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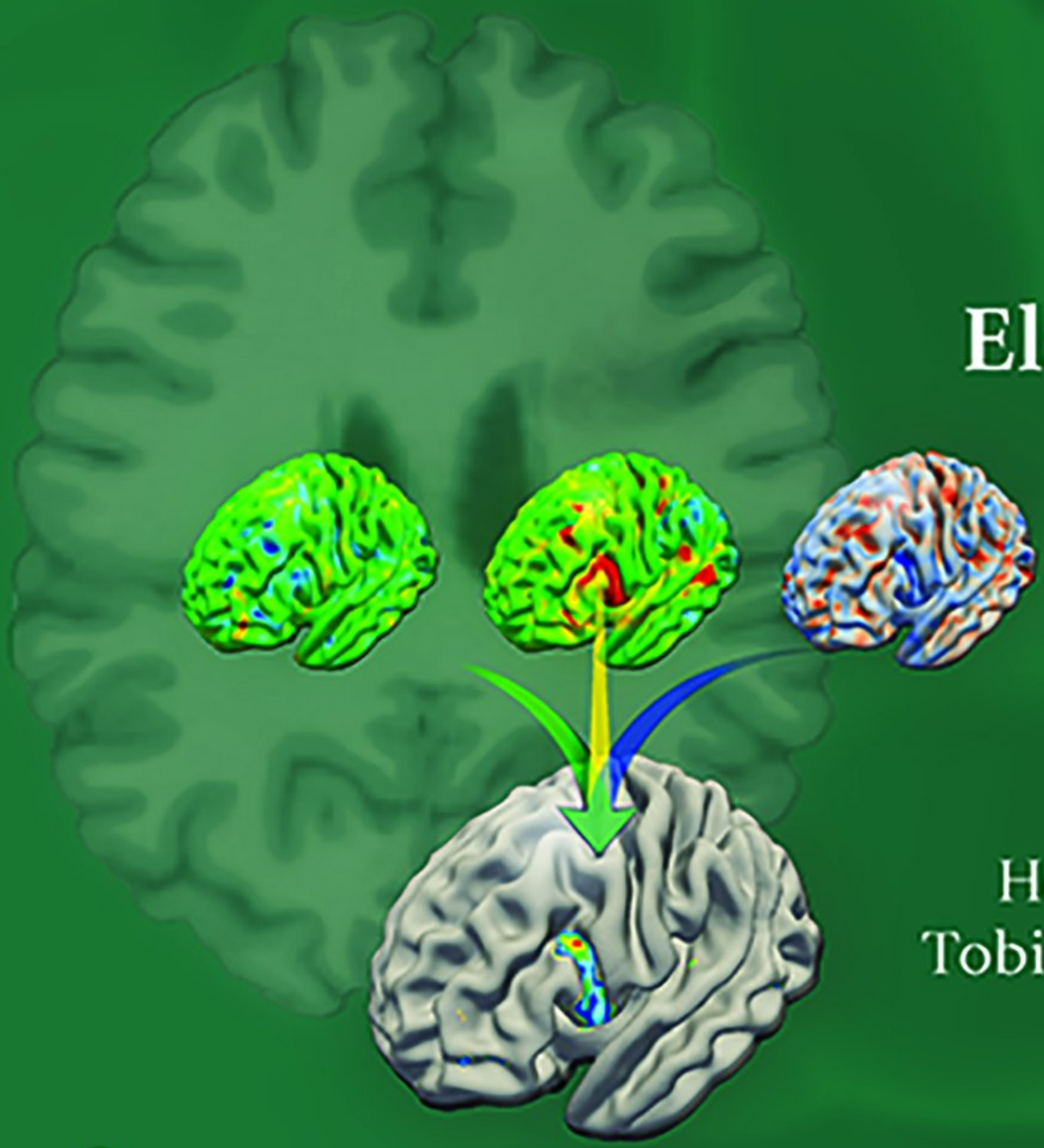
SIXTH EDITION

WYLLIE'S TREATMENT OF EPILEPSY

PRINCIPLES AND PRACTICE



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Cover Art: Exciting new research demonstrates that MRI post-processing analysis using first-order texture models may enhance localization of subtle focal cortical dysplasia, as in this illustrative case adapted from Figure 2, Chapter 77.

With thanks to Dr. Andrea Bernasconi for sharing this case, and to Mr. Jeffrey Loerch for his artistic rendition.

DEDICATION

To my dance partner, Dr. Robert Wyllie, our choreographer, Mr. Dick Blake, and all the outstanding caregivers at Cleveland Clinic.

In the pursuit of both of my two passions, medicine and dance, I have been privileged to study and practice with the very best.

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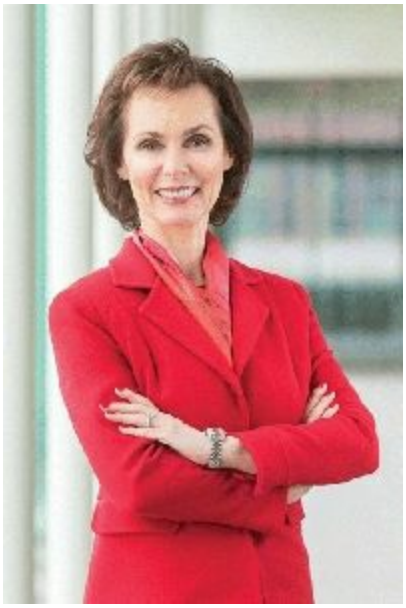

Dr. Elaine Wyllie, Professor, Lerner College of Medicine, is a pediatric epilepsy specialist at Cleveland Clinic. Presenting six editions of Wyllie's Treatment of Epilepsy is one of her proudest achievements. She has also published over 250 reports on her research in epilepsy in scientific journals and received many honors including the prestigious Epilepsy Research Award from the Milken Family Foundation and the American Epilepsy Society. Now that her two sons are grown and pursuing their own scientific careers, Dr. Wyllie's hobby is ballroom dancing with her husband on a professional level.

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FOREWORD

Epilepsy is one of the most common of all chronic neurologic disorders. An Institute of Medicine of the National Academies consensus report, Epilepsy Across the Spectrum: Promoting Health and Understanding, released on March 30, 2012, indicated that one in 26 individuals during their lifetime will develop a seizure disorder. The prevalence of epilepsy appears to be increasing and is twice the number of patients with multiple sclerosis, Parkinson disease, and autism spectrum disorders combined. Approximately 2.2 million people in the United States and 65 million individuals worldwide have epilepsy. One hundred and fifty thousand individuals develop a seizure disorder each year in the United States, the highest risk groups being in the most vulnerable people, that is, the very young and very old.

The toll of this common neurologic disorder is enormous. In addition to seizures, other comorbid conditions impacting patients' quality of life include depression and anxiety, cognitive impairment, psychosocial debilitation, lack of employment and educational opportunities, social isolation, and inability to operate a motor vehicle. These concerns are most prominent in patients with drug-resistant epilepsies that may be physically, medically, and socially disabling. Practical considerations for selected individuals with epilepsy include the cost of medications, access to appropriate epilepsy care, and limited health insurance. Finally, the care of people with epilepsy in many developing and resource-poor countries, an estimated 80% of the 65 million patients worldwide, is largely unsatisfactory and almost nonexistent.

There are still important gaps in knowledge regarding diagnosis and management of individuals with recurrent seizures, even though epilepsy has been recognized as an important illness for over 3000 years. It was first referred to as the "falling down disease" in the ancient Babylonian cuneiform medical text, the Sakikkū. Hippocrates, considered the father of medicine, made the seminal observation in the 5th century BCE that epilepsy was not a divine illness, but a malady involving the brain that may have a hereditary association. Our present understanding of epilepsy began with the pivotal studies of John Hughlings Jackson (1835–1911) and his colleagues at the National Hospital for Diseases of the Nervous System including Paralysis and Epilepsy in Queen Square, London. Jackson proposed that the cerebral cortex was an essential structure for epileptogenesis and introduced the basic tenets of focal epilepsy. The writings and teachings of Jackson in the last two decades of the 19th century (summarized in the two volume series edited by James Taylor, Selected Writing of John Hughlings Jackson, Staples Press, London, 1958) remain the foundation and cornerstone of our current understanding of clinical epileptology.

The 20th century witnessed enormous changes in our knowledge of epilepsy and in the development of diagnostic techniques and potential therapeutic modalities. Students of epileptology know well the history of the introduction and advances in EEG, antiepileptic drug therapy, neuroimaging, and epilepsy surgery in the past century. Unfortunately, despite these important contributions, approximately one-third of patients at present have drug-resistant epilepsy that may be debilitating to the people with epilepsy, their families, and caregivers. Adverse effects of therapy further may comprise the individual's quality of life.

The sixth edition of Wyllie's Treatment of Epilepsy will serve as an outstanding testimony to the

enormous progress in the evaluation and treatment of people with epilepsy that has been made by the individuals at the forefront of experimental and clinical research. Significant changes both in content and authors have been made since the fifth edition. The 95 chapters represent an international effort with the pioneers in epilepsy research and leading figures in patient care providing contemporary reviews of pivotal information as well as a glimpse into future advances. A virtual "Who's Who" in epilepsy that includes both relatively junior up-and-coming investigators and senior well-established individuals represents the contributing authors for this comprehensive textbook. The editor-in-chief and associate editors should be congratulated for identifying and properly motivating this distinguished group of experts to share their knowledge and experience in their chapters.

As has been true with prior editions of Wyllie's Treatment of Epilepsy, the volume is superbly organized into six parts each with multiple sections. Impressive leaders in epilepsy who are also prolific investigators serve as the associate editors. The reader is able with minimal effort to navigate through the textbook and identify a subject of interest and read a comprehensive but concise chapter on a wide range of material. This volume is essential for individuals involved in clinical research and patient care both in the community as well as academic centers. This should serve as a "go to" source of information in clinical epileptology. The broad contents of the sixth edition will have a putative beneficial effect on the care and management of people with epilepsy.

I am extremely honored and privileged to be invited to present the sixth edition of Wyllie's Treatment of Epilepsy and recognize that this excellent book will superbly serve the needs and goals of our patients. One century ago phenobarbital (introduced for epilepsy in 1912) was the only appropriate treatment available for the treatment of seizure disorders, and many people with epilepsy were relegated to epilepsy colonies. This textbook will both document the tremendous advances in our understanding and management of seizure disorders and also indicate ongoing areas of investigation that may result in effective therapeutic modalities. The existing gaps in knowledge in the diagnosis and treatment of epilepsy are significantly narrowed in this outstanding international effort that will inspire future research endeavors and advance the cause of patient care. The care and management of people with epilepsy must go beyond reducing seizure tendency, also attempting to enrich the lives of our patients and allowing the individuals to become productive and participating members of our society. Wyllie's Treatment of Epilepsy will assist in this task.

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Preface

Since the conception of our first edition in 1991 through our current sixth edition, we have been working diligently to perfect this text. It is considered the book with no peers, because its diverse authors are the most influential experts on the world stage today. Their informative chapters present the latest advances and authoritative research in epilepsy medicine, giving us the current state of scientific knowledge and the most up-to-date approach to clinical treatment.

It is our privilege to announce a new concept introduced with this edition. The esteemed authors have collaborated to create an electronic bank of over 500 board review-style questions spotlighting key concepts for active learning. Whether you are studying for a board examination or sharpening your clinical skills for daily practice, completing these skillfully crafted questions on-line will afford great insight and understanding.

We are honored to present this sixth edition, and trust you will find it both practical and enlightening.

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PART I PATHOLOGIC SUBSTRATES AND MECHANISMS OF EPILEPTOGENESIS

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ASSOCIATE EDITOR: HOWARD P. GOODKIN

CHAPTER 1 EPIDEMIOLOGIC ASPECTS OF EPILEPSY

CHRISTINE LINEHAN AND ANNE T. BERG

INTRODUCTION

Epidemiology is the primary research branch of public health. As such, the goal of epidemiologic investigations is to provide information about the frequency in the population of various diseases and conditions, to identify high-risk groups, to provide leads into causation and prevention, as well as to monitor trends over time and across regions or countries.

Estimations of the frequency of epilepsy within the population have recently been revised upward from an estimated 50 million people worldwide (1) to approximately 69 million people (2). The disparity in these figures may be partially explained by the fact that while the lower estimate is derived from a "best guesstimate" by key informants in 160 countries, the higher estimate is based on a meta-analysis of 65 prevalence studies, conducted in 37 countries, which met a predefined inclusion criterion. The meta-analytic study may be deemed to have a stronger empirical basis and may therefore provide a more accurate estimate of the true numbers of people worldwide with epilepsy.

A breakdown of these data by geographical location highlights the uneven distribution of epilepsy throughout the globe. Of the estimated 69 million persons worldwide who have epilepsy, 45 million (65%) are estimated to live within rural regions of countries classified by the World Bank as "developing," with a further 17 million (25%) living within urban areas of these countries. Just 7 million individuals, approximately 10% of all those with epilepsy worldwide, are estimated to live in "developed" countries (2).

The greater burden of epilepsy observed in developing regions is multifaceted, but a major contributor is the "treatment gap," that is, the difference between the number of individuals with active epilepsy on the one hand and the number who have difficulty accessing or adhering to treatment on the other. Estimates suggest that the treatment gap may exceed 75% in low-income countries, a figure that compares unfavorably with the estimated 10% gap observed in countries of high income (3). Despite the considerable skewing of prevalence within developing countries and the challenges of delivering optimal health care, epidemiologic research is hampered in these jurisdictions, most particularly given the challenges of sourcing accurate population-based denominators that are typically available in the developed world (4).

Prevalence estimates provide an important indicator of the burden of epilepsy worldwide. Mortality data are similarly used to quantify, albeit crudely, the impact of the condition within populations. The Global Burden of Disease (GBD) study, pioneered by the World Health Organization, the World Bank, and the Harvard School of Public Health and supported by the Bill and Melinda Gates Foundation (5), gathers cause of death data across the globe. Mortality data from GBD 2010 indicate that 117,600 persons with epilepsy die annually, equating to 0.3% of all deaths

worldwide. Mortality statistics, however, mask the burden of disease among those living with epilepsy. Acknowledging the need to define burden beyond mortality, the GBD study introduced a new metric to measure the burden of diseases, injuries, and risk factors—the DALY (disability-adjusted life year). DALYs were calculated in GBD 2010 as the sum of years of life lost and years lived with a disability (6). Using this algorithm, epilepsy is estimated to contribute 17,429,000 DALYs (0.7%) to the GBD.

While the GBD data provide valuable insights into the global burden of epilepsy, commentators have called for more detailed information that would breakdown these data by type of epilepsy and seizure frequency, factors that are strongly associated with quality of life (7). GBD's own disability weightings, which quantify the health loss associated with epilepsy, reflect the strong association between severity and impact. The weighting for treated epilepsy, where an individual is seizure free, is 0.072. In contrast, the weighting of "severe" epilepsy is 0.657 (8). This latter weighting was almost the highest rating allocated to any of the disabilities assessed in GBD 2010 and can be interpreted within the context of a DALY weighting of one "essentially meaning dead" (9).

The burden of epilepsy, however, extends beyond physical health status. Stigma and discrimination are common features of the condition worldwide (10,11). Profound social isolation (12), feeling of shame and discomfort (13), and higher risk of psychiatric disorder (14) are among a host of variables contributing to a compromised quality of life. Poor employment opportunities, lost work productivity, and out-of-pocket health care expenses contribute to the economic burden of epilepsy not only for the individual with epilepsy but also for the family and the wider community (15). In combination, these findings leave little doubt regarding the substantial burden of epilepsy.

The first epidemiologic study of epilepsy was conducted in 1959 by Leonard T. Kurland and reported population-based data from Rochester, Minnesota, over a 10-year period. Kurland acknowledged that data existed from "numerous reports based on proportionate hospital admission rates and selected case series" but observed that "these data are not necessarily representative of a population from which the patients are drawn" (16; p. 143). This observation was to profoundly impact not only the future of epidemiologic studies in the field but moreover the prevailing view of epilepsy and its prognosis. What Kurland had observed was that studies based on institutionalized patients suffered an inherent bias whereby those with more severe levels of epilepsy were overrepresented. Those with milder forms of epilepsy were less likely to attend specialist referral centers and were therefore less likely to be identified in these studies. The consequence of failing to include those with milder forms of epilepsy in epidemiologic studies was that epilepsy appeared an unremitting and chronic condition affecting a somewhat smaller proportion of people with epilepsy in the population (17).

Early epidemiologic studies that followed from Kurland's work contributed substantially to our current understanding of epilepsy. Additional studies exploring the Rochester longitudinal population-based datasets, for example, illustrated that the occurrence of epilepsy and isolated seizures was relatively common (18). These datasets also revealed that the probability of being in remission, as defined by 5 consecutive years of seizure freedom, was also more common than previously thought (19), an important consideration for investigators determining prevalence estimates (Fig. 1.1). These early epidemiologic findings provided an evidence base of the occurrence and prognosis of epilepsy that contributed to advances in the treatment and management of seizures (17).

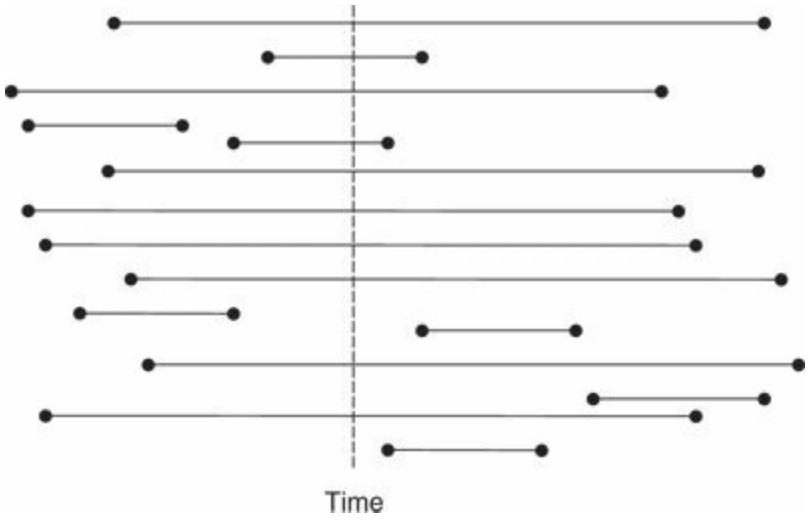

Figure 1.1. Prevalence bias. Each horizontal line represents a case with active disease (i.e., a prevalent case). The length of the line represents the time of the active disease, with onset to the left and offset or death to the right. The dashed vertical line represents the day on which prevalence is measured. Long-duration cases are oversampled (8 of 8 are ascertained on the prevalence day) relative to short-duration cases (2 of 7 are ascertained on the prevalence day).

Epidemiologic investigations since these early studies continue to inform and challenge our understanding of epilepsy. This chapter aims to outline current definitions and distinctions in epidemiologic research. In addition, findings from more recent studies and the challenges presented to investigators conducting these studies are outlined.

FREQUENCY MEASURES OF INCIDENCE AND PREVALENCE

Incidence is expressed as the number of new cases of disease in a standard-sized population per unit of time—for example, the number of cases per 100,000 population per year. Prospective studies of incidence are advocated as they permit observation of any changes in the incidence rate (20) and may therefore identify risk factors that play a causal role in the development of epilepsy (21,22). Ongoing surveillance studies of this type, however, are time consuming and costly (20,23) and are therefore less common than prevalence studies (20,23) and less likely to be conducted in resource-poor countries (24). Incidence rates for epilepsy are typically between 30 and 80 per 100,000 population per year in developed countries but have been observed to exceed these figures. Table 1.1 presents a selection of studies illustrating this trend.

Table 1.1 Incidence and Prevalence of Epilepsy as Reported in Selected Population-Based Studies Throughout the World

	First author/year	Country/region	Methodology	Age group (years)	Incidence/100,000/year	Prevalence/1000
Africa	Houinato et al. (2013) (25)	Benin	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy followed by capture–recapture method	All ages	69.4	38.4 lifetime following capture–recapture
	Mung'ala Odera et al. (2008) (26)	Kenya	Combined data from two door-to-door studies	Children	187	41 lifetime 11 active
	Dozie et al. (2006) (27)	Nigeria	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy	All ages	—	12 active
Latin America	Chong et al. (2013) (28)	Arizona–Mexico Border	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy	All ages	—	14.3 lifetime 11.8 active
	Noronha et al. (2007) (29)	Brazil	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy	All ages	—	9.2 lifetime 5.4 active
	Melcon et al. (2007) (30)	Buenos Aires	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy	All ages	—	6.2 lifetime 3.8 active
Europe	Dura-Trave et al. (2008) (31)	Spain	Cases referred to neuropediatric reference centre	Children under 15 y	62.6	—
	Christensen et al. (2007) (21)	Denmark	Data Linkage (Civil Registration and Hospital Register Databases)	All ages	68.8	5.7 lifetime
	Olafsson et al. (2005) (32)	Iceland	Cases identified via countrywide surveillance system in health care facilities with confirmatory review by neurologists	All ages	56.8 all unprovoked seizures; 23.5 single unprovoked seizures; 33.3 epilepsy	—
North America	Kaiboriboon et al. (2012) (33)	Ohio	Cases identified via Medicaid claims database	18–64 y	362	13.2 lifetime
	Benn et al. (2008) (34)	New York	Cases identified via review of local hospital and nursing home registers with follow-up interviews	All ages	41.1[a]	—
	Kobau et al. (2008) (35)	USA	Self-report omnibus health survey	Over 18 y	—	16.5 lifetime 8.4 active
Asia	Fong et al. (2008) (36)	Hong Kong	Population-based phone screening followed by neurologic validation	All ages	—	8.49 seizure disorders 3.94 active
	Tran et al. (2006) (37)	Central Lao	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy	All ages	—	7.7 active
	Mani et al. (1998) (38)	Rural South India	Door-to-door survey screening with confirmatory examination of those screening positive for epilepsy	All ages	49.3	4.19 lifetime 3.91 active

[a]First unprovoked seizure and newly diagnosed epilepsy.

Worldwide, rates vary across regions, with rates being typically higher in resource-poor countries (22), most especially in Africa and Latin America, where figures can exceed 100 per 100,000 population (39–41). Rates also differ by age, but differentially in developed and resource-poor countries. In developed countries, rates are highest among infants and older persons (31,42–44). Although incidence rates among children have fallen over the last three decades in developed countries, this decrease has been offset by an increase among older persons (45). A different age-related pattern emerges in developing countries, however, where a decrease in incidence is observed with age (22). The larger proportion of children in the population in developing countries is thought is to contribute to the higher overall incidence rates when compared with developed countries (21,22).

Prevalence studies measure the total number of persons with epilepsy at a specific moment in time. Prevalence rates are usually expressed as the number of persons with epilepsy per 1000 population. Estimates of active epilepsy are typically the focus of prevalence studies, with those in remission or who are not receiving treatment at the time of case ascertainment being excluded. A

"plethora of studies" that consistently report prevalence estimates of active epilepsy in developed countries of between 4 and 10 per 1000 population suggest that there is "little justification for further cross-sectional studies of prevalence" (46, p. 168) in these countries. Recent findings from Norway, however, of 12 per 1000 treated epilepsy and 7 per 1000 active cases in a population that excluded high-risk groups such as older persons have led investigators to suggest that the true prevalence of epilepsy in developed countries may be higher than previously reported (47). Prevalence estimates typically increase with age and are generally higher among males than females (20) although this difference may not always reach statistical significance.

Prevalence estimates in resource-poor countries are generally higher than in developed countries (46). Median prevalence of active epilepsy in Latin America is reported as 12.4 per 1000 population; however, this finding conceals widely varying findings from individual studies ranging 5.1 to 57 per 1000 population (48). This wide variation in estimates is also observed in Africa where estimates have been reported ranging from 5.2 to 58 per 1000 (49,50). While researchers note that known risk factors, such as environment, contribute to the high prevalence estimates on the African continent (26), some authors suggest that the true prevalence estimate may actually be higher again as disclosure of the condition is particularly problematic (51). Reviews of studies conducted in Asia, perhaps surprisingly, report findings aligning more closely with those in developed countries. This has led some investigators to speculate whether there is a specific protective factor as yet unknown in Asia or whether the finding reflects specific risk factors in Latin America and Africa (23). Table 1.1 presents findings from some recent studies worldwide.

Several recent studies have examined the relative frequency, if not absolute incidence, of different forms of epilepsy in well-characterized series of incident patients who were reasonably representative of the populations from which they were drawn (Table 1.2). Apart from the obvious difference between adults and children, there is a degree of variation among the studies just of children as well. Whether this represents real differences across populations or methodologic difference between studies is not clear. Certainly, patterns of referral to recruitment sources as well as diagnostic ability of the physicians who evaluate the patients could create apparent difference between studies where none exist. Such concerns aside, a few generalities can be drawn. Fewer children than adults are likely to have an unclassified form of epilepsy. In children, idiopathic focal epilepsies (largely dominated by benign rolandic epilepsy) comprise about 5% to 10% of childhood-onset epilepsy. The idiopathic generalized epilepsies comprise 20% to 40%. Finally, between 10% and 20% of childhood-onset epilepsy falls into the category of secondary generalized. These are some of the most devastating and intractable forms of epilepsy and include West and Lennox–Gastaut syndrome.

Table 1.2 Distribution of Epilepsy Syndromes in Newly Diagnosed Patients from Eight Different Countries

Syndrome	Connecticut[a] (52)	France[b] (53)		The Netherlands (54)	Italy[c] (55)	Columbia (56)	Sweden (57)	Japan (58)	Iceland (32)
	Children <16 years	Children <14 years	Adults ≥25 years	Children <16 years	Children	All ages	Children <16 years	Children <16 years	All ages
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
11 idiopathic focal	61 (10%)	47 (9%)	1 (<1%)	31 (7%)	21 (9%)	2 (2%)	46 (23%)	55 (5%)	16 (6%)
12 symptomatic focal	71 (12%)	34 (7%)	81 (27%)	74 (16%)	92 (38%)	27 (29%)	9 (4%)	345 (29%)	74 (26%)
13 cryptogenic focal	227 (37%)	121 (24%)	107 (35%)	87 (19%)	0 (0)	45 (49%)	49 (24%)	507 (42%)	78 (27%)
21 idiopathic generalized	126 (21%)	199 (40%)	15 (5%)	195 (42%)	67 (28%)	9 (9%)	37 (18%)	95 (8%)	30 (10%)
22 cryptogenic/ symptomatic generalized	43 (7%)	39 (8%)	0 (0)	29 (6%)	50 (21%)	2 (2%)	47 (23%)	173 (14%)	6 (2%)
23 symptomatic generalized	9 (1%)	14 (3%)	7 (2%)	41 (9%)	1 (<1%)	0 (0)	0 (0)	0 (0)	1 (<1%)
31 generalized and focal features	5 (1%)	13 (3%)	0 (0)	1 (<1%)	1 (<1%)	0 (0)	0 (0)	0 (0)	8 (3%)
32 unclassified	71 (12%)	34 (7%)	94 (30%)	2 (<1%)	19 (8%)	6 (7%)	17 (8%)	21 (2%)	77 (27%)
Total number of patients	613	501	305	462	251	92[d]	205	1196	290

[a]The cryptogenic and symptomatic localization–related categories were redefined to be consistent with the interpretation of other authors and to facilitate comparisons.

[b]Limited to children <14 y of age.

[c]Pediatric epilepsy center (referral) in Milan—published prior to 1989.

[d]Listed as "special syndrome."

CURRENT DEFINITIONS AND DISTINCTIONS USED IN EPIDEMIOLOGIC EPILEPSY RESEARCH

Epilepsy (recurrent, unprovoked seizures) must be distinguished from many other conditions and situations in which seizures may occur. The following definitions are generally accepted and are in widespread use.

Epileptic Seizure

An epileptic seizure is a "transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (59). Epileptic seizures must be distinguished from nonepileptic seizures and from other conditions that may produce clinical manifestations that are highly similar to those caused by epileptic seizures.

Acute Provoked Seizure

An acute provoked seizure is one that occurs in the context of an acute brain insult or systemic disorder, such as, but not limited to, stroke, head trauma, a toxic or metabolic insult, or an intracranial infection (60).

Unprovoked Seizure

A seizure that occurs in the absence of an acute provoking event is considered unprovoked (60). A history in the past of stroke, trauma, or other condition may be present; however, at the time of the seizures, no specific acute insult has occurred.

Epilepsy

The widely accepted operational definition of epilepsy requires that an individual has at least two unprovoked seizures on separate days, generally 24 hours apart. An individual with a single unprovoked seizure or with two or more unprovoked seizures within a 24-hour period is typically not at that time considered to have met the criteria for the diagnosis of epilepsy per se (60). An International League Against Epilepsy (ILAE) document from 2005 attempted to provide a conceptual definition of epilepsy, which entailed the notion of an enduring underlying predisposition to unprovoked seizures (59). The definition was presented, however, as an operational definition and engendered considerable controversy and response (61–63) precisely because there was no way to ensure that it would be consistently and validly applied across different settings by different investigators, a quality that is a prerequisite for meaningful research. A new practical clinical definition of epilepsy has now been agreed upon. Epilepsy is defined as any one of the following conditions: (a) at least two unprovoked (or reflex) seizures occurring >24 hours apart; (b) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or (c) diagnosis of an epilepsy syndrome. Epilepsy is considered to be resolved for individuals who either had an age-dependent epilepsy syndrome but are now past the applicable age or have remained seizure free for the last 10 years and off antiseizure medicines for at least the last 5 years (63). As this definition was just published in 2014, few studies have used it, and most of the literature is based on the earlier definition of two or more unprovoked seizures.

A first seizure often is the first identifiable sign of epilepsy, and in some cases, it is possible to recognize the specific underlying disorder (form of epilepsy) at its earliest presentation (53). In the case of Dravet syndrome, the first definitive sign may be a febrile seizure—typically hemiclonic and prolonged—and, with a genetic test, the epilepsy may be diagnosed before "unprovoked" seizures emerge (64). Such situations may be rare and are difficult to ascertain and handle well in many epidemiologic studies because of the relatively crude diagnostic information used. For the field of epilepsy, however, they are increasingly important and should not be ignored.

Etiology

Terminology for referring to etiology has evolved considerably in the last several years. The old, traditional terms, idiopathic, cryptogenic, and symptomatic, are gradually being abandoned in favor of clearer more descriptive language. The 2010 ILAE Commission report recommended as an initial starting point the terms "genetic," "structural–metabolic," and "unknown" to refer to classes of causal factors. Note, these are categories for causes, not the form (syndrome) of epilepsy per se. Each was carefully defined: genetic refers to causes for which, to our best understanding, the seizures are a direct result of the genetic error and seizures are the core symptom of the disorder. Evidence concerning a genetic role may come from molecular studies but may also be derived from well-conducted clinical studies (e.g., twin studies). This differs from the old idiopathic (meaning "presumed genetic") as a basis for the genetic inference is stated, and, unlike idiopathic, genetic includes disorders that do not necessarily have a "benign" outcome. The unwieldy term "structural–metabolic" is intended to identify people with known underlying brain disorders that are primary contributors to their epilepsy. As most metabolic and many structural disorders have a genetic basis, the distinction between genetic–structural–metabolic may seem fuzzy. The distinction focuses on the mechanism by which the genetic defect influences epilepsy as well as the constellation of symptoms presented by the patient, primarily seizures or seizures secondary to some other medical condition.

The role of autoimmunity, an extremely important contributor to some epilepsies is not adequately evoked by the term structural–metabolic either (65,66). As the mechanisms linking the precipitating cause to development of epilepsy become better understood, it becomes more difficult to pigeonhole some causes. For example, recent evidence suggests that some forms of cortical malformations that cause epilepsy are themselves due to viral infections in utero (67). Finally, for referring to situations in which the cause is simply unknown, the term "unknown" was suggested. This was meant to be considered as a true statement of uncertainty or ignorance, without assumptions.

The ability to identify the likely causes of epilepsy has changed dramatically over time with the introduction and increasing sophistication of neuroimaging and genetic testing. These changes are not uniformly implemented across countries or even across subpopulations within a country. Consequently, the unevenness of precision raises problems for cross population (including across time period) comparisons. For epidemiologic purposes, especially on the global level, a very pragmatic distinction could be made between what might be called complicated and uncomplicated epilepsy. Complicated epilepsy would include any epilepsy associated with a factor that is presumed to cause epilepsy (stroke, trauma, tuberous sclerosis, etc.) or any evidence of neuroimpairment (substantial developmental delay, intellectual impairment, abnormal motor or sensory exam) that can result from a cortical insult. Implicitly, uncomplicated would refer to epilepsy in which there is no clear insult or condition to which the occurrence of the epilepsy can be attributed and the individual is neurotypical (normal exams and cognition).

Grey Areas

Neonatal seizures (i.e., those occurring in an infant <28 days old) are usually differentiated from epilepsy for a variety of reasons; however, this approach makes little sense as several specific forms of epilepsy have been reported in this age group (68), and there is no good reason that factors that would be considered structural or metabolic causes of epilepsy in an older individual would be treated differently in the neonate. Unfortunately, epidemiologists often do not have the detailed information needed to distinguish the child with a seizure secondary to transient hypoglycemia from a child who seizes because of a KCNQ2 encephalopathy (69) or a brain malformation. Febrile seizures are a well-described and recognized seizure disorder, which, for historical reasons, has been distinguished (both clinically and in research) from epilepsy. For those involved in detailed genetic investigations, this may be an inappropriate distinction. For the epidemiologist, however, who may not always have the necessary clinical and particularly the genetic detail, the distinction is of value. It also has important clinical implications for the treatment of most of these children with such seizures.

Epilepsy Syndromes

Epilepsy syndromes have been alluded to above and are presented in greater detail in subsequent chapters of this book. Epilepsy, like cancer, is not a single disorder, and the efforts to identify specific forms of epilepsy reflect the importance of the diversity within the epilepsies. The epilepsy syndromes represent forms of epilepsy that have different causes, different manifestations, different implications for short- and long-term management and treatment, anticipatory guidance, genetic counseling, and long-term outcomes. Many epidemiologic studies do not attempt to identify specific forms of epilepsy; however, in large-scale population- and community-based studies, it is possible to do so, provided the investigators have access to the necessary information and the expertise needed to

diagnose these syndromes (52–54). As the questions in epileptology become increasingly sophisticated, including precise characterization of specific causes, types of seizures, and types of epilepsy, the gap between what typical epidemiologic studies can do versus the types of information needed from them has been widening.

Seizure Types

Perhaps the greatest and most relevant distinction for broad-scaled epidemiologic investigations is between convulsive and nonconvulsive seizures as a very crude marker of severity. The term tonic–clonic should generally be eschewed in epidemiologic studies as it is often misused to refer to any "big" seizure regardless of whether tonic and clonic components are both present. Diagnostic precision to identify other seizure types is generally inadequate in epidemiologic studies, and the basis of identifying other seizure types requires significant scrutiny.

EPIDEMIOLOGIC CHALLENGES

Epidemiologic studies have provided valuable insights into the frequency of seizures within the population and have provided the initial impetus for some of the distinctions outlined above. As Kurland noted, however, epidemiologists need to be vigilant to potential sources of bias that threaten the validity of their findings. The ability of diagnosticians to appropriately identify cases and the capabilities of epidemiologists to identify those cases within the population are fundamental issues within the field of epidemiology. We also note that, as the clinical and scientific field of epilepsy has grown much more sophisticated, epidemiologists must work to keep up with important diagnostic and lexical distinctions.

Diagnostic Issues and Considerations in Ascertaining Cases

Seizures and epilepsy present a complex situation because the diagnosis is not based on a single source or type of information. Rather, epilepsy is a clinical diagnosis supported to a greater or lesser extent by a wide range of data obtained from several sources: the history (both from the patient and witnesses) of the events believed to be seizures, the circumstances under which the events occur, the past medical history, medications, a neurologic examination, reliable EEG, and increasingly neuroimaging (70). To have a valid diagnosis, one must also be able to rule out many other conditions that mimic seizures. These disorders include, but are not limited to, movement disorders, parasomnias, attention deficit/hyperactivity disorder, pseudo- or nonepileptic seizures, transient ischemic attacks, and syncope (71,72).

Ideally, a diagnosis of epilepsy should be undertaken by medical practitioners with expertise in epilepsy (73). Unfortunately, access to neurologists and epilepsy specialists is generally poor in developing countries and often poor in developed countries as well. Consequently, diagnoses may be made by those with only minimal expertise in the field (35,74). Estimates of misdiagnosis rates suggest that over one-fifth of persons with a diagnosis of epilepsy may be misdiagnosed (75,76). Reevaluation of initial diagnosis of epilepsy in epidemiologic studies reports rates of 23% (77,78) with diagnostic doubt among patients diagnosed by neurologists and nonspecialists reported at 5.6% and 18.9%, respectively (79). In 2007, a UK All Party Parliamentary Group on Epilepsy convened to determine the "human and economic cost of epilepsy" in England. The report estimates that 74,000

people in England are misdiagnosed with epilepsy and are therefore receiving inappropriate treatment. The financial cost of unnecessary or incorrect treatment combined with lost employment was estimated in 2007 at £134 million per annum (80).

Epidemiologic studies that rely on medical registers for case ascertainment provide valuable insights into levels of misdiagnoses. Christensen et al. (21), for example, randomly selected 200 patients with an ICD diagnosis of epilepsy from the Danish National Hospital Register, a national register of all discharges and outpatient cases from Danish hospitals. The authors found that almost one in five (19%) of the sample did not fulfill the ILAE criteria for an epilepsy diagnosis. In fact, approximately 7% of patients were given an epilepsy diagnosis on the basis of one seizure. Christensen et al. (81) also noted that while the validity of epilepsy diagnosis from the register was moderate to high, there was low predictive value for epilepsy syndromes.

Primary care registers, a common source of case ascertainment in epidemiologic research, have also been found to include persons incorrectly diagnosed with epilepsy. Gallitto et al. (82) gathered population-based data from general practitioners (GPs) in the Aeolian Islands. All established or suspected cases of epilepsy were evaluated by epileptologists in the local outpatient services with the support of the local GPs or, for those with additional disabilities, within the family home. The evaluations comprised a review of medical notes and where necessary EEG or neuroradiologic investigation. Following the epileptologic evaluation, 30% of established and suspected cases were identified as not fulfilling the diagnostic criteria for epilepsy.

These high levels of misdiagnosis have resulted in calls for a gold standard diagnostic criterion to distinguish epilepsy from other conditions with similar clinical features (75). The UK National Institute for Health and Clinical Excellence (NICE) provides support to diagnosticians via its recently updated guidelines “The epilepsies; the diagnosis and management of the epilepsies in adults and children in primary and secondary care” (83). The NICE recommends that all individuals with a recent-onset suspected seizure be seen within a 2-week period by a specialist, defined as a medical practitioner with expertise in epilepsy. The implementation of these guidelines for children is currently being monitored by Epilepsy12, a nationwide audit aiming to ensure a standardized level of provision across the United Kingdom (84).

In addition to the determination of whether or not someone has epilepsy, adequate information is needed to identify the specific form of epilepsy and its underlying cause. While this level of detail is frequently absent from traditional epidemiologic studies, it must be incorporated in the future if epidemiologic studies are to continue to inform scientific and clinical endeavors relevant to epilepsy as it is understood and treated today. Without a meaningful diagnostic evaluation, epidemiologic studies can do little more than provide an approximate head count, which previous work has shown to be rather error prone. The lumping together of highly diverse disorders that share the diagnostic label “epilepsy” also limits the ability of epidemiologic studies to provide meaningful prognostic information.

The case ascertainment options described above, based on medical registers, may not be suitable for all epidemiologic studies. Where these registers are unavailable, or may be considered unrepresentative, other more population-based methods may be used to identify people with epilepsy. As was observed for medical registers, these methods also have their own unique challenges. Screening questionnaires, for example, are a common tool used in epidemiologic studies. Methodologies employing screening questionnaires typically comprise two phases. In the first phase, a screen is used to identify positive cases. In the second phase, these positive cases are evaluated clinically to confirm the presence of epilepsy. Noronha et al. (29), for example, used a screening tool

developed by Borges et al. (85) in the first phase of their study to determine the prevalence of epilepsy in Brazil. The screening tool reported sensitivity and specificity at 96% and 98%, respectively. Similarly, Melcon et al. (30) used a modified version of a screening tool from the Copiah County study (86) to identify potential cases for inclusion in their prevalence estimate of epilepsy in Argentina. This screening tool also reported acceptable levels of sensitivity and specificity at 95% and 80%, respectively. More recently, a three-stage survey methodology has been proposed that comprised a two-item first survey, a more extensive second survey, and a third-stage clinical validation. This methodology reported a sensitivity of 49% and specificity of 100% and was found to be 37% less expensive than the more traditional two-stage process (87).

Screening tools are advocated by the World Health Organization, whose "Global Campaign Against Epilepsy" supports those undertaking epidemiologic research in resource-poor countries. Demonstration projects managed under this program, in addition to assessments of local knowledge, attitude, and health service provision, undertake epidemiologic door-to-door studies to determine prevalence estimates. Screening tools developed by WHO (88) have been used in large-scale national epidemiologic studies (56). Notwithstanding the successful application of screening tools in many studies, the diagnostic sensitivity and specificity of these tools can, however, be poor, and the training of physicians or other health care professionals charged with validating positive screens may be compromised by poor access to such basic diagnostic tools as EEGs.

Other case ascertainment sources used in epidemiologic studies include prescription databases recording antiepilepsy drug usage. By definition, these epidemiologic studies estimate "treated epilepsy" and are more common in developed countries where the treatment gap is minimal. Prescription databases have been found to offer a suitable means by which the prevalence of epilepsy can be determined in community samples (89) as the coverage of the databases is typically far broader than medical registers. Purcell et al. (90), for example, examined rates of treated epilepsy in the United Kingdom using the General Practitioner Research Database, which provided data on prescription use of over 1.4 million persons. More recently, D'Souza et al. (91) estimated rates of treated epilepsy in Tasmania via a two-stage process of firstly, identifying all residents in Tasmania who were supplied with at least one antiepilepsy drug prescription recorded on the national prescription database over a given time period and secondly, by following up on these individuals by a postal survey to determine whether or not they were receiving this treatment for epilepsy.

A potential source of bias in identifying persons with epilepsy from prescription databases is that cases cannot be clinically validated (90,92). This bias is magnified in situations where diagnosis is not recorded on the database and where "estimates" of drug use among people with epilepsy are applied (93,94). While antiepilepsy drugs have been previously identified as "tracers" of epilepsy due to their chronic and highly specific usage (94), the growing use of antiepilepsy medication for indications other than epilepsy, such as pain, migraine, bipolar disorders, agitation, hormonal imbalance, and weight reduction, must be now considered. In general, reliance on prescription data alone is an inadequate case ascertainment method for epilepsy.

A methodology for case ascertainment that is becoming more frequently used in North American studies is the self-report survey. These studies typically include epilepsy-specific items in large population-based health surveys (95–98). The coverage of these surveys is extensive. The Canadian Health Survey, for example, was completed by over 130,000 persons, all of whom were questioned as to their health status, health care utilization, and determinants of health (95). The California Health Interview Survey 2003 provided similar data on over 41,000 persons (98).

The Behavioural Risk Factor Surveillance System (99) provides an example of the typical type of

epilepsy-specific items that can be included in these surveys: "Have you ever been told by a doctor that you have a seizure disorder or epilepsy?" A distinct advantage of this methodology is the opportunity it affords to examine not only the frequency of self-reported epilepsy among very large representative populations but also the impact of epilepsy on their health-related quality of life. Issues such as employment, education, and comorbid conditions can be examined. Most recently, the 2008 HealthStyles Survey in the United States was used to examine life satisfaction among a representative sample of community-dwelling adults with self-reported epilepsy (100).

Where these items are common to both those with and without a self-report of epilepsy, important disparities can be identified. Without doubt, this method differs from more rigorous epidemiologic studies (97). A selection bias may exist whereby, despite the broad community-dwelling population from which samples are drawn, those who agree to participate in surveys may differ in some fundamental way from those who decline. This method also faces the challenge previously observed among studies examining prescription databases whereby cases are not clinically validated. Whether those who self-disclose epilepsy do in fact have the condition cannot be determined, no more so than those who have epilepsy but chose not to disclose it. Despite these challenges, population-based surveys that are conducted on an ongoing basis as part of a health surveillance system have recently been strongly endorsed by a cross-party report published by the U.S. Institute of Medicine of the National Academies (101).

Each of the methods outlined above has its own benefits and challenges. This has led some researchers to propose that the most valid method to identify cases of epilepsy is to access multiple sources of case ascertainment (20). Data linkage studies, for example, provide opportunities to simultaneously examine both population-based and hospital-based registers (102,103). These multicase ascertainment studies make it possible "not only to estimate the number of cases missed by each source but also to indirectly estimate the number of cases missed by the combined dataset" (104, p. 134). Choice of case ascertainment, however, may not always be at the discretion of the epidemiologist. Resources of appropriately trained personnel and funding and sophistication of health care services are some of the many factors that influence how the same study might be conducted differently in different jurisdictions.

Variations in methodology have traditionally been identified as producing highly varying estimates of epilepsy (46,105). Recent research suggests that the influence of methodology on variation may have been somewhat overstated (2). Irrespective, the lack of harmonized definitions employed across studies is a cause for concern. Despite the ILAE's Commission of Epidemiology and Prognosis (60) and more recently the ILAE's Standards of Epidemiologic Studies of Surveillance of Epilepsy (106) issuing guidelines for definitions employed in epidemiologic studies, specific definitions of what constitutes "epilepsy," "active cases," and "cases in remission" differ markedly among studies. Definition of "active epilepsy," for example, vary in terms of their stated duration since last seizure, with some studies using the ILAE-recommended definition of one seizure or use of AEDs within the previous 5 years (107) and others truncating this duration to the previous 3 months (97,98). Harmonization of definitions is encouraged as it would permit valuable comparisons of findings across studies.

While the use of large-scale studies and attempts to harmonize definitions should ideally result in comparability across studies, all endeavors in clinical epilepsy research must face the challenges of epilepsy diagnosis. These are not trivial. Repeated studies from tertiary centers find that a substantial proportion of adults referred for refractory epilepsy do not have epilepsy but have nonepileptic seizures (108). These are patients who have been diagnosed by physicians, often neurologists, even

epileptologists, yet they do not have epilepsy. Nonepileptic seizures are a form of conversion disorder, a psychiatric condition. Unfortunately, distinction of nonepileptic seizures from true epilepsy requires either superb clinical acumen or admission to a monitoring unit where the events can be recorded simultaneously with EEG. The EEG, while a key tool in diagnosis, is not a test for epilepsy and is often greatly misused and misread (109–111). Without knowing the qualifications of those evaluating a patient and interpreting an EEG, the figures regarding the frequency of epilepsy in the population need to be taken with a healthy dose of skepticism. This raises further concerns regarding the epidemiologic studies that repeatedly find a relationship between other psychiatric disorders (depression, anxiety, schizophrenia, and even suicidal ideation and suicide) and epilepsy. If the epilepsy is actually a psychiatric disorder and not epilepsy, that could explain a substantial proportion of this literature. Replication of findings, if based on the same diagnostic error, should not be taken as evidence that the association is necessarily real. No obvious solution to this problem is evident at this time; however, it is a strong reminder that population-based studies may contain considerable diagnostic error, and their findings should be interpreted cautiously.

SUMMARY

Epidemiology has been key in demonstrating the relatively high frequency of seizures in the population and in challenging long-held beliefs about the uniformly poor seizure outcomes associated with seizures. Research pursuits within the epidemiology of epilepsy have come a long way from the days of simply counting how many people in a given population had seizures. Some studies are providing estimates of the frequency of specific types of epilepsy with some relatively clear patterns emerging across studies. As diagnostic technology has become more sophisticated, the methods used for ascertaining cases in a population have become appropriately more complex. Representativeness and diagnostic accuracy are increasingly at odds, especially in underdeveloped areas; however, the problem clearly exists and affects an important proportion of people considered to have “refractory” epilepsy. If these issues can be adequately addressed, cross-regional or cross-national comparisons of similarly conducted studies may help identify forms of epilepsy and causes of epilepsy that are unusually common in certain areas. This may, in turn, lead to insights into prevention. Combining the strengths of epidemiologic methods with the sophistication of new medical diagnostic technology and our growing understanding of epilepsy has the promise of advancing our knowledge of the causes, consequences, and possibly prevention of this common set of disorders.

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CHAPTER 2 THE NATURAL HISTORY OF SEIZURES

DING DING AND W. ALLEN HAUSER

It was not long ago that epilepsy was considered a lifelong condition with a low likelihood of seizure control, much less remission. This view was based largely on reports drawn from highly selected, tertiary-care center populations. However, recent retrospective and prospective epidemiologic studies based on community and hospital populations have provided more favorable information regarding the natural history of epilepsy. Appropriate counseling of people with epilepsy and their families at crucial stages during the epilepsy requires knowledge of the natural history after a first seizure, at the time of diagnosis, after a prolonged period of seizure freedom, and at time of failure of a first or second medication, which may herald the eventual onset of drug resistance or intractability. Specific important predictive factors include age of onset, gender, etiology, seizure type, electroencephalogram (EEG) pattern, number of seizures prior to treatment, early response to treatment, medication withdrawal, and epilepsy surgery. For the individual, the outcome of epilepsy strongly reflects the individual's syndromic classification and underlying etiology of the epilepsy (1).

A seizure may be the result of an acute precipitant such as a stroke or toxin (i.e., acute symptomatic) or occur in the absence of precipitating factors (i.e., unprovoked). Seizures with fever, an event occurring in 3% to 9% of children, represent a subcategory of acute symptomatic seizure. Each of these subgroups has a specific and predictable prognosis.

Seizures provoked by fever (Chapter 34), metabolic disturbance (Chapter 31), or traumatic brain injury (Chapter 28) are discussed elsewhere in the book. This chapter focuses on prognosis in persons with unprovoked seizures.

PROGNOSIS AFTER A FIRST UNPROVOKED SEIZURE

Epilepsy is a condition in which an individual has the tendency to experience recurrent unprovoked seizures. Typically, epilepsy is defined once a person experiences a second unprovoked seizure. Overall, the population risk for seizure recurrence following a first unprovoked seizure is 40% to 50% (2); however, the individual risk can vary between as low as 20% in the subsequent 5 years to higher than 80% (3–5). In one study (Table 2.1), the recurrence risk at 2 years varied from <15% in those with no identified risk factors to 100% in those with a combination of two or more risk factors (3) (Table 2.1).

Table 2.1 Seizure Recurrence After a First Unprovoked Seizure: An Extended Follow-Up

Risk factor	Recurrence in subgroups, % months of follow-up		
	12 months	24 months	36 months
Baseline ($N = 78$)	7.0	13.0	16.7
Idiopathic or cryptogenic with an affected sibling ($N = 10$)	20.0	20.0	31.0
Idiopathic or cryptogenic with a generalized spike-and-wave EEG pattern ($N = 10$)	10.0	55.0	55.0
Idiopathic or cryptogenic with prior acute seizures (all febrile) ($N = 7$)	0.0	14.0	28.6
Idiopathic or cryptogenic with abnormal neurologic examination ($N = 13$)	9.3	15.4	20.3
Idiopathic or cryptogenic with abnormal examination and additional feature ($N = 23$)	14.3	14.3	22.7
Idiopathic or cryptogenic with two or more features and normal examination ($N = 5$)	40.0	40.0	70.0
Remote symptomatic with no other features ($N = 32$)	15.9	15.9	24.8
Remote symptomatic with Todd paresis ($N = 4$)	0.0	25.0	50.0
Remote symptomatic with prior acute symptomatic seizures ($N = 3$)	100.0	100.0	100.0
Remote symptomatic with multiple seizures or SE at presentation ($N = 8$)	25.0	37.5	37.5
Remote symptomatic with two or more risk factors ($N = 12$)	41.7	75.0	75.0

EEG, electroencephalogram.
From Hauser WA, Rich SS, Annegers JF, et al. Seizure recurrence after a first unprovoked seizure: an extended follow-up. *Neurology*. 1990;40:1163–1170, with permission.

A prior neurologic insult, indicated by features such as neurologic deficits from birth (intellectual disability and cerebral palsy) or history of traumatic brain injury (TBI) or other brain injuries leading to a static lesion, is the most powerful and consistent predictor of recurrence after a first seizure (3). Other factors include an epileptiform EEG abnormality, the occurrence of previous acute symptomatic seizures, nocturnal occurrence of the seizure, and a Todd paralysis (3,6). Status epilepticus (SE), focal seizures, and a family history of epilepsy have also been identified in some but not all studies.

The risk of subsequent seizures decreases with time, with up to 80% of recurrences occurring within 2 years of the initial seizure; recurrence rates are 36% in prospective studies and 47% in retrospective studies at 2 years (7). In the National General Practice Study of Epilepsy (NGPSE) conducted in the United Kingdom, 67% of those with a single seizure had a recurrence within 12 months and 78% within 36 months (8).

There remains debate regarding the similarities between acute symptomatic seizures associated with acute brain insults and unprovoked seizures. There are many differences in terms of subsequent morbidity and mortality, and the difference in seizure recurrence among those with unprovoked seizures and individuals with a first acute symptomatic seizure is also striking. People with an acute symptomatic seizure are 80% less likely to experience a subsequent unprovoked seizure than are individuals with a first unprovoked seizure. An MRI is appropriate in the evaluation of a first presumably unprovoked seizure, but the usefulness in predicting seizure recurrence is uncertain.

In two randomized clinical trials, use of antiepileptic drugs (AEDs) in doses to maintain serum levels in the therapeutic range was associated with a reduction in the proportion of patients who experienced seizure recurrence after a first seizure (9,10). There was no benefit in terms of long-term prognosis for seizure freedom. In a prognostic model that was based on the Medical Research Council's (MRC) "Multi-center trial for Early Epilepsy and Single Seizures (MESS)" data, the estimated probability of a second seizure at 1, 3, and 5 years for individuals treated immediately following a first seizure was 26%, 35%, and 39%, respectively. In this study, no significant difference was observed between the immediate treatment group and delayed treatment group with respect to being seizure free between 3 and 5 years after randomization, quality of life outcomes, and serious complications (11). In summary, drug initiation after a first seizure decreases early seizure

recurrence but does not affect the long-term prognosis in terms of remission.

PROGNOSIS AT THE TIME OF DIAGNOSIS OF EPILEPSY

The entire natural history is modified when a diagnosis of epilepsy (recurrent unprovoked seizures) is made. Unlike the relatively low risk of a second seizure after a first unprovoked seizure (on average 40%), the risk for subsequent seizures following a second unprovoked seizure is closer to 100%, which moves the cost–benefit toward medical treatment and preparation for a much longer period for lifestyle modification. Predictors that the initial response to antiepileptic medication may be poor include multiple seizure types, a high number and density of seizures prior to treatment, and history of depression.

Initial response to treatment also provides clues to long-term prognosis. About half of newly diagnosed persons with epilepsy will obtain complete seizure control with the first antiepileptic medication, often at low doses. If failure of the first medication is related to side effects, the likelihood of control with a second medication is again excellent. However, if the failure is related to apparent ineffectiveness of the first medication, the likelihood of control with a second medication is considerably lower. Overall, about two-thirds of newly diagnosed persons with epilepsy will obtain control of seizures by either a first or a second medication. After that, changing therapy will provide control of seizures in only an additional 3% to 5% of people (12). As a corollary, the number of seizures after initiation of treatment can predict the long-term course.

It should be pointed out that failure to respond to two medications, the criteria set by the International League Against Epilepsy (ILAE) for "drug-resistant epilepsy" (13), is not tied to number of seizures or seizure density. One may have a seizure once a year or less and still qualify as "drug resistant" by this definition.

PROGNOSIS OF ESTABLISHED EPILEPSY

A community-based study of the natural history of treated epilepsy performed in Rochester, Minnesota, reported that the probability of attaining "terminal remission" (seizure free for 5 years) at 20 years after diagnosis was 75% (14). More importantly, almost 50% of the persons with epilepsy in this community-based study had entered remission at 6 years of follow-up following initial diagnosis of epilepsy, the earliest point they could be considered to be in remission. Similar data have been provided from the NGPSE. In that study, 60% of people with newly diagnosed epilepsy achieved a 5-year remission by 9 years of follow-up (15). Studies of newly diagnosed patients followed for long periods also tend to suggest a remission rate of 60% to 90% (16) (Table 2.2).

Table 2.2 Terminal Remission Data from Selected Studies

Reference	Study setting	Special study features	No. of patients	Median follow-up (years)	Years in remission	% in remission at median follow-up
Elwes et al. (17)	Hospital		106	5.5	2	79
Shafer et al. (13)	Community		432	17	5	66
Collaborative Group (18)	Hospital		280	4	1	70
Cockerell et al. (4)	Community	Definite epilepsy	564	7	5	68
Sillanpaa et al. (19)	Hospital	Children only	176	40	1	93
Lindsten et al. (20)	Community	≥1 baseline seizure	107	9	5	64
		≥2 baseline seizures	89	9	5	58

From Kwan P, Sander JW. The natural history of epilepsy: an epidemiological view. *J Neurol Neurosurg Psychiatry*. 2004;75:1376–1381, with permission.

PREDICTORS OF REMISSION IN PERSONS WITH EPILEPSY

Many studies have looked at potential predictors of seizure prognosis, including age of onset, gender, etiology, seizure type, EEG patterns, number of seizures prior to treatment, and early response to treatment (21). A diagnosis of remote symptomatic etiology, or the presence of a neurologic deficit prior to the onset of the epilepsy, has consistently been shown to be associated with a poor prognosis (19).

The number of seizures and seizure patterns in the first 6 months or first year after diagnosis has been found to be a strong determinant of the probability of subsequent remission, with 95% of those with two seizures in the first 6 months achieving a 5-year remission compared with only 24% of those with more than 10 seizures during this same time period (22). Children who experience clusters of seizures during treatment are less likely to achieve 5-year terminal remission (23). Children who continue to have weekly seizures during the first year of treatment had an eightfold increase in the risk of developing intractable epilepsy and a twofold increase in the risk of never achieving 1-year terminal remission (18).

Seizure type has not been a consistent prognostic factor (14), although persons with multiple seizure types, as is typical in the catastrophic epilepsies of childhood, have a poorer prognosis (24).

MEDICATION WITHDRAWAL IN PERSONS WITH SEIZURE REMISSION

The most comprehensive study to evaluate the success of medication withdrawal was the MRC's randomized Antiepileptic Drug Withdrawal Study. In this study, people who had been seizure free for at least 2 years were randomized to either slow withdrawal of medication or continued therapy. In the withdrawal group, 40% experienced seizure recurrence in the subsequent 2 years. The highest rate of recurrence was in the first year after the withdrawal was started. In the group continuing treatment, 25% experienced seizure recurrence by 2 years. The relapse rate was similar in the two groups after 2 years (25). The results suggest that people who need antiepileptic medication declare themselves early in the withdrawal period. The recurrence in those continuing therapy suggests that a relapse cannot be attributed solely to medication withdrawal. Even though a substantial proportion of patients in the MRC study remained seizure free after medication withdrawal, there were no powerful predictors that allowed for the identification of these individuals. In a multivariable analysis, factors

that increased recurrence risk included history of focal seizures, myoclonic seizures, and tonic–clonic seizures (primary or secondary) as well as seizures after therapy initiation. In contrast, being seizure free for over 3 years at the time of randomization decreased the risk (25).

There seemed to be little impact on quality of life associated with withdrawal, although a seizure recurrence was associated with decline in perceived quality of life. Another study of randomized withdrawal demonstrated substantial improvement in cognitive function in those for whom medication was withdrawn (26).

PROGNOSIS OF UNTREATED EPILEPSY

Although some attribute a relatively favorable prognosis to early institution of antiepileptic medication therapy, evidence from studies from resource-poor countries with significant treatment gap suggests that many patients may enter spontaneous remission with no AED treatment. In northern Ecuador, 49% of 643 patients who had never received an AED were seizure free for at least 12 months (27). A study in rural Bolivia reported that 43.7% of untreated epilepsy cases were seizure free for more than 5 years when the cohort was revisited after 10 years (28). The findings from these studies suggest that most people with epilepsy have clinical symptoms of seizures for only a few years and can successfully discontinue medication.

PROGNOSIS OF INTRACTABLE EPILEPSY

The ILAE has defined drug resistant epilepsy as "a failure of adequate trials of 2 tolerated and appropriately chosen and used AED schedules" (13). This concept is not necessarily the equivalent of intractable epilepsy, which also would seem to incorporate a concept of seizure frequency or density. Only 5% to 10% of all incidence cases of epilepsy ultimately result in truly intractable disease. These cases probably account for half the prevalence cases of epilepsy.

Intractability of epilepsy is difficult to define as it is not simply the converse of seizure freedom. Moreover, the predictors of intractability may differ from those of seizure control or remission, and the definition of drug resistance will vary with the investigator's interest and available procedures. An identified etiology, younger age at onset (younger than age 1 year), high initial seizure frequency, and intellectual disability are predictors of intractability among children. The epilepsy syndrome, specifically cryptogenic or symptomatic generalized epilepsies, is a predictor of intractability in multivariate analyses. After adjustment for epilepsy syndrome, factors correlating with an increased risk of intractability include initial seizure frequency, focal EEG slowing, and a history of a previous episode of acute symptomatic or neonatal SE (29,30).

In one of the few prospective studies that followed a cohort of children with epilepsy from time of diagnosis, it was found that about 10% of the children meet criteria for intractability at any time but that this group was fluid with individuals shifting in and out of "intractability" as defined by seizure frequency (31).

Recent studies reported that approximately 3% to 5% of patients with intractable epilepsy per year, defined as at least one (or two) seizures monthly, become seizure free for at least 12 months. This seizure freedom is not necessarily associated with changes in the therapeutic regimen. This finding highlights the fact that, irrespective of the number of previous AEDs, there is still a small possibility of inducing meaningful seizure remission in this population (32). One retrospective cohort study of 187 patients with intractable epilepsy who had been followed for a mean of 3.8 years

reported a remission rate of 4% per year with 17 of the 20 who went into remission having undergone a medication change just prior to the onset of remission and 3 of the individuals experiencing remission for no obvious reason. Five of these 20 patients subsequently relapsed after 12 months of seizure freedom although they did not necessarily revert to the high seizure frequency (33).

While this is not the optimal comparison, one might use the above data of an annual remission rate of 3% as a comparator for expected control or remission in people treated with alternative therapies.

The prognosis of intractable epilepsy may be dramatically affected by epilepsy surgery. For some procedures (cortical resection, lesionectomy, hemispherectomy), the objective is a cure of the seizures. For other procedures (corpus callosotomy), the object is to eliminate the most disabling seizures. Two randomized trials have demonstrated superiority of surgical treatment over best medical treatment for people with intractable temporal lobe epilepsy, but outcome was reported at 1 or 2 years (17,34).

Reports of long-term follow-up are now available for persons with epilepsy who have had surgery as therapy for their seizures. These findings are discussed in Chapter 90. Results following vagus nerve stimulation are discussed in Chapter 71.

SUMMARY

The prognosis in persons with a single unprovoked seizure is excellent with only about 20% of people with no risk factors experiencing further seizures. About 70% of persons with epilepsy will become seizure free, generally early in the course of their illness. About 30% of persons with epilepsy will be considered “drug resistant” sustaining incomplete control of seizures despite adequate trials of antiepileptic medication. Of this number, about 10% will be truly intractable and be candidates for therapies other than medication.

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CHAPTER 3 EXPERIMENTAL MODELS OF SEIZURES AND MECHANISMS OF STATUS EPILEPTICUS AND EPILEPTOGENESIS

TIMOTHY A. BENKE, MOLLY M. HUNTSMAN, AND AMY BROOKS-KAYAL

ANIMAL MODELS OF SEIZURES AND EPILEPSY: WHAT IS THE QUESTION?

One of the key issues in developing experimental models of seizures and epilepsy is "how close does your model need to be to the true human condition in order to reach valid, translational conclusions?" (1). In other words, is the best model for a cat actually a cat, preferably the same cat (2), or will a dog do because it also has fur? To some extent, the differences between the cat and dog are irrelevant, as our understanding of the mechanisms of brain processes from development to learning and memory in healthy and diseased states is still in its infancy.

The first step, undoubtedly, in developing a model is to define the pertinent questions. For the pediatric epilepsies, this step was approached in the "Models of Pediatric Epilepsies" workshop sponsored by NIH/NINDS, the American Epilepsy Society, and the International League Against Epilepsy (3). The pertinent questions advanced by this workshop were the following: (i) What are the long-term consequences of seizures? Can these be modified? (ii) What is the best antiseizure therapy? What is the best antiepileptogenic therapy? From these questions, the mechanisms of seizure initiation, prolongation, and termination can be addressed and their sequelae defined. Further, the mechanisms underlying the development of spontaneous repetitive seizures (SRS) (epileptogenesis) and associated cognitive dysfunction can begin to be addressed. The mechanisms by which modifiers such as genetic background, developmental stage, and other insults (hypoxia, trauma) may also be differentiated. From this, the committee proposed a table listing general strategies for model development (Table 3.1). In brief, models should be clinically relevant, developmentally appropriate, and generalized to a human condition (i.e., have validity).

Table 3.1 Strategies for Animal Model Development

1. Address a clinical need for better therapies
2. Address a key question or testable hypothesis
3. Address age specificities of developmental epilepsies, and exhibit age-specific manifestations
4. Address normal aspects of development as they relate to models of developmental epilepsies
5. Animal models of seizures and epilepsy should have EEG correlates; spontaneous seizures should be demonstrated in animal models of epilepsy
6. Investigate etiology and natural history of catastrophic/intractable epilepsies
7. Address role(s) of "multi-hit" mechanisms in epileptogenesis and epilepsies, i.e., trauma plus seizure or environment/diet plus genetic susceptibility
8. Address long-term role of seizures and other aspects of epileptic encephalopathies
9. Address model validity to clinical situation by comparisons with pharmacologic response, seizures phenotypes, outcomes, genetics, etc.
10. Allow cross-pollination from related fields: ischemia, sleep, trauma, synaptic plasticity, cancer/cell signaling, etc.

Modified from Stafstrom CE, Moshe SL, Swann JW, et al. Models of pediatric epilepsies: strategies and opportunities. *Epilepsia*. 2006;47(8):1407–1414.

While entire volumes have been devoted to the subject of model development in epilepsy (4,5), we will review the literature involving only a subset of the issues pertinent to a text on clinical epilepsy. Following an outline of techniques and the advantages and disadvantages of in vitro versus in vivo models, we will focus on the methods for invoking status epilepticus (SE) (a "prolonged" single seizure) via chemoconvulsants; single, repetitive, or prolonged seizures via hypoxia, temperature, kindling, or chemoconvulsants; and seizures induced by trauma or genetic alterations.

The process by which the initial insult (seizure, SE, or other) may lead to SRS (epilepsy) has been the subject of intense study, and multiple reviews have been put forth (6,7). Consensus regarding the relationship (cause or effect?) of hippocampal sclerosis and network reorganization to this process has not been forthcoming. Overall, the field has significantly shifted from a descriptive to a mechanistic focus involving key receptors, enzymes, and genetic regulation.

Seizures can be defined as paroxysms of abnormal, rhythmic, and synchronized discharges in the brain. Communication in the nervous system is a combination of electrical and chemical signaling with a balance between excitation and inhibition in each, primarily mediated between neurons. Glia modulate both types of communication primarily on a local basis, but frequently with distant consequences.

The resulting cascade (Fig. 3.1), beginning with receptor activation, followed by alterations in membrane polarization, potentially loops around, to result in alterations of the properties of the initial trigger of receptor activation. Consideration of this simplistic mechanism is important. Such a loop likely underlies normal plasticity associated with processes like learning and memory but perhaps becomes unstable with seizures and epileptogenesis, leading to aberrant plasticity that could result in both additional seizures and cognitive dysfunction.

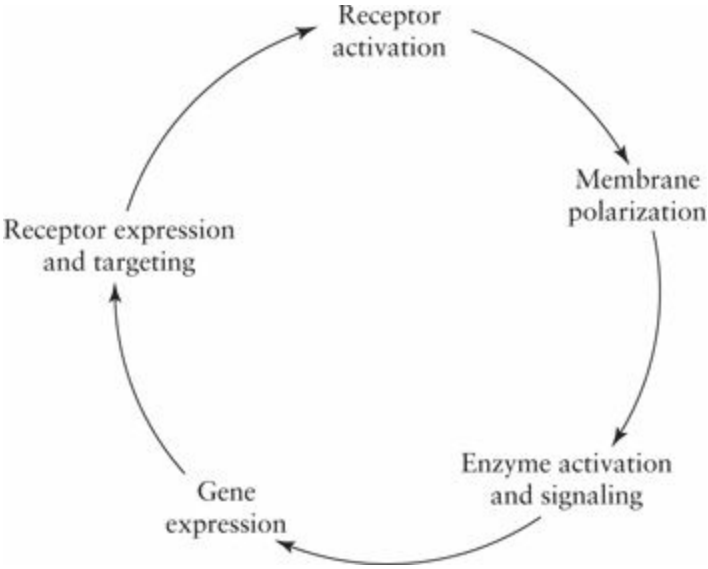

Figure 3.1. Proposed cascade of events following a seizure leading to potential adverse sequelae (medically resistant status epilepticus, epileptogenesis, learning impairment, etc.).

Review of Techniques

Experimental models can be divided into whole-animal (in vivo) versus in vitro studies (Table 3.2). Whole-animal models of acquired epilepsies typically involve single or multiple treatments to the animal that produce some form of injury or stimulation that results in later development of spontaneous seizures. Examples of these induced injuries include SE (chemoconvulsant and electrical), kindling, hypoxia, and head trauma. In genetic models, a spontaneous or induced genetic mutation or deletion results in seizures that happen spontaneously.

Table 3.2 Animal Model Summary

Model	Questions addressed
Pilocarpine and kainate	SE: consequences, treatment, role of development TLE and epileptogenesis: hippocampal networks, mechanisms, and therapies "Multi-hit" models
Pentylenetetrazol and flurothyl	Multiple brief seizure models: mechanisms of epileptogenesis Treatment of brief seizures Role of development on long-term consequences "Multi-hit" models
Temperature	Febrile seizures in children: mechanisms and therapies Role of development and long-term consequences Epileptogenesis "Multi-hit" models
HIE	True "multi-hit" model Role of development and long-term consequences Epileptogenesis: mechanisms and therapies Focal epilepsy and epileptogenesis: therapies
Toxins: tetrodotoxin and NMDA	Infantile spasms: mechanisms and therapies Role of development and long-term consequences Treatment Epileptic encephalopathies
Toxins: tetanus toxin	Focal epilepsy and epileptogenesis: therapies Role of development and long-term consequences
Trauma	True "multi-hit" model Role of development and long-term consequences Focal epilepsy and epileptogenesis: mechanisms and therapies
In vitro models	SE: consequences, treatment, role of development Role of development Synaptic and therapeutic mechanisms, especially when coupled with in vivo models
Genetic models	Catastrophic epilepsies: genesis, therapy, long-term consequences Linkage of human mutations with synaptic and electrical mechanisms in seizures and epilepsy "Multi-hit" models

Seizure "activity" must be carefully defined for several reasons. First, the definition of a seizure is often extremely variable, as in the clinical literature. Second, consciousness, routinely used as a modifier in describing clinical seizures, is arbitrarily defined in most animals used. Typically, rhythmic, stereotyped, altered behavior is observed and characterized as a seizure. As in the clinical literature, EEG has become the gold standard for correlating altered behavior with seizures, but its use is limited due to the time- and labor-intensive placement of electrodes, limitations of electrode stability over time, and the fact that electrographic seizures emanating from deeper structures can be missed when recording from the cortical surface.

In Vitro Versus In Vivo Models

In vitro models involve removal and subsequent manipulations of whole-brain structures, slices of brain structures, or isolation and culture of separated brain cells (neurons and glia). These studies allow detailed manipulations and measurements but are limited in multiple, key ways. While it is tempting to designate repetitive electrical discharges as a seizure in these models, seizures in the whole animal are associated with a change in behavior or sensation, which cannot be appreciated in these in vitro models. Therefore, to avoid confusion, the repetitive electrical discharges must be referred to as "seizure-like" events or an ictus. It is important to note that one researcher's abnormal ictal-induced phenomena may also be interpreted as another researcher's normal activity-dependent changes. In addition, certain seizures, and their sequelae, may involve the interplay of multiple brain structures and are thus difficult if not impossible to recreate in in vitro models. Finally, key processes such as development and epileptogenesis, which occur over a prolonged period of time, cannot be fully studied in in vitro models as they are limited by the length of time the in vitro preparation is viable (hours to weeks).

There are dozens of in vivo and in vitro models of seizures and epilepsy, and, as already mentioned, there is little consensus about which if any are the "optimal model." In reality, each model has its strengths and limitations, and the relative benefits depend on the specific question being asked. Below, we focus on the models that are in common use or emerging.

In Vivo Models

Pilocarpine and Kainate Models

The pilocarpine model and lithium–pilocarpine model [reviewed in (8)] involve the systemic administration of the muscarinic acetylcholine receptor agonist (pilocarpine) to induce a prolonged electrographic and behavioral seizure that requires cessation by benzodiazepines or barbiturates, typically after 1 to 2 hours, in order to prevent animal mortality. Clearly, from a clinical standpoint, muscarinic acetylcholine receptor agonism is very rarely the cause of SE in humans, with the exception of poisonings and chemical weapon exposures. Nevertheless, it is widely used because it results in severe SE, and animals eventually develop an epileptic phenotype with features very similar to those of human temporal lobe epilepsy (TLE) resulting in its widespread use for studying both of these conditions.

Kainate, a glutamate analogue that is not metabolized and can be injected either systemically or directly into the brain, results in seizures lasting several hours (9,10). Clinically, kainate originates as a shellfish poison, and human toxicity during outbreaks results in seizures and, in severe cases, hippocampal sclerosis (11). While this clinical situation is extremely rare, conditions involving glutamate overload that are known to be associated with seizures such as stroke, hypoxia (12,13), or infection may be mimicked to some degree by kainate administration. Similar to the pilocarpine model, kainate can induce an SE, and adult animals that survive kainate-induced SE may eventually develop an epileptic phenotype with features very similar to human TLE. In younger animals, kainate primarily activates the hippocampus, while in older animals, its effects are widespread (14).

Brief Seizure Models

Pentylenetetrazol and flurothyl are GABA-ergic antagonists that are administered systemically or inhaled, respectively (15). They both induce relatively short seizures, with flurothyl-induced seizures

being very brief and limited nearly to the length of exposure to the vapors. As a result, both agents are used to mimic conditions involving single or multiple brief, generalized seizures (16). The major limitations of these models are that the mechanism of seizure induction does not clearly parallel any human condition, and the animals never develop spontaneous seizures. Both agents are thought to act on all susceptible brain regions, including cortex and hippocampus (15).

Electrical kindling, whereby electrodes are implanted in order to stimulate select brain regions, can also be used to study how repeated, brief seizure-like activity can influence outcomes. Depending on the stimulation protocol, kindling can eventually lead to induced behavioral seizures. This model, however, is limited by the technicalities of long-term implantation in rodents and the fact that most kindling paradigms do not result in development of spontaneous seizures.

Clinical Models: Fever and Hypoxia/Ischemia

In models where seizures are induced in the setting of increased temperature (fever), hypoxia, and/or ischemia, the ability of these models to generalize to human pathologies is clearly evident. Hypoxia models can involve placing animals in an environment of reduced oxygen content until seizures are observed (17,18). Other methods involve single or multiple cerebral vessel occlusions, often in combination with exposure to an environment with reduced oxygen content. Methods involving vessel occlusion are often time-intensive. These methods are then limited by the elements of hypoxia and ischemia, as these may independently influence outcomes (19).

Temperature-induced seizures in developing animals (20,21) involve slowly heating the animal, typically with warmed air, until seizures are initiated. This model is gaining popularity as a model of febrile seizures but may be limited by the fact it is really a model of externally imposed hyperthermia rather than endogenous fever as occurs in the human condition. These models are particularly attractive as they may be used as preclinical models to evaluate therapies.

Toxin Models

Several models involve the direct infusion of toxins, compounds, or even genetic material into specific regions such as the hippocampus. These are each meant to model focal seizures or epileptogenesis, though the result can have distant effects. These include the tetanus toxin model [reviewed in (22)] and more recently the tetrodotoxin model (23), thought to be a model of epileptic spasms or West syndrome. The knockdown of AMPA receptor GluA2 subunit by injection of antisense probes results in acute seizures (24). Following withdrawal of direct injection of glutamate receptor antagonists, spontaneous seizures are provoked in immature animals, while systemic injection does not cause this to happen (25).

Trauma Models

Experimental models of trauma utilizing either direct impact methods (26) or surgical undercuts (27) are gaining popularity as models for studying the development of posttraumatic epileptogenesis and epilepsy. As head trauma is a common cause of acquired epilepsy in humans, these models seem very generalizable to human pathology. As a result, these models have been used to study the efficacy of antiepileptogenic compounds as well as the mechanisms underlying posttraumatic epileptogenesis.

In Vitro Models

In vitro methods involving brain slices or cultures use a variety of methods to induce seizure-like electrical events. These can involve perfusion of compounds that typically enhance or favor membrane excitability alone or in combination with electrical stimulation, akin to kindling. The resulting spontaneous neuronal-mediated discharges can then be recorded from groups of neurons or from individual neurons typically using electrophysiologic techniques. Imaging techniques using fluorescent dyes that are able to indicate changes in membrane voltage or secondary changes due to accumulations of specific ions, such as calcium, often complement electrophysiologic measurements as they are able to simultaneously record from populations of neurons that may be somewhat distant from each other. The pattern of these discharges is then interpreted in isolation, in groups or bursts, or when the bursts cluster together as an ictus. The transitions between these types of discharges are interpreted as indicative of ictal genesis and are thought to generalize to seizure genesis. When the ictus is prolonged, this event generalizes to SE. When the ability to generate an ictus becomes more facile, this situation is thought to generalize to epileptogenesis. Determining how excitation spreads through a slice of brain tissue is generalized to how it may spread in the intact preparation. Thus, application of anticonvulsants to an in vitro preparation has been used to determine their efficacy and precise mechanism(s) of action. In order to circumvent the issues of truly generalizable seizures, SE, or epileptogenesis in vitro, brain slices are often prepared at various time points after these phenomena have developed in vivo. Findings from hippocampal brain slices prepared from animals after experiencing an induced or spontaneous seizure in vivo allow examination of how overall synaptic transmission, plasticity, and seizure thresholds have become altered by these processes.

Preclinical Models and New Therapy Development: Neonatal Seizures

As an example of the use of preclinical models, the parameters for establishing an antiseizure medication as first-line treatment for neonatal seizures have recently been considered (28,29). These include utilizing relevant rodent model(s) of neonatal seizures, using EEG confirmation of seizures and drug efficacy, dose–response evaluation of efficacy, and acute and long-term aspects, including later epilepsy and behavioral consequences. Determining the relevant model is nontrivial; as noted, no model is ever perfect. These issues include face validity (similar endophenotype in humans and rodents, i.e., does the EEG and clinical picture look similar?), construct validity (similar biologic dysfunction in humans and rodents, i.e., are the triggering mechanisms similar?), and predictive ability (similar biologic response to treatments by humans and rodents, i.e., are acute and chronic aspects similar?).

We reviewed 32 studies that involved 62 separate treatment trials from 1992 to present in postnatal day (P)20 or younger rodents (Table 3.3). Most studies use pretreatment with an antiseizure medication resulting in a lack of construct validity since prophylaxis is not used clinically. Few studies validated their findings with EEG, which is important since some drugs may be proconvulsant (NMDA receptor antagonists) and because antiseizure medications are known to cause "electroclinical dissociation" in neonates, resulting in attenuation of behavioral manifestations without reduction in electrographic seizure activity. Unfortunately, no studies validated with EEG and dose response, because lower doses were sometimes found to be more effective (clinically) and earlier treatment was sometimes more effective (by EEG). Importantly, phenobarbital, the most

widely used therapy for neonatal seizures, has not been evaluated in the hypoxia model, the neonatal seizure model with likely the greatest construct validity. In the carotid artery occlusion model, phenobarbital had clinical efficacy when used as pretreatment. The efficacy of phenobarbital posttreatment has only been evaluated with EEG in the kainate model. The EEG efficacy of antidiuretic bumetanide, which is posited to overcome the depolarizing effect of GABA in the developing brain, has only been evaluated in the kainate model as pretreatment. Topiramate, levetiracetam, talampanel, and AMPA receptor antagonists have been evaluated for clinical efficacy (EEG data for levetiracetam) in the hypoxia model only when given as pretreatment.

Table 3.3 Evaluation of Preclinical Data for Anticonvulsant Efficacy for Neonatal Seizures

Rodent age	Convulsant	Anticonvulsant	Effect	Dose–response evaluation	Timing of anticonvulsant (B = before, A = after)	EEG confirmation	Ref.	Notes
7–18	ka	CBZ	neg	Yes	B	No	(30)	
		PBS	neg	Yes	B	No		
		CBZ	neg	Yes	B	No		
		VPA	neg	No	B	No		
12–18	Picrotoxin	ETX	pos	Yes	B	No	(31)	
9–15	Flurothyl	PBS	pos	Yes	B	No	(15)	
		VGB	neg	No	B	No		
		Baclofen	pos	Yes	B	No		
		CGP35348	neg	Yes	B	No		
		CGP36742	neg	Yes	B	No		
7–18	ptz	Kynurenate	pos	Yes	B	No	(32)	
		GDEE	pos	Yes	B	No		
7–18	ptz	CNQX	pos	Yes	B	No	(33)	
		DNQX	pos	Yes	B	No		
		NBQX	pos	Yes	B	No		
9–15	Flurothyl	PHT	neg	Yes	B	No	(34)	
		MK801	pos	Yes	B	No		
10	Hypoxia	NBQX	pos	No	B	No	(35)	
		MK801	?	No	B	No		
		Lorazepam	?	No	B	No		
12–18	Kindling	Ketamine	pos	Yes	B	Yes	(36)	
12–18	Kindling	GYKI52466	pos	Yes	B	Yes	(37)	
12–18	Kindling	NBQX	pos	Yes	B	Yes	(38)	
11–12	ka	MK801	neg	Yes	B	Yes	(39)	MK801 proconvulsant
10–20	tet-tox	CBZ	pos	Yes	A	Yes	(38)	
7–18	ptz	Clobazam	pos	Yes	B	No	(39a)	
9–15	Flurothyl	Ganaxolone	pos	Yes	B	No	(40)	
17	Kindling	Gabapentin	pos	Yes	B	Yes	(41)	
10	Hypoxia	Topiramate	pos	Yes	B	No	(42)	Higher dose of topiramate not effective
7–18	ptz	VGB	pos	Yes	B	No	(43)	

15	li–pilo	DZP	pos	No	A	Yes	(44)	DZP only effective early after seizure onset
12–18	ptz	MPEP	pos	Yes	B	No	(45)	
12–18	Kindling	MPEP	pos	Yes	B	Yes	(46)	
9–12	ka	PBS	pos	No	B	Yes	(47)	Bumetanide better than PBS by EEG
		Bumetanide	pos	No	B	Yes		
12–18	Kindling	MK801	pos	Yes	B	Yes	(48)	
		CGP40016	pos	Yes	B	Yes		
		AP7	neg	Yes	B	Yes		
10–15	Flurothyl	Topiramate	neg	No	B	No	(49)	
12	cao	Gabapentin	pos	Yes	B	No	(50)	
10	ka	Flupirtine	pos	Yes	B	No	(51)	
	ka	PBS	neg	Yes	B	No		
	ka	DZP	neg	Yes	B	No		
	Flurothyl	Flupirtine	pos	No	B	No		
	Flurothyl	PBS	neg	No	B	No		
	Flurothyl	DZP	neg	No	B	No		
	ka	Flupirtine	pos	No	A	Yes		EEG demonstrates efficacy of flupirtine > PBS > DZP
	ka	PBS	pos	No	A	Yes		
	ka	DZP	pos	No	A	Yes		
10	Hypoxia	Talampanel	pos	Yes	B	No	(52)	
7–18	ptz	MTEP	pos	Yes	B	No	(53)	
		AIDA	pos	Yes	B	No		
12–18	Kindling	AIDA	neg	Yes	B	Yes	(54)	
		MTEP	pos	Yes	B	Yes		
12	ptz	Allopregnanolone	pos	Yes	B	No	(55)	
		Ganaxolone	pos	Yes	B	No		
12	cao	PBS	pos	Yes	B	No	(56)	Lower dose of PBS effective; higher dose harmful
15	Flurothyl	Rapamycin	pos	No	B	No	(57)	
	ptz	Rapamycin	pos	No	B	No		
	ka	Rapamycin	neg	No	B	No		
	NMDA	Rapamycin	neg	No	B	No		
10	Hypoxia	Levetiracetam	pos	Yes	B	Yes	(58)	

Comparison of rodent ages, convulsants, anticonvulsants, and efficacy as reviewed.
ptz, pentylenetetrazol; ka, kainic acid; cao, carotid artery ligation; tet-tox, tetanus toxin; li–pilo, lithium–pilocarpine; PBS, phenobarbital; CBZ, carbamazepine; DZP, diazepam; VGB, vigabatrin; pos, positive; neg, negative.

While EEG evaluation for efficacy of antiseizure medications after onset of seizures may be the gold standard, it is important to recognize the experimental issues. Continuous video-EEG monitoring for nursing pups is technically challenging. Due to the growing skull, the recording duration is limited. The numbers and locations of electrodes are limited by the size of the skull and lack of accepted standardization. Further, details of background rhythms, seizure detection, and quantification lack widely accepted quantification and standardization.

Studies in immature rodent have demonstrated that, at relevant doses, phenobarbital, phenytoin, NMDA receptor antagonists, diazepam, valproate, and vigabatrin are proapoptotic. At higher doses, lamotrigine, carbamazepine, and topiramate are proapoptotic; in contrast, levetiracetam does not demonstrate apoptosis (59). Also, phenobarbital, phenytoin, and lamotrigine have negative behavioral consequences when administered to immature rodents (60).

In conclusion, preclinical rodent studies do not offer full evidence to recommend any antiseizure medication as efficacious for neonatal seizures as observed in clinical practice. Many drugs do affect seizure threshold, as demonstrated by those studies that administered the antiseizure medication prior to the seizure. Flupirtine shows best EEG evidence; however, phenobarbital does have efficacy. Further studies are needed that do not pretreat and that use EEG, evaluate the dose response, and fully consider short- and long-term outcomes.

MECHANISMS OF SE AND EPILEPTOGENESIS

Mechanisms of SE

Here, there are two basic questions: Why did the seizure not stop by itself, and why is SE more

difficult to stop with antiseizure medications than a single seizure? Was the underlying neuronal network susceptible to this happening, or did it become dynamically changed to allow its progression? Given that it has been found that the clinical situation is mimicked by the experimental in which benzodiazepines lose their potency as the seizure progresses (61), much effort has focused on the role of $GABA_A$ receptors and inhibitory synaptic transmission (62). These questions have been approached in a variety of ways, using in vitro brain slices or in vivo models employing pilocarpine, kainate, or kindling, sometimes in combination with in vitro brain slices prepared during or after the event. Recent studies suggest that during SE, $GABA_A$ receptors at inhibitory synapses onto granule cells of the dentate gyrus are removed from synaptic sites and moved to extrasynaptic sites and internal pools (63) in a subunit-specific manner (64). This likely minimizes their effectiveness in both self-termination of the seizure and the loss of effectiveness of benzodiazepines, in part mediated by loss of γ2 subunits, which modulate benzodiazepine sensitivity. These issues are complicated during development in the CA3 region of the hippocampus, where GABA-ergic synapses are depolarizing and thus contribute to the development of ictal activity (65,66); although recently the role of excitatory $GABA_A$ receptor-mediated currents has been questioned (67).

The alterations in $GABA_A$ receptors in the dentate gyrus are possibly mediated by NMDA receptor activation rather than by direct activation of $GABA_A$ receptors (63). It has been found that blocking NMDA receptors prevents the progression to drug-resistant SE (68). NMDARs then further contribute to the process as they are progressively recruited to synaptic sites as SE progresses (68). While in vitro studies suggest that NMDA receptors and AMPA receptors are involved in epileptogenesis (69–71), it is possible that their contribution to this process may be mediated by their effects on SE. Reductions in the AMPA receptor GluA2 subunit in CA1 and CA3 (72,73) 6 to 48 hours after SE, while implicated in cell death, may have also contribute to prolonging SE, perhaps through facilitated AMPA receptor function (74). Excess glutamate, which may occur with transporter dysfunction, has been shown to lead to NMDA receptor activation and seizures (75); however, this effect may be limited to developing animals in which glial regulation of extracellular glutamate by transporters is immature (76). Indeed, multiple genes, including those involved in transcription, are likely regulated following SE (77). Recent work has shown alterations in calcium-permeable AMPA receptors as a potential mechanism to prolong SE (78).

Mechanisms of Epileptogenesis

Epileptogenesis refers to the process by which a previously “normal” brain becomes capable of producing SRS. Animal models have typically employed prolonged SE to trigger this process; however, models of trauma and injections of toxins have also been used (see Review of Techniques). The nature and mechanisms of this process have been richly studied. Does this happen quickly or gradually, that is, what is the significance of the latent period between trigger and first SRS? This question is critical as it might represent a window of opportunity for intervention. What is the relationship of the sclerotic pathology, often seen in human TLE and animal models, to this process? How much of the process is due to network rewiring versus changes in neuronal and/or synaptic function? What are the signaling cascades mediating these processes and how can they be circumvented or reversed? Activation of group 1 metabotropic glutamate receptors, by themselves, has been shown to be epileptogenic (79,80), suggesting that the process might be less complicated.

The appearance of SRS has been taken to indicate the end of the latent period. Enhanced

excitability has been shown to gradually develop prior to the appearance of SRS (81), suggesting the end of the latent period is not a stepwise function into SRS and epilepsy. In support of this, an intensive video-EEG monitoring study has challenged the notion of the latent period by showing that the progression into SRS and epilepsy is a sigmoid function of time (82). In other words, after the first SRS, epilepsy continues to progress. Progression clearly represents a worst-case scenario, which may not always be present (83). Additional work is needed to determine where and if there is a window for interventions to prevent this progression.

Plasticity and Trafficking of $GABA_A$ Receptors in Epileptogenesis

During the process of epileptogenesis in animal models, there are alterations in the expression and membrane localization of several $GABA_A$ receptor subunits (α1, α4, γ2, and δ) in hippocampal dentate granule neurons (84–86). These alterations, which are associated with changes in phasic and tonic $GABA_A$ receptor-mediated inhibition, and in $GABA_A$ receptor modulation by benzodiazepines, neurosteroids, and zinc, begin soon after SE and continue as animals become epileptic (84–87). Several laboratories have documented similar changes in $GABA_A$ receptor subunit composition in human TLE and in animal models of TLE (84,86,88,89). Following pilocarpine-induced SE in adult rodents, $GABA_A$ receptor α1 subunit mRNA expression decreases and α4 subunit mRNA expression increases in dentate granule cells (DGCs) of the hippocampus, and animals uniformly go on to develop the recurrent spontaneous seizures that define epilepsy (84). The change in subunit expression correlates with a decreased sensitivity to zolpidem augmentation and increased sensitivity to zinc inhibition of $GABA_A$ receptor responses (84). Similar functional and subunit expression changes have been observed in DGCs isolated from surgically resected hippocampus from patients with intractable TLE (89). The changes in $GABA_A$ receptor subunit expression and function in DGCs of adult epileptic animals precede the development of epilepsy, and immature animals exposed to prolonged induced seizures show increased $GABA_A$ receptor α1 subunit expression and do not subsequently develop epilepsy (90), suggesting that $GABA_A$ receptor changes contribute to the epileptogenic process. Viral gene transfer studies demonstrating that the expression of higher α1 subunit levels inhibits development of epilepsy after SE provide further supporting evidence (91). Changes in $GABA_A$ receptor subunit expression associated with epileptogenesis vary by region and are distinct in CA1 compared to dentate gyrus (92). In addition, changes in surface expression (92) and membrane localization (93,94) of $GABA_A$ receptors related to altered receptor composition as well as loss of receptor anchoring proteins including gephyrin and GRIP (92) may play an important role in both genetic and acquired epileptogenesis.

Network Reorganization

Network reorganization in the hippocampus has been extensively studied as one of the presumed origins of SRS and because of similar findings in human TLE. Primarily, this has focused on the output of dentate granule cell neurons and has been thoroughly reviewed (8,95,96). Excitotoxic loss of mossy cells (97) in the dentate gyrus may lead to sprouting of dentate axons, known as mossy fibers (MF). The sprouted mossy fibers make aberrant excitatory connections locally in the dentate gyrus and distantly in CA3 creating an abnormal excitatory feedback circuit (98). These abnormal connections are dysfunctional, with a higher probability of activation, a larger NMDAR component

(99,100), and recruitment of kainate receptors (101). These disturbances, coupled with permanent alterations in $GABA_A$ receptors (see below), are thought to result in a circuit prone to trigger seizures in other regions, such as CA3 (95). Not without controversy, MF sprouting has not been proven to be either necessary or sufficient for development of TLE [reviewed in (7,102)]. Further aberrant circuits have also been described originating in CA3 (103) and CA1 (104–106). In trauma-induced epilepsy, aberrant connections are formed in the region of injury as well as the hippocampus [reviewed in (6,26,27)]. In the region of injury, discrete regions of apical dendrites have a selective overabundance of excitatory synaptic inputs and connectivity (107,108), which with alterations in membrane voltage-gated channel properties (109) may also contribute to the epileptic state.

Excitotoxic cell loss (which may occur following SE or other insults) throughout the hippocampus is thought to be mediated by glutamate toxicity via AMPA receptors (73,109) and NMDA receptors (110).

Secondary reactive gliosis may also contribute to synaptic dysfunction (111,112). Loss of hilar mossy cells and other neurons mediating inhibition is thought to be a critical potential contributor to the hyperexcitable steady state of the epileptic hippocampus. SE also has the paradoxical effect of inducing neurogenesis in the dentate gyrus (113). Some of the newly formed neurons may also participate in MF sprouting or other aberrant circuitry that leads to the epileptic hippocampus (114), although the exact role of newborn neurons in epileptogenesis continues to be studied.

The role of network alterations and other causative phenomena in epileptogenesis appears to be differentially regulated depending on when in development the process is initiated. Kainate-induced SE in adult animals causes, over time, SRS, CA3 cell loss, MFS into CA3 and dentate gyrus, sprouting into CA1 stratum pyramidale and stratum radiatum, and impaired learning in memory tasks (104,115,116). Similar results are found with the pilocarpine model (8,116,117). However, when animals younger than 14 days are treated with either kainate or pilocarpine, the animals do not develop spontaneous seizures (see below) (90,118,119). Single or repetitive episodes of SE in infancy caused by pilocarpine are not benign, however, and have been associated with long-term abnormalities of inhibitory neurotransmission (89). Further, single or multiple episodes of SE induced by pilocarpine at postnatal day 14 or later do result in SRS (120–122) as well as deficits in memory and learning that are inconsistently associated with cell loss and/or MFS (120,122–125). Studies in other models have not provided additional clarity regarding the association of cell loss and MF sprouting to the development of epilepsy after early-life seizures. Early-life focal administration of tetanus toxin results in a chronic epileptic state that includes memory impairment without cell loss (22) but does involve MF sprouting (126). In contrast, repetitive flurothyl seizures in early development result in MF sprouting, but they do not apparently result in SRS, only a reduced seizure threshold (127–129). Chronic perforant path kindling is associated with cell loss in the dentate gyrus (130). Similarly, in prolonged temperature-induced seizures, MF sprouting gradually develops; however, reduction in seizure thresholds is seen much earlier, and SRS have been reported only infrequently (131–133). Furthermore, MF sprouting appears in a model of early-life stress, apparently unrelated to seizures (134).

Seizure- or SE-Induced Alterations in Ion Channels

Early studies of in vitro brain slice models indicated that alterations in NMDA receptors with the successive prolongation of seizure-like discharges correlated with epileptogenesis (69–71). The mechanism of non–NMDA receptor-mediated calcium influx via calcium-permeable AMPA

receptors is also thought to underlie cell death in adult models of seizures (72,135–137) and hypoxia (18). AMPA receptor GluA1 subunit up-regulation has only been found in an adult model of electroconvulsive therapy (138). As noted previously, AMPA receptor GluA2 subunit "knockdown" studies have shown that down-regulation of this receptor subunit can lead to seizures and hippocampal injury (24). Clinical evidence from pathologic studies might support up-regulation of GluA1 expression (139–141). Seizures or SE in developing animals have found either no change (109,142) or a down-regulation of GluA2 (18,143) expression with no changes in GluA1 (144). Recurrent episodes of kainate-induced SE in developing animals are associated with a decrease in kainate binding (a reflection of AMPA receptors as well as KA receptors) in CA3 but not CA1 (119). Recurrent flurothyl seizures in developing animals have shown a long-term reduction in the expression of NMDA receptor subunits and the scaffolding protein PSD-95 (145). Transient alteration in the properties of synaptically activated AMPARs consistent with calcium-permeable AMPA receptors following hypoxic seizures in developing animals has been postulated to mediate the cascade resulting in later-life alterations in this model (146). These later-life alterations following the hypoxic-seizure cascade result from activation of the mammalian target of rapamycin (mTOR) pathway (58). Seizures induced by kainate in infant rats result in altered long-term potentiation, long-term depression, kindling, and learning associated with enhanced inhibition in the dentate gyrus (147) and mechanistically linked to reduced expression of the NMDA receptor GluN2A subunit, altered trafficking of AMPA receptor GluA1 subunit, and increased expression of PSD-95 (142). In contrast to hypoxia-induced seizures, early-life kainate seizures may not necessarily acutely involve the mTOR pathway; however, long-term consequences involve alterations in fragile X mental retardation protein–mediated signaling (148).

In adult epileptic animals induced by pilocarpine SE, GABA-ergic signaling is altered by specific reduction of $GABA_A$ receptor α1 subunits and an increase in α4 subunits in the dentate gyrus, resulting in a reduction in benzodiazepine sensitivity and enhanced inhibition by zinc (84). [This contrasts markedly to the developing hippocampus where pilocarpine SE does not result in epilepsy but results in an up-regulation of α1, overall receptor numbers and enhanced benzodiazepine sensitivity (90).] Changes in $GABA_A$ receptor subunit expression associated with epileptogenesis vary by region and are distinct in CA1 compared to dentate gyrus (92). In addition, changes in surface expression (92) and membrane localization (93,94) of $GABA_A$ receptors related to altered receptor composition as well as loss of receptor anchoring proteins including gephyrin and GRIP (92) may play an important role in both genetic and acquired epileptogenesis. Altered functions of voltage-gated sodium channels (149,150), T-type calcium channels (151,152), and potassium channels (153) have been described in epileptic animals and are thought to contribute to the epileptic state. In the hyperthermia model of febrile seizures, a single prolonged seizure results in permanent susceptibility to convulsants and enhanced in vitro kindling, mechanistically linked to enhancement of the voltage-gated potassium channel HCN (132,154,155).

The signaling pathways that regulate the plasticity in ion channel expression during epileptogenesis are just beginning to be elucidated. For example, recent studies have demonstrated that the mechanisms that regulate differential expression of $GABA_A$ receptor subunits in hippocampus after SE include the CREB/ICER, JAK/STAT, BDNF, and Egr3 signaling pathways (156,157). Targeting signaling pathways that alter the expression of genes involved in epileptogenesis may provide novel therapeutic approaches for preventing or inhibiting the development of epilepsy after a precipitating insult.

Sequelae Beyond Seizures

In adult models of epileptogenesis associated with cell loss and/or MF sprouting, uniformly, there is learning and memory impairment when assessed with the Morris Water Maze (MWM), a behavioral test used to assess spatial, long-term memory formation (158). Altered emotionality is also noted with fear conditioning (159). Mechanistically, this impairment is thought to be mediated by the anatomical damage, as similar deficits are observed in hippocampal lesion studies not associated with seizures or epileptogenesis (160). Similarly, in immature animals, abnormalities in the MWM are associated with histologic changes following repetitive SE (123–125), repetitive flurothyl seizures (129,161), tetanus toxin (22), and hypoxia/ischemia- (162) and hyperthermia- (132,154,155) induced seizures. In models where immature animals develop SRS, there is altered emotionality (121). Furthermore, kainate insult in infancy and again later in adulthood results in more prominent memory impairment than a single insult at either time (163). In immature animals following a kainate-induced seizure, there have not been any detectable problems with the MWM or histologic changes (116,164), including an absence of MF sprouting; similar findings have been reported for repeated episodes of kainate-induced SE in immature animals (119). As adults, these animals have only subtle abnormalities in the MWM (165), and in more difficult mazes, these animals have abnormalities most consistent with defective working memory (142,147,165,166); emotionality may be unaffected (165) [but see (166)]. Thus, permanent impairments in learning and memory are more severe in animal models when associated with significant histologic abnormalities. However, significant impairments can also exist without histologic abnormalities, which possibly reflect pathology limited to abnormal synaptic function isolated to the hippocampus.

Genetic Susceptibility

Advances in genetics have allowed for several human epilepsy syndromes associated with single gene defects to be further characterized [reviewed in (167)]. Following determination of the analogous gene in mice, similar defects can be introduced through cloning techniques in order to better understand how epilepsy develops in these syndromes as well as determine which treatments might be more efficacious. Often, the nature of the genetic defect, whether it represents a gain or loss of function, is not clear until the altered resulting protein is expressed in an intact, cloned animal model. In the animal model of Dravet syndrome, genetic knock-in of human mutations in voltage-gated sodium channels (NaV1.1) results in a phenotype very similar to that seen in humans (168,169). Importantly, these studies have highlighted how the balance between excitation and inhibition is a critical modifier in this disorder (170). However, this mechanism has recently been challenged (171). Similarly, genetic knock-in of human mutations in KCNQ2 and KCNQ3 has many similarities to the human phenotype of benign familial neonatal convulsions (172). Enhanced function of T-type calcium channels in thalamocortical circuits has been postulated to mediate childhood absence epilepsy. While specific mutations in T-type calcium channels have not been determined in the human condition, specific genetic targeting of enhanced expression of T-type calcium channels in this circuit has been found to mimic the human condition (173). However, genetic knock-in of human mutations in GABA receptors associated with generalized epilepsy syndromes has not uniformly resulted in phenotypes similar to the human conditions (174,175). Similarly, knock-in of human mutations in nicotinic acetylcholine receptors seen in autosomal dominant nocturnal frontal lobe epilepsy also does not reproduce features similar to the human syndromes (176). These negative results suggest not only the complexities of genetic technologies but also likely reflect basic underlying differences in

rodent and human physiology, especially susceptibility to seizures and epilepsy.

SUMMARY

Animal models, despite their limitations, have advanced our understanding of the mechanisms of seizures and epileptogenesis. Specifically, substantial gains have been made in understanding the ability of the hippocampus and cortex to rewire themselves following insults to result in circuits capable of spontaneous seizures. Developmental models have shown how significant physiologic and behavioral alterations can result without obvious histologic changes. Important questions remain to be answered in further understanding the signaling pathways, genetic programs, and subsequent synaptic modifications that underlie epileptogenesis as well as the behavioral consequences of seizures. These discoveries are crucial to determine safe and effective pharmacologic targets for stopping seizures and curing epilepsy and its consequences.

Suggested Readings

Mazarati A. The best model for a cat is the same cat…or is it? Epilepsy Curr. 2007;7:112–114.

Binder DK, Scharfman HE, eds. Recent Advances in Epilepsy Research, Vol. 548. New York: Kluwer; 2004.

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CHAPTER 4 GENETICS OF THE EPILEPSIES

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The field of epilepsy genetics continues to grow with advances in genetic sequencing technology and knowledge about normal human genomic variation. Genetics plays a role not only in causation or susceptibility to disease but also in responsiveness to medications and adverse effects. This chapter provides an overview of the genetic contribution to human epilepsy in general, the genetics of specific epilepsy syndromes, and genetic testing principles in the epilepsies.

GENETIC CONTRIBUTION TO EPILEPSY

Although suspected for centuries, the genetic contribution to epilepsy was difficult to establish historically due to difficulties defining epilepsy, misdiagnosis of seizures, inaccurate family histories due to insufficient medical information, embarrassment and concealment of seizures among family members, as well as the presence of multiple causative factors aside from genetic risk. Epidemiologic studies eventually confirmed the importance of genetics by demonstrating an increased risk of epilepsy in family members of persons with epilepsy compared to the general population (1). Offspring of individuals with focal epilepsy were found to be just as likely to have epilepsy as offspring of individuals with generalized epilepsy, and both were three times more likely than were the general population (2). These population-based studies were further supported by twin studies, which showed higher concordance among monozygotic compared to dizygotic twins (3,4), as well as heritability studies (5), segregation analyses (6,7), and linkage studies (8,9). Animal genetic models of epilepsy have lent further support, but the strongest evidence has come from the finding of specific mutations in human epilepsy syndromes. Genetics plays a disease-causing role in the progressive myoclonic epilepsies (Chapter 19), as well as those associated with malformations of cortical development (Chapter 26), neurocutaneous syndromes (Chapter 30), inherited metabolic and mitochondrial disorders (Chapter 31), and chromosomal disorders. Aside from disease genes, there also appear to be genes that mediate responsiveness and the development of adverse events to antiepileptic medications (Chapter 49). Disease genes identified in idiopathic/presumed genetic epilepsy syndromes are the focus of this present chapter.

Much of this chapter focuses on genes identified in monogenic epilepsy syndromes, genes that are not as prevalent in the common epilepsies that are thought to display more complex inheritance patterns. Genome-wide association studies have been performed to determine the role of common single nucleotide polymorphisms (SNPs) in common epilepsy syndromes, investigating the “common disease, common variant” hypothesis. Despite some successes, findings have been associated with relatively minor increments in disease risk, explaining only a small proportion of known heritability. The alternative “common disease, rare variants” hypothesis is becoming more appealing with the increasing availability of improved sequencing technology that allows detection of low-frequency

rare variants with higher penetrance. Whole-exome sequencing allows identification of functional variants in the protein-coding sequence of the genome to identify genes that contain multiple rare variants across individuals with disease. As <2% of the genome codes for protein, whole-genome sequencing is another method of capturing additional genetic information. It is likely that both common and rare variants contribute to disease risk in common epilepsy syndromes; it is also likely that other genetic factors beyond point mutations, such as epigenetic effects and genomic structural variation such as copy number variants (CNVs), play an important role yet to be defined.

GENETICS OF EPILEPSY SYNDROMES

The majority of the currently known genetic mutations associated with presumed genetic epilepsy syndromes involve genes encoding ion channels or the regulatory molecules associated with them. More recently, mutations in several additional non-ion channel genes have been linked to presumed genetic epilepsy syndromes. Of note, however, is that while the first gene mutation associated with presumed genetic epilepsy was described in 1995 and a number of other genes have been identified since then, the genetic cause of the majority of presumed genetic epilepsy syndromes remains unclear. In the sections that follow, we present an overview of the major mutations identified to date and the functional consequences.

Ion channels are critical determinants of neuronal membrane excitability. While there are specific differences in the structure and function of the various ion channels for which mutations have been described, in general, these channels are composed of primary pore-forming subunit proteins that flux ions and a number of associated proteins that serve regulatory functions. Mutations in the genes encoding any one of these proteins may disrupt channel function. The expression of ion channels in the pre- and postsynaptic membranes is highly regulated and is a dynamic, activity-dependent process. Mutations in the proteins encoding these channels can affect the biophysical properties of the channels as well as their trafficking to and from the surface membrane. Thus, mutations in ion channel proteins can have dramatic effects on the intrinsic membrane properties of a neuron. Depending on the type of cells affected, there may be marked alterations in neuronal firing patterns and the network properties of the system, which may lead to seizures or a predisposition to them.

Ion Channel Gene Mutations

Mutations in nicotinic acetylcholine receptors (nAChRs), γ-aminobutyric acid (GABA), and glutamate receptors, and in voltage-dependent sodium, potassium, calcium, and chloride channels (ClCs) have been identified in some presumed genetic epilepsy syndromes. While these receptors and ion channels are functionally and molecularly distinct, they all flux ions in response to binding of a ligand to the extracellular domains of the pore-forming regions of the channels or in response to a change in membrane potential.

Nicotinic Acetylcholine Receptors

Background.

Neuronal nAChRs are ionotropic receptors formed by a pentamer of subunits that are arranged in the lipid bilayer of the surface membrane creating a pore that fluxes cations in response to ligand (acetylcholine) binding. There have been 17 different genes identified that encode for ACh receptor

subunits, which include α1–10, β1–4, δ, ε, and γ (10). In the forebrain, α and β subunits are the most abundant, and mutations in both these subgroups have been identified in epilepsy. Under physiologic conditions, binding of the endogenous agonist acetylcholine to the receptor induces permeability of the pore region to Na^+, Ca^{2+}, and K^+ ions (Na^+ and Ca^{2+} moving inward and K^+ outward). Nicotine is an exogenous agonist of the channel as the name implies. nAChRs are ubiquitously expressed in brain and localize to presynaptic and postsynaptic regions as well as nonsynaptic domains. Presynaptic nAChRs modulate neurotransmitter release in both inhibitory and excitatory neurons (GABA and glutaminergic, respectively), while postsynaptic receptors likely contribute to fast excitatory neurotransmission, and receptors localized nonsynaptically are thought to modulate neuronal excitability (11). Nicotinic AChRs are critical to a number of physiologic processes of the central nervous system (CNS) including arousal and sleep as well as cognitive functions.

Epilepsy Genetics and Syndromes.

Gene mutations in nAChRs subunits are associated with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) and cases of sporadic nocturnal frontal lobe epilepsy (NFLE). In 1995, a mutation in CHRNA4, the gene encoding the α-4 nAChR subunit, was described in ADNFLE. This was the first gene mutation identified in association with an epilepsy syndrome. Subsequently, additional mutations have been described in CHRNA4; in the genes encoding the nAChR α-2 and β-2 subunits, CHRNA2 and CHRNB2, respectively; and in genes encoding other ion channels. The majority of the nAChRs mutations described so far involve the pore-forming region of the channel (12). At the molecular level, a number of effects have been described for the various mutations identified (13). One common effect appears to be an overall increased sensitivity of the receptor to acetylcholine, suggesting a gain of function mutation. Although several models have been proposed, exactly how the aberrant channel function leads to the clinical syndrome is unclear, particularly since the channels are ubiquitous but the disorder is of focal onset in the frontal lobes.

ADNFLE and sporadic cases of NFLE are characterized by brief motor seizures consisting of hyperkinetic limb movements with tonic or dystonic posturing of the extremities and onset in late childhood or early adolescence. However, there is significant variability in age of onset with some having onset in infancy. The seizures typically cluster during periods of nonrapid eye movement sleep and may be confused with nocturnal parasomnias. The incidence is unknown, but NFLE is thought to be underrecognized and easily misdiagnosed. In some cases, there are rare daytime seizures, including generalized tonic–clonic (GTC), generalized atonic, and complex partial seizures (CPS) (14). The ictal electroencephalogram (EEG) may demonstrate bifrontal slowing and epileptiform activity, but it also may be normal and is confounded by excessive movement artifact. ADNFLE has been associated with mutations in CHRNA4, CHRNB2, and CHRNA2 with incomplete penetrance of approximately 70% (approximately 30% of individuals who carry the mutation will never show clinical disease). Mutations in CHRNA4, CHRNB2, and CHRNA2 have been reported in about 10% to 20% of individuals with a positive family history, while these mutations are described in only about 5% of those with a negative family history of NFLE (15). Mutations in the corticotropin-releasing hormone (CRH) gene have been identified in ADNFLE (16,17). The majority of cases of ADNFLE/NFLE have seizures that respond well to antiepileptic medications, particularly to carbamazepine; however, resistance to antiepileptic drugs (AEDs) in roughly 30% of these patients is reported requiring trials of additional AEDs [for review, see (18)]. Indeed, those cases of sporadic NFLE that have been associated with mutations in CHRNA4 tend to be more refractory (19,20). The

neurologic exam and imaging studies were normal in individuals with ADNFLE/NFLE; however, neuropsychological assessment of patients with ADNFLE and mutations in the nAChR revealed impairments in cognitive function involving executive tasks and memory (21). Furthermore, there have been recent reports of autism associated with intellectual disability in a kindred with ADNFLE and CHRNA4 mutation (S252L) (22). ADNFLE and coexistent pervasive developmental disorder have been reported in an individual coexpressing a CHRNB2 mutation and also an SCN1A mutation (23).

$GABA_A$ Receptors

Background.

There are three classes of GABA receptors; however, thus far mutations associated with epilepsy have only been described in $GABA_A$ receptors, which are ionotropic receptors that flux chloride (Cl^-) in response to ligand binding. $GABA_A$ receptors underlie fast inhibition and regulate neuronal activity at a cellular and network level. The balance of inhibitory and excitatory neurotransmission is critical to physiologic functions of the CNS. There are 18 genes encoding a number of different $GABA_A$ receptor subunits (α1–6, β1–3, γ1–3, δ, ε1–3, θ, π). Various combinations of these subunits associate to compose the pentameric pore-forming functional $GABA_A$ channels in the CNS. Pentamers of two α, two β, and one γ or one δ subunit compose most $GABA_A$ receptors (24). The heterogeneity in the subunit composition of the receptor contributes to the pharmacologic profile and localization at a subcellular and regional level in the brain. These receptors are activated through ligand binding to the extracellular domains of the receptor. The endogenous ligand is GABA; however, the channels are well-known targets for a number of exogenous drugs, including benzodiazepines, barbiturates, and other sedative agents such as alcohol, which enhance inhibitory neurotransmission (25). Importantly, the pharmacology of these channels has been critical to the medical management of a number of neurologic disorders including epilepsy. Application of an antagonist of these receptors can evoke seizures, which is a phenomenon that has been exploited in basic science epilepsy laboratories.

Epilepsy Genetics and Syndromes.

Mutations in $GABA_A$ receptors have been associated with a variety of epilepsy syndromes, including childhood absence epilepsy (CAE), juvenile myoclonic epilepsy (JME), febrile seizures (FS), generalized/genetic epilepsy with febrile seizures plus (GEFS+), and severe myoclonic epilepsy of infancy (SMEI). Clinical descriptions of these syndromes can be found in Chapters 18, 19, and 34. Mutations in $GABA_A$ receptors include genes encoding: (i) the α1 and α6 subunits, GABRA1 and GABRA6, respectively; (ii) the β3 subunit, GABRB3; (iii) the γ2 subunit, GABRG2; and (iv) the δ subunit, GABRD.

GABRA1 mutations have been described in familial JME, with one family of 14 affected individuals over four generations, all with a similar phenotype of myoclonic and GTC seizures and generalized spike–wave complexes on EEG (26). Mutations in GABRA1 have also been described in a sporadic case of CAE. Out of 98 individuals with presumed genetic generalized epilepsy (GGE), one individual with clusters of daily absence seizures from 3 to 5 years of age was identified as

having a heterozygous mutation in GABRA1; there was no history of FS and no family history of seizures (27). A missense mutation in GABRA6 was described in a patient with CAE and atonic seizures (28). GABRB3 genetic abnormalities also have been associated with CAE. Twenty-eight of forty-five patients with CAE had polymorphisms in the promoter region of exon 1a of the GABRB3 subunit that reduced binding of transcriptional activators (29). Functionally, this mutation would lead to a reduction in GABRB3 subunit expression. A later report screening families of CAE probands revealed three missense mutations (at positions 11, 15, and 32) in GABRB3 associated with absence seizures and eyelid myoclonia, or grand mal seizures, or atonic seizures and vomiting, depending upon the mutation. However, incidental presence of the mutation at position 32 was found in two siblings of the proband who had generalized spike and wave activity with or without FS, and asymptomatic carriers were found in the relatives of the proband with a mutation at the 15 position.

GABRG2 mutations were identified by two independent groups in families with GEFS+ and CAE. Shortly thereafter, additional mutations in GABRG2 were described in families with GEFS+, SMEI or Dravet syndrome (DS), CAE, and FS. GEFS+ is a familial epilepsy syndrome, with at least two affected family members, encompassing a wide range of phenotypes from simple FS to FS persisting beyond 6 years of age (FS+), to afebrile GTC seizures, absence, myoclonic, or atonic seizures, and even focal seizures. While many patients have seizures that remit spontaneously, others may develop refractory epilepsy, including SMEI or DS. Separate mutations in GABRG2 also have been identified in several families with CAE and FS (30,31). In two other families, with isolated FS or FS with associated other seizure types, mutations in GABRG2 have been described (32,33). These families are arguably still within the spectrum of the GEFS+ phenotype.

GABRD is thought to be a susceptibility locus for GGE, and a mutation has been identified in one small family with GEFS+ (34). Clinical features of affected individuals in the families described above do not differ significantly from nonfamilial forms of GGE.

Functionally, the $GABA_A$ receptor mutations have been characterized in a number of laboratories, and a variety of functional effects have been identified including alterations in GABA sensitivity, reduced surface expression, alterations in the biophysical properties of the receptor, and dominant negative as well as loss of function effects. The net result of these alterations is a reduction in GABA-activated Cl^- currents and thereby alterations in inhibitory neurotransmission (12). As mentioned above, mutations in GABRD, the gene encoding the δ subunit, have been suggested as susceptibility alleles in GEFS+ and JME. The δ subunit is found in $GABA_A$ receptors localized exclusively to the extra- or perisynaptic regions, while those containing γ subunits are found both in the synaptic and extrasynaptic regions. These channels contribute to the tonic inhibitory current, and studies have shown that the mutations described in epilepsy reduce this current and the surface expression of the channels (12,35).

Sodium Channels

Background.

Voltage-gated sodium channels (Na_v) are composed of a complex formed by a large α subunit and smaller auxiliary β subunits. The Na_v α subunit consists of four internally repeated domains that each have six transmembrane spanning regions and a pore loop, which together form the ion-conducting pore that fluxes Na^+ ions. The β subunits associate with the α subunit complex and modify the channel

biophysical properties and interact with the cytoskeleton. Four of the nine genes encoding the Na_v channel α subunits are expressed in the mammalian CNS. These are SCN1A, SCN2A, SCN3A, and SCN8A, which encode $Na_v1.1$, $Na_v1.2$, $Na_v1.3$, and $Na_v1.6$, respectively. The $Na_v1.x$ channels are responsible for action potential initiation and propagation in neurons. The subcellular localization varies depending upon the subunit composition (36,37). These channels are critical to physiologic functions of the CNS, and the aberrant regulation or genetic mutation of the sodium channel α and β subunits has been associated with neuropathology, including epilepsy. Furthermore, these channels have been the target of therapeutics in epilepsy. The mechanism of action of some anticonvulsant drugs such as phenytoin, oxcarbamazepine, and lacosamide is thought to be in part through modulation of these channels.

Epilepsy Genetics and Syndromes.

Mutations in SCN1A, SCN2A, and SCN1B (encoding the β1 subunit) are well- described genetic causes of epilepsy. The first sodium channel mutation in epilepsy was described in 2000 in SCN1A (38) with two families with GEFS+. Subsequently, approximately 650 mutations have been described in this channel subunit in GEFS+ variants and SMEI or DS variants (35,39,40). Missense mutations are thought to account for the majority of SCN1A variants, while nonsense mutations and other genetic variants account for a relatively smaller proportion. Furthermore, the majority of known SCN1A mutations are de novo (88%). To date, over 20 mutations in SCN2A have been described in association with benign familial neonatal/infantile seizures (BFNIS), GEFS+, and SMEI/DS. More frequently, SCN2A missense mutations have been described in BFNIS, and nonsense or truncation mutations have been described in SMEI/DS. The mutations in SCN1A and SCN2A that led to more dramatic alteration in the protein product were associated with the more severe phenotype (DS). SCN1B mutations have been described in GEFS+, FS, early-onset absence epilepsy, and temporal lobe epilepsy (TLE) (12).

There is phenotypic variability with the sodium channel subunit mutations and complex genotype–phenotype relationships, suggesting that modifier genes play a role. As mentioned above, GEFS+ is a familial epilepsy syndrome with a highly variable phenotype, typically involving FS persisting beyond 6 years of age, followed by afebrile seizures. The afebrile seizures that follow FS can be either generalized or focal, including mesial TLE. Affected family members can have isolated FS, afebrile seizures, or both. Mutations in SCN1A, SCN2A, and SCN1B have been described in GEFS+. At the more severe end of the GEFS+ spectrum is SMEI or DS. While roughly 70% to 80% of Dravet patients will have SCN1A mutations (both missense and truncation), the etiology for the remaining affected individuals is unknown. De novo mutations in SCN1A have also been identified in cases of alleged pertussis vaccine–induced encephalopathy, which can resemble SMEI clinically (41). Furthermore, the diphtheria–tetanus–pertussis vaccine may be associated with earlier onset of SCN1A-associated DS (42). Mutations in SCN3A, SCN8A, and SCN9A (encoding Nav1.9) sodium channel α subunits also have been described in association with epilepsy and may be considered disease-modifying genes [for review, see (35)].

There is an increased incidence of sudden unexpected death in epilepsy (SUDEP) in DS compared to other chronic epilepsies (43). SCN1A mutations and SUDEP have been reported in some families, and recently, a frameshift duplication mutation in SCN1A was reported in association with SUDEP. While this channel has greatest expression in the brain, there are reports of SCN1A expression in the mammalian heart (44). Interestingly, mutation of the SCN5A channel, which has high

cardiac expression levels, causes Brugada syndrome. There is a report of SUDEP in an individual with epilepsy and long QT syndrome syndrome associated with a missense mutation in SCN5A (45).

Potassium Channels

Background.

Potassium channels are major determinants of the intrinsic membrane excitability of neurons and thus alterations in these channels will have profound effects on network behavior within the CNS. These channels are critical to physiologic functions of the CNS including development, plasticity, learning and memory, and many other functions. Mutations or aberrant regulation of a number of the K^+ channels expressed within the CNS has been described in neurologic disorders, including epilepsy. These channels are extremely diverse, and there are many different subunits described. The functional channel complexes flux K^+ ions outward. There are three major classes of K^+ channels that are defined by the number of transmembrane domains within each α subunit. Mutations in channels falling into two of these classes have been described in epilepsy. These include the voltage-dependent potassium (K_v) channel α subunits that are characterized by six transmembrane domains and the inward-rectifier K^+ (K_{ir}) channels that are characterized by two transmembrane domains. Each of these groups is characterized by subfamilies encoded by numerous genes. The functional channel is formed by multimerization of the α subunits and a host of associated or auxiliary subunits that influence the channel properties and trafficking (12,37).

Epilepsy Genetics/Syndromes.

KCNQ2 and KCNQ3 from the K_v family, which encode K_v7 α subunits, have been clearly linked to epilepsy. Channels composed of these subunits underlie the M-current, named so due to the observation that stimulation of muscarinic cholinergic receptors suppresses the current. M-channels contribute to a portion of the afterhyperpolarization (AHP), known as the medium AHP (mAHP). These channels are expressed early during development in the human brain. Recent reports indicate that over 50 mutations have been identified in KCNQ2 and KCNQ3 in families with benign familial seizures in the first year of life (35). The nomenclature for this disorder is based upon age of onset of seizures and includes benign familial neonatal convulsions/seizures (BFNC/BFNS) also known as benign familial neonatal convulsions or benign familial epilepsy type 1 occurring before day of life 5, benign familial neonatal/infantile convulsions/seizures (BFNIC/BFNIS) occurring between 2 days and 6 months of age, and benign familial infantile convulsions/seizures (BFIC/BFIS) occurring between 3 and 8 months of age. The seizures are focal with or without secondary generalization, with clustering of seizures at times. A small percentage of these individuals go on to have seizures later in life. The familial cases are autosomal dominant, but de novo mutations also have been identified. Compared to KCNQ2, relatively fewer mutations in KCNQ3 have been identified in families with this syndrome (46). The described mutations are predicted to result in truncation of the channel protein, and others are missense mutations. Evidence suggests that the net effect of these mutations is a loss of function. The decreased level of functional M-channels is predicted to lead to increased excitability within the CNS, particularly during the neonatal period. Indeed, under physiologic conditions, these likely play an important inhibitory role early postnatally when GABA neurotransmission is depolarizing and thereby excitatory. The epilepsy remission seen in affected

individuals is thought to be due to the developmental switch in GABA when it changes to become inhibitory (12). Myokymia later in life has been described in one family with KCNQ2 mutation and BFNS (47) . KCNQ2 mutations have recently emerged as a cause of neonatal epileptic encephalopathy with intractable tonic seizures evolving during the first week of life that eventually subside, but residual intellectual disability and motor impairment are present (48). The electroclinical features of the benign familial seizure subtypes are similar, and KCNQ2 mutations account for the majority of BFNS and BFNIS cases, although SCN2A mutations are another important cause of BFNIS, as already discussed. While KCNQ2 and KCNQ3 mutations are also seen in BFIS, mutations in the proline-rich transmembrane protein (PRRT2) gene are much more frequent, as discussed below. (49).

KCNA1 encodes the $K_v1.1$ α subunits. The K_v1 subfamily of K^+ channels is found throughout the brain and is localized to axonal regions where it contributes to repolarization and shaping of the action potential. Kv1.1 α subunits heteromultimerize with other K_v1 subunits, and the channels may be dramatically altered in their properties by inclusion of the $K_v\beta1.1$ auxiliary subunit in the supramolecular channel complex (37). Mutations in KCNA1 underlie autosomal dominant episodic ataxia type 1 (EA1), and some families with this disorder have epilepsy. The effect of this mutation on channel function is an overall loss of function with altered channel assembly, trafficking, and kinetics (12). KCNA1 mutations have been described in families with EA1, which is a rare disorder that is characterized by intermittent episodes of ataxia and myokymia as well as partial seizures in a few kindreds (50). Because not all families with this gene defect exhibit epilepsy as part of the phenotype, this gene locus is considered a susceptibility gene or risk factor for epilepsy.

KCNMA1 encodes the α subunit of the large-conductance voltage- and Ca^{2+}-activated K^+ channel, also called the BK channel (KCa1.1). The BK channel is distinct from other K^+ channels in that it can be activated by both intracellular Ca^{2+} and membrane depolarization. BK channels are highly conserved throughout evolution and are widely expressed in multiple mammalian cells including smooth muscle, inner ear hair cells, and neurons throughout the brain. The channels consist of a pore-forming α subunit (KCNMA1), which has at least nine splice variants in the human brain (51), and a regulatory β subunit, of which there are four isoforms (KCNMB1-4). A mutation in KCNMA1 has been identified in a family with generalized epilepsy and paroxysmal dyskinesia (GEPD) (52). Sixteen affected individuals developed epileptic seizures (n = 4), paroxysmal nonkinesigenic dyskinesia (n = 7), or both (n = 5). The mutation increases the sensitivity of the channel to calcium compared to the wild-type channel. This gain of function appears to cause more rapid action potential repolarization. The end result is that neurons fire at a higher sustained rate, likely due to a reduction of action potential width (53).

A mutation in KCND2, the gene encoding the $K_V4.2$ α subunit, has been described in an individual with medically intractable TLE. This same mutation was present in the father, suggesting that this gene may be considered a susceptibility locus (54). Missense variations in the gene encoding the K_{ir} 4.1 potassium channel (KCNJ10) have been associated with susceptibility to GGE syndromes of absence epilepsy and JME (34). Recently, mutations in the potassium channel tetramerization domain–containing protein 7 gene (KCTD7) have been described in association with progressive myoclonic epilepsy (35). The molecular function of the KCTD7 protein product is unclear; however, it is homologous to the tetramerization domain of voltage-gated potassium channels, and overexpression of this protein hyperpolarizes the cell and decreases excitability, suggesting a role for this molecule in dampening excitability.

Calcium Channels

Background.

Voltage-dependent calcium (Ca_v) channels flux calcium intracellularly in response to depolarization and thereby mediate a number of physiologic processes in the CNS including the activation of signaling pathways, gene transcription, and neurotransmitter release. Calcium channels consist of two families: high-voltage-activated (HVA) family and low-voltage-activated (LVA) family. The HVA family includes Ca_v1 (L-type) and Ca_v2 (P/Q-, N-, and R-type) channels, which are heterotrimers of subunits α, β, α_2-δ, and γ. The LVA family includes Ca_v3 (T-type) channels, which are monomers and are composed only of α subunits. HVA and LVA channels differ in function and electrophysiologic properties. Ca_v1 channels are typically localized postsynaptically in the somatodendritic regions and contribute to calcium signaling in response to action potential backpropagation, synaptic activity, and activity-dependent gene regulation. Ca_v2 channels are localized both pre- and postsynaptically with both axonal and somatodendritic expression. An important function for these channels is the regulation of presynaptic neurotransmitter release. Ca_v3 channels underlie a transient calcium current that activates at subthreshold potentials and is critical for the regulation of calcium flux at near resting membrane potential and also during action potentials. These channel subfamily members are fairly broadly distributed within the CNS (37). A number of AEDs mediate an anticonvulsant effect through altering the function of these channels (see Chapter 43).

Epilepsy Genetics.

Mutations in the genes encoding Ca_v channels and their auxiliary subunits were first described in mice; naturally occurring mutations in these channels were associated with generalized spike and wave activity (55). Subsequently, mutations in Ca_v channels associated with presumed genetic epilepsy in humans have been described. The most common mutations in Ca_v channels associated with epilepsy involve CACNA1H, which encodes the $Ca_v3.2$ channels, also known as T-type calcium channels. $Ca_v3.2$ channels are localized primarily in dendritic regions where they modulate neuronal excitability by promoting burst firing and boosting synaptic inputs. These channels contribute to the thalamocortical circuitry with expression both in neurons in cortical layer V and in reticular thalamic nuclei, and over 30 mutations have been described in families with GGE and CAE. T-type channels and low-threshold burst firing in the thalamocortical circuit are involved in the generation of thalamocortical oscillations during spike–wave discharges. A variety of different mutations have been described for CACNA1H in epilepsy. Some are associated with a gain of function, but others have effects on channel kinetics, trafficking, or decrease the underlying current. In addition, a number of sites for alternative splicing of $Ca_v3.2$ are present, and some of the identified mutations occur in these regions (12). Additional work is required to understand how these gene mutations contribute to the epilepsy phenotype.

The CACNA1A gene encodes the $Ca_v2.1$ α subunit, which underlies the P/Q-type calcium current, and is widely expressed in the CNS both in regions of the forebrain such as cortex and hippocampus and in the cerebellum (37). Subcellularly, these channels are localized presynaptically where they play a critical role in initiating neurotransmitter release. The channels are also localized in the somatodendritic regions where they modulate excitability of the postsynaptic membrane in neurons

(37). Mutations in CACNA1A have a strong link with familial hemiplegic migraine (FHM), episodic ataxia type 2, and spinocerebellar ataxia type 6 (56). Some families with mutations in this gene express a phenotype that also includes epilepsy. There are different mutations described, and functional characterization of some of them suggests that channel function is impaired in the mutant channel.

The CACNB4 gene encodes the Ca_v auxiliary β_4 subunit, a non–pore-forming modulatory subunit. Inactivation of the CACNB4 gene in the mutant "lethargic" mouse results in a neurologic phenotype resembling absence epilepsy with ataxia (57). Subsequently, mutations in CACNB4 were described in humans with GGE/JME and episodic ataxia (38).

In mouse models with mutations in HVA channel subunits, there is a compensatory increase in thalamic LVA (T-type channel) current, which is thought to contribute to the epilepsy phenotype (58). This is consistent with the finding of gain-of-function mutations in Cav3.2, an LVA channel subunit, in individuals with familial GGE.

Epilepsy Syndromes.

Susceptibility to GGE/CAE is associated with variants in the CACNA1H gene. In one study, missense mutations were identified in 12% of children of Chinese descent with CAE, with each child inheriting the missense mutation from one of his or her unaffected parents; there was no difference in clinical CAE phenotypes between individuals with and without mutations (59). Two possible explanations for the presence of missense mutations in unaffected parents are (i) the parents might have had CAE early in life that was undetected, and (ii) the missense mutations only increase susceptibility to CAE but alone are not sufficient to cause CAE. Variants in CACNA1H were also identified among 240 Caucasian individuals in Australia, from 167 unrelated GGE and GEFS+ families, with a wide variety of individual epilepsy syndromes including CAE, juvenile absence epilepsy (JAE), JME, myoclonic astatic epilepsy, GEFS+, FS, and TLE (60). All variants were also observed in some unaffected individuals, suggesting that the variants are susceptibility alleles. The types of variants identified in the studies above are population specific and present at low frequencies. Mutations in the CACNA1A gene have also been found to be associated with epilepsy. In one Swedish family of three mutation carriers, all had FHM and ataxia, and two had CPS (61). In a second family, five members had absence epilepsy with 3-Hz spike and wave activity and cerebellar ataxia (62). In a study of 48 individuals with SMEI or DS due to SCN1A mutations, the presence of CACNA1A variants appeared to modify the epileptic phenotype; those individuals with both SCN1A and CACNA1A mutations were more likely to have an earlier onset of seizures, absence seizures before 6 years of age, and more frequent prolonged seizures in the first year of life, compared to individuals who only had SCN1A mutations (63). Finally, coding variants in the CACNB4 gene were identified in two families with GGE and one family with episodic ataxia (38). Similar to CACNA1A variants, mutations in CACNB4 may be a genetic modifier in individuals with SCNA1 mutations and SMEI or DS (17).

Chloride Channels

Background.

This section is focused on voltage-gated ClCs, which contrasts an earlier section in this chapter covering ligand-gated chloride ($GABA_A$) receptors. There are a number of mammalian genes

encoding ClCs. This section focuses on the CLCN family of genes (CLCN1-7), which encode voltage-gated ClCs or chloride transporters; these channels flux chloride and serve a number of important functions throughout the organism. Voltage-gated ClCs have four subunits surrounding a pore, which fluxes Cl^- as well as other inorganic anions. The channels are composed of dimeric multisubunit proteins that are gated by multiple factors. For instance, channel opening to flux Cl^- out of the cell occurs in response to hyperpolarization and acidic extracellular pH (64). The channel is expressed in the CNS and has a critical role in GABA inhibition through maintaining a low intracellular concentration gradient (65,66).

Epilepsy Genetics and Syndromes.

Three mutations in the CLCN2 gene were identified in 3 of 46 unrelated families with GGE (67). In a reevaluation of two of the families reported, discrepancies were identified in family structure, phenotype, and genetic analysis (68), and as result, the paper was retracted. Other studies have reported CLCN2 mutations in individuals with epilepsy (69–72), but the evidence for their functional role is lacking (73–75). A study that used exome sequencing of 237 ion channel genes in 152 individuals with sporadic epilepsy of unknown origin found an excess of variation in CLCN1, which encodes the ClC-1 chloride channel, in those with epilepsy compared to controls (76). They also reported a CLCN1 truncation mutation in an individual with intractable generalized epilepsy and mild myotonic features, as well as demonstrated the presence of CLCN1 mRNA transcripts and ClC-1 protein in human brain autopsy specimens and in mouse brain, suggesting a role for CLCN1 in human epilepsy. While CLCN1 mutations have long been associated with autosomal dominant and autosomal recessive forms of myotonia congenita, ClC-1 protein previously was not believed to be expressed in the brain. This study also identified more missense variants in CLCN2, CLCN5, and CLCN7 in individuals with epilepsy compared to controls, but the significance of these findings remains to be seen.

Glutamate Receptors

Background.

The N-methyl-D-aspartate (NMDA) receptor is a glutamate-activated excitatory ion channel permeable to Na^+, K^+, and Ca^{2+}. NMDA receptors are composed of NMDA receptor 1 (NR1 or GRIN1) and NMDA receptor 2 subunits (NR2 or GRIN2). NMDA receptor antagonists have been investigated as potential anticonvulsant medications. Autoantibodies to NMDA receptors have been associated with limbic encephalitis, which is often characterized by seizures and status epilepticus.

Epilepsy Genetics and Syndromes.

Mutations in GRIN2A have been identified in patients with presumed genetic focal epilepsies with rolandic spikes and epilepsy-aphasia spectrum disorders. In a study of individuals with Landau–Kleffner syndrome, continuous spike and wave during slow-wave sleep (CSWS), and atypical rolandic epilepsy associated with speech disturbance, GRIN2A mutations were identified in about 20% of both familial and sporadic cases (77). Large 16p13.2 deletions that included GRIN2A were previously reported in individuals with severe cognitive impairment, dysmorphic features, and rolandic seizures (78). Mutations in GRIN2A were also identified in individuals with both familial

and sporadic childhood epilepsy associated with various degrees of cognitive impairment (79). In a separate study, GRIN2A mutations were identified in 4.9% of individuals with benign epilepsy with centrotemporal spikes and in 17.6% of individuals with CSWS (80). In another large study, screening individuals with epileptic encephalopathy of various causes, GRIN2A mutations were identified in 9% of individuals with epilepsy-aphasia spectrum disorders but not in other epileptic encephalopathies (81).

Na^+, K^+-ATPase Pump Gene (ATP1A2)

Background.

The Na^+, K^+-ATPase catalyzes the ATP-driven exchange of three intracellular Na^+ ions for two extracellular K^+ ions across the plasma membrane. The enzyme plays a crucial role in maintaining the transmembrane cation gradients that are dissipated in the propagation of action potentials. In addition, the Na^+ gradient produced by Na^+-K^+-ATPase is required for clearance of extracellular glutamate by astrocytes. ATP1A2 encodes the α-2 isoform of the major subunit of the Na^+, K^+-ATPase and is predominantly found in neural and muscle tissues. The ATP1A2 gene encodes a protein that is thought to play a role in calcium signaling during cardiac muscle contraction. In the CNS, ATP1A2 is expressed in neurons throughout the brain in the neonatal period, becoming more abundant in glia in adulthood. In the CNS, the α-2 isoform is thought to play a critical role in calcium signaling, although the exact mechanism of its pathogenesis is still unclear.

Epilepsy Genetics and Syndromes.

In a five-generation Dutch–Canadian family with FHM and BFIC/BFIS, a mutation was identified in the ATP1A2 gene, regardless of whether the affected family member had FHM, BFIC/BFIS, or both (82). In another study of 20 families with epilepsy and migraine, two families were found to have novel ATP1A2 mutations; six mutation carriers had both epilepsy and migraine, two had only epilepsy, and six had only migraine (83). While other similar families have been described, the most prominent phenotype is that of migraine or migraine and seizures with very few mutation carriers having epilepsy alone. In a case–control study of 152 German individuals with nonfamilial GGE and 111 healthy German controls, no significant association was found with seven polymorphisms of the ATP1A2 gene and GGE compared to controls, suggesting that ATP1A2 was not a major susceptibility gene in this particular epilepsy population (84). The ATP1A2 gene appears to play a more significant role in FHM.

Non-ion Channel Gene Mutations

Leucine-Rich, Glioma-Inactivated-1 (LGI1) Gene

Background.

The LGI1 gene was the first non-ion channel gene identified in human idiopathic/genetic epilepsy. LGI1 encodes a secreted protein with two distinct structural domains: the C-terminal region, which consists of seven copies of a 40-43-residue named EAR (epilepsy-associated repeat) or epitempin

(EPTP) domain, and the N-terminal region, which contains leucine-rich repeats (LRRs), surrounded by conserved cysteine-rich clusters. The function of the LGI1 gene product is not clear, but studies suggest a role in synaptic transmission (85–87), as well as in neuronal development (88,89). Other LRR-containing proteins are involved in signal transduction, cell growth regulation, adhesion, and migration.

Epilepsy Genetics.

The LGI1 gene product enhances AMPA receptor–mediated synaptic transmission in hippocampal slices. Mutations in LGI1 have been identified in individuals with autosomal dominant partial epilepsy with auditory features (ADPEAF) (90), also referred to as autosomal dominant lateral temporal lobe epilepsy (ADLTE). There is evidence for allelic heterogeneity, as 25 different mutations have been described in various families with ADPEAF or in sporadic individuals with lateral TLE. Most LGI1 mutations tested by cell transfection assay using HEK293 or 293T cell lines, regardless of whether they occur in the N-terminal LRR domain or the C-terminal EPTP domain, cause a significant reduction in protein secretion (91). CNV analysis identified a heterozygous 81-kb microdeletion of the LGI1 gene in affected members of an ADLTE family after exon sequencing failed to identify a point mutation (92). Beyond genetics, antibodies against LGI1 have been associated with limbic encephalitis.

Epilepsy Syndrome.

ADPEAF is characterized by focal seizures with auditory auras ranging from unformed sounds, such as humming or ringing, to distortions and volume changes, to more organized sounds, such as singing and music. Some affected individuals have seizures provoked by auditory stimuli. Age of onset can vary from 4 to 50 years, with mean age of onset in the late teens. Interictal EEG is often normal, as is magnetic resonance imaging (MRI). Seizures are generally well controlled with medications, but intractable epilepsy has also been reported (93). ADPEAF exhibits incomplete penetrance, estimated at 67%, regardless of the specific LGI1 mutation (94) . LGI1 mutations have been described in approximately 30% to 50% of the families tested, with no clear clinical distinction between those families with and without mutations (95,96). A subset of affected individuals with LGI1 mutations has GGE (95). De novo LGI1 mutations have been described in about 2% of sporadic partial epilepsy with auditory features (97,98). In an analysis of clinical and molecular information from the 36 published ADPEAF families with LGI1 mutations reported in the literature, disease-causing mutations were more likely to occur in the N-terminal LRR domain compared to the C-terminal EPTP domain, and auditory symptoms were less frequent in individuals with truncation mutations in the EPTP domain compared to mutations in other regions (99).

Myoclonin1/EFHC1 Gene

Background.

Myoclonin1/EFHC1 encodes a 640-amino acid protein, also called EFHC1, that consists of three DM10 domains of unknown function and a C-terminal region with a single calcium-binding EF hand motif. Mutations in Myoclonin1/EFHC1 occur in JME and JAE. There are several putative functions for the EFHC1 protein. In hippocampal neurons, EFHC1 overexpression induced apoptotic cell death, possibly through modulation of R-type calcium currents (100). More recent work suggests that

EFHC1 potentiates the activity of the transient receptor potential M2 channel TRPM2, a calcium-permeable channel that is linked to cell death (101). Another putative role is that of EFHC1 as a ciliary protein, as suggested by the presence of EFHC1 in cilia of ependymal cells lining the cerebral ventricles, and abnormal ciliary function in EFHC1-deficient mice (102–104). Intact ependymal ciliary function is required for normal CSF flow and the directional migration of neuroblasts, which depends on normal CSF flow. Yet another function attributed to EFHC1 is that of a microtubule-associated protein (MAP) involved in cell division and neuronal migration during development (105).

Epilepsy Genetics and Syndrome.

Heterozygous missense mutations in EFHC1 were first described in individuals with familial JME in 2004 (100). Numerous additional missense, nonsense, and deletion mutations have been described in various families as well as in sporadic cases of JME (106). Some mutation carriers without epilepsy were found to have epileptiform abnormalities on EEG, with an overall rate of 3% to 9% of JME patients seen in clinic having EFHC1 mutations (106). Mutations in the EFHC1 gene have also been identified in JAE and sporadic GGE (107). A homozygous mutation in EFHC1 was also discovered in a family with three of seven children presenting with intractable epilepsy beginning in the neonatal period (108).

Proline-Rich Transmembrane Protein 2 (PRRT2) Gene

Background.

The PRRT2 gene is located on chromosome 16; it consists of four exons encoding 340 amino acids, and the protein is predicted to have two transmembrane domains. In mice, high levels of PRRT2 mRNA are detected in the brain with lower levels in the spinal cord, with peak expression during postnatal development. The PRRT2 protein is poorly characterized, but it appears to interact with SNAP-25, a synaptosomal-associated protein involved in the release of neurotransmitters from synaptic vesicles at the presynaptic membrane.

Epilepsy Genetics and Syndromes.

PRRT2 mutations were first identified in families with paroxysmal kinesigenic dyskinesia (PKD) (109). Subsequently, different heterozygous truncating mutations in PRRT2 were found in families with PKD and infantile convulsions (110). Heterozygous PRRT2 mutations have also been reported in individuals with BFIC/BFIS, as well as additional families with the infantile convulsions and choreoathetosis (ICCA) syndrome or the co-occurrence of BFIC/BFIS and PKD (111). Although the ICCA syndrome was first linked to a region on chromosome 16 in 1997, the causative gene was not identified until 2011. In the 2 years following the original 2011 reports, over 50 mutations in over 300 individuals were identified, with the majority of families harboring the same recurrent frameshift mutation: PRRT2 c.649-650insC. Several de novo mutations were also reported. Most mutations led to protein truncation. Mutant truncated proteins showed loss of membrane targeting with the truncated proteins remaining in the cytoplasm. Mutations in PRRT2 appear to account for 40% to 80% of familial cases of BFIC/BFIS, PKD, or ICCA. The phenotypic variability, in which the same mutation can cause BFIC/BFIS, PKD, or both in different individuals in the same family, remains unexplained.

DEP Domain–Containing Protein 5 (DEPDC5) Gene

Background.

The Dishevelled, Egl-10 and Pleckstrin (DEP) domain–containing protein 5 (DEPDC5) gene is located on chromosome 22; there are several isoforms of approximately 1600 amino acids in length. In mice, expression occurs in neurons and GABAergic interneurons throughout brain development. The gene is strongly expressed in both the developing and adult human brain, and the encoded protein contains a DEP homology domain found in other proteins involved in G-protein signaling and membrane targeting, but the exact function of DEPDC5 is unknown.

Epilepsy Genetics and Syndromes.

Autosomal dominant familial focal epilepsy with variable foci (FFEVF) was first described in 1998 (112). FFEVF is characterized by marked intrafamilial variability in age of onset, ictal semiology and localization, seizure severity, cognitive function, and psychiatric comorbidity. Linkage studies mapped FFEVF to a region on chromosome 22q, but the causative gene was not identified until 2013. Mutations in DEPDC5 were identified in seven of eight large families with FFEVF, with an estimated penetrance of 66%; mutations were also identified in 10 of 82 (12%) small families with two or more individuals with nonlesional focal epilepsy (113). Most mutations introduced a premature stop codon leading to protein truncation (113). In another series of families with autosomal dominant focal epilepsies including FFEVF, ADNFLE, and familial TLE, DEPDC5 mutations were identified in 6 of 16 (37%) families, with most mutations causing premature protein truncation and loss of function (114).

GENETIC TESTING

Genetic testing is available for a number of the presumed genetic epilepsy syndromes described above (for information on currently available genetic tests, check www.genetests.org). Prior to ordering, it is important to differentiate genetic testing to establish a diagnosis in a patient with epilepsy or suspected epilepsy (diagnostic testing) from genetic testing in asymptomatic individuals to identify future risk of developing epilepsy (screening or predictive testing). It is also important to differentiate genetic testing in monogenic disorders (caused by a single “major” gene) versus genetic testing in complex genetic disorders, which may be caused by multiple genes and/or environmental factors. The ethical implications of genetic testing are complex and need to be addressed before testing is ordered, ideally with a geneticist or genetic counselor. Genetic testing has implications for the entire family, and yet each individual family member has the right to decide whether to participate in testing. The testing can involve the analysis of DNA, RNA, chromosomes, proteins, or metabolites. Genetic testing of symptomatic individuals (diagnostic testing) is most helpful when the test has high sensitivity and specificity, when the results will influence clinical management, when the disease is preventable or treatable, or when the results provide important information for other family members. Even without effective treatment, genetic testing can be valuable by establishing the diagnosis and excluding other possibilities, thus limiting further testing.

Complicating genetic testing in the epilepsies is incomplete penetrance and genetic heterogeneity. Many of the mutations identified to date have <100% penetrance; some individuals who carry the disease mutation will never have clinical disease. Most genetic epilepsy syndromes also display

genetic heterogeneity in that they can be caused by mutations in more than one gene; this clearly complicates the interpretation of a "negative" test of a single gene. Consider the case of a child diagnosed clinically with SMEI, whose parents request genetic testing to determine the risk to future offspring. Approximately 70% to 80% of patients with SMEI will have SCN1A mutations, with the vast majority occurring de novo. Mutations in GABRG2 have also been identified in SMEI patients, and SCN1A mutations have also been identified in patients with GEFS+, a typically more benign phenotype. If an SCN1A mutation is identified in the affected child, and not in the parents, the mutation is likely to have occurred de novo, and the risk to future offspring is low. However, it is difficult to exclude the possibility of gonadal mosaicism (the presence of the mutation in a subset of the gametes of one parent), in which case there would be increased risk to future offspring. If an SCN1A mutation is not identified in the affected child, one cannot rule out the possibility of a gene mutation in another gene, such as GABRG2. If an SCN1A mutation is identified in both the affected child and one parent, there is a 50% chance of transmitting that SCN1A mutation to future offspring, but the clinical phenotype would be difficult to predict, as SCN1A mutations have been identified in a wide range of phenotypes, from benign FS to severe intractable epilepsy.

As another example, consider the case of a 28-year-old woman with intractable NFLE. Her brother, father, paternal uncle, and paternal grandfather all have similar seizures at night. She plans to have children, and she wants to know the risk of epilepsy in her offspring. Based on her family history, her diagnosis is most likely ADNFLE, which has been associated with mutations in CHRNA4, CHRNB2, CHRNA2, as well as other genes. Mutations in CHRNA4 and CHRNB2 account for only a small percentage of all patients with ADNFLE, implying that other genes are involved. As with many autosomal dominant epilepsies, there is incomplete penetrance, estimated at 50% to 70%. If a CHRNA4 mutation is identified in this patient, there is a 50% chance of transmitting the mutation and a 25% to 35% chance of transmitting NFLE to her offspring. If a CHRNA4 mutation is not identified in this patient, she may still have a mutation in another gene, with a similar risk of transmitting the disease. In a patient with a clinical diagnosis of NFLE and a family history consistent with autosomal dominant inheritance, genetic testing would not necessarily change treatment or genetic counseling.

There are certain specific clinical scenarios in which genetic testing is playing an increasingly important role, such as in the evaluation of a child with an epileptic encephalopathy, with onset of medically refractory seizures in the first year of life associated with marked developmental delay. When neuroimaging for structural brain malformations, karyotyping for chromosomal abnormalities, and screening for inherited metabolic disorders are unrevealing, additional genetic testing can provide important information for diagnosis and treatment. Specific gene defects to consider are listed in Table 4.1, but the table is not meant to be exhaustive, particularly as new mutations continue to be identified at a rapid rate. In particular, in cases of Dravet syndrome, mutations have been described in SCN1A, SCN1B, SCN2A, PCDH19, and GABRG2. In children diagnosed with West syndrome characterized by infantile spasms and hypsarrhythmia, mutations have been identified in CDKL-5, ARX, STXBP-1, and PLCB1, as well as others. Ohtahara syndrome, an epileptic encephalopathy with onset in the first few days or weeks of life, characterized by burst suppression on EEG, has been associated with mutations in STXBP-1, ARX, SLC25A22, and SCN2A, as well as others. An epileptic encephalopathy similar to Ohtahara syndrome has been associated with KCNQ2 mutations, characterized by intractable tonic seizures in the first week of life associated with a burst suppression pattern on EEG and severe cognitive impairment, but, unlike Ohtahara syndrome, which often evolves to West syndrome, seizures resolve by 3 years of age. GLUT1 deficiency was first

described as a cause of epileptic encephalopathy, but the phenotypic spectrum has grown to include milder phenotypes including paroxysmal movement disorders and milder forms of epilepsy, including GGEs such as absence epilepsy. GLUT1 deficiency is caused by mutations in the solute carrier family 2 (facilitated glucose transporter) member 1 (SLC2A1) gene, and mutations in SLC2A1 have been identified in 10% of patients with early-onset absence epilepsy (115) and 1% of more common GGE syndromes including with JME, JAE, CAE, and epilepsy with GTC seizures (116). Diagnosing GLUT1 deficiency has important treatment implications, as the ketogenic diet is an effective therapy. Rare CNVs appear to play an important role in the epileptic encephalopathies (117). The role of CNV detection by SNP microarray or array comparative genomic hybridization (CGH) has become routine in the evaluation of nonsyndromic intellectual disability (children with global developmental delay) (118). Whole-exome sequencing is another powerful tool to detect genomic variation, but the results are complex and should be interpreted with the help of a genetic counselor or medical geneticist.

Table 4.1 Selected Inherited Human Epilepsy Syndromes

Epilepsy syndrome	Seizure types/clinical features	Chromosomal segment	Associated genes
Idiopathic/genetic focal			
Benign focal epilepsy of childhood; benign rolandic epilepsy; epilepsy-aphasia spectrum disorders	Focal and secondarily GTC seizures, nocturnal	15q14 16p13	Unknown *GRIN2A*
Benign familial infantile convulsions/seizures (BFIC/BFIS)	Onset between 3 and 8 mo of age. Focal and secondarily GTC seizures.	19q (BFIS1) 16p12-q12 (BFIS2) 2q23-q24 (BFIS3) 1p36-p35 (BFIS4) 20q13 8q24	Unknown *PRRT2* *SCN2A* Unknown *KCNQ2* *KCNQ3*
Benign familial neonatal-infantile convulsions/seizures (BFNIC/ BFNIS)	Onset between 2 d and 6 mo of age. Focal and secondarily GTC seizures.	2q24 20q13	*SCN2A* *KCNQ2*
Benign familial neonatal convulsions/seizures (BFNC/ BFNS)	Onset in the first few days of life. Tonic or secondarily GTC seizures. Spontaneous remission.	20q13.3 (BFNS1) 8q24 (BFNS2) inv(5)p15q11 (BFNS3)	*KCNQ2* *KCNQ3* Unknown
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	Focal and secondarily GTC seizures, nocturnal	20q13.2-q13.3 (ENFL1) 15q24 (ENFL2) 1q21(ENFL3) 8p21 (ENFL4) 8q11-q13 22q11	*CHRNA4* Unknown *CHRNB2* *CHRNA2* *CRH* *DEPDC5*
Autosomal dominant partial epilepsy with auditory features (ADPEAF)	Focal seizures, often with auditory auras	10q24 (ETL1) 12q22-q23 (ETL2) 4q (ETL3) 9q21-q22 (ETL4) 8q13 (ETL5)	*LGI1* Unknown Unknown Unknown *CPA6*
Familial focal epilepsy with variable foci (FFEVF)	Focal seizures, arising from different foci within the same family	22q11	*DEPDC5*
Familial occipitotemporal lobe epilepsy and migraine with visual aura	Visual, cognitive, and autonomic auras; focal motor seizures, CPS, secondarily GTC; migraine with aura	9q21-q22 (ETL4)	Unknown
Familial temporal lobe epilepsy	Febrile seizures with childhood afebrile focal and GTC seizures, déjà vu aura; relatively benign course, normal MRI	12q22-q23 (ETL2) 4q13-q21 (ETL3) 8q13 (ETL5) 22q11	Unknown Unknown *CPA6* *DEPDC5*
Idiopathic/genetic generalized			
Childhood absence epilepsy (CAE)	Typical absence, GTC seizures	8q24 (ECA1) 5q31.1 (ECA2) 5q34 (ECA4) 15q11-q12 (ECA5) 16p13 (ECA6)	Unknown *GABRG2* *GABRA1* *GABRB3* *CACNA1H*
Juvenile myoclonic epilepsy (JME)	Myoclonic, absence, and GTC seizures	6p12-p11 (EJM1) 15q14 (EJM2) 6p21 (EJM3) 5q12-q14 (EJM4) 5q34 (EJM5) 2q23 (EJM6) 3q26 (EJM8)	*EFHC1* Unknown Unknown Unknown *GABRA1* *CACNB4* *CLCN2*
Genetic generalized epilepsy (IGE/GGE) comprised CAE, JAE, JME, epilepsy with grand mal seizures on awakening (EGMA)—*other potential susceptibility alleles have been reported that are not listed here*	Absence, myoclonic, GTC seizures	8q24 (IGE1/EIG1) 14q23 (IGE2/EIG2) 9q32-q33 (EIG3) 10q25-q26 (EIG4) 10p11 (EIG5) 16p13 (EIG6) 15q13 (EIG7) 3q13-3q21 (EIG8) 2q23 (EIG9) 1p36 (EIG10) 3q27 (EIG11) 1p34 (EIG12)	Unknown Unknown Unknown Unknown Unknown *CACNA1H* Unknown *CASR* *CACNB4* *GABRD* *CLCN2* *SLC2A1*

Epilepsy syndrome	Seizure types/clinical features	Chromosomal segment	Associated genes
Generalized/genetic epilepsy with febrile seizures plus (GEFS+)	Febrile seizures often beyond 6 y of age, followed by GTC, absence, myoclonic, atonic seizures	19q13 (GEFSP1) 2q24 (GEFSP2) 5q34 (GEFSP3) 2q24 1p36 (GEFSP5) 8p23-p21 (GEFSP6) 2q24 (GEFSP7)	*SCN1B* *SCN1A* *GABRG2* *SCN2A* *GABRD* Unknown *SCN9A*
Familial adult myoclonic epilepsy	GTC seizures, myoclonus	8q24 (FAME1) 2p11-q12 (FAME2) 3q26-q28 (FAME4) 1q32 (FAME5)	Unknown Unknown Unknown *CNTN2*
Familial infantile myoclonic epilepsy (FIME)	Febrile seizures, myoclonic and GTC seizures	16p13	*TBC1D24*
Other epilepsy syndromes			
Familial febrile seizures	GTC seizures with fever	8q13-q21 (FEB1) 19p (FEB2) 2q23-q24 (FEB3) 5q14-q15 (FEB4) 6q22-q24 (FEB5) 18p11.2 (FEB6) 21q22(FEB7) 5q34 (FEB8) 3p24-p23 (FEB9) 3q26 (FEB10) 8q13 (FEB11)	Unknown Unknown *SCN1A* *GPR98* Unknown Unknown Unknown *GABRG2* Unknown Unknown *CPA6*
Generalized Epilepsy with Paroxysmal Dyskinesia (GEPD)	Absence and GTC seizures, paroxysmal dyskinesia	10q22	*KCNMA1*
Infantile convulsions with choreoathetosis (ICCA)	Infantile convulsions, paroxysmal kinesigenic dyskinesia	16p11	*PRRT2*
BFIC and Familial Hemiplegic Migraine (FHM)	Infantile convulsions, migraine, or hemiplegic migraine	1q23	*ATP1A2*
Epileptic encephalopathies			
Dravet syndrome (Severe myoclonic epilepsy of infancy)	Onset in the first year of life. Febrile seizures followed by afebrile seizures later in life. Developmental delay.	2q24 (EIEE6) Xq22 (EIEE9)	*SCN1A* *PCDH19*
Early infantile epileptic encephalopathy (EIEE)		5q31 19q13 2q24 (EIEE11)	*GABRG2* *SCN1B* *SCN2A*
Ohtahara syndrome	Onset in the first few days or weeks of life. Tonic spasms but focal seizures can also be seen. Burst suppression pattern on EEG. With KCNQ2 mutations, seizures typically resolve by 3 y of age, but developmental delay persists.	Xp21 (EIEE1) Xp22 (EIEE2) 11p15 (EIEE3) 9q34 (EIEE4) 20q13 (EIEE7) 2q24 (EIEE11)	*ARX* *CDKL5* *SLC25A22* *STXBP1* *KCNQ2* *SCN2A*
West syndrome	Infantile spasms, severe global developmental delay. Hypsarrhythmia on EEG.	Xp21 (EIEE1) Xp22 (EIEE2) 9q34 (EIEE4) 20p12 (EIEE12) 9q34 (EIEE14) 1p34 (EIEE15)	*ARX* *CDKL5* *STXBP1* *PLCB1* *KCNT1* *ST3GAL3*
Epilepsy of infancy with migrating focal seizures	Refractory focal seizures, severe developmental delay, regression. Poor prognosis.	2q24 9q34 20p12	*SCN1A* *KCNT1* *PLCB1*
Myoclonic-astatic epilepsy	Onset between 2 and 5 y of age. Myoclonic, astatic/atonic, absence, and tonic–clonic seizures. Variable prognosis.	2q24 19q13 5q31 1p34	*SCN1A* *SCN1B* *GABRG2* *SLC2A1*
Epilepsy and mental retardation limited to females (EFMR)	Onset in the first year of life. Multiple focal and generalized seizure types, often associated with fever. Mental retardation. Poor language development, ataxia. Only seen in females.	Xq22.1 (EIEE9)	*PCDH19*
GLUT1 deficiency		1p34	*SLC2A1*

GTC, generalized tonic–clonic.

CONCLUSION

Genetics plays a role in virtually all epilepsy syndromes, through a diversity of mechanisms. The identification of specific mutations in ion channel subunits has contributed significantly to our knowledge of underlying pathogenic pathways leading to seizures and epilepsy, but clearly, non-ion channel genes are involved. Further work in the identification of gene defects and their functional characterization will continue to advance our understanding of basic mechanisms. Work toward improving phenotype–genotype correlations and delineating the functional significance of both common and rare polymorphisms in "epilepsy genes" will allow us to make better use of genetic testing in epilepsy.

The eventual hope is that understanding the genetics of human epilepsy will improve recognition, diagnosis, and treatment of individuals with epilepsy. In the search for new strategies to reduce the burden of disease, the discovery of epilepsy genetic risk factors offers a novel opportunity to identify individuals susceptible to epilepsy before it develops and to treat and prevent seizures and associated comorbidities in those individuals at risk.

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CHAPTER 5 PICTORIAL ATLAS OF EPILEPSY SUBSTRATES

AJAY GUPTA AND RICHARD A. PRAYSON

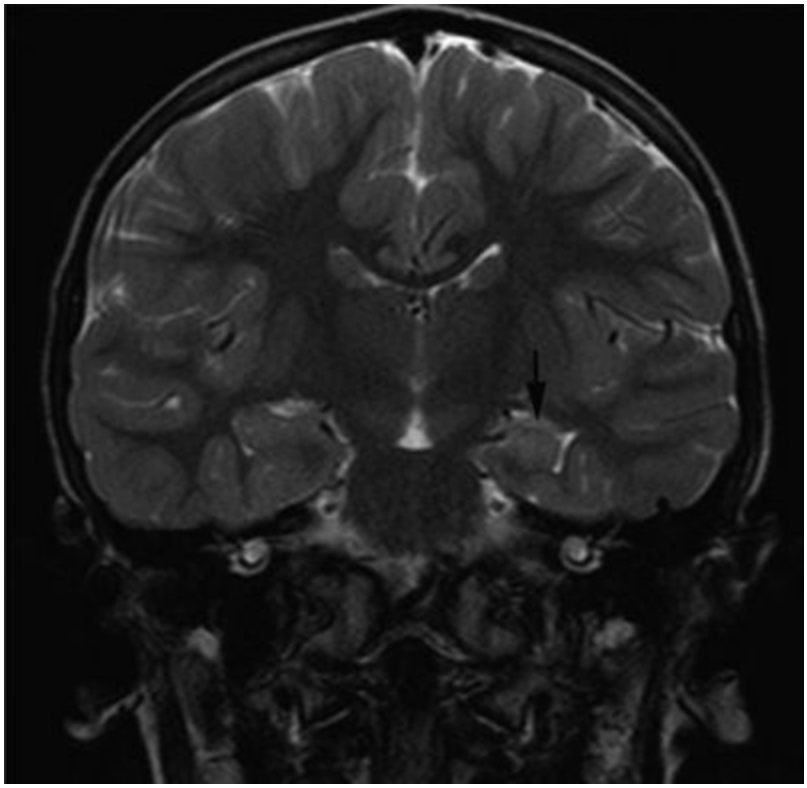

Figure 5.1. Mesial temporal sclerosis. Coronal T2-weighted image from MRI without gadolinium in a 7-year-old male with temporal lobe epilepsy shows increased signal intensity and decreased size of the left hippocampal formation (arrow).

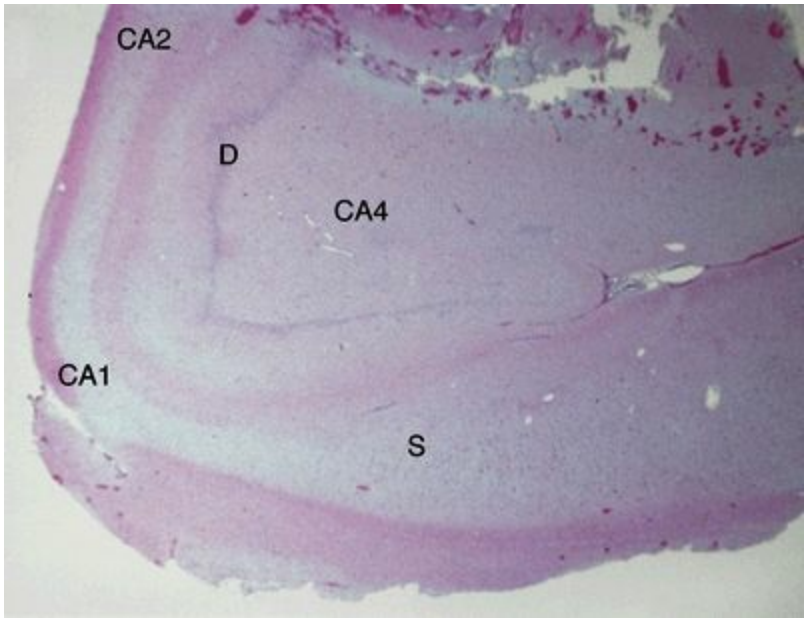

Figure 5.2. Low-magnification appearance of hippocampus in **hippocampal sclerosis** (HS). An adult patient who underwent anterior temporal lobectomy for treatment of intractable temporal lobe epilepsy. HS is the most common cause of intractable partial epilepsy in adults. HS is generally marked by preferential loss of neurons in the dentate (D), CA4 region, CA1 region, and subiculum (S). A lesser degree of neuronal loss may be observed in the CA3 and CA2 regions. Loss of neurons is accompanied by gliosis and, in severe cases, grossly evident atrophy.

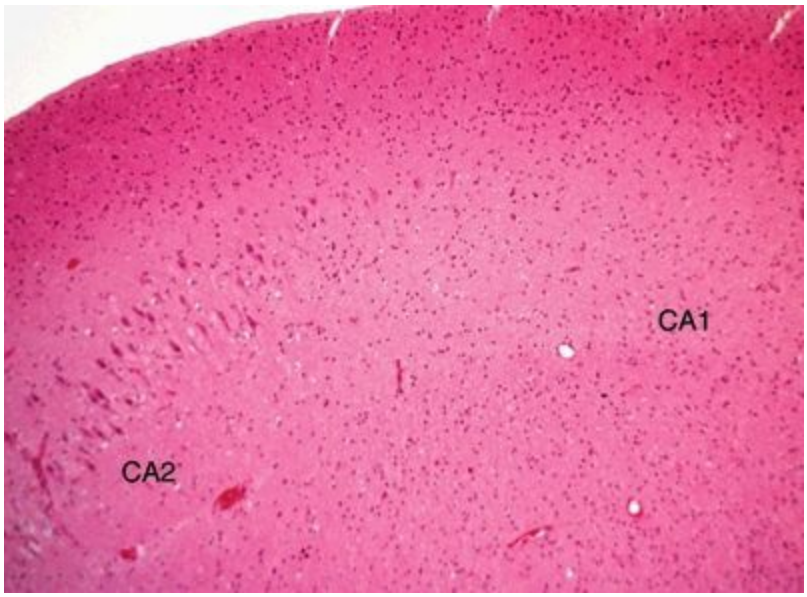

Figure 5.3. Higher-magnification appearance of the hippocampus in **hippocampal sclerosis** at the interface between CA2 and CA1 regions. There is a marked loss of neurons in the CA1 region with gliosis.

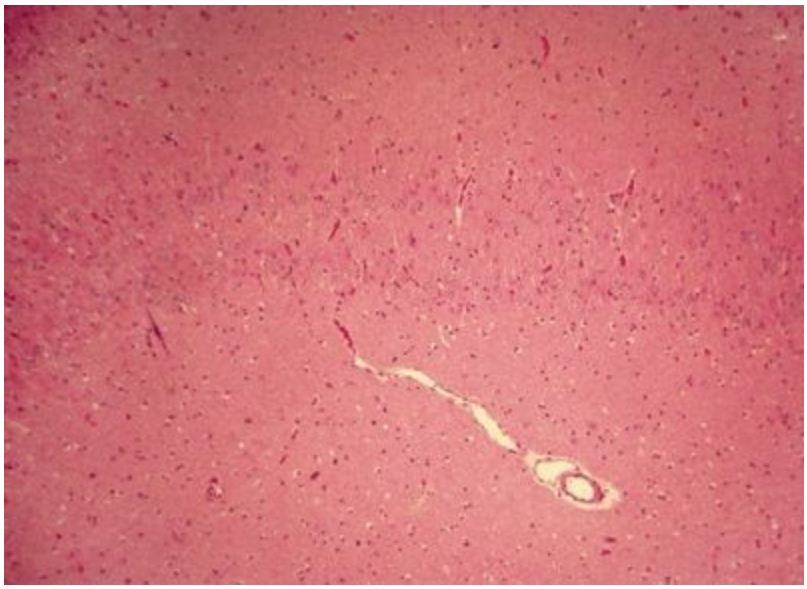

Figure 5.4. Histologic appearance of **double dentate** marked by two bands of neurons in the hippocampus. This represents a form a hippocampal dysplasia. Hippocampal dysplasia is an infrequent cause of temporal lobe epilepsy and may be seen as a dysmorphic hippocampal formation on a high-definition three-dimensional volume acquisition sequences on brain MRI.

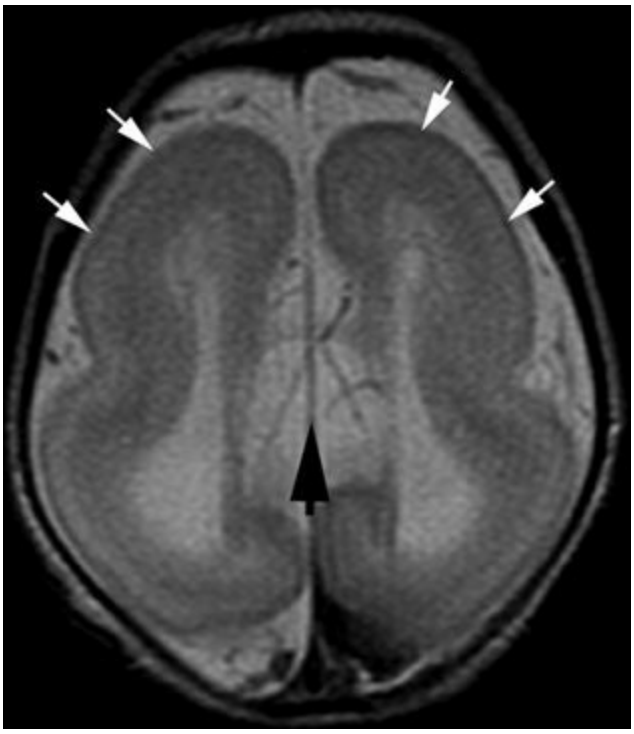

Figure 5.5. Lissencephaly. Axial T2-weighted image from MRI without gadolinium in a newborn shows lack of normal sulcation (white arrows), parallel lateral ventricles, and absence of the corpus callosum (black arrow). Children with lissencephaly usually present with epileptic spasms, severe global developmental delay, microcephaly, and marked hypotonia during early infancy.

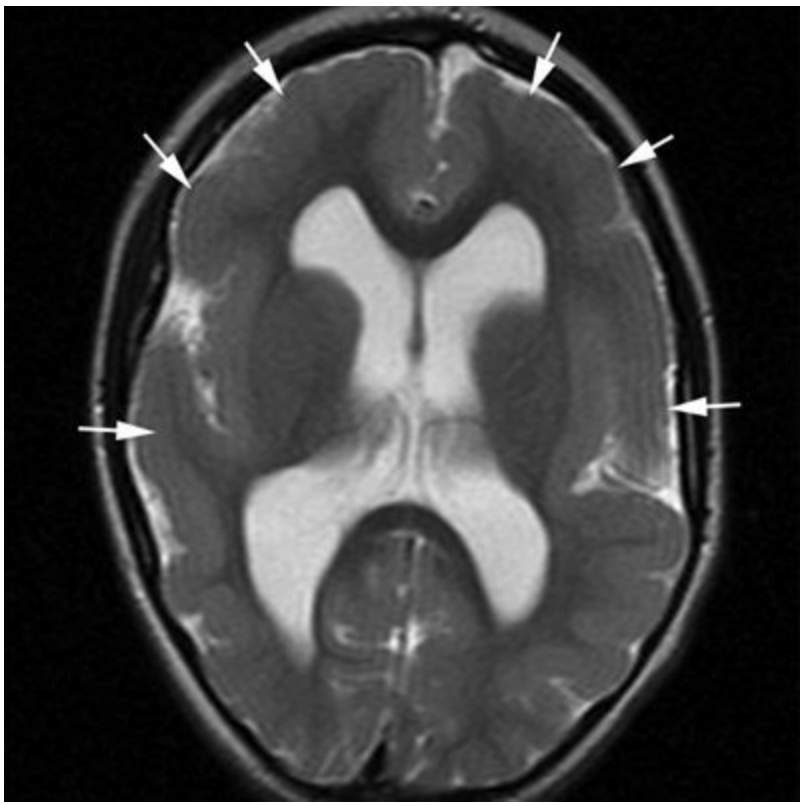

Figure 5.6. Pachygyria. Axial T2-weighted image from MRI without gadolinium in a 4-year-old with spastic quadriplegia and generalized seizures shows a paucity of sulcal markings and thickened cortex bilaterally (arrows).

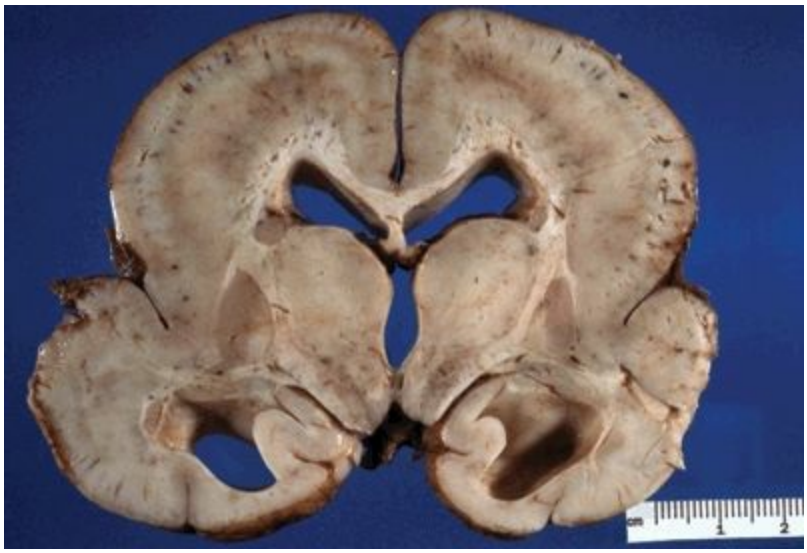

Figure 5.7. The gross appearance of **lissencephaly (agyria)** characterized by a lack of gyral formation and a decreased number of sulci. Note enlargement of ventricles, suggesting parenchymal volume loss. The cortex is usually thickened on cross-section. Microscopically, there is an abnormally layered cortex, typically three to five layers.

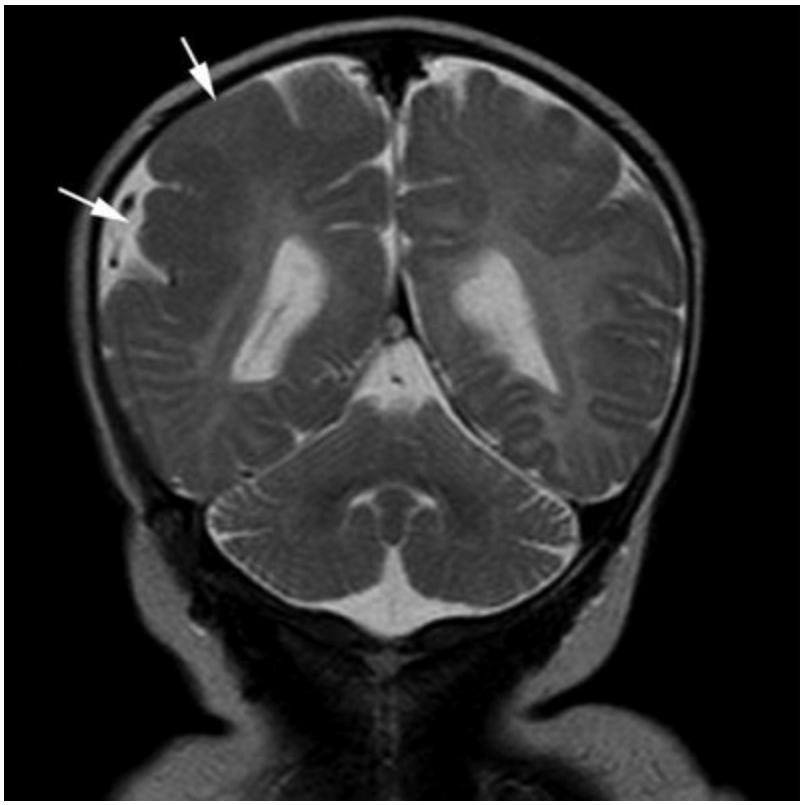

Figure 5.8. Polymicrogyria. Coronal T2-weighted image from MRI without gadolinium in a newborn with motor seizures shows generalized thickening of the cortex of the right parietal lobe characterized by multiple small gyri (arrows). Polymicrogyria are usually epileptogenic lesions, sporadic or familial in occurrence, and various brain MRI patterns have been recognized that help in making an accurate diagnosis.

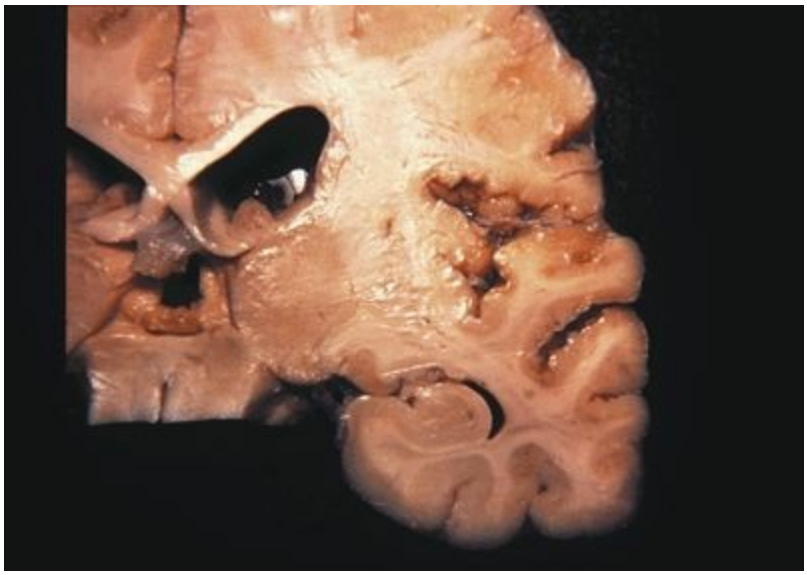

Figure 5.9. Gross appearance of **perisylvian polymicrogyria (micropolygyria)** marked by the focal presence of small, irregular gyri separated by shallow sulci. The cortex is often thinned and microscopically is composed of two- to four-layered cortex. The leptomeninges overlying polymicrogyria may be abnormally hypervascular due to a persistence of fetal leptomeningeal vascularization. Congenital bilateral perisylvian polymicrogyria (CBPP) usually presents with seizures during childhood. Other clinical findings in the patients with CBPP include pseudobulbar paresis, dysarthria, swallowing difficulties, and tongue paresis with inability to protrude tongue and to perform lateral tongue movements. (Photograph courtesy of Dr. Bette Kleinschmidt-DeMasters.)

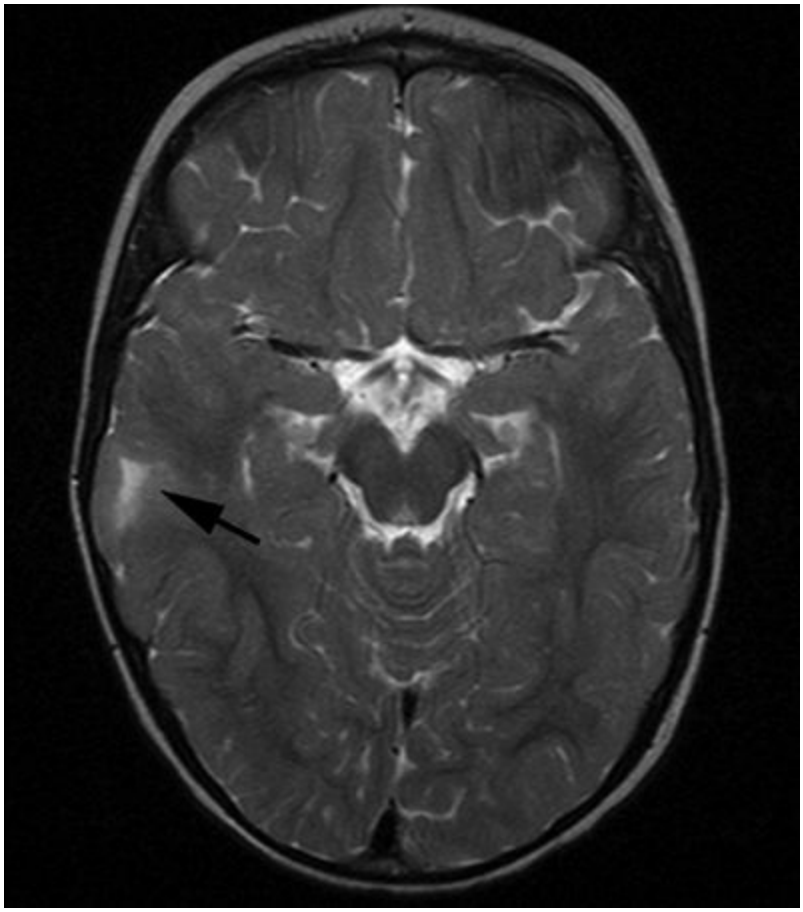

Figure 5.10. Balloon cell dysplasia. Axial T2-weighted image from MRI without gadolinium in an 18-month-old male with intractable seizures shows high signal in the right parietal subcortical white matter subtending a broad-based gyrus (arrow). Most focal cortical dysplasias are sporadic congenital malformations and, as a group, are one of the most important causes of intractable epilepsy that is surgically remediable.

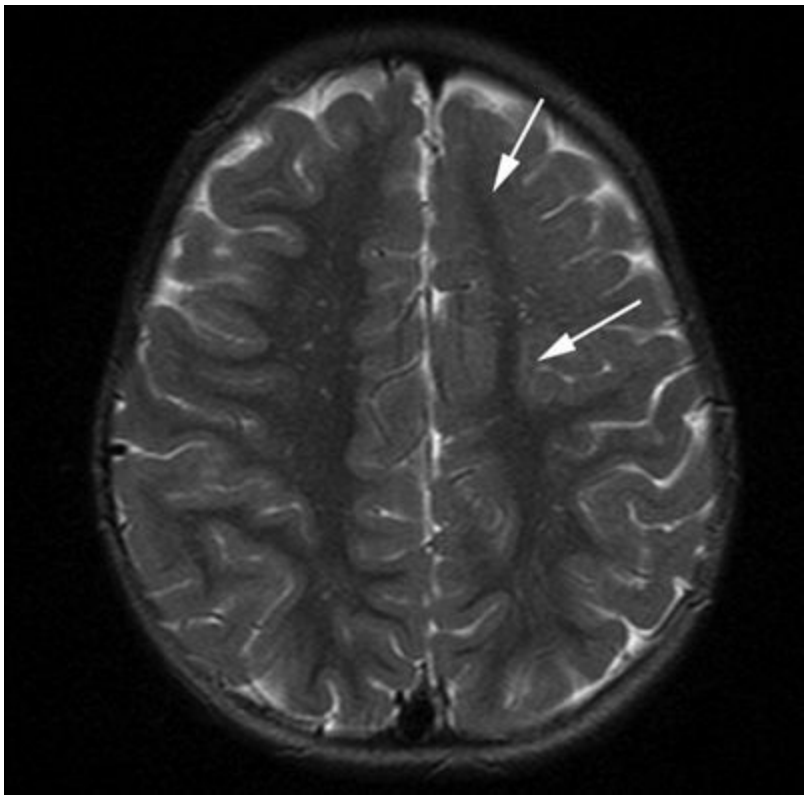

Figure 5.11. Lobar cortical dysplasia. Axial T2-weighted image from MRI without gadolinium in a 3-year-old with infantile spasms shows generalized blurring of the gray–white interface with lack of normal white matter arborization in the left frontal lobe (arrows).

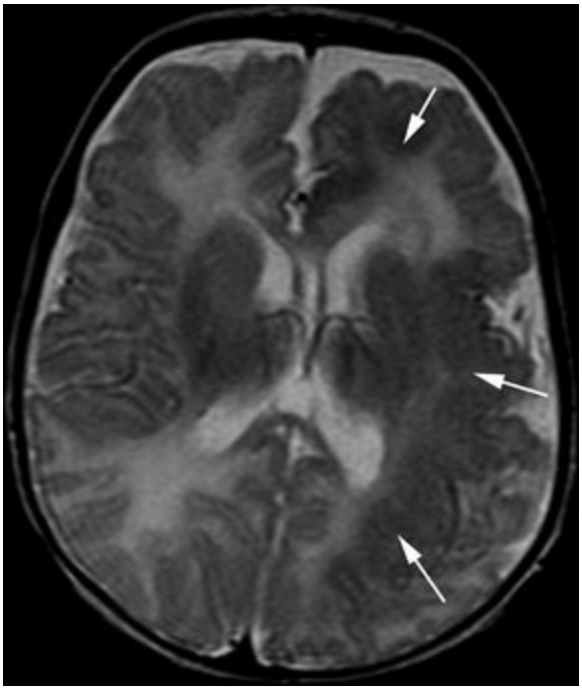

Figure 5.12. Hemispheric malformation of cortical development. Axial T2-weighted image from MRI without gadolinium in a 4-year-old boy with intractable infantile spasms since birth shows diffuse left hemispheric cortical thickening with lack of normal arborization of white matter (arrows).

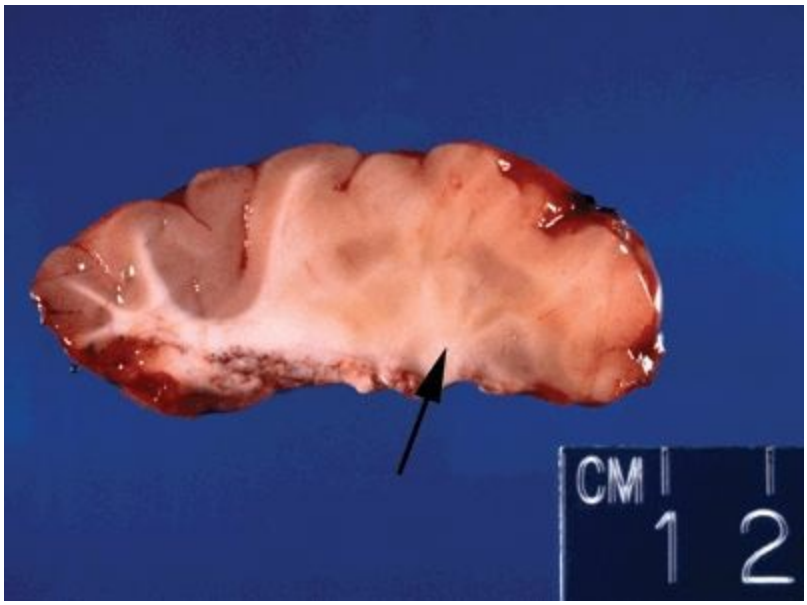

Figure 5.13. Gross appearance of **cortical dysplasia** marked by an indistinct gray/white interface (right portion of cross section —arrow) with evidence of gray matter tissue abnormally placed in white matter (**nodular heterotopia**).

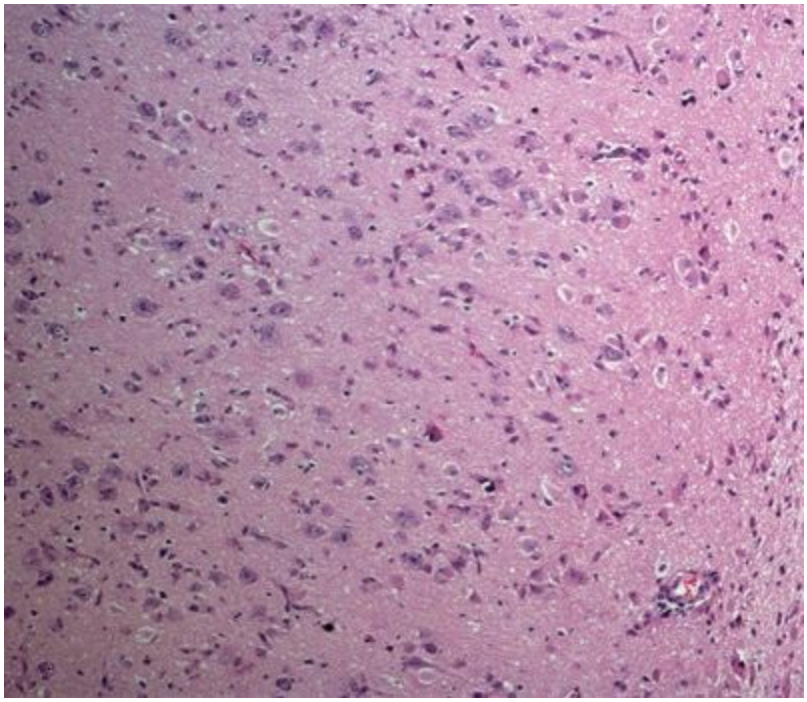

Figure 5.14. Histologic appearance of **cortical dysplasia** marked by a loss of normal cortical lamination, increased cellularity, and malpositioning of neurons within the cortex. Neurons normally have their apical dendrites oriented perpendicular with respect to the surface of the brain.

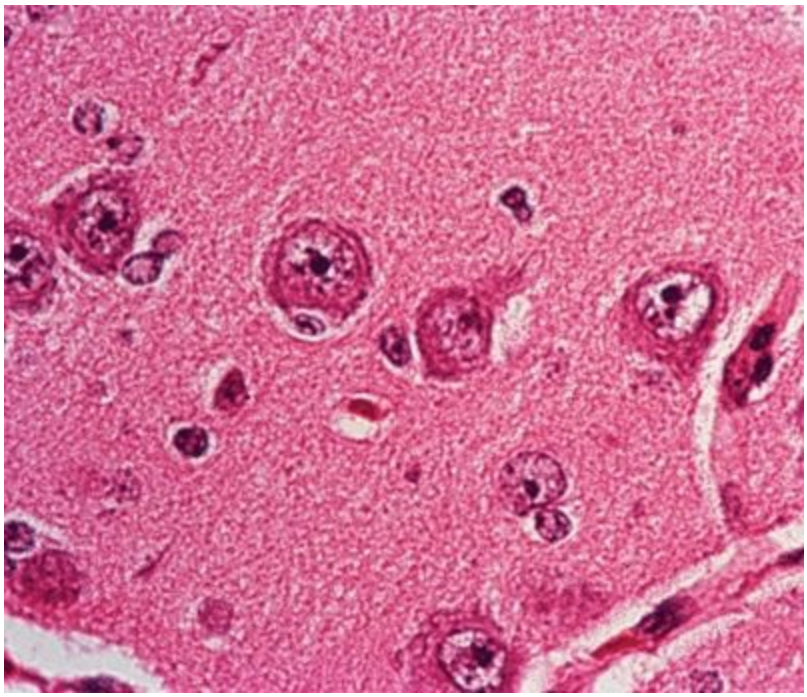

Figure 5.15. High-magnification appearance of neurons in cortical layer II of the parietal lobe in a patient with **cortical dysplasia**. The neurons are abnormally enlarged in size (**neuronal cytomegaly**) without any other evidence of dysmorphic features.

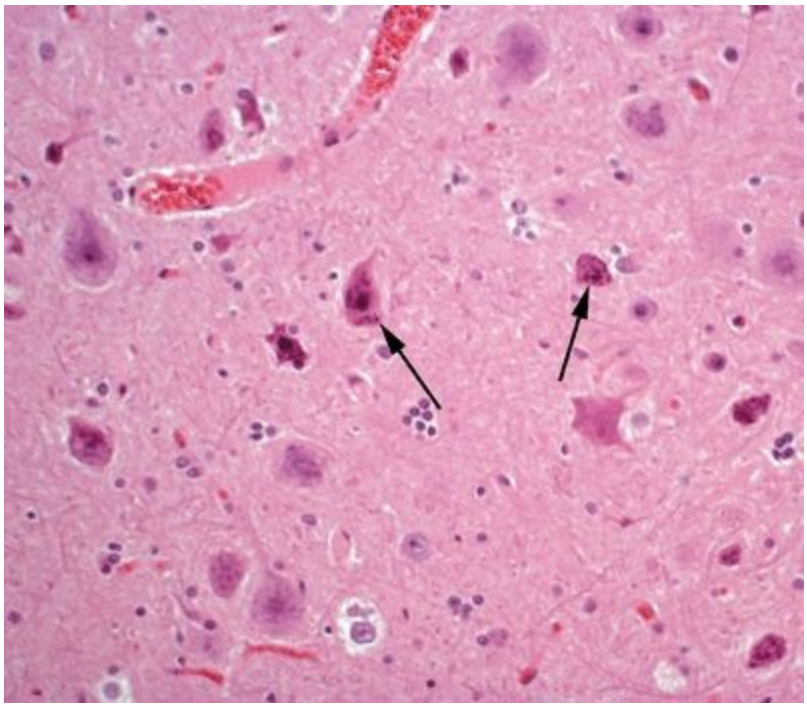

Figure 5.16. Histologic appearance of neurons in cortical layer III of the temporal lobe in a patient with **cortical dysplasia**. The neurons are marked by abnormal cytologic appearance (**dysmorphic neurons**) (arrows), including abnormal nuclear morphology and atypical distribution of Nissl substance. In addition, neurons are haphazardly arranged within the cortex.

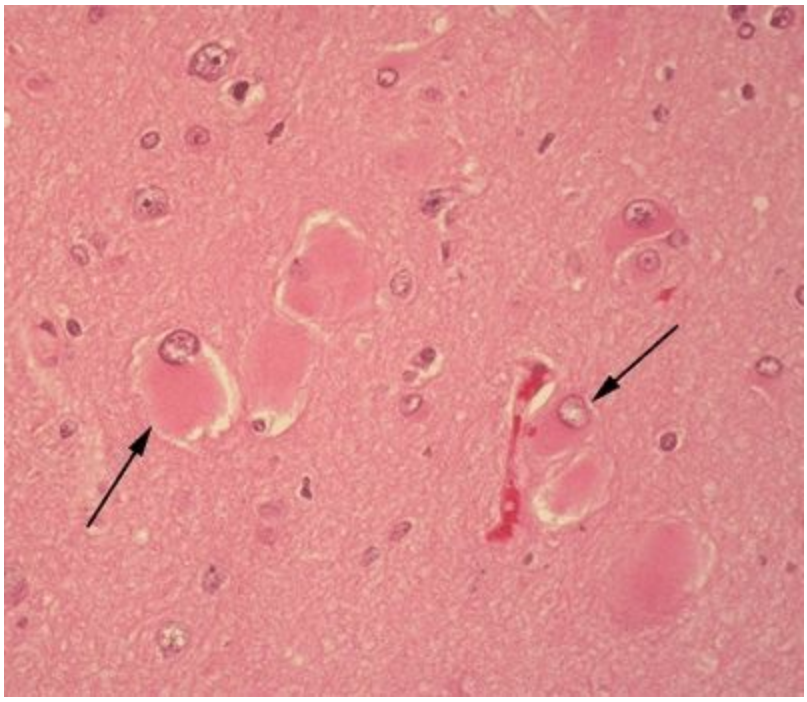

Figure 5.17. Histologic appearance of **balloon cells** (arrows) in the setting of **cortical dysplasia**. Balloon cells are marked histologically by the presence of abundant eosinophilic cytoplasm and eccentrically placed nuclei. Multinucleation may be observed. The derivation of these cells is still debated. A subset of balloon cells stain with markers of both glial differentiation (glial fibrillary acidic protein) and neural differentiation (neuron-specific enolase).

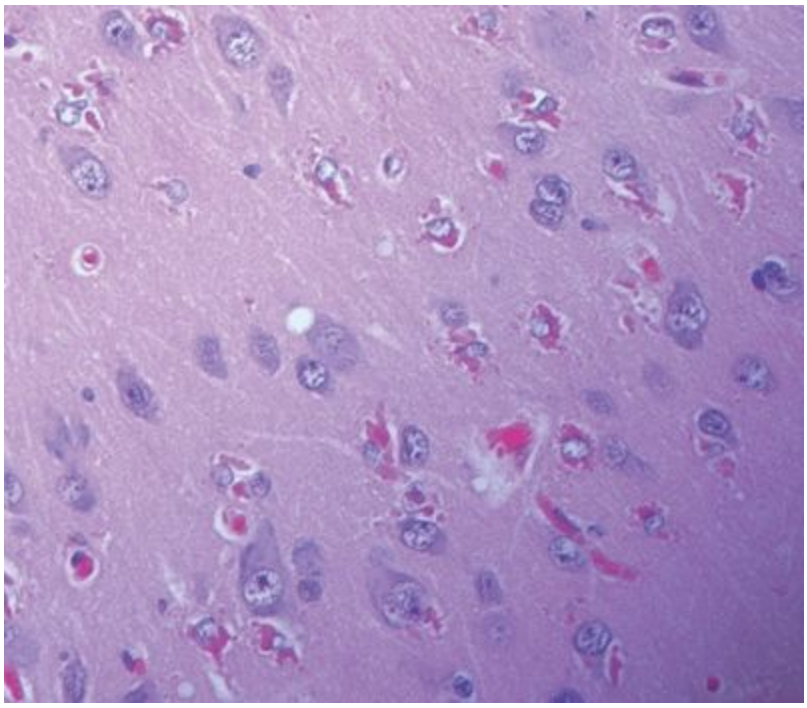

Figure 5.18. Hyaline protoplasmic astrocytopathy of the neocortex may be seen in cases of focal cortical dysplasia. This lesion is marked by eosinophilic inclusions in the cytoplasm of protoplasmic astrocytes in the neocortex, representing a filaminopathy.

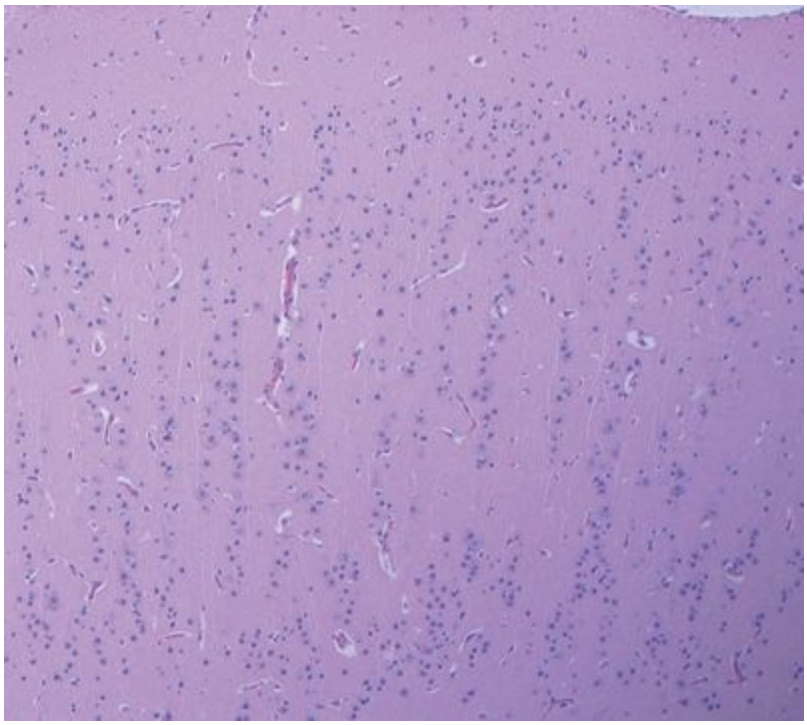

Figure 5.19. Focal cortical dysplasia marked by a linear array or columnar arrangement of cortical neurons. This pattern may rarely occur in isolation or more frequently occurs in conjunction with disorganization in the horizontal orientation in the cortical architecture.

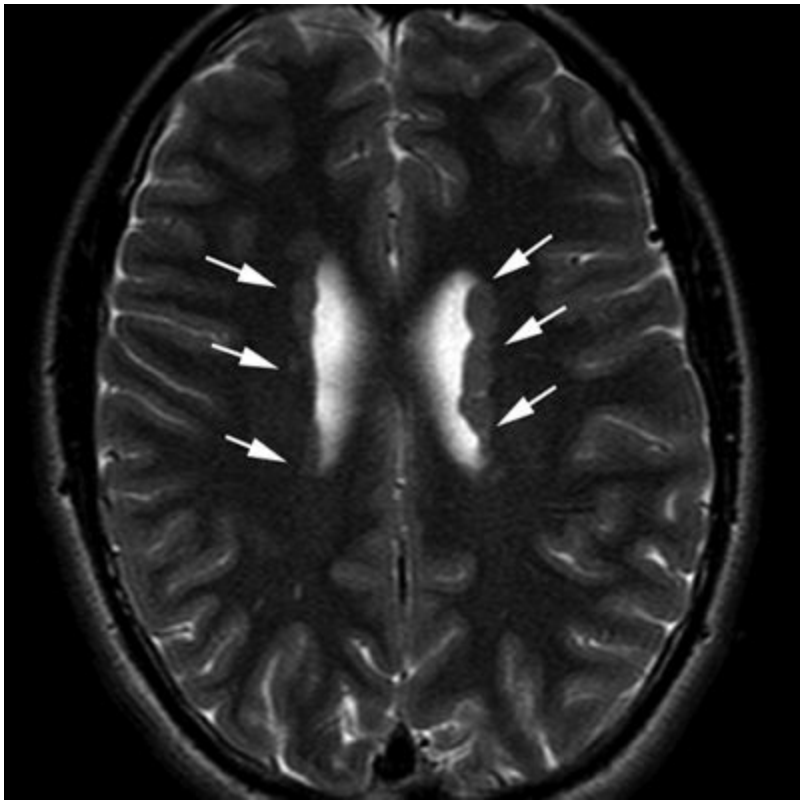

Figure 5.20. Subependymal (periventricular) heterotopia. Axial T2-weighted image from MRI without gadolinium in a 14-year-old female with history of ptosis and tremors shows gray matter nodularity lining the lateral ventricles bilaterally (arrows). Bilateral periventricular nodular heterotopica could be an X-linked dominant condition due to filamin A gene mutations.

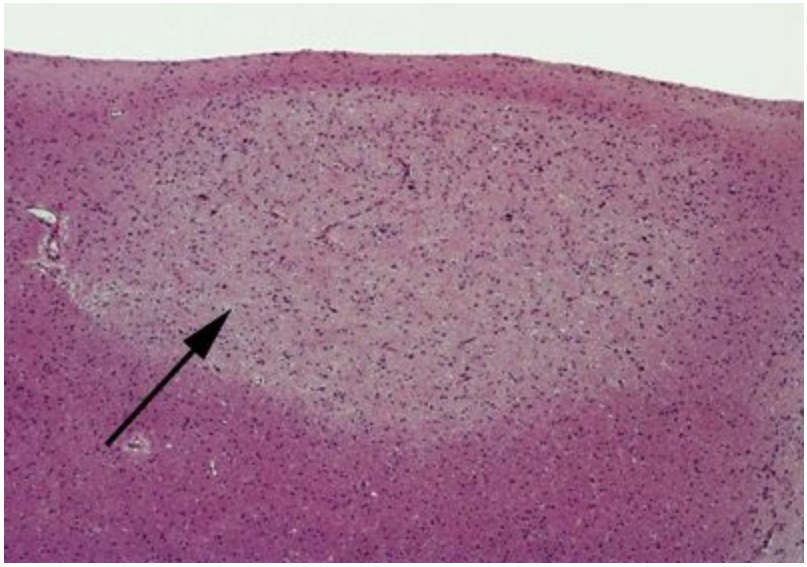

Figure 5.21. Microscopic appearance of a **subependymal (periventricular) nodular heterotopia** of gray matter (arrow). The nodule microscopically is marked by a mixture of neural and glial cells arranged in a disorganized fashion. Heterotopias are collections of mostly normal-appearing neurons in abnormal location presumably due to a disturbance in migration.

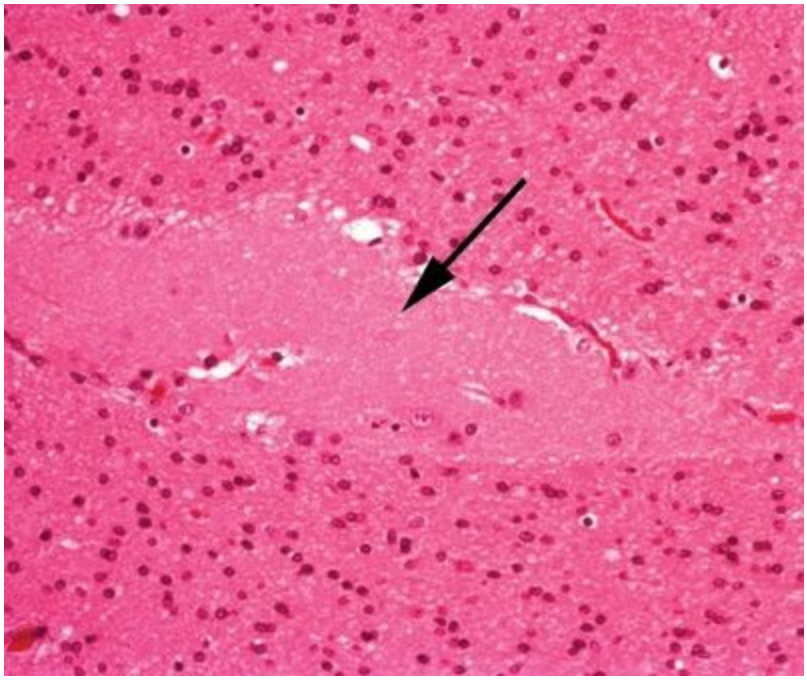

Figure 5.22. Small focus of the **heterotopic gray matter** situated in the deep white matter of the frontal lobe region (arrow).

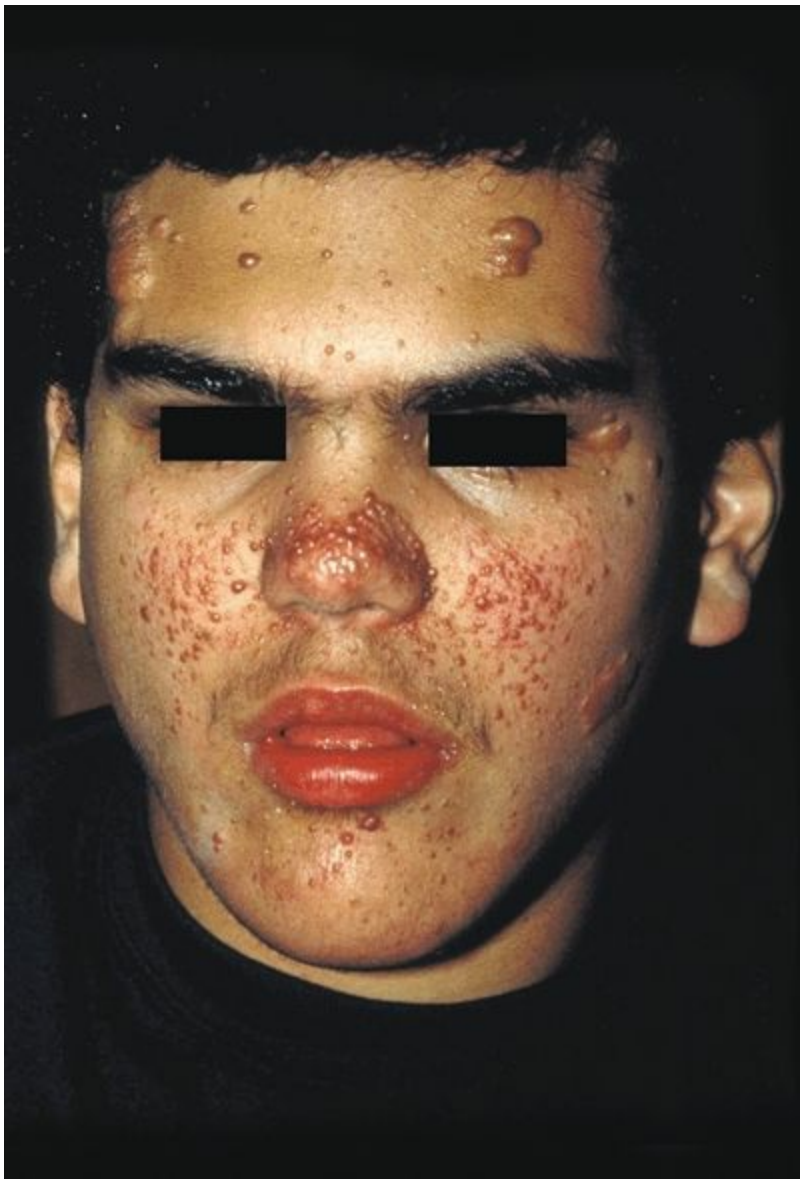

Figure 5.23. A patient with **facial adenoma sebaceum**, a diagnostic finding in tuberous sclerosis (TS). TS is an autosomal dominant condition that involves multiple organs and systems besides the central nervous system. Clinical spectrum is highly variable, and the diagnosis is usually made by looking for other findings like hypomelanotic skin patches, fibromatous skin plaques, dental pits, ungual fibromas, retinal hamartomas, cardiac rhabdomyomata, and renal cysts. TS is caused by mutations in the TSC 1 (hamartin) and 2 (tuberin) genes located on chromosomes 9 and 16, respectively. The phenotype due to TSC 1 and 2 mutations is generally difficult to distinguish clinically.

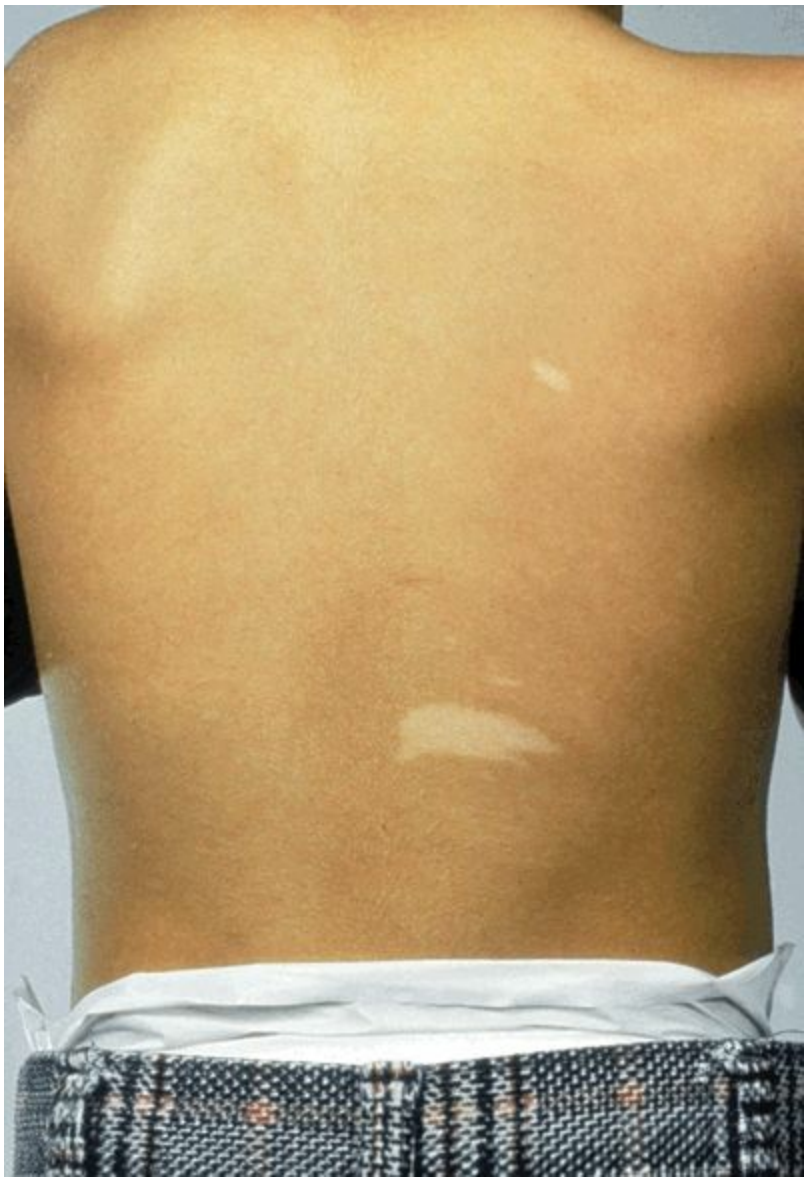

Figure 5.24. "Ash leaf macule" in a patient with **tuberous sclerosis**. Hypopigmented macules may only be visible under ultraviolet light in patients with fair skin color.

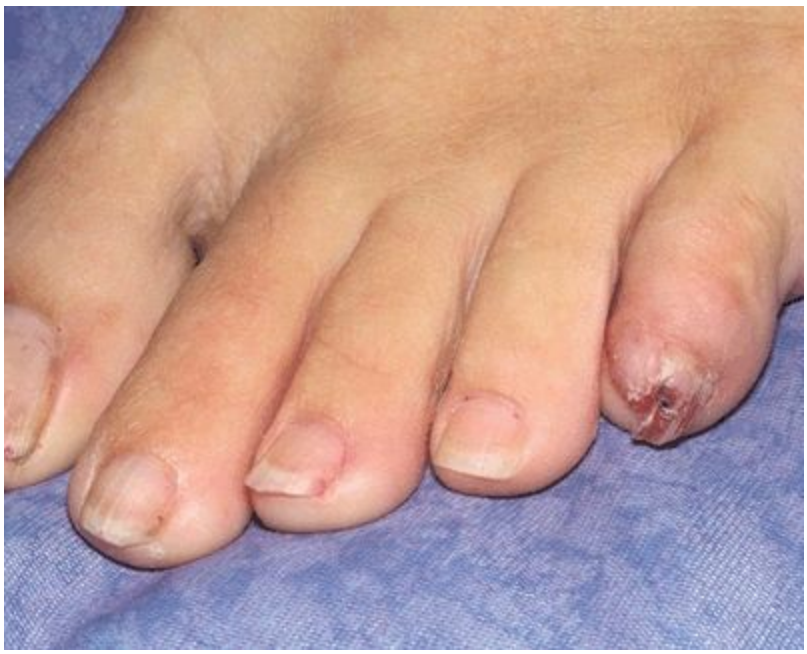

Figure 5.25. Ungual fibroma involving the little toe.

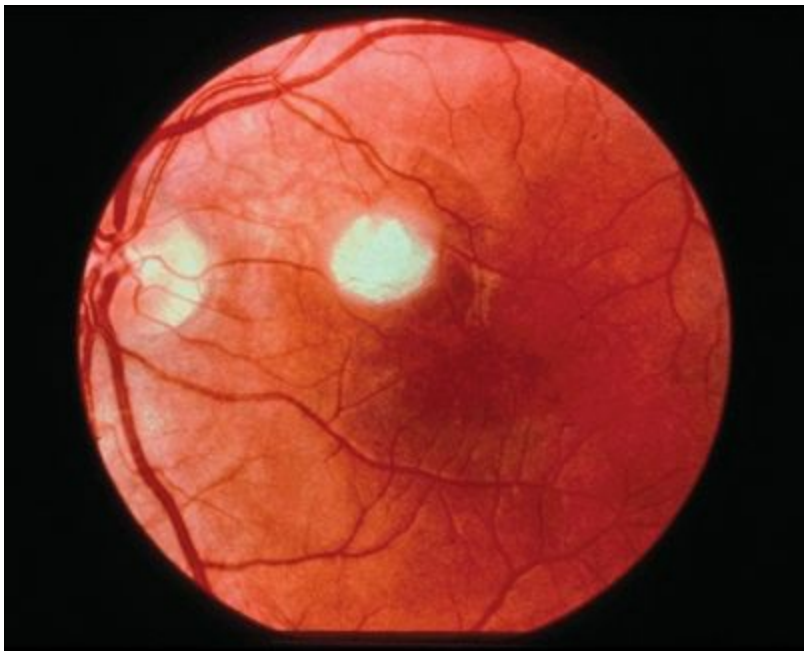

Figure 5.26. Retinal hamartoma seen on funduscopic examination.

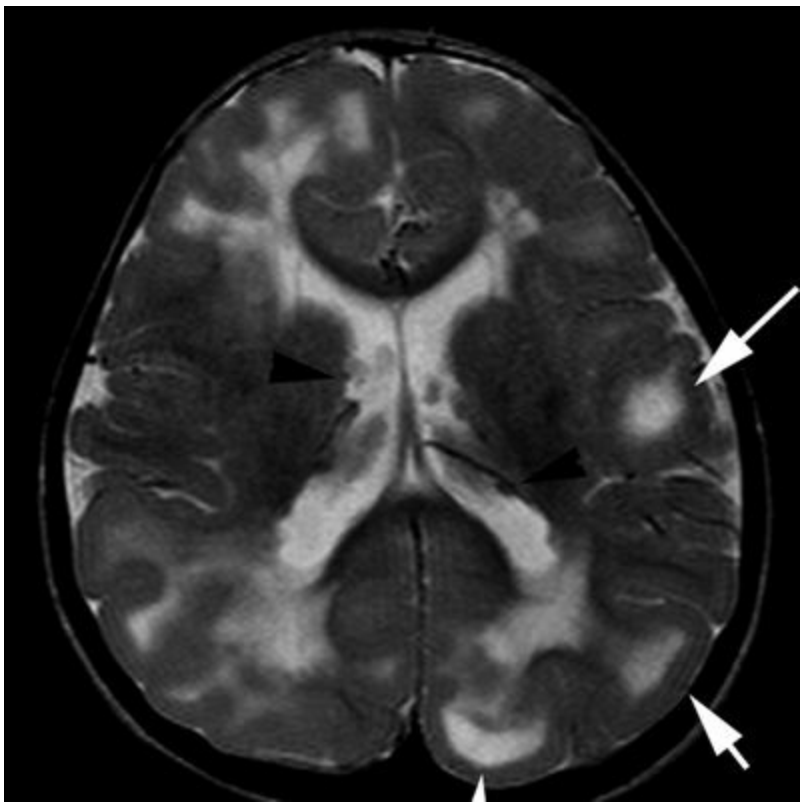

Figure 5.27. Tuberous sclerosis. Axial T2-weighted image from MRI without gadolinium in a 9-year-old male with over 20 seizures per day shows multiple subependymal low-signal-intensity nodules (black arrowheads) and multiple bilateral malformations of cortical development characterized by gyral broadening and subcortical white matter hyperintensity (white arrows).

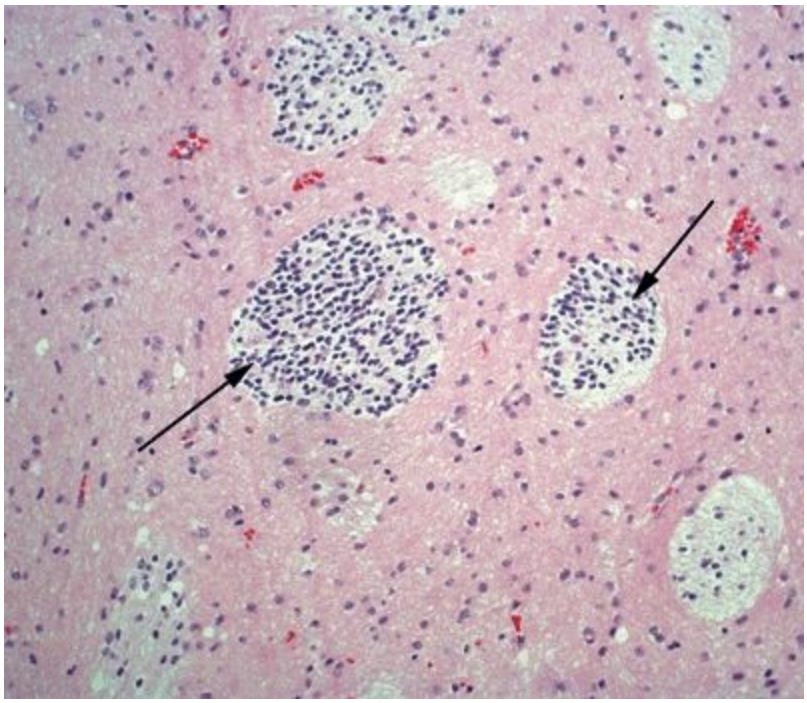

Figure 5.28. Histologic appearance of **hamartia** (arrows) characterized by an aggregation of small, immature-appearing neurons. This lesion most likely represents a form of cortical dysplasia and is seen in patients with tuberous sclerosis.

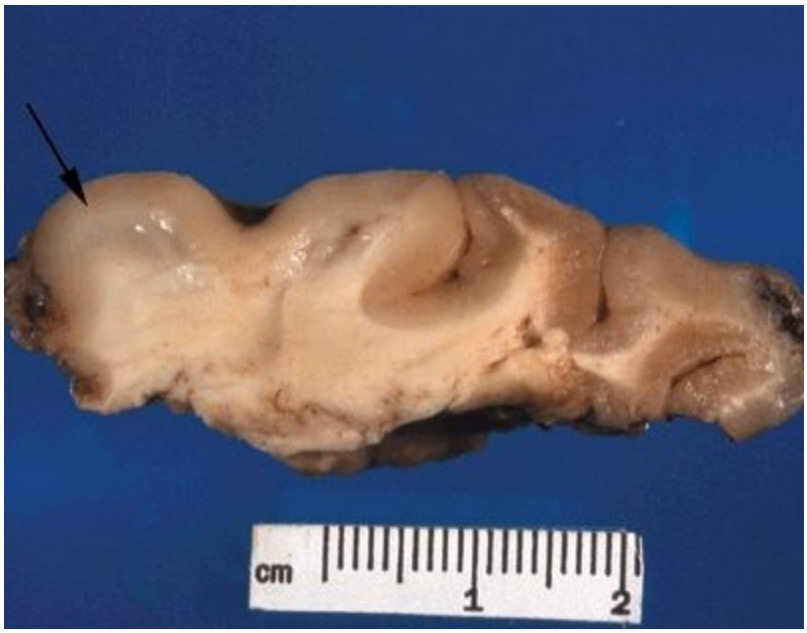

Figure 5.29. Gross appearance of a **cortical tuber** marked by obliteration of the gray/white interface (left most gyrus—arrow). Cortical tubers often have a firm consistency related to gliosis and microcalcifications. Other pathologic findings in the brain of tuberous sclerosis patients include subependymal nodules and giant cell astrocytomas typically located at the foramen of Monro, leading to obstructive hydrocephalus in some patients.

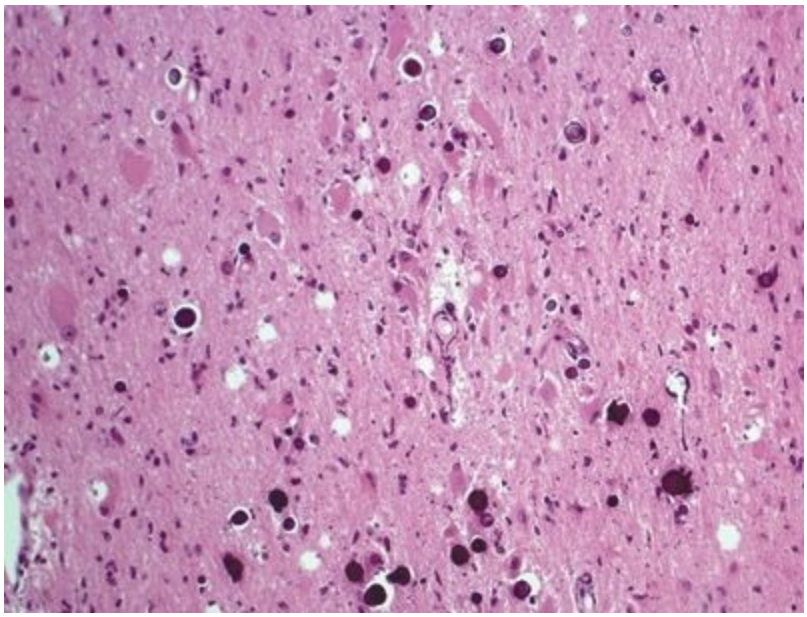

Figure 5.30. Histologic appearance of parenchyma from a **cortical tuber** of tuberous sclerosis. The histologic findings are generally that of a cortical dysplasia and are marked by abnormal cortical lamination, a malorientation of neurons within the cortex and dysmorphic neurons frequently accompanied by ballooned cells. Microcalcifications are also prominently noted in this particular microscopic field.

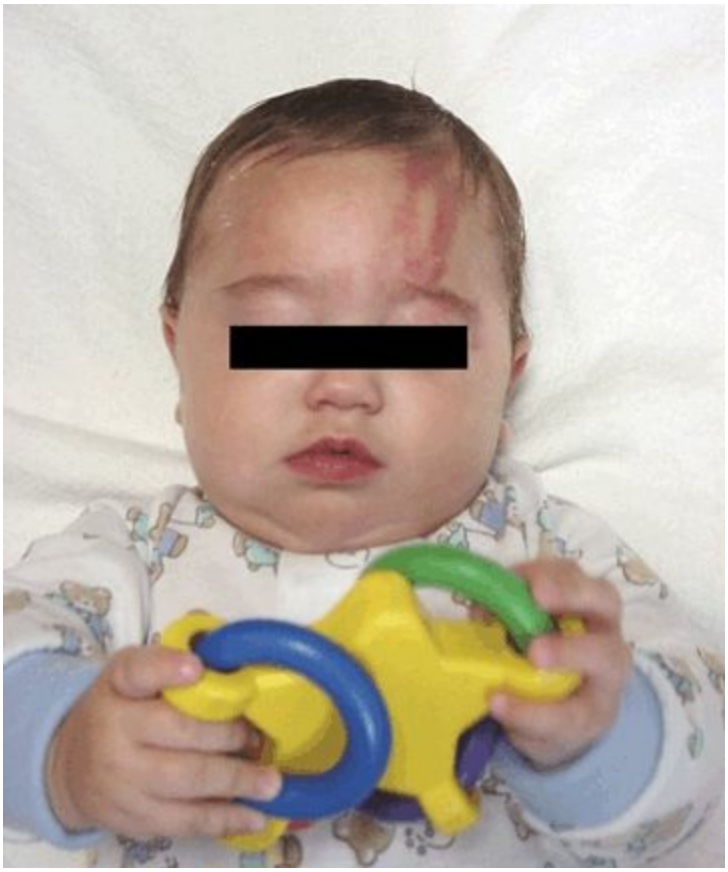

Figure 5.31. A child with **Sturge–Weber syndrome**. The presence of nevus flammeus in the distribution of the first division (ophthalmic) of the trigeminal nerve highly correlates with the central nervous system involvement.

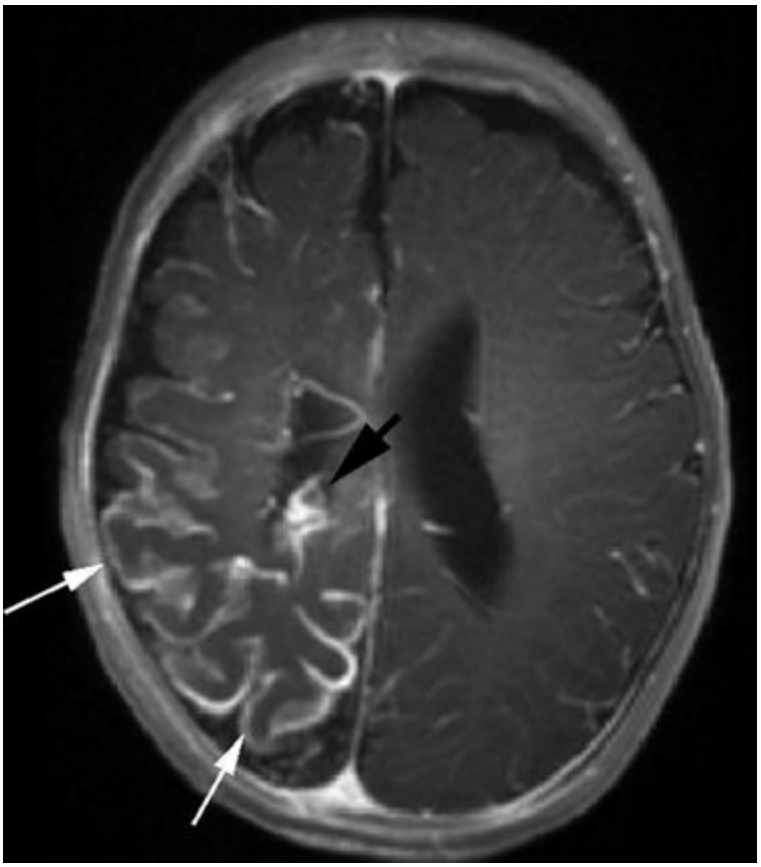

Figure 5.32. Sturge–Weber syndrome. Axial MPRAGE image from MRI with gadolinium in a 12-month-old girl with left tonic–clonic seizures shows diffuse gyriform enhancement (white arrows) with enlargement of the glomus of the right choroid plexus (black arrow).

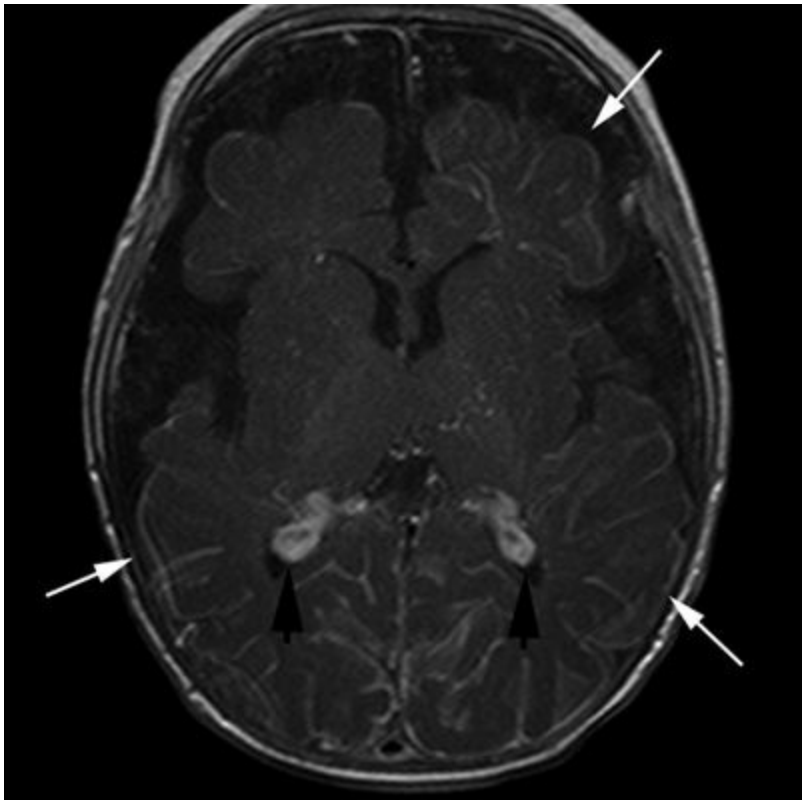

Figure 5.33. Sturge–Weber syndrome. Axial T1-weighted image from MRI with gadolinium in a 4-month-old girl with bilateral facial port-wine stains shows left frontal and bilateral parietooccipital gyriform enhancement (white arrows) with bilateral enlargement of the glomus of the choroid plexus (black arrows).

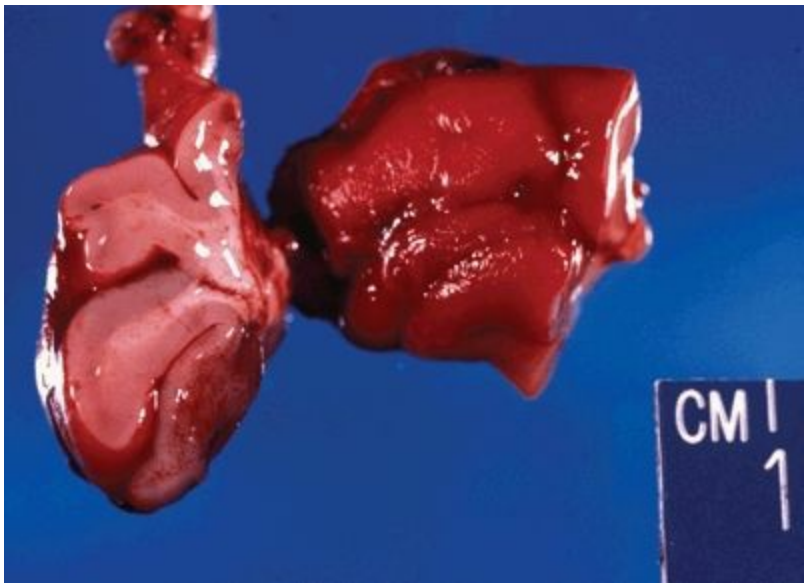

Figure 5.33. Cross-sectional **(left)** and external **(right)** views from a resection in a patient with **Sturge–Weber disease**. The leptomeninges appear hemorrhagic due to a proliferation of vessels.

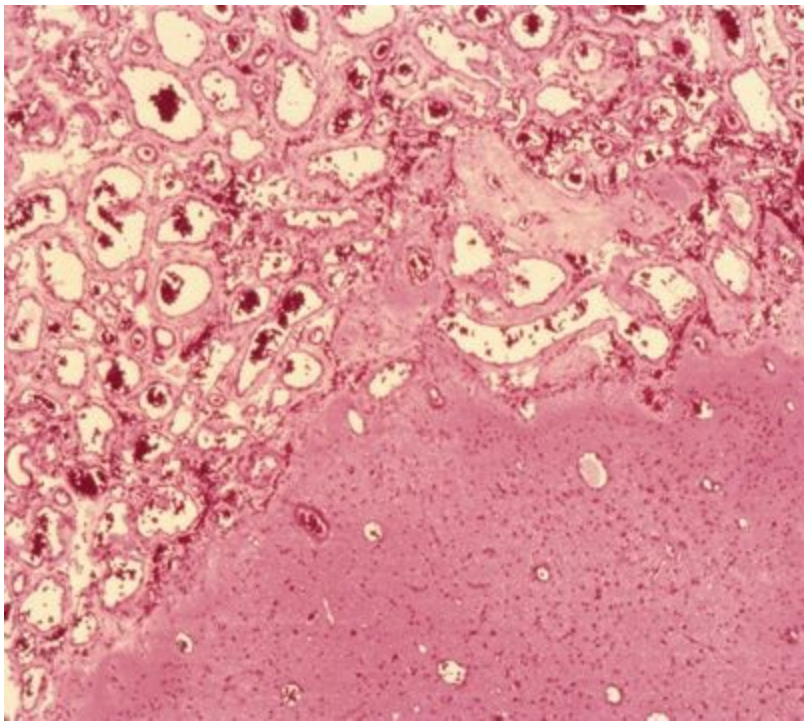

Figure 5.35. Histologic appearance of the leptomeninges in the setting of **Sturge-Weber disease**. The leptomeninges are marked by a proliferation of venous and capillary vessels arranged in a hemangiomatous configuration. There is no malignant potential to the lesion. The underlying cortex often demonstrates gliosis with prominent microcalcifications.

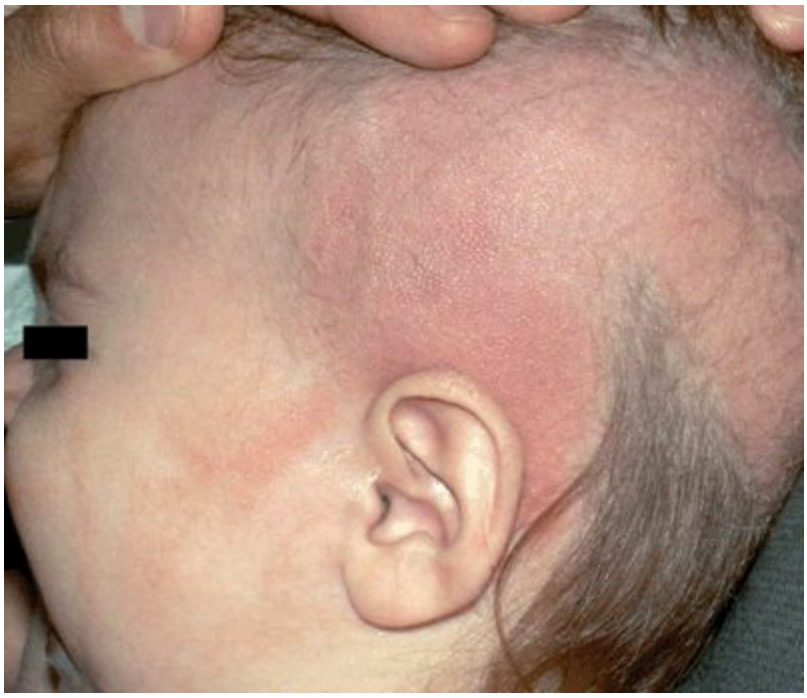

Figure 5.36. A child with a nevus on the cheek and left temple extending on to the scalp with loss of hair. She presented with partial seizures. Her brain MRI showed an extensive malformation of cortical development in the left temporoparietooccipital region. The constellations of findings suggest **epidermal nevus syndrome**, which is a sporadic condition. Epidermal nevus syndromes may be associated with hemimegalencephaly ipsilateral to the facial cutaneous findings.

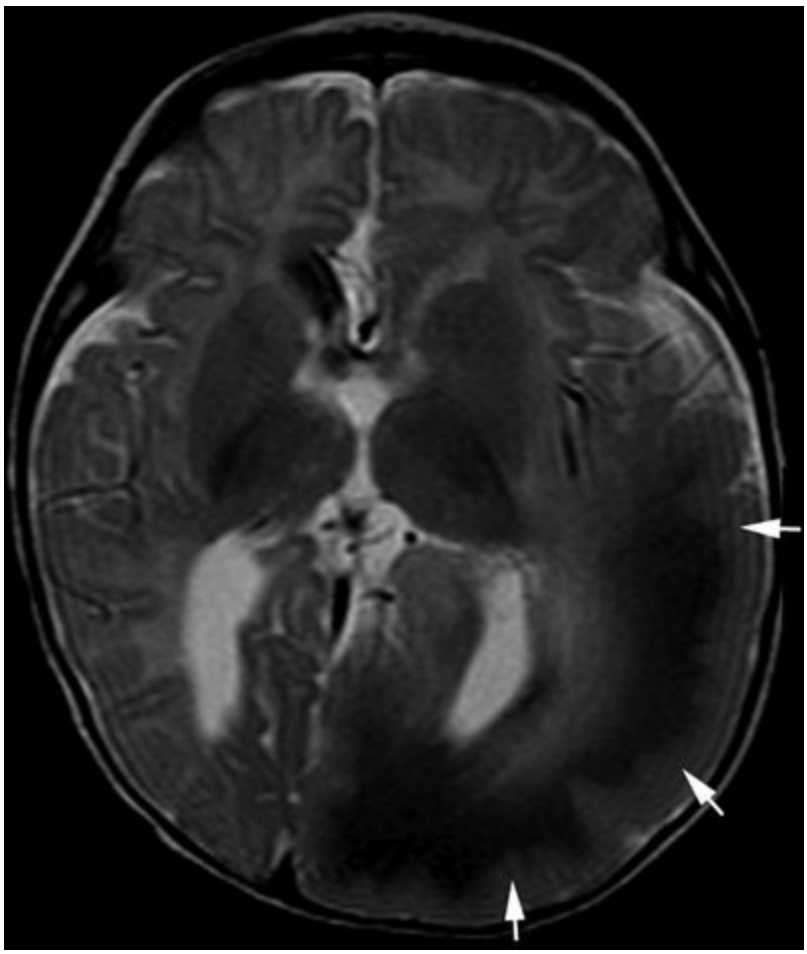

Figure 5.37. Epidermal nevus syndrome with hemimegencephaly. Axial T2-weighted image from MRI without gadolinium in a 6-month-old child with facial linear shows generalized enlargement of the left hemisphere with gyral thickening, decreased cortical signal, and blurring of the gray–white interface (arrows).

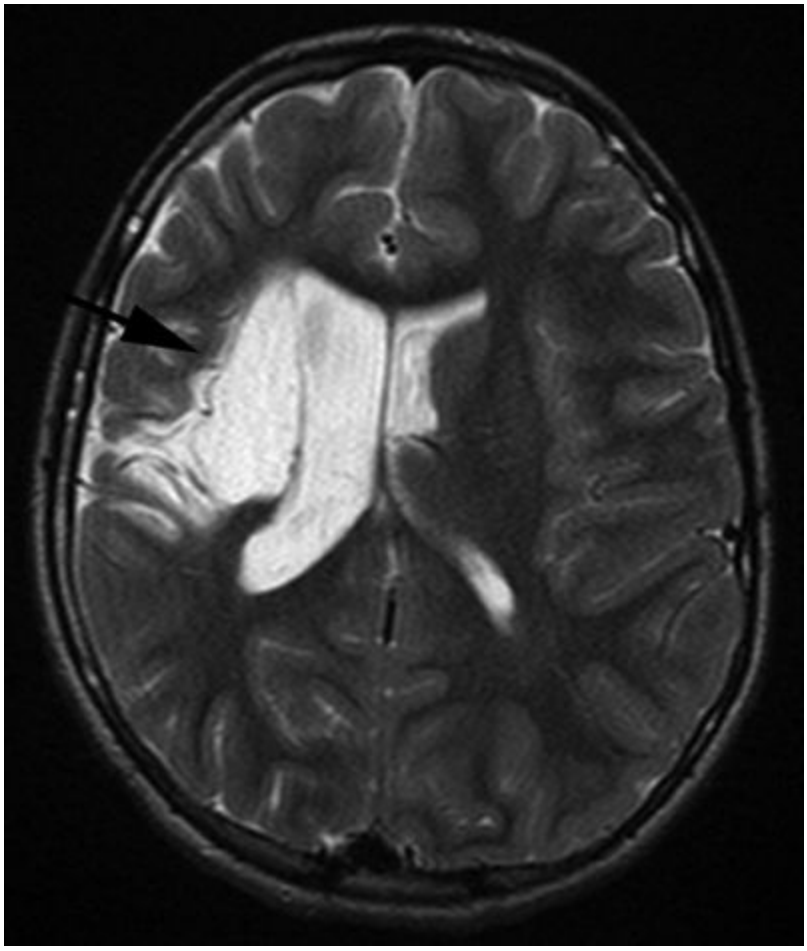

Figure 5.38. Remote infarction. Axial T2-weighted image from MRI without gadolinium in a 9-year-old boy with a history of posttraumatic occlusion of the right internal carotid artery as the infant shows cystic encephalomalacia in the right MCA territory (arrow).

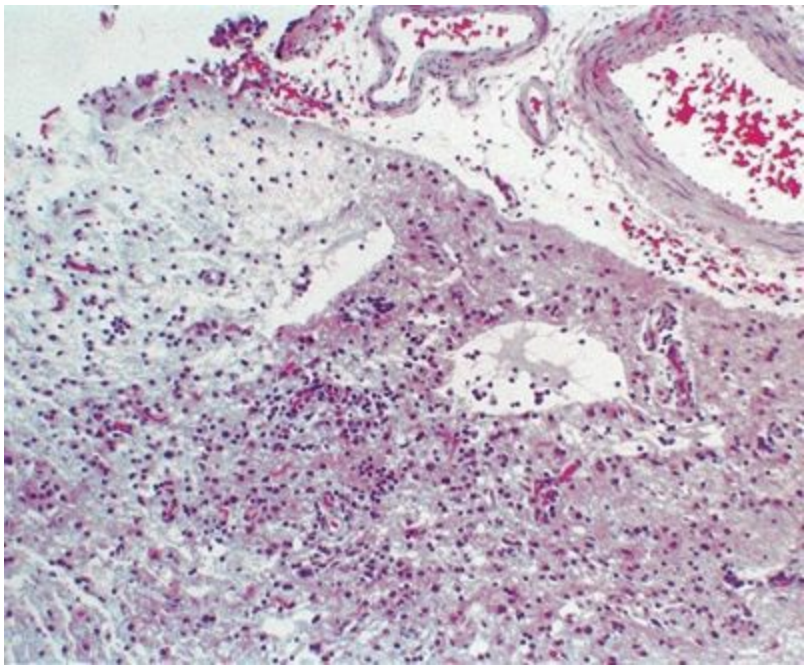

Figure 5.39. Histologic appearance of a **remote infarct** resulting in chronic epilepsy. The parenchyma is marked by cystic degeneration accompanied by macrophages and gliosis. Note the relative sparing of the molecular layer, which is more commonly observed with infarcts versus contusion.

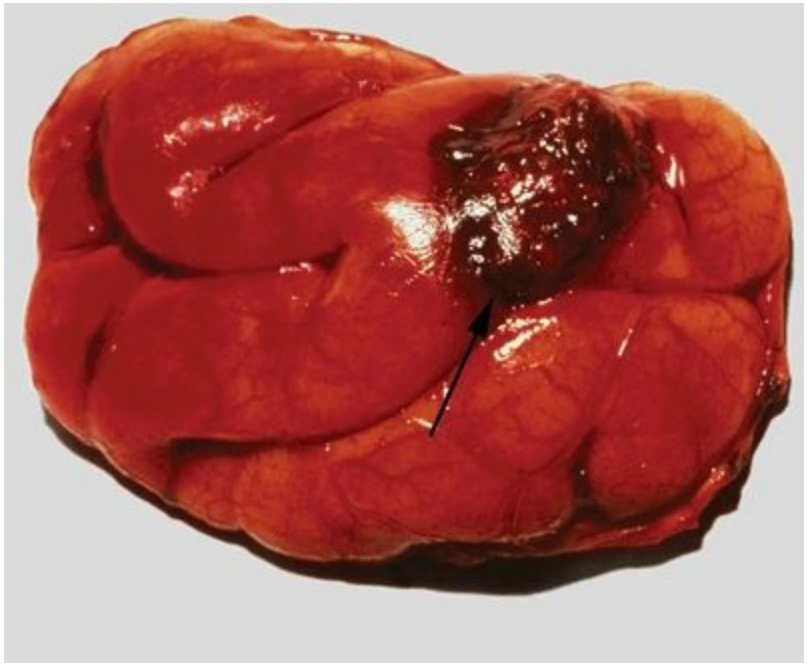

Figure 5.40. Gross appearance of a circumscribed hemorrhagic-appearing lesion situated in the temporal lobe corresponding to a **cavernous angioma** (arrow).

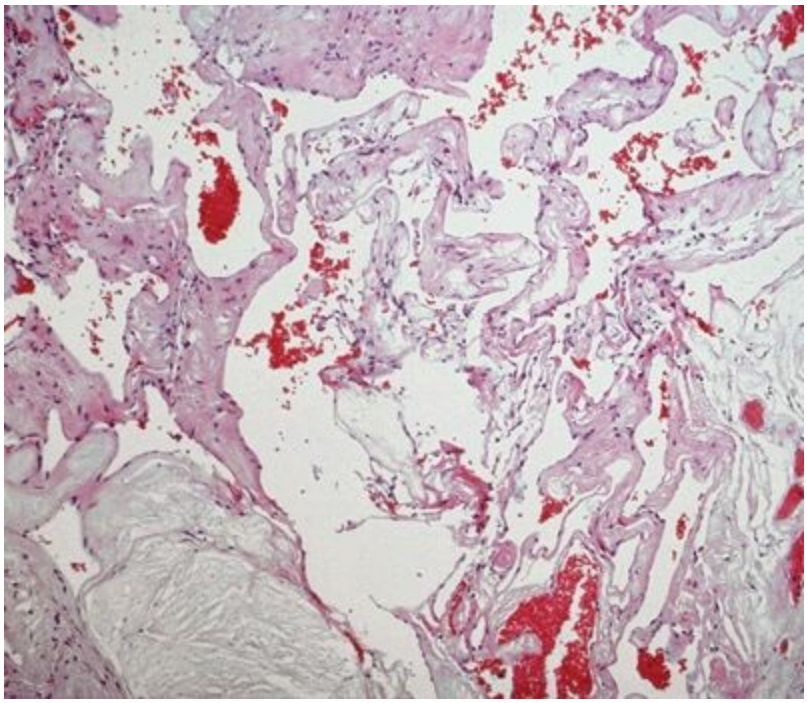

Figure 5.41. Microscopic appearance of the **cavernous angioma** in Figure 5.40. Cavernous angiomas are marked by a proliferation of dilated venous vessels, typically arranged in back-to-back fashion, without intervening neural parenchyma. Thickening of venous vessel walls may be observed. The lesions are often accompanied by adjacent gliosis and hemosiderin deposition.

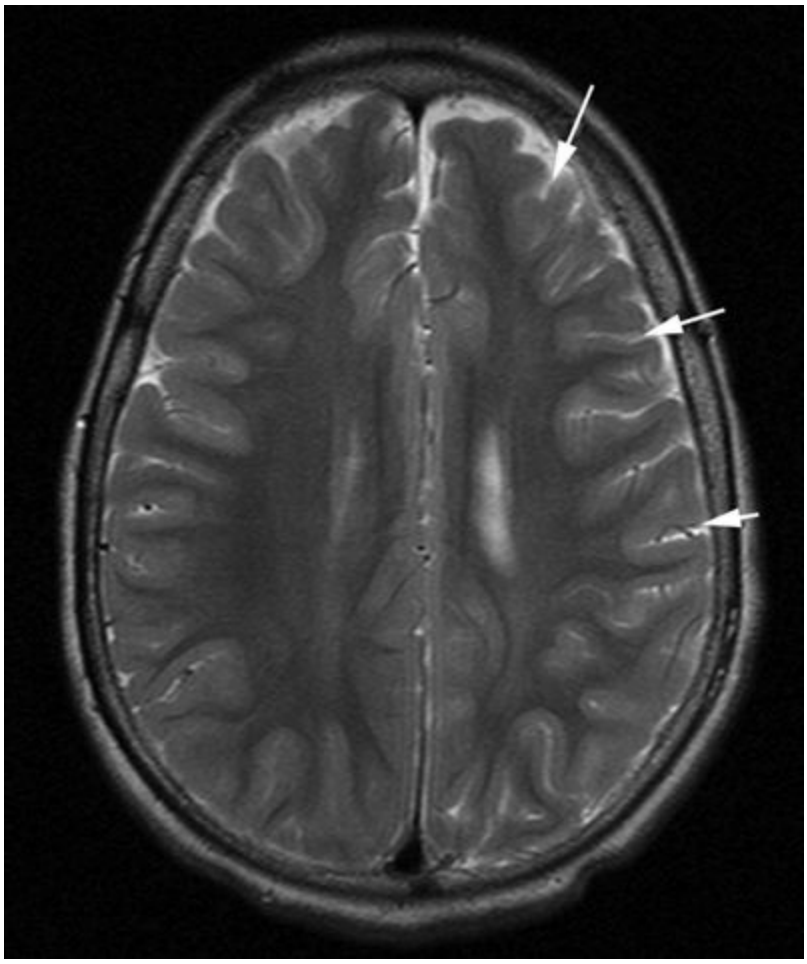

Figure 5.42. Rasmussen encephalitis. Axial T2-weighted image from MRI without gadolinium in a 3-year-old boy with a 1-year history of right tonic–clonic seizures progressive hemiparesis shows widening of the left frontal sulcal markings consistent with mild volume loss (arrows). Rasmussen encephalitis typically presents with intractable partial seizures (usually focal motor seizures and epilepsia partialis continua), progressive hemiparesis, cognitive decline, and unilateral cerebral atrophy with early and prominent involvement of the insular region.

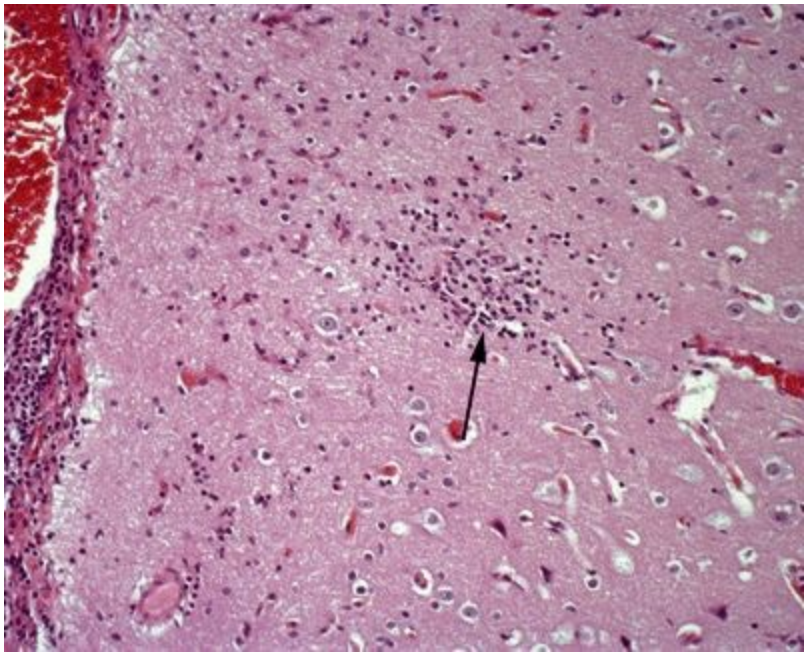

Figure 5.43. The histopathologic findings of **Rasmussen's encephalitis** often resemble those of viral encephalitis. These findings that are illustrated here include leptomeningeal chronic inflammation, perivascular parenchymal inflammation with microglial nodule formation (arrow), and gliosis.

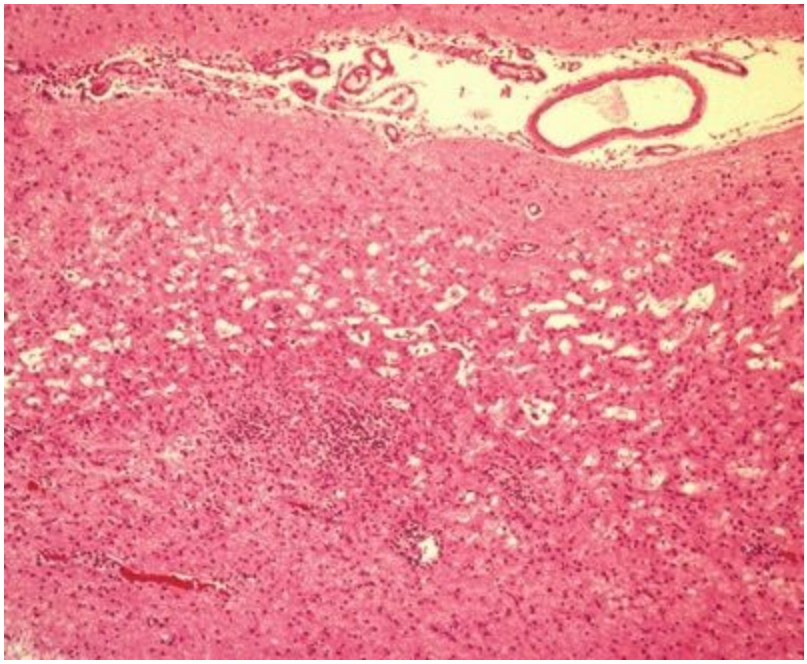

Figure 5.44. Many patients with **Rasmussen's encephalitis** demonstrate cortical atrophy, which microscopically is seen here and is marked by prominent gliosis, inflammation, and vacuolar degenerative changes in the cortex.

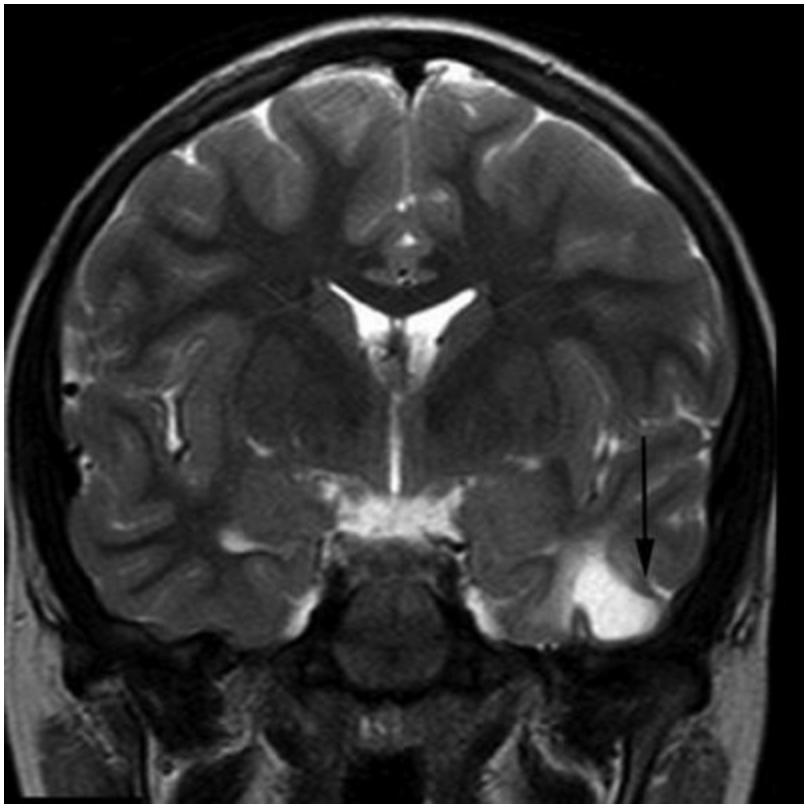

Figure 5.45. Ganglioglioma. Coronal T2-weighted image from MRI without gadolinium in a 9-year-old boy with a 6-year history of seizures consisting of staring spells shows a cystic cortical lesion of the left inferior temporal gyrus (arrow).

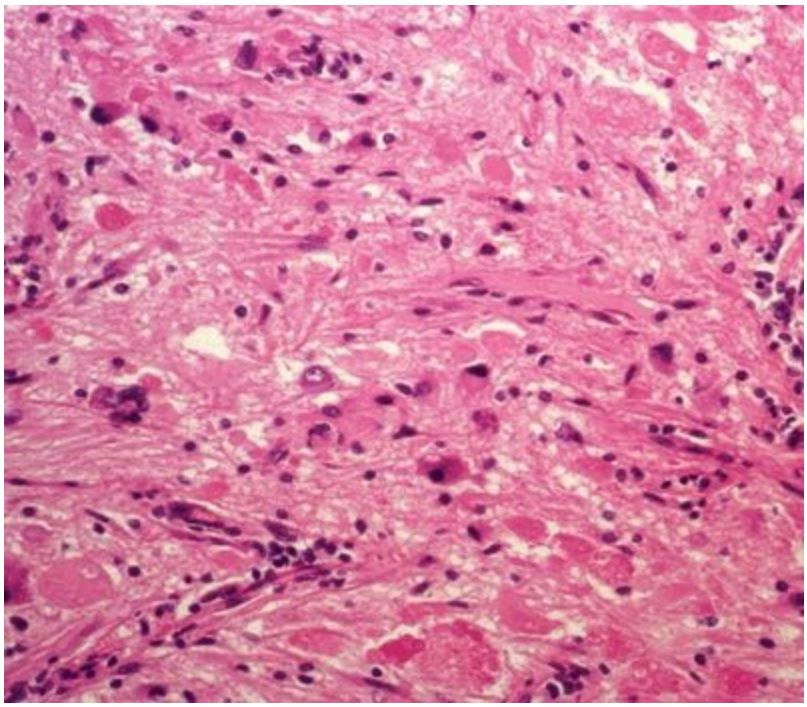

Figure 5.46. Histologic appearance of a **ganglioglioma**. The tumor represents a low-grade neoplasm (WHO grade I). It is marked by a proliferation of atypical ganglion cells intermixed with an atypical gliomatous component, most commonly resembling low-grade astrocytoma. Gangliogliomas most commonly arise in the temporal lobe, often in childhood, and are associated with cortical dysplasia. Perivascular chronic inflammation and eosinophilic granular bodies are also common features of this tumor type. This photomicrograph shows rare atypical large neuronal cells intermixed with a more spindle cell glioma component.

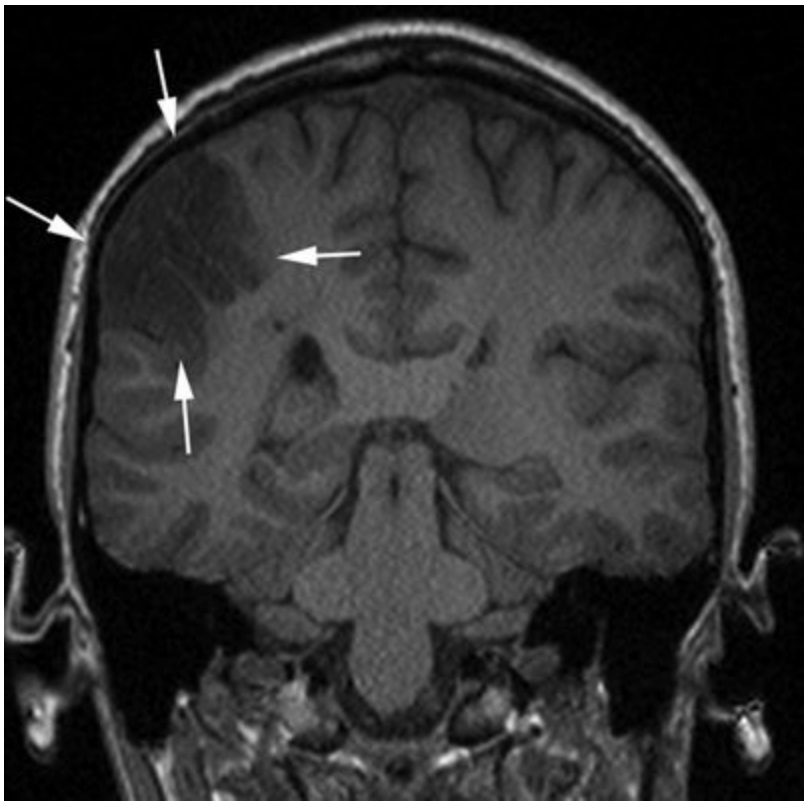

Figure 5.47. Dysembryoplastic neuroepithelial tumor. Coronal MPRAGE image from MRI without gadolinium in a 13-year-old girl with a 1-year history of left arm somatosensory progressing to dialeptic seizures shows a cortical lesion involving the right inferior parietal lobule characterized by multiple cystic structures, gyral broadening, and mild inner table scalloping (arrows).

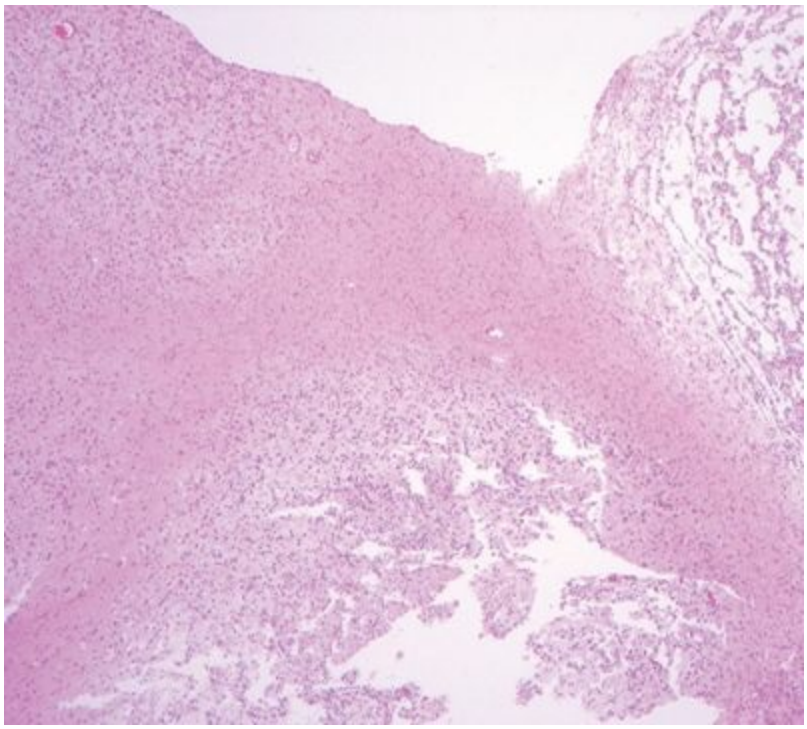

Figure 5.48. Low-magnification appearance of a temporal lobe **dysembryoplastic neuroepithelial tumor**. These WHO grade I lesions most commonly arise in the temporal lobe and are predominantly cortical based. Typically, they have multinodular architectural pattern and a microcystic appearance as seen in this photomicrograph.

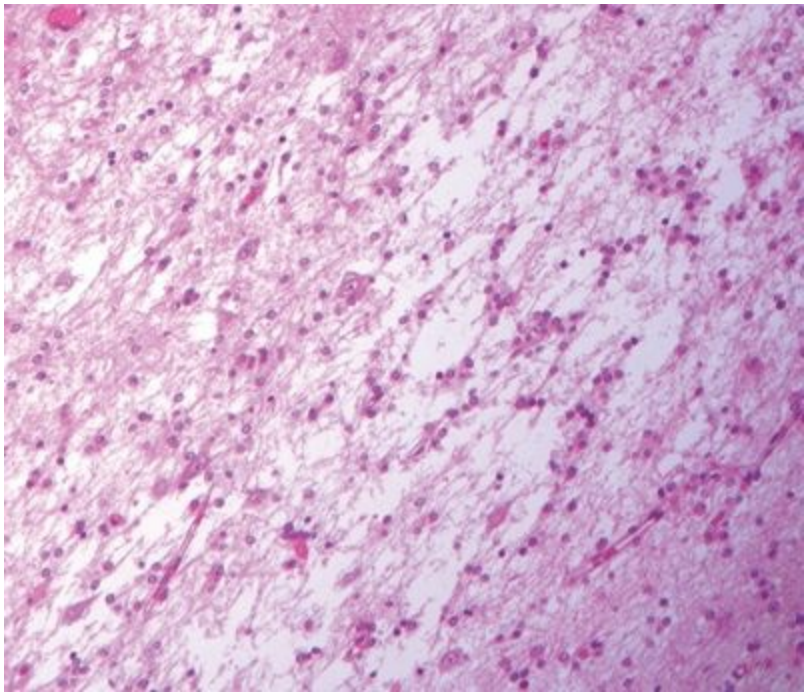

Figure 5.49. Higher-magnification appearance of a **dysembryoplastic neuroepithelial tumor** showing a proliferation of predominantly oligodendroglial-like rounded cells arranged against a mucoid background. Intermixed with these cells are smaller numbers of major appearing neuronal cells and astrocytic cells. Dysembryoplastic neuroepithelial tumors are also frequently accompanied by adjacent cortical dysplasia.

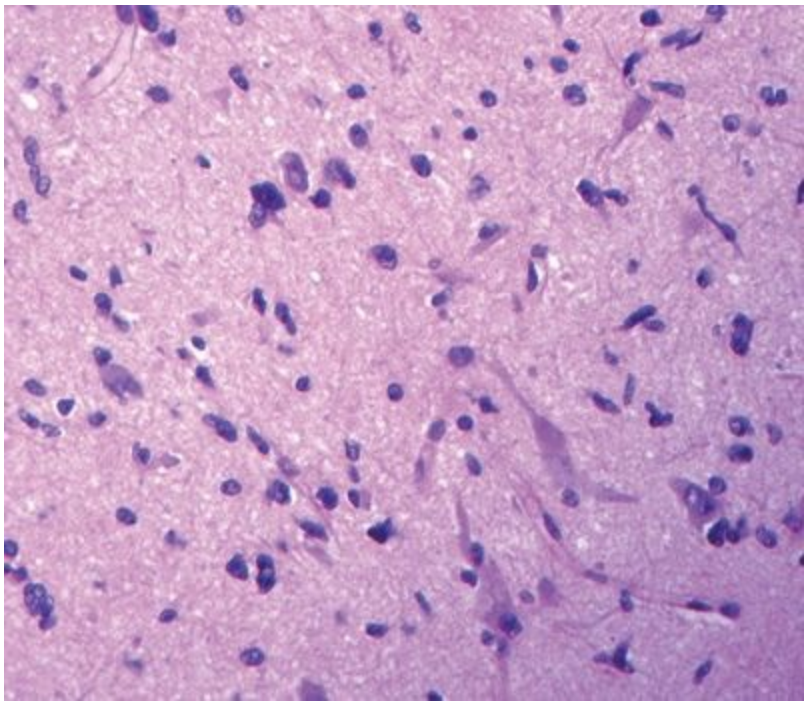

Figure 5.50. Histologic appearance of a **low-grade diffuse fibrillary astrocytoma** (WHO grade II). The tumor is marked by a mildly hypercellular parenchyma and cytologic atypia, as evidenced by nuclear enlargement and hyperchromasia and angularity to the nuclear contours. Areas of ganglioglioma may resemble low-grade astrocytoma, underscoring the importance of tissue sampling in order to identify the atypical ganglion cell component that helps define ganglioglioma. This tumor has the potential of degenerating into a higher- grade lesion over time (glioblastoma multiforme).

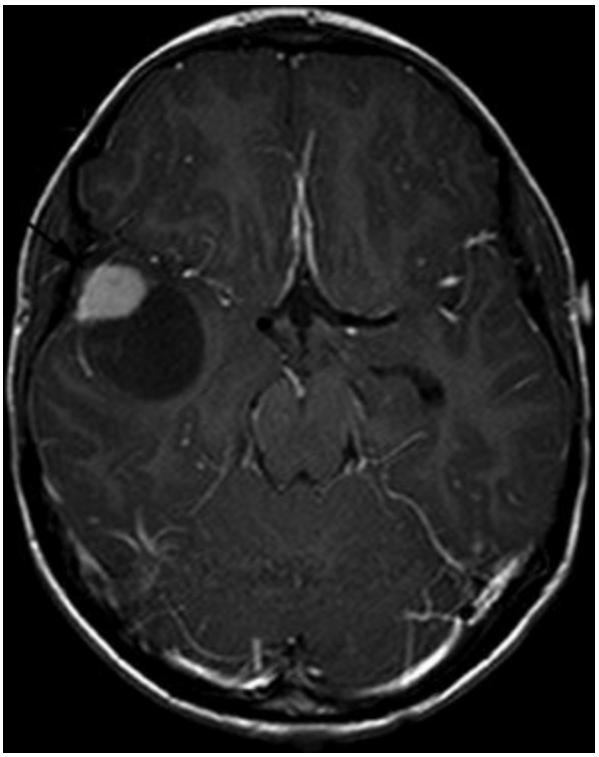

Figure 5.51. Pleomorphic xanthoastrocytoma. Axial T1-weighted image from MRI with gadolinium in a 10-year-old boy with a 1-year history of headache shows a lesion involving the cortex and subcortical white matter of the right temporal pole characterized by a large cyst with an enhancing mural nodule (arrow) without significant surrounding edema.

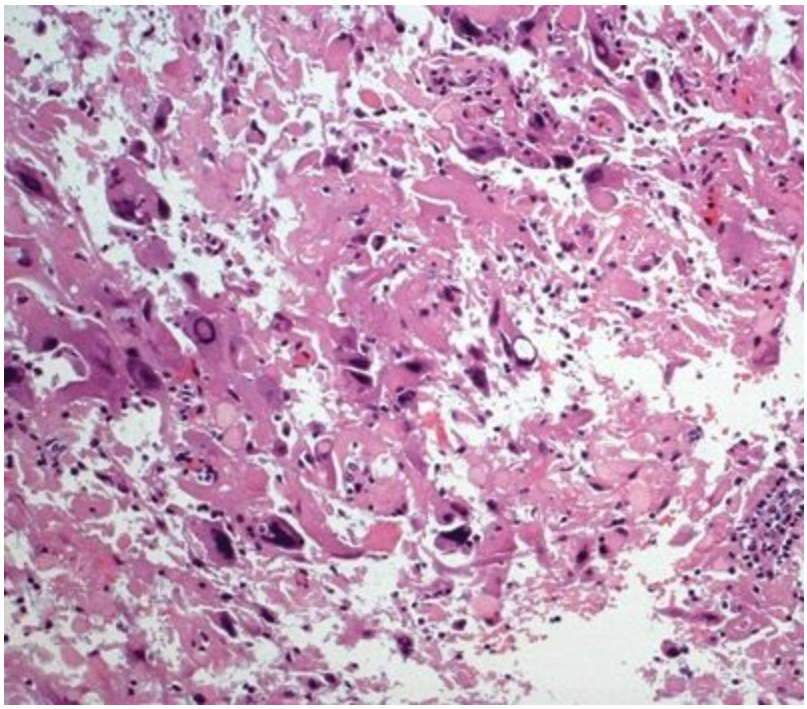

Figure 5.52. Pleomorphic xanthoastrocytomas are generally low-grade astrocytic tumors (WHO grade II) marked by prominent hypercellularity and nuclear pleomorphism, lipidized astrocytic cells, perivascular lymphocytes, and increased reticulin staining between individual tumor cells. In contrast to high-grade astrocytic tumors, most pleomorphic xanthoastrocytomas lack appreciable mitotic activity or necrosis. Most of these tumors arise either in the temporal or in the parietal lobe region in younger patients.

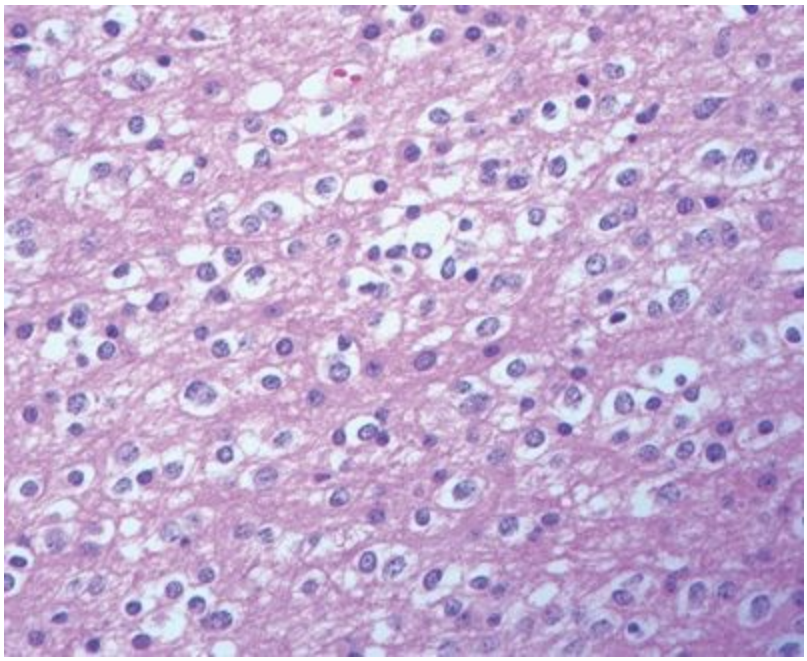

Figure 5.53. Low-grade oligodendroglioma: The histologic appearance of a low-grade oligodendroglioma (WHO grade II) arising in the temporal lobe is marked by a proliferation of cells with rounded nuclei, scant cytoplasm, and pericellular clearing ("fried egg" appearance). The pericellular clearing results from a delay in formalin fixation. These tumors, in contrast to dysembryoplastic neuroepithelial tumors, arise in the white matter and infiltrate into the overlying cortex. They are frequently calcified and have a prominent arcuate capillary vascular pattern. Many of these tumors demonstrate large deletions on chromosomes 1p and 19q and, like low-grade astrocytomas (WHO grade II), stain with IDH-1 antibody.

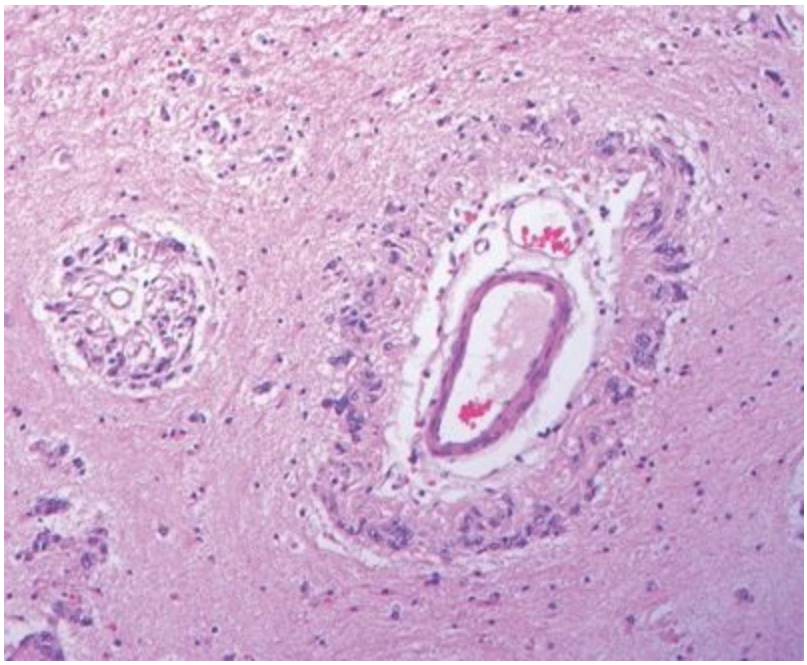

Figure 5.54. Angiocentric gliomas (WHO grade I) typically arise in young patients with chronic epilepsy in the temporal lobe. Microscopically, these tumors are marked by a striking perivascular pseudorosette-like pattern. The tumor frequently has an infiltrative margin.

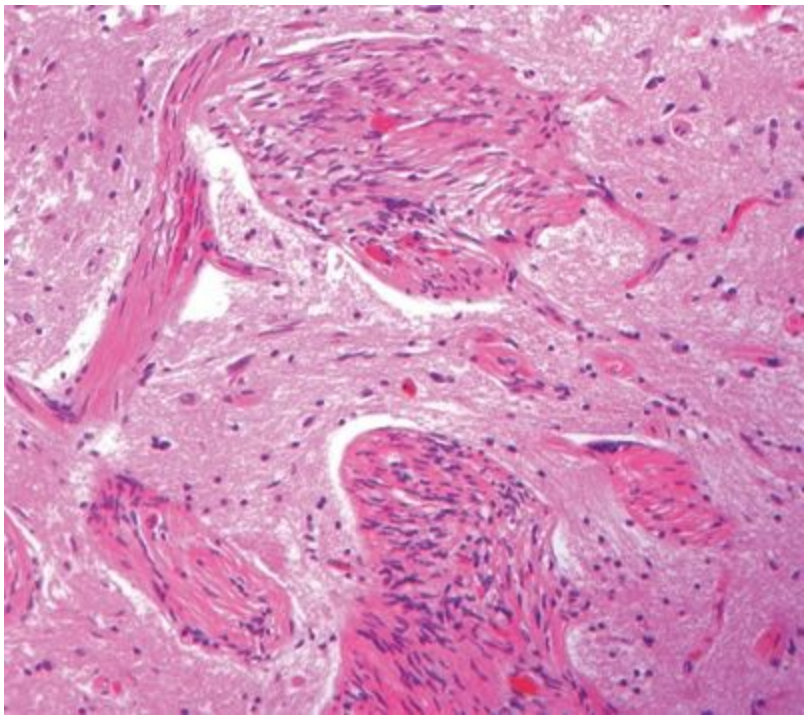

Figure 5.55. Meningioangiomatosis is a rare maldevelopmental lesion marked by a proliferation of blood vessels rimmed by a collar of spindled meningothelial cells. The lesion is usually primarily situated in the cortex but can extend to involve the underlying white matter. A subset of cases demonstrate an overlying meningioma. This lesion is associated with neurofibromatosis type II.

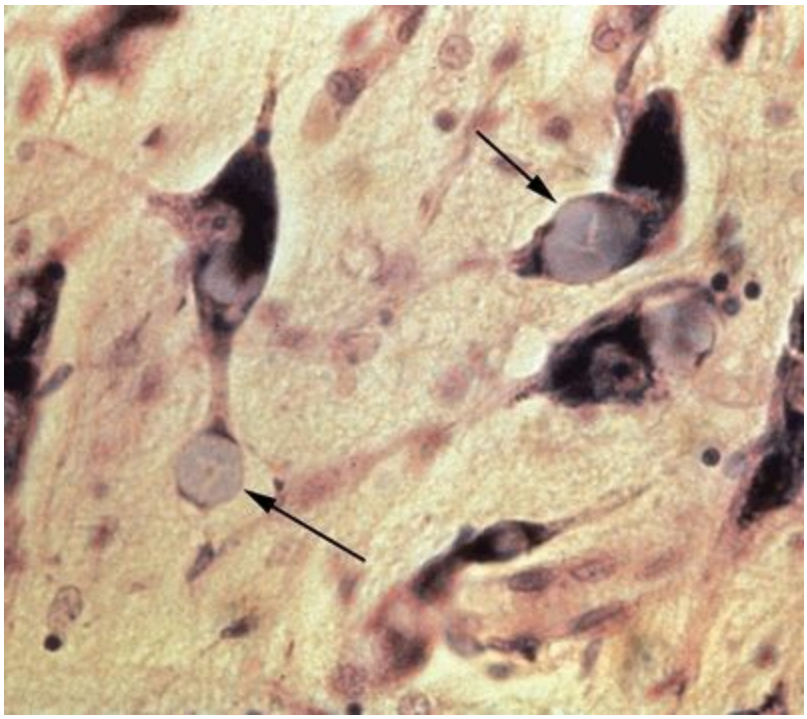

Figure 5.56. Lafora bodies (arrows) are intracytoplasmic neuronal polyglucosan structures that are seen in Lafora disease, which is an inherited progressive myoclonic epilepsy syndrome. It is an autosomal recessive disorder with onset in late childhood and adolescence. Characteristic seizures include myoclonic and occipital lobe seizures with visual hallucinations, scotomata, and photoconvulsions. The disease leads to an inexorable decline in the cognitive and neurologic functions, resulting in dementia and death usually within 10 years of onset.

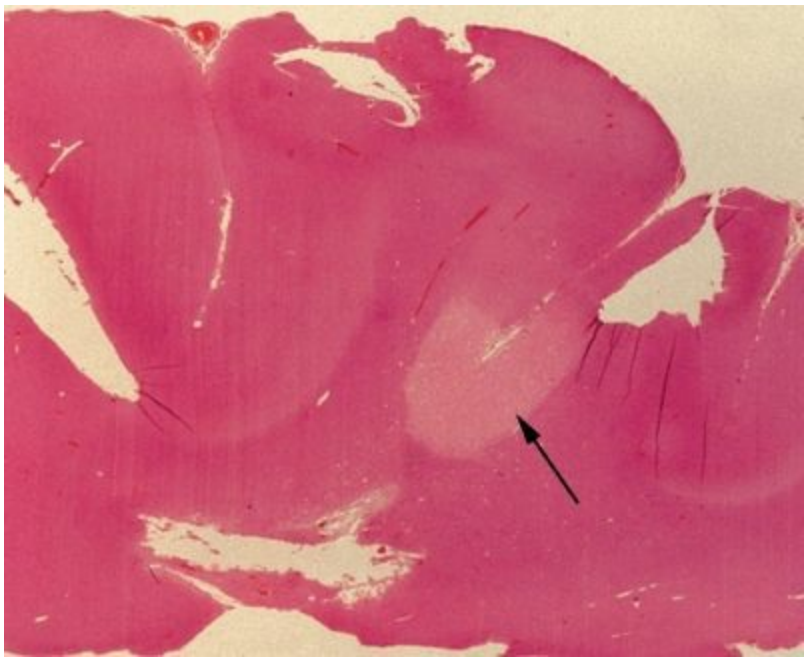

Figure 5.57. Invasive seizure monitoring with depth electrodes may occasionally result in infarcts associated with disruption of vessels. This low-magnification photomicrograph shows a pale zone of cortex (arrow) representing acute infarct due to placement of electrodes (**electrode-related infarct**).

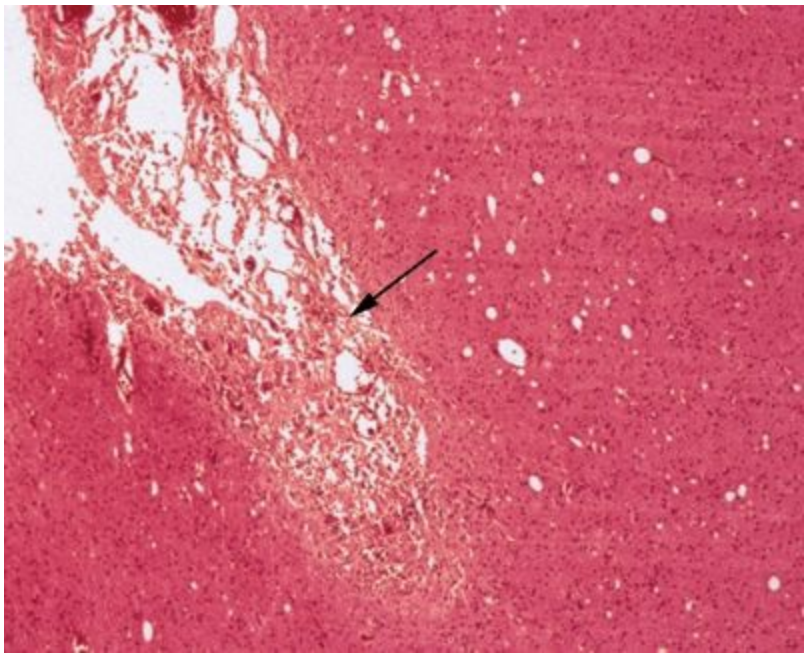

Figure 5.58. The tract along which a depth electrode was placed is observed. Evidence of **infarct/contusion along the electrode tract** as marked by vacuolated changes, surrounding gliosis, and a macrophage infiltrate (arrow).

PART II BASIC PRINCIPLES OF ELECTROENCEPHALOGRAPHY

ASSOCIATE EDITOR: HOWARD P. GOODKIN

CHAPTER 6 NEUROPHYSIOLOGIC BASIS OF THE ELECTROENCEPHALOGRAM

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Field potentials appear and are detectable in the space surrounding cellular elements of the nervous system. They comprise rapid waves and baseline shifts; the former correspond to the conventional electroencephalogram (EEG), and both phenomena are included in the so-called direct current (DC) potential. Field potentials are essential in the diagnosis and classification of epileptic seizures as well as in the control garnered by antiepileptic therapy. This chapter describes the elementary mechanisms underlying the generation of field potentials and the special functional situations leading to "epileptic" field potentials.

BIOELECTRICAL ACTIVITY OF NEURONAL AND GLIAL CELLS

The cells of the nervous system are generally differentiated into neurons and glial cells, whose processes intermingle and form a dense, highly complex matrix (Fig. 6.1). Because the actual interactions of these cellular elements are barely recognizable in spatiotemporal dimensions, principles of their structure and function inevitably are taken into account.

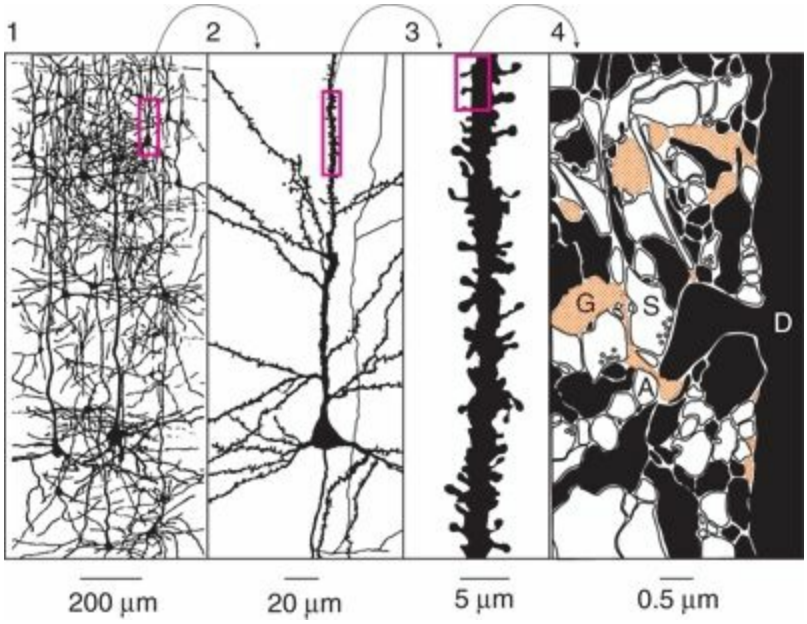


Figure 6.1. Morphology and histology of neuronal and glial elements in the neocortex. Rectangles and arrows indicate extended sections. In section 1, only a minor portion of the neurons is stained. A, axon; D, dendrite; G, glial cell; S, synapse. (Modified from Gaze RM. The Formation of Nerve Connections. New York: Academic Press; 1970; Purpura DP. Dendritic differentiation in human cerebral cortex: normal and aberrant developmental patterns. In: Kreutzberg GW, ed. Advances in Neurology. Vol. 12. New York: Raven Press; 1975:91–116; Valverde F. The organization of area 18 in the monkey: a golgi study. Anat Embryol. 1978;154:305–334;

Westrum LE, Blackstad TW. An electron microscopic study of the stratum radiatum of the rat hippocampus (regio superior, CA1) with particular emphasis on synaptology. J Comp Neurol. 1962;113:281–293, with permission.)

Neurons

A typical neuron consists of a soma (body, perikaryon) and fibers (dendrites and axons). In functional terms, with respect to information input, the relatively short and highly arborized dendrites can be considered extensions of the soma, as reflected in their being covered by thousands of synaptic endings. Axons are relatively long and, especially in their terminal regions, branch into collaterals. These neuronal output structures carry information into the terminal regions. Information is transferred to other neurons by way of synaptic endings (1–9).

Neuronal function is closely correlated with bioelectrical activity, which can be studied with intracellular microelectrode recordings. When a neuron is impaled by a microelectrode, a membrane potential of approximately 70 mV with negative polarity in the intracellular space becomes apparent. This resting membrane potential, existing in the soma and all its fibers, is based mainly on a potassium outward current through leakage channels. If the resting membrane potential is critically diminished, that is, if a threshold is surpassed, an action potential (AP) is triggered, which is based on sodium inward and potassium outward currents through voltage-dependent membrane channels. APs are conducted along the axons to the terminations, where they lead to a release of transmitter substances at the chemical synapse. These transmitters open another class of membrane channels in the postsynaptic neuron. Dependent on the ionic composition of the currents flowing through the transmitter (ligand)-operated channels, two types of membrane potential changes, commonly called postsynaptic potentials (PSPs), are induced in the postsynaptic neuron. When a sodium inward current prevails, depolarization of the postsynaptic neuron occurs. This synaptic depolarization is called an excitatory postsynaptic potential (EPSP) because it increases the probability that an AP will be triggered. When a potassium outward current or a chloride inward current prevails, hyperpolarization of the postsynaptic neuron occurs. Because hyperpolarization increases the distance between membrane potential and threshold, the synaptic hyperpolarization is called an inhibitory postsynaptic potential (IPSP) (10–12).

The EPSPs and IPSPs can interact with each other (Fig. 6.2). Electrical stimulation of an axon (ST1 in Fig. 6.2A) forming an excitatory synapse on a postsynaptic neuron can induce an AP at the site of stimulation. Conducted along the axon, the AP finally induces an EPSP in the postsynaptic neuron (ST1 in Fig. 6.2B). When only one synapse separates the site of stimulation from the site of EPSP generation, a monosynaptic EPSP appears. One way in which a summation of EPSP takes place is when the stimulation is repeated with an interstimulus interval shorter than the duration of the EPSP. With this temporal summation, the second EPSP can surpass the threshold and induce an AP (ST1 in Fig. 6.2B). A summation of EPSPs also can occur when monosynaptic EPSPs are evoked simultaneously at several locations on the postsynaptic neuron (spatial summation). Temporal and spatial summations are often combined with each other and are essential for information processing in the central nervous system, as when the AP reaches the target neuron by different ways. With stimulation at ST2 in Figure 6.2A, the triggered APs pass through varying numbers of relays before reaching their target. As APs are delayed with each synaptic transmission, they appear with temporal dispersion at the postsynaptic neuron and induce a long- lasting depolarization (ST2 in Fig. 6.2B). Because many synapses are involved, such a depolarization is called a polysynaptic EPSP. When a polysynaptic network is activated repeatedly, EPSPs of considerable amplitude and duration can appear, as demonstrated by the original recording in Figure 6.2C. As with EPSPs, IPSPs can be

induced both monosynaptically and polysynaptically and also are subject to temporal and spatial summation (ST3 and ST4 in Fig. 6.2A and B) (5,11,12).

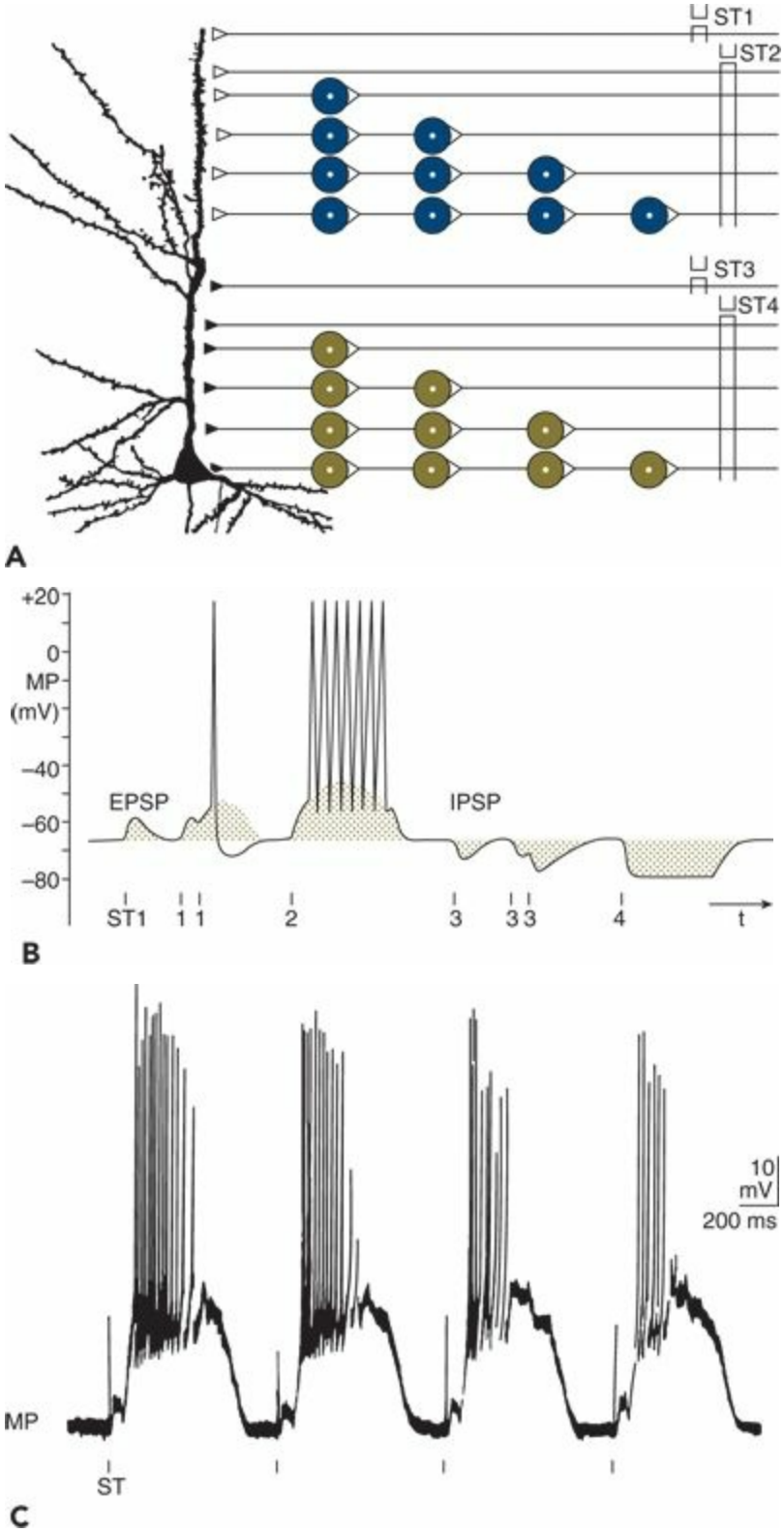


Figure 6.2. Bioelectrical activity of neuronal elements: membrane potential (MP), action potential (AP), excitatory postsynaptic potential (EPSP), and inhibitory postsynaptic potential (IPSP). **A:**Indicated are stimulation sites and the pyramidal neuron from which the recording was made. Open symbols represent excitatory synapses and filled symbols inhibitory synapses. Up to four interneurons are schematically drawn between stimulation sites (ST1 to ST4) and the neuron. **B:**Intracellular recording from the pyramidal neuron in **(A)** is shown. Single electrical stimuli applied at ST1 and ST3 evoked monosynaptic EPSP and IPSP, respectively. Paired stimulation at ST1 and ST3 led to a summation of the corresponding monosynaptic responses. After stimulation at ST2 and ST4, polysynaptic EPSP and IPSP, respectively, were elicited. **C:**Original tracing of synaptically mediated neuronal depolarizations in a spinal motoneuron of the cat is shown. Stimulation (ST) of pathways oligosynaptically and polysynaptically linked to the neuron led to early (oligosynaptic) and late (polysynaptic) potentials. (**A** and **B** adapted from Speckmann E-J. Experimentelle Epilepsieforschung. Darmstadt, Germany:

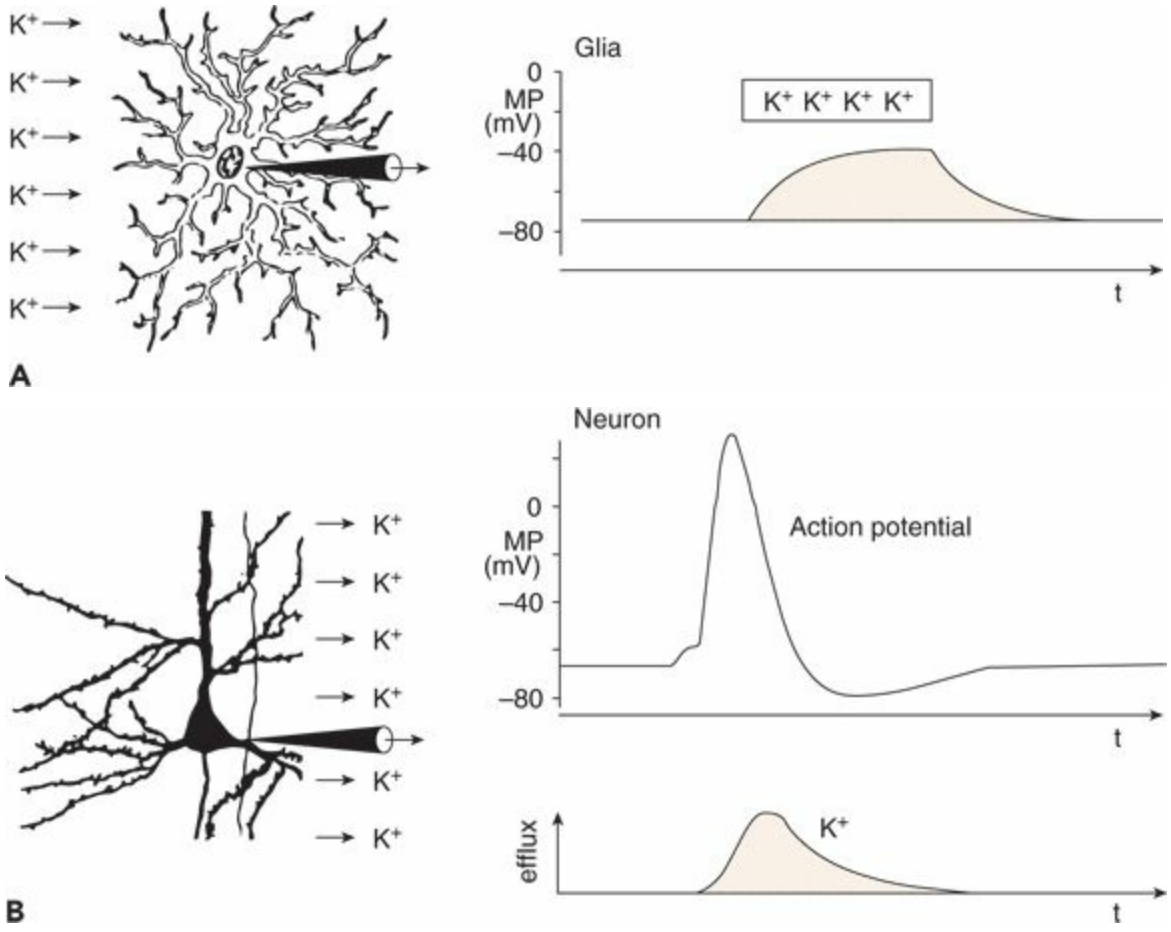
Wissenschaftliche Buchgesellschaft; 1986:13, with permission.)

In complex neuronal systems, EPSPs and IPSPs are often superimposed and induce long-lasting sequences of fluctuations of the membrane potential. These kinds of postsynaptic responses play a prominent role in the generation of extracellular potential fields, such as the EEG.

Glial Cells

Consisting of a soma and fibers, glial cells intermingle with the neuronal structures. Glial cell fibers are electrically coupled, building up an extended functional network (3,8,13).

Glial cells also show a membrane potential (Fig. 6.3A). Unlike neurons, glial cells do not generate APs and PSPs. Because their resting membrane potential is based exclusively on potassium outward current through leakage channels, its value is close to the potassium equilibrium potential. With an increase and a subsequent decrease in extracellular potassium concentration, glial cells depolarize and repolarize, respectively (Fig. 6.3A). Changes in the extracellular concentration of other cations have only small effects on the membrane potential of glial cells (14,15).



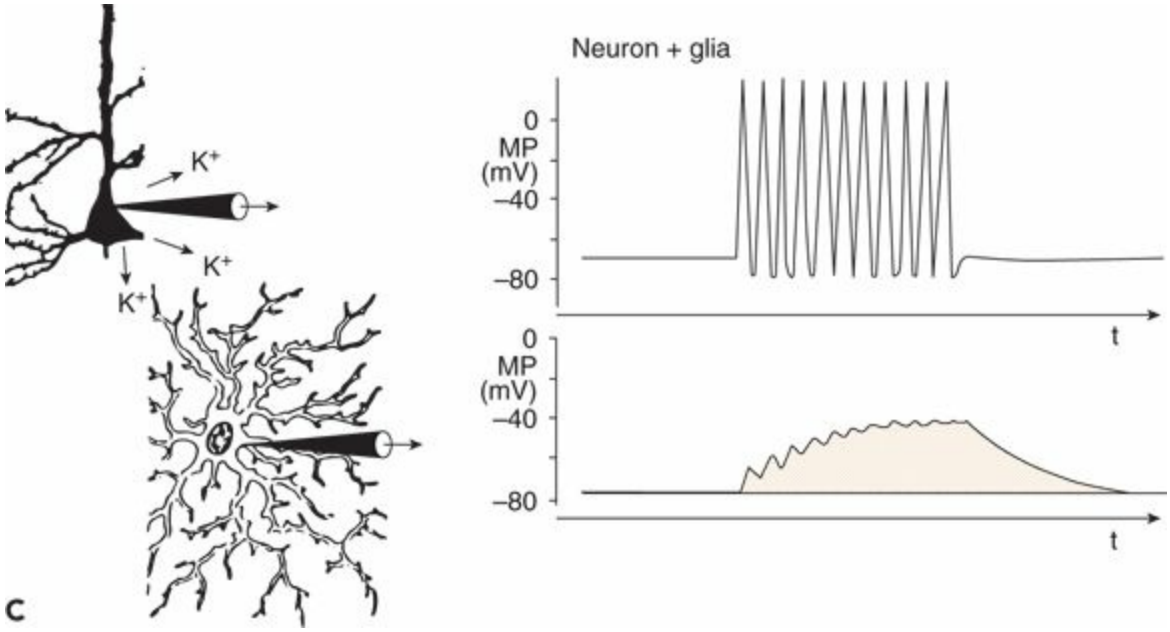


Figure 6.3. Changes in membrane potential (MP) of a glial cell induced by an increase in extracellular potassium concentration **(A)** and functional linkage between neuronal and glial activity **(B)** and **(C)**. **A:** The increased extracellular concentration of K^+ led to a sustained depolarization of the glial cell. **B:** During a neuronal action potential, an efflux of K^+ occurred. **C:** The K^+ concentration in the extracellular space close to the glial cell was raised during the repetitive firing of a neuron. This led to sustained depolarization of the neighboring glial cell. (**A** and **C** adapted from Zenker W. Feinstruktur des Nervengewebes. In: Zenker W, ed. Makroskopische und Mikroskopische Anatomie des Menschen. Vol. 3. Munich, Germany: Urban & Schwarzenberg; 1985:3–55, and **B** and **C** adapted from Valverde F. The organization of area 18 in the monkey: a golgi study. Anat Embryol. 1978;154:305–334.)

Glial cells and neurons are functionally linked by way of the extracellular potassium concentration (Fig. 6.3B and C). As mentioned, neuronal APs are associated with an outflow of potassium ions (see Fig. 6.3B). Thus, with an increase in the repetition rate of neuronal APs, the extracellular potassium concentration increases, resulting in depolarization of glial cells adjacent to the active neurons (see Fig. 6.3C) (11,14–16).

PRINCIPLES OF FIELD POTENTIAL GENERATION

Changes in membrane potential of neurons and glial cells are the basis of changes in extracellular field potential. The mechanisms involved can be described as follows: (i) primary transmembranous ion fluxes at a restricted membrane area of cells and consequent localized membrane potential changes; (ii) development of potential gradients between sites of primary events and the remaining areas of the membrane; and (iii) secondary ion currents because of the potential gradient along the cell membrane in the intracellular and extracellular spaces. The secondary current flowing through the extracellular space is directly responsible for the generation of field potentials (9,17). Because EPSPs and IPSPs are important in the generation of the EEG findings, the processes are explained in greater detail using the examples of an excitatory synaptic input (2,12,18,19).

A vertically oriented neuronal element, shown schematically in Figure 6.4, is impinged on by a single excitatory synapse whose afferent fiber can be stimulated. The resulting net influx of cations leads to depolarization of the membrane, that is, to an EPSP. Consequently, a potential gradient exists along the neuronal membrane and evokes an intracellular and extracellular current flow. As a result of the intracellular current, the EPSP spreads electrotonically; the extracellular current induces field potentials. The polarity depends on the site of recording. The electrode near the synapse "sees" the inflow of cations (a negativity), whereas the electrode distant from the synapse "sees" the outflow of

cations (a positivity). Between the two electrodes is the reversal point of the field potentials (12,20).

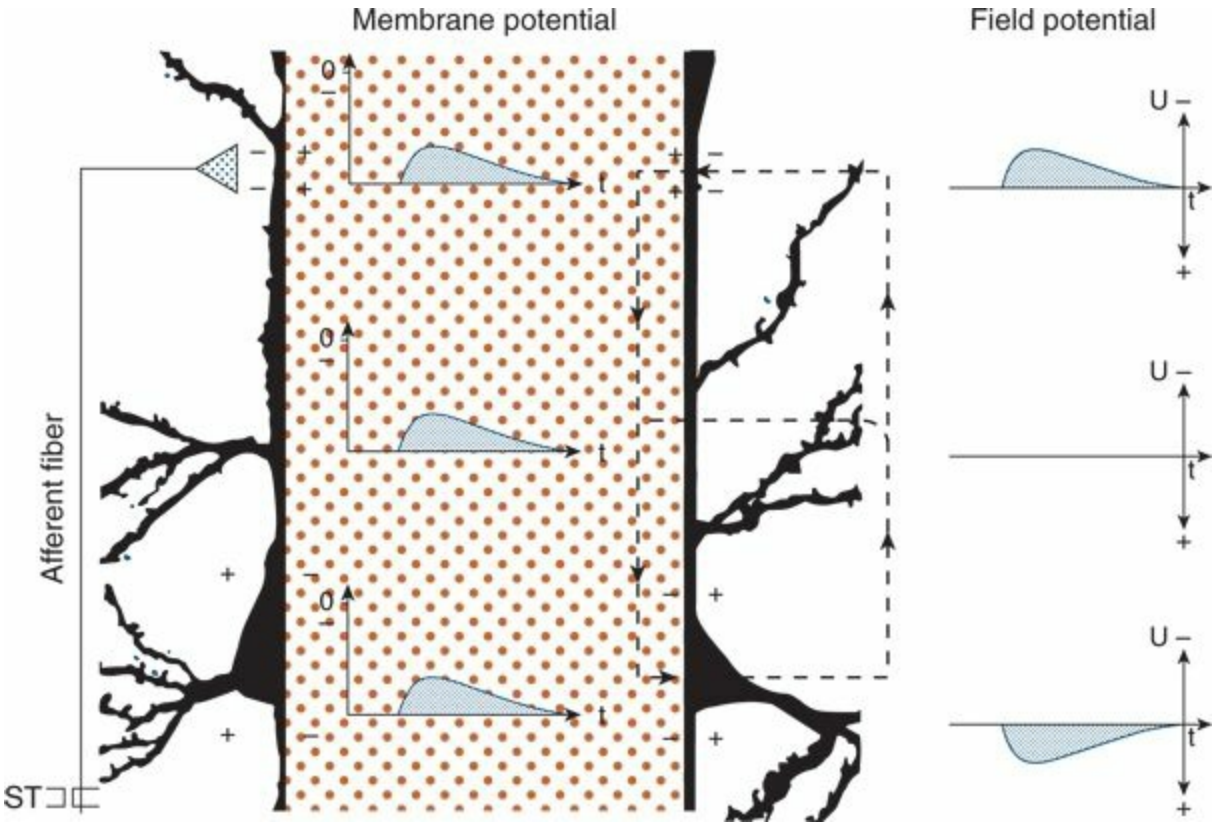


Figure 6.4. Principles of field potential generation in the neocortex. A perpendicular pyramidal neuron with an extended intracellular space (hatched area) is shown. An afferent fiber **(left)** formed an excitatory synaptic contact at the superficial aspect of the apical dendrite. Changes in membrane potential and in corresponding field potential are given in the intracellular and extracellular spaces, respectively. After stimulation of the afferent fiber (ST), an excitatory postsynaptic potential developed in the upper part of the dendrite and spread electrotonically to the lower parts. The local excitation (+ and −) led to tangential current flows (broken lines) and to the field potential changes in the extracellular space.

Corresponding effects occur with the generation of IPSPs. Activation of an inhibitory synapse induces an outflow of cations or an inflow of anions at the synaptic site. In this way, the membrane potential is increased at the synaptic site, and a potential gradient develops along the cell membrane, similar to that described for EPSPs. The potential gradient evokes a current flow from the synaptic site to the surrounding regions of the membrane. Compared with EPSPs, the extracellular current flow is inverted, as is the polarity of field potentials. Thus, the electrode near the synapse "sees" a positivity and the electrode distant from the synapse a negativity.

Field potentials are generated by extracellular currents, and their polarity depends on the direction of the current as well as on the positions of the extracellular electrodes. Figure 6.5 illustrates the generation and polarity of field potentials, as elicited by excitatory and inhibitory inputs to superficial and deep regions of vertical neuronal elements. Negative field potentials at the cortical surface may be based on superficial EPSPs as well as on deep IPSPs, and positive field potentials at the surface may be based on superficial IPSPs as well as on deep EPSPs (Fig. 6.6) (12,19,20).

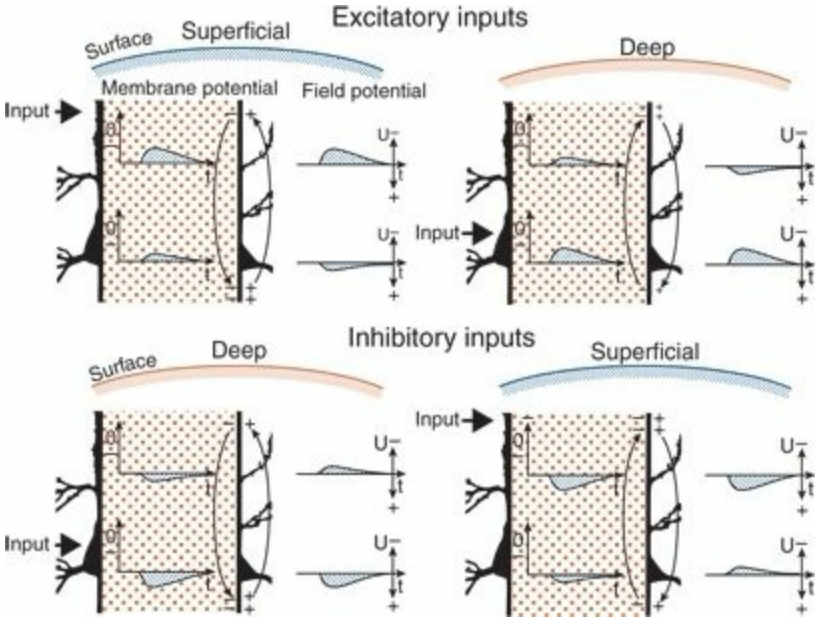


Figure 6.5. Generation of field potential in the neocortex by excitatory and inhibitory synaptic inputs reaching the superficial and deep parts of perpendicular pyramidal neurons. The intracellular space is extended (hatched areas). Changes in membrane potential and in the corresponding field potential are given in the intracellular and extracellular spaces, respectively. Locations of active inputs are indicated (heavy arrows). EPSP and IPSP, excitatory and inhibitory postsynaptic potentials, respectively. Excitatory inputs: With superficial excitation, an inward current generated an EPSP in upper and lower regions. Because of the direction of the extracellular current flow (light arrows), the field potential had negative polarity at the surface and positive polarity in the deep recording (cf. Fig. 6.4). With deep excitation, the current flow—and the field potentials—had inverse direction to that elicited by superficial excitation. Inhibitory inputs: With deep inhibition, an outward current generated an IPSP in lower and upper regions. Because of the direction of the extracellular current flow (arrows), the field potential had positive polarity in the deep recording and negative polarity at the surface. With superficial inhibition, the direction of current flow was inverse to that seen with deep inhibition; the field potentials were inverted as well. Differences in the shape of the various potentials were caused by the electrical properties of the tissue.

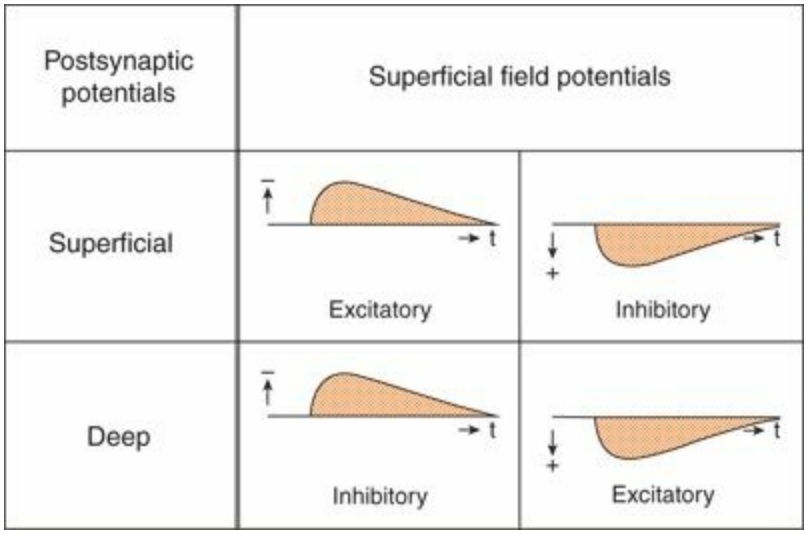


Figure 6.6. Synopsis of the synaptic processes underlying the generation of superficial field potentials in the cerebral cortex. Different mechanisms may lead to uniform superficial field potentials.

POTENTIAL FIELDS IN NEURONAL NETWORKS

Many neuronal elements contribute to the extracellular currents that generate field potentials recorded at the surface of central nervous system structures. The spatial arrangement of the neuronal elements and the positions of the recording electrodes play an essential role in establishing and detecting extracellular potential fields (2,12,21).

Two principal types of neuronal arrangements can be identified (Fig. 6.7). In the parallel type, the somata are in one layer and the dendrites are in opposite layers (see Fig. 6.7A). In the other type, the somata are in the center of a pool and the dendrites extend to its periphery (see Fig. 6.7B). The first arrangement is realized in the cortex and the second in brainstem nuclei.

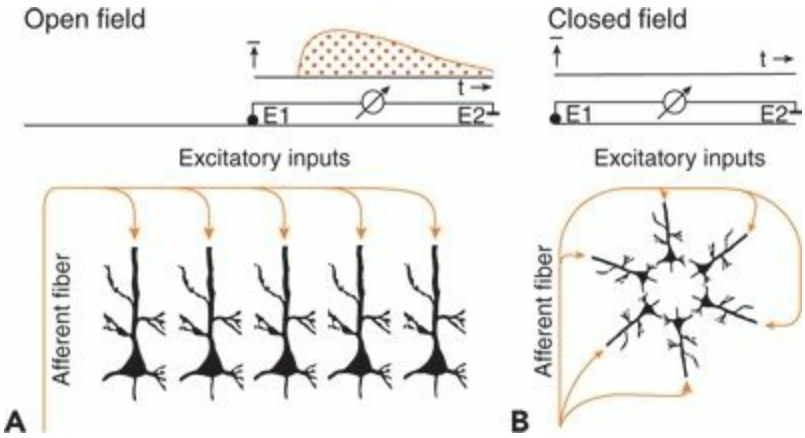


Figure 6.7. Neurons arranged to give open **(A)** and closed **(B)** fields. Field potentials are present **(A)** or missing **(B)** during excitatory inputs by way of afferent fibers. E1 and E2 indicate different and reference electrodes.

The two neuronal arrangements build up the so-called open and closed fields. In open fields, one electrode (E2 in Fig. 6.7A) largely integrates the potentials of the population (i.e., it is near the zero potential line), and the other electrode (E1 in Fig. 6.7A) sees only the positive or negative field, permitting the recording of a field potential. In closed fields, external electrodes do not see significant potential differences because the current flows within the pool compensate for each other (see Fig. 6.7B) (2,21).

TYPES OF FIELD POTENTIAL CHANGES

With respect to the time course, two types of field potentials can be differentiated, depending on the time constant of the amplifying recording device. The conventional EEG is recorded with a time constant of 1 second or less. Amplification with an infinite time constant, that is, by a DC amplifier, permits additional recording of baseline shifts and wavelike potentials (EEG/DC) (22–24).

Wave Generation (Conventional Electroencephalogram)

The generation of wavelike potentials is described in Figure 6.8, a representation of a column of neocortex. In its upper dendritic region, the neuron is activated by an afferent fiber by way of an excitatory synapse. The superficial EEG and the membrane potentials of the dendrite and afferent fiber are recorded. The afferent fiber shows grouped, followed by regular, discharges. With grouped discharges prominent, summated EPSPs occur in the dendrite; with sustained regular activity, a depolarizing shift of the membrane potential appears. The changes in membrane potential in the upper dendrite lead to field potentials. When amplifiers with a finite time constant are used, only fluctuations in field potential are recorded, corresponding to findings on conventional EEG. The shift of the membrane potential is not reflected (21,25).

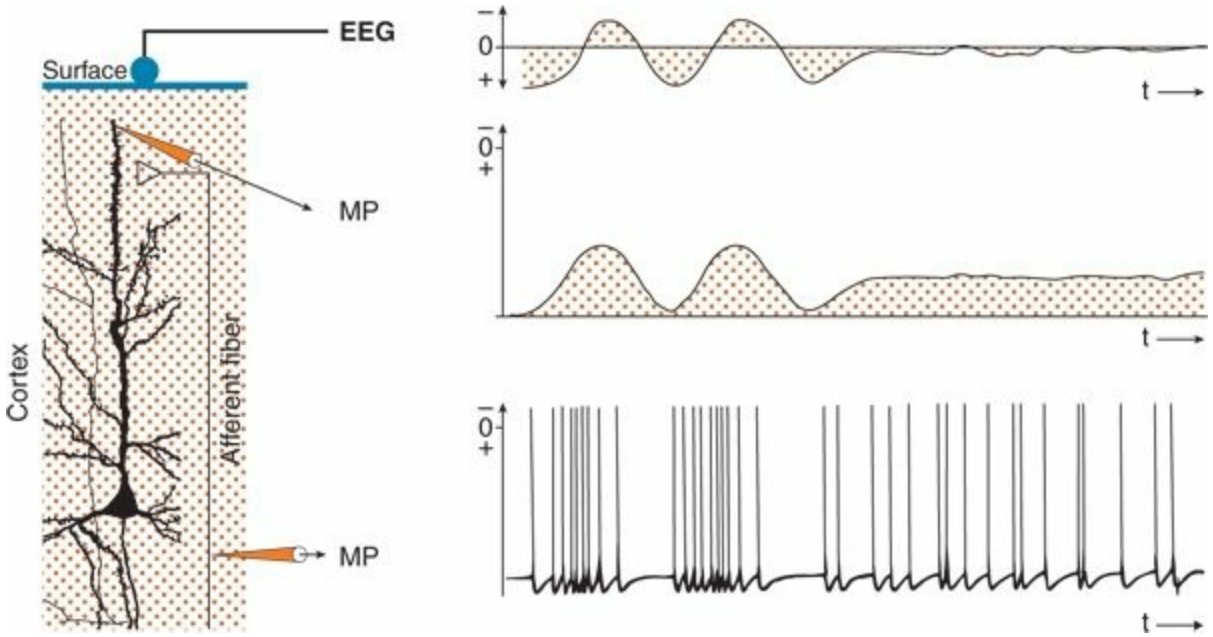


Figure 6.8. Wave generation in the electroencephalogram (EEG) at the surface of the cerebral cortex. A perpendicular pyramidal neuron is shown. An afferent fiber formed an excitatory synaptic contact at the superficial part of the apical dendrite. Simultaneous recordings of the membrane potentials (MPs) of the afferent fiber and the dendritic element, as well as of the EEG, are displayed. Groups of APs in the afferent fiber generate wavelike excitatory postsynaptic potentials (EPSPs) in the dendritic region and corresponding waves in the EEG recording. Tonic activity in the afferent fiber results in long-lasting EPSP with only small fluctuations. The long-lasting depolarization is not reflected on the conventional EEG recording.

Baseline Shifts (Electroencephalogram/Direct Current)

The generation of baseline shifts is described in Figures 6.9 and 6.10. In a column of the neocortex (see Fig. 6.9), a neuron is activated in its upper dendritic region by an afferent fiber by way of an excitatory synapse. In this case, the afferent fiber displays three levels of sustained activity. Medium regular activity is interrupted by periods of high repetition and silence. Consequently, owing to facilitation, the upper dendrite is depolarized during the high discharge in the afferent fiber and is hyperpolarized in the silent period because of disfacilitation. This results in corresponding field potential shifts. When amplifiers with an infinite time constant are used, these baseline shifts, which reflect sustained values of the membrane potential of neuronal elements, are recorded. With a sufficiently high upper frequency limit, the DC recording comprises conventional EEG waves as well as slow potential deviations (26–32).

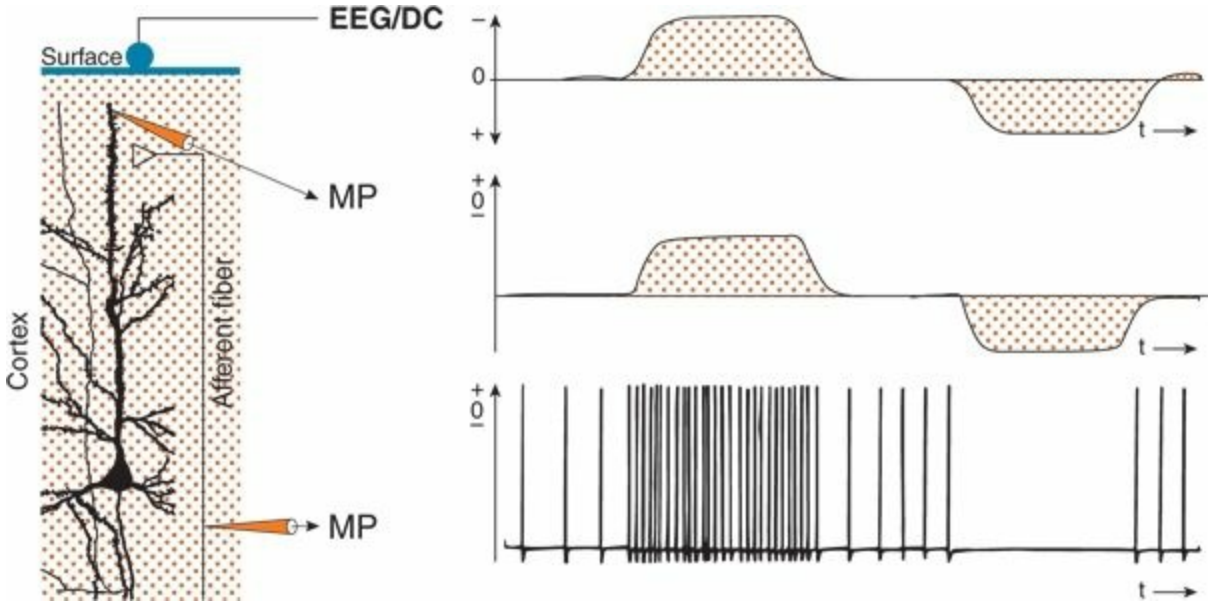


Figure 6.9. Sustained shifts in the electroencephalogram (EEG) at the surface of the cerebral cortex resulting from sustained neuronal activities. If recordings are performed with a direct current (DC) amplifier (EEG/DC), sustained potentials can also be recorded at the surface. In the perpendicular pyramidal neuron depicted, an afferent fiber formed an excitatory synaptic contact at the superficial part of the apical dendrite. The membrane potentials (MPs) of the afferent fiber and the dendritic element were recorded simultaneously, as was the EEG/DC. Increased and decreased sustained activity in the afferent fiber generated sustained depolarizations and hyperpolarizations of the dendritic region and corresponding negative and positive shifts of the EEG/DC recording.

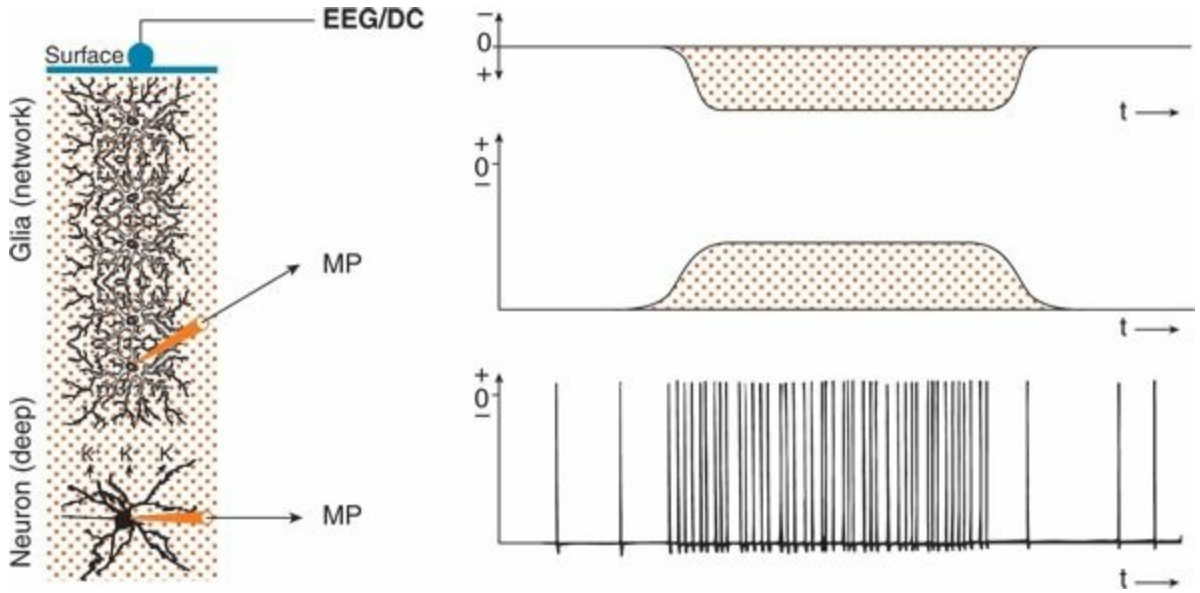


Figure 6.10. Sustained shifts in the electroencephalogram (EEG) performed with a direct current (DC) amplifier (EEG/DC) at the surface of the cerebral cortex generated by neuronal activity and mediated by a glial network. If recordings are performed with a DC amplifier, sustained potentials can also be recorded. A deep neuron functionally coupled to a perpendicularly oriented glial network is shown. The membrane potentials (MPs) of the deep neuron and of a glial cell as well as the EEG/DC were recorded simultaneously. Sustained increased activity of the deep neuron induced an increase in extracellular K^+ concentration and a corresponding depolarization of the glial cells. Because of the electrotonically coupled network of glial cells, a sustained positive potential was induced in the surface EEG/DC recording.

Glial cells also are involved in the generation of baseline shifts (Figs. 6.10 and 6.11). As noted, a functional coupling between neurons and glial cells exists (see Fig. 6.3). Figure 6.10 shows a neuron in deep cortical layers and a network of electrically coupled glial cells extending to the surface. The superficial EEG/DC and the membrane potentials of a glial cell and the neuron are recorded. With increased discharge frequency of the neuron, extracellular potassium concentration rises, evoking a

depolarization of the adjacent glial cell. The potassium- induced depolarization is conducted electrotonically within the glial network. A functional situation is present similar to that in a perpendicular neuron with a deep excitatory synaptic input (see Figs. 6.5 and 6.6). The superficial EEG/DC electrode sees a long-lasting positivity because of an outflow of cations from the glial cells in the upper layers. In other respects, this corresponds to the well-known spatial buffering of potassium. In principle, the aforementioned mechanism can make visible the activity of closed fields (see Fig. 6.7B) in baseline shifts of field potentials (31,33,34).

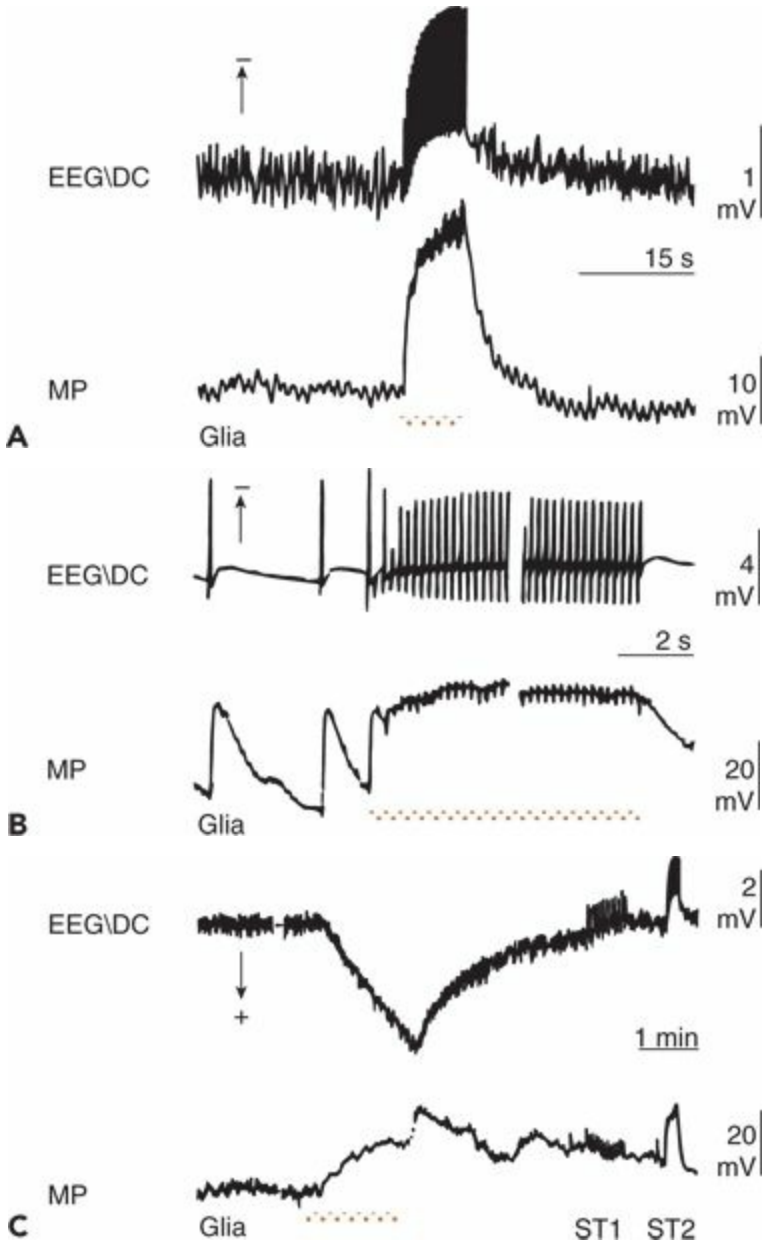


Figure 6.11. Simultaneous recordings of the electroencephalogram (EEG) potential performed with a direct current (DC) amplifier (EEG/DC) at the surface of the cerebral cortex and of the membrane potential (MP) of glial cells in an anesthetized and artificially ventilated rat. **A:**High-frequency electrical stimulation of the cortical surface (horizontal bar) is indicated. **B:**Focal epileptic activity induced by penicillin is indicated. Repetitive cortical stimulation (horizontal bar) increased the frequency of epileptic discharges (interruption, approximately 5 seconds). **C:**Increase of the local partial pressure of carbon dioxide (PCO_2) during apnea (horizontal bar) is shown. ST1 and ST2, low- and high-frequency electrical stimulation of the cerebral cortex, respectively. Depolarization of glial cells can be associated with both a positive **(C)** and a negative **(A** and **B)** shift in the EEG/DC. (**A** adapted from Caspers H, Speckmann E-J, Lehmenkühler A. DC potentials of the cerebral cortex. Seizure activity and changes in gas pressures. Rev Physiol Biochem Pharmacol. 1987;106:127–178; **B** adapted from Speckmann E-J. Experimentelle Epilepsieforschung. Darmstadt, Germany: Wissenschaftliche Buchgesellschaft; 1986; and **C** adapted from Caspers H, Speckmann E-J, Lehmenkühler A. Electrogenesis of slow potentials of the brain. In: Elbert T, Rockstroh B, Lutzenberger W, et al., eds. Self-regulation of the Brain and Behavior. New York :

Springer; 1984:26–41, with permission.)

Glial cells contribute to the generation of field potentials, although this mechanism is not dominant. Thus, the original recordings of cortical EEG/DC and membrane potentials of cortical glial cells demonstrate that glial depolarization occurs parallel to negative (see Fig. 6.11A and B) and positive (see Fig. 6.11C) baseline shifts of field potentials. On the whole, field potential changes can be thought to be generated primarily by neuronal structures (16,31).

BASICS OF EPILEPTIC FIELD POTENTIALS

As described, field potentials recorded during epileptic activity are based on changes in neuronal membrane potential. The amplitudes of field potentials exceed those of nonepileptic potentials because the underlying neuronal activity is highly synchronized. As a result of the synchronization, the activity of a single element represents that of the entire epileptic population. On that basis, changes in field potentials and neuronal membrane potential can clearly be related to one another (12,35–39).

Figure 6.12 shows typical recordings of epicortical EEG and of the membrane potential of a neuron in upper cortical layers. During the development of epileptic activity, flat depolarizations superimposed by APs appear first. These membrane potential changes evolve into typical paroxysmal depolarizations that consist of a steep depolarization triggering a burst of APs, a plateau-like diminution of the membrane potential, and a steep repolarization followed by an afterhyperpolarization or an afterdepolarization. With the appearance of the epileptic neuronal depolarizations, negative fluctuations of the local field potential develop. As Figure 6.12 shows, a close temporal relationship exists between development of the intracellularly recorded membrane potential and the extracellularly generated field potentials. Later, the duration and amplitude of the neuronal depolarizations and of the negative field potentials increase and reach a final level. The transition from epileptic to normal activity is also associated with a parallelism between field potentials and membrane potential changes. Thus, the epileptic negative field potentials represent the activity of an epileptic neuronal network (35–37,39).

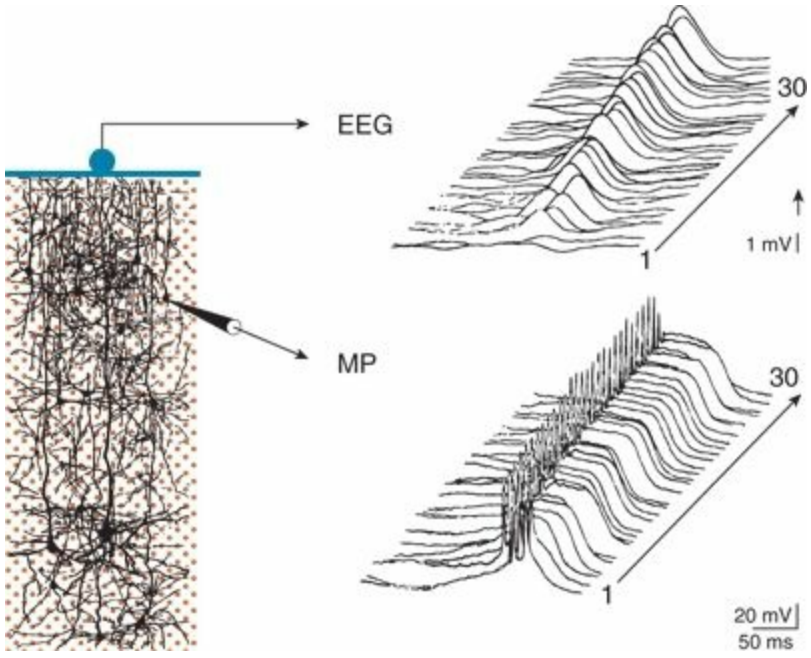


Figure 6.12. Simultaneous establishment of paroxysmal depolarizations of a neuron in superficial cortical layers and of sharp waves in the electroencephalogram at the cortical surface during development of an epileptic focus. Focal epileptic activity was induced by local

penicillin application. MP, membrane potential. Graphic superposition of 30 successive potentials with the commencement of focal epileptic activity is shown. (Adapted from Elger CE, Speckmann E-J. Vertical inhibition in motor cortical epileptic foci and its consequences for descending neuronal activity to the spinal cord. In: Speckmann E-J, Elger CE, eds. Epilepsy and Motor System. Baltimore, MD: Urban & Schwarzenberg; 1983:152–160, with permission.)

Epileptic foci can induce evoked potentials (EP) in nonepileptic areas (Fig. 6.13). In Figure 6.13A, two cortical columns generate epileptic activity, as indicated by the neuronal paroxysmal depolarizations and the concomitant negative spikes in the EEG. The epileptic activities at both sites are not necessarily synchronous. In Figure 6.13B, only one column is epileptically active. The epileptic discharges elicit synaptic potentials in the neighboring nonepileptic area. The synchronized burst discharges induced in the nonepileptic column then give rise to "epileptic evoked potentials."

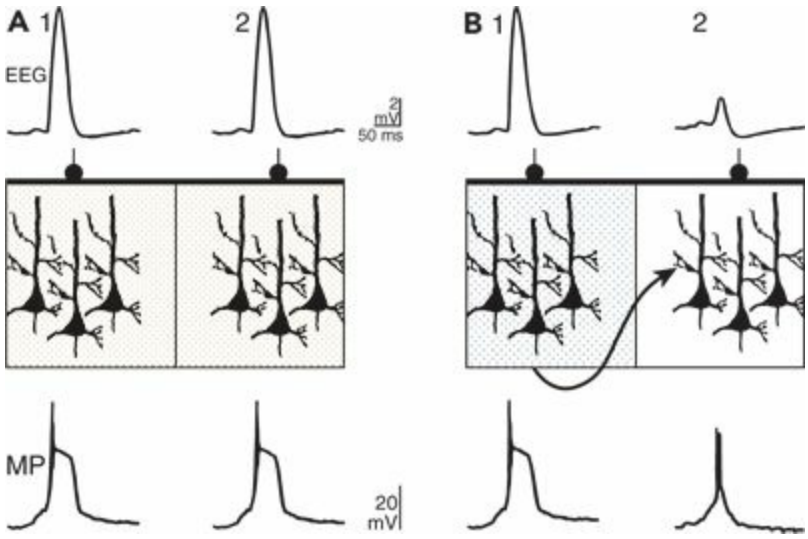


Figure 6.13. Electroencephalographic waves at the cortical surface representing locally generated **(A1** and **A2** and **B1)** and synaptically transmitted **(B2)** epileptiform neuronal discharges. Cortical columns with (hatched areas) and without (open area) locally generated epileptic activity are shown. Both **A1** and **A2** potentials represent directly epileptiform neuronal depolarizations. The potential in **B1** represents directly epileptiform neuronal discharges, and that in **B2** represents indirectly epileptiform discharges in the primary nonepileptic neighboring column, that is, a potential synaptically evoked by the epileptically active neurons (arrow). MP, membrane potential.

FIELD POTENTIALS WITH FOCAL EPILEPTIC ACTIVITY

For practical reasons, the description of field potential generation with focal epileptic activity takes into account the functional significance of an epileptic focus, especially motor phenomena (12,35,38,40,41).

The relationship between epileptic field potentials in motor cortical areas and their output to the spinal cord is detailed in Figure 6.14. In Figure 6.14A, the epicortical EEG spike is associated with a defined high-amplitude spinal field potential, indicating synchronized descending neuronal activity. These events result finally in muscular clonus. Superficial EEG potentials and spinal output are not always closely related, however. Each of these motor phenomena may be present without the other (see Fig. 6.14B and C) (42–47).

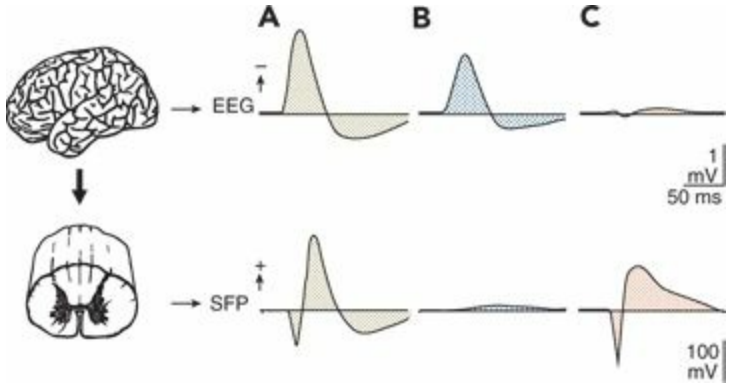


Figure 6.14. Dissociation in occurrence of epileptiform potentials on the surface EEG and of spinal field potentials (SFPs). Focal epileptiform activity was restricted to motor cortical layers. **A:**Simultaneous appearance of cortical and spinal activity is indicated. **B:**Presence of cortical activity and failure of spinal activity are shown. **C:**Failure of cortical activity and presence of spinal activity are shown. (Adapted from Elger CE, Speckmann E-J, Prohaska O, et al. Pattern of intracortical potential distribution during focal interictal epileptiform discharges (FIED) and its relation to spinal field potentials in the rat. Electroencephalogr Clin Neurophysiol. 1981;51:393–402, with permission.)

The aforementioned discrepancies between superficial EEG potentials and cortical output can be clarified by recording field potentials from within the cortex. In Figure 6.15, the superficial EEG was recorded simultaneously with intracortical field potentials at three depths, including layer V, and with spinal field potentials. With positive field potentials in layer V, spinal field potentials are missing (see Fig. 6.15A and B). Synchronized motor output appears only when the typical epileptic negative spike occurs in layer V (see Fig. 6.15C). In all these cases, the EEG spikes at the cortical surface are identical (42–44,46,47).

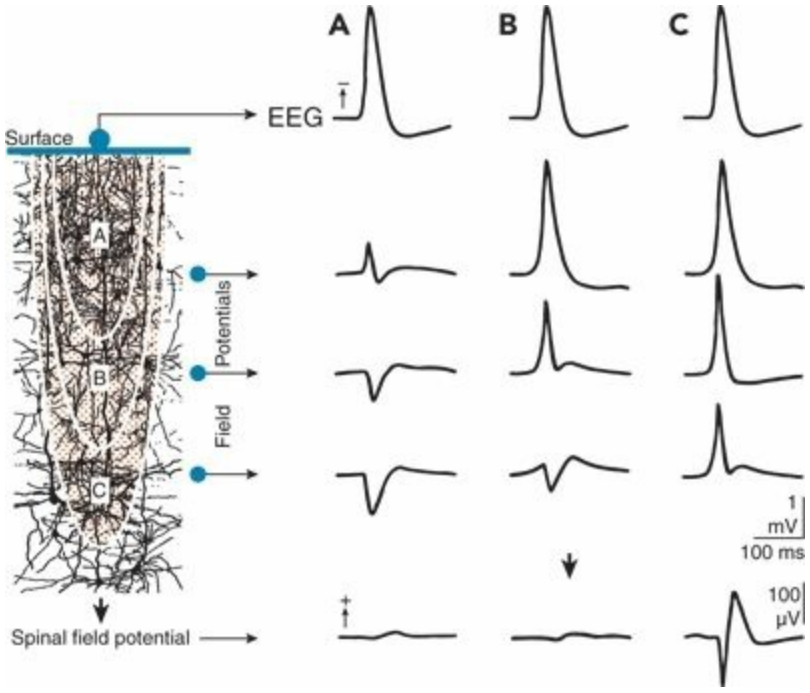


Figure 6.15. Epicortical (electroencephalogram), intracortical, and spinal field potentials during focal epileptiform activity. The actual vertical extension of the focus is indicated on the left and related to the tracings by letters. The occurrence of synchronized spinal field potentials is linked to the appearance of negative field potentials in lamina V **(A–C)**. (Adapted from Elger CE, Speckmann E-J, Caspers H, et al. Focal interictal epileptiform discharges in the cortex of the rat: laminar restriction and its consequences for activity descending to the spinal cord. In: Klee MR, Lux HD, Speckmann E-J, eds. Physiology and Pharmacology of Epileptogenic Phenomena. New York: Raven Press; 1982:13–20, with permission.)

The situations presented in Figure 6.15A and C are shown at the level of intracellular recordings in Figure 6.16. The positive field potentials in layer V parallel long-lasting and highly effective neuronal inhibitions, and the negative field potentials at the same site are based on typical neuronal paroxysmal depolarization shifts. Thus, the synchronized excitation of pyramidal neurons in layer V is a prerequisite for epileptic motor output. This excitation is not necessarily reflected in the superficial EEG, however (see Fig. 6.14C). Epileptic motor reactions based on a cortical focus may occur without appropriate signs on such a recording (43,44,46–48).

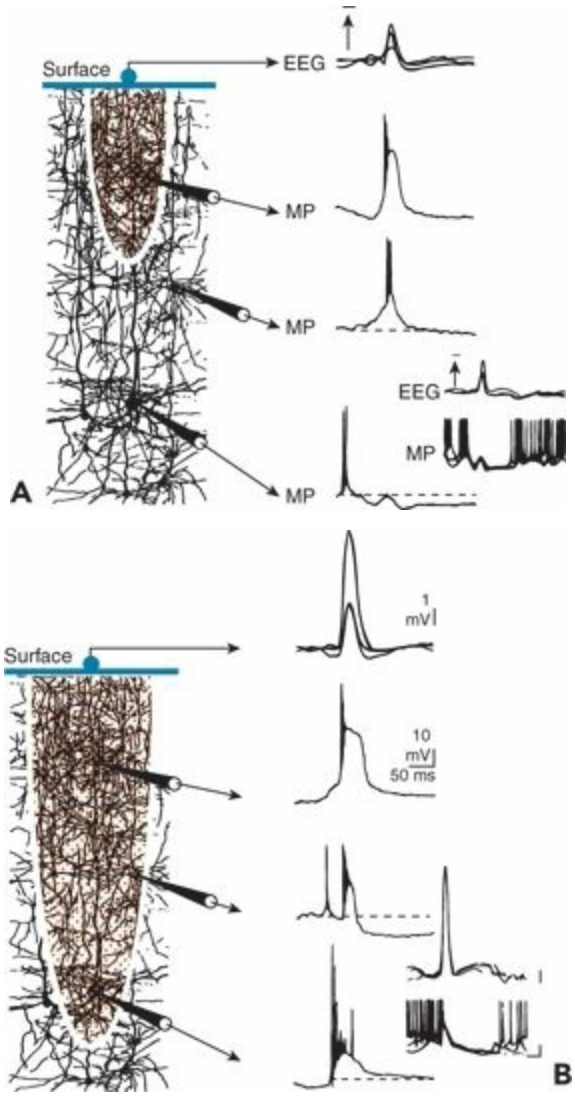


Figure 6.16. Membrane potential (MP) changes of single neurons in layers of the motor cortex during focal epileptic activity with different vertical extensions. Epileptic activity was recorded 5 **(A)** and 15 **(B)** minutes after local application of penicillin to the cortical surface. The drawings indicate vertical extension of the focus. The MP changes were recorded simultaneously with the electroencephalographic changes, which are superimposed to show the relationship of the curves to each other. **Insets:** Shown are three superimposed superficial electroencephalographic and deep MP recordings. (Adapted from Speckmann E-J. Experimentelle Epilepsieforschung. Darmstadt, Germany: Wissenschaftliche Buchgesellschaft; 1986:122, with permission.)

The difference between bioelectrical activity at the cortical surface and in deeper cortical layers becomes very clear when voltage-sensitive dyes are used instead of field potential recordings (49–51). With this technique, neuronal activity can be seen, although the requirements for the generation of field potentials are not fulfilled (cf. Fig. 6.7).

FIELD POTENTIALS WITH GENERALIZED

TONIC–CLONIC ACTIVITY

Observations made during tonic–clonic seizures in experimental animal studies are used to explain the generation of field potentials during generalized seizures. After repeated injections of pentylenetetrazol, typical tonic–clonic seizures appear (Fig. 6.17) accompanied by field potential changes consisting of baseline shifts and superimposed rapid waves. The latter allow the differentiation between the tonic and clonic phases (see Fig. 6.17C) (12,35–38,41).

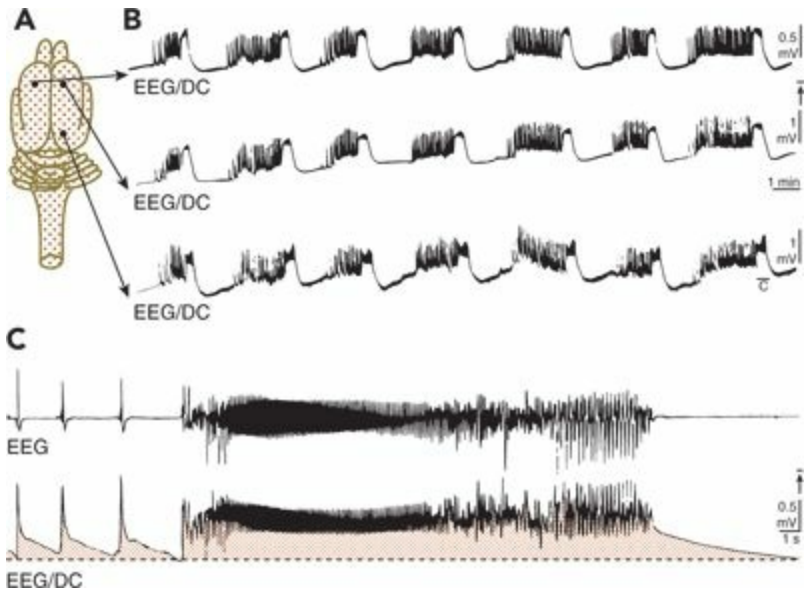


Figure 6.17. Experimental animal model of generalized tonic–clonic seizures elicited by repeated systemic administration of pentylenetetrazol. **A:** The recording arrangement is shown. **B:**Simultaneous recordings of the epicortical direct current (DC) potential from the motor regions of both hemispheres and from an occipital area are presented. **C:**Part **C** in **B** is displayed as a conventional electroencephalogram (EEG) and EEG/DC potential with an extended timescale. (Adapted from Speckmann E-J. Experimentelle Epilepsieforschung. Darmstadt, Germany: Wissenschaftliche Buchgesellschaft; 1986:69, with permission.)

Baseline Shifts (Electroencephalogram/Direct Current)

Figure 6.18 shows the relationship between baseline shifts of field potentials, from both surface and deep recordings, and membrane potential changes of pyramidal neurons in layer V. During tonic–clonic seizures, a series of paroxysmal depolarizations occurs in pyramidal tract neurons. This means that neuronal depolarization parallels a negative shift of the baseline of field potentials on superficial and deep recordings. The close temporal relationship can be discerned also on recordings with an extended timescale. Although the bioelectrical events are similar, discrepancies exist in the commencement of seizures and in the postictal phase. With seizure onset, a monophasic negative shift always occurs on deep recordings of field potentials. In contrast, the superficial EEG/DC findings can start with a monophasic negative or positive as well as a biphasic negative–positive fluctuation. In the postictal period, deep recordings always show a positive displacement of the baseline of field potentials and superficial recordings a negative displacement. Comparison of the different simultaneous recordings of field potentials and membrane potential reveals the following findings: The initial negative fluctuation and the postictal positive displacement of the field potential in deeper layers correspond, respectively, to the initial highly synchronized depolarization and to the postictal hyperpolarization of pyramidal tract neurons. This close correspondence is missing when superficially recorded EEG/DC shifts and neuronal membrane potential changes are compared. Thus, the mean neuronal activity is well represented in the baseline shift of deep field potentials. As far as

the superficial field potentials are concerned, additional generators, for example, glial networks, must be taken into account (14–16,18,52–54).

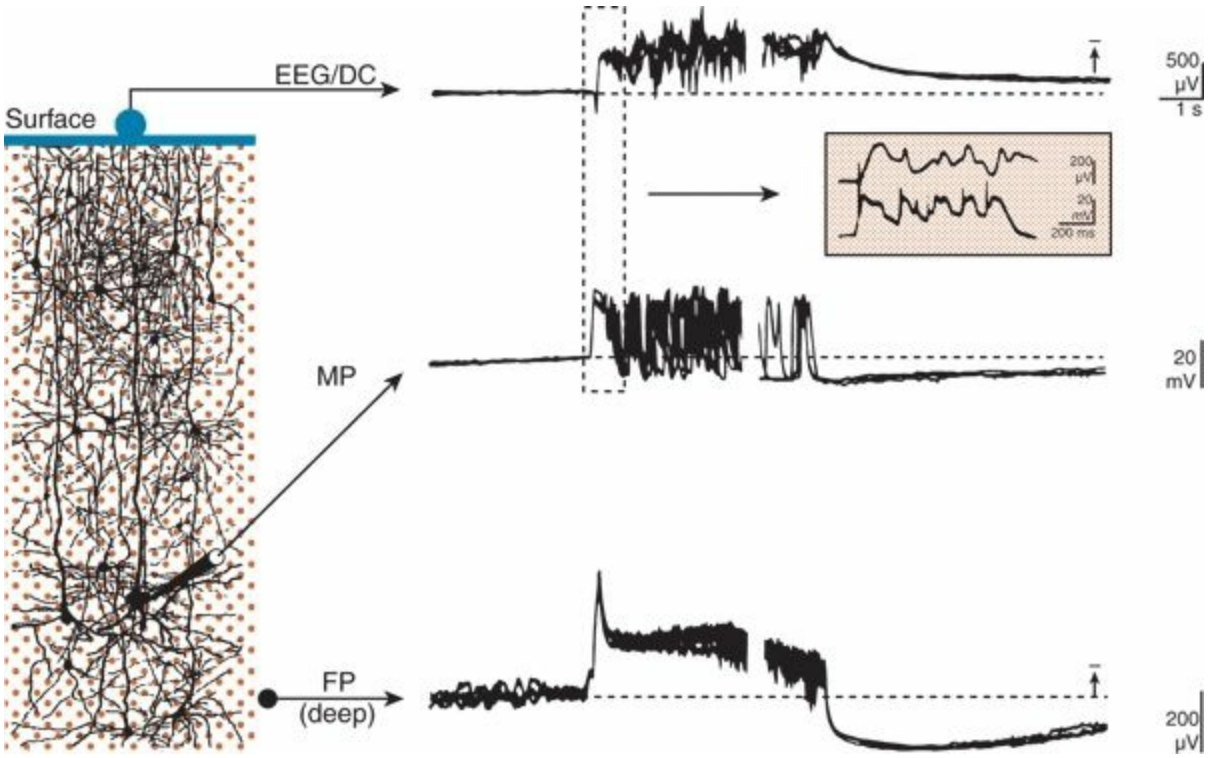


Figure 6.18. Relationship between shifts of the epicortical (electroencephalogram [EEG] performed with a direct current [DC] amplifier [EEG/DC]) and laminar field potentials (FPs) and changes in the membrane potential (MP) of a pyramidal tract cell during tonic–clonic seizures (inkwriter recordings with graphic superpositions). Epileptic activity was elicited by repeated systemic administrations of pentylenetetrazol. Interruptions were 30 to 60 seconds. **Inset:** Shown are parts of the EEG/DC and MP recordings displayed on an oscilloscope with an extended timescale.

Waves (Conventional Electroencephalogram)

The rapid waves superimposed on the baseline shifts of the EEG/DC can best be interpreted when the afferent impulse inflow to the upper cortical layers is evaluated. Figure 6.19 represents a cortical column with a perpendicularly oriented neuron. An afferent fiber forms an excitatory synapse in upper dendritic regions. The discharge frequency of the afferent fiber was recorded simultaneously with the surface EEG/DC. For further description, three types of waves were selected: monophasic negative (see Fig. 6.19A), monophasic positive (see Fig. 6.15C), and biphasic positive–negative (see Fig. 6.19B) waves. With the commencement of negative waves, the discharge rate increased from a low initial level (see Fig. 6.15A and B); during positive waves, the discharge rate decreased from a high level (see Fig. 6.19C). Thus, the generation of superficial waves can be explained as resulting from facilitation (negative waves) and disfacilitation (positive waves) of neuronal structures in upper cortical layers (20,22–24,40,46,47).

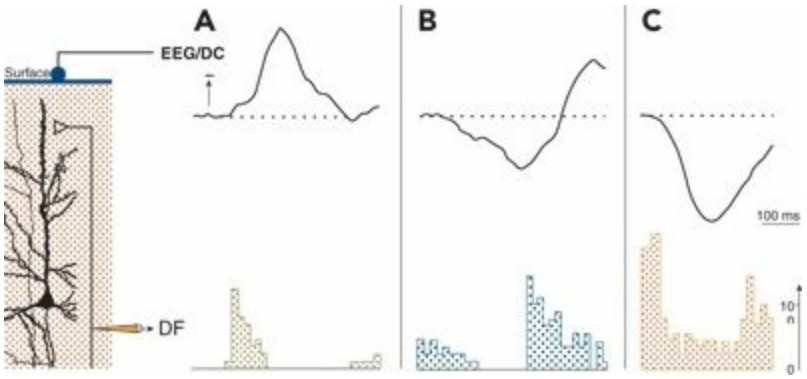


Figure 6.19. Relationship between different patterns of fluctuations of the epicortical field potential (electroencephalogram [EEG] performed with direct current [DC] amplifier [EEG/DC]) and changes in discharge frequency (DF) of neuronal elements in superficial cortical layers during tonic–clonic seizures. Epileptic activity was elicited by repeated systemic administrations of pentylenetetrazol. Up to 16 single events were averaged: monophasic negative **(A)** and positive **(C)**, as well as biphasic positive–negative **(B)**, fluctuations of EEG/DC. N, number of action potentials. (Adapted from Speckmann E-J. Experimentelle Epilepsieforschung. Darmstadt, Germany: Wissenschaftliche Buchgesellschaft; 1986:143, with permission.)

CORRELATIONS OF MEMBRANE POTENTIAL CHANGES IN A NEURONAL POPULATION AND OF EEG SIGNALS

In addition to electroencephalography, there is a variety of other methods for detecting brain activity. Among these, single photon emission tomography, positron emission tomography, functional magnetic resonance imaging, and intrinsic optical imaging are based on metabolic changes associated with increases of local neuronal activity. Besides the latter "very indirect" methods, EEG including EP and magnetoencephalography represent "more direct ones" since they measure the field effects of the proper neuronal activity and therewith of the information processing brain activity. For the analysis of neuronal network functions, the immediate and simultaneous recording of membrane potentials of all neurons in a population by application of voltage-sensitive dyes is the "only direct" method available yet (49–51,55–57). Without doubt, all these methods have advantages and disadvantages. Thus, the functional imaging using voltage-sensitive dyes cannot be applied in patients for several reasons, for example, prerequisite of direct access to the brain structure to be investigated, photo toxicity, and pharmacologic side effects of the dyes. But this method is helpful to analyze the functional meaning of field potentials in living human brain slices in vitro, especially with spontaneously occurring epileptic discharges.

Principle and schematic example of recording neuronal membrane potentials using voltage-sensitive dyes are displayed in Figures 6.20 and 6.21. The living brain slices are stained with fluorescence (or absorption) dyes (A1 in Fig. 6.20). With depolarization and hyperpolarization, the fluorescence is decreased and increased, respectively (A2 and A3 in Fig. 6.20). The changes in fluorescence are measured via a microscope by an array of detectors and therewith the actual membrane potentials of the neurons are observed (B1 and B2 in Fig. 6.20).

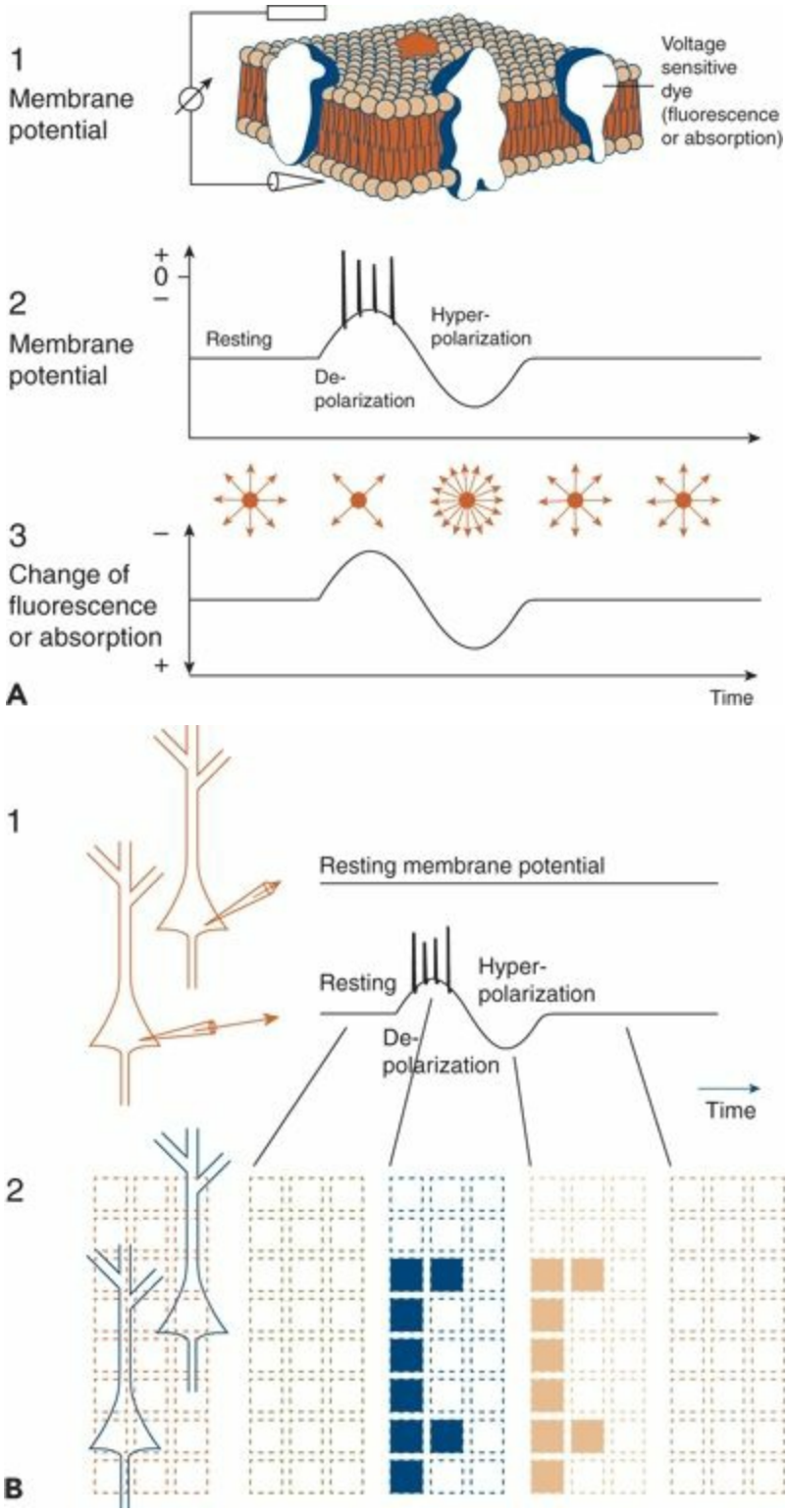


Figure 6.20. Recording of neuronal membrane potentials using voltage-sensitive dyes, principles and schematic example of application. **A:**(1) A dye is incorporated into the double lipid membrane of nerve cells and illuminated by light with dye-specific wavelength; simultaneously, the membrane potential is recorded with an intracellular microelectrode against a reference electrode in the extracellular space. (2) Changes of the membrane potential (MP) starting from the resting level passing a decrease (depolarization) with APs superimposed and a subsequent increase (hyperpolarization) and eventually returning to resting level. (3) In correspondence to the different MP levels, fluorescence and absorption of the dye changes. With fluorescent dyes, a depolarization is associated with decrease and a hyperpolarization with an increase of fluorescence (symbols). **B:**(1) Two neurons in a population; one stays in the resting state, the other changes its MP as in A (2). (2) By the aid of a microscope and a connected array of diodes (squares), the different MP changes of both neurons can be detected via the different optical behaviors. (Adapted from Speckmann E.-J. Das Gehirn meiner Kunst—Kreativität und das selbstbewusste Gehirn. Münster, Germany: Daedalus; 2012:176, with permission.)

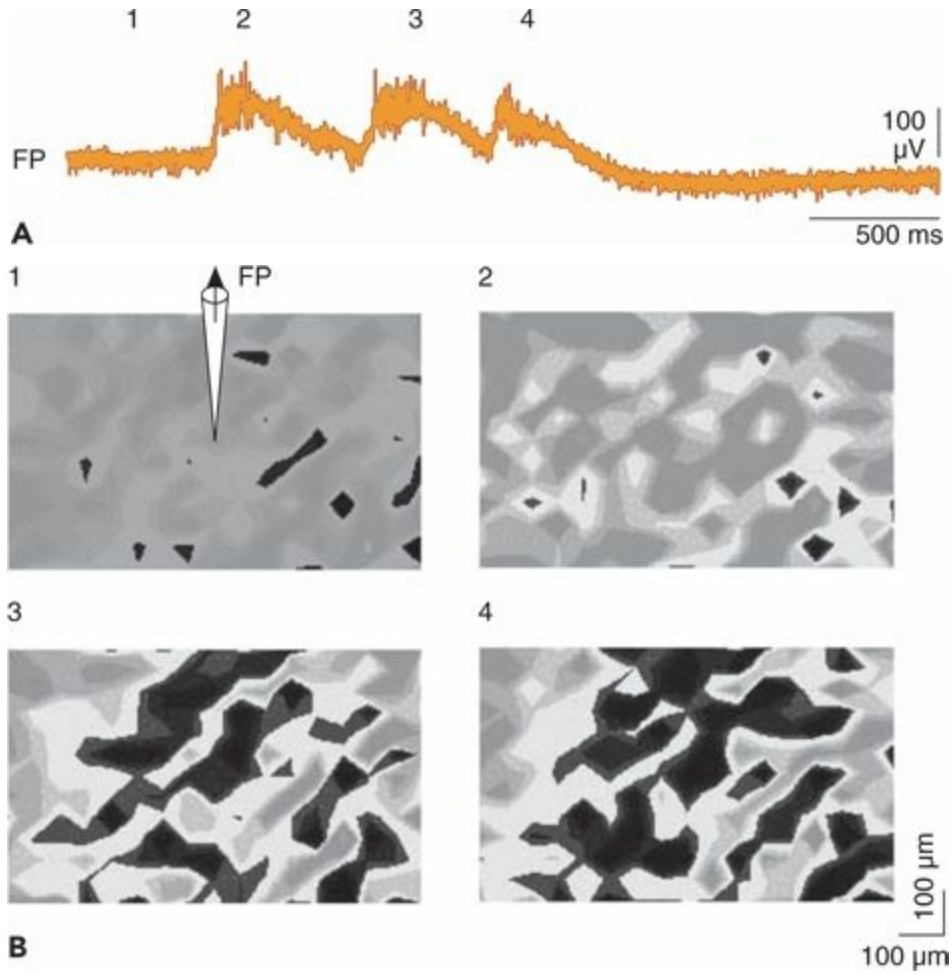


Figure 6.21. Simultaneous detection of membrane potentials (MP) of all neurons in a population (voltage- sensitive dye) and conventional recording of the local field potential (FP) at the same time. Living brain tissue (0.5 mm thick) from the temporal lobe of a patient who underwent epilepsy surgery. **A:**Recording of the local FP ("local EEG"). (1) Resting state, (2–4) epileptic discharges of different intensities. Epileptic discharges appeared spontaneously, that is, they were not induced experimentally. **B:**MP changes indicated by the intensity of fluorescence of the dye (black = decrease of the MP, depolarization). Similar epileptic potentials in the FP (2 and 3) are associated with different extents of neuronal depolarizations and similar extents of neuronal depolarizations with different epileptic potentials in the FP (3 and 4). (Adapted from Speckmann E.-J. Das Gehirn meiner Kunst—Kreativität und das selbstbewusste Gehirn. Münster, Germany: Daedalus; 2012: 176, with permission).

The method of simultaneous measurement of neuronal membrane potentials of all neurons in a population is successfully applied in living human brain slices (0.5 mm thick) in vitro obtained from neurosurgical interventions (tumor and epilepsy surgery) (49–51,58,59).

A comparison of the field potentials, that is, the local EEG, and of the neuronal membrane potentials detected by the aid of voltage-sensitive dyes is given in Figure 6.21. The tissue is a slice preparation from the temporal neocortex resected from a patient suffering from pharmacoresistent complex partial seizures. Most of these living human brain slices show spontaneous epileptic EEG potentials, that is, epileptic discharges not induced by experimental procedures. One can derive the following from the recordings:

1. During epileptic discharges, only a certain portion of the neurons in the population is active simultaneously, that is, a complete synchronization is missing (Fig. 6.21, numbers 2 through 4).
2. Similar epileptic potentials in the EEG (Fig. 6.21, numbers 2 and 3) are associated with different extents of neuronal depolarizations and similar extents of neuronal depolarizations with different epileptic potentials in the EEG (numbers 3 and 4).

CONCLUSION

Changes of neuronal activity associated with net current flows in the extracellular space produce field potentials. In clinical practice, a synchronization of the activity of neuronal elements is needed to recognize signals. As seen in superficial and deep potential fields, field potentials are generated in functionally different structures and may be based on different elementary mechanisms. Field potentials at the cortical surface, for example, can be interpreted in a variety of ways because they are not constantly related to neuronal activity in deep cortex.

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CHAPTER 7 LOCALIZATION AND FIELD DETERMINATION IN ELECTROENCEPHALOGRAPHY

RICHARD C. BURGESS

LOCALIZATION AND MAPPING

The word "electroencephalogram" (EEG) is derived from Greek roots to create a term meaning an electrical picture of the brain. While interpreting an EEG, electroencephalographers maintain a three-dimensional picture of the brain/head in their minds. In principle, there are an infinite number of different source configurations of an electrical event within the head that may give rise to the same electrical field distribution at the scalp. Despite this theoretical constraint, one of the key functions of the electroencephalographer is to conceptualize the generators in relationship to this vision and to build an increasingly clear mental image of the foci of these generators. Methods for localization and field determination are tools to help the electroencephalographer infer the location, strength, and orientation of generator sources within the cortex, based on their manifestation at 21 or more EEG recording sites.

Scalp electrical activity arises from both physiologic and pathologic brain generators. Localization of epileptiform potentials from scalp EEG is critically important to pinpoint the epileptic focus and identify the region of brain pathology (1). Many electroencephalographers have taken a simplistic approach, assuming that the generator source must be close to the point where the maximum voltage is recorded. Attempts to systematize the localization of specific EEG activity date back to the early years of electroencephalography. In the mid-1930s, Adrian and Matthews (2) as well as Adrian and Yamagiwa (3) employed phase reversal techniques to localize normal rhythms, and Walter (4) used phase reversals for localization of abnormal EEG activity, as did Gibbs and Gibbs (5) in 1941 in their classic atlas. More recently, a variety of reviews have outlined general principles for the use of polarity, montages, and localization (5–11). It should be emphasized that phase reversals are not inherently an indicator of abnormality. Phase reversals occur as a result of both normal and abnormal activities. Phase reversals are most obvious for sharply contoured transient activity and therefore in the case of epileptiform abnormalities provide a dramatic visual clue.

Despite the critical importance of accuracy in localization, there has been an absence in the literature of descriptions of systematic methods for accomplishing this localization in a simple, manual fashion (12,13). Most textbooks emphasize the distribution that would occur as a result of an assumed generator (i.e., the "forward" problem). With the evolution of digital EEG (14), a variety of methods for computerized source localization have become available (15,16) at the push of a button within the EEG machine itself or as stand-alone software (17,18). These techniques are model based and have significant limitations; they have generally not been employed in routine clinical practice. A

practical guide for the step-by-step identification of the origin of epileptiform activity has been developed at the Cleveland Clinic Foundation (19) and is covered in some detail here.

The principles of source localization apply to any type of brain electrical activity; however, this review concentrates primarily on defining the electrophysiologic origin of epileptiform activity. While epileptologists generally rely heavily on the location of interictal discharges in the workup of patients leading up to epilepsy surgery (20,21), the relationship of the irritative zone (as manifest by interictal spikes) to the epileptogenic zone (identification of which is obviously crucial for surgical success) has been the subject of much debate (22,23). Nevertheless, the majority of the points covered in this review are illustrated using interictal spikes.

There are two steps in the interpretation of epileptiform discharges: surface field determination and source localization. Proper determination of the electrical field results from knowledge of the electrode positions and head shape and has only one answer. Accurate field determination is essential not only for accurate source localization but also for discrimination of epileptic activity from other nonepileptic transients. For source localization, on the other hand, no single unique solution exists. In order to arrive at a plausible solution for the source location, several assumptions are useful. In this chapter, practical neurophysiologic concepts that relate the generator to the surface electrical fields are described in the first section. Then, the next three sections describe important conventions used in visual interpretation of EEG regarding instrumentations, the field determination, and the source localization. Lastly, the application of computer-based techniques that aim to assist in the localization problem is briefly discussed.

PRACTICAL CONCEPTS OF ELECTRICAL FIELDS APPLIED TO BRAIN GENERATORS

Sources

The electrical activity recorded during an EEG is a scalp representation of the current dipoles generated by the underlying intracranial local field potentials (24–28). These intracranial sources, either focal dipoles or sheets of dipoles, represent the postsynaptic potentials originating from vertically oriented neurons. A unit current dipole is created by the intercellular laminar currents in the apical dendrites arising from the pyramidal cells in the outer layer of the cerebral cortex. Specifically, superficial excitatory postsynaptic potentials and deep inhibitory postsynaptic potentials generate almost all spontaneous EEG activities (29), particularly the epileptogenic abnormalities. When populations of neurons are more or less synchronously activated for relatively long durations, the activity can be macroscopically recorded from a certain distance as a linear summation of the unit dipoles (26–28). This summated activity may also be represented as a dipole or sheet of dipoles along the cortex. Thus, the generator of epileptic activity can be explained by a single or multiple equivalent current dipoles (8,13,30,31). The surface potential can be thought of as a two-dimensional projection or shadow of a complex three-dimensional electrical object residing inside the head.

Fundamental to scalp localization is the concept of the “inverse” problem, which entails an estimate, based on surface data, of the magnitude, location, and distribution of electrical fields throughout the brain. Whereas the forward problem is solvable with unique solutions, the inverse problem is not. The mathematical representation of the biophysics underlying volume conduction is covered by Nunez (9).

The forward problem can be stated as follows: Given known charge distributions and volume conductor geometries and properties, predict the resulting surface potential distribution. The solution involves applying numerical or analytical methods for any known set of geometries and boundary conditions (9,32) to solve the linear Poisson equation:

$$\nabla^2\Phi = -\frac{\rho}{\varepsilon}$$

where ∇^2 is the second spatial gradient operator, Φ is the scalar potential in volts, ρ is the free charge density, and ε is the permittivity of the mass of tissue. Multiple sources can be shown to combine linearly, so that a combination of sources results in the arithmetic sum of the potential distributions that each would produce individually.

The corresponding inverse problem can be stated as follows: Given a surface potential distribution and the volume conductor geometries and properties, determine the underlying charge distribution. Unfortunately, a given surface map can be produced by any of an infinite number of possible source distributions. EEG records at a distance from the sources and employs only a limited number of sensors—typically 20 to 30 in a routine scalp EEG. Therefore, this problem generally has no unique solution (33). Nevertheless, simplifying assumptions are usually made: (i) The source dipole is near the surface; (ii) the source dipole is perpendicular to the surface; (iii) the head is a uniform, homogeneous volume conductor; (iv) at least one recording electrode is essentially over the source; and (v) the reference is not contained in the active region.

On the basis of these assumptions, one generally looks for a single predominating potential maximum on the surface, with the source lying directly below it; however, a variety of nondipolar source configurations could produce the same observation. For example, a simple monopolar charge buildup, a curved dipole sheet, or a finite-thickness dipole "pancake" would all produce a single well-defined maximum. In addition, signals originating from confined but deep-seated generators will be broadly distributed when recorded from the surface (34,35), and these cannot be reliably distinguished from more superficial but widespread epileptic regions.

In addition to these "equivalent" source possibilities, others are physiologically similar but generate very different surface maps. Through variations in orientation and shape, dipole sheets can produce charge reorientation and cancellation. The resultant range of possible scalp distributions serves as a reminder that observed scalp maxima do not necessarily lie directly above maximal brain activity. Jayakar et al. (36) have pointed out the difficulties in localizing epileptic foci on the basis of simple models, owing to effects from dipolar orientation, anatomic variations, and inhomogeneities, among other factors.

Volume Conduction

In a volume conductor, the electrical field spreads instantaneously over an infinite number of pathways between the positive and negative ends of the dipole. Outside the neuron, the circuit is completed by the current flowing through the extracellular fluid in a direction opposite to the intracellular current. Through the process of volume conduction, electrical activity originates from a local field generator and spreads through a conductive medium to be picked up by a distant recording electrode. Volume conduction is passive—that is, it does not involve active regeneration of the signal by intervening neurons or synaptic relays—and occurs as easily through saline as through brain parenchyma. Potentials recorded by way of volume conduction are picked up synchronously and at

the speed of light at all recording electrodes. Although attenuated with distance by the medium, volume-conducted components preserve their original polarity and morphology.

The attenuation factor is defined by the inverse square law: That is, the recorded electrical potential falls off in direct proportion to the square of the distance from the generator (37,38). For example, a 100-μV potential seen at the electrode directly overlying a cortical generator (assume a distance of 1 cm away) will be reflected as a 4-μV potential at an electrode that is 5 cm away and as only a 1-μV potential at 10 cm away. The rapidity of this falloff is a function of the depth of the generator, with more superficial generators falling off much more rapidly. Distant generators have a "flat" falloff, one of the hallmarks of a "far-field" potential (Fig. 7.1).

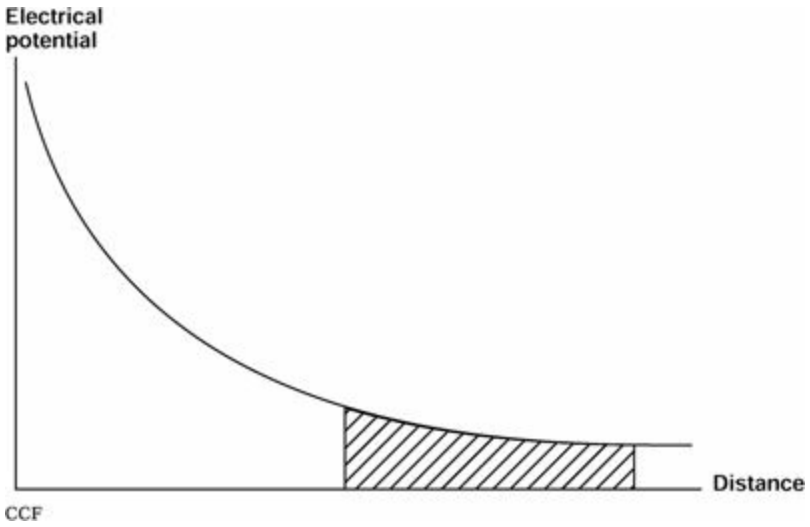

Figure 7.1. The electrical potential recorded by an electrode decreases in a parabolic fashion the farther away from the source it is. The difference recorded between two electrodes close to the source (near-field potentials) will be greater than the differential recordings from the tail of the curve. These far-field potentials (in the shaded region) are also lower in absolute amplitude.

The medium through which current travels to reach the recording electrode is not homogeneous but rather exhibits a variety of conductivities (39). As the current attempts to complete its circuit by following the path of least resistance, these differences in conductivities, especially differences among cerebrospinal fluid (CSF), skull, and scalp, and their associated boundaries, affect the electrical potential recorded on the scalp. The signal is not only altered in amplitude but is also stretched out during its passage to the surface because of the spatial summation and shunting effects of the intervening layers. In the skull, the conductivity in a tangential direction is higher than in a direction perpendicular to the surface. This produces a "smearing effect" on the surface potential distribution (40). Although the current tends to flow along the path of least resistance, there is still some flow throughout the volume conductor, thereby permitting recording of the electrical potential at all sites on the volume conductor, albeit with the amplitude inversely related to the square of the distance from the source (see Fig. 7.1).

The head also contains normal or abnormal openings that present low-resistance paths to conducted currents. The current tends to flow toward skull defects, whether physiologic (such as foramina) or acquired through trauma or surgery, and around cavities (such as the ventricles), markedly distorting the field in the region of the defect. The resistivity of scalp or brain tissue is many times smaller than that of bone (41–43). As a result, surface potentials near these openings will be unusually high, and the largest potentials can be seen at the location of the defect even when the source is several centimeters away from the defect (40,44,45).

Surface Electrical Manifestations

A variety of real-world considerations complicate the interpretation of surface recordings. Because the dipoles measured at the scalp ordinarily are oriented radially, scalp electrodes see primarily the positive or the negative pole—but usually not both. Although generators located at the apex of a gyrus lie perpendicular to the scalp (i.e., vertical dipoles), any generator within a cortical fissure will present a dipole at an angle to the scalp. Nearly 70% of the cortical surface lies within the sulcal depths (46). In addition, many brain areas—most notably the mesial frontal, parietal, occipital, and basal temporal cortex—are diversely oriented and lie at varying distances from surface electrodes. Hence, it is not sufficient to assume that the generator must be close to the point where the maximum potential is recorded (7). Finally, the choice of reference affects the form of the EEG measurements.

When a generator dipole is oblique or parallel to the scalp, the resulting surface potentials can lead to false localization of the potential maximum. The typical bell-shaped distribution of the electrical field is replaced by one shaped like a sideways "S" in this circumstance. Because both the positive and the negative ends of the dipole may be recorded at the scalp, the surface potential can exhibit two "maxima" of opposite polarity. Between the two ends will be a zero isopotential boundary where the generator will not be picked up at all (Fig. 7.2).

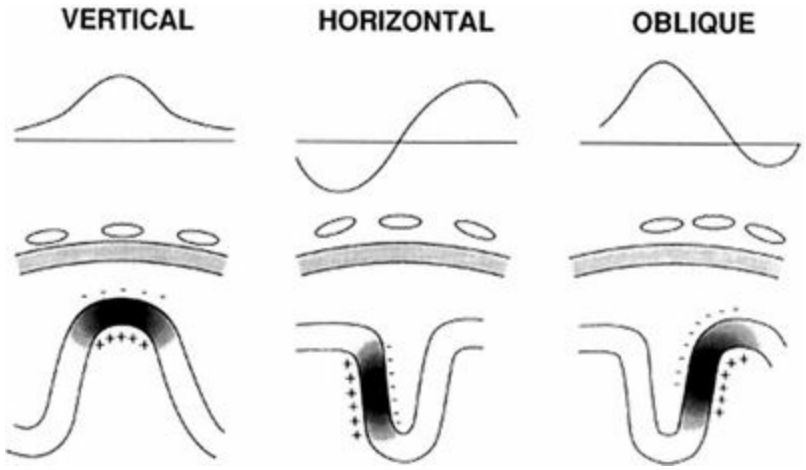

Figure 7.2. There are unusual sources wherein both the negative and the positive poles are recorded on the surface. The bottom row of figures shows a patch of cortex containing gyri and sulci. The darker areas represent the cortical mantle that is activated by an epileptic discharge, with negative and positive poles highlighted. In the middle row of illustrations, the positions of the electrodes on the scalp, relative to the discharging cortex, are shown. The top row illustrates the voltage that would be recorded on the EEG as a function of the distance along the scalp right below it.

It is important to distinguish true horizontal dipoles, such as those arising at a sulcus or the interhemispheric fissure, from field distributions resulting from widely separated activity but giving rise to distinct negative and positive maxima. For example, bisynchronous temporal spikes differing slightly in phase, such that the negative component on the left aligns with the positive component on the right, may appear to represent huge transverse dipoles (36); however, careful evaluation with an alternative reference (or the demonstration that the spikes also occur asynchronously) can prove that the fields represent not the source and sink of a single dipole but rather two generators (47) linked by corticocortical propagation.

When a source lies deeper in the brain, two changes occur: The surface potential becomes smaller and the field becomes more widespread relative to the surface maximum (34,35,48). Although the shape of the electrical field gradient can indicate the type of field and the distance of the

generator, identifying the source on the basis of the potential difference between any scalp electrodes becomes increasingly difficult. When the potential field gradient is relatively flat, as is the case in the far-field potential from a deep-seated source, a bipolar montage will display the waveform at relatively smaller amplitude (see Fig. 7.1). Diffuse discharges may be better appreciated on referential montages, assuming that the reference is not involved. An adequate "vantage point" may be impossible with surface electrodes when the focus is deep. It may be impossible to find a scalp electrode reference that is not electrically involved in the active region, and some cases can only be resolved by invasive electrode placements that can monitor more limited areas (see Chapter 82) (32,49–52).

The combination of multiple sources can produce a variety of results. A superficial source can overshadow a deep one, distorting or even hiding it. Because the amplitude of a measured potential is inversely proportional to the square of the distance from the recording electrode, nearby sources can appear significantly higher at the recording electrodes. A given electrode thus has a "view" of the nearby generators, such that dipoles that combine to reinforce each other will have a large net effect, whereas those that cancel will produce a smaller or null potential (53).

Complicating this problem is the fact that the equivalent dipole is an abstraction. In reality, only sources that extend over multiple layers of several square centimeters of cortical tissue have sufficient energy to generate detectable scalp discharges (48,54). An epileptogenic zone almost always consists of a continuum of dipoles, resulting in a sheet or "patch" (55) dipole. Such a source may cover an extended brain region, with the constituent areas lying at various depths and orientations. Since each surface electrode has a three-dimensional cone of pick-up, both reinforcement and cancellation are possible to produce a variety of surface potential distributions. Overall, the conduction phenomena leading to surface potentials follow the "solid-angle" rule (56), that is, the net surface potential is proportional to the solid angle of the cone subtended by the recording electrode, that is, $V_{electrode} = V_{source}\ (\Omega/4\pi)$. Unless a dipole sheet parallels the surface, the maximum surface potential may be elsewhere than directly over the affected area, as illustrated in Figure 7.3. The solid angle theorem helps to explain the results of multiple synchronously discharging pyramidal neurons arrayed over a cortical region containing both sulci and gyri.

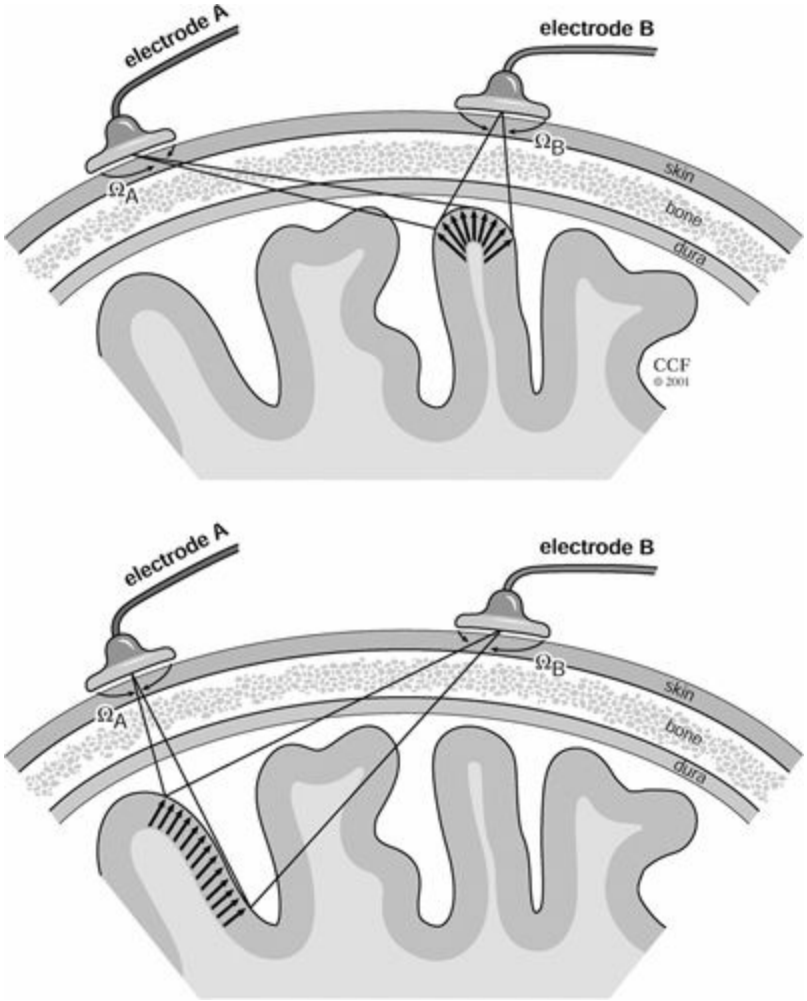

Figure 7.3. Use of the solid-angle rule to ascertain the signal measured on the scalp surface relative to the orientation of the dipole. **Top:**Surface electrode B sees a large electrical potential because of the orientation and proximity of the dipole layer, as borne out by the solid angle Ω_B. **Bottom:**: In this case, the potential seen by electrode A is actually lower than that measured by the more distant electrode B because of the arrangement of the dipoles in the discharging region. The smaller solid angle, Ω_A, is proportional to the voltage measured on the scalp.

In the same way that opposing dipoles can cancel each other relative to a distant electrode, a sheet of nonparallel dipoles can produce a "closed" field (57) whose potential contributions will cancel, resulting in a negligible potential at the surface (58). These generators, usually not visible on scalp EEG, are observed primarily on invasive recordings (53). Even when not a completely closed field, multipolar source–sink configurations tend to produce more cancellation than dipolar generators and to attenuate more quickly as a function of distance (9). This irregular structure is particularly likely in the basal and mesial areas of the temporal cortex and the hippocampus, where cortical infolding is so prevalent (59).

The head consists of a series of roughly concentric layers that separate the brain from the scalp surface. Each of these layers—CSF, meninges, bone, and skin—presents different electrical characteristics to the currents that conduct the EEG to the surface. These layers occasion considerable current spreading, which causes the potential from localized foci to appear in a much broader scalp area (9,60). Spreading in itself would not be an insurmountable problem, because it is theoretically possible to recover deep dipole sources based on observed surface potentials, using appropriate mathematical transformations. Such recovery, however, is guaranteed only in a perfectly spherical concentric conductor, onto which electrodes can be placed in any location. The head is not a perfect globe, however, and significant constraints disqualify the face or neck, which may be preferred for

certain sources, as electrode sites.

Electrode Placement as Spatial Sampling

Placement of scalp electrodes should be considered an exercise in spatial sampling. Electrode density must be generous enough to capture the available information but not so closely spaced as to overwhelm with redundant data. Inability to precisely locate a cortical generator may be the result of spatial undersampling ("aliasing"). The assumption that a potential will decrease monotonically as distance increases from the involved electrode is based not only on an uncomplicated electrical field, that is, a monopole (61), but also on an electrode placement sufficiently dense to accurately represent the spatial contours of the field. Cooper et al. (54) suggested that at least 6 cm^2 of cortex discharging simultaneously is required to reflect a visible potential on the scalp surface, and more recently, it has been suggested that the required area for surface detectability is even larger, based on simultaneous intracranial and scalp EEG recordings (22,62). Because most epileptogenic potentials seen on the scalp are visible at multiple electrodes, a considerably larger cortical area must be synchronously discharging to produce these potentials (24).

Especially controversial is the detectability of spikes generated in the mesial temporal lobe. Some authors believe that scalp EEG recording of deep sources is possible (63), while others have found it impossible to record spikes from the mesial temporal structures (64,65). Sphenoidal electrodes provide a significantly better view of the mesial area, as shown in Figure 7.4, and are frequently employed in epilepsy monitoring units.

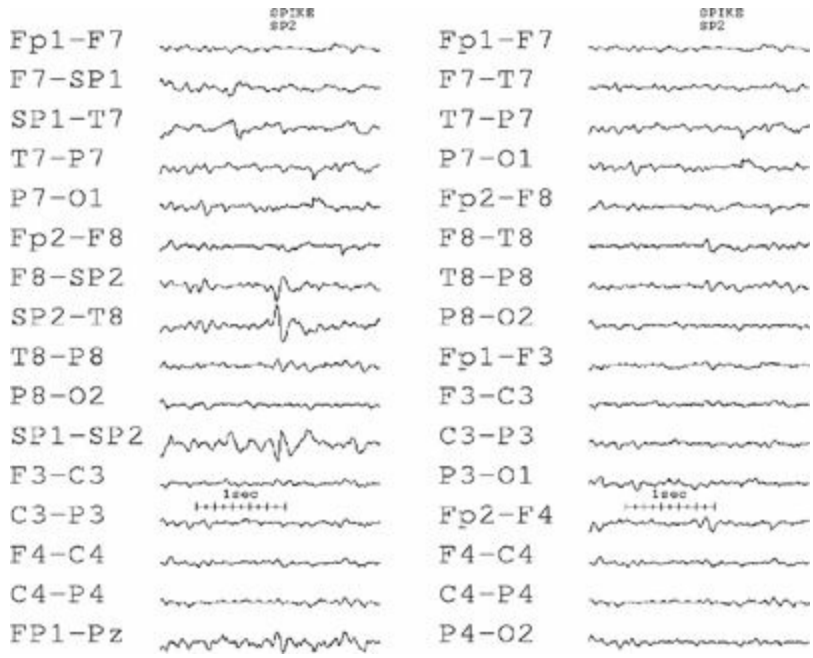

Figure 7.4. This EEG shows an example of a spike that is highly focal in the right sphenoidal electrode. Note that in the conventional double-banana longitudinal montage without the sphenoidals, this discharge is almost invisible.

The widely accepted International 10–20 Electrode Placement System (66), although relatively easy to apply reproducibly, has some inherent limitations in terms of the accuracy of localization (67). When more precise localization is indicated to avoid spatial aliasing, scalp electrodes should be placed at least once every 2.5 cm (68). The maximum spacing can be determined theoretically (24) as well as experimentally, and as many as 128 electrodes (spaced approximately 2 cm apart) may sometimes be necessary (69).

Boundary Problems

Regardless of the fineness of the scalp electrode grid, boundary effects will occur at the edges of the array. The maximum potential must be well within the scope of the recording electrodes to ascertain that a physiologic gradient exists away from the electrode. For example, epileptic sharp waves arising from mesial temporal structures are frequently localized outside the area covered by the 10–20 placement (70–73). It is impossible to determine the complete extent of the maximum fields unless the area is surrounded by regions of lesser activity. Recordings in which the activity is large all the way to the boundary of the region defined by the montage must be "remontaged" to include, if possible, all the relevant electrodes, or further recording must be carried out with additional electrodes. This may be especially complicated when it is difficult to position electrodes inferior to the customary borders of scalp coverage.

A significant portion of the head cannot be practically surveyed, and important brain areas such as the basomesial temporal cortex and other deep sources are only indirectly accessible with standard scalp electrodes. Additional electrodes inferior to the 10–20 system (66) must be employed to provide a better view. In certain circumstances, the information obtained from a combination of closely spaced scalp electrodes such as the international 10–10 system (74–76) and sphenoidal electrodes can obviate the need for more invasive recordings (77).

EEG INSTRUMENTATION CONSIDERATIONS RELATED TO LOCALIZATION

Differential Amplifiers

Amplifiers used in clinical neurophysiology measure the difference between two potentials at the inputs to the amplifier and provide an amplified version of this difference at the output. These devices, called differential amplifiers, eliminate unwanted signals that are identical at both inputs, called common-mode signals. The two terminals at the input to a differential amplifier are sometimes labeled G1 and G2, recalling when a screened "grid" within the vacuum tube amplifier controlled the flow of electrons from cathode to plate. Modern opamp-based differential amplifiers employ complex integrated circuits, and the terms "input 1" and "input 2" are used throughout this chapter.

The amplifier itself has no concept of polarity; it simply does the subtraction and the gain multiplication and then provides an output voltage that is a linear function of the input voltages, according to the following equation:

$$V_{output}(t) = G \times \left[V_{input1}(t) - V_{input2}(t) \right]$$

where $V_{output}(t)$ and $V_{inputN}(t)$ are the output and input voltages, and G is the gain of the amplifier. Only during interpretation of the EEG waveform in the context of the underlying generators does the concept of polarity have any meaning. Inexperienced electroencephalographers often mistakenly ascribe a polarity at the input to a specific waveform deviation at the output (12). It should be remembered that there are no positive deflections and no negative deflections. There are only upward and downward deflections (12). Figure 7.5 illustrates four different input conditions that give rise to exactly the same deflection.

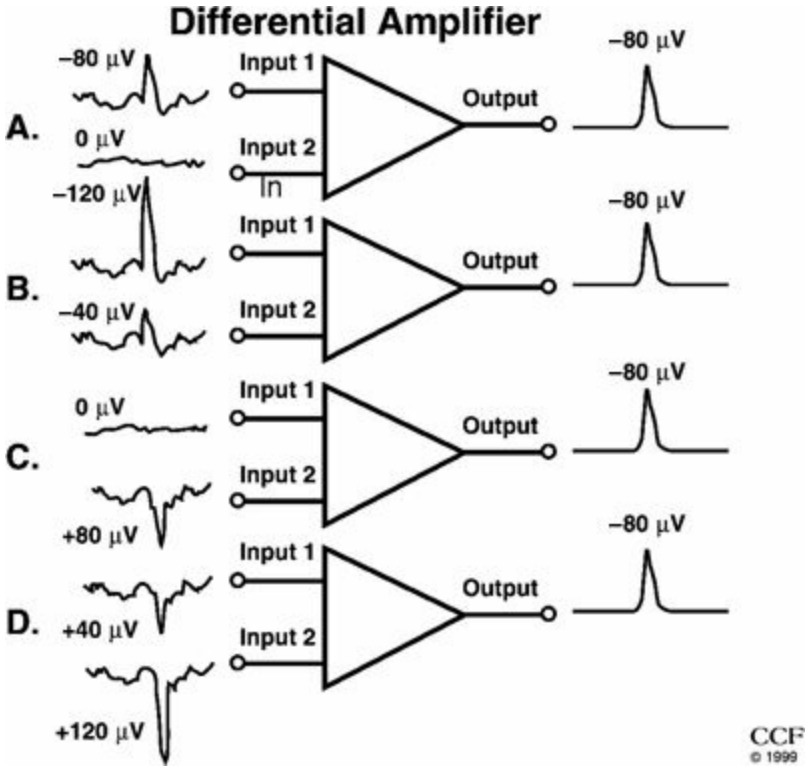

Figure 7.5. A and **B:**Illustrate a surface-negative spike. Input 1 is more negative than input 2. Because a differential amplifier responds only to the difference between the two inputs (input 1 – input 2), the spikes illustrated will yield identical output voltages; (−80) – (0) is the same as (−120) – (−40). The background electroencephalogram activity, because it is more widespread than the spikes and therefore almost the same at both inputs, is largely canceled out. In **(C)** and **(D)**, the spike is surface positive, that is, input 2 is more positive than input 1. The calculations (0) – (+80) and (+40) – (+120) both result in an answer of −80, and the background is still canceled out. All four circumstances yield identical outputs despite the differing amplitudes and polarities.

Polarity Conventions

Deflection refers to the vertical direction on the page or display screen in which the waveform component under study appears to go, and it is a function only of the display instrumentation. By EEG convention, upward deflections are caused by input 1 being more negative than input 2. Downward deflections are caused by input 1 being more positive than input 2 (78). These relationships imply nothing about the underlying polarity of the signals at inputs 1 and 2—only the polarity of their differences. When the name of electrode connected to input 1 is written above the deflection and the name of input 2 below, the deflection will point to the electrode with the “relative” negativity as has been done in Figure 7.6.

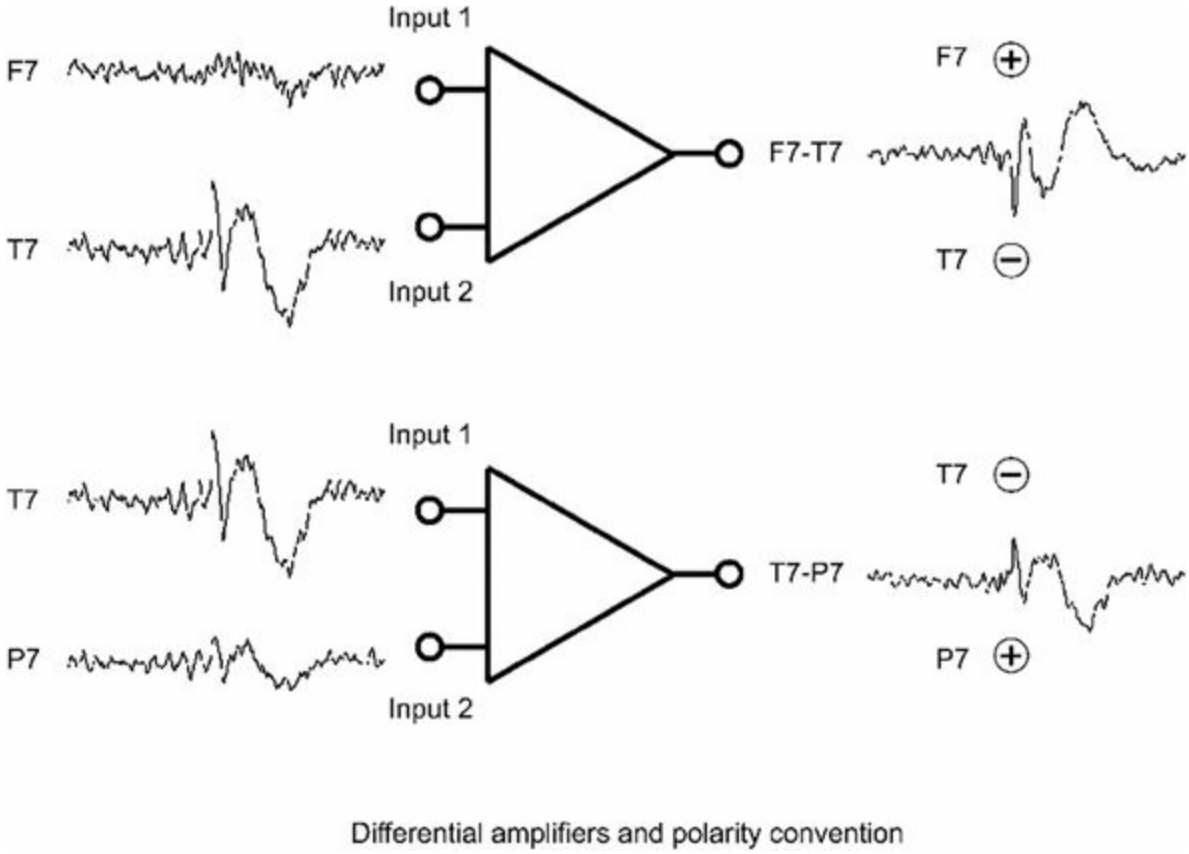

Figure 7.6. Differential amplifier and polarity conventions. The differential amplifier is designed to amplify only the difference between the signals at the two inputs. An upward deflection appearing at the output is caused by input 1 being more negative than input 2. A downward deflection results from input 1 being more positive than input 2. This convention is common to all clinical EEG machines. When the name of the electrode (i.e., its "derivation") connected to input 1 is written above the waveform and that connected to input 2 is written below as in this figure, the deflection always points to the electrode of higher "relative" negativity.

If the difference between the two signals at the input is 0, no deflection will occur. When two electrodes (no matter how close to the source of the sharp wave or spike) that lie along the same isopotential line (typically at the same distance from the generator) are input to a differential amplifier, the output will reflect no activity, even though both electrodes may be measuring high amplitudes in an absolute sense. Some amplifiers used in basic neurophysiology research and in clinical evoked potentials employ another convention, designed to display positive input 1 as an upward deflection.

Derivations and Montages

A derivation describes the connections of the electrodes to the amplifier inputs. A montage is a combination of derivations arranged down the EEG page to display many amplifier channels simultaneously in a way that aids in the identification and localization of abnormalities (79). Each amplifier could be connected to any pair of electrodes available. Likewise, these amplifier outputs could be arranged in any fashion on the screen; the arrangement in chains assists our visual localization capabilities.

The arrangement of derivations into a montage determines whether it is called bipolar or referential. Derivations in bipolar montages are established between neighboring electrodes to emphasize focal activity. They take advantage of the subtractive nature of differential amplifiers to effect a high degree of cancellation. Any montage can be analyzed to locate the maximum of a sharp wave or spike, provided that the montage has a logical order (6,80,81). It is convenient to link the

electrodes in a systematic "chain" of bipolar derivations. Because input 1 of each succeeding channel in the montage is the same as input 2 of the preceding channel, the electrodes are all electrically linked in a structured way and—more importantly—algebraically.

Bipolar montages are of maximum advantage when attempting to pick out localized potentials, as they help to cancel out more widespread activity. Bipolar montages are most logically arranged in a longitudinal or transverse direction. In a referential montage, the same electrode is connected to input 2 of every channel, while each channel has a different electrode connected to input 1. In contrast to bipolar montages, referential montages do a better job (as long as the reference is judiciously chosen) of picking up activity that has a more widespread distribution.

ELECTRICAL FIELD DETERMINATION ON THE SCALP

Identification of Peaks; Measurement of the Amplitude

Interictal epileptiform abnormalities are recognized by their morphology—an impression of "standing out" from the background—and by their electrical field distribution, which must demonstrate a realistic relationship between the electrical potentials at topographically associated electrode positions. In choosing an abnormality to localize, the peak selected must be representative of the patient's population of spikes, and the sample must be as clean as possible.

It is assumed that an activity starts from "zero" and reaches its maximum after a certain time. The amplitude of the activity is measured between the zero and the maximum peak. However, it is often difficult to identify the level of the "zero" in each EEG channel correctly, because the activity is superimposed on the background, arises from the noise level, or continues from the preceding activity. Sometimes sharp activity can be separated from a slower background, if the frequency of the epileptic activity is clearly different, by using filtering.

Practically, the amplitude is measured as peak to peak or baseline to peak. Identification of the baseline and peak may be particularly troublesome in the case of polyphasic discharges, in which each phase is brief and difficult to line up temporally. When analyzing a peak, the maximum value in each EEG channel should be identified at exactly the same time point. During visual analysis of a waveform, the montage selected will influence identification of the peak, resulting in different, or sometimes erroneous, field determinations. Multiple peaks or phase reversals with small time shifts reflect sequential change in the location of the maximum. In the EEG tracings shown in Figure 7.7, note that the peaks of several of the channels were reached on different phases of the waveform, giving the erroneous appearance of a phase reversal. Computerized source localization techniques are especially sensitive to the selection of the appropriate time frame. Errors in identifying the peaks that are to be mapped can cause extraordinary displacements in the apparent localization of the sources (82,83).

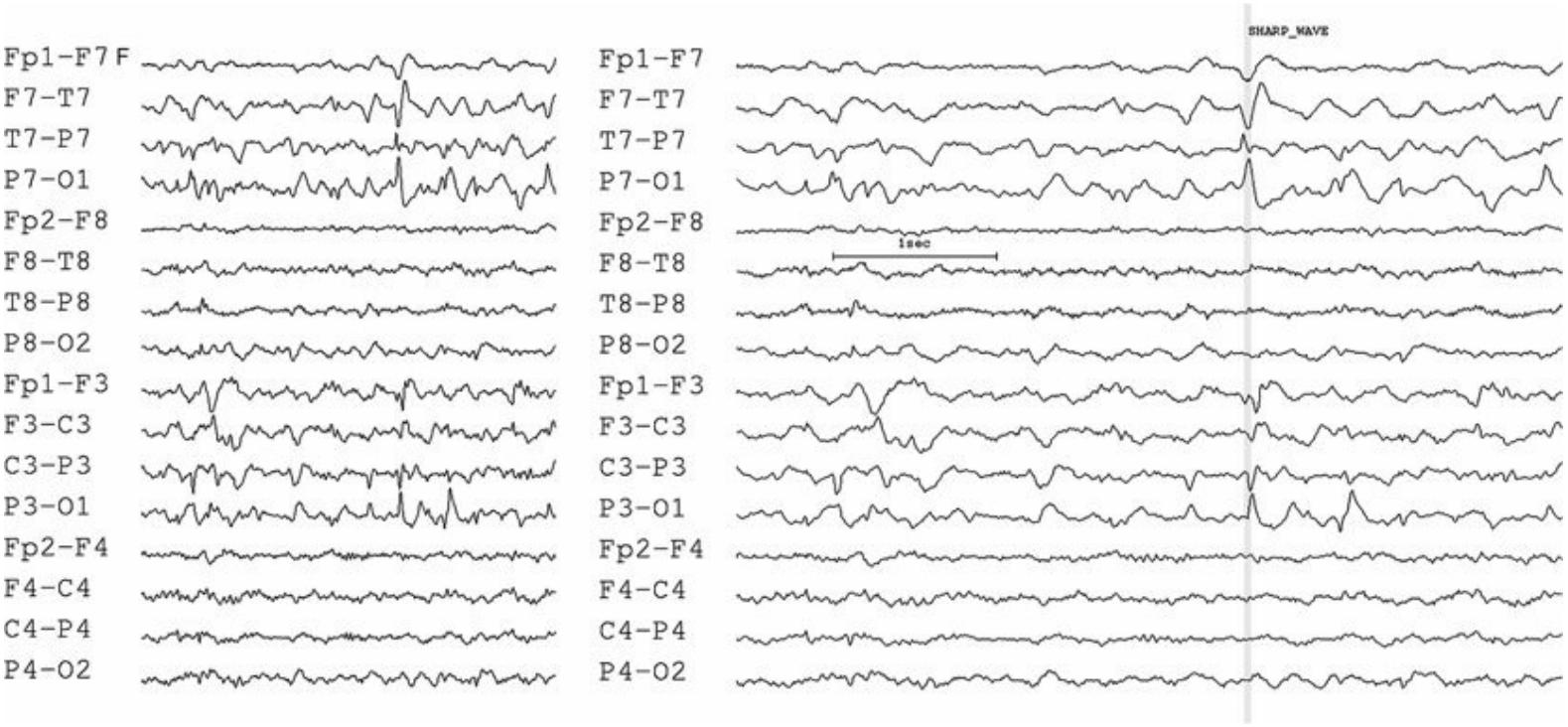

Figure 7.7. Phase reversals—choosing the same component. Be certain to select the proper phase of the discharge. The EEG on the left appears to show a confusing distribution, at first glance, with phase reversals at multiple sites. On the right, the timescale of the same epoch has been doubled. The vertical marker reveals that the discharge actually consists of three phases, with each peak at a slightly different time. The phase reversal at T_7–P_7 occurs prior to the phase reversal at P_3.

The peak of the sharp wave (i.e., the negative extrema) generally has the highest amplitude at the electrode closest to the involved cortical epileptogenic neurons (7). The main component of an epileptic discharge may be preceded by a smaller deflection of the opposite polarity. Early components show a more localized field than later ones (84,85), and they are more synchronous than the slow wave that frequently follows a spike. Thus, the initial deflection probably contains more localizing information (36), and employing the lower- frequency waves for localization may not always represent the epileptogenic region.

Mapping the Electrical Field

The two-dimensional display of the scalp regions involved in epileptiform or other activity is called mapping. Isopotential lines are drawn on a representation of the scalp to specify the topography of equivalent electrical potentials, similar to the isocontour lines drawn by a surveyor on a land map. From the area where the activity is maximum, succeeding regions that are further away will show a lower amplitude and can be divided into convenient isopotential contours. Because EEG amplitude is always measured with respect to a reference, the absolute amplitude will be dependent on the reference. But as shown in Figure 7.8, the shape of the contour distribution does not change with the reference.

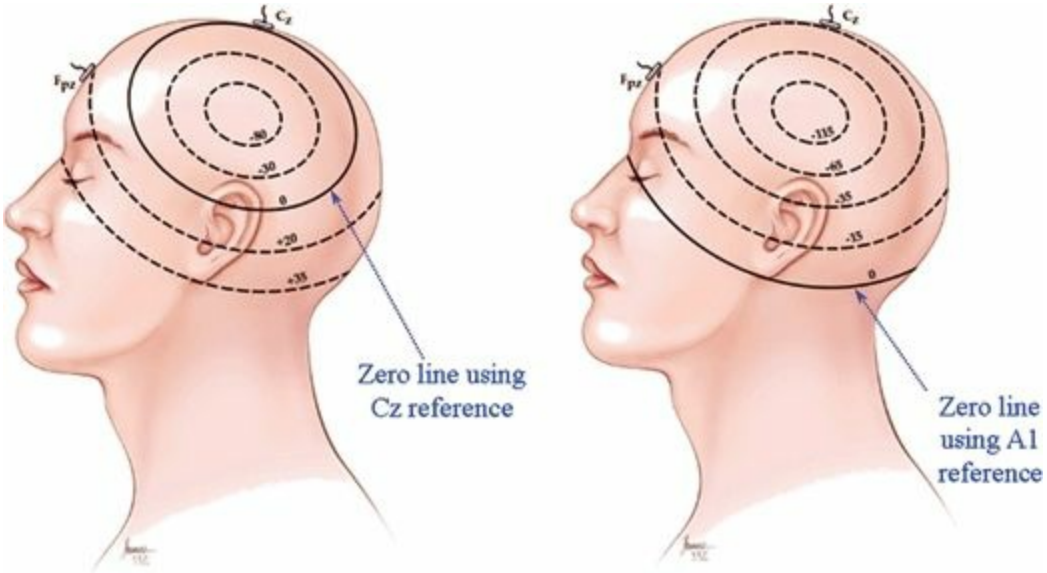

Figure 7.8. Topographical distribution of electrical potentials (in microvolts). EEG amplitudes are always measured relative to another reference. Note that the specific choice of reference electrode does not affect the shape of the isocontours of this left temporal discharge.

The potential fields of spikes and sharp waves can be mapped even without electronic assistance by tracking the relationships of the electrical potential level between electrodes. As the initial step, a longitudinal or transverse chain of the electrodes is used to map the one-dimensional relationship of voltage level to electrode position, as illustrated in Figure 7.9, top. Then, two chains are connected to each other through a common electrode to obtain the two-dimensional relationship. To create an isopotential contour map, a 100% value is assigned to the maximum and a 0% value is assigned to the minimum. However, as discussed later, the polarity of the maximum depends on an assumption about the generator. The "maximum" may be the highest negative point or the highest positive point. Similarly, the "minimum" may be negative or positive or may have a mid-curve value when two maxima of opposite polarity are assumed, for example, a horizontal dipole generator. Depending on the polarity of the maximum, that is, the point given a 100% value, at least two different isocontour maps can be obtained, as shown in Figure 7.10. To make the correct choice, some assumptions must be introduced, as described later.

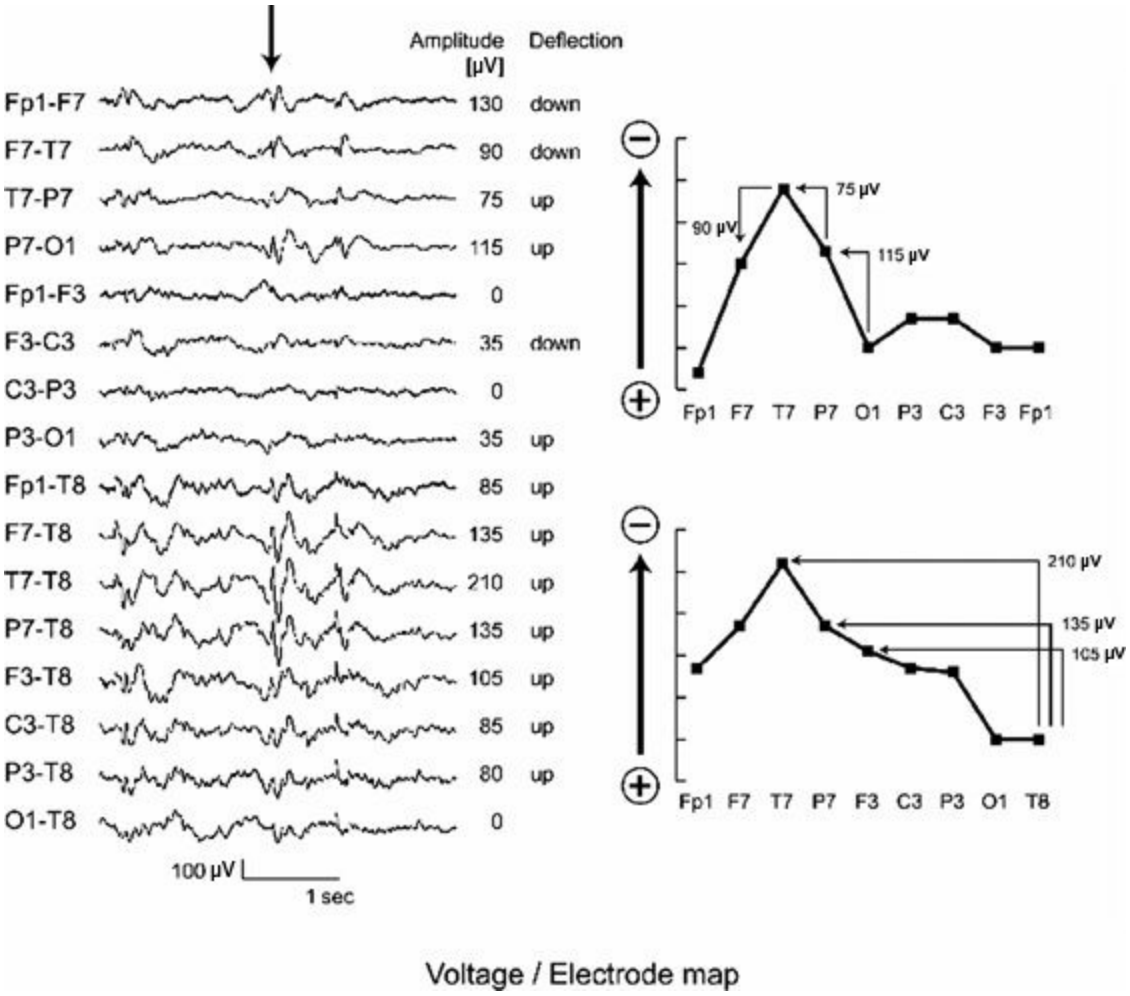

Figure 7.9. Voltage/electrode map. The EEG shows the same activity in two different montages: A bipolar montage in the top eight traces and a referential montage in the bottom eight. Two voltage/electrode maps for the spike indicated by the arrow are reconstructed manually from the two montages, respectively. In the bipolar montage, the difference of the potential level (amplitude) and relative polarity (deflection) between neighboring electrodes is sequentially tracked along the "chain" of the montage. Here, the potential mapping was started from a common electrode O_1 with a value of 0 μV assumed. Employing the algebraic relationships between the electrode derivations, the calculated amplitudes at each individual electrode are graphed. The resulting voltage level at Fp_1 differed slightly between the two bipolar chains, owing to minor differences in manual measurement of the amplitudes. For the referential montage, the measured amplitudes are written down directly, as no calculations are necessary. If all the deflections are in the same direction and the referential electrode (input 2) is located at the minimum, as seen in this example, then the amplitude of the deflection simply reflects the voltage level of the electrode. No matter which montage is used, the field determination should be same in terms of location of the maximum. The voltage/electrode maps may differ in detail, however, reflecting a varying degree of visibility of the spike between montages.

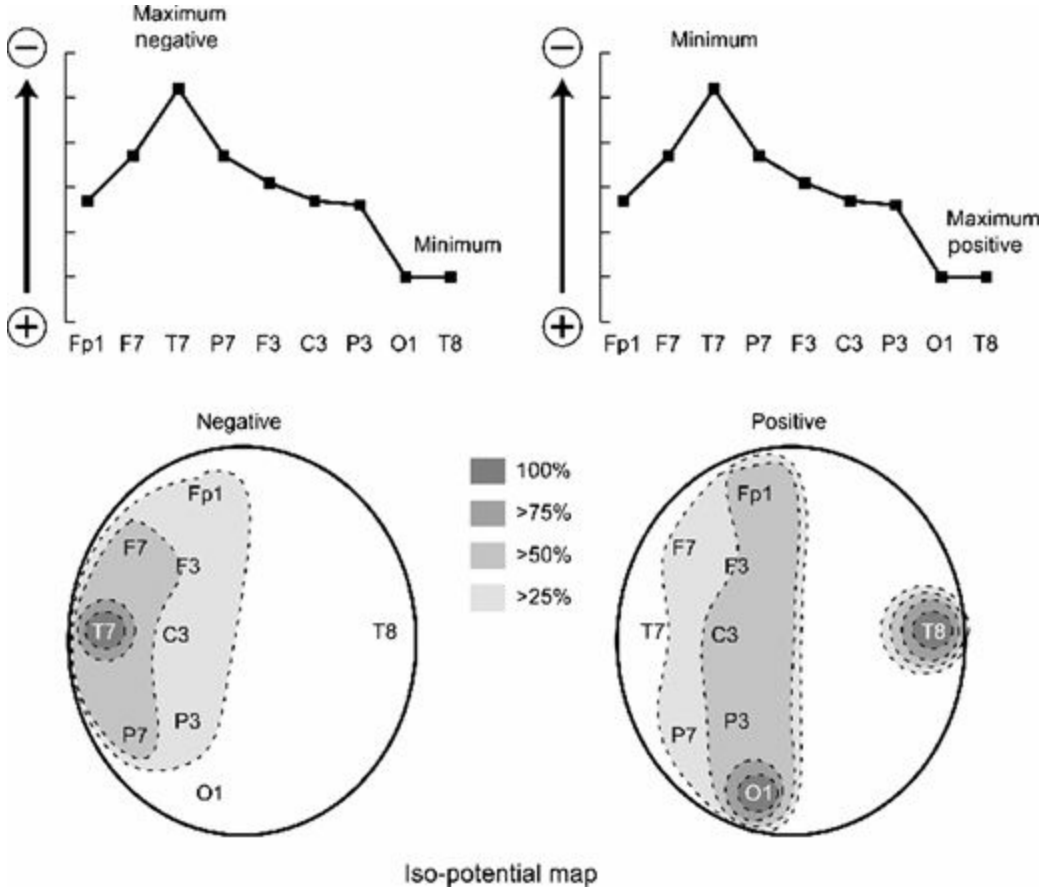

Figure 7.10. Isopotential map. As in Figure 7.9, the vertical axis of the top figures represents electrical potential, and the horizontal axis shows electrode location. A 100% value is assigned to the maximum, and a 0% value is assigned to the minimum. Depending on the polarity of the maximum, at least two different maps can be obtained, illustrated on the bottom row. In the map on the left side, the maximum is assumed to be negative, and the falloff of potential with distance is physiologic. On the right, the opposite assumption was made, that is, the maximum is a positive potential, resulting in a very unphysiologic distribution. Thus, it was deduced that this spike has maximum negativity from the left temporal area.

The ideal situation in referential recording occurs when the reference electrode is totally inactive or picks up activity of negligible amplitude. In this situation, those channels showing some activity will deflect in one direction only, as illustrated in Figure 7.9, bottom. The electrode closest to the generator will show the largest waveform deflection, and the amplitude of the deflection in all the other channels will be directly proportional to the magnitude of the activity recorded from each of those electrodes. This situation makes it especially easy to find the maximum and to assess the extent of the field distribution (see Fig. 7.9). To achieve this ideal situation, a contaminated reference must be recognized and a "distribution montage" constructed instead, typically with a reference electrode from the other hemisphere (Fig. 7.11).

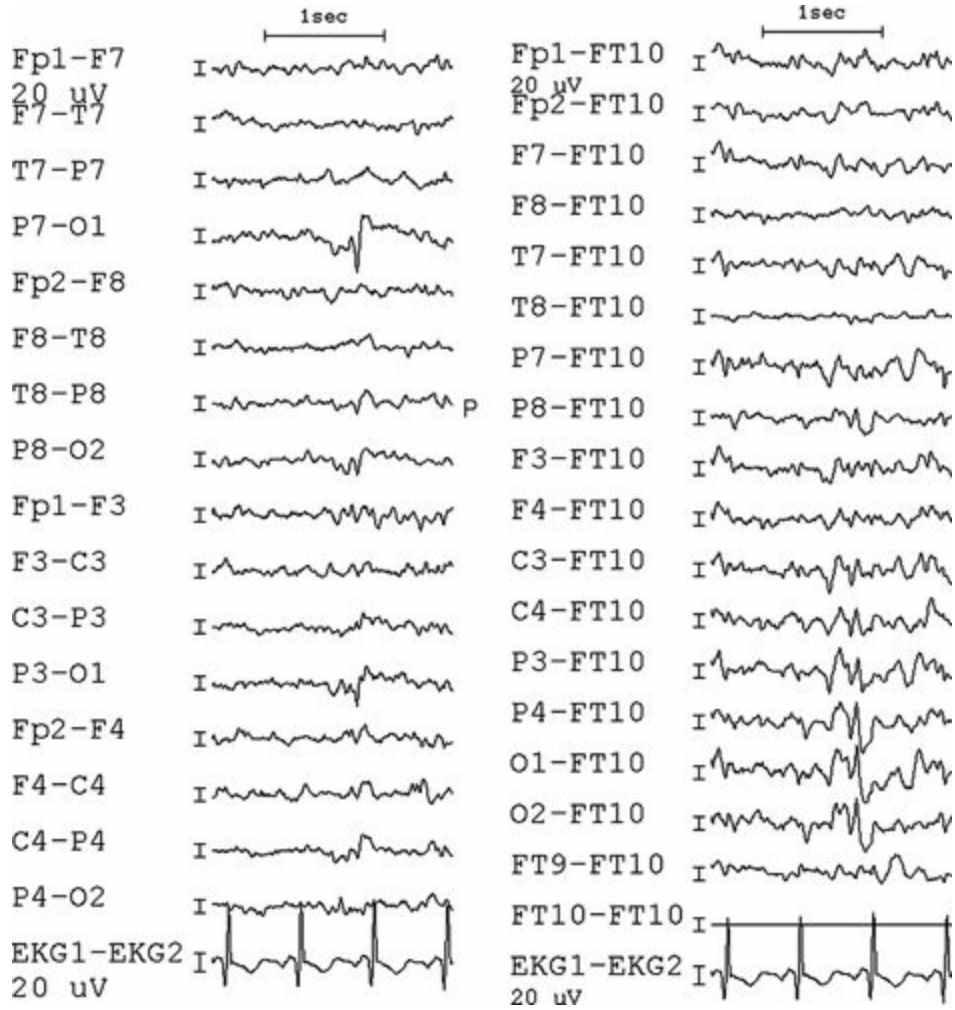

Figure 7.11. On the left, a bipolar montage with no phase reversal suggests that the activity is either at the beginning or at the end of the chain. The same time period is shown on the right, and the distribution montage to an uninvolved contralateral electrode confirms the left posterior maximum of this surface-negative discharge.

In mapping potentials measured from a bipolar recording, the bipolar measurements first must be converted to voltages relative to a selected "reference" electrode. The wisest choice usually is to select the least involved electrode at the beginning or end of the chains, taking advantage of the fact that certain electrodes are common to more than one chain. For instance, in the "double-banana" longitudinal montage, the frontal polar and occipital electrodes occur in both ipsilateral chains. These common electrodes provide an electrical connection between chains and allow an algebraic determination of the potential gradient of the electrical field over the entire area covered by the two chains. Because all the electrodes in both chains are related to each other by a sequence of subtractions, one can determine the relative amplitude at any electrode to the reference electrode. Of course, the exact amplitude (in absolute terms) at any scalp electrode is unknown. However, electrodes relatively distant from the site of maximum activity "see" a negligible potential, hence the assumption that the potential of the particular transient under study at these uninvolved electrodes is zero. The fact that the potential at this uninvolved electrode may not be exactly zero is unimportant because the relative differences between electrodes will be appropriately preserved.

Although it is possible to localize a spike or sharp wave from a single montage if electrical connections between the chains (or appropriate assumptions) exist, recording from multiple montages, especially "crisscrossing" montages, will help to confirm the topography of the discharge and can better define the topographic distribution. When the amplitudes of the potential distribution do not match exactly between chains or montages, the discrepancies most likely arise from errors in

visual measurement, erroneous assumptions of zero potential, or difficulty recognizing the same waveform in different montages. Generally, referential montages with uninvolved references will be better able to map the distribution of the activity.

The procedure for mapping the potential field, illustrated in Figures 7.9 and 7.10, can be summarized as follows:

1. Measure the amplitude of the component of interest in each channel.
2. Select an electrode that appears to be uninvolved. Assume a value of 0 for that electrode.
3. Calculate the amplitude of all the electrodes relative to the selected electrode, based on the algebraic relationship established by the montage.
4. Follow this procedure for all the chains connected by common electrodes.
5. Assume another zero electrode to calculate the distribution in chains not connected by a common electrode.
6. If the resulting distribution has potentials both above and below zero, start with another "zero" electrode.
7. Draw isopotential contours around the resulting distribution.
8. If the topographic distribution is unphysiologic, assume the opposite polarity for the waveform.

These principles can be applied most profitably when electrode montages are simple and systematic, as recommended by the American Clinical Neurophysiology Society (79).

Rules for Field Identification

A practical set of rules for identification of the electrical fields seen on the EEG is outlined in Table 7.1. The following sections provide more detailed instructions for the application of these rules.

Table 7.1 Rules for Potential Distribution

Montage type	Phase reversal	Conclusion
Bipolar	No	Maximum or minimum is located at the end of the chain
Bipolar	Yes	Maximum or minimum is located at the electrode of the phase reversal
Referential	No	Referential electrode is either maximum or minimum
Referential	Yes	Referential electrode is neither maximum nor minimum

Bipolar Montage

Derivations in a bipolar montage are customarily arranged in chains (6,79,80); that is, the electrode connected to input 2 of one channel is also connected to input 1 of the next channel. Electrode chains

are usually parallel, along transverse or sagittal axes, and contain no single electrode common to all channels.

When the deflections of two channels move simultaneously in opposite directions, this defines a "phase reversal." The presence or absence of phase reversals provides useful and immediate clues to localize maxima and minima. Whether the montage is bipolar or referential radically alters the meaning of the phase reversal (Table 7.1). In bipolar montages, there are two types of phase reversals: negative phase reversals (wherein the deflections point toward each other) and positive phase reversals (wherein they point away from each other).

If there is a phase reversal, the electrode where it occurs is either the minimum or the maximum of the electrical field. (The term "maximum" denotes absolute value, not necessarily maximum negativity.) The location of the maximum depends on the assumed polarity of the generator. Phase reversals involving surface-negative activity generate a negative phase reversal, in which the deflections "point" toward each other. However, the same picture theoretically could result from a positive electrical field that is minimum at the site of the phase reversal and larger at the ends of the chain. Conversely, a positive potential maximum at an electrode in the middle of a bipolar chain will cause the deflections to point away from each other, that is, a positive phase reversal.

If there is no phase reversal, then the electrical field maximum must be located under either the first or the last electrode of the chain (Fig. 7.12). The potential field minimum must then be at the opposite end of the chain. Because the potential gradient for each pair of electrodes in the chain is in the same direction, the potential decreases progressively from the electrode with the highest potential to the one with the lowest potential.

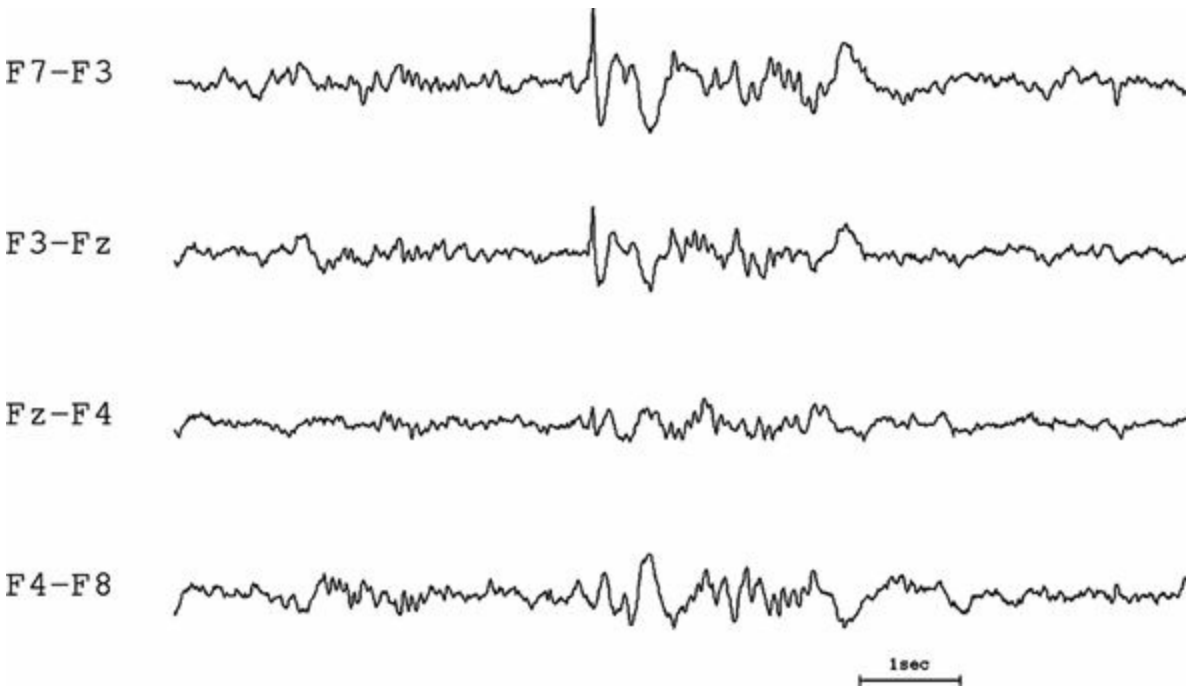

Figure 7.12. Bipolar montage with no phase reversal. Electroencephalographers are used to looking for phase reversals in a bipolar montage. In this tracing, there is no phase reversal; therefore, the discharge must be coming from either the beginning or the end of the chain. If the sharp wave is negative, implying that the activity is at the beginning of the chain (F_7), the distribution has a much more realistic falloff (i.e., it has a single peak with a monotonic decline). If the sharp wave is assumed to be positive, then the maximum would have to be at the end of the chain (F_8) with an oddly flat distribution on the right and a rapid falloff on the left.

In a bipolar montage, the amplitude may be misleading because it indicates differences in electrical potential and not the electrode of maximal involvement (Fig. 7.13). Because the gradients

tend to be steeper in regions of highest activity, the electroencephalographer may habitually but unwisely determine the maximum on the basis of amplitude. Inexperienced electroencephalographers will often (erroneously) localize by a cursory impression of the "maximum field." It is very important, however, to keep in mind that recordings made between a pair of electrodes (a derivation) are actually measuring the electrical gradient.

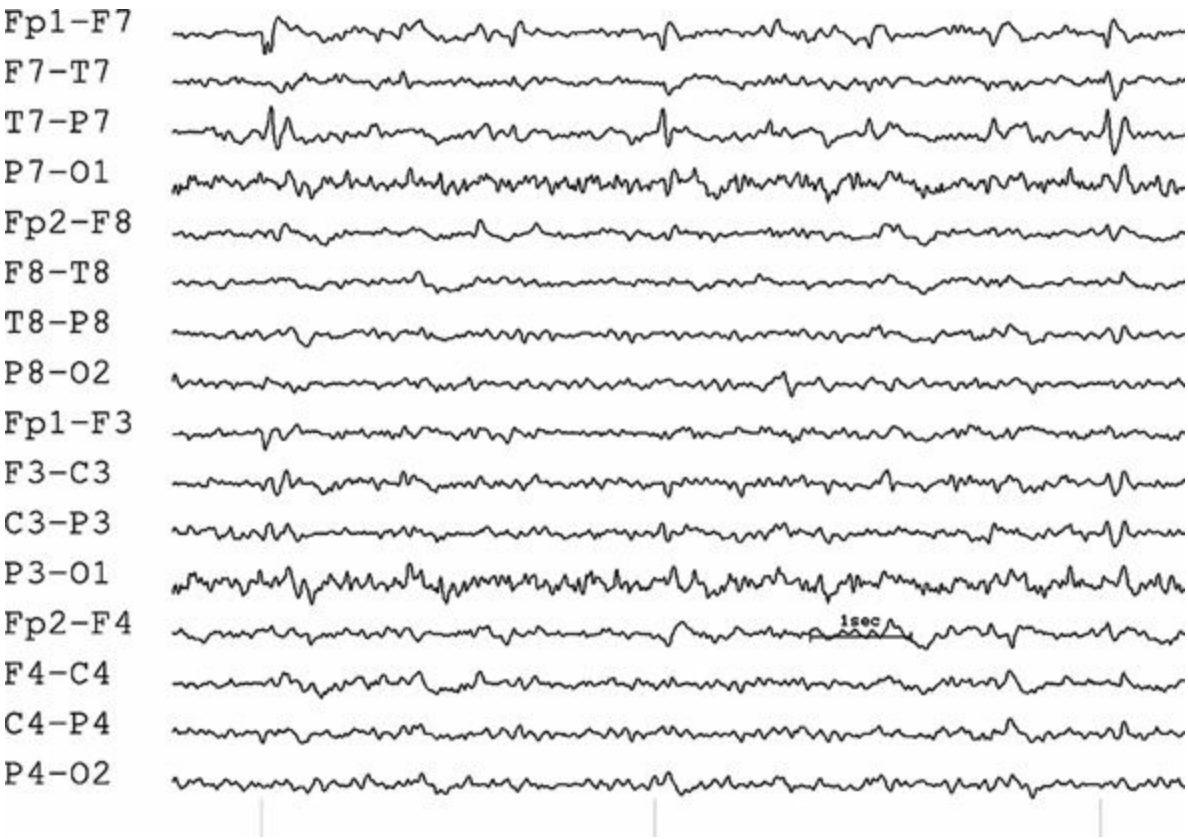

Figure 7.13. Bipolar montage with phase reversal. The amplitudes of the differences between the voltages at input 1 and input 2 do not indicate the maximum of the electrical field. In this circumstance, the amplitude of the sharp wave is actually maximum at F_7 and T_7, but approximately equal in those two adjacent electrodes, so the discharge is localized to both electrodes.

Referential Montage

All derivations in a referential montage connect the same electrode (or electrode combination) to input 2. If some derivations within a given montage use one reference electrode (e.g., the left ear) whereas others use a different reference (e.g., the right ear), only those sets of channels with a common reference should be analyzed together.

If there is no phase reversal (as shown in Fig. 7.14), the reference electrode (i.e., the one connected to input 2) is either the minimum or the maximum of the electrical field. If the reference electrode is the minimum of the electrical field, the maximum will be at the electrode with the largest amplitude. This situation is the easiest to analyze, because the amplitude of the deflection in each channel directly reflects the level of activity in input 1 of the channel.

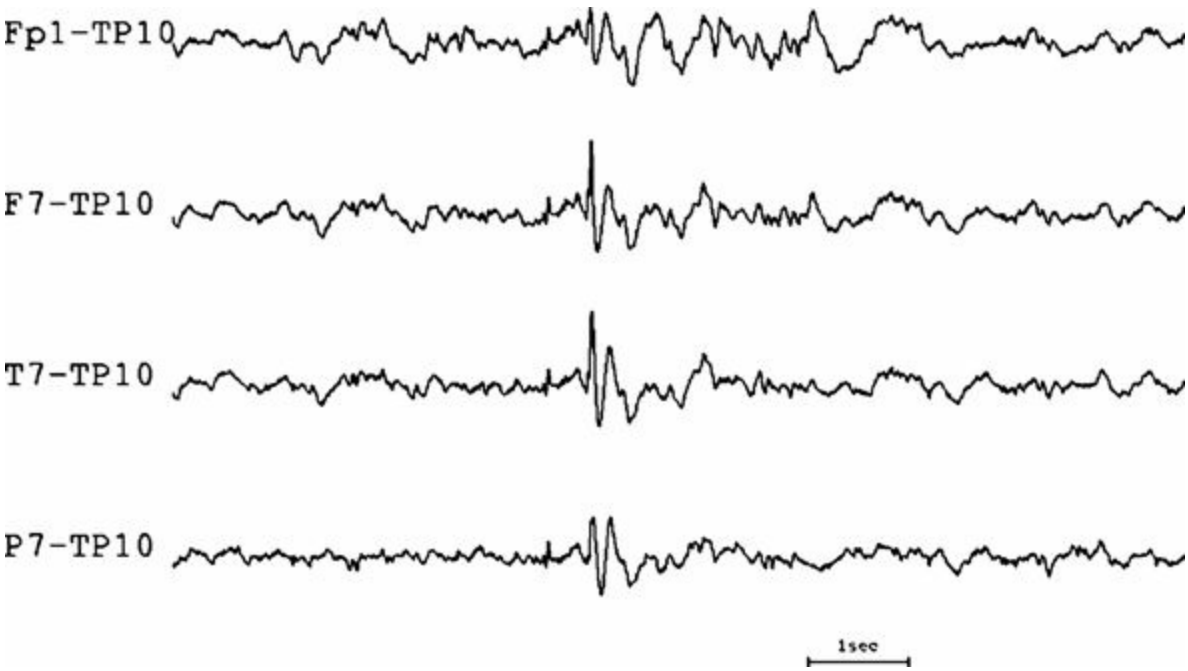

Figure 7.14. Referential montage with no phase reversal. This montage, which employs a contralateral reference chosen because it appeared to be uninvolved in the discharge, helps to clarify the location of a spike widely distributed across the left temporal region.

If the reference is maximum, the electrode at input 1 of the largest amplitude channel is at the minimum of the electrical field. If the reference is maximum and some channels show no deflection, the electrodes connected to input 1 of those channels are also maximum.

If there is a phase reversal, then the reference electrode is neither the minimum nor the maximum of the electrical field (Fig. 7.15). Hence, the reference is "involved," that is, at some intermediate potential. This indicates that some electrodes connected to input 1 have a greater potential and some a lower potential than the reference. If, for instance, the polarity of the discharge is negative, those electrodes connected to input 1 that have a higher potential than the reference will point upward, whereas those less negative than the reference will point downward. The channels that show no activity (isopotential with the reference) measure a negativity at input 1 equal to that at the reference. If the recorded potential has two maxima of opposite polarity, such as seen in tangential dipole sources, then referential montages will show phase reversals even if the reference is the minimum.

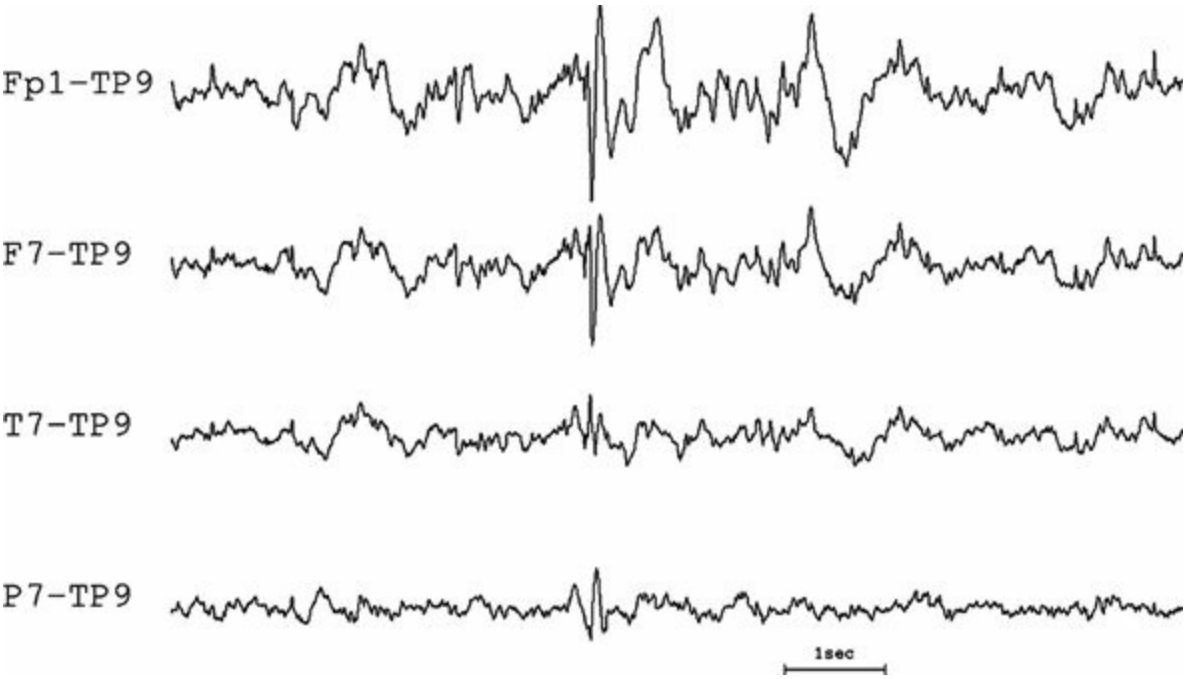

Figure 7.15. Referential montage with phase reversal. Since there is a phase reversal between channels 2 and 3, the reference is neither minimum nor maximum, that is, it must be "involved." This tracing is actually of the same discharge as shown in Figure 7.14, employing a less wisely chosen reference.

Choice of a Reference

In a referential montage, any electrode may be the reference, but a reference that is one uninvolved in the electrical field will best suit the electroencephalographer's purpose. The voltage difference between any pair of electrodes is entirely unrelated to the choice of reference (86,87); subtracting the voltage measured referentially at electrode B from that measured referentially at electrode A will produce exactly the voltage measured bipolarly from the A–B derivation, regardless of the reference chosen. This is true for a single electrode or a mathematically calculated one such as the average reference (88–90) and is the principle of computer-aided montage reformatting.

The amplifiers in a reference montage perform their differential function exactly as in a bipolar montage. Referential recordings measure not the absolute potential under the various scalp electrodes but the potential difference, as do bipolar recordings. Specifically, however, they measure the difference between each electrode and a chosen common reference. Instead of chains of electrodes, with each succeeding amplifier sharing one input from the previous amplifier, all the amplifiers share a common input 2. What the amplifier "sees" depends on the electrical relationship between the reference and the field of the waveform. The reference may be completely uninvolved in the field (a minimum), may be in an area that picks up a higher value of the waveform than any of the other electrodes (a maximum), or may lie somewhere in between (neither a maximum nor a minimum).

When mapping the distribution of a particular wave, the choice of reference electrode will affect the appearance of the traces as well as the electroencephalographer's ability to localize. For evaluating epileptic foci, the reference is normally chosen to be completely uninvolved in the electrical field distribution of the spike or sharp wave (all deflections should point in the same direction). Typically, the electrode most distant from the activity of interest will be the least involved reference. "Standard" referential montages occasionally include the reference in the field distribution (some deflections pointing upward, some downward). An electrode at the vertex (C_z) is an excellent reference for displaying temporal spikes but may be a poor choice during sleep when it is very

active. In the linked-ears reference (91) (frequently used to decrease electrocardiographic artifact), the reference electrode (A_1 connected to A_2) connects the two brain regions. This electrical shunt changes the field generated (92), decreasing, for example, asymmetries between the temporal regions (9) and producing other distortions (93). The "weighting" applied to activity from each side will depend entirely on the electrode impedances, with the ear having the lower impedance predominating. When temporal lobe epileptiform activity spreads to the ipsilateral ear, the linked-ear reference will inappropriately reveal spikes in both hemispheres.

A common average reference has been advocated (89) to avoid the problem of an "active reference." Using passive summing networks, active amplifier configurations, or combinatorial software, it is possible to devise a reference that combines all the electrodes applied to the head, the so-called common average reference (88,89). The disadvantages of this system are threefold: (i) The common average reference is, by definition, contaminated because the abnormal potential will influence all of the channels (94); (ii) depending on the number of electrodes included in the average, the potential under study will be reduced by a small proportion; and (iii) large-amplitude focal pathologic activities will be reflected proportionally in all the inactive channels as well, albeit with apparently opposite polarity.

A variety of calculated references and transformations are available, but these must be used with caution. The "source derivation" provides useful "deblurring" by arithmetically estimating the cortical sources that generate a scalp distribution; however, this method gives increasing weight to distant electrodes and can produce erroneous results when these sites are active (36,38,95,96). Because there is no ideal reference for all cases, it is usually best to distribute the electrical field potentials by manual selection of an uninvolved and quiet electrode as a reference.

SOURCE LOCALIZATION

Assumptions

After determination of the electrical field, the sources responsible for the production of the field can be localized with the aid of a number of simplifications. The procedure for determining the polarity and location of the generator is based on the following four specific assumptions:

1. Epileptogenic sources are simple dipoles or sheets of dipoles obeying a simple principle of superposition (48).
2. Dipoles are fundamentally oriented perpendicularly, with only one pole generally detectable on the scalp (78) and therefore can be treated as if they were monopoles. When both the positive and the negative poles are recorded from the surface, the localization system outlined below will not apply.
3. Epileptiform discharges are chiefly surface-negative phenomena. In the absence of a skull defect, a transverse- lying dipole (as in benign focal epileptiform discharges of childhood), or other evidence of an unusual discharge, the assumption of surface negativity will usually result in the proper distribution.
4. The head is essentially a uniform, homogeneous volume conductor.

Choosing Between Two Possibilities

The application of the rules above will yield two possible hypotheses in each case. In a bipolar chain, for example, a downward deflection with no phase reversals may be generated by either a negativity maximum at the last electrode of the chain (Fig. 7.16) or a positivity maximum at the first electrode of the chain. To choose between the two possibilities in any given case, one must guess about the polarity of the source generator or the relative likelihood of one of the two electrodes being the more active.

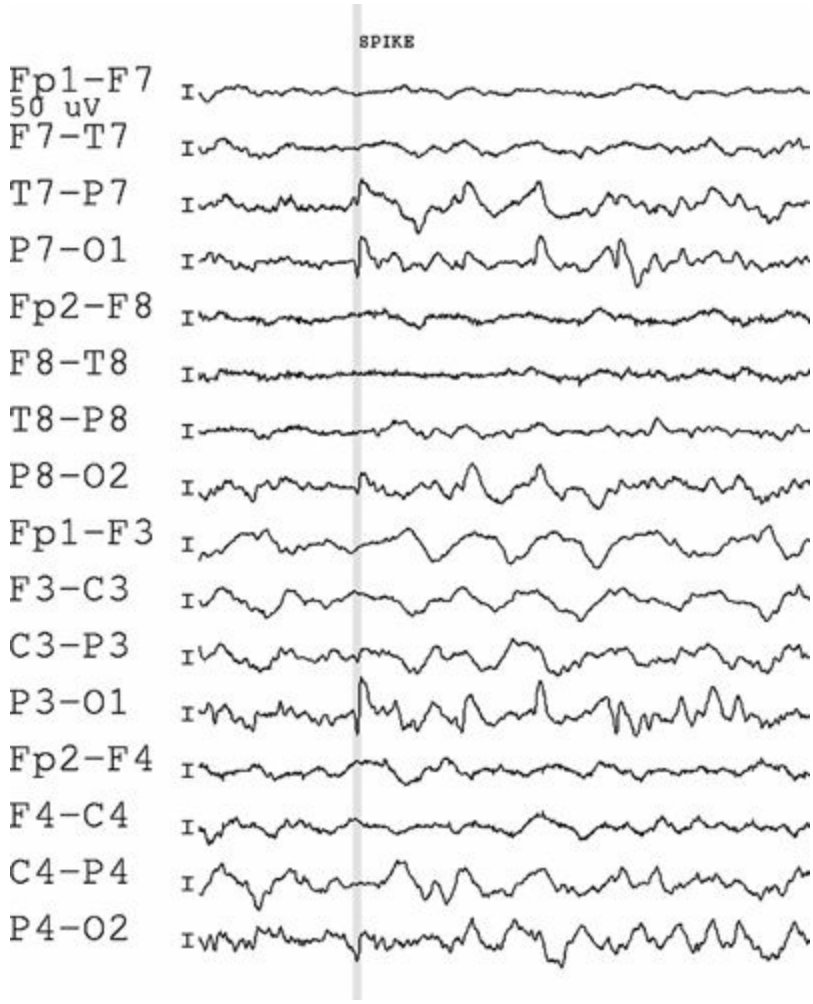

Figure 7.16. Bipolar montage with maximum negativity at the end of the chain. The marker brackets the downgoing negative component.

Because the localization of a transient will depend on a correct assumption about its polarity, all possible clues must be used to make an educated guess about polarity. For example, if the transient appears to be epileptiform, it is most likely to be surface negative, whereas if morphology and location suggest a positive occipital sharp transient (POST), it can be expected to be surface positive (Fig. 7.17). The best strategy is to see if the distribution based on the assumed polarity makes physiologic sense; if not, the opposite polarity will have to be tried. In Figure 7.10, the isopotential map based on an assumption that the polarity of the maximum is negative displays a more logical potential falloff for focal activity than the opposite assumption. Therefore, it is most likely that this activity has negative polarity with a maximum at electrode T_7.

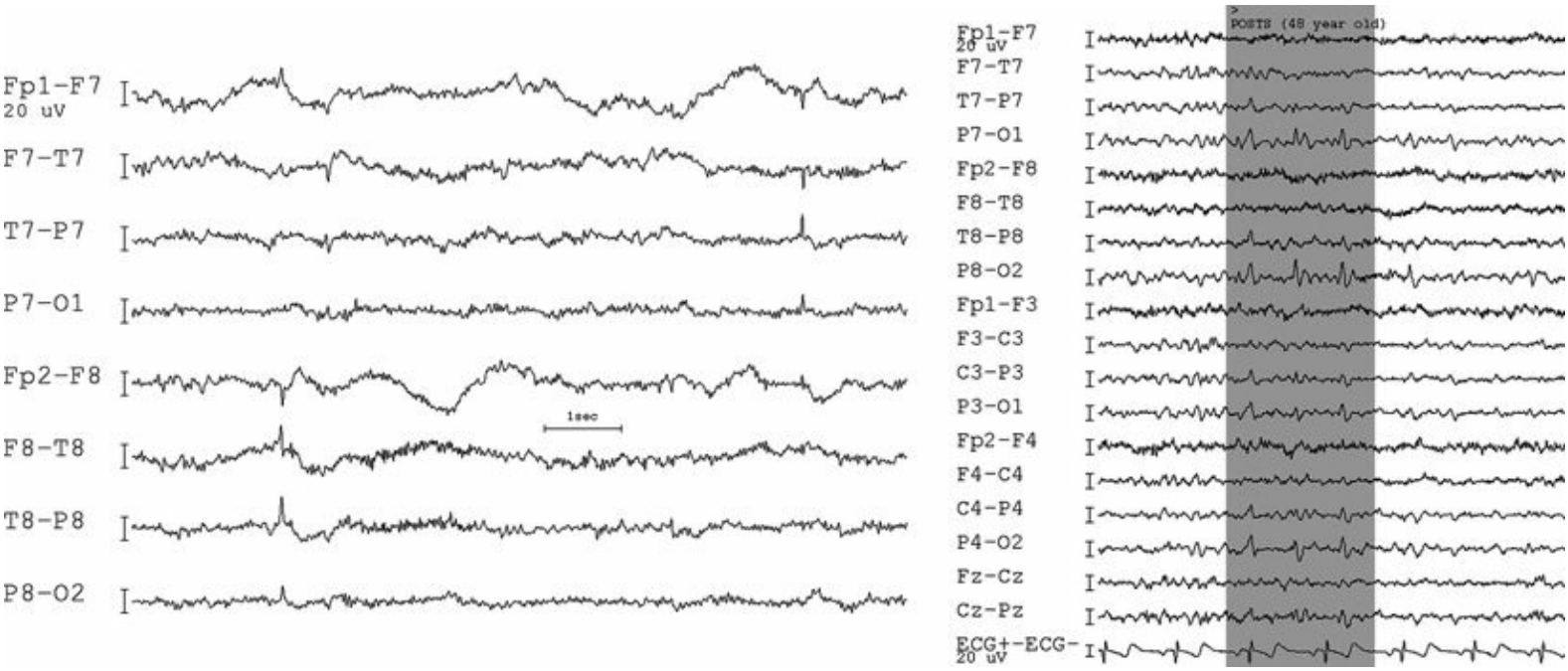

Figure 7.17. Clues to identifying the origin of sharply contoured waveforms. **Left:**Although these discharges stand out dramatically from the background, their presence during sleep and their very brief duration suggest that the transients here are "benign epileptiform transients of sleep (BETS)." BETS are often multiphasic, but the predominant component is negative, as in this example. **Right:** The electrical field distribution of these sharply contoured waves is consistent with POSTS (positive occipital sharp transients), that is, a positivity at the end of the chain. If the electroencephalographer assumed instead that they were negative, suggesting epileptiform discharges, their distribution across the entire head would have been more difficult to explain physiologically.

Determination of the electrical field of a discharge may help to differentiate artifacts or extracortical physiologic activity from abnormal brain activity (Fig. 7.18). Because the electrical gradient is steepest at the electrodes closest to the source, the electrical potential difference between inputs 1 and 2 becomes smaller as one moves farther away from the generator source (97). For this reason, the steepest potential gradient, and the largest deflection, will most often appear in the channels nearest the source.

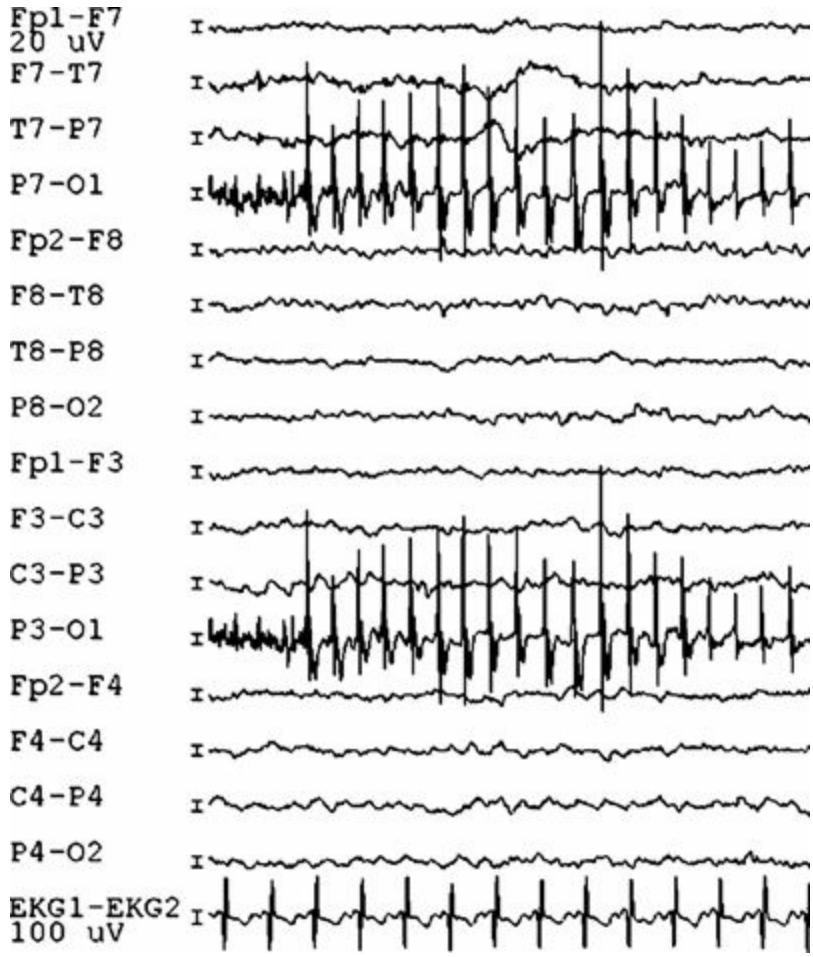

Figure 7.18. Artifacts. The sharply contoured discharges emanating from the left posterior region cannot be dismissed as artifacts on the basis of morphology alone nor do they match up with the EKG artifact. However, since they appear only in channels 4 and 12, they must be arising solely from electrode O_1. If these large-amplitude occipital "spikes" were epileptogenic, electrical field theory would dictate a much more gradual falloff. Because the field shows a precipitous, and therefore impossible, distribution, these discharges must be artifacts.

When dealing with an invariant spike, seen in various chains and montages, analyses based on any of the multiple electrode chains or montages should all reach the same conclusion (see Figs. 7.9 and 7.19). Corroborating a potential localized on a longitudinal montage by using a transverse montage (i.e., montages that are at right angles to each other), for example, can be helpful. If different conclusions result from the analysis of different montages, the assumptions about polarity or location were probably incorrect on one of the montages. Nevertheless, consistent conclusions across montages do not prove that the assumptions were correct, as the same error about polarity or location may have been made throughout the analysis.

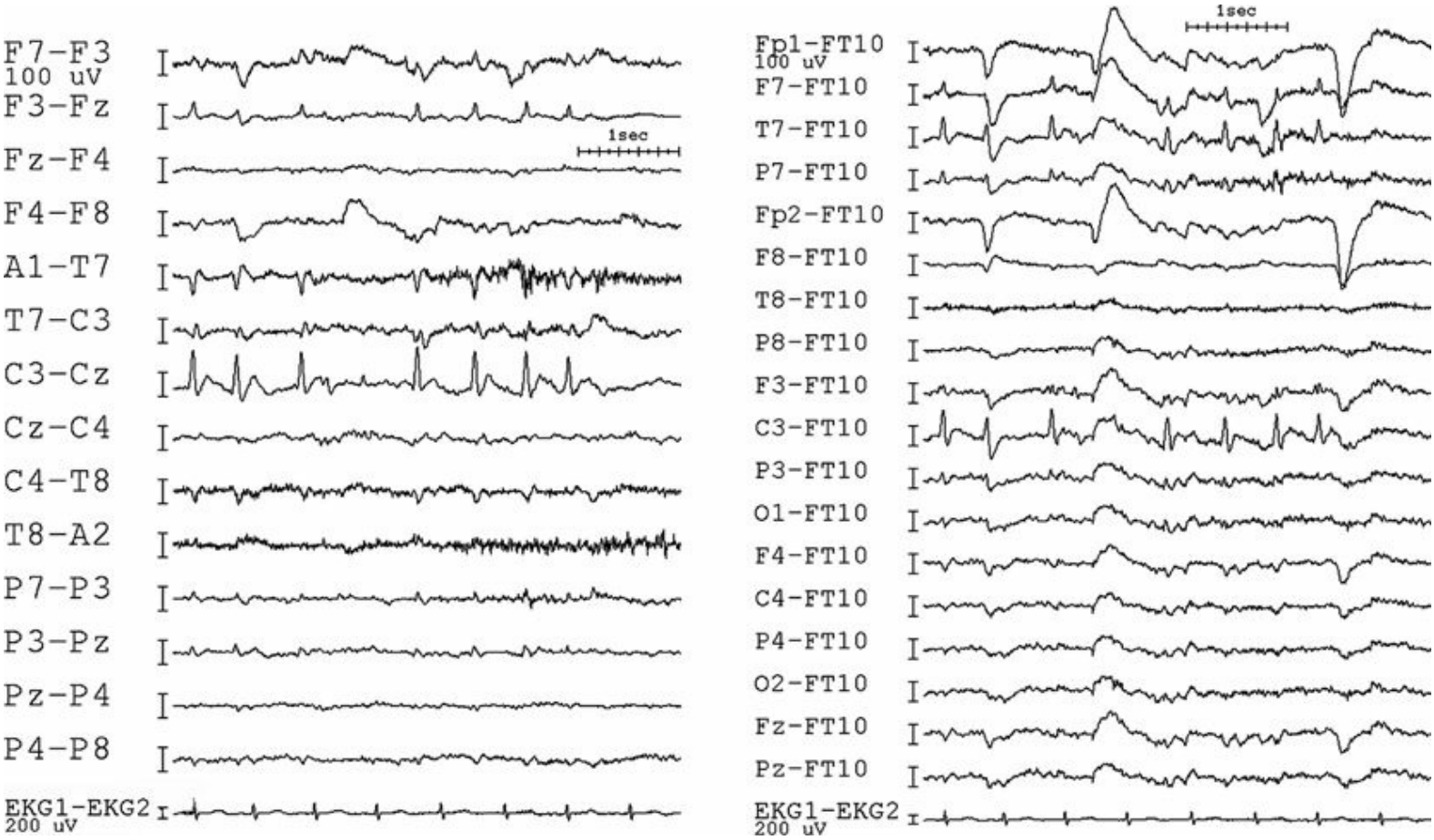

Figure 7.19. The phase reversals in the transverse montage shown on the left suggest the possibility of benign rolandic spikes. On the right, an ad hoc distribution montage employing a contralateral electrode clearly shows a typical centrotemporal distribution. It is also easier to distinguish the eye movement artifacts from the sharp waves in this montage.

Localization Rules: Cautions and Limitations

While the majority of this explanation has focused on the distribution of isolated transients, typically epileptiform activity, the same rules apply to the distribution of more prolonged or rhythmic activities, such as the wicket rhythm in Figure 7.20. Regardless of which component is chosen for analysis, the same principles can be applied. The simple rules and procedures for manual localization of electrical activity on the basis of bipolar or referential montages, outlined above, are valid only for single sources; that is, they presuppose a single monopolar generator. Regional abnormalities such as those encountered in focal epilepsy quite frequently satisfy this assumption as an approximation. Some EEG patterns, however, are produced by two or more generators of the same or different polarity acting simultaneously. When multiple sources or horizontal dipoles are involved, even highly sophisticated mathematical source localization techniques may not enable us to identify the exact composition of such generators.

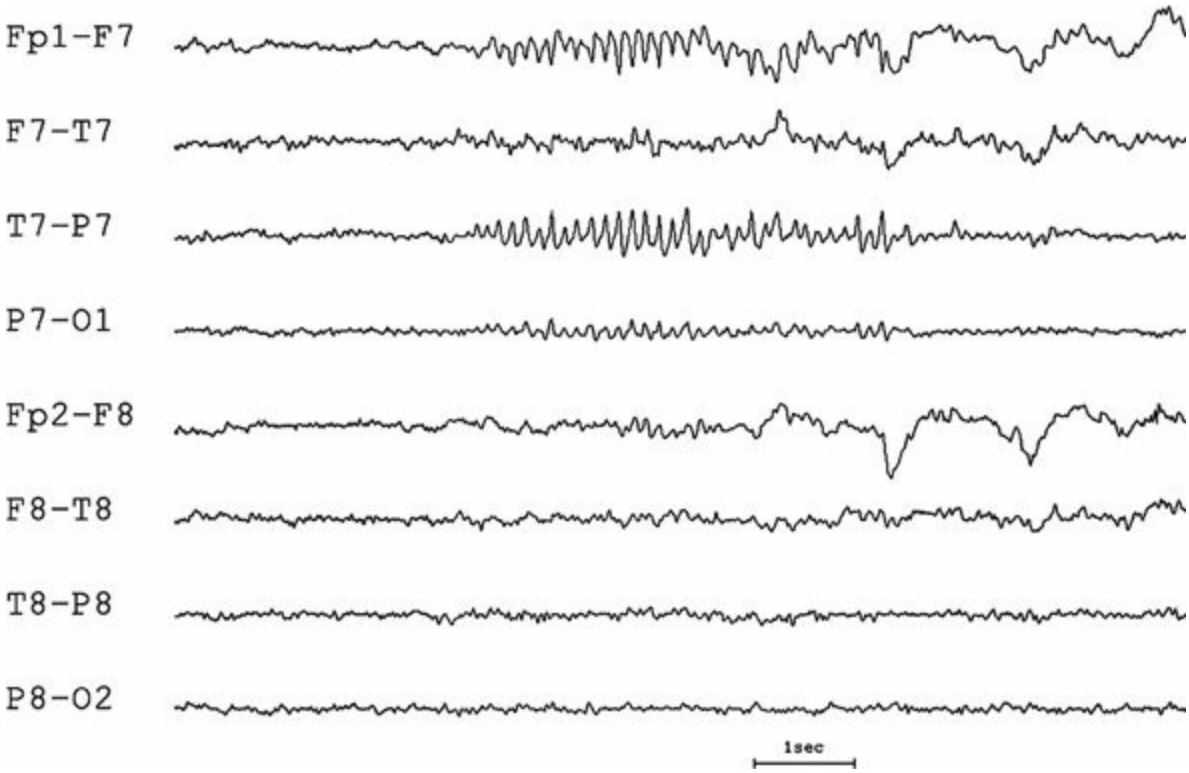

Figure 7.20. Bipolar montage with phase reversal. Phase reversals need not always occur in adjacent channels. This EEG shows the phenomenon for some normal activity rather than the abnormal discharges seen in Figure 7.13. The phase reversal of this arciform activity spans the isoelectric temporal channels, consistent with the broad distribution of a wicket rhythm.

Although both poles of the dipolar generator must be present by definition, one of them is oriented deep within the head, allowing assumption of a monopole. On occasion, however, both poles may be represented on the scalp surface, precluding the use of these rules. This occurs, for example, in the case of an epileptogenic focus originating from the superior mesial portion of the motor strip (98). Cortical regions involving the interhemispheric fissure, such as the foot area or the calcarine cortex, are especially likely to produce these horizontal dipoles. Specifically, the end of the dipole traditionally at the surface will be buried within the fissure with its maximum seen on the contralateral scalp, and the ordinarily deep end of the dipole may be close to the scalp surface on the ipsilateral side. Because of their location, horizontal dipoles also can be seen in benign focal epileptiform discharges of childhood (99).

The electrical fields resulting from these transverse dipoles are characterized by a simultaneous surface-negative and surface-positive potential seen at different electrodes on the scalp or by a double-phase reversal (13,100). Note that when double-phase reversals or other factors indicate, for example, a huge anteroposterior dipole or a transverse dipole extending from one hemisphere to the other (47), the physiologic meaning of such an unusual field must be questioned. A horizontal dipole should not be the first thought when the electroencephalographer confronts deflections pointing in opposite directions. An involved reference, the most common cause for this phenomenon, must be excluded.

As noted, in a bipolar montage, the channels of highest amplitude must not be confused with the area of greatest activity. This mistake is most likely to occur when the chain has no phase reversals, indicating that the maximum of the discharge originates from either the beginning or the end of the chain or when the maximum is broadly distributed across several channels (Fig. 7.20). A greater amplitude seen in one or more channels is solely a manifestation of a greater potential difference.

Obviously, determining whether a phase reversal is present is a key aspect of the localization

procedure. Multiple fast components may be confusingly mixed when viewed from a bipolar montage and are more accurately represented in a referential montage to identify the individual components that are phase reversing across channels. A discharge with an extremely broad field can result in rather tiny differences between adjacent electrodes.

Because the brain, skull, and scalp do not have homogeneous conductivity, current pathways from active epileptogenic areas can vary dramatically among the recording sites. This variability may lead to a site of maximal scalp activity considerably distant from the fundamental generator (101).

Although general physiologic and physical principles can explain the phenomena involved, clinical interpretation of a particular set of measurements often will have to be based on experience and information that is not easily derivable from first principles. Nevertheless, by remaining aware of alternative possibilities, the electroencephalographer can avoid misinterpreting unusual recordings.

COMPUTER-AIDED METHODOLOGY FOR LOCATING EEG SOURCES

Topographic Mapping of Voltage and Other Parameters

Topographic EEG mapping is the generation of a pictorial representation based on measurements obtained from multichannel EEG analysis—usually simultaneous, instantaneous amplitudes of some parameter. Computer-aided mapping can accurately summarize the field distribution and may help to highlight locally originating activity (102). Computed topographic maps can be used (i) to describe an already known localization (perhaps for communication with nonneurophysiologists), (ii) to confirm a conventionally determined localization, (iii) to identify changes not detected in the original interpretation, and (iv) to display statistical differences between patient populations (so-called Z scores) (103). These maps should always be used in conjunction with the raw EEG data (104,105).

Automated mapping may be used to represent the topographic distribution of any variable, whether derived from complex calculations or simply displaying electrical field distributions as shown in Figure 7.21, depending on the application. In the evaluation of epileptic patients, the topographic distribution of sharp waves may present a valuable display, once their characteristics have been reduced to a metric (106). It is important to remember that a computerized system is unlikely to perform the measurement in every case as it would have been done manually, so that visual inspection of the waveform is essential for each map (104).

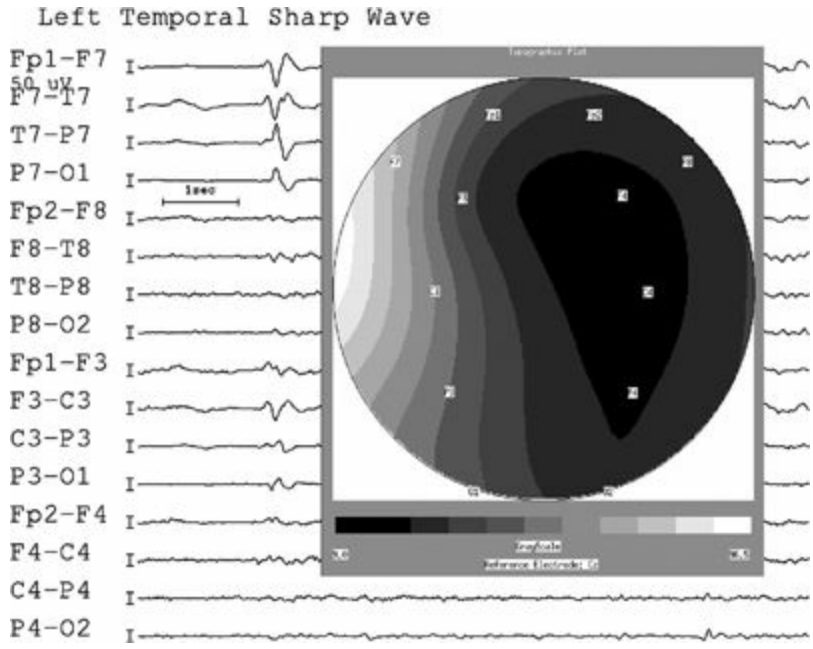

Figure 7.21. Topographic mapping. Digitization of the electroencephalogram offers the opportunity for interactive postprocessing that may help to convey location in an easy to understand way. In this figure, the electrical field of the sharp wave seen phase reversing at T_7 in the EEG has been automatically mapped onto a top view of a spherical model of the head. Using baseline-to-peak amplitude measurements from a C_Z reference, interpolating the amplitudes at every scalp location between electrodes, dividing into 10 isocontours, the amplitude map has been plotted as a gray-scale intensity. Koszer et al. (113) have demonstrated relatively good congruence between the manual process carried out by electroencephalographers described in the text and computerized topographic mapping methods.

When used to map the amplitude of the EEG or evoked potential at a specific point in time, interpolation between the voltages measured at the electrodes must be carried out to present a smooth contour on the map. The most practical interpolation method is the one based on spherical splines (107). Unlike magnetic resonance imaging and computed tomography, in which the intensity of every pixel is based on a measurement, topographic maps are derived from measurements at only 16 to 32 points, with the balance obtained via interpolation, creating the illusion of a higher resolution than actually exists.

Once the computer has associated the amplitude information with its topographic location, mathematical techniques even more powerful than electrical field mapping can be brought to bear. As a result of volume conduction, potentials generated within a small brain region will be seen over a wide area of scalp. The spreading of the field to the scalp can be mathematically reduced by current source derivation methods (102,108). These spatial deblurring techniques such as the Laplacian operator (109) can narrow the apparent distribution of the electrical field, thereby emphasizing discrete foci (94). The Laplacian operator supplies information about the locally occurring activity in a "reference-free" manner (81), taking into account the direction of the field along the scalp to define the differences between adjacent electrodes.

Commercial instrumentation for topographic mapping is relatively easy to use. Many EEG machines produce in real-time a topographic display, synchronized with the cursor positioned and continuously updated. Although much attention has been paid to the algorithms for generating and presenting these displays, there is a danger that the relatively complex calculations that go into generating these maps will lead to gross misinterpretation as a result of the wide range of variables (101,105,110,111). There are a number of pitfalls and caveats associated with topographic mapping (111,112) that have prevented widespread acceptance of this technique for most clinical applications

(101). Jayakar et al. (36) have described several limitations of these methods.

Computer-aided topographic mapping actually is not well suited to display epileptiform EEG elements owing to their rapid time course. Because not all the channels may be at their peak simultaneously, the maps may show an unexpected result, that is, the maps may demonstrate spike progression but will not necessarily reflect the manually determined localization (113). Moreover, computer topographic mapping of the amplitude of the EEG signal (or of evoked potentials, spectral measurements, or statistical analysis) provides no new information and cannot be used to make classifications not apparent in the raw data. Topographic mapping techniques, even with sophisticated enhancements such as the Laplacian operator or spatial deblurring, do not provide any conclusive three-dimensional information about the source of scalp-recorded signals (114). Nevertheless, they can make it easier to grasp the special relationships existing between electrodes in various neighborhoods of the scalp or to chart the progress of an epileptic discharge across the scalp as shown in Figure 7.22. To decrease errors, several restrictions imposed by the interpolation methods and the boundary value problem dictate the use of more electrodes than are conventionally placed. Indeed, adding closely spaced electrodes alone may reveal new information.

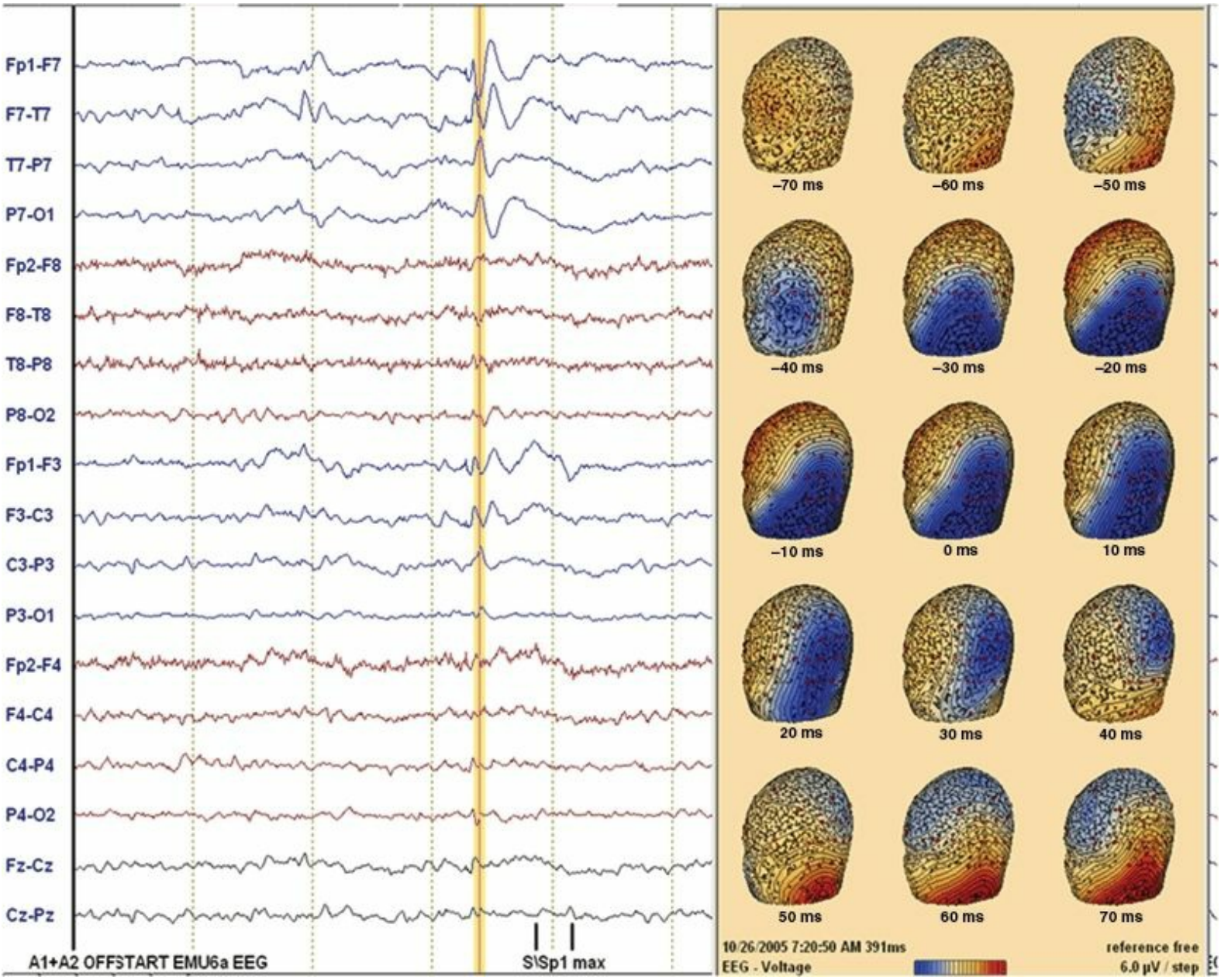

Figure 7.22. A sequence of topographic maps can show the evolution and subsequent dissipation of the electrical field of a spike.

Each of the snapshots illustrates the extent of the electrical field of this left temporal discharge in 10 msec time increments, spanning the 140-msec epoch swept out in yellow. On a computer screen, this can even be presented as a slow-motion cine loop.

Dipole Modeling and Source Localization

Visual inspection, aided by simple enhancements such as distribution montages and the rules outlined above, is the time-honored method to identify the location from which epileptic EEG activity arises. There are, however, difficulties in identifying the source of a scalp potential that derive, in part, from the fact that the amplitude seen on the scalp is a function of not only its distance from the generator but also the orientation of the dipolar generator. Not only do the generators of the EEG dipoles possess an orientation but also they are complex sheets of dipoles arranged on a convoluted surface, following the contours of the cortex. The other problem that distorts the relationship between scalp potentials and the underlying cortical generators is the nonhomogeneity of the cerebral tissue, scalp, and skull.

There are computerized methods for EEG source localization that attempt to address some of these difficulties. These packages (such as BESA) (15) and CURRY (115,116) were initially developed in the realm of research, and they provide myriad tools to calculate and extract quantities from electrophysiologic data (117–121). Computerized source analysis is an attempt to identify the origin of electrical potentials seen on the scalp by solving the "inverse problem." Source analysis is most commonly carried out by postulating a single or multiple spatiotemporal dipole models chosen to account for the surface signals and their timing relationships (122–124). Although the sources of electrical activity recorded by the EEG are actually folded sheets of dipolar pyramidal neurons, the traditional computer model typically uses only a single dipole with no spatial extent. In order to explain a widespread scalp distribution, the computer model tends to locate these dipoles deep to the actual cortical location. Solutions to the inverse problem involve simplifications and approximations and, even when well-defined dipoles using implanted sources in the human brain are employed, often produce errors of a few centimeters (63,125). Although it is not possible to uniquely identify the positions of the electrical sources in the brain from the scalp electrodes (126), appropriate assumptions can yield useful information in some cases (16,127). An illustration of the practical use of the equivalent current source dipole method to localize three epileptic discharge is shown in Figure 7.23.

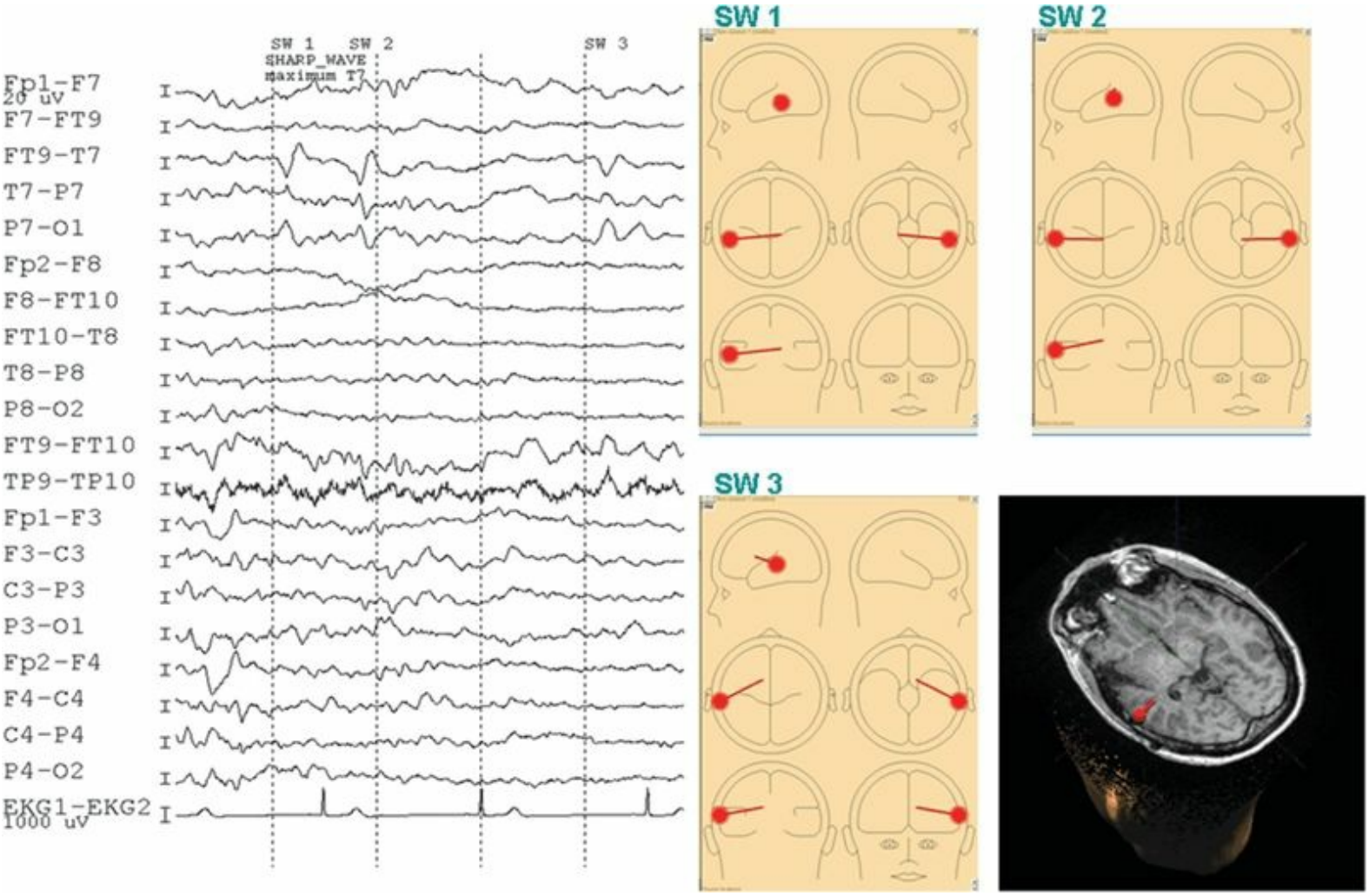

Figure 7.23. Source analysis of three broad, left temporal sharp waves using a single equivalent dipole. The location of sharp wave 3 is shown coregistered with the MRI.

Localization using dipole source analysis has been the subject of many validation (128) and comparison studies (129). In recent years, purveyors of these packages have enhanced their offerings to be of more use in clinical medicine. Several journals have dedicated special issues to the various aspects of this methodology (130), and there have even been some large prospective studies evaluating its value in presurgical epilepsy evaluation (131). Although computerized "source analysis" was applied beginning in the mid-1980s to identify single or multiple foci (122,123) and has been continuously developed for more than 25 years, the extra time and effort required have discouraged use of these techniques in EEG on a routine basis. This software methodology is sometimes limited, because in clinical use only the simplest of models of the source (e.g., equivalent current dipole) and the head (e.g., concentric spheres) are employed. While other source models exist that are perhaps more visually pleasing and can illustrate the activity of more broadly distributed activity (as illustrated by the min-norm example shown in Figure 7.24), they are still subject to the inherent limitations of the head model for EEG. The temporal dynamics of the source and the intracranial anatomic pathology associated with epilepsy often make these models inexact, and the results may be misleading (132). Even when artificial dipoles with known locations are localized, the errors in location range from 13 to 22 mm (133).

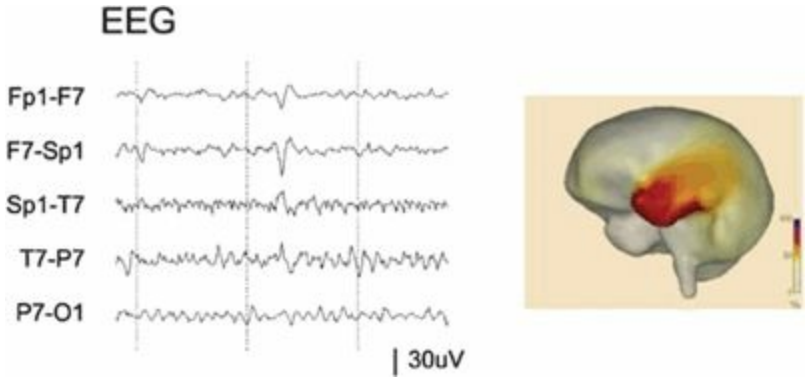

Figure 7.24. Distributed source modeling attempts to overcome the "point source" assumption of the single equivalent dipole model. A common method is the minimum-norm estimate, which postulates a large number (typically 5000 to 15,000) of fixed dipole sources arrayed throughout the active portions of the brain. The strength of each dipole is estimated and displayed as a color-coded intensity, as in this example of a left temporal sharp wave.

The source localization procedure attempts to account for all of the activity recorded by the electrodes. Therefore, activity that is unrelated to the waveform under study will have to be explained by the model as well, such activity as normal background (alpha rhythm, vertex waves, spindles), noncerebral signals (EKG, EMG), and artifacts (instrumentation, external machinery, electrodes). The effects of these other activities are difficult to recognize in the source localization results. Accuracy hinges on assumptions, and depending on the models and the procedure, there are multiple opportunities for errors (134,135):

1. Inadequate head model shape—nonspherical head, irregularity of concentric layers
2. Insufficient compartments in the head model—neglecting the skull in the spherical model
3. Anatomic layer conductivity and thickness measurement errors—especially the bone
4. Inhomogeneity of brain regions—such as ventricles, cystic, or resected areas
5. Measurement location error—differences between the actual locations and assumed locations of electrodes, fiducials, sources
6. Source modeling errors—differences between the actual source and the source model in shape and extent

It has been shown that even the conductivity anisotropy of brain tissue causes field distortions, for example, in the vicinity of large fiber tracts (136). It is important to remember that the results of source localization are, in the signal processing chain, considerably distant from the raw data. For this reason, it is important to apply these computerized methods with caution and to always display and review with the raw EEG. Despite the automated nature of computerized source localization, the electroencephalographer's expert judgment about a priori constraints and which sources to reject as possible solutions is of critical importance.

The different tissues that the EEG signal has to traverse on its way to the scalp have very different conductivities, thereby influencing the representation on the surface and consequently the accuracy of computerized source localization. These differences in conductivity between the brain, CSF, bone, and scalp have a negligible effect on the magnetic field. The modeling required for source localization of magnetoencephalography (MEG) signals—which arise from the same neuronal activity that generates EEG signals—is therefore much simpler, providing a generally more accurate computerized solution to this sophisticated inverse problem. The volume conductor model that represents the physical properties of the medium between the sources and the sensors is especially

complex for the electroencephalography of patients with highly distorted head anatomy. MEG, on the other hand, is unaffected by the tissue variations inherent in scalp, skull, CSF, dura, and brain parenchyma. The use of MEG for evaluation of epileptic patients is covered in detail in Chapter 76.

While new imaging techniques have decreased the importance of EEG for many neurologic disorders, EEG is still the sine qua non for the diagnosis of epilepsy. If the seizure semiology, ictal scalp EEG features, and the neuroimaging fail to produce a consensus regarding the focus localization, then further studies—usually including even more EEG from intracranial recordings—will be required in order to outline a target for surgical resection.

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CHAPTER 8
ELECTROENCEPHALOGRAPHIC ATLAS OF EPILEPTIFORM ABNORMALITIES

SOHEYL NOACHTAR AND ELAINE WYLLIE

Electroencephalography (EEG) is generally considered the single most important laboratory tool in the evaluation of patients with epilepsy. This atlas of material from patients seen at the Cleveland Clinic Foundation and the University of Munich illustrates some of the EEG findings discussed throughout this book. Additional EEG atlases and textbooks are listed in the bibliography at the end of this chapter.

METHODS

These tracings were made following American Electroencephalographic Society guidelines (1), with electrodes placed according to the International 10-20 Electrode Placement System (2). Additional closely spaced electrodes according to the 10-10 system (Fig. 8.1) were used in some cases to better define a focal epileptogenic zone. The combinatorial electrode nomenclature used here is that recently proposed by the American Electroencephalographic Society (3) and the International Federation of Clinical Neurophysiology (2). The EEG terminology used in this chapter follows the recommendation of the International Federation of Clinical Neurophysiology (4).

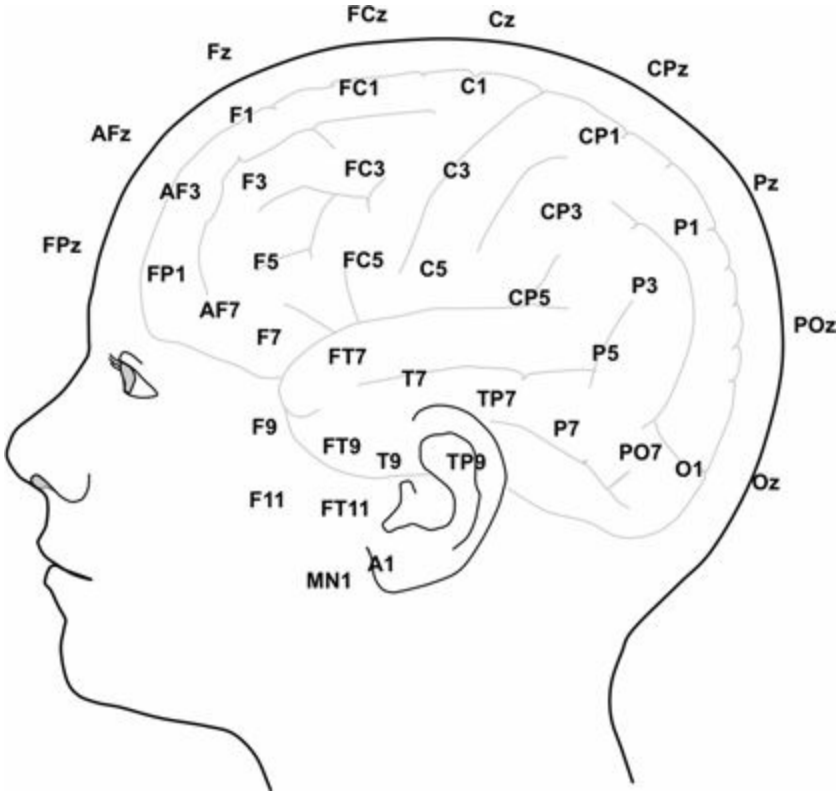

Figure 8.1. Electrode positions and nomenclature of the combinatorial 10-10 system proposed by the American Electroencephalographic Society (1) and the International Federation of Clinical Neurophysiology (2).

For consistency and ease of interpretation, we displayed most tracings with the same longitudinal bipolar montage (Fig. 8.2). Occasionally, the activity was best shown with a transverse bipolar montage (Fig. 8.3), a longitudinal bipolar montage with anterior temporal or sphenoidal electrodes (see Fig. 8.2), or a referential montage (Fig. 8.4).

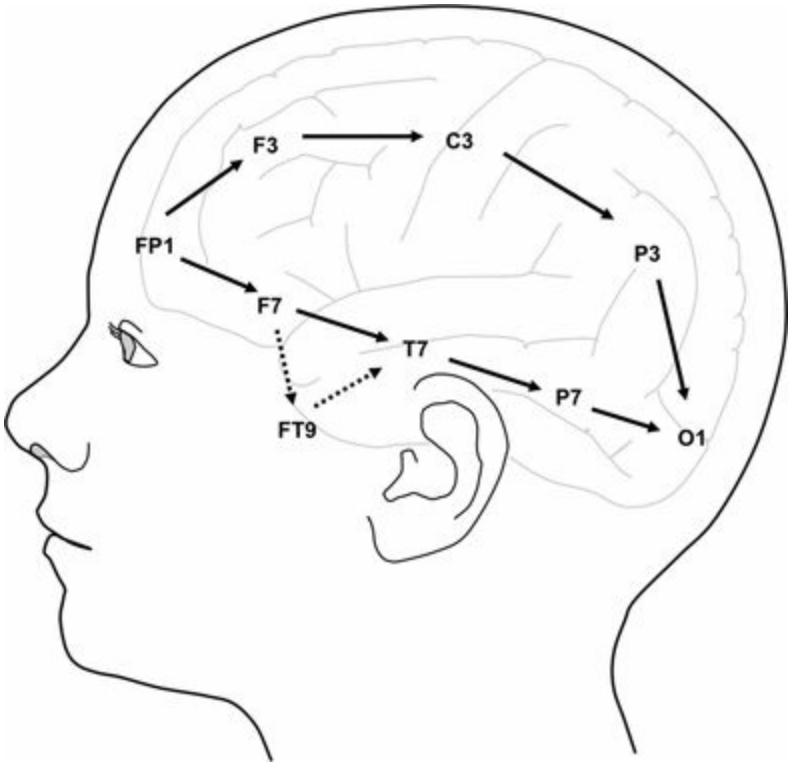

Figure 8.2. Longitudinal bipolar montage, left-sided electrodes. The "double-banana" montage used for almost all the tracings in this atlas includes the channels shown with filled arrows, ordered as follows: right temporal chain, left temporal chain, right parasagittal chain, and left parasagittal chain. The "anterior temporal" montage used in some of the tracings is modified to include the channels

shown with broken arrows to reflect anterior, basal, or mesial temporal discharges with anterior temporal (FT9, FT10) or sphenoidal (SP1, SP2) electrodes.

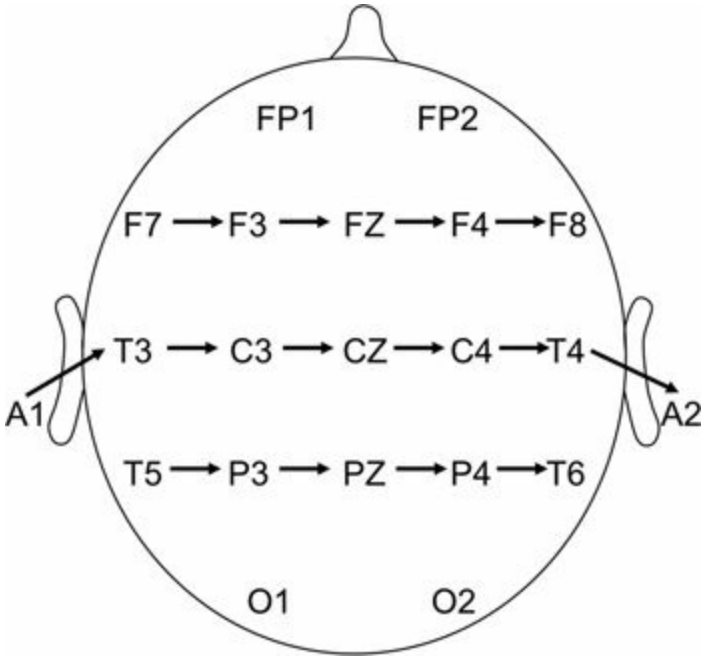

Figure 8.3. Transverse bipolar montage, vertex view. Channels are arrayed in order, as follows: frontal chain, temporocentral chain, and parietal chain.

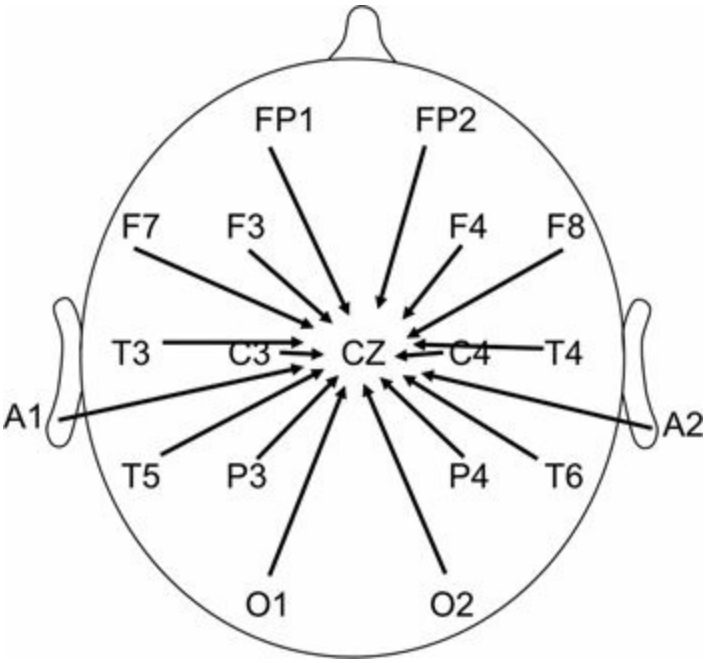

Figure 8.4. Reference montage to vertex.

PART I: NORMAL ELECTROENCEPHALOGRAPHIC PATTERNS AND VARIANTS SOMETIMES CONFUSED WITH EPILEPTIFORM ACTIVITY

For epileptologists to fulfill the basic obligation to "do no harm," they must avoid "overreading" normal variants on EEG (5,6). This section includes several normal patterns that may be easily mistaken for epileptiform discharges, resulting in an incorrect diagnosis of epilepsy and inappropriate recommendations for antiepileptic medication.

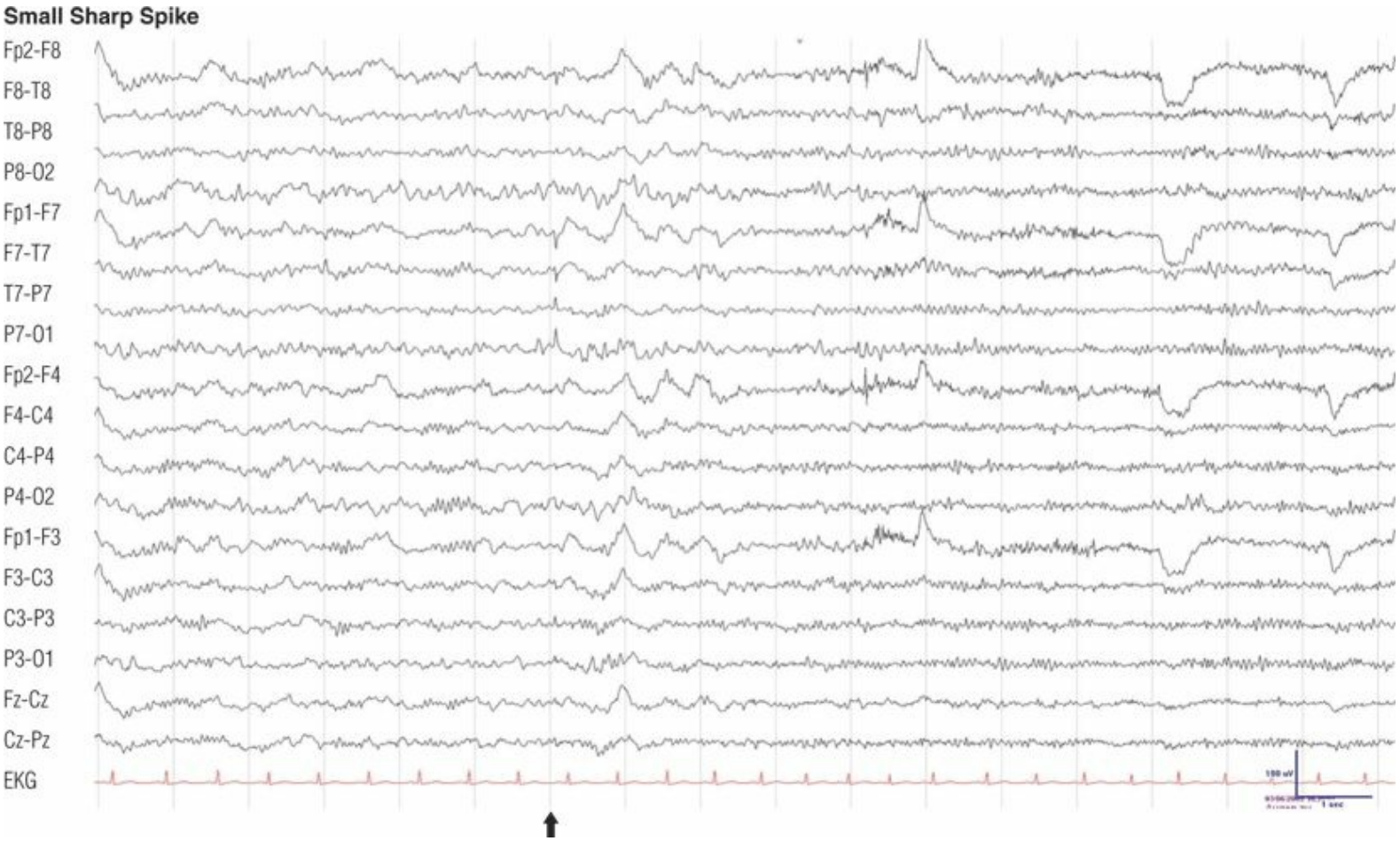

Figure 8.5. Forty-two–year-old man, otherwise normal, with chronic tension headache. Note the low-amplitude monophasic sharp transient (arrow) followed by a minimal slow wave, maximum negativity in the left posterior temporal region (electrode P7), undisturbed background rhythms, during light sleep. During the second half of the EEG, the patient is awake. Small, sharp spikes have also been called benign epileptiform transients of sleep (7).

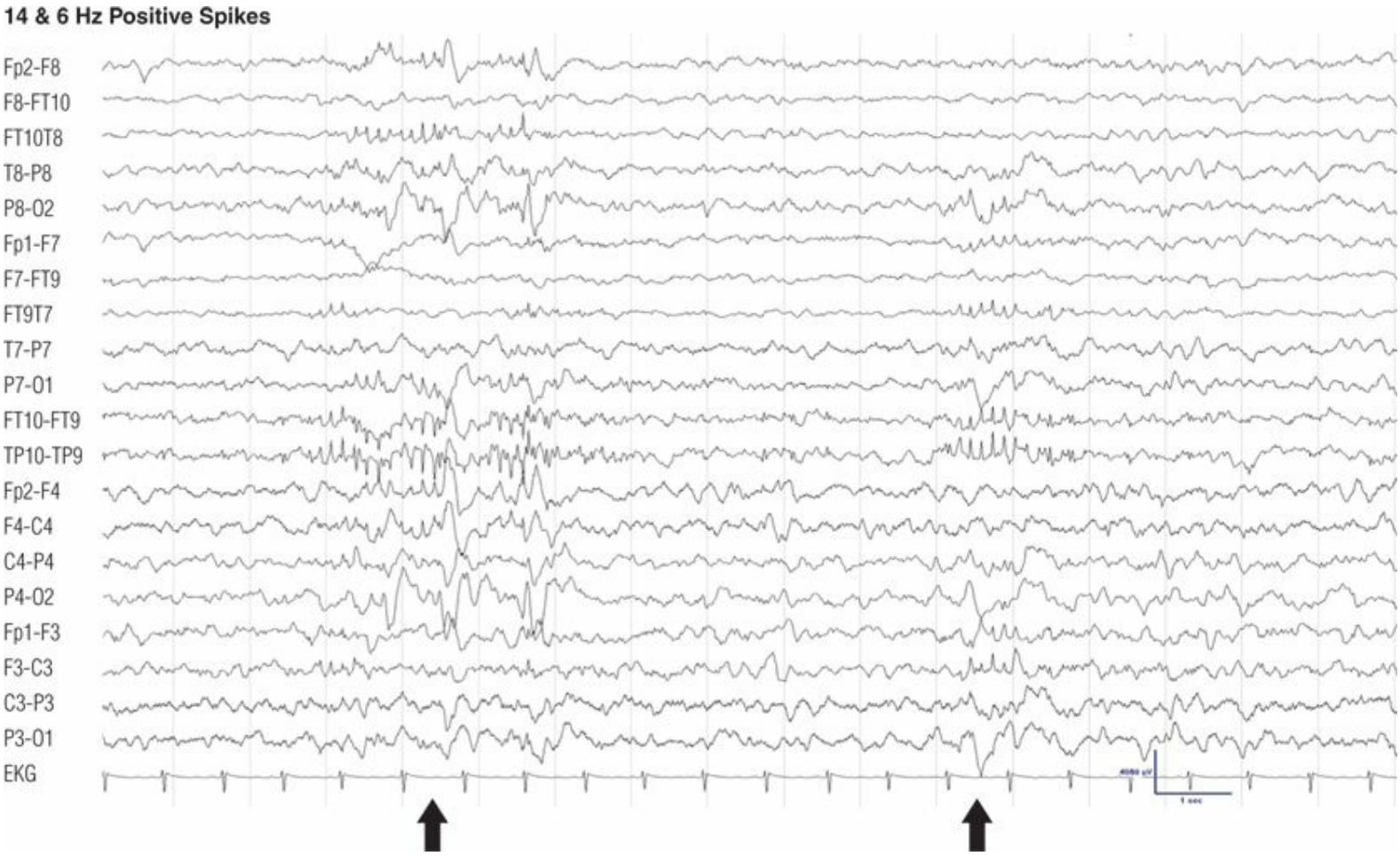

Figure 8.6. Thirteen-year-old girl, otherwise normal, with vasovagal syncope. Note the burst of sharply contoured 14- and 6-Hz activity with maximum positivity in the left and right posterior temporal regions, occurring in light sleep (8). The transhemispheric montage TP10-TP9 depicts the highest amplitude of the positive spikes. Positive spikes of 14 and 6Hz have also been called ctenoids.

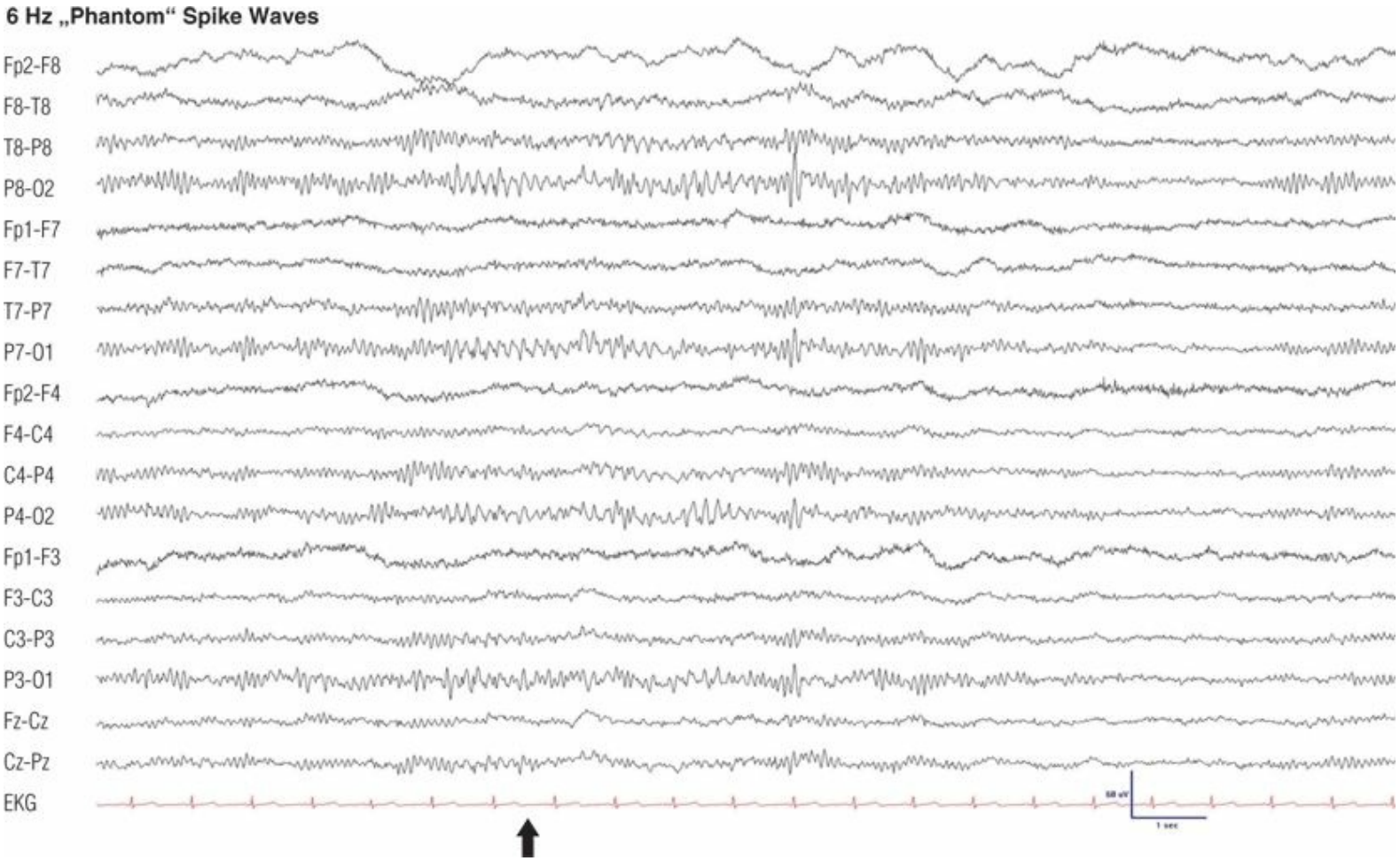

Figure 8.7. Twenty-two–year-old woman with vasovagal syncope. Note the generalized burst of 6-Hz low-amplitude spikes with 6-Hz slow waves occurring during drowsiness in the posterior regions (6).

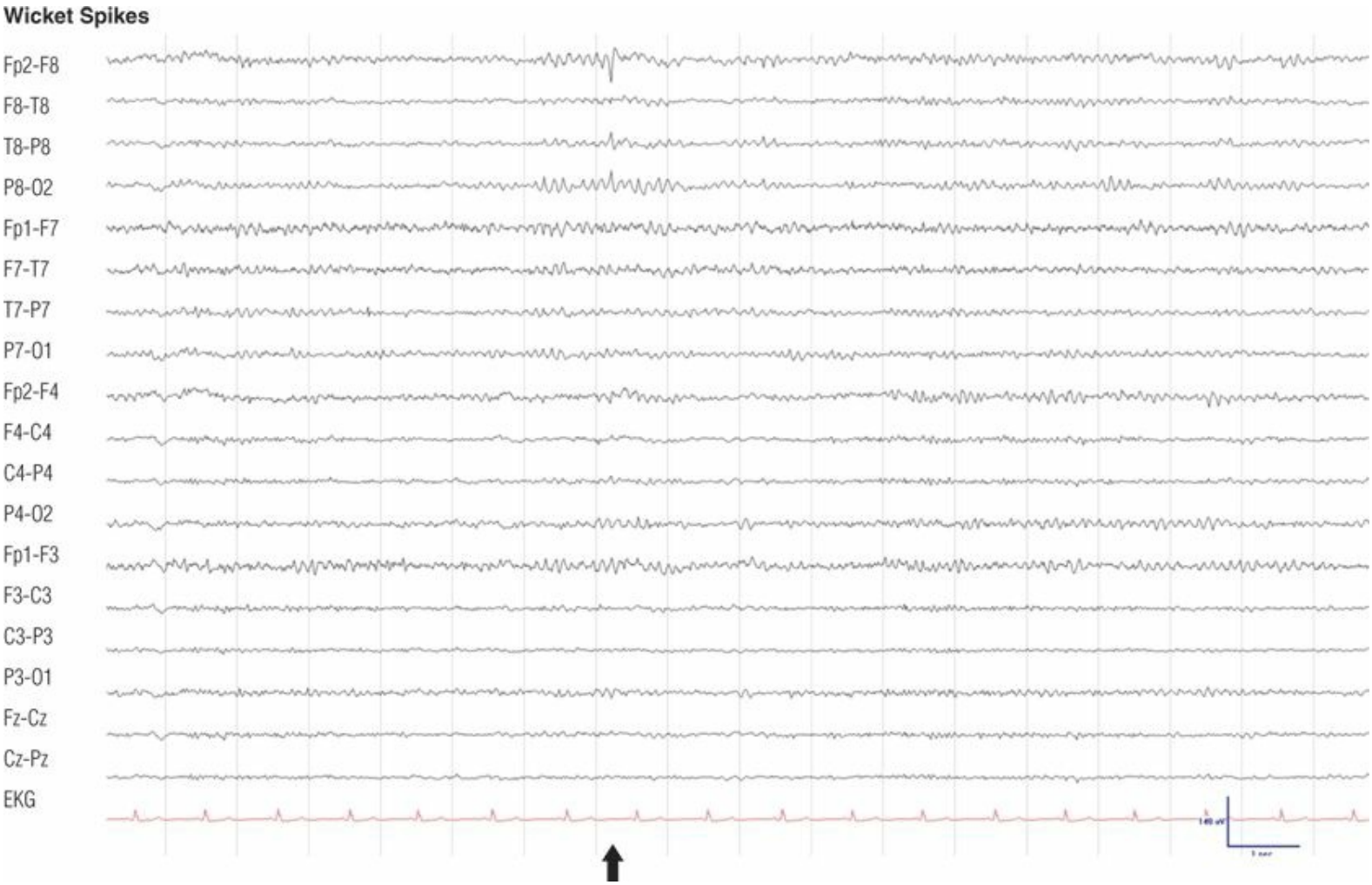

Figure 8.8. Fifty-four–year-old woman with migraine. Note the 7-Hz, rhythmic, sharply contoured waves with maximum negativity in midtemporal regions, occurrence during drowsiness, and undisturbed background rhythms. The typical frequency of wicket spikes is 6 to 11 Hz (9).

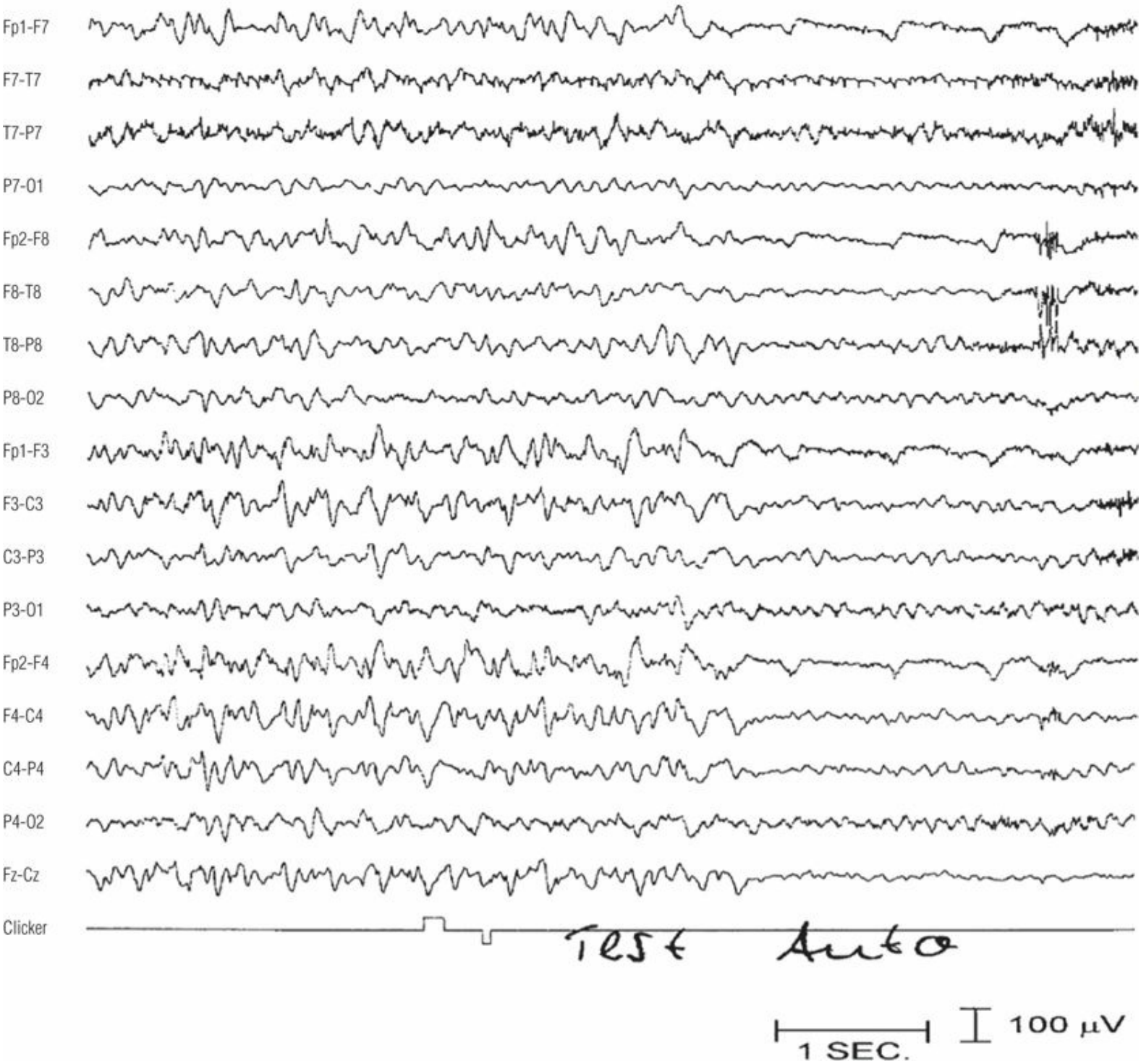

Figure 8.9. Sixty-one–year-old woman with depression. Note the diffuse frontal-maximum, rhythmic, sharply contoured theta and delta activity (10) that ended after 34 seconds and was immediately followed by a normal posterior dominant alpha rhythm. During the rhythmic activity, the patient responded appropriately to an auditory stimulus (clicker). In the last channel, the upward deflection was from the technician's sound stimulus, and the subsequent downward deflection was from the button pressed by the patient in response. The patient remained awake and responsive throughout the recording and afterward recalled the test word ("auto").

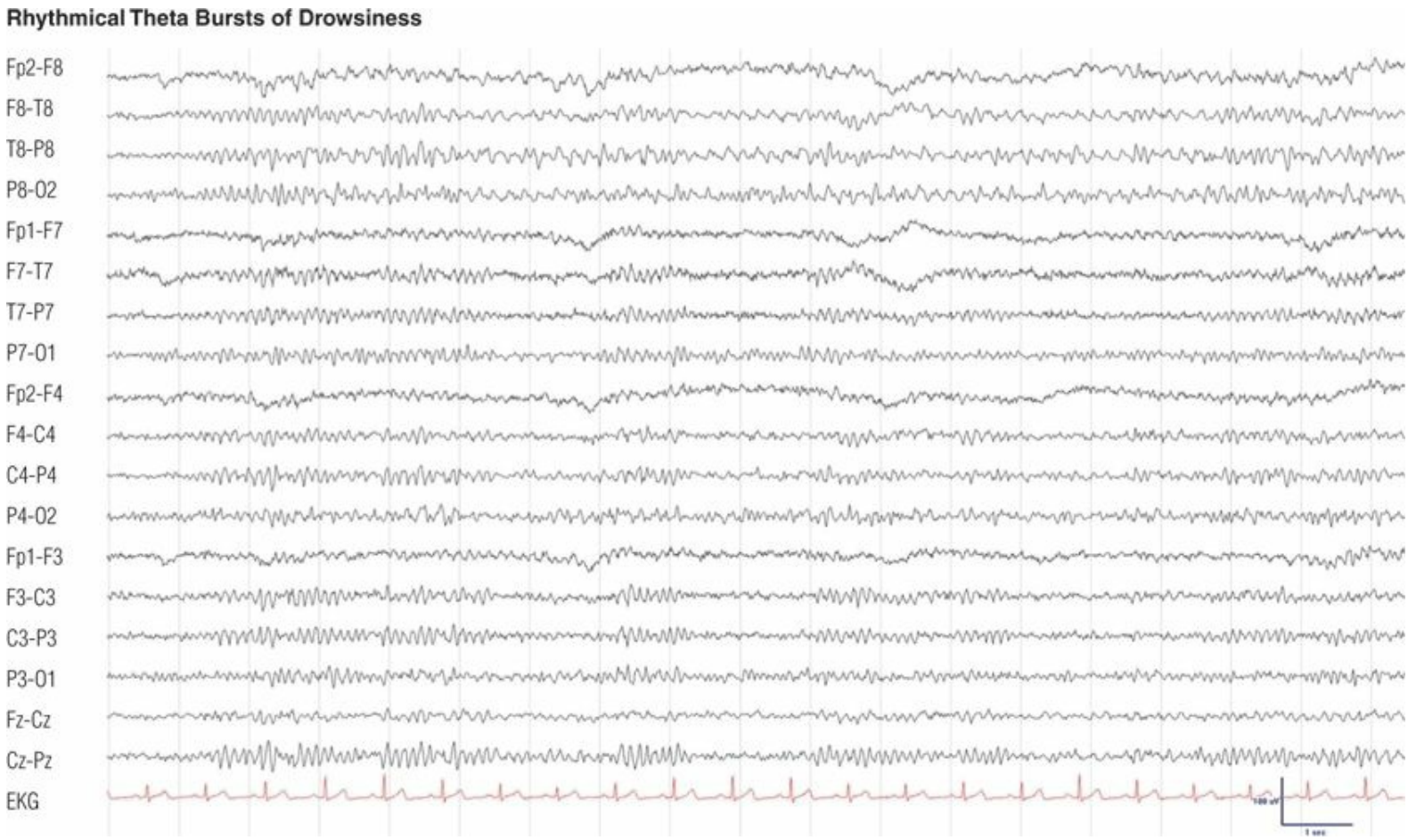

Figure 8.10. Thirty-three–year-old woman with depression. This rhythmic theta activity during drowsiness, with sharply contoured waves maximal in the left midtemporal region, has also been called psychomotor variant (6,11).

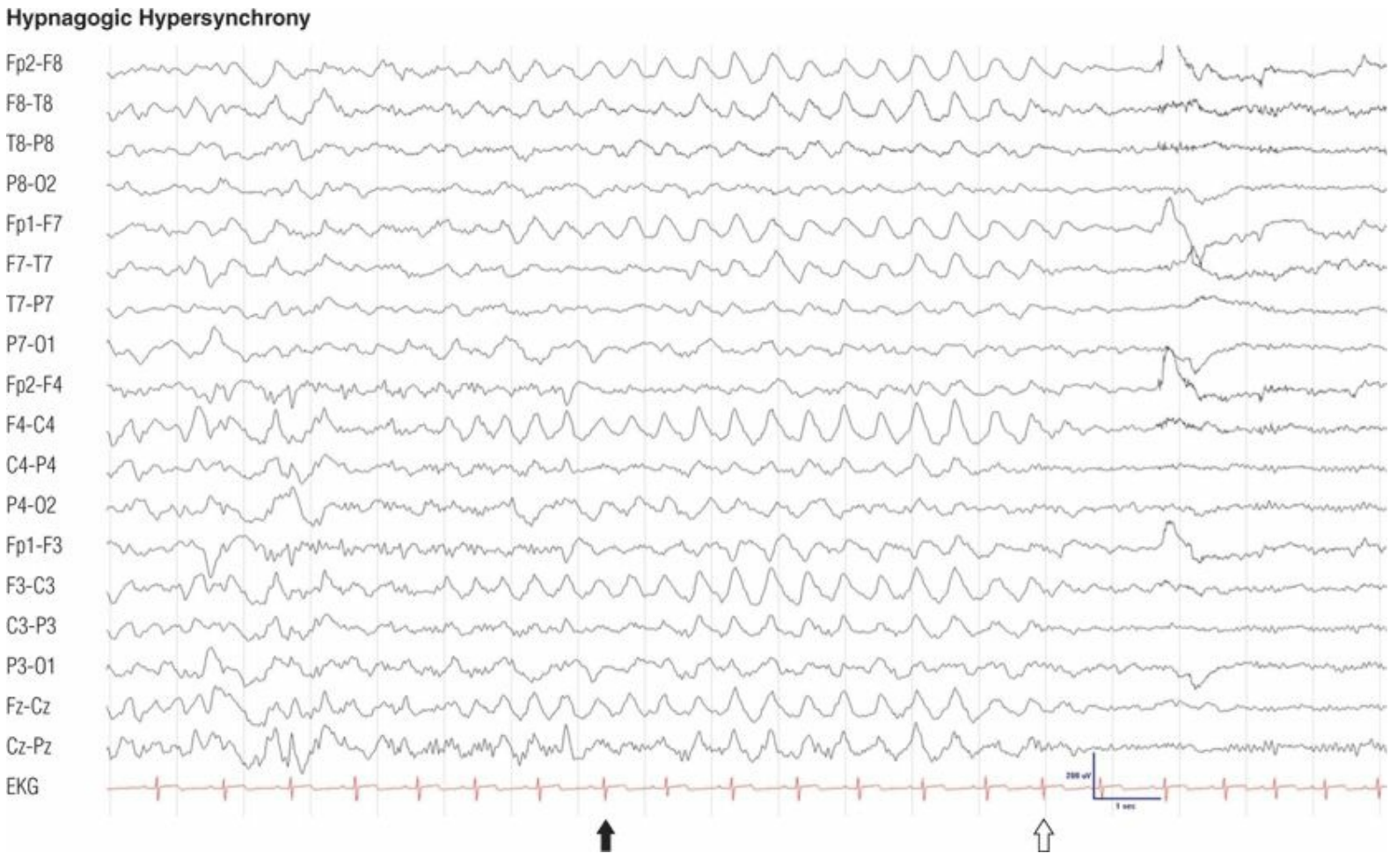

Figure 8.11. Eleven-year-old normal boy. Note the generalized, rhythmic, high-amplitude delta waves during drowsiness (black arrow), which cease with arousal (open arrow).

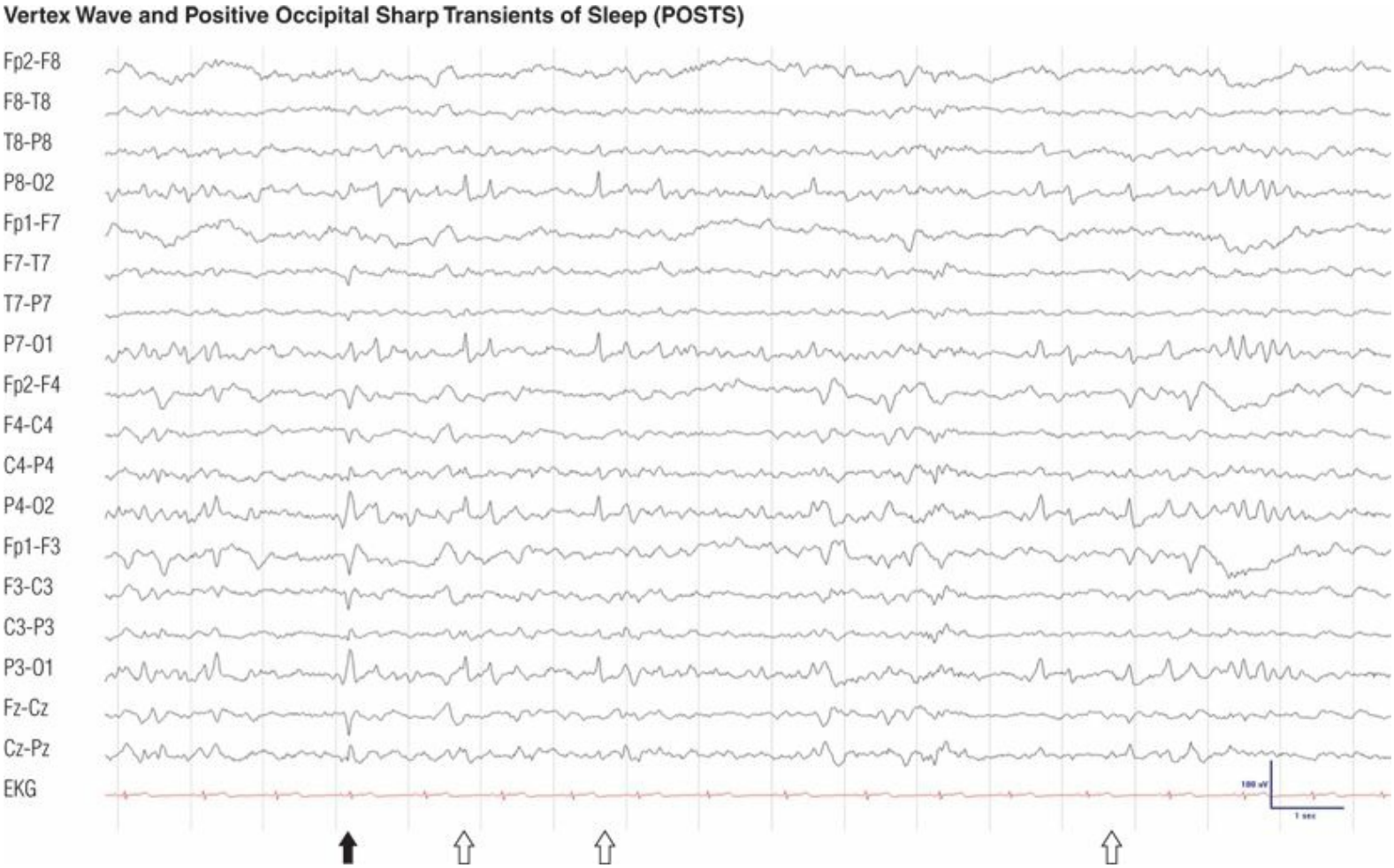

Figure 8.12. Sixteen-year-old girl with vasovagal syncope. Note the central vertex waves (black arrow) and runs of positive occipital sharp transients of sleep (POSTS) (open arrows) (channels 4, 8, 12, and 16), both normal features of stage I or II non–rapid eye movement (non-REM) sleep.

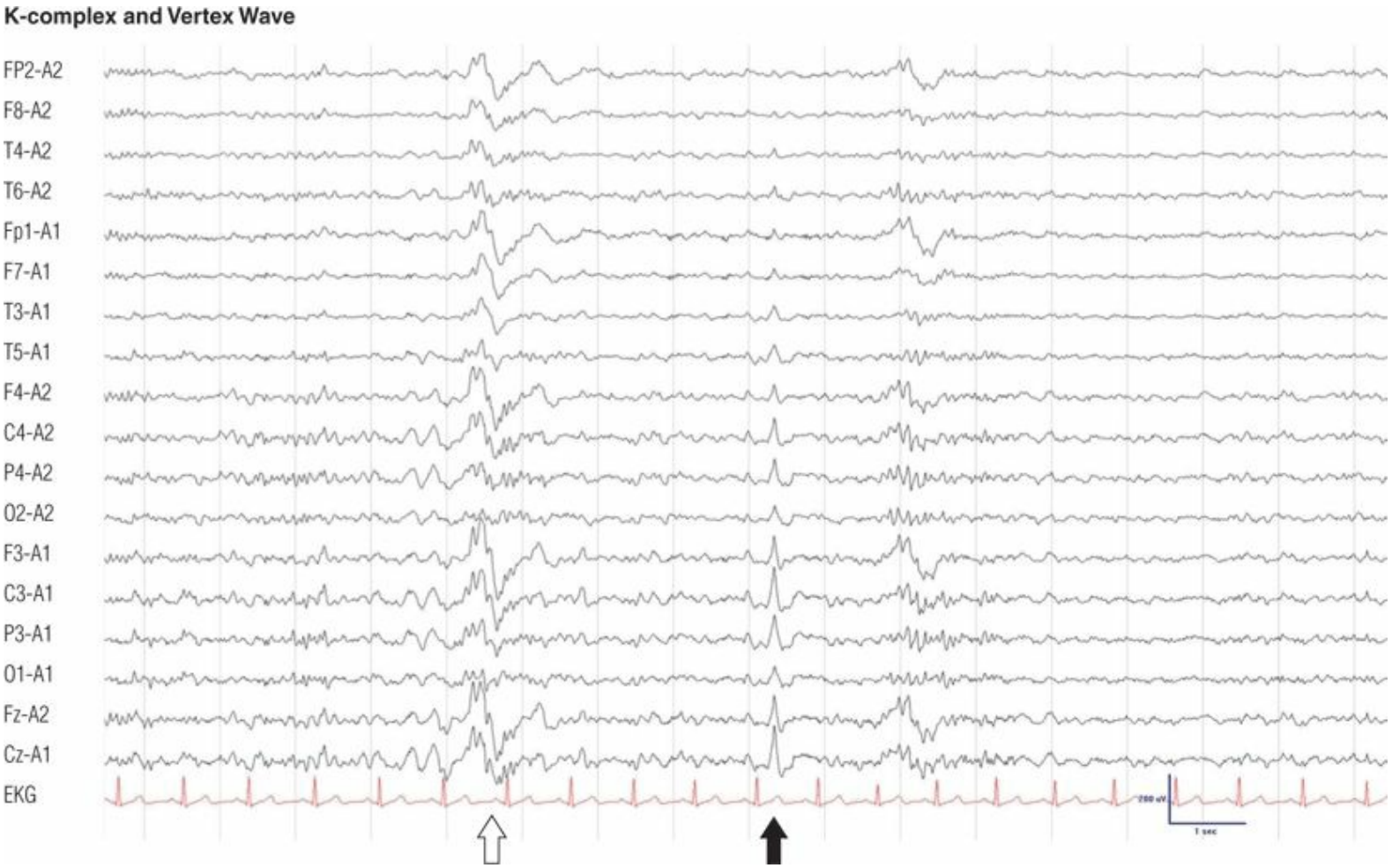

Figure 8.13. Twenty-four–year-old man. K-complexes (open arrow) and vertex wave (solid arrow). Note the sleep spindle, which is associated with the K-complex during stage II non-REM sleep.

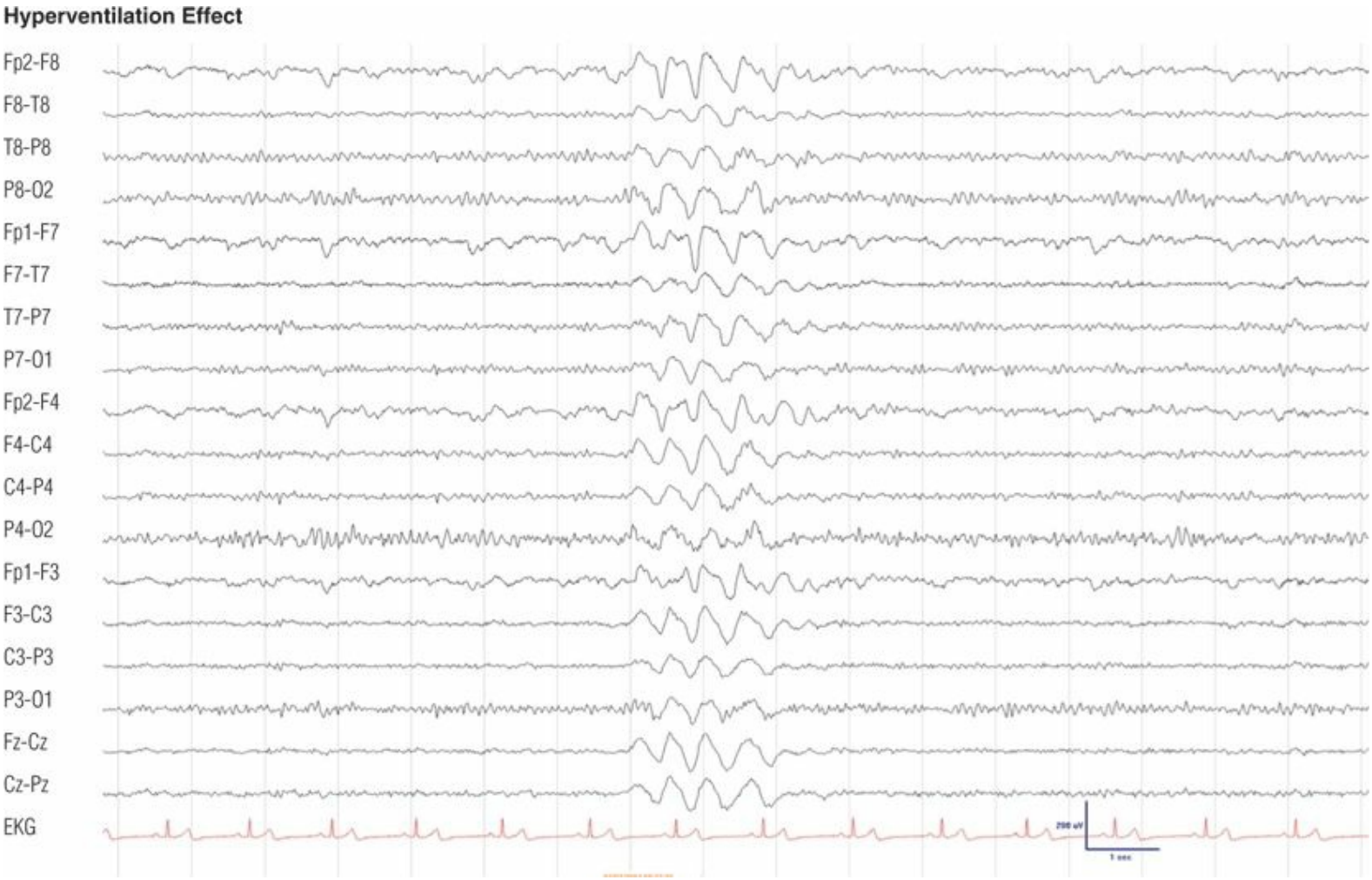

Figure 8.14. Eighteen-year-old girl with school tension headache. Hyperventilation-induced high-amplitude rhythmic delta slowing is a normal response. The girl was alert and responsive during this tracing, which was obtained after 1 minute of hyperventilation.

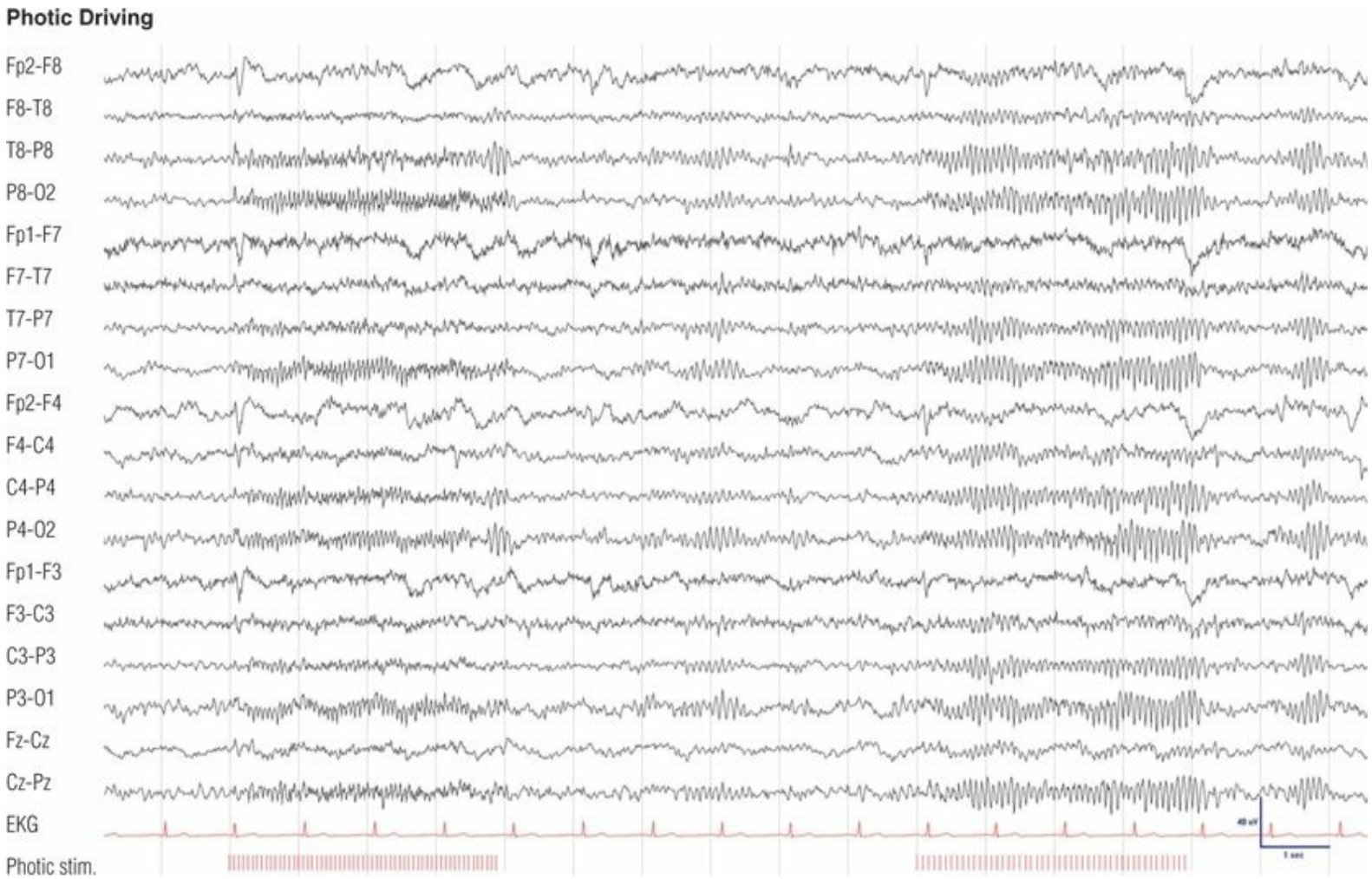

Figure 8.15. Sixteen-year-old boy with childhood absence epilepsy since 7 years of age, seizure free on medication for the last 3 years. Note the time-locked, unsustained, bioccipital response to 8- and 4-Hz photic stimulation, separated by normal posterior background activity. Photic driving represents a normal response to photic stimulation and is not related to the epilepsy of the patient.

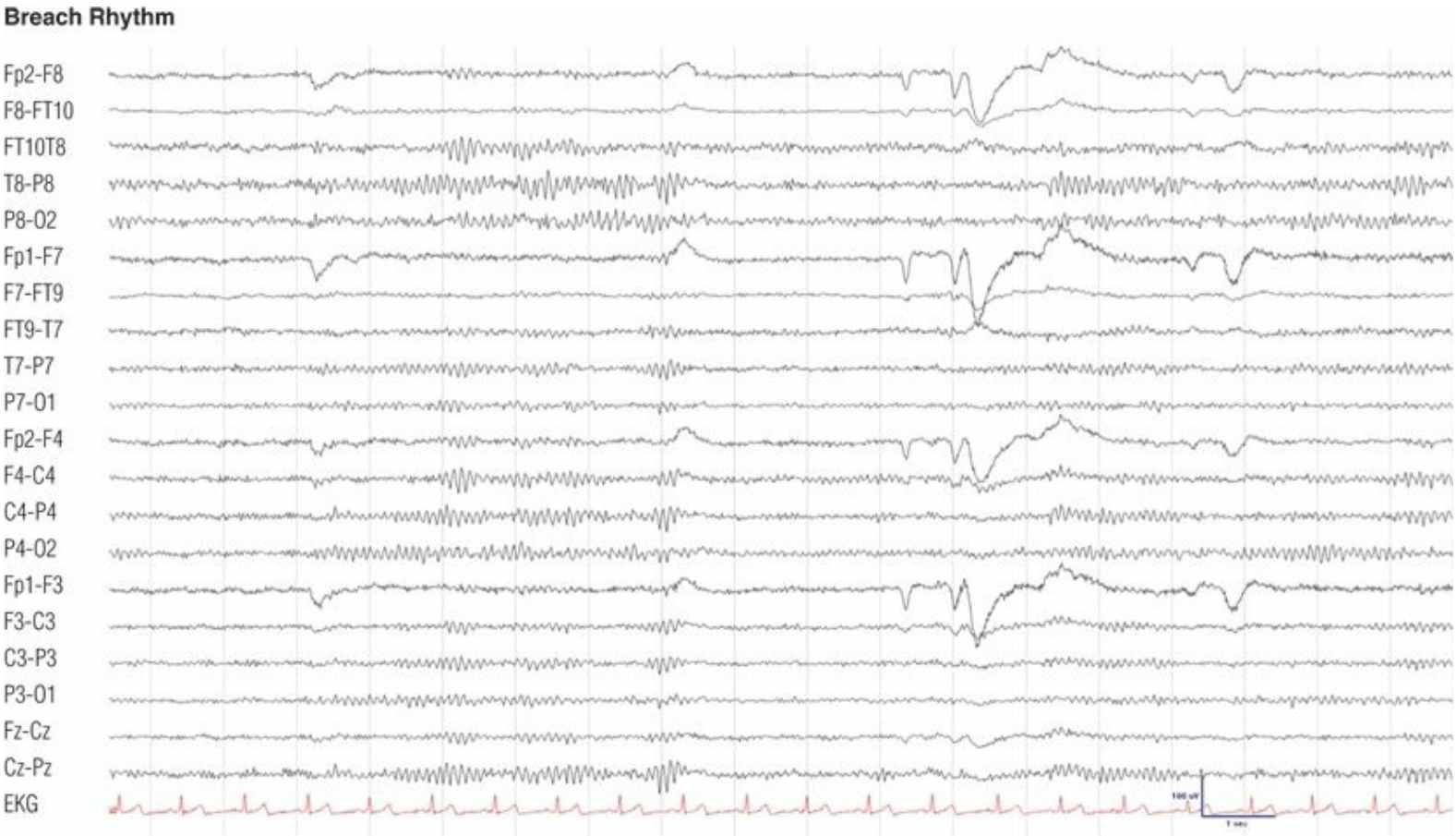

Figure 8.16. Fifty-one–year-old woman with trigeminal neuralgia, status after right parietotemporal craniotomy for vascular decompression. Note the asymmetry of background rhythms owing to the skull defect (12), maximum at the right temporal (T8, P8) electrodes.

PART II: ELECTROENCEPHALOGRAPHIC ABNORMALITIES OF THE GENERALIZED EPILEPSIES

Childhood Absence Epilepsy

Generalized spike–wave complexes	Figure 8.17

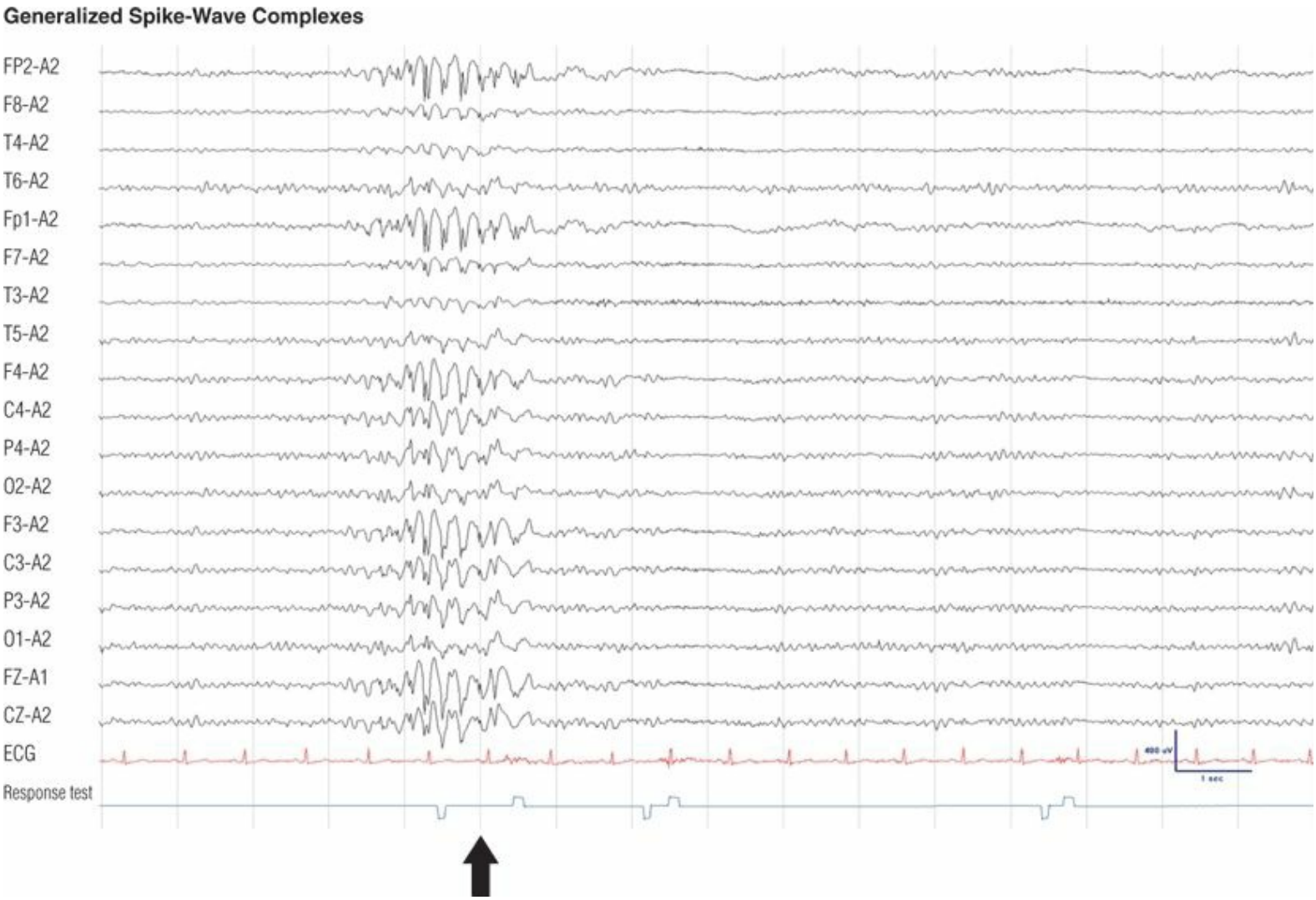

Figure 8.17. Twelve-year-old boy, otherwise normal, with recent onset of absence seizures. These irregular generalized spike-and-wave complexes were precipitated by hyperventilation and lasted for almost 2 seconds. Note that the patient failed to press a button (black arrow) as a response to an auditory stimulus (clicker test) given to him during the SWC, but he responded to a second stimulus at the end of the discharge. These episodes would go unnoticed if not tested.

Juvenile Absence Epilepsy

Absence status epilepticus	Figures 8.18 and 8.19

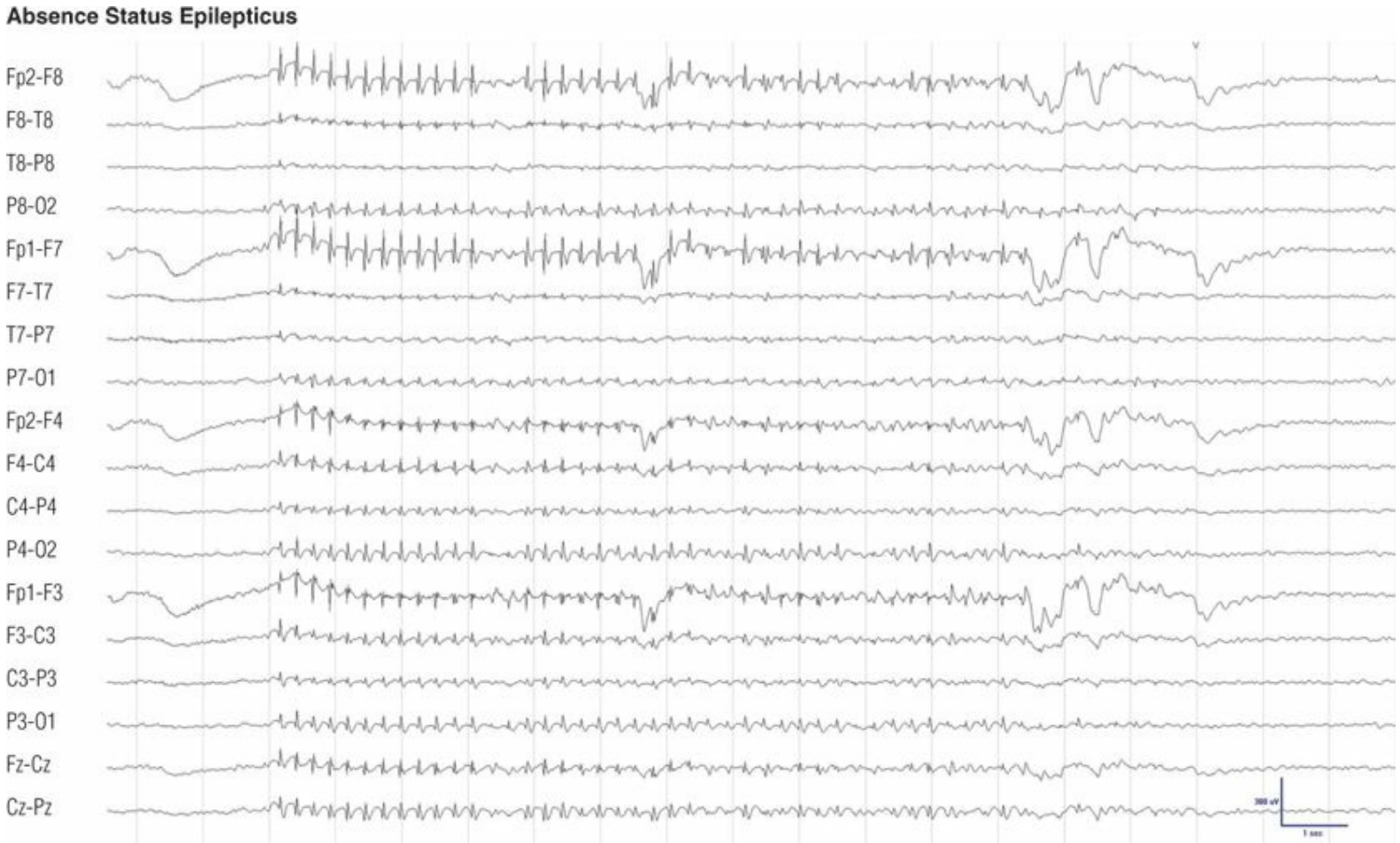

Figure 8.18. Thirty-six–year-old woman with absence seizures during childhood. She was seizure free throughout adulthood off medication until recently absence status epilepticus began during drug treatment with imipramine for depression. During this episode, with generalized spike-and-wave complexes, she was unresponsive. Electroencephalographic findings and behavior returned to normal after intravenous injection of lorazepam.

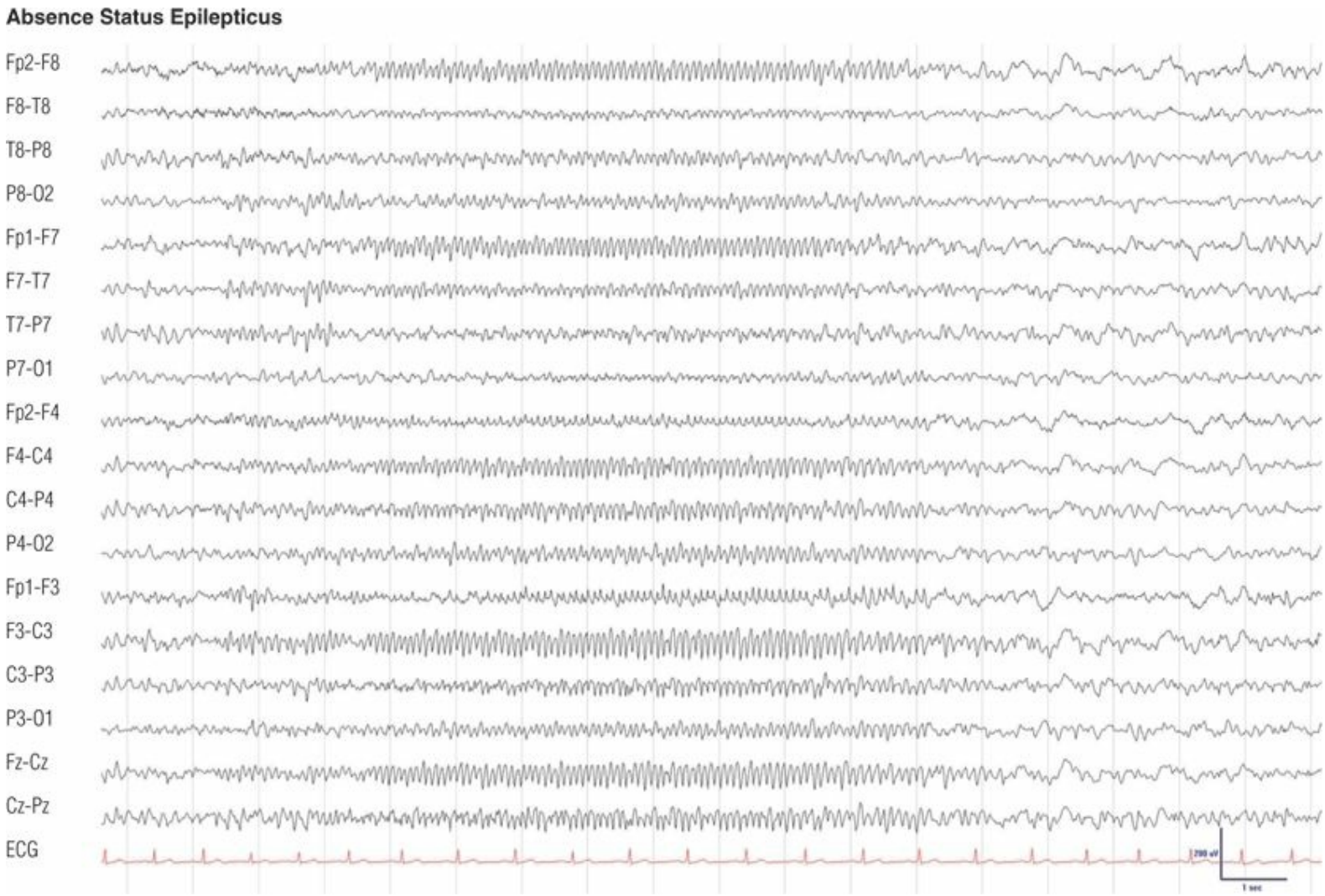

Figure 8.19. Fifty-eight–year-old man with juvenile absence epilepsy with a 2-day history of confusion and agitation prior to this electroencephalogram (EEG). He was switched to topiramate and stopped valproic acid erroneously. EEG findings and behavior returned to normal after intravenous injection of clonazepam.

Myoclonic Epilepsy

Photoparoxysmal response in juvenile myoclonic epilepsy	Figure 8.20
Generalized myoclonic seizure	Figure 8.21

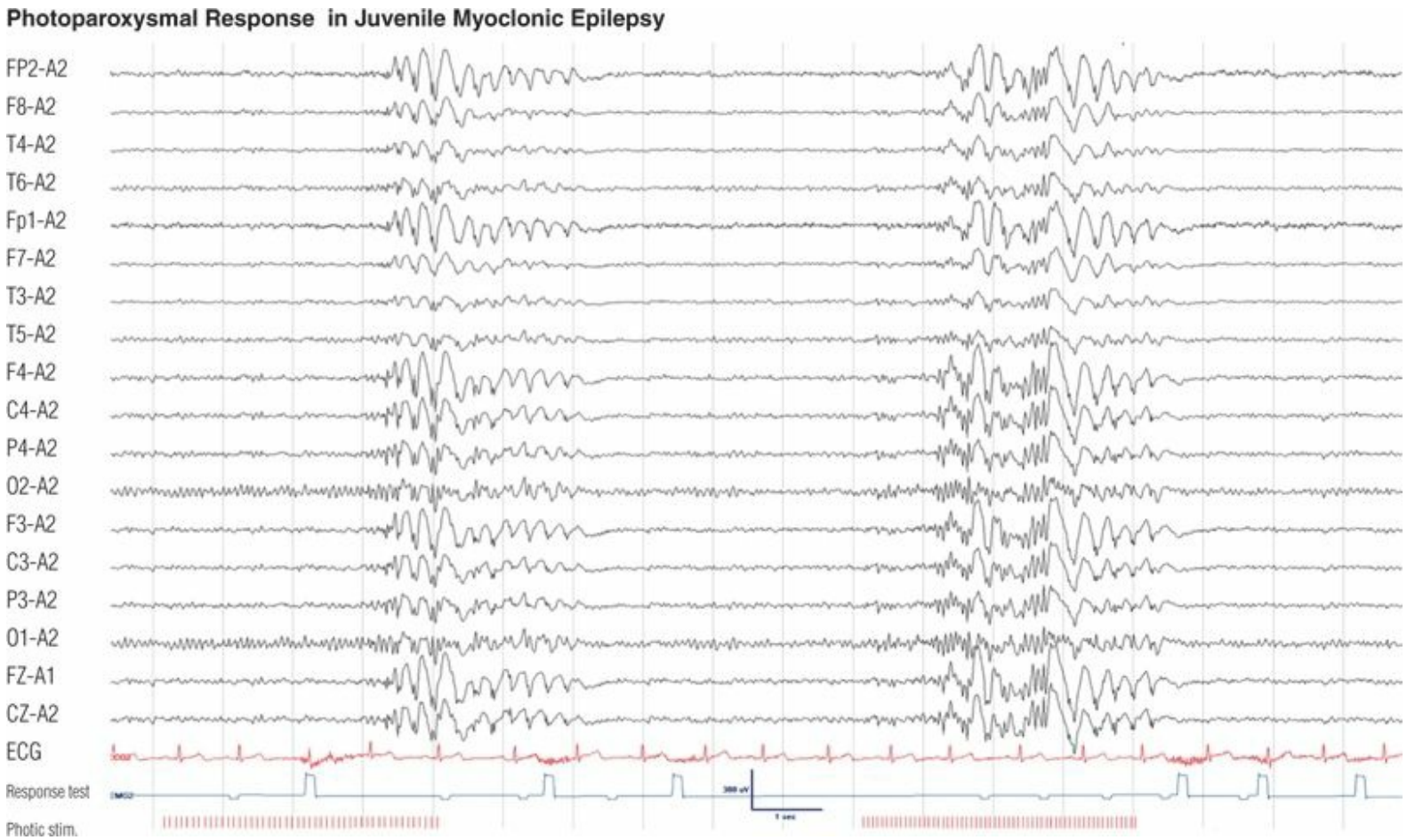

Figure 8.20. Sixteen-year-old boy with a 4-year history of myoclonic jerks of the upper extremities and a few generalized tonic–clonic seizures in the morning after awakening. Photic stimulation elicited generalized polyspikes and spike–wave complexes at 12 and 15 Hz. His responses to auditory stimuli during these discharges were either absent or delayed (absence seizure) (see clicker test).

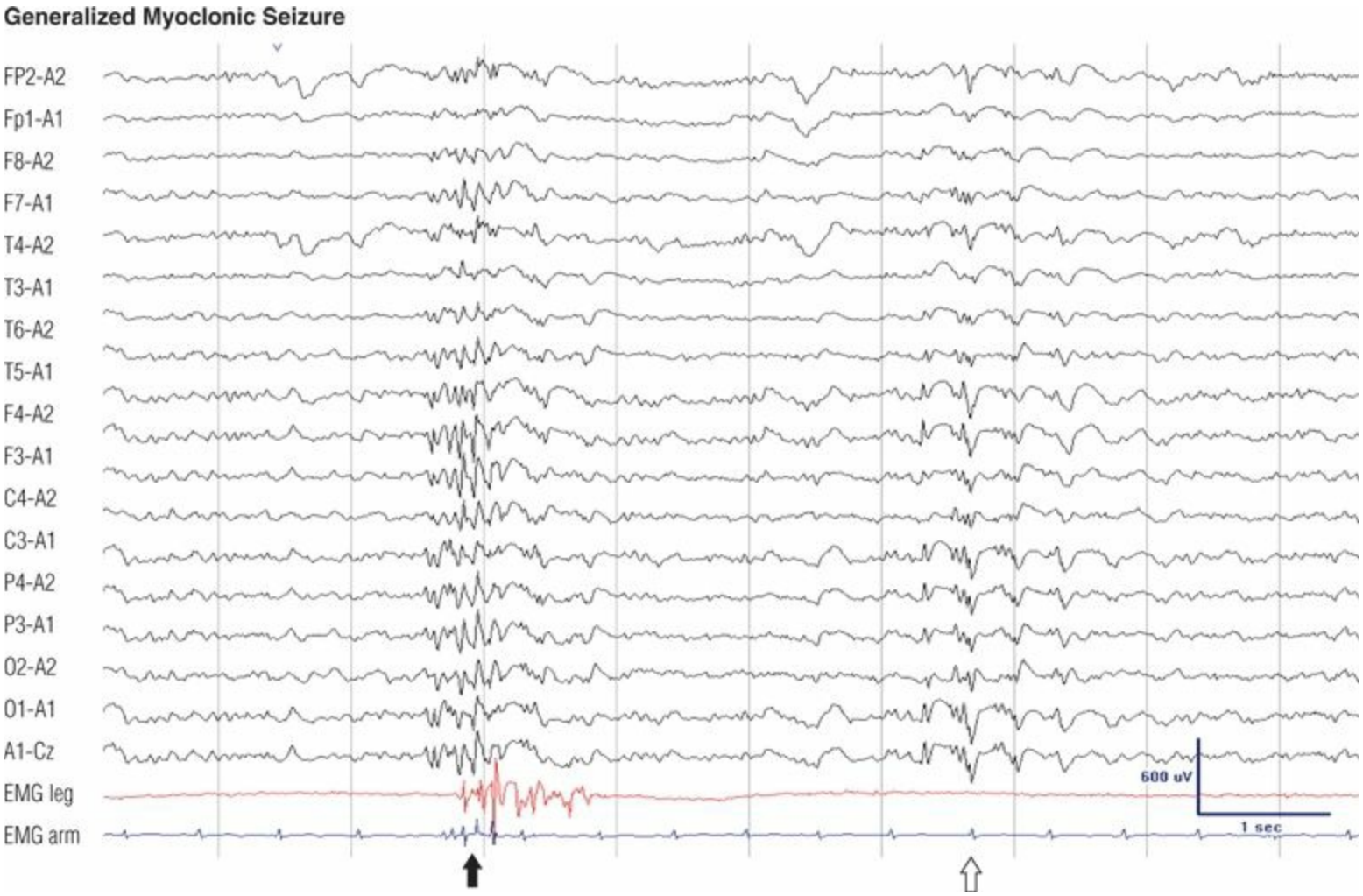

Figure 8.21. Twenty-two–year-old man, otherwise normal, with generalized myoclonic and generalized tonic–clonic seizures on awakening since adolescence. His generalized myoclonic seizures consisted of jerks of the arms. EEG during drowsiness. Note the dense generalized polyspikes were associated with jerks (solid arrow), whereas the other discharges (open arrow) were not.

Infantile Spasms

Hypsarrhythmia	Figure 8.22
West syndrome: infantile spasm	Figure 8.23

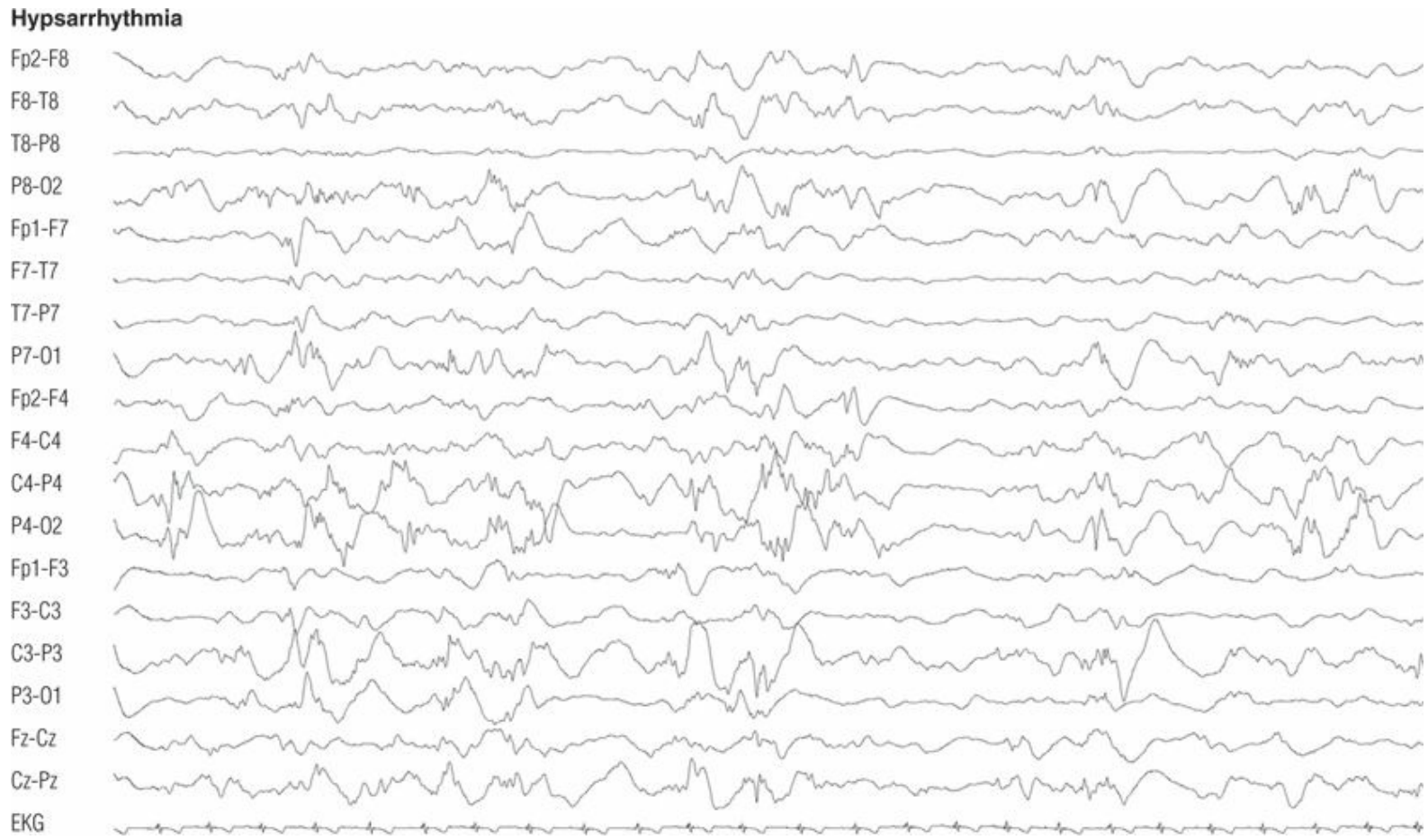

Figure 8.22. Ten-month-old boy with infantile spasms and developmental delay. Awake electroencephalographic record showed disorganized background rhythms dominated by multifocal spikes and high-amplitude slowing.

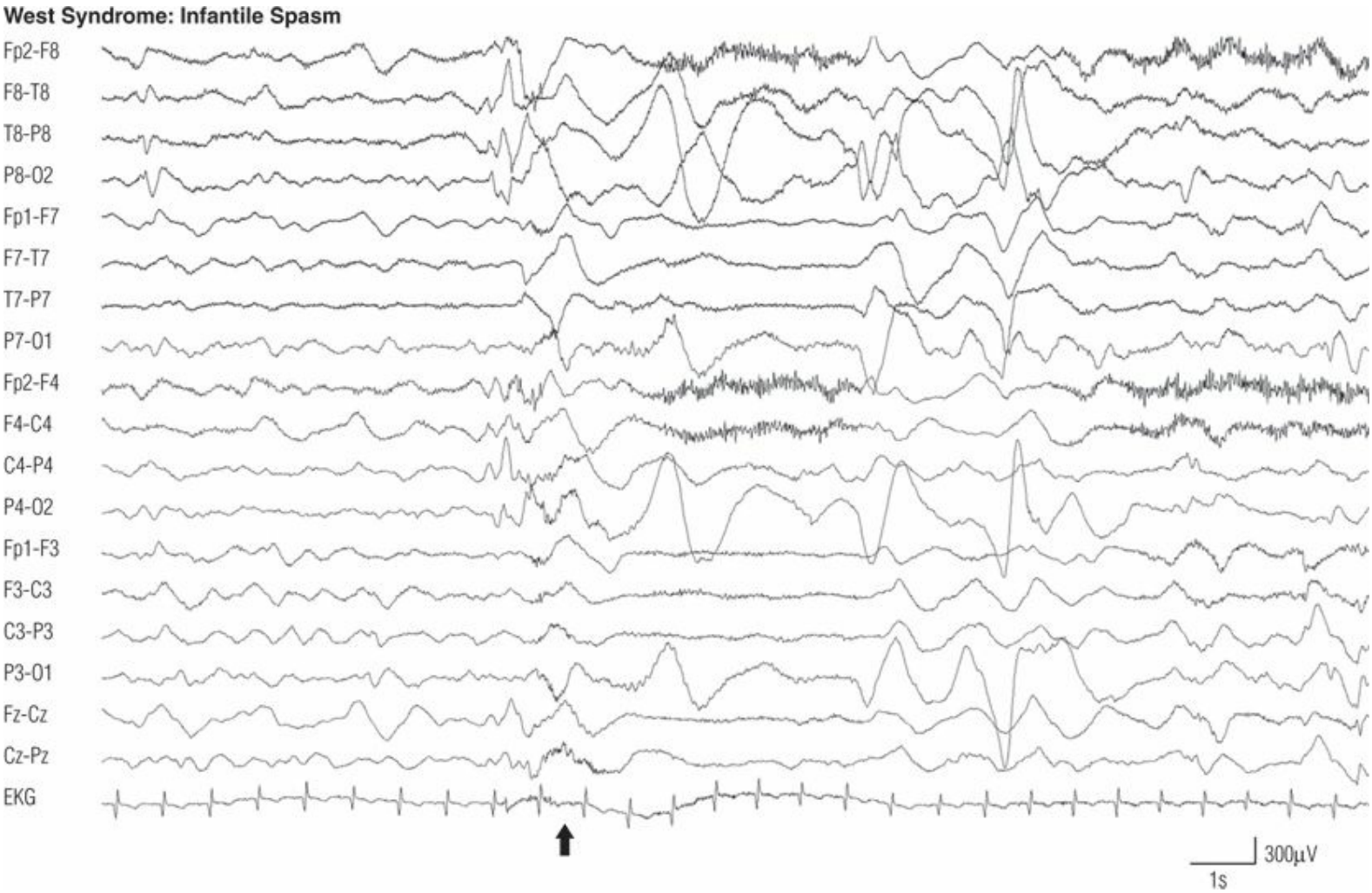

Figure 8.23. EEG during a spasm (arrow), from the same infant as in Figure 8.22. Note the generalized electrodecremental pattern for 3 seconds. The spasm involved tonic abduction and extension of both arms with flexion of the trunk and neck.

Lennox–Gastaut Syndrome

Generalized slow spike–wave complexes	Figure 8.24
Generalized paroxysmal fast and polyspikes in sleep	Figures 8.25 and 8.26
Atonic seizures	Figure 8.27

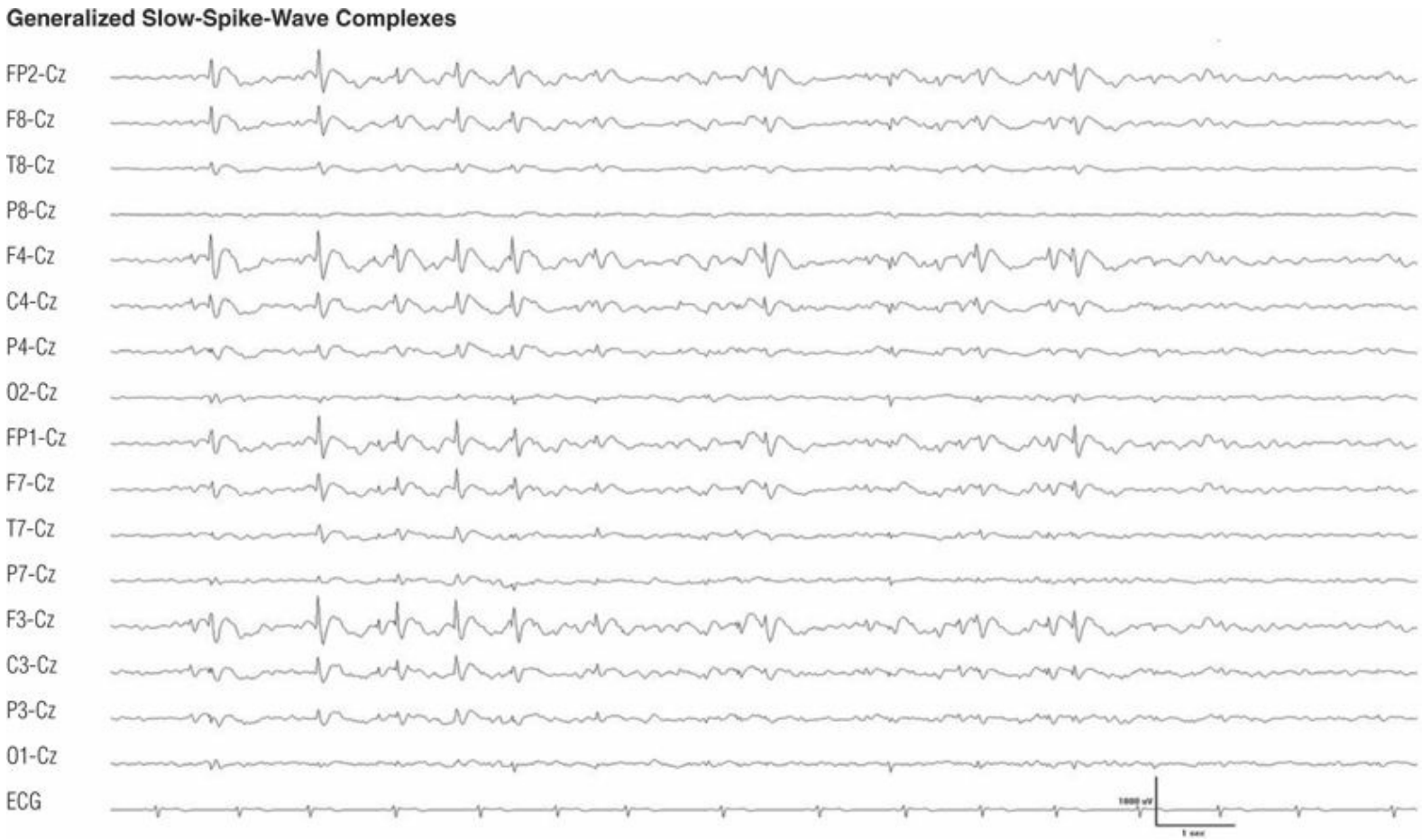

Figure 8.24. Seven-year-old boy with developmental delay and intractable generalized tonic, atonic, myoclonic, tonic–clonic, and atypical absence seizures since age 3 years. Note the bifrontal maximum of the generalized sharp– and slow–wave complexes (5), also called slow spike-and-wave complexes.

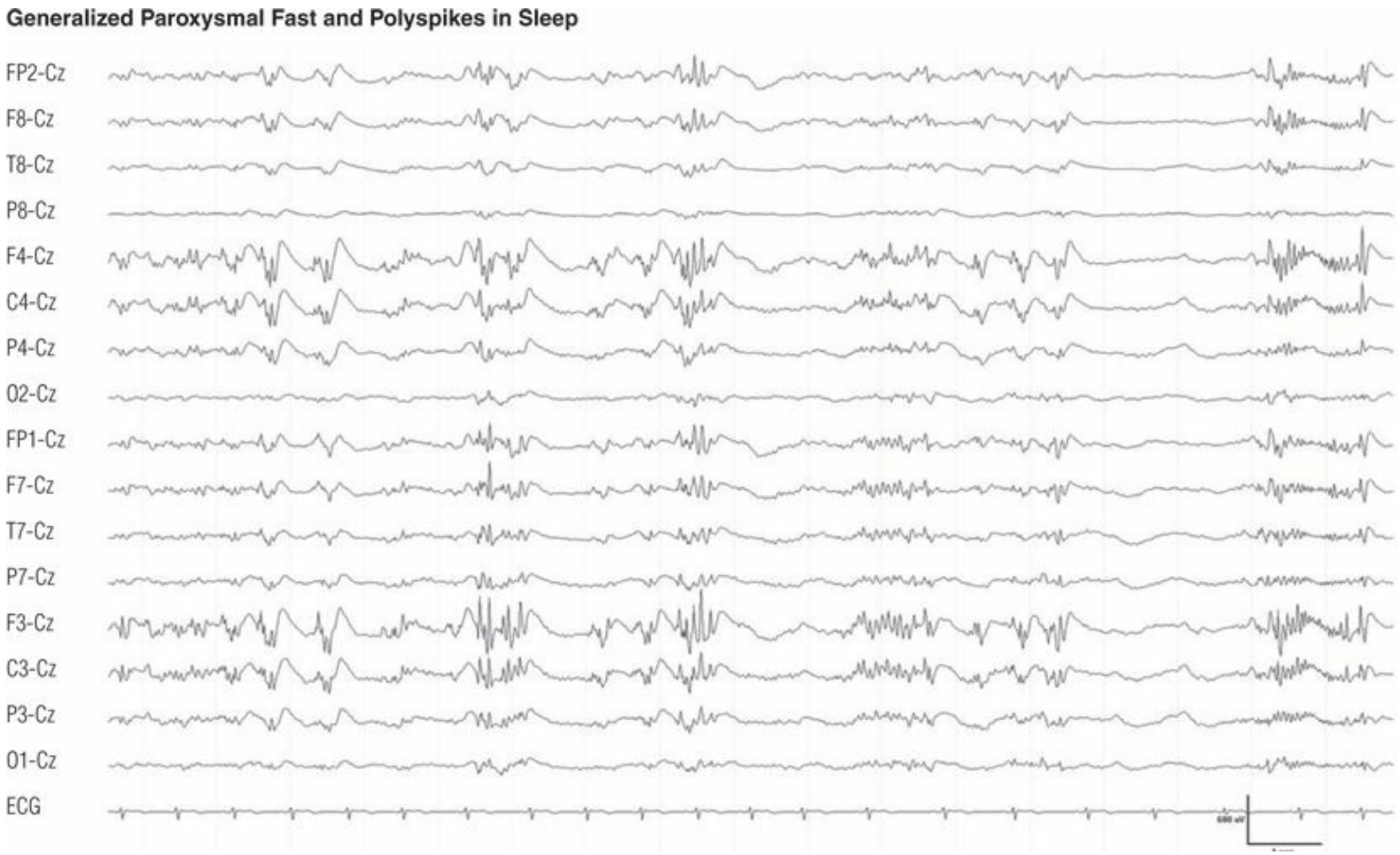

Figure 8.25. Same patient as in Figure 8.24. Generalized polyspikes and paroxysmal fast during drowsiness.

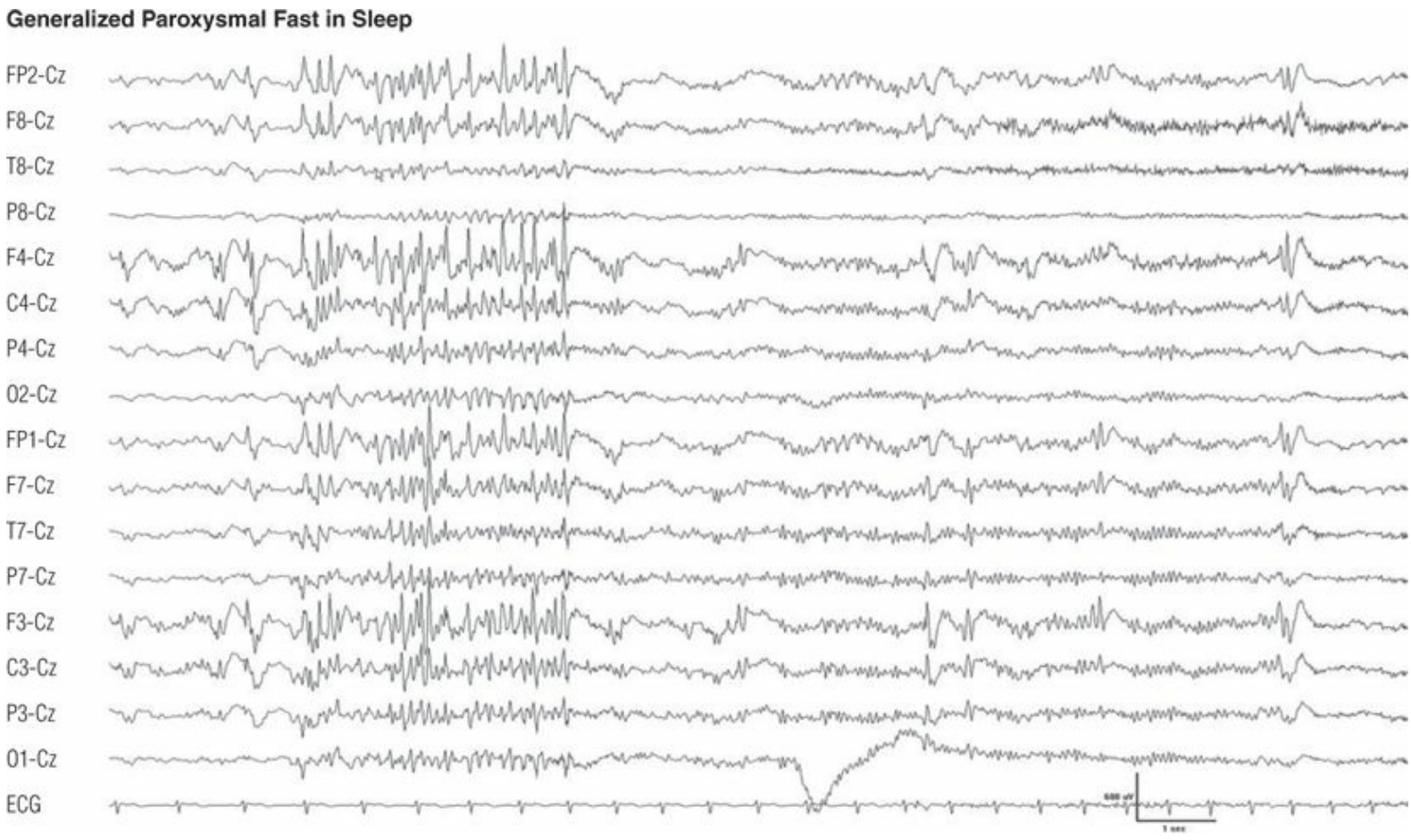

Figure 8.26. Same patient as in Figures 8.24 and 8.25. During drowsiness, generalized paroxysmal fast occurred. When the

paroxysmal fast lasted longer than 5 to 6 seconds, generalized tonic seizure was observed.

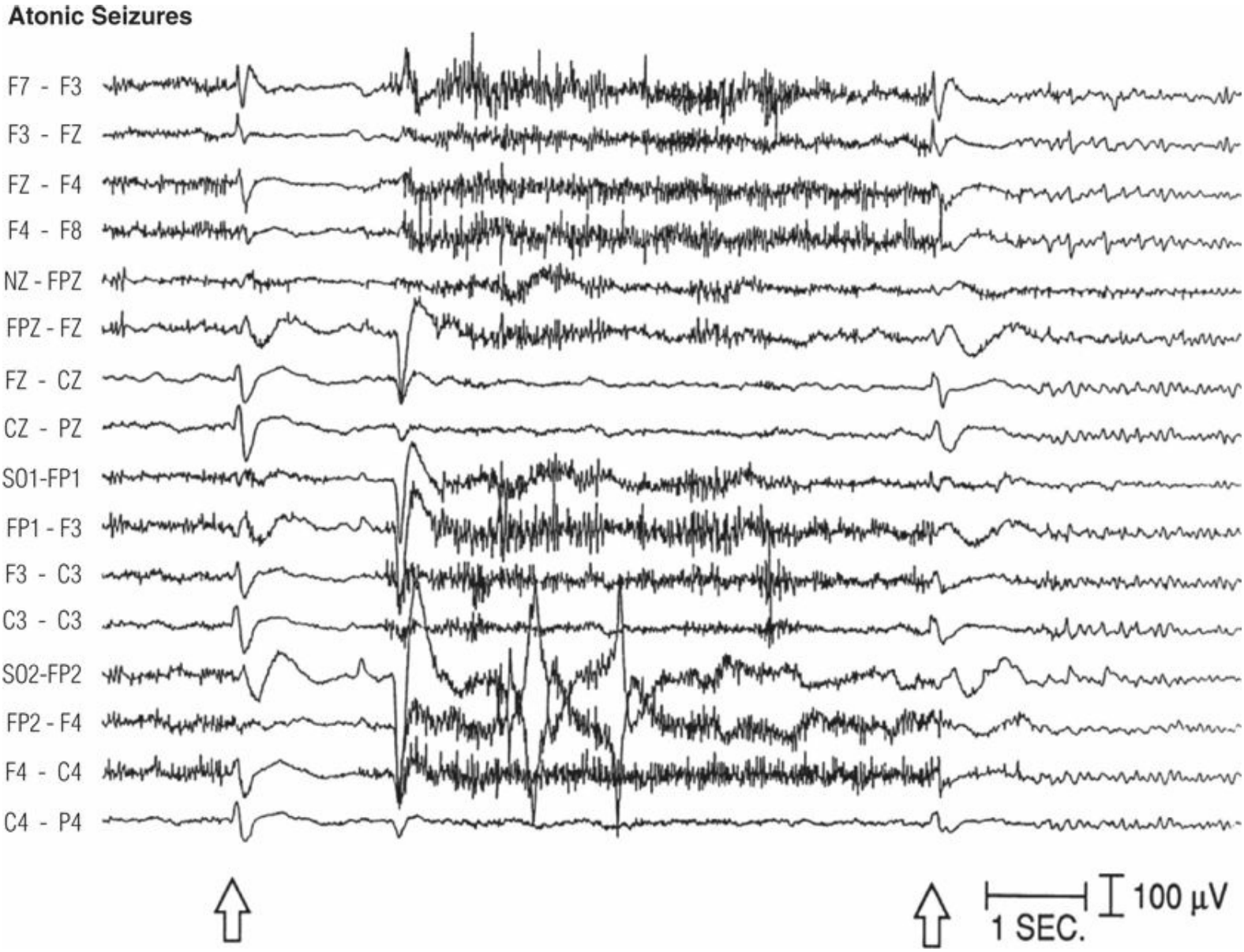

Figure 8.27. Forty-one–year-old man with borderline intelligence and intractable generalized tonic, atonic, generalized tonic–clonic, and atypical absence seizures since age 3 years. Interictal electroencephalogram showed generalized sharp– and slow–wave complexes. Two seizures are recorded here, with limp head nodding plus tonic stiffening and elevation of both arms. Each seizure began with a generalized sharp wave (open arrows) followed by attenuation of electroencephalograph activity and cessation of muscle artifact.

Intractable Epilepsy with Multifocal Spikes

Intractable epilepsy with multifocal spikes	Figure 8.28

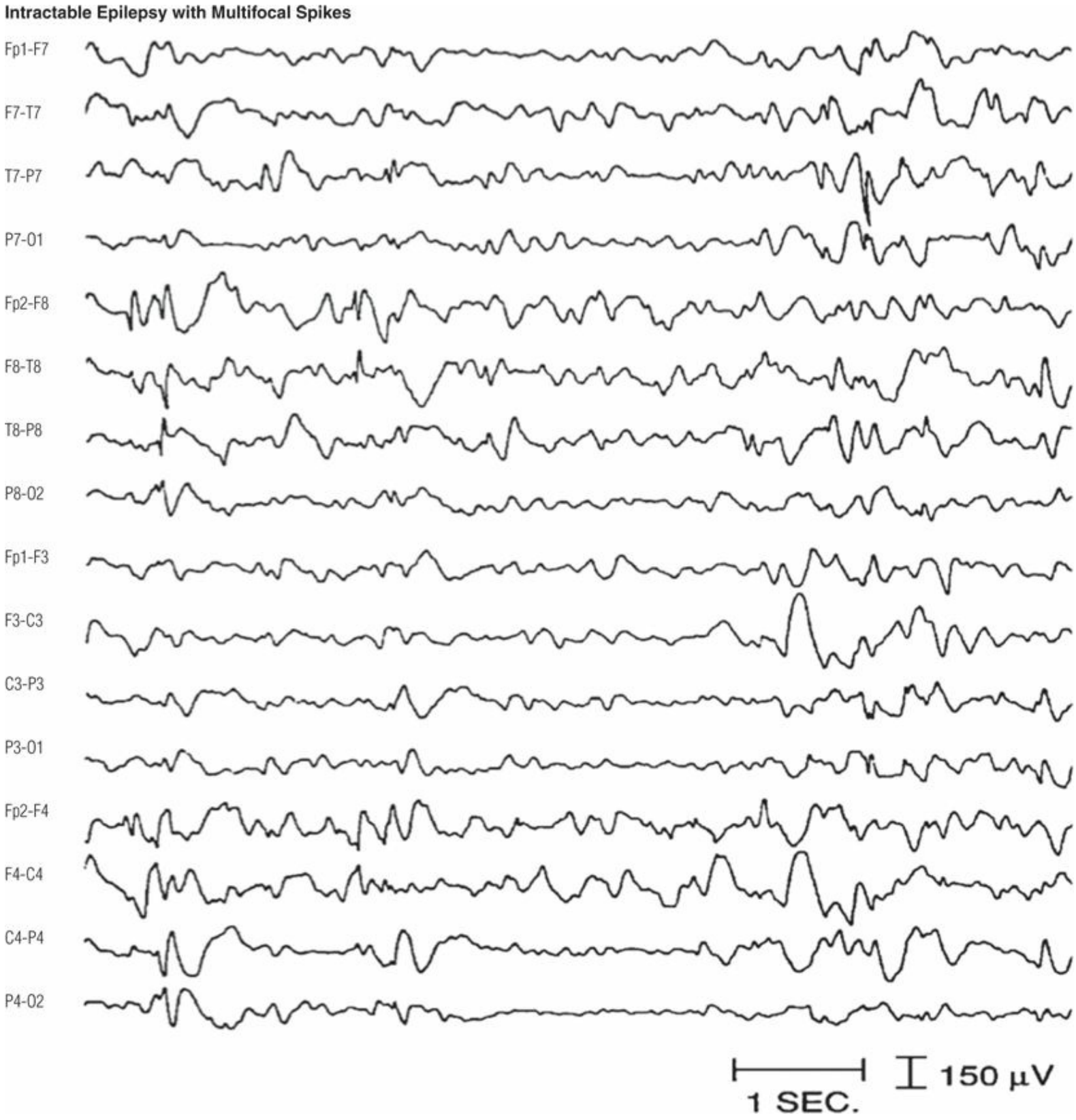

Figure 8.28. Three-year-old boy with developmental delay and intractable clusters of generalized tonic, myoclonic, and atypical absence seizures. This electroencephalographic pattern is not uncommon in children with clinical features similar to those of Lennox–Gastaut syndrome (13).

Stimulation-Related Epilepsy

Cognitive (Soduko)-induced spikes	Figures 8.29 and 8.30

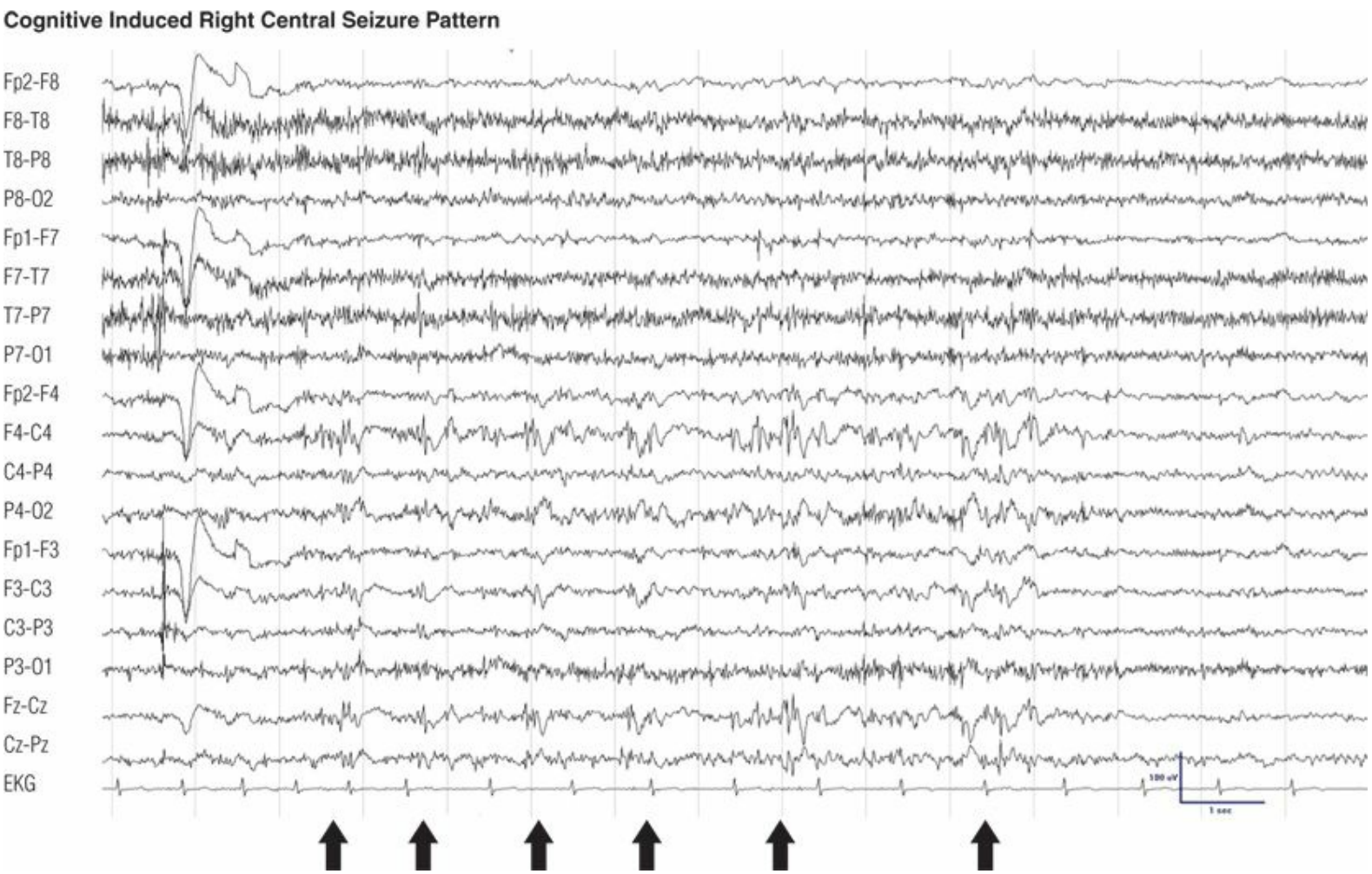

Figure 8.29. Twenty-five–year-old right-handed man with focal clonic seizure induced by cognitive tasks. He developed Lance–Adams syndrome after he was buried by an avalanche resulting in 15 minutes of hypoxia. When the patient was trying to solve Sudoku puzzles, he developed clonic seizures of the left arm (14). These evolved into GTCS in case he continued with the riddle. The unilateral clonic seizures stopped immediately when the sudoku was discontinued. During this EEG, the patient was solving a sudoku; note the initial eye movement artifact that is followed by repetitive right central polyspike bursts.

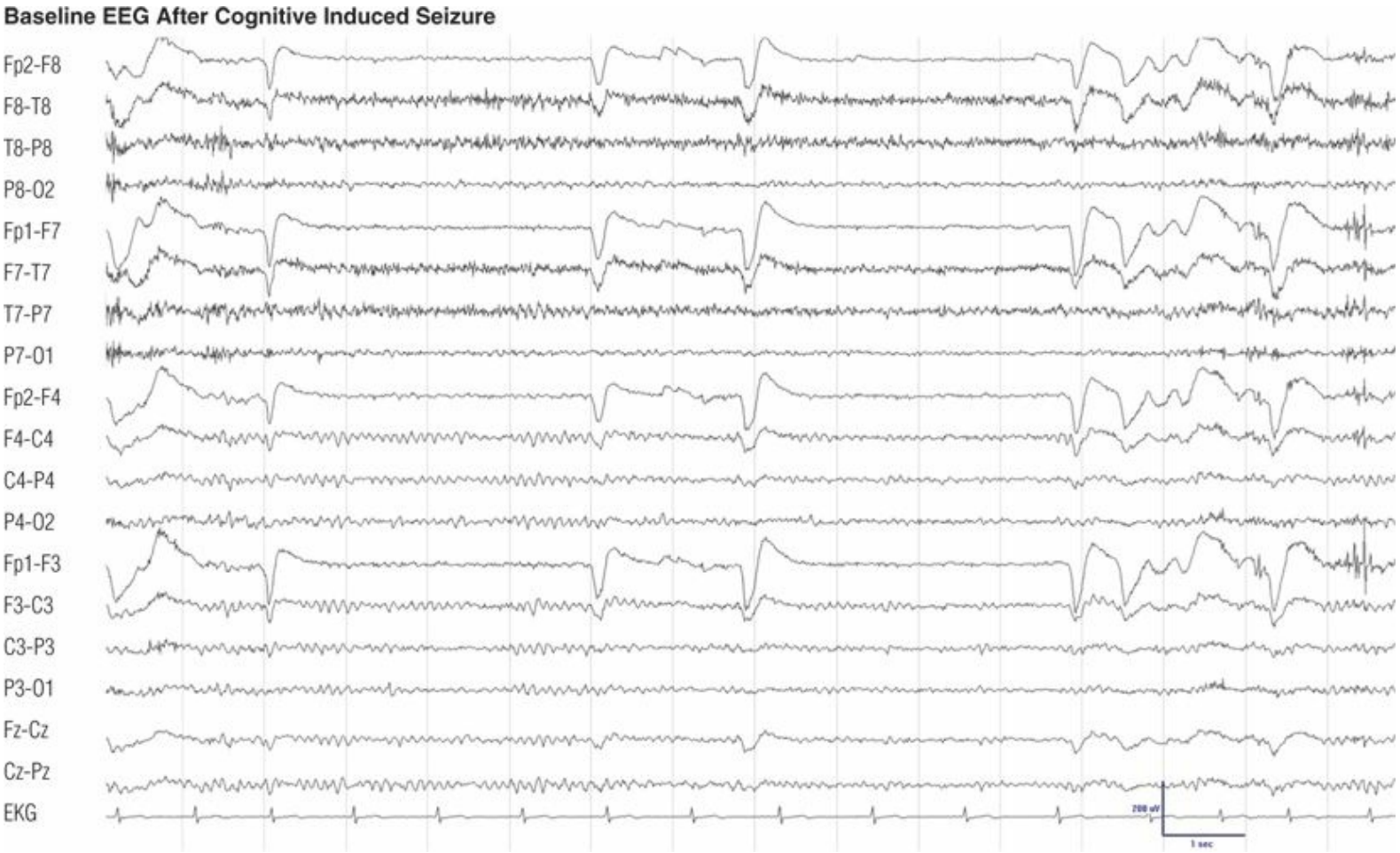

Figure 8.30. Same patient as in Figure 8.29. The EEG normalized and the left arm clonic seizure ceased immediately after cessation of the sudoku.

PART III: ELECTROENCEPHALOGRAPHIC ABNORMALITIES OF THE FOCAL EPILEPSIES

Localization-related (partial, focal, or local) epilepsies (15) involve seizures arising from a cortical region within one hemisphere. The first several illustrations are from children who had benign epileptiform discharges of childhood on EEG, with or without clinical seizures. The rest of the figures are from patients with symptomatic epilepsy and focal seizures arising from specific cortical regions, grouped by location of the epileptogenic zone. For most of the titles and legends, we use terminology from the most recent seizure and epilepsy classification systems of the International League Against Epilepsy (16). Some additional terms are also used here, such as "aura" instead of "simple partial seizure with special sensory symptoms" and "focal clonic seizure" instead of "simple partial seizure with focal motor signs." Some newer terms were also included (17); these are discussed further in Chapter 9.

Benign Focal Epileptiform Discharges of Childhood

Centrotemporal sharp waves	Figure 8.31
Dipole potential	Figure 8.32
Occipital sharp waves	Figure 8.33
Left and right central sharp waves	Figure 8.34
Temporal Lobe EpilepsyTemporal sharp waves	Figure 8.35
Bitemporal sharp waves	Figure 8.36
Lateral (neocortial) temporal lobe epilepsy: left temporal polyspikes and right temporal spikes	Figure 8.37
Complex partial ("automotor") seizure	Figures 8.38–8.40
Positive polarity spikes after resection	Figure 8.41
Frontal lobe epilepsyFrontal sharp waves	Figure 8.42
Frontal polyspikes	Figure 8.43
Bilateral secondary synchrony	Figure 8.44
Bilateral tonic seizure from sleep	Figure 8.45
Unilateral negative myoclonic seizure	Figure 8.46

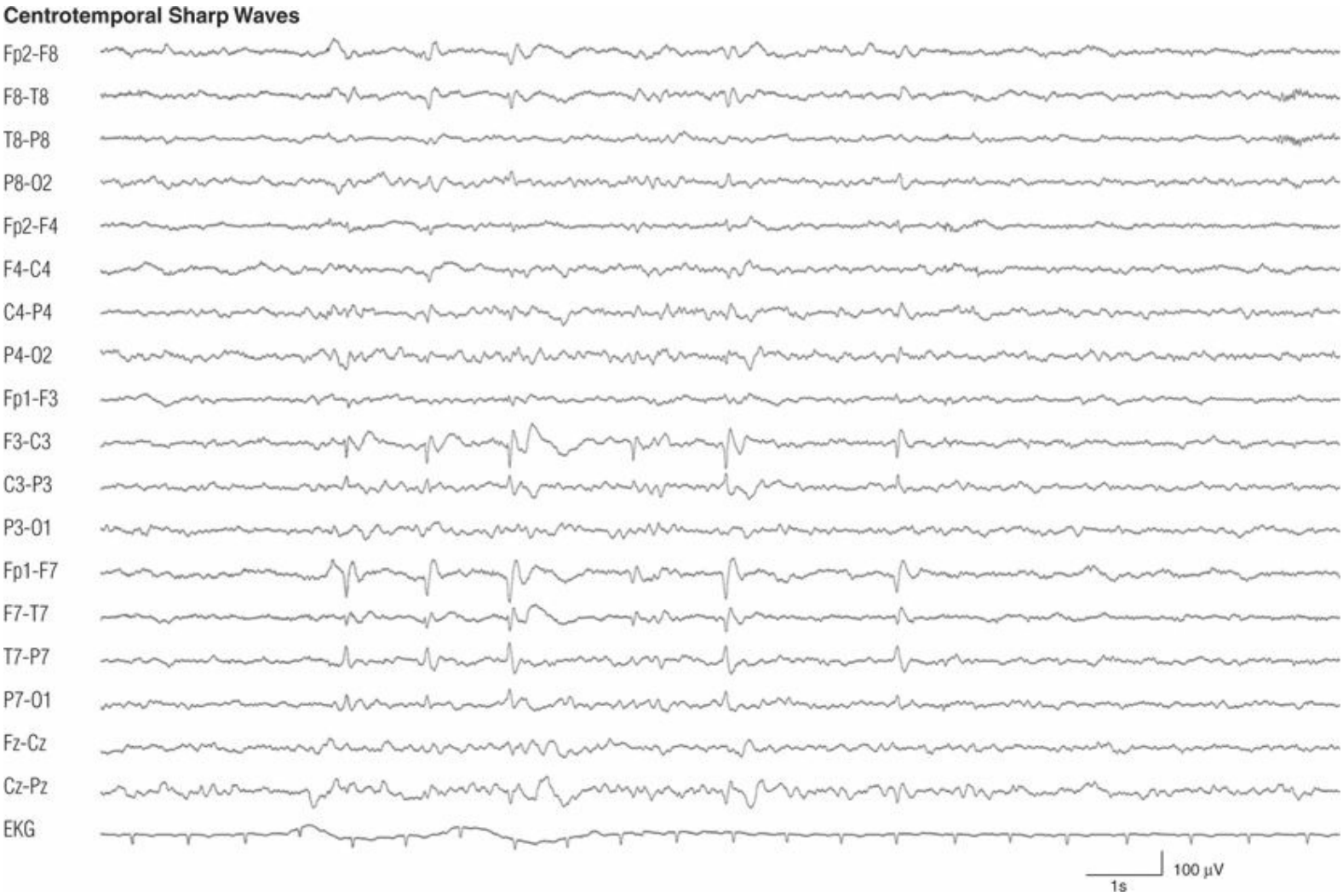

Figure 8.31. Nine-year-old boy with benign focal epilepsy of childhood. Awake electroencephalogram showed normal findings, but recording during drowsiness and light sleep showed left centrotemporal sharp waves (benign focal epileptiform discharges of childhood) (18). Many children with benign focal epileptiform discharges of childhood do not have seizures (19), and the finding may be incidental.

Centrotemporal Sharp Waves – Dipole potential

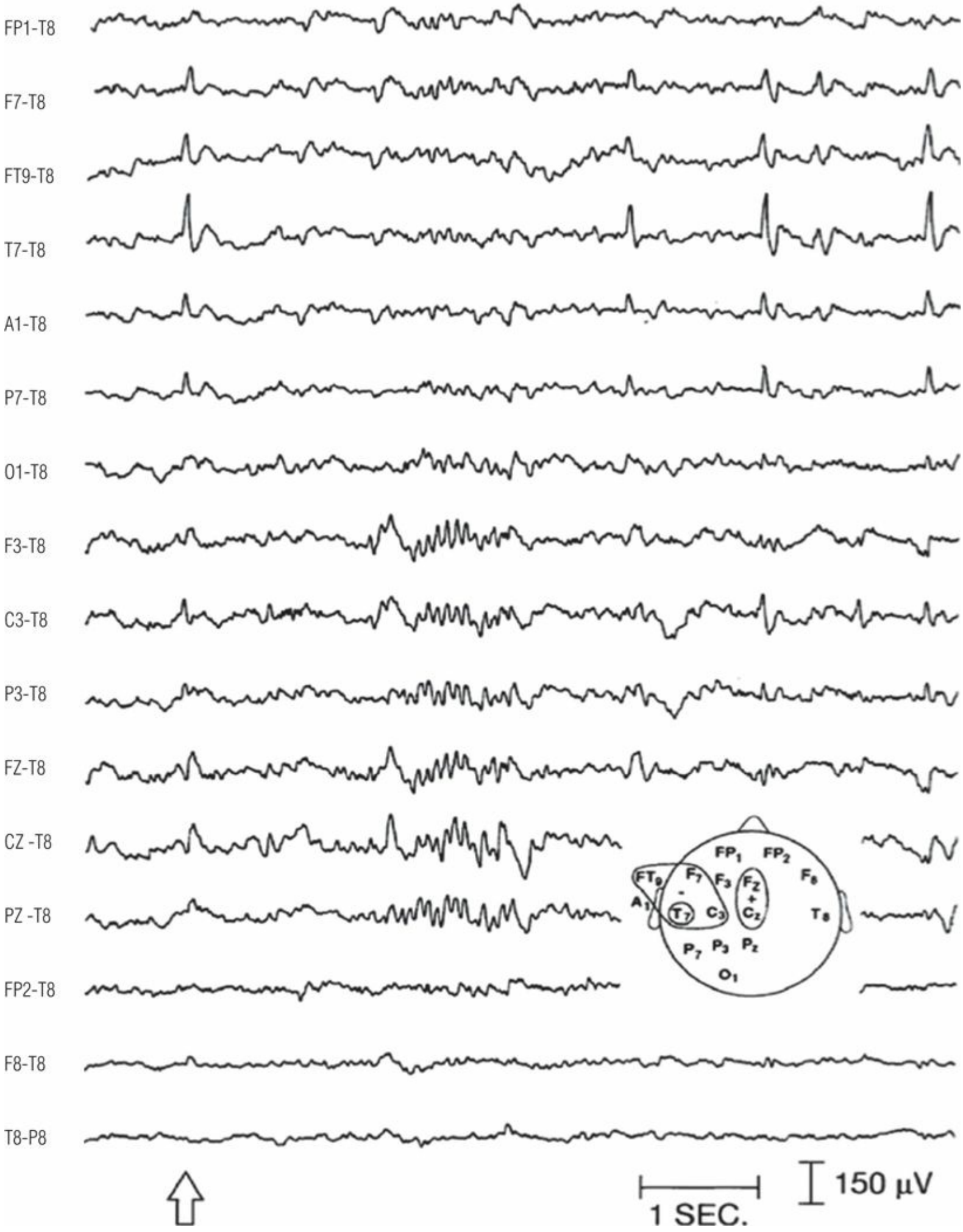

Figure 8.32. Referential electroencephalogram from a 8-year-old patient with attention deficit hyperactivity disorder and no history of seizures. Note that the sharp waves were reflected at the scalp as dipoles, with maximum negativity over the left centrotemporal region and maximum positivity over the vertex. Dipole potentials are typical of benign focal epileptiform discharges of childhood, possibly as a result of horizontal orientation along banks of the sylvian or rolandic fissures (18).

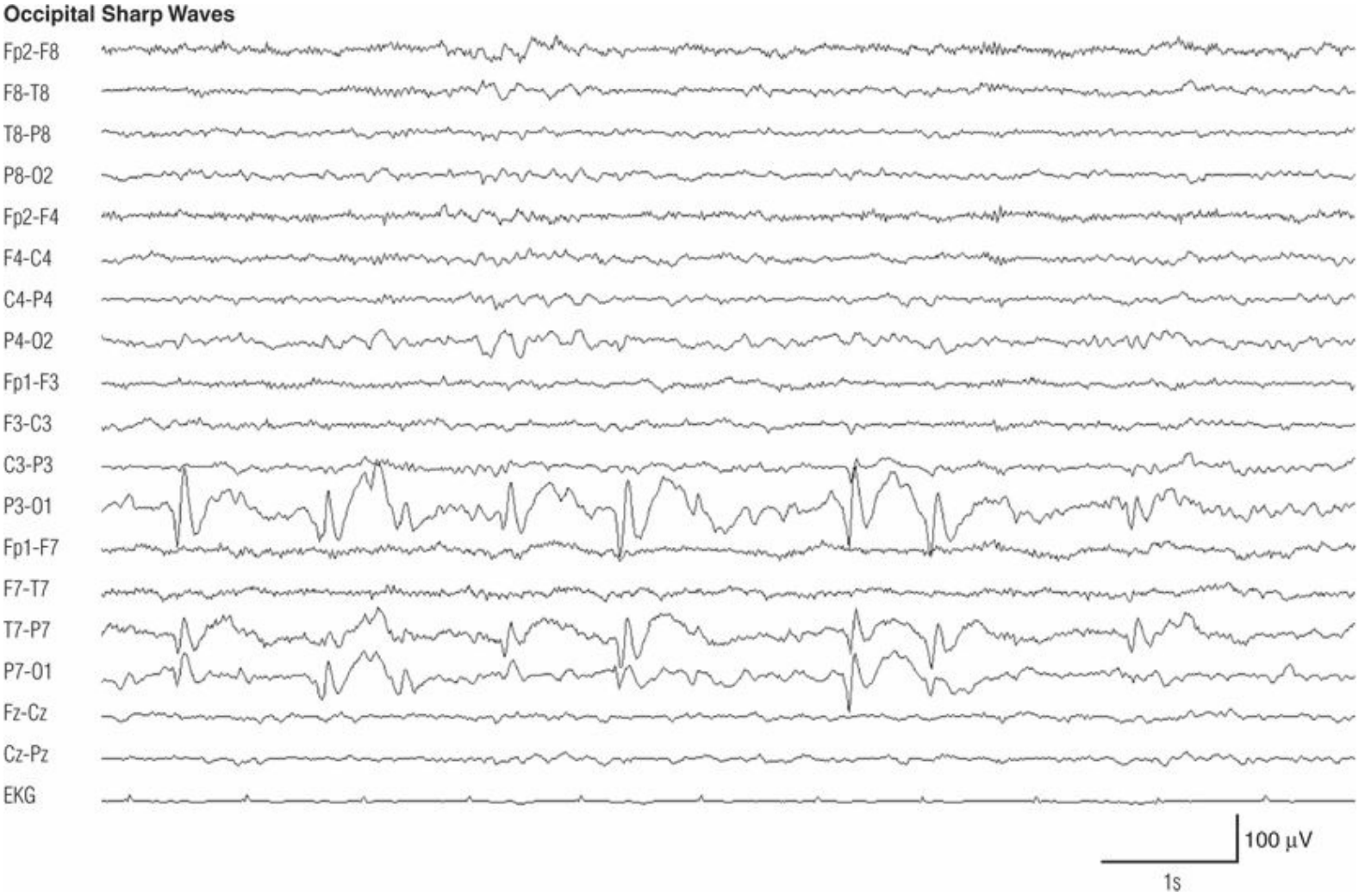

Figure 8.33. Ten-year-old boy with migraine and no history of seizures. The right occipital sharp waves with typical morphology of benign focal epileptiform discharges of childhood (18) were abundant in light sleep but rare during wakefulness.

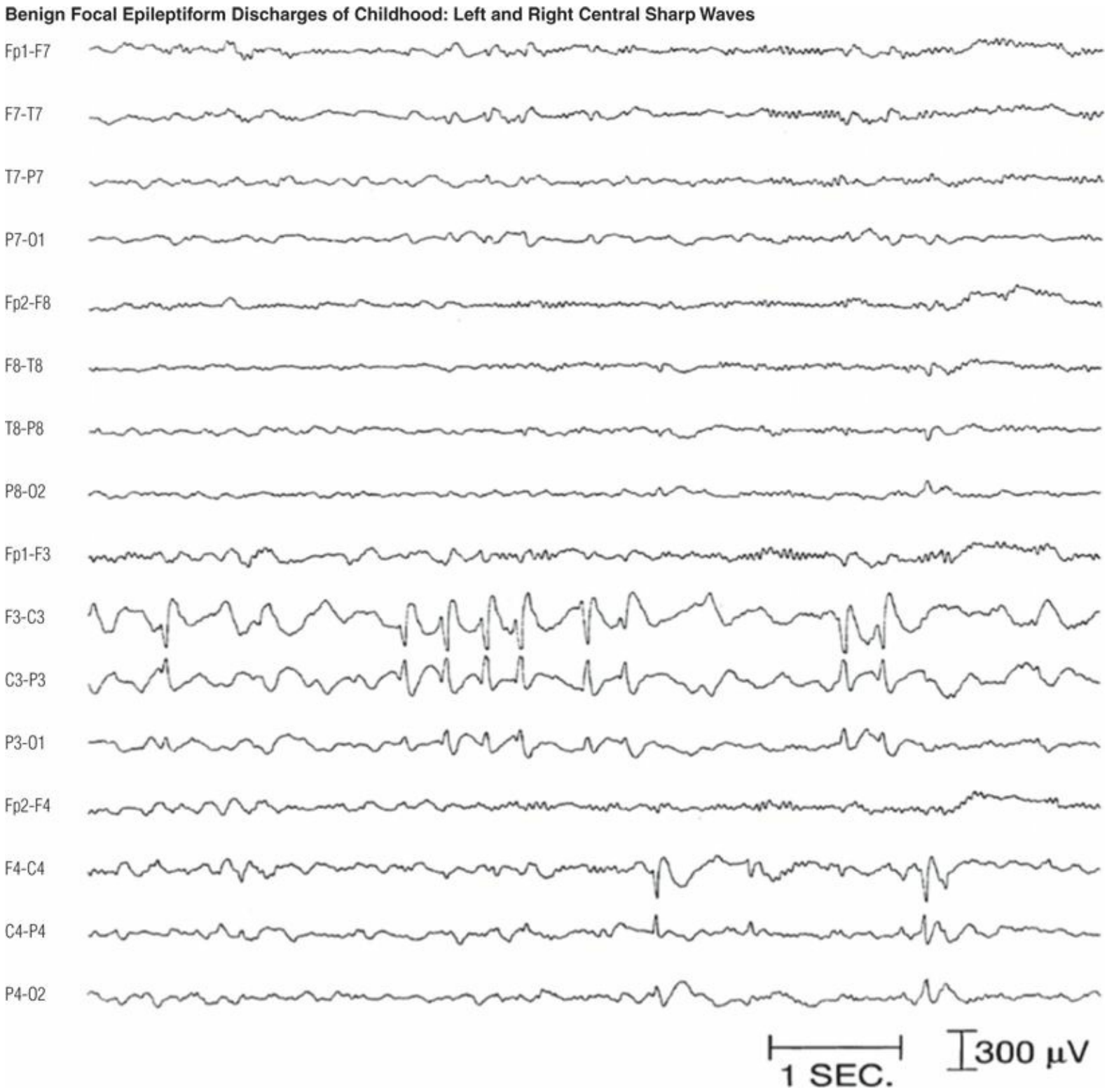

Figure 8.34. Eight-year-old boy, otherwise normal, with rare nocturnal generalized tonic–clonic convulsions since age 4 years. Benign focal epileptiform discharges of childhood are commonly bifocal or multifocal, often from homologous areas of both hemispheres (18).

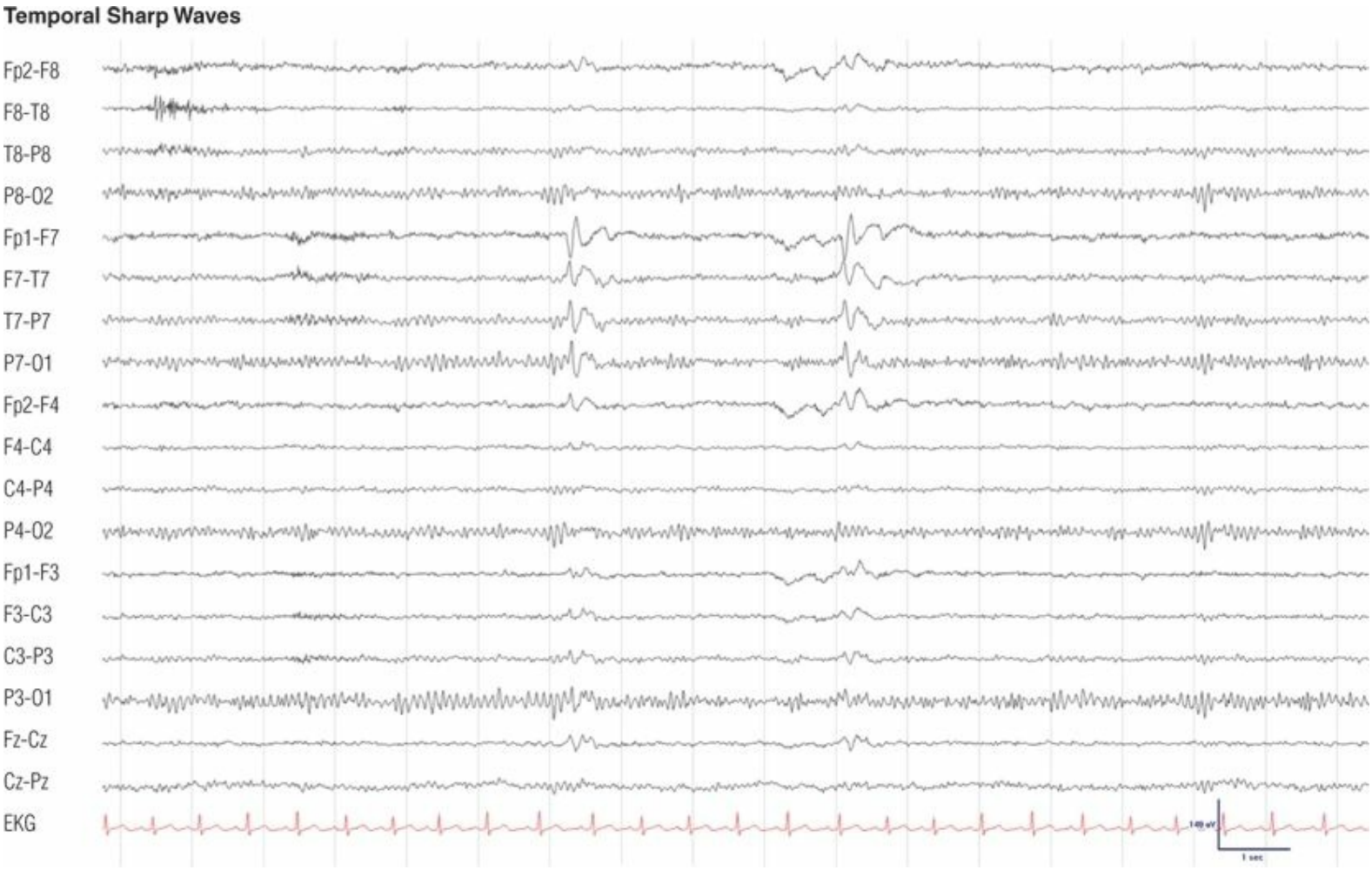

Figure 8.35. Thirty-seven–year-old woman with complex partial seizures with automatisms since age 8 years. Interictal electroencephalogram showed sharp waves from the left anterior temporal region, with maximum amplitude at electrode F7.

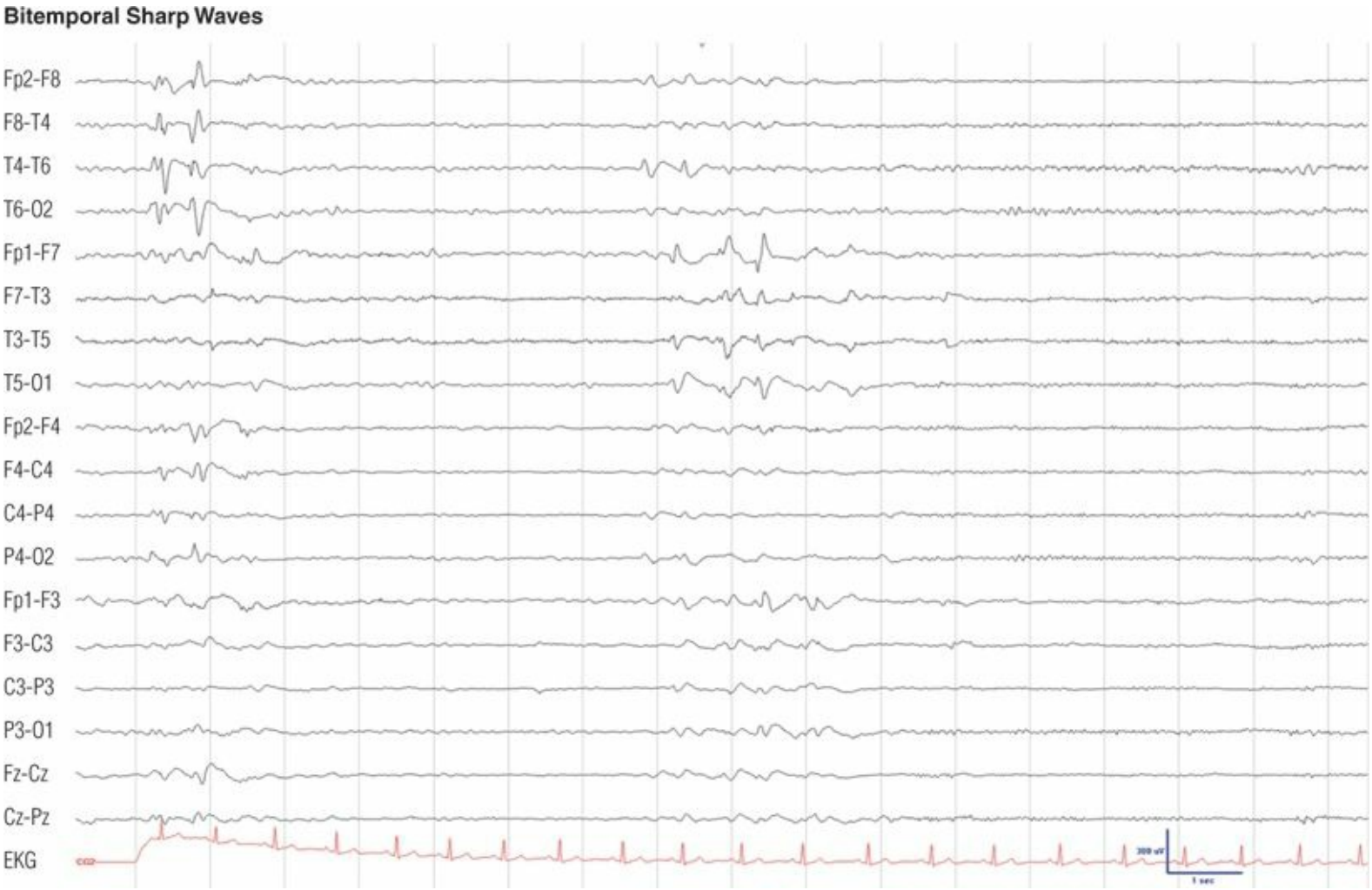

Figure 8.36. Thirty-four–year-old man with onset of complex partial seizures with automatisms at age 4. Interictally, sharp waves were recorded over the right and left temporal region, but all recorded seizures arose from the right temporal lobe.

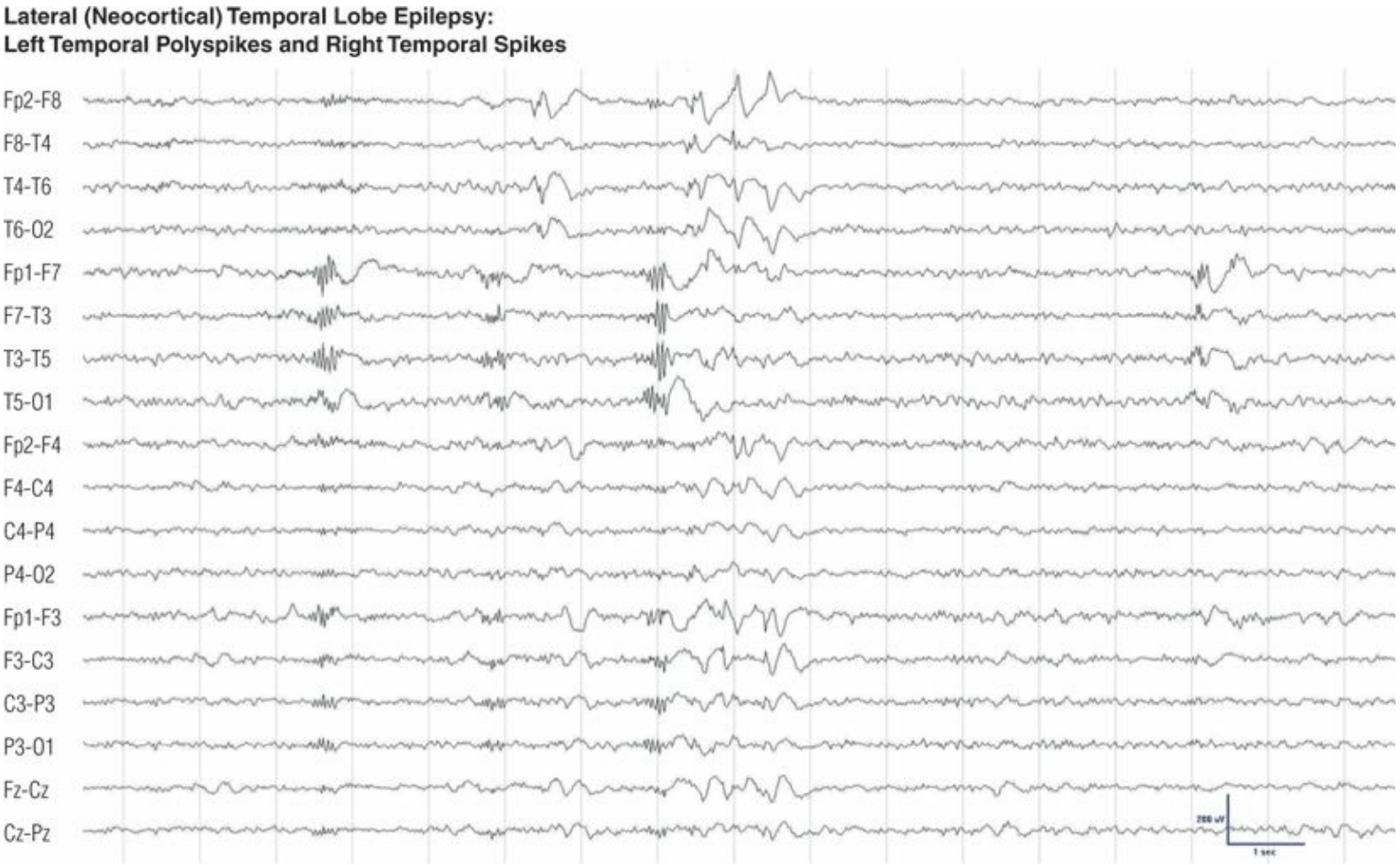

Figure 8.37. Twenty-five–year-old man with complex partial seizures with automatisms since age 5 years due to bilateral perisylvian dysplasia (20). Note the frequent left temporal polyspike bursts and right temporal spikes and slowing.

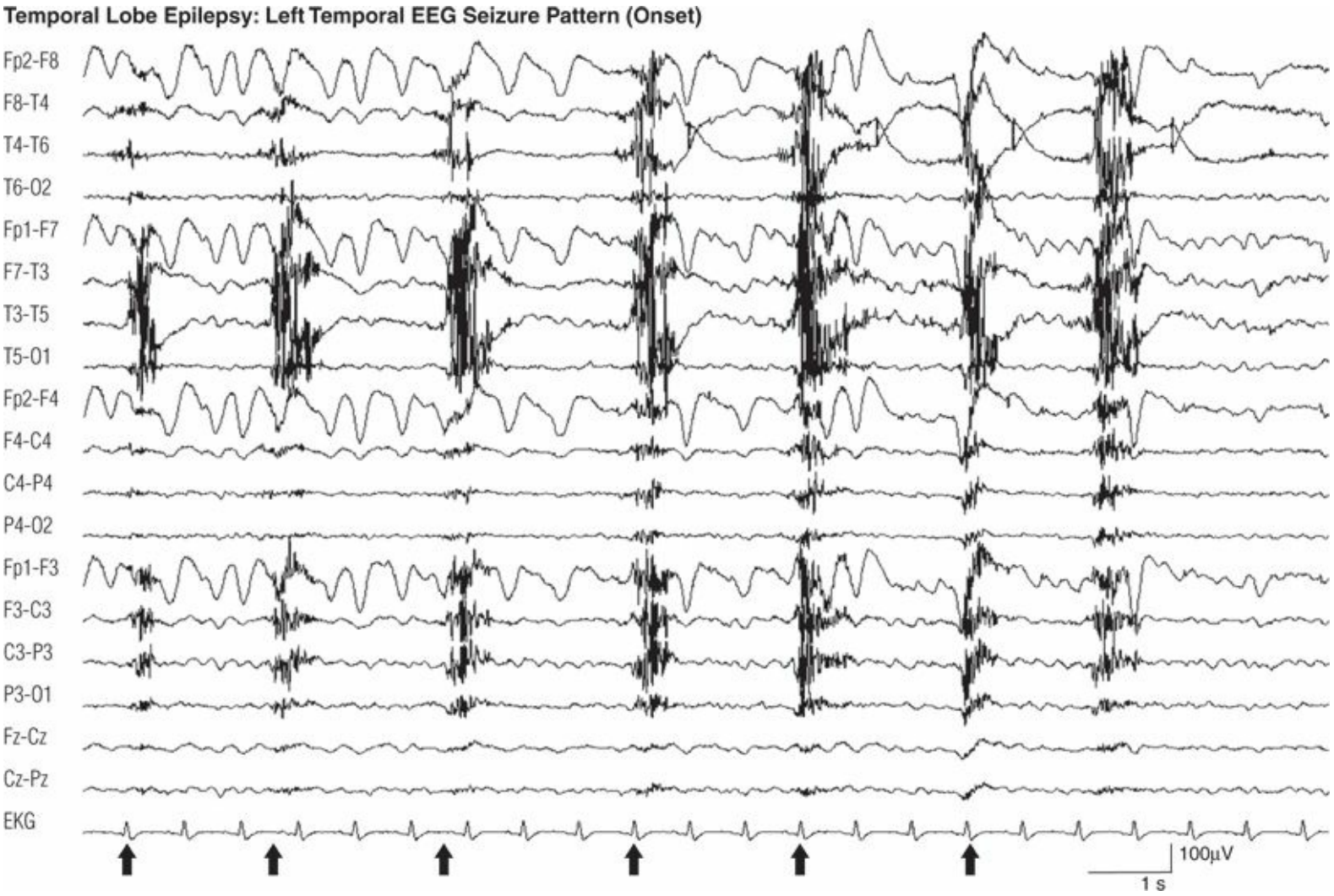

Figure 8.38. Forty-two–year-old man with left temporal lobe epilepsy due to mesial temporal sclerosis. Note the rhythmical left temporal theta waves indicating the EEG onset of a seizure characterized by oral automatisms. The EMG artifacts reflect the chewing movements (arrows).

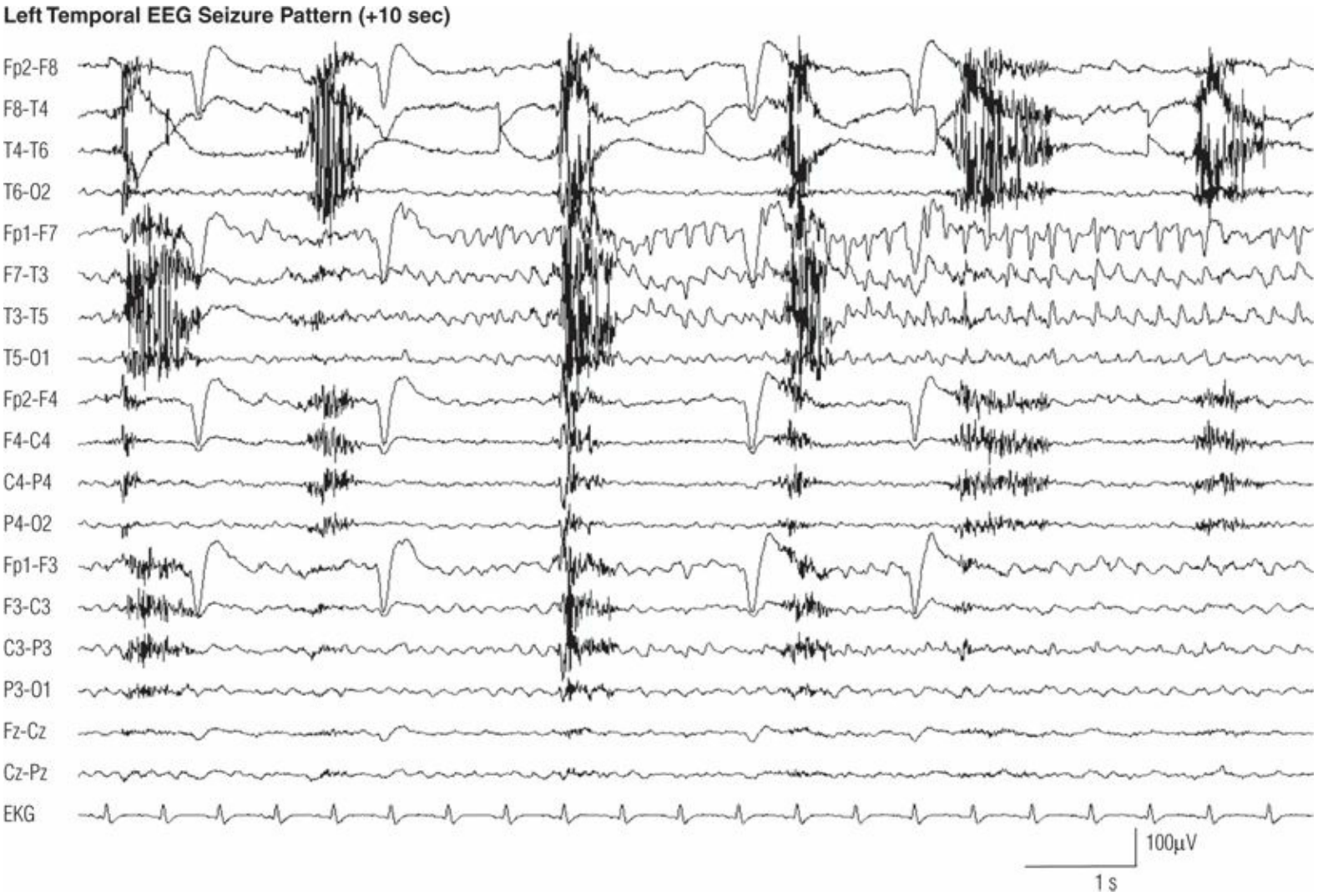

Figure 8.39. Continuation of the seizure shown in Figure 8.38. The rhythmical left temporal theta waves slow down and evolve into repetitive spikes. Clinical features included staring, unresponsiveness, and oral automatisms. The patient is seizure free following left anterior and mesial temporal resection.

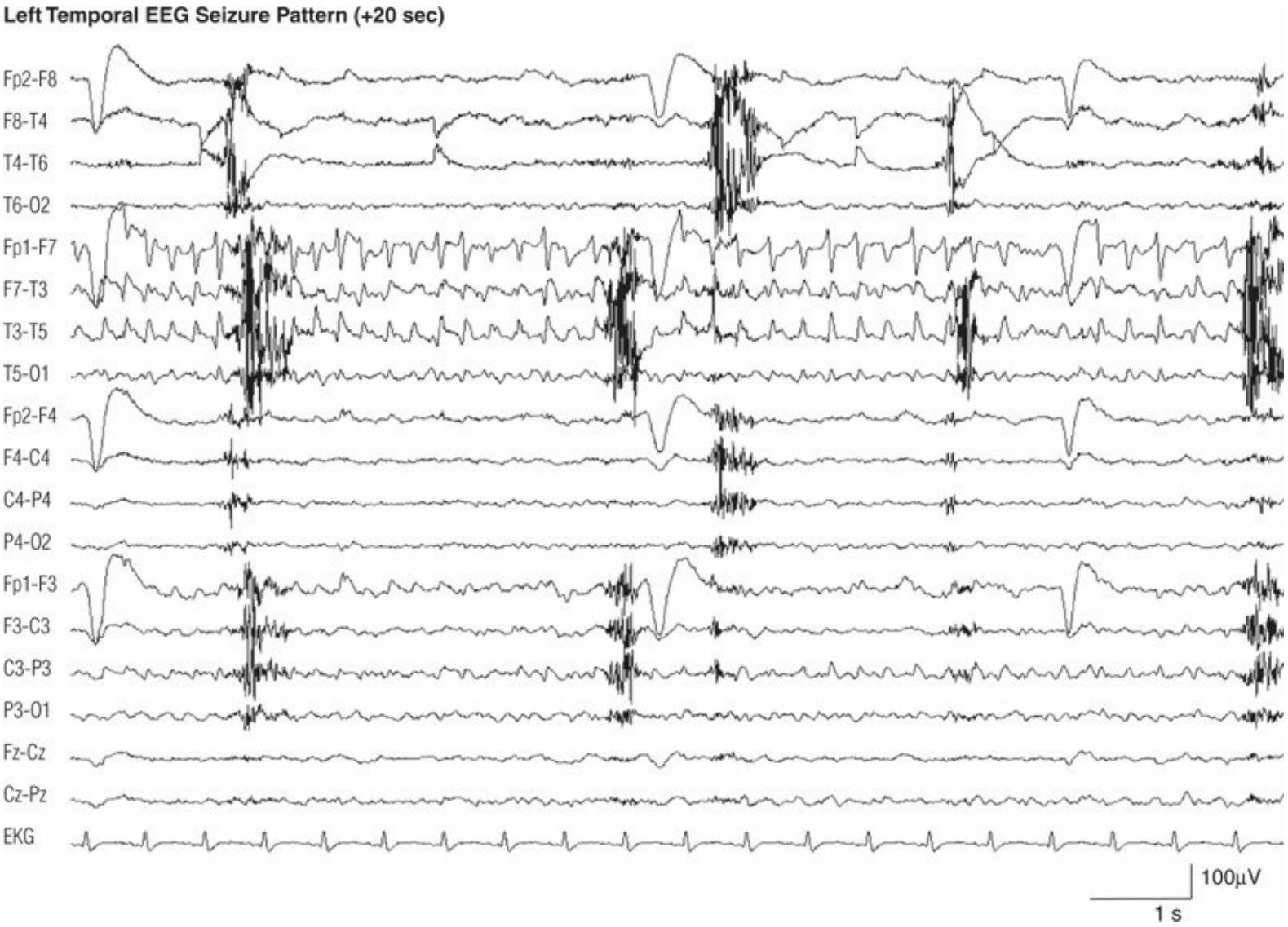

Figure 8.40. Continuation of the seizure shown in Figure 8.39.

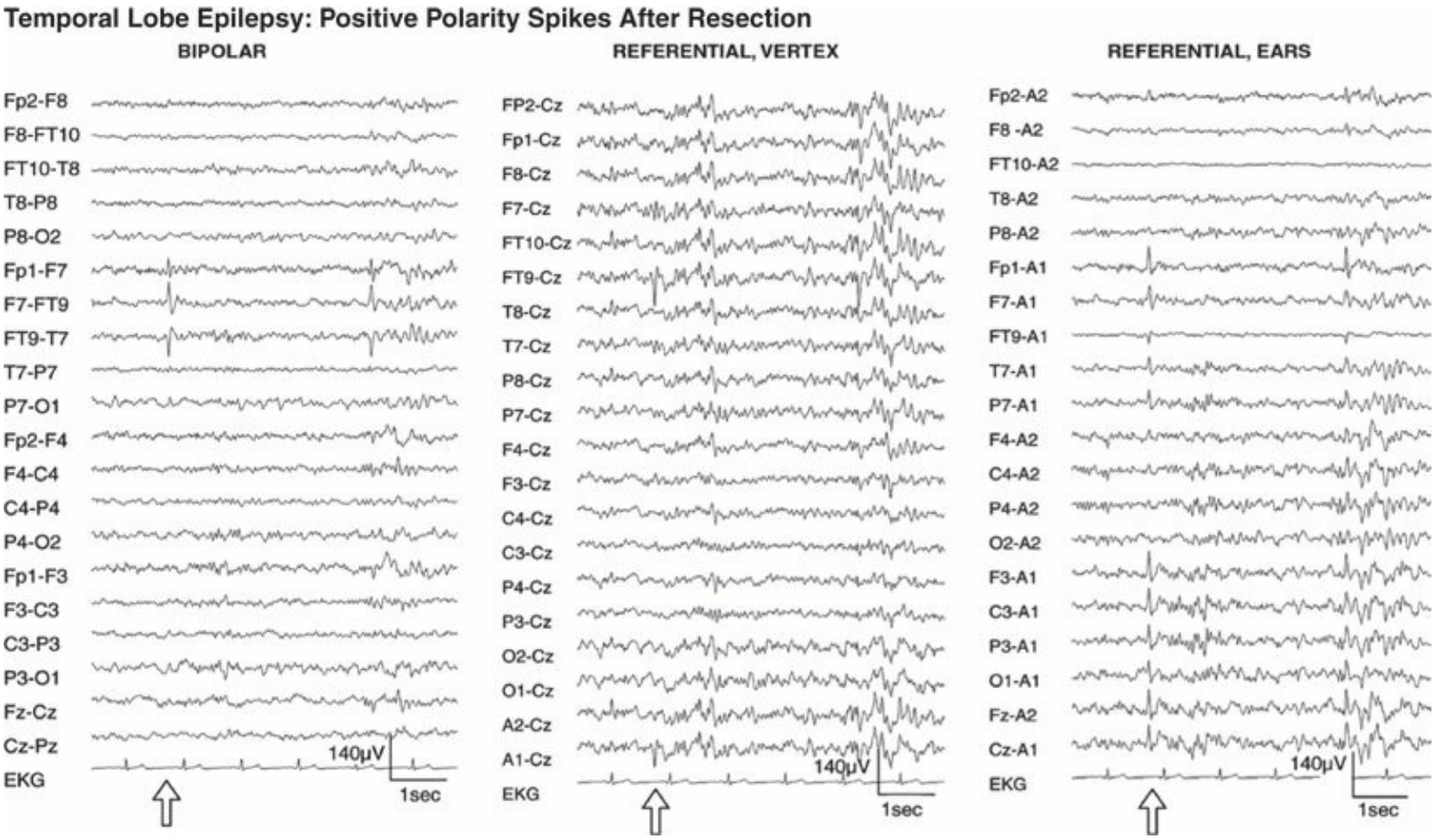

Figure 8.41. Bipolar and referential montages of the same spike (arrows) of a patient who underwent left anterior temporal lobe resection for medically intractable temporal lobe epilepsy. Note that the left anterior spike (electrode FT9) has a positive polarity. This is a rare finding in patients following temporal resections. The downward deflection in the vertex reference (Cz) in the electrodes FT9 and A1 reflects the positivity. The ear reference montage shows that the electrode FT9 shows the maximum positivity (downward deflection), whereas the other left-sided electrodes are relatively negative with regard to left ear electrode (A1) and, therefore, point upward. This may give rise to the false impression of a negative spike in the left frontal region in the ipsilateral ear reference montage.

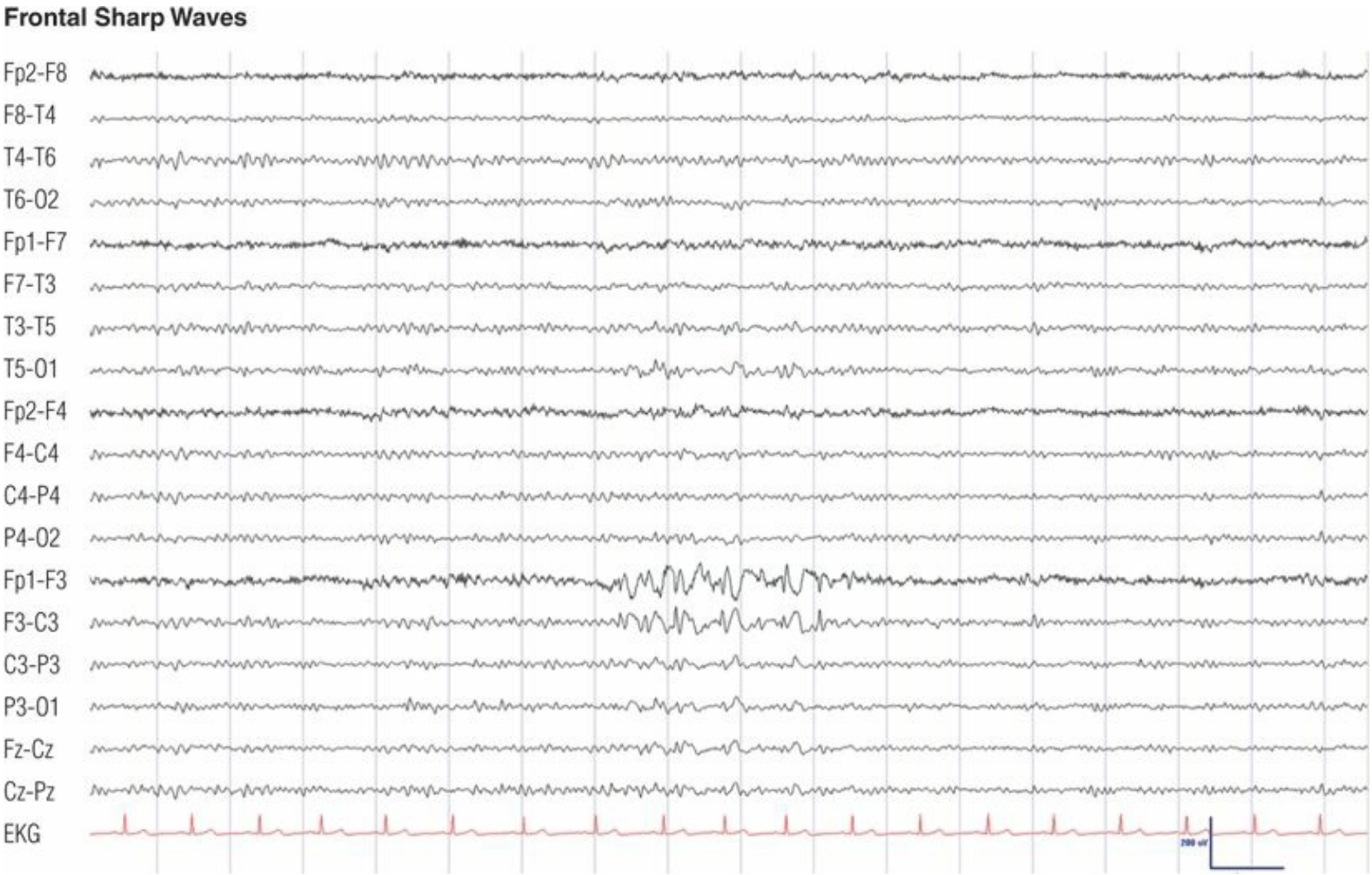

Figure 8.42. Thirty-year-old man with intractable right versive and generalized tonic–clonic seizures due to left frontal cortical malformation. Interictal sharp waves were maximum in the left frontal region at electrode F3.

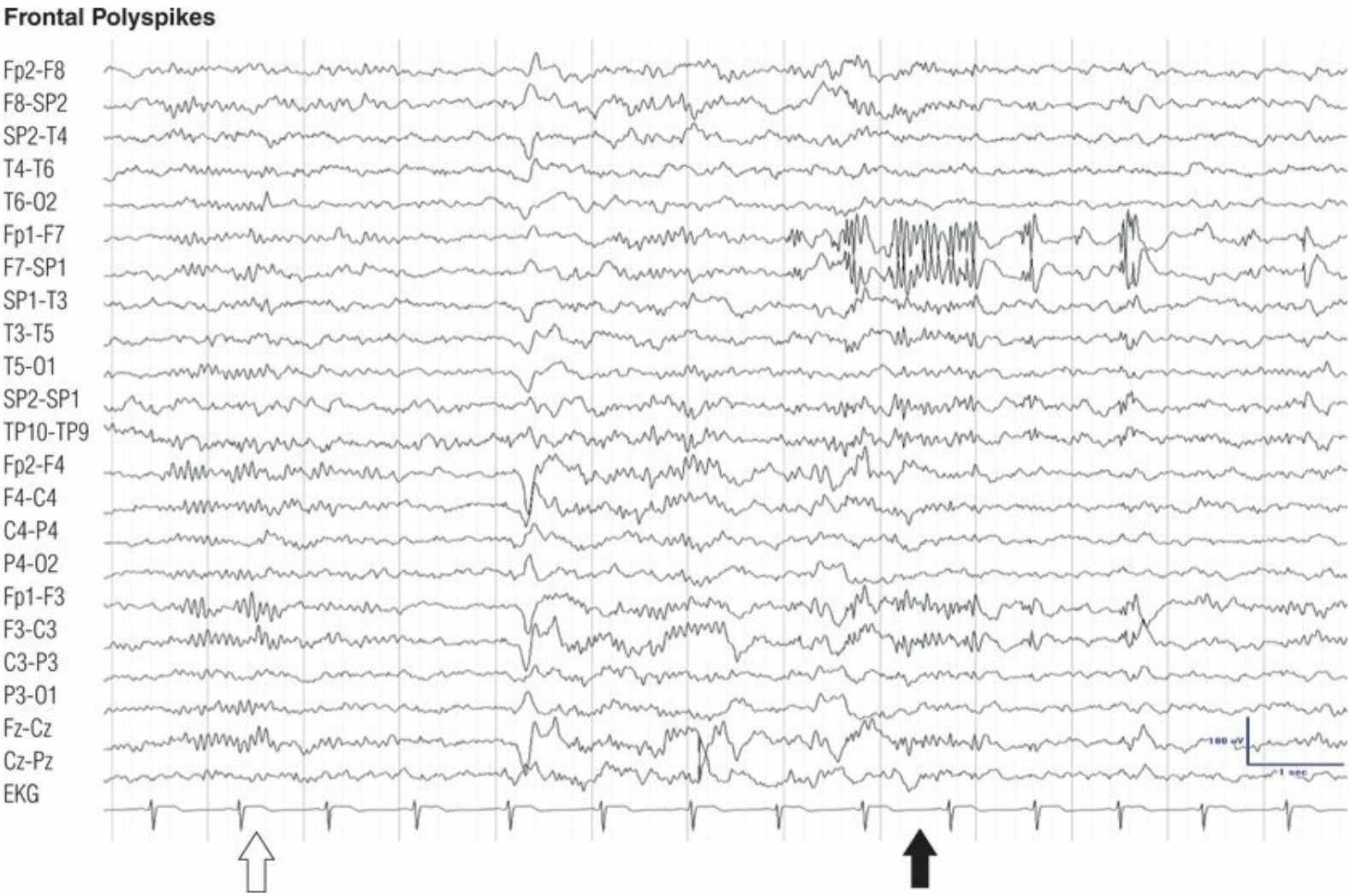

Figure 8.43. Twelve-year-old boy with bilateral asymmetric tonic seizures evolving into the right arm clonic seizures due to left fontal cortical malformation. Note the polyspikes with maximum at electrode F7 (solid arrow) (20) during light sleep characterized by sleep spindles and vertex wave (open arrow).

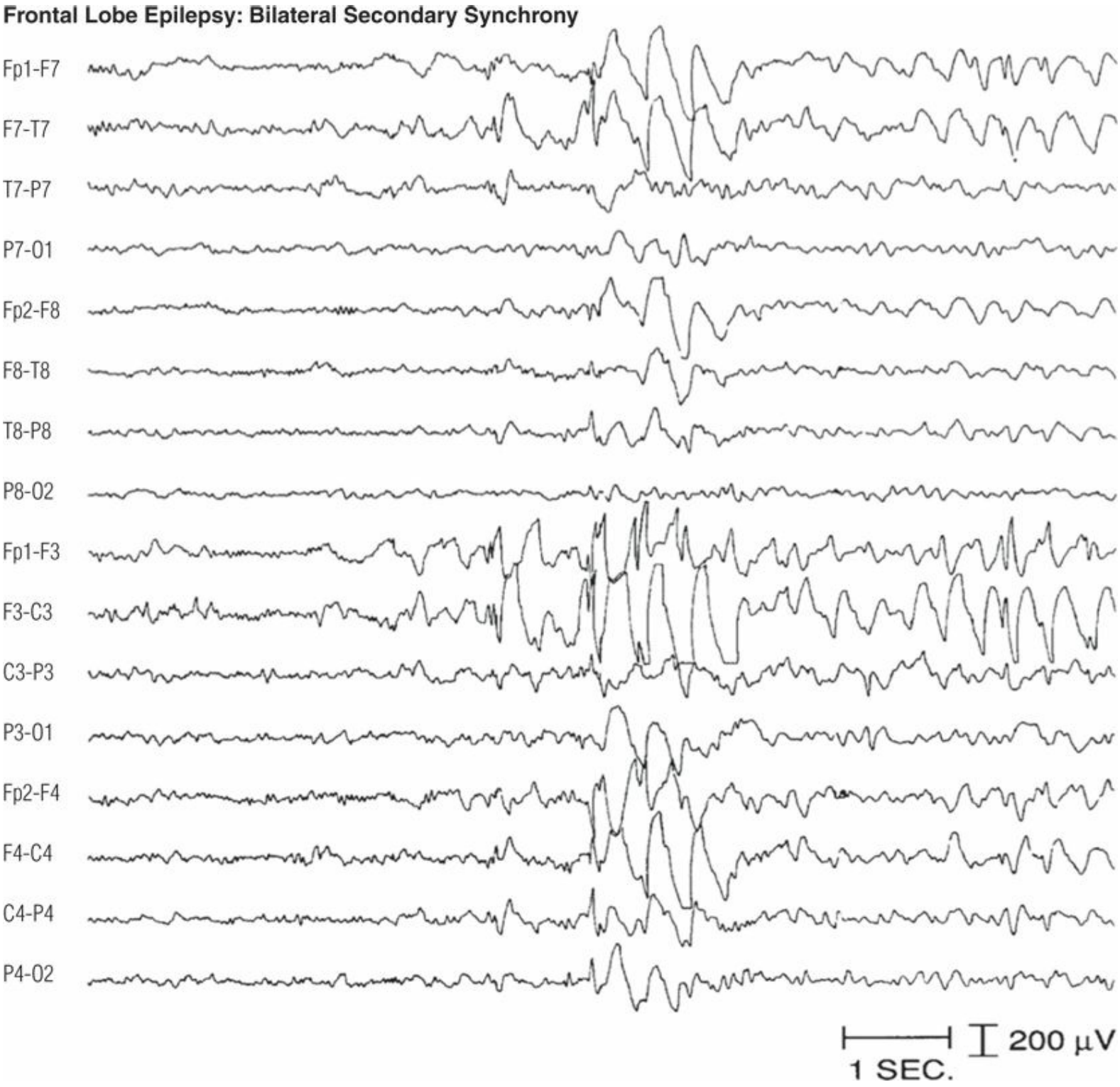

Figure 8.44. Seventeen-year-old boy with intractable frontal lobe epilepsy due to encephalomalacia of the left frontal lobe as a result of head trauma at age 13 years. Interictal sharp waves were maximum in the left frontal region but frequently showed secondary bilateral synchrony with generalization.

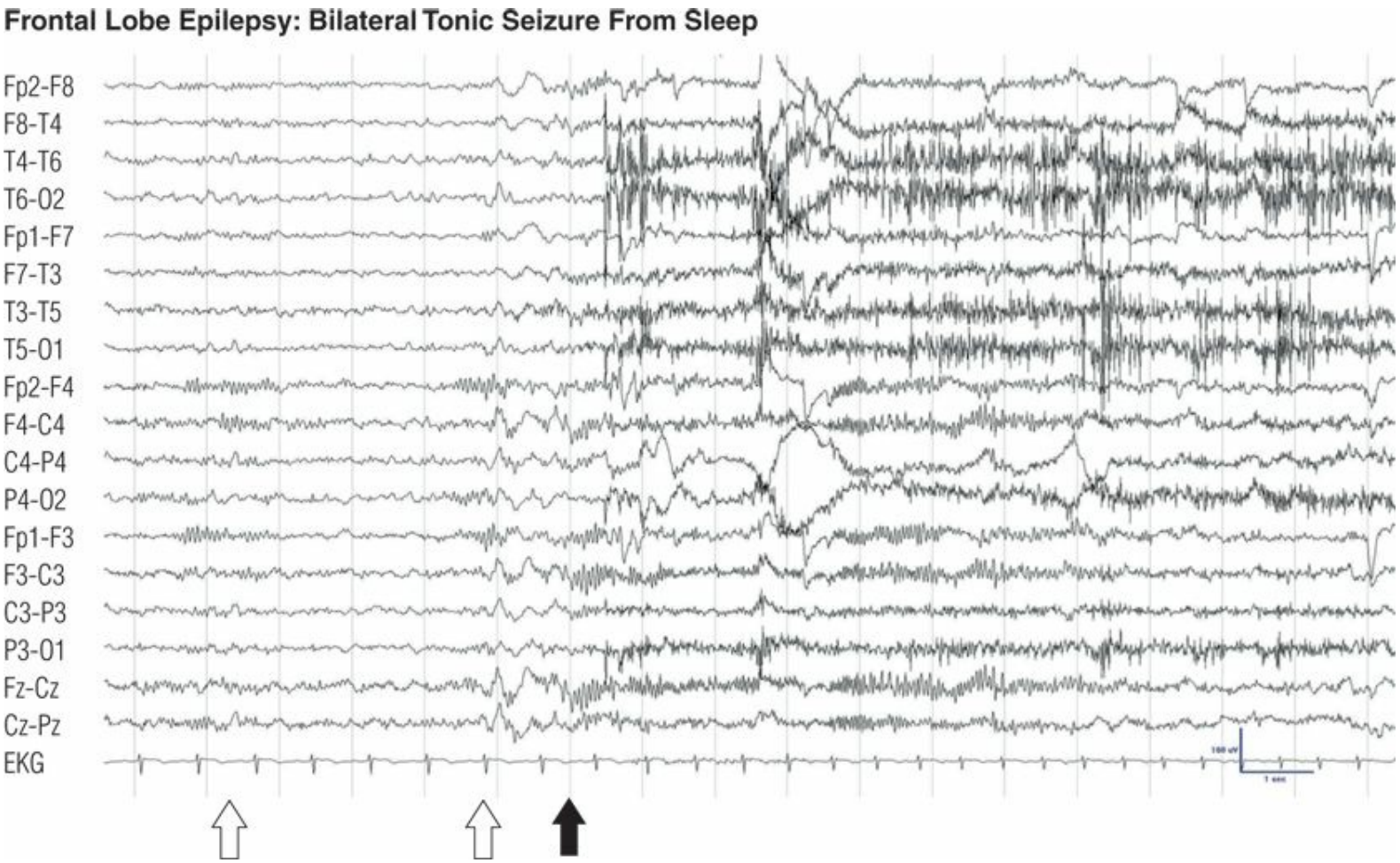

Figure 8.45. Twenty-four–year-old man with MRI–negative focal epilepsy. Note the high-frequency discharge in the left mesial frontal region (electrodes F3 and Fz) (solid arrow) arising out of light non-REM sleep characterized by sleep spindles (open arrows). Abundant EMG artifacts are caused by a bilateral asymmetric tonic seizure.

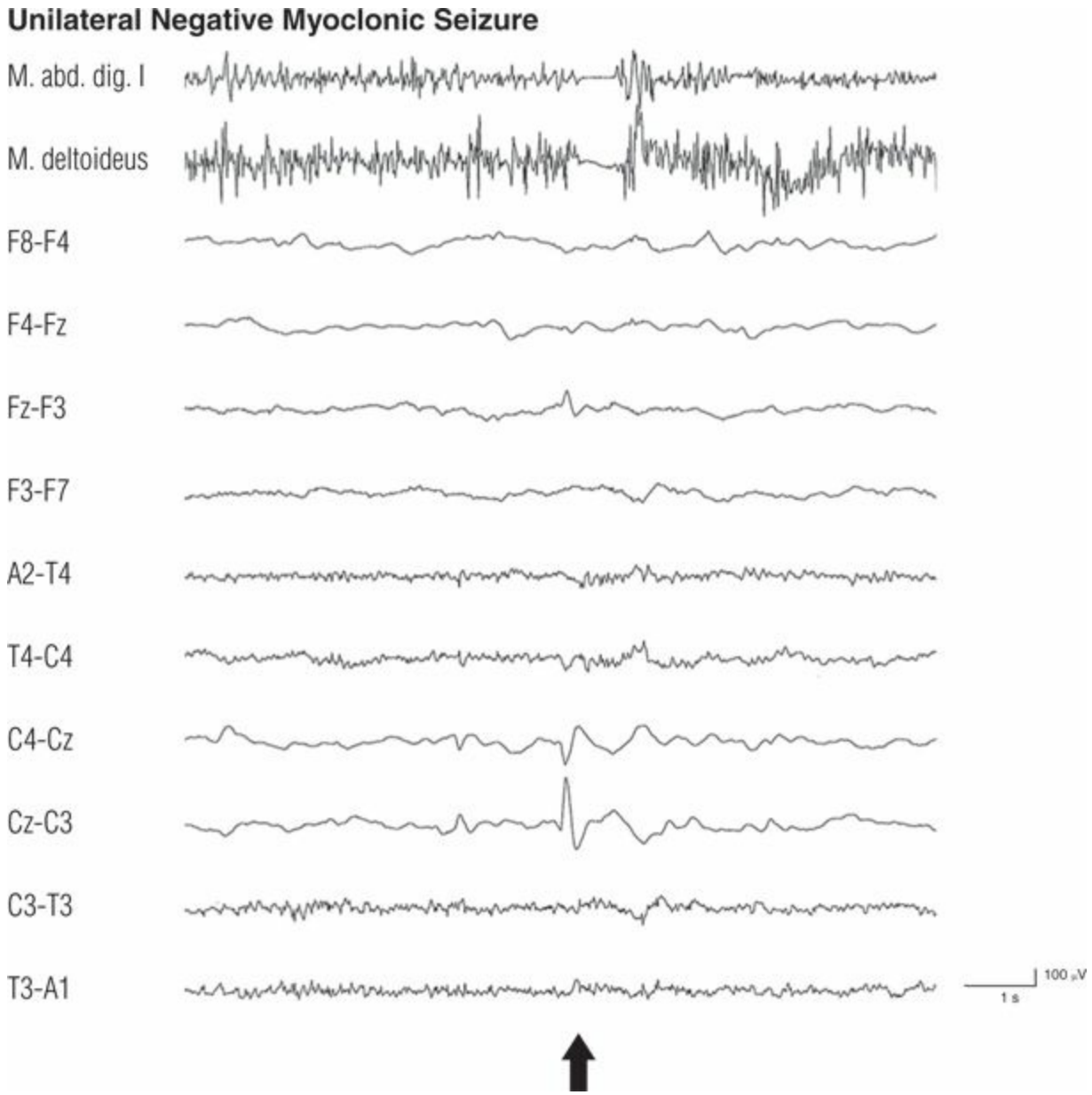

Figure 8.46. Nineteen-year-old man with a perinatal left frontotemporal encephalomalacia. Since the age of 3 years, he has had bilateral asymmetric tonic seizures that evolved into generalized tonic–clonic seizures. Later, negative myoclonic seizures occurred. Note the EMG silent period in the right hand (m. abd. dig I) and right shoulder (m. deltoid) associated with the right central sharp wave (arrow). Negative myoclonus occurs only during tonic muscle contraction. This EEG reflects a so-called paradoxical lateralization since the sharp wave shows maximum negativity ipsilateral to the negative myoclonus of the arm (21). Paradoxical lateralization in this case is most likely due to a left mesial frontal generator (21).

Mesial Frontal Lobe Epilepsy

Sharp waves at vertex	Figure 8.47
Bilateral tonic seizure	Figure 8.48

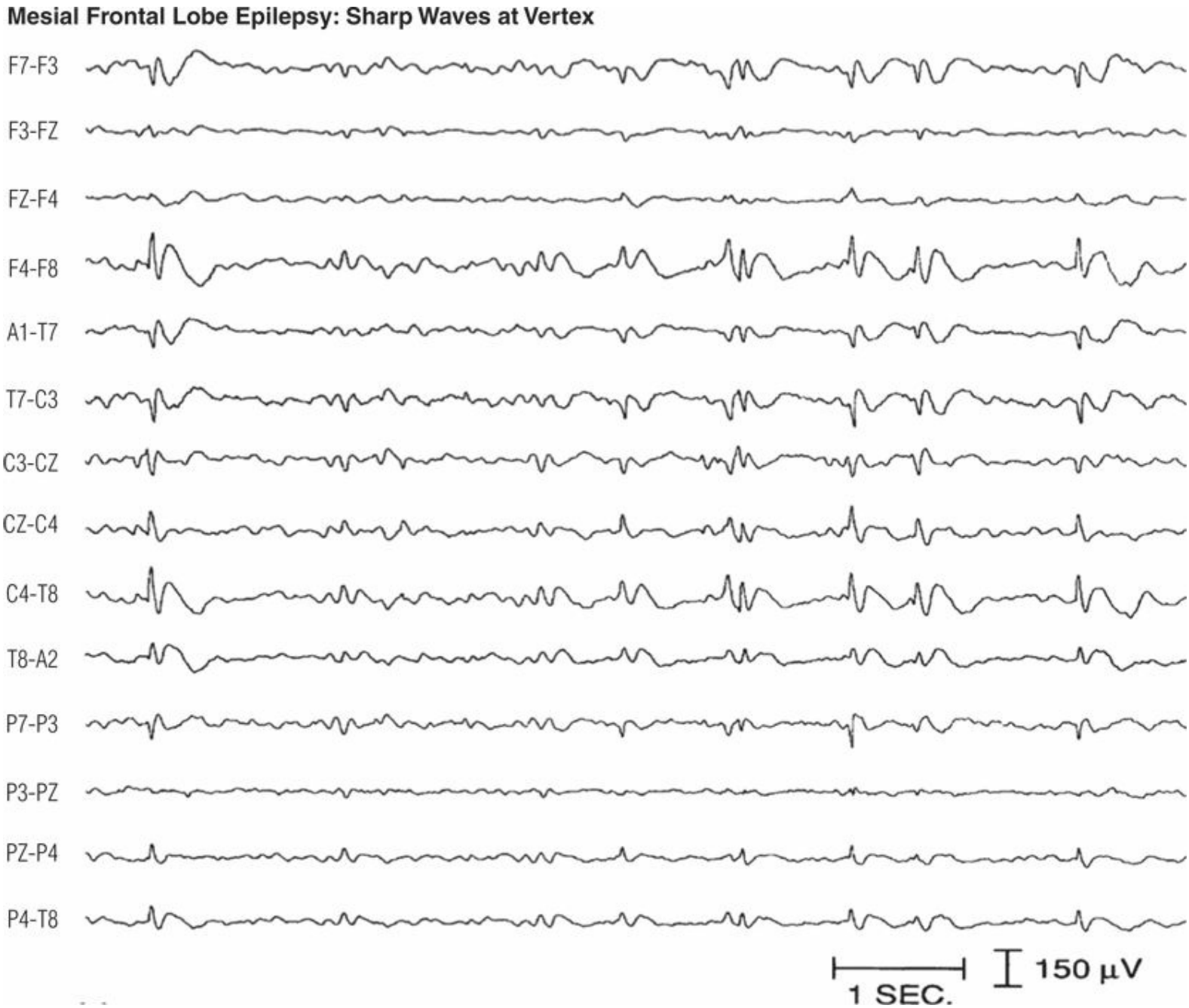

Figure 8.47. Seventeen-year-old woman with a low-grade astrocytoma in the left mesial frontal lobe (paracentral lobule). Intractable seizures involved brief tonic abduction of both arms, version of head and eyes to the right, and falling backward without loss of consciousness. Note the frequent sharp waves at the vertex.

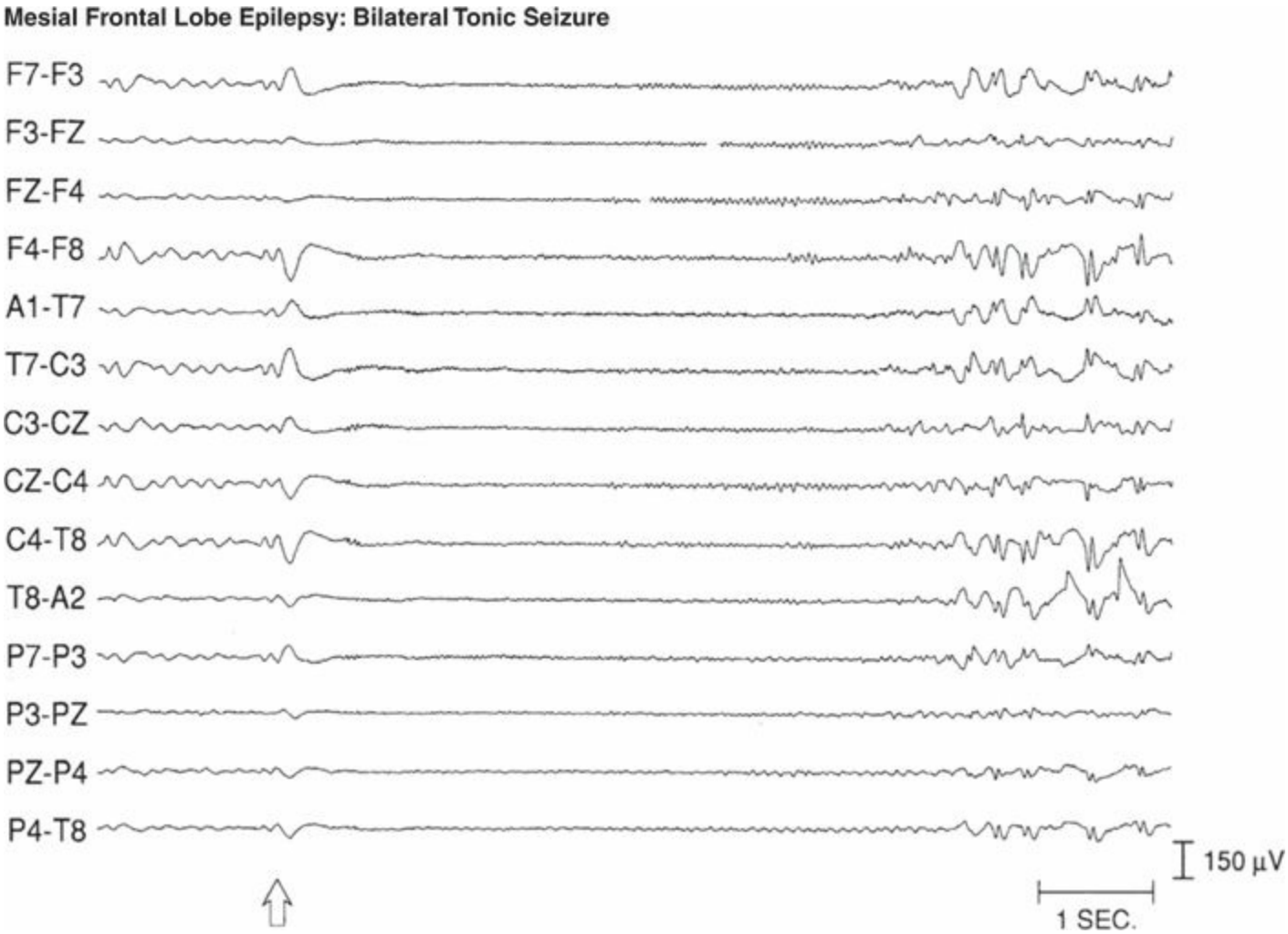

Figure 8.48. Electroencephalogram during a typical seizure from the patient described in Figure 8.47. At clinical onset (arrow), a vertex slow transient and then a generalized electrodecremental pattern with paroxysmal fast activity were recorded, followed by paroxysmal vertex sharp waves.

Paracentral Epilepsy

Focal clonic seizure	Figures 8.49 and 8.50
Frontocentral sharp waves	Figure 8.51
Epilepsia partialis continua	Figure 8.52

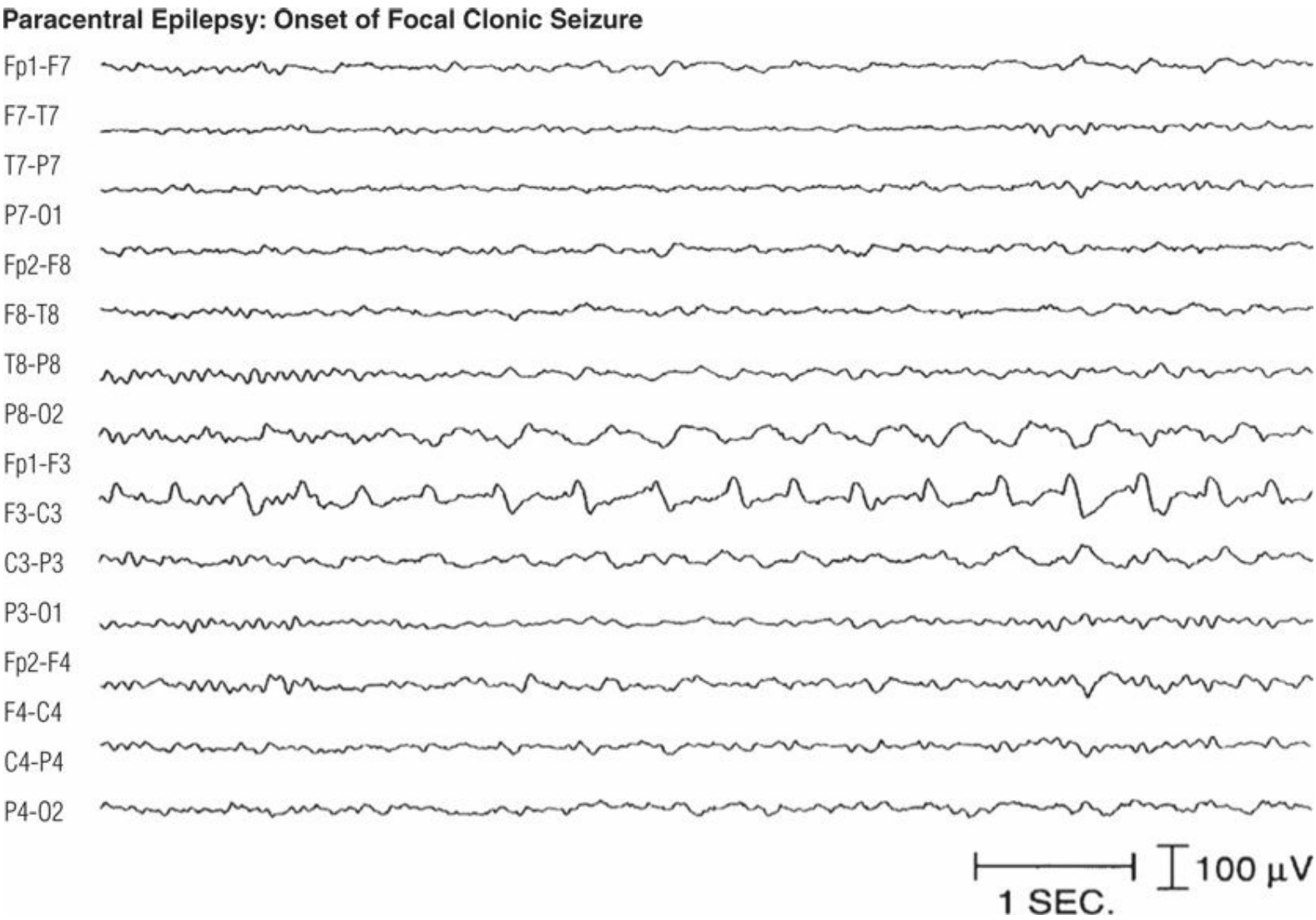

Figure 8.49. Four-year-old girl with frequent nocturnal focal clonic seizures with Jacksonian spread. Seizures began with twitching of the right shoulder and thoracic wall, followed by version of the head to the right and clonic jerking of the right arm and leg without loss of consciousness. Seizure pattern on electroencephalogram was maximum at the left central region.

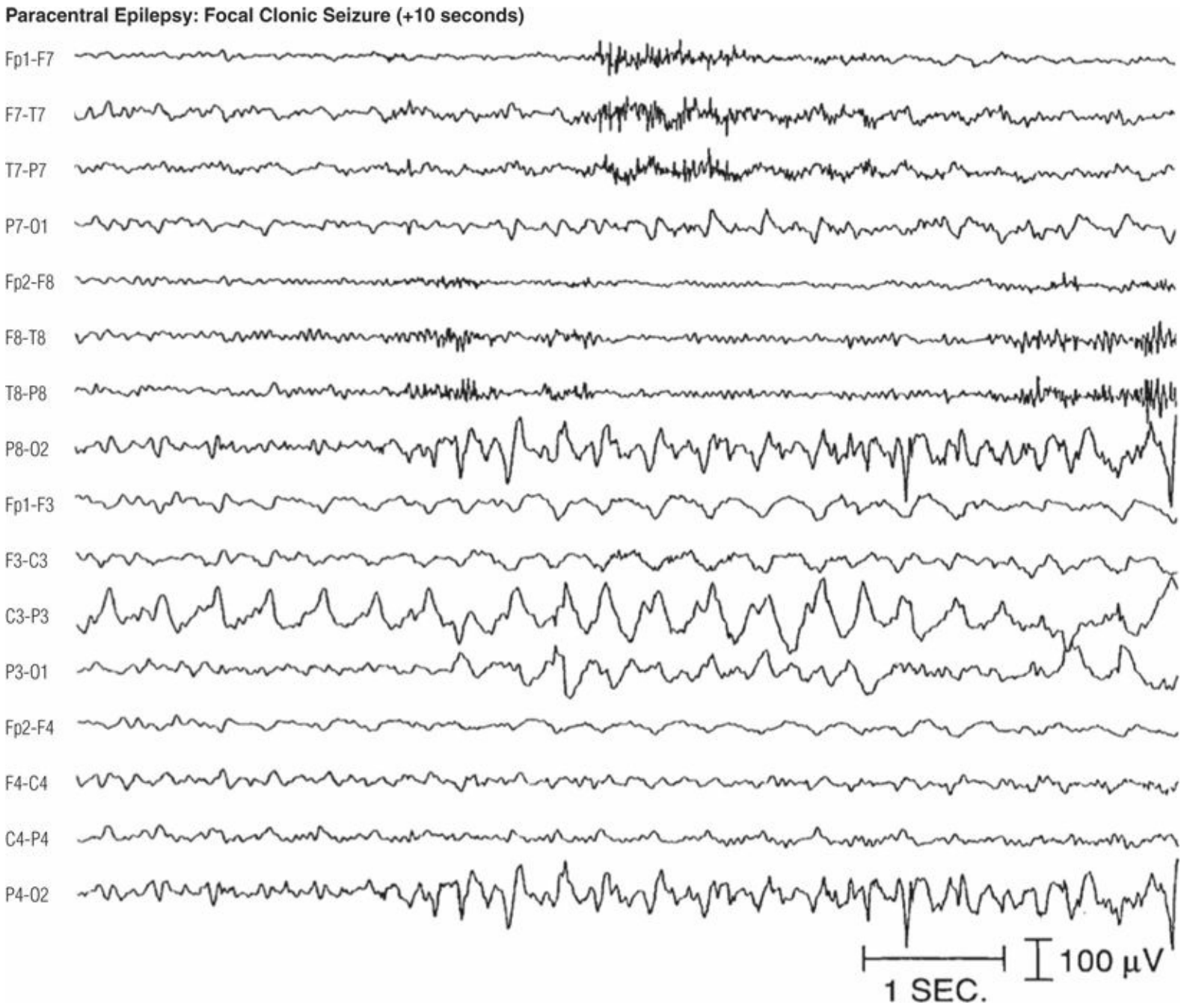

Figure 8.50. Evolution of the seizure in Figure 8.48, with spread of the ictal discharge into left parietal and occipital regions.

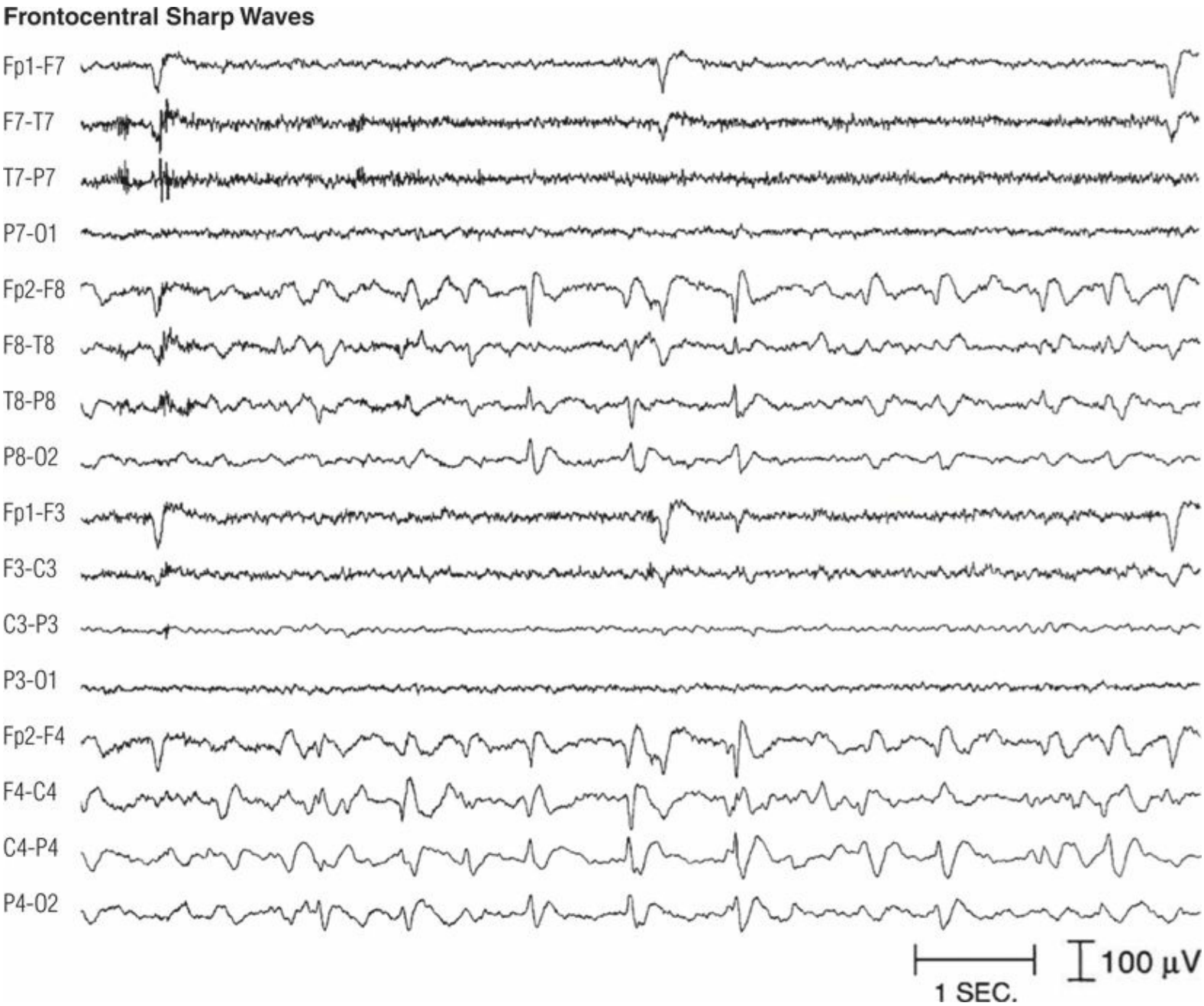

Figure 8.51. Eight-year-old boy with left hemiparesis and posttraumatic encephalomalacia in the right frontocentral white matter as a result of a motor vehicle accident at age 3 months. Interictal electroencephalogram showed right hemisphere slowing with sharp waves over the right frontocentral region (maximum at the C4 electrode).

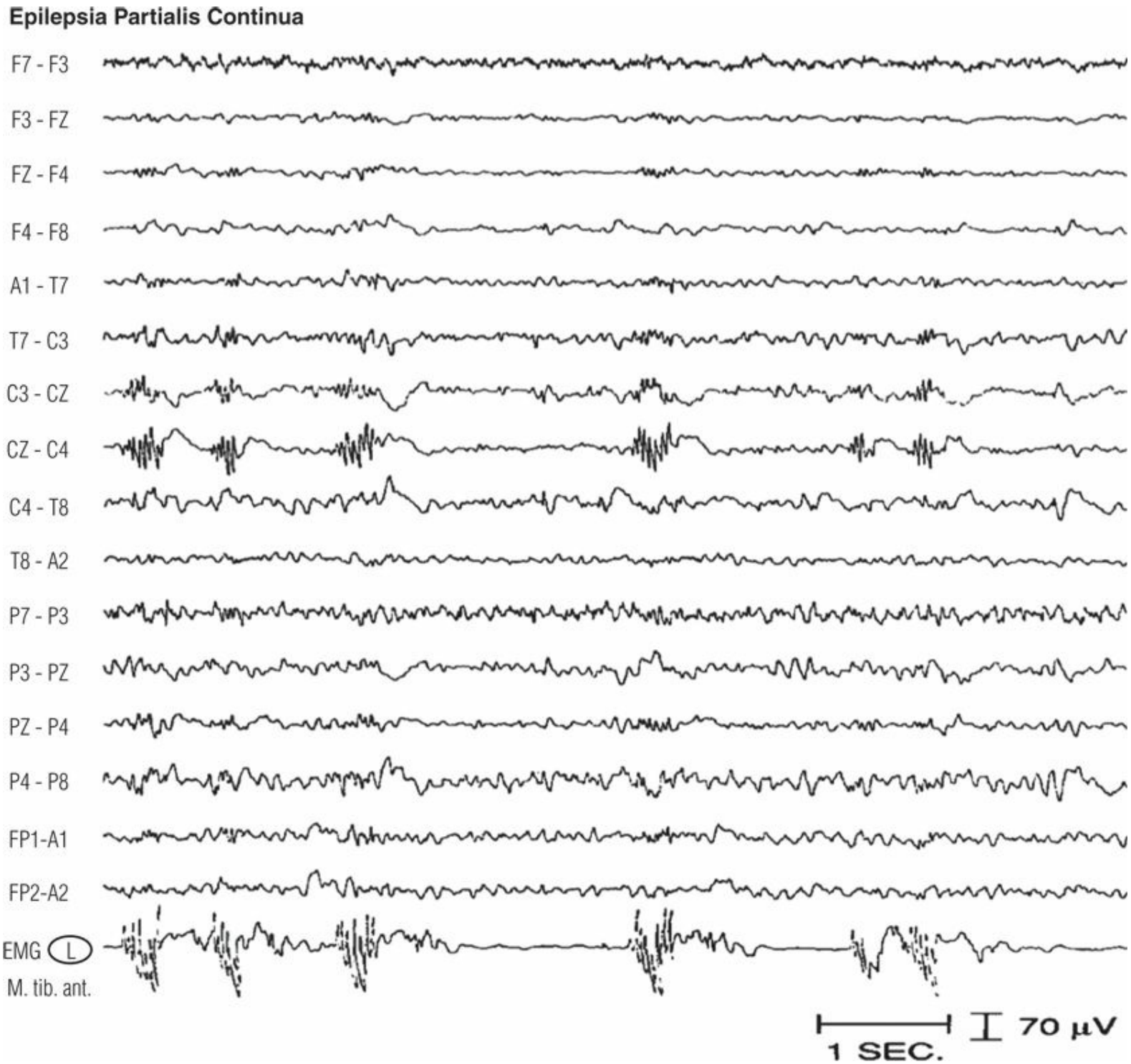

Figure 8.52. Sixty-nine–year-old man with continual jerking of the left foot and leg for 6 weeks, without loss of consciousness. Electromyography from the left tibialis anterior muscle showed that jerks occurred synchronously with each burst of polyspikes on electroencephalogram. Polyspikes were maximum at left vertex electrodes, presumably as a result of paradoxical lateralization of the discharge from the right interhemispheric region (21).

Occipital Lobe Epilepsy

Occipitotemporal spikes	Figure 8.53
Visual aura and left versive seizure	Figure 8.54

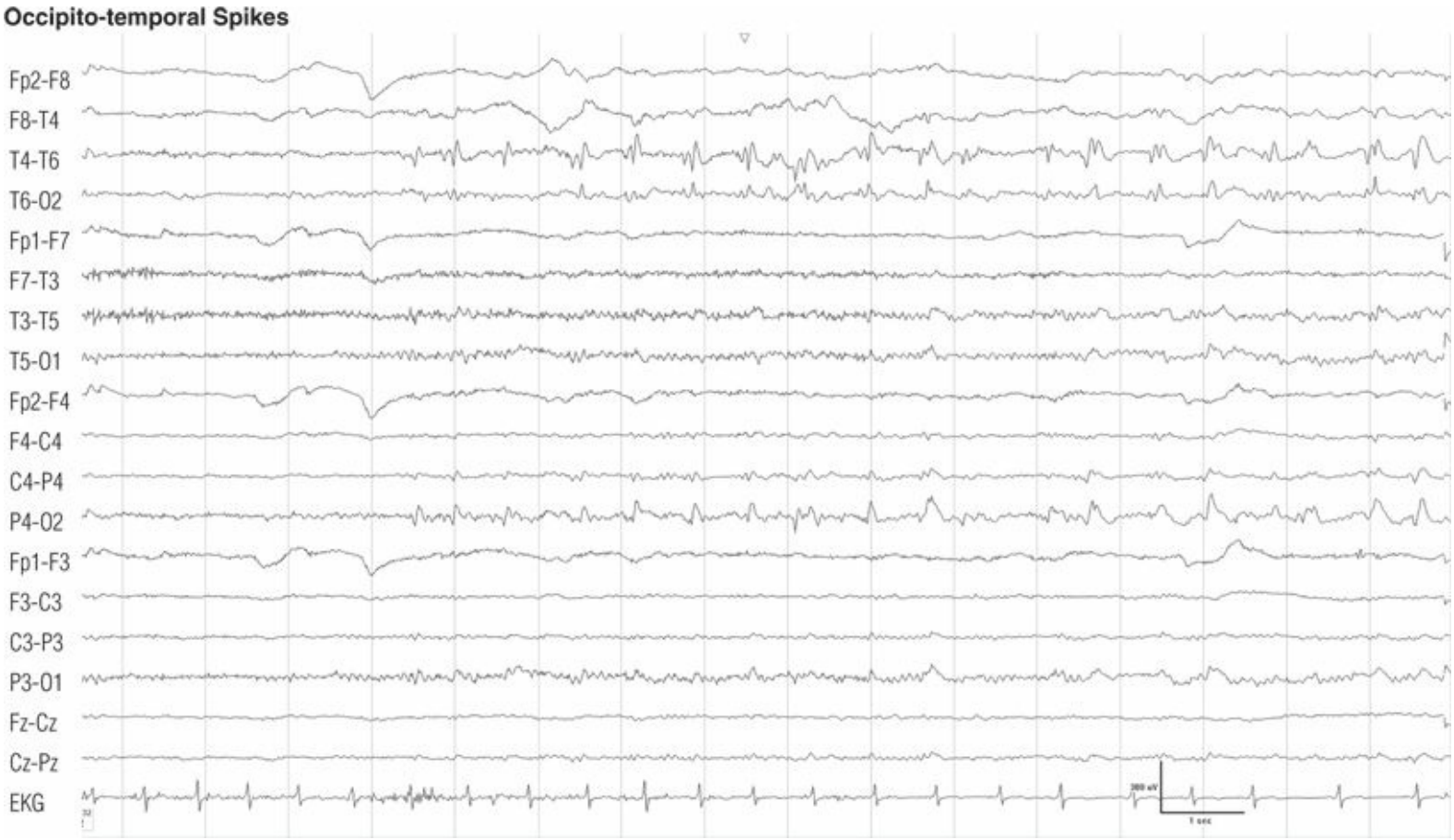

Figure 8.53. Seventeen-year-old boy with right occipital lobe epilepsy due to cortical malformation. Note the frequent spikes and polyspikes in the right occipital region maximum at electrodes O_2 and P8 (20).

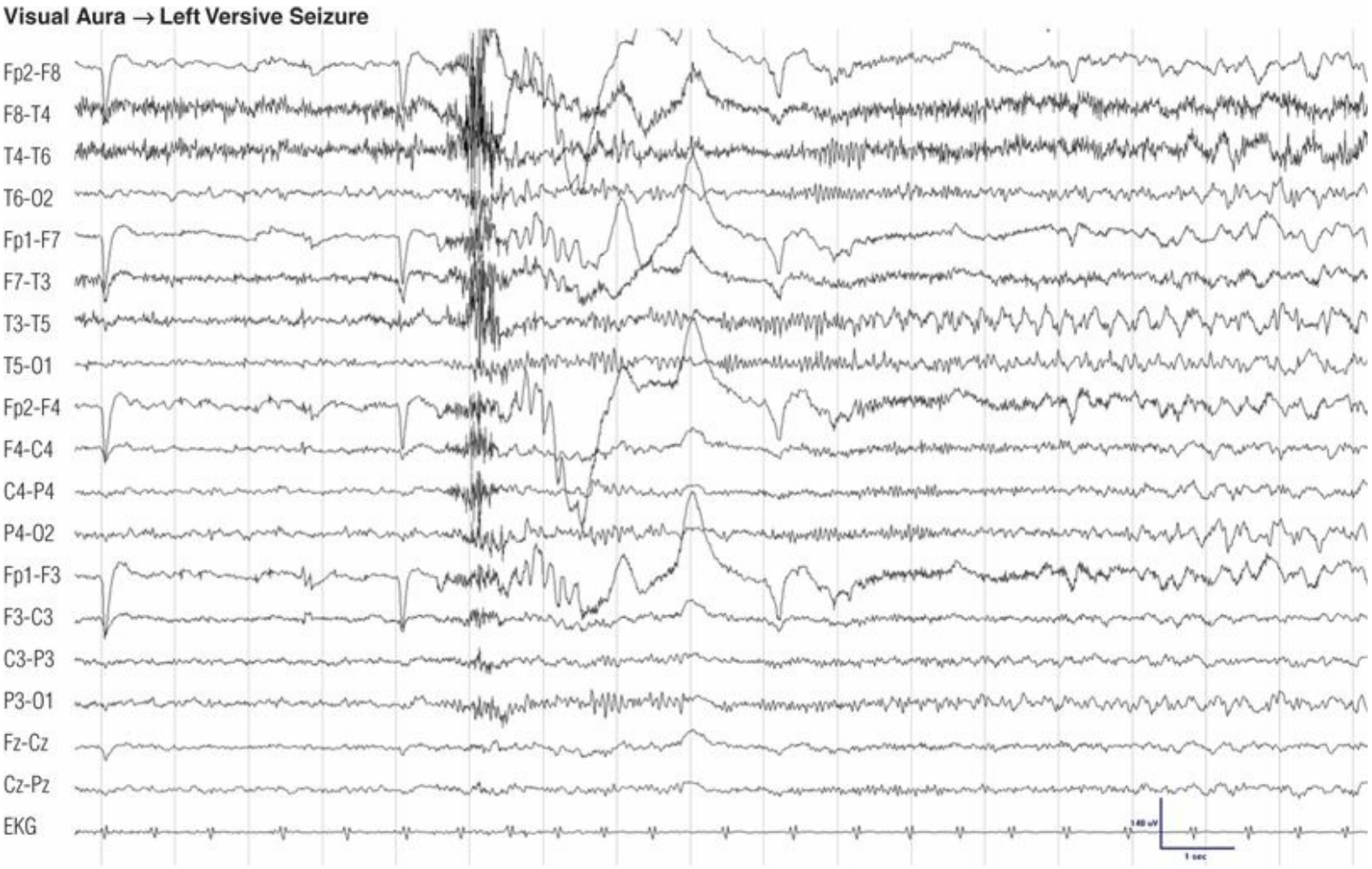

Figure 8.54. Recording of a left visual aura that evolved into a left versive seizure in the same patient as in Figure 8.54. Note the high-frequency discharge in the occipital regions at seizure onset (arrow), which can hardly be lateralized overlapping with a burst of EMG artifact.

PART IV: ELECTROENCEPHALOGRAPHIC FINDINGS IN NONEPILEPTIC PAROXYSMAL DISORDERS

The differential diagnosis of epilepsy includes a wide variety of paroxysmal disorders (see Chapter 40 and 41). During a clinical episode, the EEG recording may be crucial to clarifying the exact nature of the spells. In most of these disorders, the ictal electroencephalogram is normal. Three nonepileptic paroxysmal disorders with abnormal EEG findings are syncope, breath-holding spells, and sleep attacks caused by narcolepsy.

Pallid infantile syncope	Figures 8.55 and 8.56
Cyanotic breath-holding spell	Figures 8.57 and 8.58
Narcolepsy	Figure 8.59

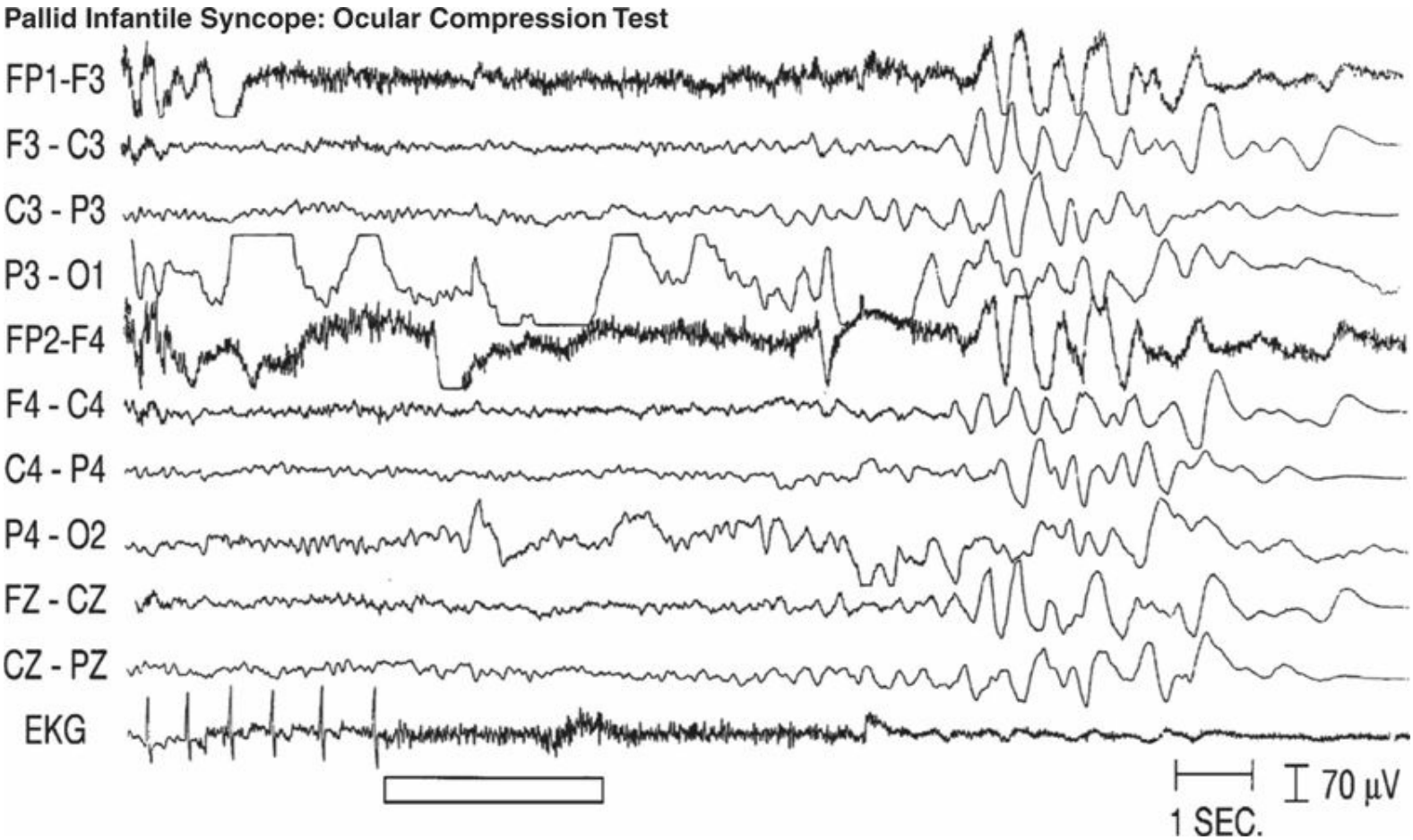

Figure 8.55. Two-year-old boy with pallid infantile syncope. Ocular compression (22,23) (bar), a controversial provocative maneuver, resulted in syncope with cardiac asystole for 12.5 seconds. Electroencephalography showed diffuse high-amplitude slowing followed by cerebral suppression as a result of global cerebral ischemia.

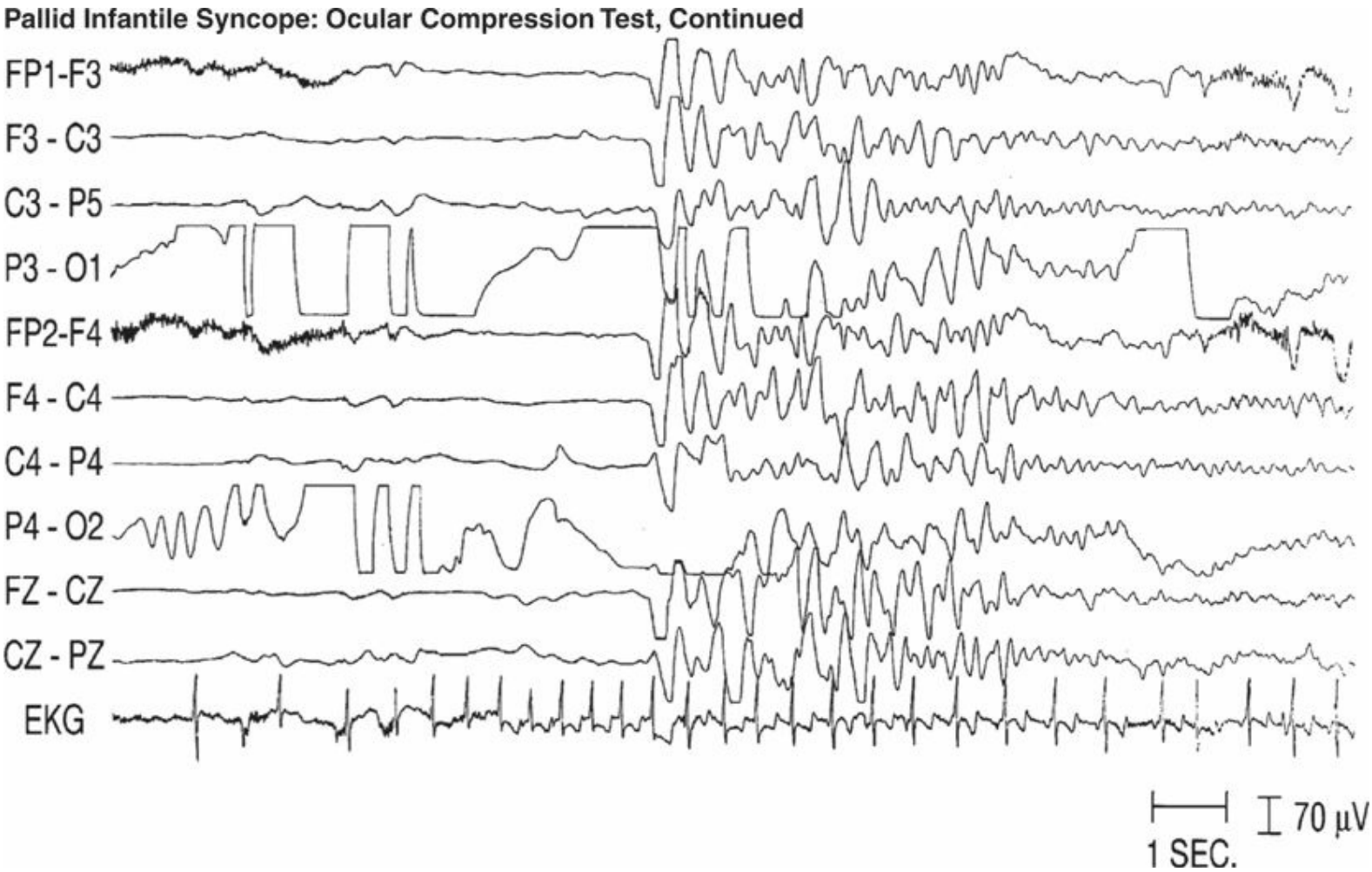

Figure 8.56. With recovery of the patient shown in Figure 8.56, electroencephalogram showed high-amplitude slowing followed by normal rhythms. Asystole with ocular compression may be caused by activation of the oculocardiac reflex (trigeminal afferent, vagal efferent pathways) (22,23).

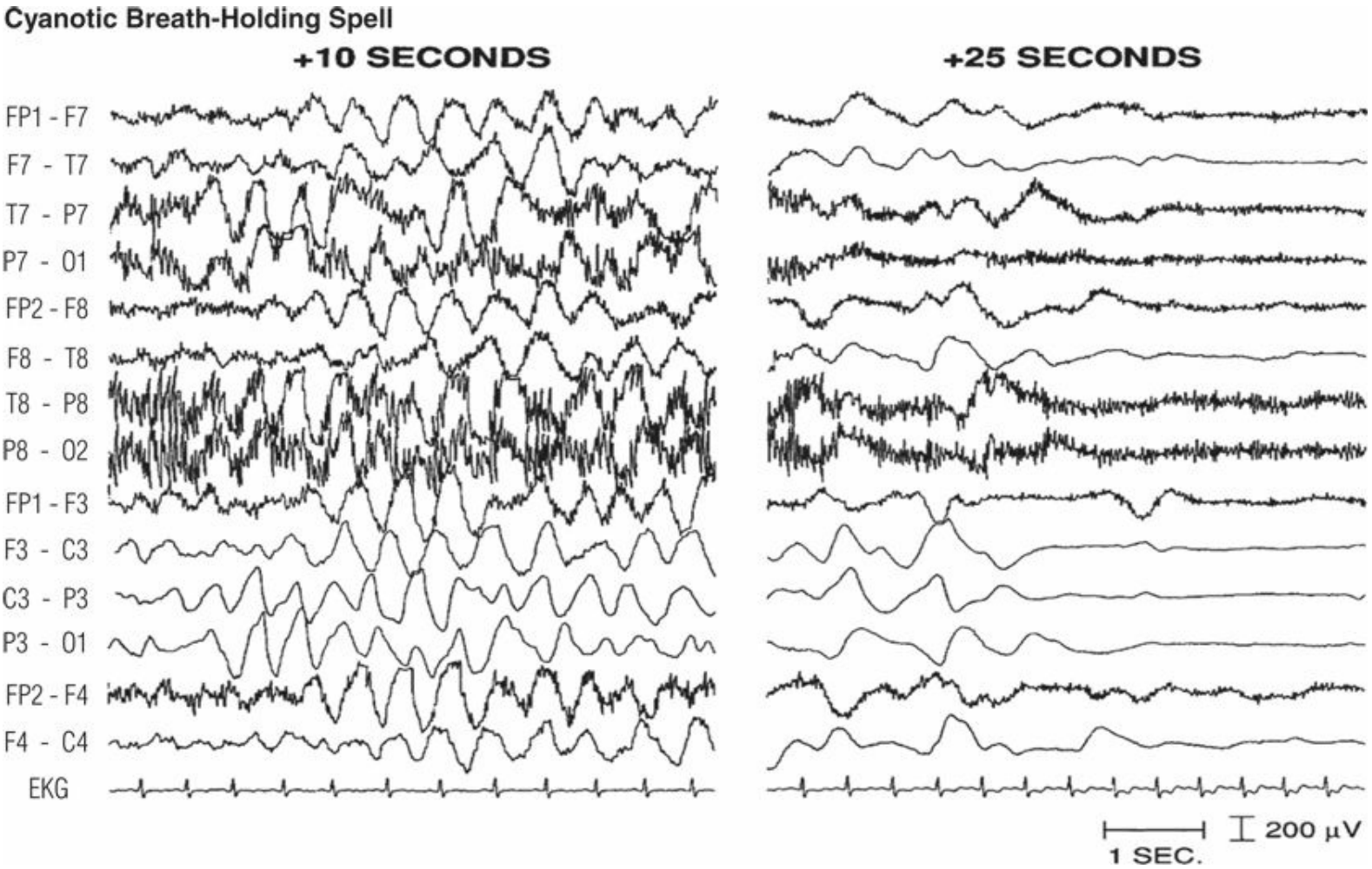

Figure 8.57. Two-year-old boy with cyanotic breath-holding spells sometimes followed by generalized tonic–clonic seizures. This episode occurred during crying and involved cessation of respiration for 40 seconds, oxygen desaturation to 73%, cyanosis, loss of consciousness, opisthotonic posturing, and urinary incontinence.

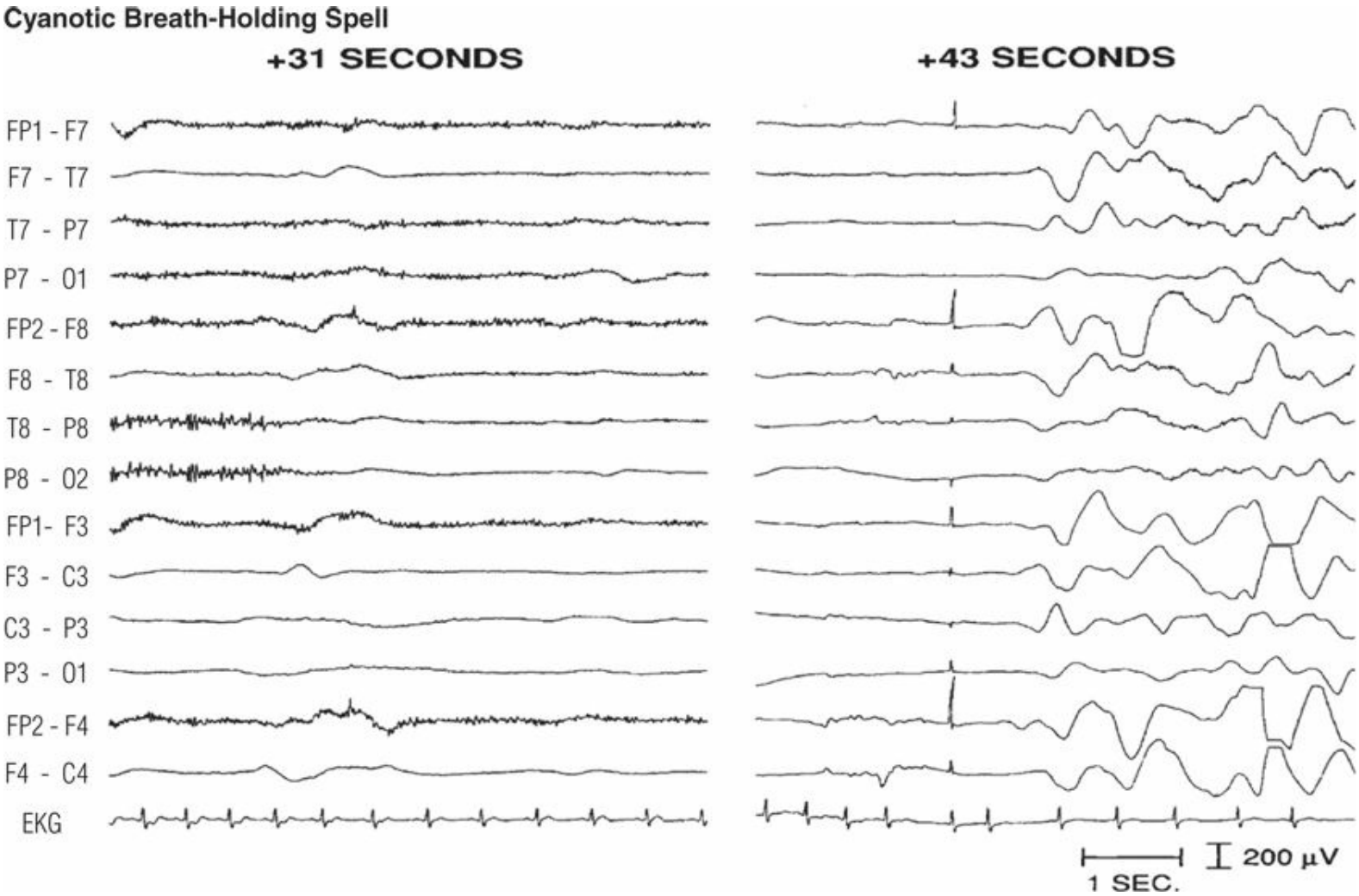

Figure 8.58. As the episode continued in the patient shown in Figure 8.58, electroencephalographic activity was similar to that during the syncopal attack in Figures 8.56 and 8.57, but the electroencephalogram showed tachycardia instead of asystole.

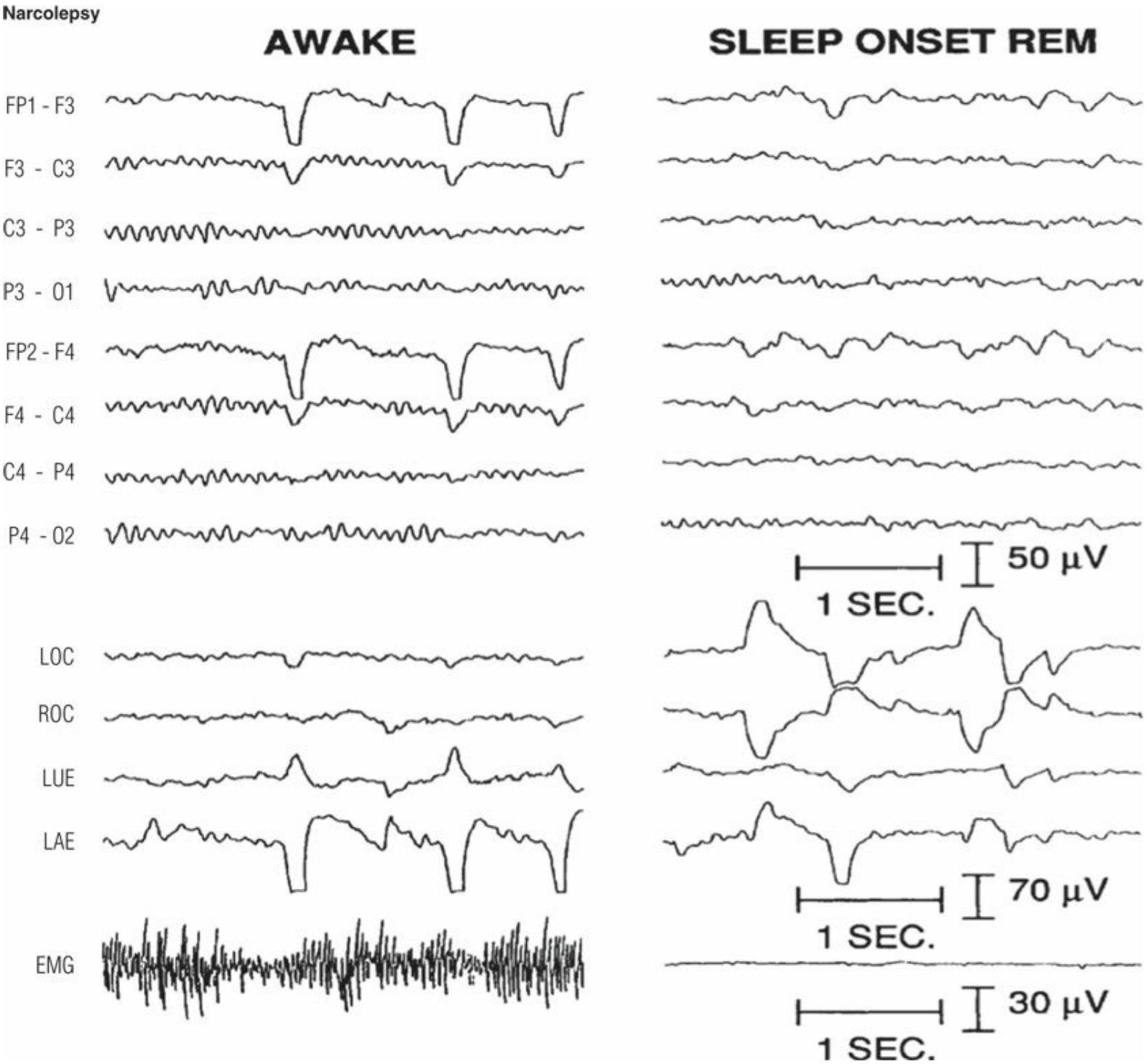

Figure 8.59. Fifty-six–year-old man with episodes of loss of consciousness (sleep attacks) and automatic behavior (minisleeps). Multiple sleep latency test gave evidence of narcolepsy with short sleep latency (2 minutes) and sleep-onset rapid eye movement periods (REM latency, 1 minute). Typical features during rapid eye movement sleep included rapid eye movements, absent muscle artifact, and drowsy electroencephalographic pattern. LOC and ROC, left and right outer canthus; LUE and LAE, under and above left eye. Ocular electrodes were referential to A1/A2. EMG is at the chin.

PART I: NORMAL ELECTROENCEPHALOGRAPHIC PATTERNS AND VARIANTS SOMETIMES CONFUSED WITH EPILEPTIFORM ACTIVITY

PART II: ELECTROENCEPHALOGRAPHIC ABNORMALITIES OF THE GENERALIZED EPILEPSIES

PART III: ELECTROENCEPHALOGRAPHIC ABNORMALITIES OF THE FOCAL EPILEPSIES

PART IV: ELECTROENCEPHALOGRAPHIC FINDINGS IN NONEPILEPTIC PAROXYSMAL DISORDERS

ACKNOWLEDGMENTS

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PART III EPILEPTIC SEIZURES AND SYNDROMES

SECTION A EPILEPTIC SEIZURES

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CHAPTER 9 TERMINOLOGY FOR SEIZURES AND EPILEPSIES

TOBIAS LODDENKEMPER AND ANNE T.BERG

INTRODUCTION

The international efforts to provide common terms and concepts for classifying seizures and epilepsy were first formalized in the late 1960s in the reports of Merlis (1) and Gastaut (2). Over time, these were revised culminating in the most widely used system for classification of epilepsies that was proposed in 1989 by the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) (3). This epilepsy classification remains in place despite ongoing discussions and proposals and is appended to this chapter. ILAE's 1981 seizure classification (4) and its 1985 and 1989 classifications of the epilepsies (3,5) have given physicians around the world a common language. These ILAE classifications rested on earlier classification approaches in 1969 and 1970 (1,2) and reflected concepts and understandings dating back to the late 1800s. These classifications were mainly based on two features: (a) the distinction between generalized and focal features and (b) etiologic considerations, although this latter was largely aligned with neurodisability as it greatly predated modern genetics. To bring terminology and concepts up to date and reflect advances in the neurosciences such as imaging and genetics and the advances in understanding of brain function, new approaches have been suggested (2010 report). An overview of the timeline of different proposals and classifications is given in Table 9.1.

Table 9.1 Timeline of Epilepsy Classifications

1969: Gastaut, Proposals—Seizures and Epilepsies
1970: Gastaut, Classification—Seizures
1970: Merlis, Classification—Epilepsies
1981: Commission, Classification—Seizures
1985: Commission, Classification—Epilepsies
1989: Commission, Classification—Epilepsies
1993: Commission, Epidemiologic standards
2001: Blume, Glossary of ictal semiology
2001: Engel, Proposed diagnostic scheme
2005: Fisher, Definition of seizure and epilepsy
2006: Task Force, Report—Seizures and epilepsies
2010: Commission report—Terminology and organization
2014: Pending update

TERMINOLOGY AND DEFINITIONS

It is critical to differentiate between epilepsy, epilepsy syndrome, and seizure types and acknowledge that these are different entities.

Seizure: Hughlings Jackson was among the first to outline the distinction between seizures and epilepsy. According to Jackson, "A convulsion is but a symptom, and implies only that there is an occasional, an excessive, and a disorderly discharge of nerve tissue on muscles. This discharge occurs in all degrees; it occurs with all conditions of ill health, at all ages, and under innumerable circumstances" (6). This definition has not changed in the last 150 years. According to the ILAE, an epileptic seizure "is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain." Defining features include "mode of onset and termination, clinical manifestations, and abnormal enhanced synchrony" (7).

Epilepsy: The term epilepsy initially characterized both the disease and its attacks (8). An operational definition was provided 20 years ago by the ILAE: "A condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause. Multiple seizures occurring in a 24-h period are considered a single event. An episode of status epilepticus is considered a single event. Individuals who have had only febrile seizures or only neonatal seizures as herein defined are excluded from this category" (9). In 2005, the ILAE attempted to provide a conceptual definition although the report may have overstated this summary in referring to this as an operational definition: "epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure. Elements in the definition of epilepsy include history of at least one seizure, enduring alteration in the brain that increases the likelihood of future seizures, and associated neurobiologic, cognitive, psychological, and social disturbances" (7). Most recently in 2014, the epilepsy definition was revised and now includes "(1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome" (10).

Epilepsy Syndrome: The concept of epilepsy syndromes was introduced over many years and was firmly ensconced in the ILAE report of 1989. An epilepsy syndrome is defined as "a complex of signs and symptoms that define a unique epileptic condition. This must involve more than just a seizure type: thus frontal lobe seizures per se, for instance, do not constitute a syndrome" (11). The ILAE furthermore distinguishes epileptic diseases, which are defined as "a pathologic condition with a single, specific, well-defined etiology. Thus progressive myoclonic epilepsy is a syndrome, but Unverricht-Lundborg is a disease" (11).

EARLY ILAE CLASSIFICATIONS

The first ILAE classification in 1969/1970 (1,2) distinguished primary or secondary epilepsy (based on identification of causes but largely in association with neurodisability) and partial or generalized (based on seizure manifestations). If the cause was not known, the term "primary" was used, whereas "secondary" alluded to a known cause. "Partial" indicated onset from a focal area in the brain, either based on semiologic features or based on clinical evaluation, and generalized included epilepsy with no clear single area of onset in the brain.

The 1981 seizure classification (4) further distinguished seizures into partial or generalized and took into account more than two types of features for a given partial or generalized seizure.

Specifically, the classification outlined partial and generalized seizures. Among partial seizures, simple partial, complex partial, and secondary generalized seizures were recognized. Among generalized seizures, absence, myoclonic, atonic, tonic, and tonic–clonic seizures were included.

Partial seizures could be "simple" and "complex" depending on the preservation or loss of consciousness during the events. Secondarily generalized was used, when a partial seizure spreads and involves the whole brain (and both sides of the body simultaneously with loss of consciousness). Generalized epilepsies were characterized by specific seizures in the form of absence (i.e., staring spells), myoclonic (muscle jerks), loss of tone (atonic), increased tone (tonic), and tonic plus clonic movements. Notably, epileptic spasms were excluded from this classification.

A revised epilepsy classification was published in 1985 (5). Because the term secondary generalized epilepsy was sometimes confused with the different concept of "secondary" or "secondarily" generalized tonic–clonic seizures, it was abandoned in the subsequent revision. The terms primary and secondary were replaced with idiopathic (there is no cause except a possible genetic predisposition), symptomatic (the epilepsy is secondary to an underlying disorder of the brain), and cryptogenic (the cause is not known but presumed to be symptomatic). Both terms were applied to partial and generalized epilepsies. Furthermore, the recognition of "benign" rolandic epilepsy necessitated a category of "primary partial" epilepsies. Furthermore, this publication introduced the new concept of epilepsy syndromes as "Epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together."

THE 1989 ILAE CLASSIFICATION

The 1989 ILAE epilepsy classification is used worldwide and is reproduced in the appendix to this chapter. It was revised from proposals made in 1970 (1,2) and 1985 (5) and, like the 1981 ILAE seizure classification (4), is based primarily on the definition of electroclinical syndromes. In 1969, Henri Gastaut proposed the first classification of epilepsies (2), which was used as the basis of the first ILAE epilepsy classification system that was proposed one year later (1). This classification provided the major division between "partial" (focal) and generalized epilepsies. Each seizure type was grouped according to this dichotomy and associated with interictal and ictal electroencephalographic (EEG) findings, etiology and pathologic findings, and age of manifestation.

About 15 years later, a revision introduced the concept of epilepsy syndromes "defined as an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together. The signs and symptoms may be clinical (e.g., case history, seizure type, modes of seizure recurrence, and neurologic and psychological findings) or as a result of findings detected by ancillary studies (e.g., EEG, x-ray, CT [computed tomography], and NMR [nuclear magnetic resonance])" (5). This revision divided many specific epilepsy syndromes under the major dichotomy of generalized and "localization-related" (focal) epilepsies and associated them with clinical and EEG findings, etiologies, and disease severity.

The primary dichotomy of these classification systems was set between localization-related (focal) epilepsies, "in which seizure semiology or findings at investigation disclose a localized origin of the seizures" (3), and generalized epilepsies, characterized by "seizures in which the first clinical changes indicate initial involvement of both hemispheres… [and] the ictal encephalographic patterns initially are bilateral" (3). EEG findings are the laboratory results that carry the most weight for defining a focal epilepsy syndrome.

In addition to localizing information, previous epilepsy classifications also contained etiologic

information. The 1970 epilepsy classification (1) further divided the generalized epilepsies into primary, those occurring in the setting of normal neurologic status, with seizures that begin in childhood or adolescence and lack any clear cause, and secondary, those involving abnormal neurologic or psychological findings and diffuse or multifocal brain lesions. Because the term secondary generalized epilepsy was sometimes confused with the different concept of "secondary" or "secondarily" generalized tonic–clonic seizures, it was abandoned in the 1985 (5) and 1989 (3) revisions. Primary and secondary were replaced with idiopathic and symptomatic. The 1970 classification (1) applied the etiologic dichotomy only to generalized epilepsies because all focal epilepsies were assumed to be associated with some type of brain lesion. This did not include the idiopathic syndrome of benign epilepsy of childhood with centrotemporal spikes, and therefore, the 1985 (5) and 1989 (3) revisions applied idiopathic and symptomatic to the focal epilepsies as well. The term cryptogenic was added in the 1989 (3) classification to describe epilepsy syndromes that are presumed to be symptomatic but are of unknown cause in specific patients.

In spite of its widespread use, the 1989 proposal has been criticized because of its separation between "partial" and "generalized" epilepsies, and therefore, it does reflect our growing appreciation for the complex manifestations of epilepsy in the brain or how that can change over time, especially in the developing brain. Furthermore, the terms "idiopathic," "cryptogenic," and "symptomatic" are based on assumption and lack of knowledge rather than actual evidence. Now that the ability to collect the necessary evidence has developed, those assumptions are being called into question. Additionally, the system accommodates didactic grouping purposes but has limitation when used in clinical practice during the process of data acquisition: A working diagnosis is usually assigned first, and subsequently, etiologies are explored. A final diagnosis and classification is frequently not possible before workup was completed. Furthermore, the systems description of seizure semiology is limited and is thought to mingle seizure semiology and epilepsy type or syndrome and only allows a strict one-to-one relationship between seizure type and epilepsy. In all, the 1989 classification rests on concepts developed over the past century and does not readily incorporate our rapidly expanding knowledge about the causes and manifestations of epilepsy afforded to us by advances in neuroimaging, molecular cell genetics, neuroimmunology, and other fields.

SEMIOLOGIC SEIZURE CLASSIFICATION

A seizure classification based only on clinical semiology, so-called semiologic seizure classification, was proposed by Hans Lüders et al. in the late 1990s (12,13). This considered the following clinical seizure features:

1. Auras: Ictal manifestations having sensory, psychosensory, and experiential symptoms.
2. Autonomic seizures: The main ictal manifestations are objectively documented autonomic alterations.
3. "Dialeptic" seizures: Their main ictal manifestation is an alteration of consciousness independent of ictal EEG manifestations. The term "dialeptic" seizure has been introduced to distinguish this concept from absence seizures (as dialeptic seizures with a generalized ictal EEG) and complex partial seizures (as dialeptic seizures with a focal ictal EEG).
4. Motor seizures: Motor symptoms and are subclassified as simple or complex. Simple motor seizures are characterized by simple, unnatural movements that can be triggered by

electrical stimulation of the primary and supplementary motor area (such as myoclonic, tonic, clonic and tonic–clonic, versive seizures). Complex motor seizures are characterized by complex motor movements resembling natural movements but occurring in an inappropriate setting (definition of "automatisms").

5. Special seizures: Seizures characterized by "negative" features (so named atonic, astatic, hypomotor, akinetic, and aphasic seizures). The semiologic seizure classification identifies in detail the somatotopic distribution of ictal semiology and seizure evolution and paved the way for an ILAE glossary of seizure semiology.

GLOSSARY OF SEIZURE SEMIOLOGY

Terms from the semiologic seizure classification were incorporated in an ILAE glossary of seizure semiology terms in 2001 (11). This glossary delineates descriptive terms that provide additional details on clinical seizure presentation. The glossary contained terms for reference to semiology, as well as terms for indicating seizure timing and duration, severity, prodromes, and postictal phenomena. According to this glossary, seizures can be termed "motor" when they involve musculature in any form. The motor event could consist of an increase (positive) or decrease (negative) in muscle contraction to produce a movement. Seizures can be called "tonic" when consist in a sustained increase in muscle contraction lasting a few seconds to minutes; "atonic" when appearing as a sudden loss or diminution of muscle tone without apparent preceding myoclonic or tonic event lasting 1 to 2 seconds, involving the head, trunk, jaw, or limb musculature; or "myoclonic" if they present with a sudden, brief (usually <100 milliseconds) involuntary single (or multiple) contraction of muscles or muscle groups of variable topography. The term "clonic" was used to refer to myoclonus that is regularly repetitive, involves the same muscle groups at a frequency of about 2 to 3 Hz, and is prolonged. "Tonic–clonic" refers to a sequence consisting of a tonic followed by a clonic phase (14). The glossary also contains details on automatisms and associated features of semiology. The term "automatism" is recommended for a more or less coordinated, repetitive, motor activity mostly occurring when cognition is impaired. Automatisms often resemble a voluntary movement and may consist of an inappropriate continuation of ongoing preictal motor activity. Lip smacking, lip pursing, chewing, licking, teeth grinding, and swallowing are termed "oroalimentary" (14). The term "dyscognitive" refers to events in which [1] disturbance of cognition is the predominant feature, and [2a] two or more of the components of cognition are involved, or [2b] involvement of such components is undetermined. Components of cognition were defined as follows:

1. Perception: symbolic conception of sensory information
2. Attention: appropriate selection of a principal perception or task
3. Emotion: appropriate affective significance of a perception
4. Memory: ability to store and retrieve percepts or concepts
5. Executive function: anticipation, selection, monitoring of consequences, and initiation of motor activity including praxis and/or speech

2001 ILAE PROPOSAL: A SYNDROME-ORIENTED

CLASSIFICATION

To resolve these existing controversies surrounding the 1989 epilepsy classification, the ILAE's Commission on Classification and Terminology published a common terminology for ictal semiology (14) and a revised five-axis classification scheme of epilepsies (11). This proposal (11) was also based on epilepsy syndromes that appeared in previous classifications. The authors defined an epileptic syndrome as "[a] complex of signs and symptoms that define a unique epilepsy condition" (11). However, due to ongoing discussions, this proposal was again revised and another progress report was issued 5 years later (15).

Axes of the 2001 ILAE Proposal

The different axes in the 2001 ILAE proposal included seizure description (axis 1), seizure type (axis 2), epilepsy syndrome (axis 3), etiology (axis 4), and impairment (axis 5).

Axis 1 described ictal seizure semiology through a standardized glossary of descriptive ictal terminology (14). This terminology was independent of pathophysiologic mechanisms, epilepsy focus, or seizure etiology.

Axis 2 was based on a list of accepted epileptic seizure types constructed by the task force. These seizure types were closely related to diagnostic epilepsy entities or indicated underlying mechanisms, pathophysiology, or etiology or implicated related prognosis and therapy.

Axis 3 identified the epilepsy syndrome diagnosis and separated epilepsy syndromes from entities with epileptic seizures. Epilepsy syndromes were divided into "syndromes in development" and fully characterized syndromes (16).

Axis 4 delineated the etiology of epilepsies, which included pathologic and genetic causes as well as diseases frequently associated with epilepsy, and this list was a work in progress at the time of publication.

Axis 5 was incomplete at the time of publication and was intended to include an optional classification of the degree of disability and impairment caused by the epilepsy.

Compared with the 1989 version of epilepsy classification, the diagnostic scheme of the 2001 proposal attempted to overcome shortcomings among EEG features, clinical seizure semiology, and syndromic classification efforts. By dividing the seizure classification into several axes, the ILAE responded to the criticism that a strict one-to-one relationship is lacking between epilepsy syndromes and seizure types. The introduction of a multiaxial diagnostic scheme reflected the recognition of epilepsy as a clinical symptom that can manifest with different semiologic seizure types and be intertwined with different etiologies. It also tried to respond to criticism that seizure semiology was not sufficiently emphasized in previous classifications. Furthermore, it tried to address the more and more confluent borders between generalized and focal epilepsies. The term partial was replaced by focal. Additionally, it attempted to model epilepsy syndromes more flexible by defining "accepted syndromes" versus "syndromes in development." However, critics highlighted an incomplete and preliminary presentation, lack of inclusion criteria for "accepted" syndromes, redundancy among classification axes, lack of information on age of onset, and inability to use this classification in all patients and lack of applicability (17–20). Due to ongoing discussions, the ILAE core group on classification revised this approach and provided an update in 2006 (15).

THE 2006 REPORT OF THE ILAE CLASSIFICATION

CORE GROUP

This proposal aimed to outline "scientifically rigorous criteria for identification of specific epileptic seizure types and specific epilepsy syndromes as unique diagnostic entities" (15). Criteria included epileptic seizure types, age of onset, progressive nature, interictal EEG, associated interictal signs and symptoms, pathophysiologic mechanisms, anatomical substrate, and etiologic categories, as well as genetic basis. Subsequently, the group scored epilepsy syndromes listed in the 2001 proposal on a scale from 1 to 3, with 3 being the most clearly and reproducibly defined. The proposal mentioned that this was a very preliminary method and intended to ignite further research and category suggestions or possible cluster analysis of signs and symptoms (15). Based on this proposal, epilepsy syndromes could be assigned in up to 70% of cases in a first comparison (21). However, persistent inter- and intra-axial discordance was noted necessitating further revision in 2010.

THE 2010 REVISED TERMINOLOGY AND CONCEPTS FOR ORGANIZATION OF SEIZURES AND EPILEPSIES

This additional update is an "interim organization" and tries to address ongoing criticisms to concepts and terminology (22). Classification is not treated as a rigid doctrine but a guide to summarize our current understanding about seizures and epilepsies in a useful manner. This revision includes the concept of electroclinical syndromes and essentially leaves the suggested syndrome list from 2006 unchanged although it incorporated additional, well-documented syndromes (22). It also addresses the variable degrees of precision of diagnosis and attempts to include the natural evolution. Epilepsies are now organized by specificity into three major divisions of electroclinical syndromes, nonsyndromic epilepsies with structural–metabolic causes, and epilepsies of unknown cause. This organization allows further description within divisions by dimensions as previously suggested (17). These may include cause, seizure types, age at onset, and others. Furthermore, it emphasizes the descriptive seizure terminology from 2001 (14) within these dimensions, specifically for focal epilepsies. Seizures are now recognized as "occurring in and rapidly engaging bilaterally distributed networks (generalized) and within networks limited to one hemisphere and either discretely localized or more widely distributed (focal)" and terms such as complex partial and simple partial have been abandoned. It also rekindles the terminology "focal" and differentiates from "generalized" seizures, while recognizing that generalized epileptic seizures do not necessarily include the entire cortex. Suggested etiologic concepts within the causal dimension include genetic, structural–metabolic, and unknown replacing idiopathic, symptomatic, and cryptogenic. Further changes in terminology and classification remain work in progress.

DO NOT CLASSIFY—DIAGNOSE!

While the ILAE efforts still continue to revise this epilepsy classification, clinicians continue to take care of epilepsy patients and make clinical epilepsy diagnoses, largely unaffected by the Ivory Tower, theoretical discussions, and deliberations on epilepsy classification. Like any other neurologic condition, the general neurologic diagnostic approach to diagnosis of characterizing the clinical presentation (namely, the seizures), followed by localization in the CNS, and investigating

underlying etiologies and comorbidities can also be applied to epilepsy. The diagnostic approach to seizures and epilepsy involves five independent steps:

1. How old is the patient?
2. Is it epilepsy?
3. What is the clinical presentation? (What are the seizure symptoms/the neurologic exam findings/cognitive or developmental status?)
4. What are the results of investigational tests?
5. Can you localize the source of the seizures, can you identify one or several epilepsy causes, or can you identify an epilepsy syndrome? (Is there a functional or structural lesion and if so, where is it? Is there a genetic factor? A vascular, infectious, toxic, autoimmune, metabolic, idiopathic/unknown, neoplastic, congenital, degenerative, and endocrine component (mnemonic: VITAMIN CDE)? This process requires comparison of all collected evidence in the setting of previously described findings and literature categories. Interpretation of above collected clinical findings and test results may allow localization or syndrome diagnosis. Also, are there other related features that may assist with diagnosis making or fit with known syndromes? Ongoing synopses of independent investigational techniques include synthesis and integration of all results into a working and ultimately final diagnosis during the process of collection of a detailed history and clinical course, seizure semiology analysis either by history or video review, physical examination, electrophysiologic studies, structural neuroimaging and functional and metabolic neuroimaging, and laboratory testing including genetic and histopathologic studies, and these studies aid in answering the questions outlined above.

1. How Old Is the Patient?

Perhaps the single most important overriding factor in the diagnosis of a patient with epilepsy is the age at onset. This is because different types of epilepsies, seizures, and causes of epilepsy manifest at different ages. If one begins with age, the field of diagnostic possibilities rapidly simplifies and one can focus on a relatively restricted range of possibilities. That said, there are fundamental principles to guide diagnosis at any age.

2. Is It Epilepsy?

Any given patient may present with nonepileptic seizures. Therefore, it is always crucial to consider the option that events may be nonepileptic. The differentiation between epileptic and nonepileptic events is often challenging. Video–EEG monitoring can help capture clinical semiology and an EEG correlate—or lack thereof. In infants and children, overdiagnosis of epilepsy is often seen in the context of breath-holding spells, gastroesophageal reflex, excessive startling, or parasomnias among others. In older adolescents and adults, a phenomenon known as nonepileptic (sometimes psychogenic) seizures is seen. This is a conversion disorder and ideally should result in the involvement of a psychiatrist.

Diagnosis is recognized as an ongoing interactive and iterative process. Once further evidence and results become available, patients can be diagnosed with an increasing degree of precision or

results may inform further, more targeted testing. If it is uncertain whether the patient has epilepsy or nonepileptic seizures, we prefer the term paroxysmal event. As further information becomes available through the steps outlined previously (e.g., an electroencephalogram [EEG] demonstrating left mesial temporal sharp waves, left temporal EEG seizures, and an MRI showing left hippocampal atrophy), the diagnosis becomes more precise (left mesial temporal lobe epilepsy). Therefore, it is helpful to document progress in diagnostic workup and diagnosis as well as a revised diagnostic hypothesis with every patient encounter. Additional details on localizing and lateralizing evidence of clinical seizures as well as diagnostic syndromic features are also outlined in several other chapters in this book.

3. What Is the Clinical Presentation?

A detailed account of the episodes in question is crucial. Specific questions may focus on who witnessed the event, when and where events occur, whether they are triggered by external stimuli, how they begin, how they evolve, and how they end, which are essential to determining the type of seizure.

The seizure setting includes a reliable witness who can provide a detailed account of the event in question. Alternatively, a video recording of the event may also be extremely helpful, especially in circumstances if the patient cannot recall the event or parts of the event. Emphasis should also be placed on the immediate period prior to the seizure, as a detailed account of that time period may reveal potential seizure triggers or prodrome. Examples may include the patient's baseline activity, changes in the setting or patient behavior immediately before the event (i.e., occurrence out of sleep), or clinical symptoms that the patient experienced prior to seizure onset, such as a headache or fever.

Onset: Detailed reconstruction of the seizure onset may divulge further information about potential auras, although auras do not necessarily need to be present. However, the first clinical symptom often provides most information regarding the ictal onset zone and epileptogenic zone as the initial symptomatogenic zone is usually closest to the actual seizure onset (23).

Evolution: Further clinical seizure features and evolution may present with a variety of different presentations, including motor, language, automatisms, autonomic manifestations, and alteration of consciousness among others. The clinical signs and symptoms are the most important pieces of information for localizing a lesion in the central nervous system (23). Seizures and seizure semiology are the clinical manifestation of epilepsy. The ILAE epilepsy terminology from 2001 (14), based on clinical seizure descriptions (12,13,24–29), provides a helpful framework for this description. This glossary uses only the clinical semiology and does not require any additional diagnostic techniques other than analysis of an observed or videotaped seizure. Of note, data from other investigational techniques, such as EEG, MEG, MRI, or nuclear imaging, are not necessary to utilize the glossary.

Postictal: Events that happen after the seizure may also provide additional information. Lateralizing signs, such as postictal hemiparesis (Todd palsy) or postictal nose wiping, may continue to provide additional clinical information.

In between and after seizures, the physical examination can add information regarding etiology, type of epilepsy, and epilepsy syndrome (i.e., a hemiparesis may point toward a large hemispheric lesion; progressive hemiparesis over time may implicate a tumor or Rasmussen encephalitis in the appropriate clinical setting) (23).

Frequency, patterns, and seizure clusters: It may also be crucial to inquire about seizure frequency; seizure patterns, such as predominant occurrence at night; or seizure occurrence in

clusters, as seen during epileptic spasms.

4. What Are the Results of Investigational Tests?

An EEG helps in the evaluation of seizure type and localization and possible diagnosis of an epilepsy syndrome and aids in the estimation of seizure recurrence risk. Activation procedures (hyperventilation, photic stimulation, sleep/sleep deprivation) can be performed to provoke epileptiform abnormalities (23).

Neuroimaging, including MRI, can investigate a possible cause of seizures, such as the identification of a structural abnormality. In general, as a practical guideline, persistent postictal focal deficits and the lack of return to baseline within a few hours after a seizure should suggest the need of neuroimaging to rule out additional neurologic structural lesions.

Further investigations to determine the etiology of seizures including genetic testing through laboratory blood tests may also be considered if clinically indicated.

5. Do the Presentation and Investigational Findings Fit with a Specific Epilepsy Localization, Known Genetic Cause, or Well-Described Epilepsy Syndrome?

Seizures are caused by the co-occurrence of multiple triggering factors. On the basis of investigational methods used to determine the cause of the epilepsy (e.g., histopathology, metabolic testing, MRI imaging, genetic testing) or localization to a certain area in the brain, factors responsible for the generation of seizures can be found simultaneously at different diagnostic levels. To account for multiple coexisting etiologic factors, the etiology dimension permits the classification of several factors in one patient. Other diagnostic techniques, such as genetics, have led to the identification of other coexisting causes and, with the results from further research in newer fields, will gain in importance in the future. A large proportion of children with epilepsy and a smaller proportion of adults have epilepsies that may fit criteria for specific electroclinical syndromic diagnoses. Such diagnoses are not independent of any of the other features discussed above, but they do provide a clinical gestalt that allows some confidence regarding the preferred treatments, likely neurologic consequences, and long-term outcomes for the patient. These syndromes are addressed in several different chapters in this text.

CONCLUSION

The classification of epilepsies is an ongoing process. While the terminology of the 1989 ILAE proposal (3) is in widespread use (and is reproduced here as an Appendix), it does not reflect the current approach, terminology, and concepts used in the contemporary diagnosis and treatment of patients with epilepsy. Newer proposals attempt to provide adjust for scientific progress and implement language that directly applies the advances from neuroimaging, genetics, and other areas of neuroscience to the patient and—in doing so—provide a transparent translation of discoveries to patient care. While the classification of epilepsy continues to be revised, we urge the readers not to waste time with classification, but to diagnose their patients, to be able to provide the most appropriate treatment. The general neurologic approach of seizure description, localization and etiology, and comorbidity confirmation works also well in epilepsy, in particular when approaching

and diagnosing a new epilepsy patient.

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CHAPTER 9 APPENDIX PROPOSAL FOR REVISED CLASSIFICATION OF EPILEPSIES AND EPILEPTIC SYNDROMES

(COMMISSION ON CLASSIFICATION AND TERMINOLOGY OF THE INTERNATIONAL LEAGUE AGAINST EPILEPSY 1989). REPRODUCED WITH PERMISSION FROM EPILEPSIA. 1989;30:389–399.

PART I: INTERNATIONAL CLASSIFICATION OF EPILEPSIES AND EPILEPTIC SYNDROMES

1. Localization-related (focal, local, partial) epilepsies and syndromes
   1.1 Idiopathic (with age-related onset)At present, the following syndromes are established, but more may be identified in the future:

- Benign childhood epilepsy with centrotemporal spike
- Childhood epilepsy with occipital paroxysms
- Primary reading epilepsy

1.2 Symptomatic (Part III)

- Chronic progressive epilepsia partialis continua of childhood (Kojewnikow syndrome)
- Syndromes characterized by seizures with specific modes of precipitation (see Part IV)

Apart from these rare conditions, the symptomatic category comprises syndromes of great individual variability, which are based mainly on seizure types and other clinical features, as well as anatomic localization and etiology—as far as these are known.

The seizure types refer to the International Classification of Epileptic Seizures. Inferences regarding anatomic localization must be drawn carefully. The scalp EEG (both interictal and ictal) may be misleading, and even local morphologic findings detected by neuroimaging techniques are not necessarily identical with an epileptogenic lesion. Seizure symptomatology and, sometimes, additional clinical features often provide important clues. The first sign or symptom of a seizure is often the most important indicator of the site of origin of seizure discharge, whereas the following sequence of ictal events can reflect its further propagation through the brain. This sequence, however, can still be of high localizing importance. One must bear in mind that a seizure may start in a clinically silent region, so that the first clinical event occurs only after spread to a site more or less distant from the locus of initial discharge. The following tentative descriptions of syndromes related to anatomic localizations are based on data that include findings in studies with depth electrodes.

Temporal Lobe Epilepsies

Temporal lobe syndromes are characterized by simple partial seizures, complex partial seizures, secondarily generalized seizures, or combinations of these. Frequently, there is a history of febrile seizures, and a family history of seizures is common. Memory deficits may occur. On metabolic imaging studies, hypometabolism is frequently observed [e.g., positron emission tomography (PET)]. Unilateral or bilateral temporal lobe spikes are common on EEG. Onset is frequently in childhood or young adulthood. Seizures occur in clusters at intervals or randomly.

General Characteristics

Features strongly suggestive of the diagnosis when present include:

1. Simple partial seizures typically characterized by autonomic and/or psychic symptoms and certain sensory phenomena such as olfactory and auditory (including illusions). Most common is an epigastric, often rising, sensation.
2. Complex partial seizures often but not always beginning with motor arrest typically followed by oroalimentary automatism. Other automatisms frequently follow. The duration is typically >1 minute. Postictal confusion usually occurs. The attacks are followed by amnesia. Recovery is gradual.

Electroencephalographic Characteristics

In temporal lobe epilepsies, the interictal scalp EEG may show the following:

1. No abnormality.
2. Slight or marked asymmetry of the background activity.
3. Teporal spikes, sharp waves and/or slow waves, unilateral or bilateral, synchronous but also asynchronous. These findings are not always confined to the temporal region.
4. In addition to scalp EEG findings, intracranial recordings may allow better definition of the intracranial distribution of the interictal abnormalities.

In temporal lobe epilepsies, various EEG patterns may accompany the initial clinical ictal symptomatology, including (a) a unilateral or bilateral interruption of background activity and (b) temporal or multilobar low-amplitude fast activity, rhythmic spikes, or rhythmic slow waves. The onset of the EEG may not correlate with the clinical onset depending on methodology. Intracranial recordings may provide additional information regarding the chronologic and spatial evolution of the discharges.

Amygdalohippocampal (Mesiobasal Limbic or Rhinencephalic) Seizures

Hippocampal seizures are the most common form; the symptoms are those described in the previous paragraphs except that auditory symptoms may not occur. The interictal scalp EEG may be normal, may show interictal unilateral temporal sharp or slow waves, and may show bilateral sharp or slow waves, synchronous or asynchronous. The intracranial interictal EEG may show mesial anterior temporal spikes or sharp waves. Seizures are characterized by rising epigastric discomfort, nausea, marked autonomic signs, and other symptoms, including borborygmi, belching, pallor, fullness of the face, flushing of the face, arrest of respiration, pupillary dilatation, fear, panic, and olfactory–gustatory hallucinations.

Lateral Temporal Seizures

Simple seizures characterized by auditory hallucinations or illusions or dreamy states, visual misperceptions, or language disorders in case of language dominant hemisphere focus. These may progress to complex partial seizures if propagation to mesial temporal or extratemporal structures occurs. The scalp EEG shows unilateral or bilateral midtemporal or posterior temporal spikes, which are most prominent in the lateral derivations.

Frontal Lobe Epilepsies

Frontal lobe epilepsies are characterized by simple partial, complex partial, secondarily generalized seizures, or combinations of these. Seizures often occur several times a day and frequently occur during sleep. Frontal lobe partial seizures are sometimes mistaken for psychogenic seizures. Status epilepticus is a frequent complication.

General Characteristics

Features strongly suggestive of the diagnosis include

1. Generally short seizures
2. Complex partial seizures arising from the frontal lobe, often with minimal or no postictal confusion
3. Rapid secondary generalization (more common in seizures of frontal than of temporal lobe epilepsy)
4. Prominent motor manifestations, which are tonic or postural
5. Complex gestural automatisms frequent at onset
6. Frequent falling when the discharge is bilateral

A number of seizure types are described below; however, multiple frontal areas may be involved rapidly, and specific seizure types may not be discernible.

Supplementary Motor Seizures

In supplementary motor seizures, the seizure patterns are postural, focal tonic, with vocalization, speech arrest, and fencing postures.

Cingulate

Cingulate seizure patterns are complex partial with complex motor gestural automatisms at onset. Autonomic signs are common, as are changes in mood and affect.

Anterior Frontopolar Region

Anterior frontopolar seizure patterns include forced thinking or initial loss of contact and adversive movements of the head and eyes, with possible evolution including contraversive movements and axial clonic jerks and falls and autonomic signs.

Orbitofrontal

The orbitofrontal seizure pattern is one of complex partial seizures with initial motor and gestural automatisms, olfactory hallucinations and illusions, and autonomic signs.

Dorsolateral

Dorsolateral seizure patterns may be tonic or, less commonly, clonic with versive eye and head

movements and speech arrest.

Opercular

Opercular seizure characteristics include mastication, salivation, swallowing, laryngeal symptoms, speech arrest, epigastric aura, fear, and autonomic phenomena. Simple partial seizures, particularly partial clonic facial seizures, are common and may be ipsilateral. If secondary sensory changes occur, numbness may be a symptom, particularly in the hands. Gustatory hallucinations are particularly common in this area.

Motor Cortex

Motor cortex epilepsies are mainly characterized by simple partial seizures, and their localization depends on the side and topography of the area involved. In cases of the lower prerolandic area, there may be speech arrest, vocalization or dysphasia, tonic–clonic movements of the face on the contralateral side, or swallowing. Generalization of the seizure frequently occurs. In the rolandic area, partial motor seizures without march or jacksonian seizures occur, particularly beginning in the contralateral upper extremities. In the case of seizures involving the paracentral lobule, tonic movements of the ipsilateral foot may occur, as well as the expected contralateral leg movements. Postictal or Todd paralysis is frequent.

Kojewnikow Syndrome

Two types of Kojewnikow syndrome are recognized, one of which is also known as Rasmussen syndrome and is included among the epileptic syndromes of childhood noted under symptomatic seizures. The other type represents a particular form of rolandic partial epilepsy in both adults and children and is related to a variable lesion of the motor cortex. Its principal features are (a) motor partial seizures, always well localized; (b) often late appearance of myoclonus in the same site where somatomotor seizures occur; (c) an EEG with normal background activity and a focal paroxysmal abnormality (spikes and slow waves); (d) occurrence at any age in childhood and adulthood; (e) frequently demonstrable etiology (tumor, vascular); and (f) no progressive evolution of the syndrome (clinical, EEG, or psychological, except in relation to the evolution of the causal lesion). This condition may result from mitochondrial encephalopathy (MELAS). NOTE: anatomical origins of some epilepsies are difficult to assign to specific lobes. Such epilepsies include those with pre- and postcentral symptomatology (perirolandic seizures). Such overlap to adjacent anatomic regions also occurs in opercular epilepsy.

In frontal lobe epilepsies, the interictal scalp recordings may show (a) no abnormality; (b) sometimes background asymmetry, frontal spikes, or sharp waves; or (c) sharp waves or slow waves (either unilateral or frequently bilateral or unilateral multilobar). Intracranial recordings can sometimes distinguish unilateral from bilateral involvement.

In frontal lobe seizures, various EEG patterns can accompany the initial clinical symptomatology. Uncommonly, the EEG abnormality precedes the seizure onset and then provides important localizing information, such as (a) frontal or multilobar, often bilateral, low-amplitude fast activity, mixed spikes, rhythmic spikes, rhythmic spike waves, or rhythmic slow waves or (b) bilateral high-amplitude single sharp waves followed by diffuse flattening.

Depending on the methodology, intracranial recordings may provide additional information

regarding the chronologic and spatial evolution of the discharges; localization may be difficult.

Parietal Lobe Epilepsies

Parietal lobe epilepsy syndromes are usually characterized by simple partial and secondarily generalized seizures. Most seizures arising in the parietal lobe remain as simple partial seizures, but complex partial seizures may arise out of simple partial seizures and occur with spread beyond the parietal lobe. Seizures arising from the parietal lobe have the following features: Seizures are predominantly sensory with many characteristics. Positive phenomena consist of tingling and a feeling of electricity, which may be confined or may spread in a jacksonian manner. There may be a desire to move a body part or a sensation as if a part were being moved. Muscle tone may be lost. The parts most frequently involved are those with the largest cortical representation (e.g., the hand, arm, and face). There may be tongue sensations of crawling, stiffness, or coldness, and facial sensory phenomena may occur bilaterally. Occasionally, an intraabdominal sensation of sinking, choking, or nausea may occur, particularly in cases of inferior and lateral parietal lobe involvement. Rarely, there may be pain, which may take the form of a superficial burning dysesthesia or a vague, very severe, painful sensation. Parietal lobe visual phenomena may occur as hallucinations of a formed variety. Metamorphopsia with distortions, foreshortenings, and elongations may occur and are more frequently observed in cases of nondominant hemisphere discharges. Negative phenomena include numbness, a feeling that a body part is absent, and a loss of awareness of a part or a half of the body, known as asomatognosia. This is particularly the case with nondominant hemisphere involvement. Severe vertigo or disorientation in space may be indicative of inferior parietal lobe seizures. Seizures in the dominant parietal lobe result in a variety of receptive or conductive language disturbances. Some well-lateralized genital sensations may occur with paracentral involvement. Some rotatory or postural motor phenomena may occur. Seizures of the paracentral lobule have a tendency to become secondarily generalized.

Occipital Lobe Epilepsies

Occipital lobe epilepsy syndromes are usually characterized by simple partial and secondarily generalized seizures. Complex partial seizures may occur with spread beyond the occipital lobe. The frequent association of occipital lobe seizures and migraine is complicated and controversial. The clinical seizure manifestations usually, but not always, include visual manifestations. Elementary visual seizures are characterized by fleeting visual manifestations that may be either negative (scotoma, hemianopsia, amaurosis) or, more commonly, positive (sparks or flashes, phosphenes). Such sensations appear in the visual field contralateral to the discharge in the specific visual cortex, but can spread to the entire visual field. Perceptive illusions, in which the objects appear to be distorted, may occur. The following varieties can be distinguished: a change in size (macropsia or micropsia) or a change in distance, an inclination of objects in a given plane of space, and distortion of objects or a sudden change of shape (metamorphopsia). Visual hallucinatory seizures are occasionally characterized by complex visual perceptions (e.g., colorful scenes of varying complexity). In some cases, the scene is distorted or made smaller, and in rare instances, the subject sees the subject's own image (heautoscopy). Such illusional and hallucinatory visual seizures involve epileptic discharge in the temporoparietooccipital junction. The initial signs may also include tonic and/or clonic contraversion of eyes and head or eyes only (oculoclonic or oculogyric deviation),

palpebral jerks, and forced closure of eyelids. Sensation of ocular oscillation or of the whole body may occur. The discharge may spread to the temporal lobe, producing seizure manifestations of either lateral posterior temporal or hippocampoamygdala seizures. When the primary focus is located in the supracalcarine area, the discharge can spread forward to the suprasylvian convexity or the mesial surface, mimicking those of parietal or frontal lobe seizures. Spread to contralateral occipital lobe may be rapid. Occasionally, the seizure tends to become secondarily generalized.

1.3 CryptogenicCryptogenic epilepsies are presumed to be symptomatic, and the etiology is unknown. Thus, this category differs from the previous one by the lack of etiologic evidence (see definitions).

2. Generalized epilepsies and syndromes

2.1 Idiopathic (with age-related onset—listed in order of age)

- Benign neonatal familial convulsions
- Benign neonatal convulsions
- Benign myoclonic epilepsy in infancy
- Childhood absence epilepsy (pyknolepsy)
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy (impulsive petit mal)
- Epilepsy with grand mal (GTCS) seizures on awakening
- Other generalized idiopathic epilepsies not defined above
- Epilepsies with seizures precipitated by specific modes of activation

2.2 Cryptogenic or symptomatic (in order of age)

- West syndrome (infantile spasms, Blitz–Nick– Salaam–Krämpfe)
- Lennox–Gastaut syndrome
- Epilepsy with myoclonic astatic seizures
- Epilepsy with myoclonic absences

2.3 Symptomatic

2.3.1 Nonspecific etiology

- Early myoclonic encephalopathy
- Early infantile epileptic encephalopathy with suppression burst
- Other symptomatic generalized epilepsies not defined above

2.3.2 Specific syndromes

- Epileptic seizures may complicate many disease states. Under this heading are included diseases in which seizures are a presenting or predominant feature.

3. Epilepsies and syndromes undetermined whether focal or generalized

3.1 With both generalized and focal seizures

- Neonatal seizures
- Severe myoclonic epilepsy in infancy

- Epilepsy with continuous spike waves during slow-wave sleep
- Acquired epileptic aphasia (Landau–Kleffner syndrome)
- Other undetermined epilepsies not defined above

3.2 Without unequivocal generalized or focal features. All cases with generalized tonic–clonic seizures in which clinical and EEG findings do not permit classification as clearly generalized or localization related, such as in many cases of sleep grand mal (GTCS), are considered not to have unequivocal generalized or focal features.

4. Special syndromes

4.1 Situation-related seizures (Gelegenheitsanfälle)

- Febrile convulsions
- Isolated seizures or isolated status epilepticus
- Seizures occurring only when there is an acute metabolic or toxic event due to factors such as alcohol, drugs, eclampsia, and nonketotic hyperglycemia

PART II: DEFINITIONS

Localization-Related (Focal, Local, Partial) Epilepsies and Syndromes

Localization-related epilepsies and syndromes are epileptic disorders in which seizure semiology or findings at investigation disclose a localized origin of the seizures. This includes not only patients with small circumscribed constant epileptogenic lesions (anatomic or functional), i.e., true focal epilepsies, but also patients with less well-defined lesions, whose seizures may originate from variable loci. In most symptomatic localization-related epilepsies, the epileptogenic lesions can be traced to one part of one cerebral hemisphere, but in idiopathic age-related epilepsies with focal seizures, corresponding regions of both hemispheres may be functionally involved.

Generalized Epilepsies and Syndromes

According to the International Classification of Epilepsies and Epileptic Syndromes, generalized epilepsies and syndromes are epileptic disorders with generalized seizures, i.e., "seizures in which the first clinical changes indicate initial involvement of both hemispheres.... The ictal encephalographic patterns initially are bilateral."

Epilepsies and Syndromes Undetermined as to Whether They Are Focal or Generalized

There may be two reasons why a determination of whether seizures are focal or generalized cannot be made: (a) the patient has both focal and generalized seizures together or in succession (e.g., partial seizures plus absences) and has both focal and generalized EEG seizure discharges (e.g., temporal spike focus plus independent bilateral spike-and-wave discharges), and (b) there are no positive signs of either focal or generalized seizure onset. The most common reasons for this are the seizures occur during sleep, the patient recalls no aura, and ancillary investigations, including EEG, are not revealing.

Idiopathic Localization-Related Epilepsies

Idiopathic localization-related epilepsies are childhood epilepsies with partial seizures and focal EEG abnormalities. They are age related, without demonstrable anatomic lesions, and are subject to spontaneous remission. Clinically, patients have neither neurologic and intellectual deficit nor a history of antecedent illness, but frequently have a family history of benign epilepsy. The seizures are usually brief and rare, but may be frequent early in the course of the disorder. The seizure patterns may vary from case to case, but usually remain constant in the same child. The EEG is characterized by normal background activity and localized high-voltage repetitive spikes, which are sometimes independently multifocal. Brief bursts of generalized spike waves can occur. Focal abnormalities are increased by sleep and are without change in morphology.

Benign Childhood Epilepsy with Centrotemporal Spikes

Benign childhood epilepsy with centrotemporal spikes is a syndrome of brief, simple, partial, hemifacial motor seizures, frequently having associated somatosensory symptoms that have a tendency to evolve into GTCS. Both seizure types are often related to sleep. Onset occurs between the ages of 3 and 13 years (peak, 9 to 10 years), and recovery occurs before the age of 15 to 16 years. Genetic predisposition is frequent, and there is male predominance. The EEG has blunt high-voltage centrotemporal spikes, often followed by slow waves that are activated by sleep and tend to spread or shift from side to side.

Childhood Epilepsy with Occipital Paroxysms

The syndrome of childhood epilepsy with occipital paroxysms is, in general respects, similar to that of benign childhood epilepsy with centrotemporal spikes. The seizures start with visual symptoms (amaurosis, phosphenes, illusions, or hallucinations) and are often followed by a hemiclonic seizure or automatisms. In 25% of cases, the seizures are immediately followed by migrainous headache. The EEG has paroxysms of high-amplitude spike waves or sharp waves recurring rhythmically on the occipital and posterior temporal areas of one or both hemispheres, but only when the eyes are closed. During seizures, the occipital discharge may spread to the central or temporal region. At present, no definite statement on prognosis is possible.

Idiopathic Generalized Epilepsies (Age Related)

Idiopathic generalized epilepsies are forms of generalized epilepsies in which all seizures are initially generalized, with an EEG expression that is a generalized, bilateral, synchronous, symmetrical discharge (such as is described in the seizure classification of the corresponding type). The patient usually has a normal interictal state, without neurologic or neuroradiologic signs. In general, interictal EEGs show normal background activity and generalized discharges, such as spikes, polyspike, spike wave, and polyspike waves ≥3 Hz. The discharges are increased by slow sleep. The various syndromes of idiopathic generalized epilepsies differ mainly in age of onset.

Benign Neonatal Familial Convulsions

Benign neonatal familial convulsions are rare, dominantly inherited disorders manifesting mostly on the 2nd and 3rd days of life, with clonic or apneic seizures and no specific EEG criteria. History and investigations reveal no etiologic factors. About 14% of these patients later develop epilepsy.

Benign Neonatal Convulsions

Benign neonatal convulsions are very frequently repeated clonic or apneic seizures occurring at about the 5th day of life, without known etiology or concomitant metabolic disturbance. Interictal EEG often shows alternating sharp theta waves. There is no recurrence of seizures, and the psychomotor development is not affected.

Benign Myoclonic Epilepsy in Infancy

Benign myoclonic epilepsy in infancy is characterized by brief bursts of generalized myoclonus that occur during the first or second year of life in otherwise normal children who often have a family

history of convulsions or epilepsy. EEG recording shows generalized spike waves occurring in brief bursts during the early stages of sleep. These attacks are easily controlled by appropriate treatment. They are not accompanied by any other type of seizure, although GTCS may occur during adolescence. The epilepsy may be accompanied by a relative delay of intellectual development and minor personality disorders.

Childhood Absence Epilepsy (Pyknolepsy)

Pyknolepsy occurs in children of school age (peak manifestation, ages 6 to 7 years), with a strong genetic predisposition in otherwise normal children. It appears more frequently in girls than in boys. It is characterized by very frequent (several to many per day) absences. The EEG reveals bilateral, synchronous symmetrical spike waves, usually 3 Hz, on a normal background activity. During adolescence, GTCS often develop. Otherwise, absences may remit or, more rarely, persist as the only seizure type.

Juvenile Absence Epilepsy

The absences of juvenile absence epilepsy are the same as in pyknolepsy, but absences with retropulsive movements are less common. Manifestation occurs around puberty. Seizure frequency is lower than in pyknolepsy, with absences occurring less frequently than every day, mostly sporadically. Association with GTCS is frequent, and GTCS precede the absence manifestations more often than in childhood absence epilepsy, often occurring on awakening. Not infrequently, the patients also have myoclonic seizures. Sex distribution is equal. The spike waves are often >3 Hz. Response to therapy is excellent.

Juvenile Myoclonic Epilepsy (Impulsive Petit Mal)

Impulsive petit mal appears around puberty and is characterized by seizures with bilateral, single, or repetitive, arrhythmic, irregular myoclonic jerks, predominantly in the arms. Jerks may cause some patients to fall suddenly. No disturbance of consciousness is noticeable. The disorder may be inherited, and sex distribution is equal. Often, there are GTCS and, less often, infrequent absences. The seizures usually occur shortly after awakening and are often precipitated by sleep deprivation. Interictal and ictal EEG have rapid, generalized, often irregular spike waves and polyspike waves; there is no close phase correlation between EEG spikes and jerks. Frequently, the patients are photosensitive. Response to appropriate drugs is good.

Epilepsy with GTCS on Awakening

Epilepsy with GTCS on awakening is a syndrome with onset occurring mostly in the second decade of life. The GTCS occur exclusively or predominantly (>90% of the time) shortly after awakening regardless of the time of day or in a second seizure peak in the evening period of relaxation. If other seizures occur, they are mostly absence or myoclonic, as in juvenile myoclonic epilepsy. Seizures may be precipitated by sleep deprivation and other external factors. Genetic predisposition is relatively frequent. The EEG shows one of the patterns of idiopathic generalized epilepsy. There is a significant correlation with photosensitivity.

Generalized Cryptogenic or Symptomatic Epilepsies (Age Related)

West Syndrome (Infantile Spasms, Blitz–Nick–Salaam–Krämpfe)

Usually, West syndrome consists of a characteristic triad: infantile spasms, arrest of psychomotor development, and hypsarrhythmia, although one element may be missing. Spasms may be flexor, extensor, lightning, or nods, but most commonly they are mixed. Onset peaks between the ages of 4 and 7 months and always occurs before the age of 1 year. Boys are more commonly affected. The prognosis is generally poor. West syndrome may be separated into two groups. The symptomatic group is characterized by previous existence of brain damage signs (psychomotor retardation, neurologic signs, radiologic signs, or other types of seizures) or by a known etiology. The smaller, cryptogenic group is characterized by a lack of previous signs of brain damage and of known etiology. The prognosis appears to be partly based on early therapy with adrenocorticotropic hormone (ACTH) or oral steroids.

Lennox–Gastaut Syndrome

Lennox–Gastaut syndrome manifests itself in children ages 1 to 8 years, but appears mainly in preschool-aged children. The most common seizure types are tonic axial, atonic, and absence seizures, but other types such as myoclonic, GTCS, or partial are frequently associated with this syndrome. Seizure frequency is high, and status epilepticus is frequent (stuporous states with myoclonias, tonic, and atonic seizures). The EEG usually has abnormal background activity, slow spike waves <3 Hz, and, often, multifocal abnormalities. During sleep, bursts of fast rhythms (approximately 10 Hz) appear. In general, there is mental retardation. Seizures are difficult to control, and the development is mostly unfavorable. In 60% of cases, the syndrome occurs in children suffering from a previous encephalopathy but is primary in other cases.

Epilepsy with Myoclonic Astatic Seizures

Manifestations of myoclonic astatic seizures begin between the ages of 7 months and 6 years (mostly between the ages of 2 and 5 years), with (except if seizures begin in the first year) twice as many boys affected. There is frequently hereditary predisposition and usually a normal developmental background. The seizures are myoclonic, astatic, myoclonic astatic, absence with clonic and tonic components, and tonic–clonic. Status frequently occurs. Tonic seizures develop late in the course of unfavorable cases. The EEG, initially often normal except for 4- to 7-Hz rhythms, may have irregular fast spike wave or polyspike wave. Course and outcome are variable.

Epilepsy with Myoclonic Absences

The syndrome of epilepsy with myoclonic absences is clinically characterized by absences accompanied by severe bilateral rhythmical clonic jerks, often associated with a tonic contraction. On the EEG, these clinical features are always accompanied by bilateral, synchronous, and symmetrical discharge of rhythmical spike waves at 3 Hz, similar to childhood absence. Seizures occur many times a day. Awareness of the jerks may be maintained. Associated seizures are rare. Age of onset is approximately 7 years, and there is a male preponderance. Prognosis is less favorable than in pyknolepsy owing to resistance to therapy of the seizures, mental deterioration, and possible

evolution to other types of epilepsy such as Lennox–Gastaut syndrome.

Symptomatic Generalized Epilepsies and Syndromes

Symptomatic generalized epilepsies, most often occurring in infancy and childhood, are characterized by generalized seizures with clinical and EEG features different from those of idiopathic generalized epilepsies. There may be only one type, but more often there are several types, including myoclonic jerks, tonic seizures, atonic seizures, and atypical absences. EEG expression is bilateral but less rhythmical than in idiopathic generalized epilepsies and is more or less asymmetrical. Interictal EEG abnormalities differ from idiopathic generalized epilepsies, appearing as suppression bursts, hypsarrhythmia, slow spike waves, or generalized fast rhythms. Focal abnormalities may be associated with any of the above. There are clinical, neuropsychological, and neuroradiologic signs of a usually diffuse, specific, or nonspecific encephalopathy.

Generalized Symptomatic Epilepsies of Nonspecific Etiology (Age Related)

Early Myoclonic Encephalopathy

The principal features of early myoclonic encephalopathy are onset occurring before age 3 months, initially fragmentary myoclonus, and then erratic partial seizures, massive myoclonias, or tonic spasms. The EEG is characterized by suppression burst activity, which may evolve into hypsarrhythmia. The course is severe, psychomotor development is arrested, and death may occur in the first year. Familial cases are frequent and suggest the influence of one or several congenital metabolic errors, but there is no constant genetic pattern.

Early Infantile Epileptic Encephalopathy with Suppression Burst

This syndrome is defined by very early onset, within the first few months of life, frequent tonic spasms, and suppression burst EEG pattern in both waking and sleeping states. Partial seizures may occur. Myoclonic seizures are rare. Etiology and underlying pathology are obscure. The prognosis is serious with severe psychomotor retardation and seizure intractability; often, there is evolution to the West syndrome at age 4 to 6 months.

Epilepsies and Syndromes Undetermined as to Whether They Are Focal or Generalized

Neonatal Seizures

Neonatal seizures differ from those of older children and adults. The most frequent neonatal seizures are described as subtle because the clinical manifestations are frequently overlooked. These include tonic, horizontal deviation of the eyes with or without jerking, eyelid blinking or fluttering, sucking, smacking, or other buccal–lingual–oral movements, swimming or pedaling movements, and, occasionally, apneic spells. Other neonatal seizures occur as tonic extension of the limbs, mimicking

decerebrate or decorticate posturing. These occur particularly in premature infants. Multifocal clonic seizures characterized by clonic movements of a limb, which may migrate to other body parts or other limbs, or focal clonic seizures, which are much more localized, may occur. In the latter, the infant is usually not unconscious. Rarely, myoclonic seizures may occur, and the EEG pattern is frequently that of suppression burst activity. The tonic seizures have a poor prognosis, because they frequently accompany intraventricular hemorrhage. The myoclonic seizures also have a poor prognosis, because they are frequently a part of the early myoclonic encephalopathy syndrome.

Severe Myoclonic Epilepsy in Infancy

Severe myoclonic epilepsy in infancy is a recently defined syndrome. The characteristics include a family history of epilepsy or febrile convulsions, normal development before onset, seizures beginning during the first year of life in the form of generalized or unilateral febrile clonic seizures, secondary appearance of myoclonic jerks, and often partial seizures. EEGs show generalized spike waves and polyspike waves, early photosensitivity, and focal abnormalities. Psychomotor development is retarded from the 2nd year of life, and ataxia, pyramidal signs, and interictal myoclonus appear. This type of epilepsy is very resistant to all forms of treatment.

Epilepsy with Continuous Spike Waves During Slow-Wave Sleep

Epilepsy with continuous spike waves during slow-wave sleep results from the association of various seizure types, partial or generalized, occurring during sleep, and atypical absences when awake. Tonic seizures do not occur. The characteristic EEG pattern consists of continuous diffuse spike waves during slow-wave sleep, which is noted after onset of seizures. Duration varies from months to years. Despite the usually benign evolution of seizures, prognosis is guarded because of the appearance of neuropsychological disorders.

Acquired Epileptic Aphasia (Landau–Kleffner Syndrome)

The Landau–Kleffner syndrome is a childhood disorder in which an acquired aphasia, multifocal spike, and spike-and-wave discharges are associated. Epileptic seizures and behavioral and psychomotor disturbances occur in two-thirds of the patients. There is verbal auditory agnosia and rapid reduction of spontaneous speech. The seizures, usually GTCS or partial motor, are rare and remit before the age of 15 years, as do the EEG abnormalities.

Special Syndromes

Febrile Convulsions

Febrile convulsions are an age-related disorder almost always characterized by generalized seizures occurring during an acute febrile illness. Most febrile convulsions are brief and uncomplicated, but some may be more prolonged and followed by transient or permanent neurologic sequelae, such as the hemiplegia–hemiatrophy–epilepsy (HHE) syndrome. Febrile convulsions tend to recur in about one-third of affected patients. Controversy about the risks of developing epilepsy later has largely been resolved by some recent large studies; the overall risk is probably not more than 4%. The indications for prolonged drug prophylaxis against recurrence of febrile convulsions are now more

clearly defined, and most individuals do not require prophylaxis. Essentially, this condition is a relatively benign disorder of early childhood.

PART III: SYMPTOMATIC GENERALIZED EPILEPSIES OF SPECIFIC ETIOLOGIES

Only diseases in which epileptic seizures are the presenting or a prominent feature are classified. These diseases often have epileptic pictures that resemble symptomatic generalized epilepsies without specific etiology, appearing at similar ages.

Malformations

Aicardi syndrome occurs in females and is noted for retinal lacunae and absence of the corpus callosum; infantile spasms with early onset; and often asymmetric, diffuse EEG abnormalities generally asynchronous with suppression burst and/or atypical hypsarrhythmia.

Lissencephaly–pachygyria is characterized by facial abnormalities and specific CT scan features, axial hypotonia, and infantile spasms. The EEG shows fast activity of high-voltage "alpha-like" patterns without change during wakefulness and sleep.

The individual phacomatoses have no typical electroclinical pattern. We emphasize that West syndrome is frequent in tuberous sclerosis and that generalized and partial seizures may follow the otherwise typical course of infantile spasms. Sturge–Weber syndrome is a frequent cause of simple partial seizures followed by hemiparesis.

Hypothalamic hamartomas may present with gelastic seizures, precocious puberty, and retardation.

Proven or Suspected Inborn Errors of Metabolism

Neonate

Metabolism errors in the neonate include nonketotic hyperglycinemia and D-glyceric acidemia, showing early myoclonic encephalopathy with erratic myoclonus, partial seizures, and suppression burst EEG patterns.

Infant

The classical phenylketonuria can express itself as a West syndrome. A variant of phenylketonuria with biopterin deficiency causes seizures starting in the second 6 months of life in infants who have been hypotonic since birth. The seizures are generalized motor seizures associated with erratic myoclonic jerks and oculogyric seizures.

Tay–Sachs and Sandhoff disease present with acoustic startle or myoclonus in the first months of life, without EEG manifestations. In the 2nd year, myoclonic jerks and erratic partial seizures occur, along with marked slowing of the background rhythms.

Another type of metabolic error is early infantile type of ceroid lipofuscinosis (Santavuori–Haltia–Hagberg disease). Massive myoclonus begins between the ages of 5 and 18 months, with a highly suggestive EEG pattern of vanishing EEG.

Pyridoxine dependency is manifested by seizures that have no suggestive characteristics, but this condition must always be suspected since therapeutic intervention is possible.

Child

Late infantile ceroid lipofuscinosis (Jansky–Bielschowsky disease) is characterized by onset between the ages of 2 and 4 years of massive myoclonic jerks, atonic, or astatic seizures. The EEG shows slow background rhythms, multifocal spikes, and a characteristic response to intermittent photic stimulation at a slow rate.

An infantile type of Huntington disease appears after age 3 years, with a slowing of mental development, followed by dystonia, GTCS, atypical absence seizures, and myoclonic seizures. The EEG shows discharges of generalized spike waves and polyspike waves, with the usual photic stimulation rate.

Child and Adolescent

A juvenile form of Gaucher disease is marked by onset at approximately 6 to 8 years of age, with epileptic seizures of various types, most commonly GTCS or partial motor. The EEG shows progressive deterioration of background activity, abnormal photic response, diffuse paroxysmal abnormalities, and multifocal abnormalities with a clear posterior predominance.

The juvenile form of ceroid lipofuscinosis (Spielmeyer–Vogt–Sjögren disease) is characterized by onset between the ages of 6 and 8 years, a decrease in visual acuity, slowing of psychomotor development, and appearance of cerebellar and extrapyramidal signs. After 1 to 4 years, GTCS and fragmentary, segmental, and massive myoclonus occur. The EEG shows bursts of slow waves and slow spikes and waves.

Onset of Lafora disease occurs between the ages of 6 and 19 years (mean 11.5 years) and is characterized by generalized clonic and GTCS, with a frequent association of partial seizures with visual symptomatology, constant myoclonic jerks (fragmentary, segmental, and massive myoclonus), and rapidly progressive mental deterioration. The EEG shows discharges of fast spike waves and polyspike waves, photosensitivity, deterioration of background activity, and the appearance of multifocal abnormalities, particularly posteriorly. On the average, death occurs 5.5 years after onset.

The so-called degenerative progressive myoclonic epilepsy (Lundborg type) also falls into this category. The only significant well-individualized group is the Finnish type, described by Koskiniemi et al. Onset occurs between the ages of 8 and 13 years, with myoclonus (segmental, fragmentary, and massive) and GTCS, associated cerebellar ataxia, and slowly progressive although generally mild mental deterioration. The EEG shows slow abnormalities (theta rhythms and later, delta rhythms), with generalized spike waves predominantly in the frontal area and photosensitivity. Patients survive ≥15 years.

Dyssynergia cerebellaris myoclonica (DCM) with epilepsy (Ramsay Hunt syndrome) appears between the ages of 6 and 20 years (mean 11 years) with myoclonias or GTCS. Above all, the myoclonic syndrome is characterized by action and intention myoclonus. The GTCS are rare and sensitive to therapy. Mental deterioration, when present, is slow. Most of the neurologic manifestations are limited to cerebellar signs. In the EEG, the background activity remains normal, with generalized paroxysmal abnormalities (spikes, spike waves, and polyspike waves) and photosensitivity. During REM sleep, rapid polyspikes appear, localized in the central and vertex regions.

The clinical picture for the cherry-red spot myoclonus syndrome (sialidosis with isolated deficit in neuraminidase) is very similar to that of the Ramsay Hunt syndrome, with myoclonus, photosensitivity, and cerebellar syndrome. Other characteristics include the nearly constant existence

of amblyopia and presence of a cherry-red spot on funduscopic examination. The EEG is similar to that of DCM with the following specific features: the polyspike-wave discharges always correspond to a massive myoclonus, and there is no photosensitivity.

A Ramsay Hunt–like syndrome can also be associated with a mitochondrial myopathy, with abnormalities of lactate and pyruvate metabolism (7).

Adult

Kufs disease (adult ceroid lipofuscinosis) is a relatively slow, progressive storage disease with frequent generalized seizures that may be very intractable. Unlike juvenile storage disease, the optic fundi may be normal. The main characteristic is an extreme photic sensitivity on slow photic stimulation.

A large number of epilepsy-related diseases in childhood, adulthood, and old age are not enumerated here because the seizures are not distinctively different from other seizure types and are not critical for diagnosis.

PART IV

Precipitated seizures are those in which environmental or internal factors consistently precede the attacks and are differentiated from spontaneous epileptic attacks in which precipitating factors cannot be identified. Certain nonspecific factors (e.g., sleeplessness, alcohol or drug withdrawal, or hyperventilation) are common precipitators and are not specific modes of seizure precipitation. In certain epileptic syndromes, the seizures clearly may be somewhat more susceptible to nonspecific factors, but this is only occasionally useful in classifying epileptic syndromes. An epilepsy characterized by specific modes of seizure precipitation, however, is one in which a consistent relationship can be recognized between the occurrence of one or more definable nonictal events and subsequent occurrence of a specific stereotyped seizure. Some epilepsies have seizures precipitated by specific sensation or perception (the reflex epilepsies) in which seizures occur in response to discrete or specific stimuli. These stimuli are usually limited in individual patients to a single specific stimulus or a limited number of closely related stimuli. Although the epilepsies that result are usually generalized and of idiopathic nature, certain partial seizures may also occur following acquired lesions, usually involving tactile or proprioceptive stimuli.

Epileptic seizures may also be precipitated by sudden arousal (startle epilepsy); the stimulus is unexpected in nature. The seizures are usually generalized tonic but may be partial and are usually symptomatic.

Seizures precipitated by integration of higher cerebral function such as memory or pattern recognition are most often associated with complex partial epilepsies but are occasionally observed in generalized epilepsies (such as reading epilepsy). Seizures also occur spontaneously in most such patients.

Primary Reading Epilepsy

All or almost all seizures in this syndrome are precipitated by reading (especially aloud) and are independent of the content of the text. They are simple partial motor-involving masticatory muscles, or visual, and if the stimulus is not interrupted, GTCS may occur. The syndrome may be inherited. Onset is typically in late puberty, and the course is benign with little tendency to spontaneous seizures. Physical examination and imaging studies are normal, but EEG shows spikes or spike waves in the dominant parietotemporal region. Generalized spike and wave may also occur.

CHAPTER 10 EPILEPTIC AURAS

NORMAN K. SO

The word "aura" (from Greek for air, Latin for breeze) was first applied to epilepsy by Galen's teacher, Pelops (1), who interpreted reports of altered sensations ascending to the head from an extremity as support for a humoral mechanism in which a vapor passed up the blood vessels and, therefore, a peripheral origin of epileptic seizures.

The aura, of course, is a seizure, not the cause, as Erastus pointed out around 1580. Jackson's systematic study of auras ushered in a new era when he correlated the sensations with functional localization in the brain (2). The 1981 International Classification of Epileptic Seizures (3) defined the aura as "that portion of the seizure which occurs before consciousness is lost and for which memory is retained afterwards." Furthermore, an aura in isolation constitutes a sensory seizure (4). Conventional usage limits the aura to the initial sensations of a seizure that the patient is aware of in the absence of observable signs. This definition specifically separates an aura from other focal seizures and is the definition used in this chapter. For example, with autonomic phenomena, when cold shivering is experienced at seizure onset, the sensation of shivering would be an aura; but if accompanied by observable signs like piloerection, the observable sign would exclude classifying this focal seizure as an aura.

The aura usually only lasts seconds to minutes. On occasion, auras can be longer lasting, continuous, or recurrent with short interval breaks. Intracranial electroencephalographic (EEG) studies have shown that prolonged auras (aura continua) can represent continuous or recurrent seizures, a form of focal status epilepticus (5).

Auras should be separated from prodromal symptoms that can last for hours or days before a seizure. The symptoms are typically different, comprising symptoms such as nervousness, anxiety, dizziness, and headache, which do not have the same potential localizing significance as auras. Sometimes, the patient may not be conscious of anything untoward, but family members or friends may describe irritability or other personality change. Such prodromes resemble those recounted by some patients before a migraine attack. Gowers' speculation (1) that the prodrome is "indicative of slight disturbance of the nerve centers" has not been improved on.

Some patients with generalized epilepsy experience stereotyped sensations before or during a generalized seizure. Like an aura, these premonitory symptoms can be varied but usually lack the character that suggests activation of a circumscribed area of the cortex. Sensations include dizziness, warmth, cold, generalized tingling, anxiety, and a "spaced-out" or confused feeling. Some of the sensations likely correspond to a buildup of absence (dizziness, light-headedness, and confusion) or myoclonic seizures (anxiety, restlessness, jumpiness, and jerking) before loss of consciousness or convulsive activity. However, elementary visual hallucinations and abdominal sensations indistinguishable from those in focal epilepsy have been reported preceding seizures in several genetic (idiopathic) generalized epilepsies (6,7).

An early onset of epilepsy, lower intelligence quotient, male gender, and right temporal lobe focus have been associated with a higher incidence of "simple primitive" auras, whereas complex

"intellectual" auras with illusions or hallucinations accompanied male gender and a verbal intelligence quotient of >100 (8). Aura content may relate to the patient's individual psychological makeup. Stimulation of various mesial limbic structures elicited auras with features that were intimately related to ongoing psychopathologic processes (9). Emotional responses and hallucinations produced by electrical stimulation were reported to depend on the background affective state (10). Patients who experienced anxiety or fear during temporal lobe electrical stimulation scored higher on the "psychasthenia" scale of the Minnesota Multiphasic Personality Inventory, whereas those experiencing dreamlike or memory-like hallucinations scored higher on the "schizophrenia" scale (11).

PRESENCE AND ABSENCE OF AURAS

The incidence of auras in large populations is imprecise. In the 32-year epidemiologic study from Rochester, Minnesota (12), epilepsy with focal sensory seizures was seen in 3.7% of all patients. A further 26.4% were classified to have temporal lobe epilepsy, but the incidence of aura in this group was not separately reported. In the two large series of clinic- and office-based epileptic patients studied by Gowers (1) and by Lennox and Cobb (13) (Table 10.1), an aura was present in 56% of patients. Although notable discrepancies exist between the two series in relative frequencies of unilateral somatosensory auras, bilateral general sensations, and visual auras, other categories are remarkably consistent. Differences are most likely explained on the basis of definitions of aura type. The incidence of auras ranged from 46% to 77% in patients who either underwent presurgical evaluation by long-term monitoring with scalp or intracranial EEG electrodes (14–16) or had temporal lobe surgery (17).

Table 10.1 Incidence of Aura in Two Series of Clinic- and Office-Based Epileptic Patients

Aura	Gowers (1) %[a] (n = 2013)	Lennox and Cobb (13) % (n = 1359)
Present	1145 (57%)	764 (56%)
Somatosensory[b]	18.0	8.5
Bilateral sensations	4.5	38.0
Visceral/epigastric	18.0	14.5
Vertiginous	19.0	12.0
Cephalic	8.0	5.5
Psychic	8.0	11.0
Visual[c]	16.0	6.5
Auditory	6.0	2.0
Olfactory	1.0	1.0
Gustatory	1.5	0.1

[a]Percentages apply to patients with aura.
[b]Includes motor phenomena at onset.
[c]Includes illusions and hallucinations.
From Gowers WR. *Epilepsy and Other Chronic Convulsive Diseases: Their Causes, Symptoms & Treatment*. 2nd ed. London, UK: J & A Churchill; 1901; Lennox WG, Cobb S. Aura in epilepsy: a statistical review of 1,359 cases. *Arch Neurol Psychiatry*. 1933;30:374–387.

Lennox and Cobb (13) reported that a long disease duration correlated with an increase in the incidence of auras and wrote that "It is more accurate to speak of the recollection of aura(s) rather than of their presence." Young children may lack the verbal capacity to describe the sensations that herald a seizure, even though their actions indicate some awareness of the impending event. Similarly, adults who deny any warning, nevertheless, may press the seizure alarm button during video–EEG monitoring but have no recollection of having done so. Some patients without auras might have had them earlier in the illness. Anecdotal experience suggests that auras may disappear as the disease progresses. The seizure either induces an amnesia so immediate that there is no memory of a warning or causes retrograde amnesia. This is supported by a study that showed that amnesia for auras depended on the severity of the seizure (18). An isolated aura is nearly always recollected when there is a unilateral EEG ictal discharge. The aura is more likely to be forgotten if the seizure becomes secondarily generalized or involves a bilateral EEG ictal discharge.

Isolated auras can persist after epilepsy surgery despite the complete cessation of complex partial (focal seizures with dyscognitive features) or secondarily generalized seizures. Isolated postoperative auras occurred in 15% to 35% (19–21) of patients after surgery for temporal lobe epilepsy and in 22% of a series after focal resective surgery unselected for location (22). Persistent auras after temporal lobe surgery may relate to incomplete removal of epileptogenic tissue in residual temporal lobe structures or neighboring areas of the operculum and insula. When epigastric auras persist after functional hemispherectomy, the insula is again implicated as it is the only cortical structure still connected on the side of surgery. Although isolated postoperative auras are often regarded as of little significance, and classified among the "seizure-free" outcomes, they may portend a reduced chance of complete seizure control (23) even if published studies do not all agree on this point, and a reduced quality of life on self-assessment (22). A small number of patients may lose their aura after temporal lobectomy even as they continue to have postoperative seizures leaving them with no warning; yet others may experience a different aura (19).

CLINICAL LOCALIZATION

An aura provides evidence of focal seizure onset and can help to localize the epileptogenic zone, provided the symptoms share a certain stereotypy and consistency even if they may vary from time to time in the same patient. Caution though is advised when interpreting the report of preceding sensation in the evaluation of a first seizure owing to the limited reliability of a single observation (24).

Patients with psychogenic nonepileptic seizures (PNES) can report a range of sensations, sometimes difficult to distinguish from that of an epileptic aura with alterations in smell, taste, vision, or tingling; but more often, the symptoms are long lasting and nonspecific, with headache, pain, and confusion prominent. Rarely, a PNES starts with an epileptic aura (25) in a patient whose epileptic seizures are well controlled. The PNES that follows an epileptic aura can be interpreted to represent a learned response or an example of psychogenic elaboration.

Current concepts on the localizing value of auras rely heavily on the pioneering studies of Penfield and Jasper (26) who correlated sensations and signs obtained through electrical stimulation of the awake patient with those of the patient's spontaneous seizures. Subsequent studies with long-term intracranial electrodes for the recording of spontaneous seizures and extraoperative electrical brain stimulation have extended early observations (27–29).

Although an aura may help to localize the epileptogenic zone, an important point must be kept in

mind. The initial sensation of an aura is related to the first functional brain area affected by the seizure that has access to consciousness, but this may not be the site of seizure origin. A seizure starting in the posterior parietal region may be initially asymptomatic until ictal activity spreads to adjacent functional areas. Spread to the postcentral gyrus may elicit a somatosensory sensation as the first warning; propagation to parietooccipital association cortex may give rise to initial visual illusions or hallucinations. Furthermore, it remains unclear whether experience of an aura is contingent on direct ictal activation of the cortical areas subserving those functions or whether an aura sensation may also be evoked by remote excitation or decoupling of inputs within a larger functional network. A sensory jacksonian march cannot be explained by other than ictal spread along the somatosensory cortex. The sometimes indistinguishable auras found in patients with hippocampal sclerosis and temporal neocortical pathology support the role of a distributed network that functionally links the limbic and neocortical structures in the temporal lobe. Cortical stimulation in extratemporal epilepsy also showed that sites at which an aura is reproduced can extend well beyond the expected functional map for those sensations (29).

The localizing value of auras has been studied in a number of ways. Penfield and Kristiansen (30) recorded the initial seizure phenomenon in 222 patients with focal epilepsy and commented on the likely localization of different auras. Auras reported in patients with well-defined epileptogenic foci in different brain regions can be compared from different series (Table 10.2) or, better yet, prospectively (35) (Table 10.3). Data from patients (31,32) who become seizure free after localized brain resections are particularly important. Making comparisons from different series in the literature is hampered by several problems: Terminology of aura type is not uniform, auras can be grouped together in dissimilar ways, and classification rules are unclear when multiple sensations occur in the same aura. In spite of the different approaches, retrospective and prospective series yielded a similar conclusion: Auras have localizing significance. Patients with temporal lobe epilepsy have the highest incidence of epigastric, emotional, and psychic auras (31,35,36). Frontal lobe epilepsy is distinguished by frequent reports of no aura (32,35). When an aura is present in frontal lobe epilepsy, cephalic, somatosensory, and general body sensations predominate. Perirolandic epilepsy with centroparietal foci and parietal lobe epilepsy are most likely to experience somatosensory aura (33,37). Not surprisingly, occipital lobe epilepsy has the highest incidence of visual aura (34,38). No single aura sensation is necessarily restricted to a single lobe, however.

Table 10.2 Relative Incidence of Auras in Focal Epilepsies (%)

	Temporal[a] Rasmussen (31) (n = 147)	Frontal[a] Rasmussen (32) (n = 140)	Parietal Salanov (33) (n = 82)	Occipital Salanova (34) (n = 42)
Somatosensory	5	17.5	61[b]	5
Epigastric/emotional	52[b]	12.5	1	—
Cephalic	5	12.5	5	5
General body	8	12.5	1	—
Psychic	15	7.5	15	—
Visual	11	5.0	7	74[b]
Auditory	11	—	1	—
Olfactory	11	—	—	—
Gustatory	11	—	—	—
Vertiginous	11	2.5	9	—
None	15	42.5[b]	7	16

[a]Seizure free after surgery.
[b]Indicates highest incidence for location.
Adapted and reanalyzed from Rasmussen T. Localizational aspects of epileptic seizure phenomena. In: Thompson RA, Green JR, eds. *New Perspectives in Cerebral Localization*. New York: Raven Press; 1982:177–203; Rasmussen T. Characteristics of a pure culture of frontal lobe epilepsy. *Epilepsia*. 1983;24:482–493; Salanov V, Andermann F, Rasmussen T, et al. Parietal lobe epilepsy. Clinical manifestations and outcome in 82 patients treated surgically between 1929 and 1988. *Brain*. 1995; 118:607–627; Salanova V, Andermann F, Oliver A, et al. Occipital lobe epilepsy: electroclinical manifestations, electrocorticography, cortical stimulation and outcome in 42 patients treated between 1930 and 1991. *Brain*. 1992;115:1655–1680.

Table 10.3 Frequency of Auras in Focal Epilepsies

		Retrospective series			Prospective series		
	n	Temporal	Frontal	Postero-occipital	Temporal	Frontal	Postero-occipital
Somatosensory	32	1	8	15	0	1	7
Epigastric	47	20	3	3	20	0	1
Cephalic	22	5	13	1	3	0	0
Diffuse warm sensation	10	1	9	0	0	0	0
Psychic	51	27	2	2	19	0	1
Elementary visual	13	1	0	12	0	0	0
Elementary auditory	3	3	0	0	0	0	0
Vertiginous	7	0	1	2	1	1	2
Conscious confusion	11	4	3	1	2	1	0
Total	196	62	39	36	42	3	11

Adapted from Palmini A, Gloor P. The localizing value of auras in partial seizures: a prospective and retrospective study. *Neurology*. 1992;42:801–808.

While most auras cannot lateralize the side of seizure onset, there are exceptions. Unilateral somatosensory aura in an extremity and lateralized visual aura are contralateral to the side of seizure onset. A lateralized auditory aura (sound in one ear) may also refer to the contralateral hemisphere. Pilomotor seizures, if unilateral, however, point to the ipsilateral hemisphere. Ictal headaches, if lateralized, are likewise ipsilateral to the site of seizure onset.

FUNCTIONAL CORRELATIONS

The EEG signature of auras depends on the recording technique. An isolated aura is a focal seizure of restricted extent and may not be apparent in scalp EEGs. In a study of temporal lobe epilepsy (39) studied by a combination of surface and depth electrodes, only 19% of auras confirmed by depth recordings had a surface ictal EEG correlate. In the same study, 10% of depth electrode recorded subclinical EEG seizures, and 86% of clinical seizures were accompanied by surface changes. An EEG that incorporates sphenoidal electrodes may have a better chance (28%) of detecting an

electrographic change during auras in patients with temporal lobe epilepsy (15). The surface EEG ictal pattern is often subtle as compared with that of a complex partial seizure and may appear as low-frequency rhythmic sharp waves, sudden attenuation of the ongoing background, or abrupt cessation of ongoing interictal spikes sometimes followed by rhythmic slow waves.

Depth electrodes targeted directly at mesial limbic structures (where the majority of temporal lobe seizures originate) have been more successful in demonstrating EEG ictal activity in temporal lobe auras than were simultaneous recordings from subdural electrodes over the lateral temporal convexity (40,41). Nevertheless, even in patients with clinical seizure onset in one temporal lobe localized by depth electrodes, only about half of isolated auras showed an ictal EEG correlate (16,42). In the same patient, some auras may be associated with ictal EEG changes, whereas others show no change (43). This suggests that seizures may arise dynamically from different discrete areas within a larger epileptic zone. In neurophysiologic terms, these observations support the belief that only a very small portion of the brain is activated to produce aura sensations. On the basis of firing patterns of limbic neurons recorded by microelectrode techniques in patients with temporal lobe epilepsy, only 14% of neurons at the epileptogenic zone are estimated to increase their firing rate in an aura. The corresponding estimate for a subclinical seizure is 7% and for a clinical complex partial seizure 36% (43). In agreement, an ictal–interictal subtraction single photon emission computed tomography study of isolated auras showed no clear dominant or reproducible areas of hyperperfusion in most cases (44).

Although an aura reflects activation of functional cortex by a circumscribed seizure discharge, the seizure discharge frequently spreads. A seizure that spreads along a single functional area as the postcentral gyrus produces the sensory equivalent of a jacksonian march. An aura can also spread across different functional regions. A seizure that starts in the primary visual area of the occipital lobe and spreads to the temporal limbic structures may present with initial transient blindness followed by other sensations referable to the temporal lobe.

Multiple sensations can occur even when seizure activity is relatively confined to one region, as at the start of temporal lobe seizures. Anxiety, epigastric, and “indescribable” sensations commonly precede the more complex phenomena of déjà vu and other illusions of vision or sound (45). When multiple auras can be dissected out along a sequence, they likely correlate with propagation of the ictal discharge within the temporal lobe, as recorded in a subdural EEG study (46). In other cases, a time series cannot be discerned, and the multiple sensations seem to occur simultaneously or vary in order from one seizure to another in the same patient. An alternative explanation for multiple auras could be that they are secondary to activation of a distributed network of several functional areas (47). The temporal limbic system, with extensive connections to the septum, hypothalamus, temporal neocortex, insula, and parieto-occipital association cortex, is precisely such a system. In support of this hypothesis, electrical stimulation of temporal limbic structures by depth electrodes can produce different sets of sensations at different times, despite stimulation of the same contacts (11).

SOMATOSENSORY AURAS

Tingling, numbness, and an electrical feeling are common, whereas absence of sensation or a sensation of movement is less. A sensation that starts focally in an extremity or shows a sensory march, such as an ascent from the hand up the arm to the face, points to a seizure discharge in the primary somatosensory area of the contralateral postcentral gyrus (26). A clinically identical seizure may have started more posteriorly in “silent” parietal cortex and caused symptoms only after it

spread to the postcentral gyrus. A primary somatosensory aura can be interrupted by clonic jerking of the affected part and reflects spread from the postcentral to the precentral gyrus. A seizure starting in the primary motor area of the precentral gyrus can also cause a somatosensory aura, rapidly accompanied by clonic motor phenomena. Indeed, the precentral gyrus accounted for 25% of the sites producing a somatic sensation during intraoperative stimulation of the rolandic cortex (26).

Somatic sensations with a wide segmental (whole limb or side of body) or bilateral distribution indicate seizure activity outside the primary somatosensory area. Seizures arising from or involving the second sensory area, situated in the superior bank of the sylvian fissure and parietal operculum (26,48), evoke somatic sensations of the contralateral or ipsilateral sides of the body or both. The sensation can be rudimentary, but second sensory auras include pain, coldness, and a desire for movement (26).

Seizures arising from the supplementary motor area were preceded by an aura in nearly half the patients in one study (49). Penfield and Jasper (26) elicited somatic sensations from the supplementary sensory area, a part of the mesial cortex in the interhemispheric fissure, posterior to the supplementary motor area. Extraoperative stimulation using chronically implanted subdural electrodes not only confirmed the existence of supplementary sensory areas but also showed that they intermingle and overlap with the supplementary motor area, so that the two regions can best be regarded as a single functional entity (50,51). Auras from the supplementary motor and sensory areas include nonspecific tingling, desire for or sensation of movement, and feelings of stiffness, pulling, pulsation, and heaviness. These sensations usually involve extensive areas of a contralateral extremity or side of the body or bilateral body parts. They may be perceived as a generalized body sensation as well. Penfield and Jasper (26) also elicited epigastric sensations on stimulation of the supplementary motor area.

Chronic recordings and stimulation studies of depth electrodes implanted into the posterior insular cortex revealed a fourth brain region that can give rise to contralateral somatosensory sensations (52,53). The sensations include those of tingling, electrical shock, heat, and sometimes pain. They can involve more localized or more extensive regions on the contralateral side of the body. Somatosensory auras occur in a small percentage of patients with temporal lobe epilepsy (17) (Table 10.2). Since the temporal lobe is devoid of representation for somatic sensation, these auras are thought to occur secondarily to propagation of the ictal discharge into the second sensory area, the insula, or postcentral gyrus.

As an aura, a general body sensation, including diffuse warm and cold thermal sensations, has little value in cortical localization, having been reported as seizure aura from all regions of the brain. Besides the supplementary motor area, the mesial temporal structures (54) have responded to stimulation with such diffuse sensations.

Ictal pain as aura can be classified according to the affected parts: cephalic, abdominal, and somatosensory. Ictal headache will be discussed with other cephalic auras and abdominal pain with epigastric aura. Painful body sensations may represent the initial aura or occur as a component of an aura or seizure. The pain may be sharp, burning, electric, cold, or cramp-like and may be focally to diffusely distributed. Pain as an isolated symptom is much less common than as an association of paresthesias and other somatic sensations (55,56). Some patients experience cramp-like pain with tonic muscle spasm of an affected part. Well-localized and unilateral ictal pain generally occurs contralateral to an epileptic focus in the postcentral gyrus or neighboring parietal lobe (55–59). Electrical stimulation of the postcentral gyrus can elicit contralateral pain (57,60). Resection of the parietal cortex with the epileptic focus has successfully abolished painful seizures (56,57). Other

areas reported to produce painful somesthetic auras are the second sensory area (26,61) and insular cortex (53). The localization of heat, cold, warmth, and flushing is variable or poorly understood. When these sensations are focal and unilateral, the same cortical regions described above are presumed responsible. When they are felt over wide segmental areas, on both sides of the body or in a generalized distribution, they lack reliable localizing or lateralizing value.

There are further somatic sensory alterations, which are distinctive with possible localizing value. Pharyngeal dysesthesias of tingling and burning or laryngeal discomfort to the point of a choking sensation are uncommon auras, sometimes reported in patients with seizures arising from the insula (53) or spreading from the temporal lobe to the insula. Aura sensations of body deformation, when a limb or part of the body is felt altered in size, twisted, or absent, suggest ictal alteration of sensory integration, a parietal lobe phenomenon (33).

VISUAL AURAS

Spots, stars, blobs, bars, or circles of light, monochromatic or variously colored, implicate seizure activity in the visual areas of the occipital lobes and occur in a majority of seizure arising there (26,34,38). These stationary or moving images may be lateralized to the visual field contralateral to the involved lobe but also may appear directly ahead. When they are lateralized and move across the field of vision, the patient's head may turn to follow them. Some patients describe darkness proceeding to blindness, which can also occur as a postictal phenomenon in those with visual auras. Such ictal blindness or amaurosis occurs in up to 30% of occipital seizures. An occipital seizure may propagate to the temporal lobe or the parietal cortex. In the former instance, a visual aura may be followed by psychic experiences, epigastric aura, or emotional feelings, whereas a somatosensory aura may follow in the latter case. Auras with formed visual hallucinations are discussed under psychic auras, as are visual illusions such as macropsia and micropsia.

AUDITORY AURAS

The auditory cortex lies in the transverse gyrus of Heschl in the superior bank of the superior temporal gyrus or temporal operculum. Electrical stimulation there and in the adjacent superior temporal gyrus produces simple sounds variously described as ringing, booming, buzzing, chirping, or machinelike (26). Similar elementary auditory phenomena are described with auditory auras. At other times, partial deafness may occur, with impairment of auditory comprehension if the language dominant hemisphere is involved. Auras with such characteristics suggest seizure activity in the superior temporal neocortex, Heschl gyrus, or temporal operculum (26,62) and are usually noted in patients with lateral neocortical temporal lobe epilepsy rather than mesial temporal lobe epilepsy. Auditory aura is a defining feature in patients with autosomal dominant partial epilepsy with auditory features associated with LGI1 gene mutation (63). If the sounds in an aura are lateralized to one ear, the focus is usually in the contralateral hemisphere. Because seizures can spread to other portions of the temporal lobe, auditory auras are frequently accompanied by other temporal lobe phenomena. Other auditory illusions and formed hallucinations are discussed later on in this chapter.

VERTIGINOUS AURAS

Stimulation of the posterior extent of the superior temporal gyrus can elicit feelings of displacement

or movement, including rotatory sensations (26). True vertiginous auras are probably uncommon but may be localized to the posterior part of the superior temporal neocortex (62) and experienced as one of several aura sensations that may arise together or in succession. True vertigo must be distinguished from nonspecific dizziness, which, on questioning, may resolve to cephalic sensations, light-headedness, or sense of impending loss of awareness, none of which has reliable localizing value. Early reports of patients with so-called vertiginous seizures probably included a large number with such nonspecific dizziness (64).

OLFACTORY AURAS

Jackson and Beevor (65) reported a "case of tumor of the right temporosphenoidal lobe bearing on the localization of the sense of smell and on the interpretation of a particular variety of epilepsy." The patient experienced a "very horrible smell which she could not describe." The term "uncinate fits" has been used to describe seizures with this aura because pathologic lesions are frequently found in the medial temporal lobe. The smell of an olfactory aura is often unpleasant or disagreeable (26,66) with odors akin to burning rubber, sulfur, or organic solvents. However, the smell can be neutral or even pleasant (67). The incidence of olfactory aura is low at about 1% (see Table 10.1). Whether patients with this symptom are disproportionately likely to have temporal lobe tumor is open to debate (66,68), as nonneoplastic lesions such as mesial temporal sclerosis can also be found responsible (67,69).

Other than the medial temporal lobe, the olfactory bulb is the only structure that can produce an olfactory sensation on electrical stimulation, and rarely, seizures starting in the orbitofrontal cortex can produce an olfactory aura (27). Olfactory aura rarely occurs in isolation; gustatory or other sensations referable to the temporal lobe frequently occur together or follow.

GUSTATORY AURAS

Usually disagreeable, the taste experienced may be described as sharp, bitter, acid, or sickly sweet. The incidence is low (see Table 10.1). Penfield and Jasper (26) ascribed the representation of taste deep in the sylvian fissure adjacent to and above the insular cortex. Hausser-Hauw and Bancaud (70) localized gustatory hallucinations to the parietal or rolandic operculum. They also recorded spontaneous and electrically induced seizures from the temporal limbic structures that were associated with gustatory phenomena but believed that the aura resulted from seizure propagation to the opercular region. Temporal lobectomies failed to abolish the gustatory hallucinations in three of their patients. The course of seizures with gustatory aura depends on the site of the epileptogenic zone. Suprasylvian seizures are likely to involve salivation, second sensory area sensations, and clonic facial contractions. Seizures of temporal origin may have epigastric aura in addition and develop automatisms.

EPIGASTRIC OR ABDOMINAL AURAS

Under this heading are various sensations localized to the abdomen or lower chest that may move to the throat and head but rarely descend in the opposite direction. "Visceral" and "viscerosensory" are other terms to describe this aura. Commonly characterized as a feeling of nausea, epigastric aura may also be reported as butterflies in the stomach, emptiness, queasiness as "going over a hill," tightness,

and churning; occasionally, it may be painful (58,71). This aura is frequently associated with or preceded or followed by other sensory, psychic, emotional, or autonomic phenomena (72). The sensation cannot be considered secondary to altered gastroesophageal function, as direct intraesophageal and intragastric pressure recording showed its occurrence with and without peristalsis (72,73). Although an abdominal aura is most common in temporal lobe epilepsy, it has been associated with epilepsies from all lobes of the brain (see Tables 10.2 and 10.3). Epigastric sensations can be elicited in epileptic and nonepileptic individuals by electrical stimulation of the amygdala, hippocampus, anteromedial temporal region, sylvian fissure, insula, supplementary motor area, pallidum, and centrum medianum of the thalamus (14,72).

CEPHALIC AURAS AND ICTAL HEADACHES

Cephalic aura includes a range of sensations felt in the head that includes dizziness, electrical shock, tingling, fullness, pressure, or other ill-defined sensations. It should not be confused with a somatosensory aura arising from the different cortical sensory areas. Moreover, electrical stimulation studies have provided no clear localization, and cephalic sensations have been reported as auras in focal seizures arising from all brain regions but may be more common in frontal lobe epilepsy (see Tables 10.2 and 10.3).

The relationship of headache to seizures is complex and is still the subject of considerable debate. Most common are postictal headaches, which can be diffuse or lateralized. Headaches can occur as an epileptic prodrome. Some patients with both migraine and epilepsy report that their seizures seem to be triggered by a headache. A headache of abrupt onset at the beginning of a seizure can be considered an aura or an ictal headache. An ictal headache can be pounding like a migraine but also sharp and steady. The pain may build gradually, but several patients studied with scalp or intracranial recording showed abrupt pain onset and offset synchronous with EEG seizure activity (74,75). Ictal headache is not well localized to any specific region and has been described also in generalized epilepsy. A lateralized headache is likely to be ipsilateral to the side of the epileptogenic focus (56,71,74,76). Many well-studied patients had temporal lobe epilepsy, possibly reflecting the increased likelihood of intensive presurgical EEG monitoring in this group. Patients with occipital lobe epilepsy represent the other major population with ictal headache, and when associated with a visual aura need to be differentiated from classic migraine. Ictal or postictal headache is often a striking symptom in benign epilepsy of childhood with occipital paroxysms (77) and in occipital seizures of patients with Lafora disease (78) and other progressive myoclonus epilepsies. It is possible that ictal headaches are not auras in the sense of a perception linked to localized neuronal activation, but the result of “an alteration in intracranial circulation either preceding the attack or coincidental with its onset” (26), akin to what occurs during migraine aura.

EMOTIONAL AURAS

Ictal fear describes pronounced anxiety or intense terror that is out of proportion to, and separable from, the understandable apprehension that can accompany any seizure. In some patients, the fear resembles a real-life experience, such as suddenly finding a stranger standing close behind, or is associated with an unpleasant psychic hallucination of past events. Others seemingly localize the sensation to the chest or stomach in association with an epigastric aura (79). Ictal fear may be accompanied by symptoms and signs of autonomic activation, such as mydriasis, tachycardia, and

hyperventilation, and behavioral manifestations of screaming, calling for help, and agitated movements. An aura of fear has been linked to temporal lobe epilepsy (80) and can be elicited on stimulation of the mesial temporal structures (28,81). An aura of fear can be difficult to separate from a panic attack when it occurs in isolation, and correct identification relies on the associated ictal clinical and EEG findings.

Elation and pleasure are infrequent auras. The preictal happiness and ecstasy reported by Dostoyevski are cited as an example. Electrical stimulation of the left amygdala appeared able to produce either pleasant or unpleasant emotions, while right amygdala stimulation induced mainly negative emotions of fear and sadness (82). But in general, pleasurable sensations are rarely elicited by electrical stimulation. Depression as an aura or ictal phenomenon is debatable. In the largest series, reported by Williams (79), many of the patients had depression that lasted for hours to days, making it likely that this state constituted a prodromal mood change rather than an aura.

PSYCHIC AURAS

In 1880, Hughlings Jackson (2) described "certain psychical states during the onset of epileptic seizures" that included "intellectual aurae…reminiscence…dreamy feelings…dreams mixing up with present thoughts…double consciousness…'as if I went back to all that occurred in my childhood'… These are all voluminous mental states and yet of different kinds." Both Gowers (1) and Penfield and Jasper (26) included emotional auras under the heading of psychic auras. Others used the term "experiential" phenomena for these events (28,81).

An illusion results from faulty interpretation of present experience in relation to the environment. Aware of the error in perception, the patient has "mental diplopia" in the jacksonian sense. A hallucination is a lifelike experience unrelated to present reality. Psychic hallucinations include dreamlike events or memory flashbacks that are complex and "formed," in contrast to the elementary "unformed" hallucinations that characterize excitation of the primary sensory areas. Nevertheless, epileptic patients invariably sense that the hallucinations are not real.

The nature of psychic auras is as varied as their complexity. Many attempts at classification have been made (Table 10.4), but it may be fruitless to adhere to an overly rigid categorization of these rich phenomena that offer glimpses into the workings of human consciousness. For example, déjà vu can be considered an illusion of familiar memory; the converse, when what should have been a familiar visual experience becomes unfamiliar, is called jamais vu. The corresponding auditory illusions are déjà entendu and jamais entendu. Despite reports that psychic auras can occur with focal seizures from elsewhere in the brain, the consensus ascribes them to epileptic activation of the temporal lobe. Penfield and Perot (83) found that the sites eliciting psychic phenomena during acute intraoperative stimulation were nearly all in the lateral temporal neocortex, particularly along its superior border, and only occasionally in basal or mesial temporal regions. In contrast, later studies (28,84,85) identified both mesial temporal limbic (amygdala, hippocampus, entorhinal cortex) and temporal neocortex structures as capable of producing psychic phenomena, even in the absence of an electrical afterdischarge. To reconcile these differences, Gloor (47) proposed a hypothesis based on the model of a neuronal network with reciprocal connections—in this case, between the limbic structures and the temporal neocortex. Psychic phenomena arising "from the activation of matrices in distributed neuronal networks" could presumably be elicited from different locations within the temporal lobe, including temporal isocortex and various limbic structures. Signal analysis during déjà vu upon stimulation of the entorhinal cortex in epileptic patients found increased EEG signal

correlations between medial temporal structures (86).

Table 10.4 Psychic Auras

	Illusion	Hallucination
Memory	Déjà vu, jamais vu, déjà entendu, jamais entendu, strangeness	Memory flashbacks, dreams of past
Vision	Macropsia, micropsia, objects nearer or farther, clearer or blurred	Objects, faces, scenes
Sound	Advancing or receding, louder or softer, clearer or fainter	Voices, music
Self-image	Mental diplopia, depersonalization, derealization, remoteness	Autoscopy
Time	Standstill, rushing, or slowing	—
Others	Increased awareness, decreased awareness	—

Forced thinking refers to an awareness of intrusive stereotyped thoughts, fixation on, or crowding of thoughts. Penfield and Jasper (26) separated it from psychic auras and localized it to the frontal lobe. Autoscopy, a hallucination of self-image, is seeing oneself as a "double," or as an external entity observed from a distance after the mind is felt to have left the body (87,88), and has been associated with localization of the ictal focus in the temporal lobe or right parietal lobe.

AUTONOMIC AURAS

There is no consensus on the range of phenomena to be included in this category. Epigastric sensations are considered an autonomic aura by some, although there is insufficient evidence for implication of autonomic afferent or efferent pathways. One of the commonest autonomic sensations is that of palpitations with an accompanying tachycardia. It is often associated with auras of fear, anxiety, or epigastric sensation. These are frequent symptoms in temporal lobe epilepsy. When palpitation occurs alone as aura and is the dominant symptom, it would be appropriate to classify it as an aura. However, tachycardia occurs not just with the aura, but even more frequently during the clinical seizure, and it would be redundant and misleading to call it an autonomic seizure.

Respiratory symptoms experienced as an aura include such sensations as not being able to breathe, a need to breathe more deeply, and of a breath filling the chest that would not expire. Alterations in respiratory rhythms have been reported on stimulation of temporal limbic structures and in seizures of insular origin (53).

Cold shivering and associated piloerection as auras can be experienced over diffuse or extended areas or localized and lateralized to one part of the body. This aura is probably not unique to a single cortical area, but seems most common in temporal lobe epilepsy (89–91). When unilateral, the side of piloerection is more likely ipsilateral to the side of the epileptic focus.

Urinary urgency has been reported both at seizure onset and afterward. It is uncommon as an aura and may be more common postictally. The localization of these sensations implicates the nondominant frontal lobe in the vicinity of the cingulate gyrus or the nondominant temporal lobe (92,93).

SEXUAL AURAS

These uncommon erotic feelings may or may not be accompanied by genital sensations or symptoms or signs of sexual arousal. They are distinguished from the sometimes unpleasant superficial genital sensations without sexual content that arise from stimulation of the primary somatosensory area at the parasagittal convexity or interhemispheric fissure and possibly the perisylvian region. Sexual auras seem to arise from the temporal lobe (94) with other cases reported from the parasagittal area implicating the sensory cortex. The cases reported thus far have shown a female preponderance. Of those patients whose sexual aura resulted in orgasm, a right hemisphere lateralization has been found in one review (95).

CONCLUSION

Epileptic auras are rich in symptomatology. As the earliest or only symptom of an epileptic discharge, it can convey information on possible sites of seizure onset. A familiarity of different aura symptoms and their anatomico-functional relationships will reward the clinician and neurophysiologist.

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CHAPTER 11 FOCAL MOTOR SEIZURES

ANDREAS V. ALEXOPOULOS AND STEPHEN E. JONES

In memoriam: Dudley S. Dinner, MD (1947–2007)
"One who is the giver of knowledge is the giver of life."

HISTORY

Focal motor seizures have been recognized since the time of Hippocrates, who first observed seizures affecting the body contralateral to the side of head injury (1). Hughlings Jackson was the first to theorize that focal seizures are caused by "a sudden and excessive discharge of gray matter in some part of the brain" and that the clinical manifestations of the seizure depend on the "seat of the discharging lesion" (2,3).

During the second half of the 19th century, Fritsch and Hitzig (4) pioneered stimulation of the brain in animals. They discovered that electrical stimulation of the exposed cerebral cortex produced contralateral motor responses in dogs (5,6). Experimental faradic stimulation of the human cerebral cortex was first performed by Bartholow in 1874 (7). In 1909, Cushing (8) reported that faradic stimulation of the postcentral gyrus could be used to determine the anatomic relationship of the sensory strip to an adjacent tumor. Motor responses elicited by electrical stimulation in humans were first described by Krause in the beginning of the 20th century (9) and by Foerster more than 70 years ago (2). These early observations led to the fundamental work of Penfield and Brodley (10), who used electrical stimulation to elucidate the motor and sensory representation of the human cerebral cortex and pioneered the techniques for the functional localization of the sensorimotor cortex during surgery.

FUNCTIONAL ANATOMY OF THE MOTOR CORTEX

Strictly speaking, the motor cortex (Fig. 11.1) consists of three motor areas: the primary motor area (PMA or M1) in the precentral gyrus, which houses a complete representation of body movements; the supplementary sensorimotor area (SSMA or SMA) on the mesial surface rostral to the PMA, also containing a complete motor representation (hence the term supplementary); and a more loosely defined premotor cortex (PreMC) on the lateral convexity (11).

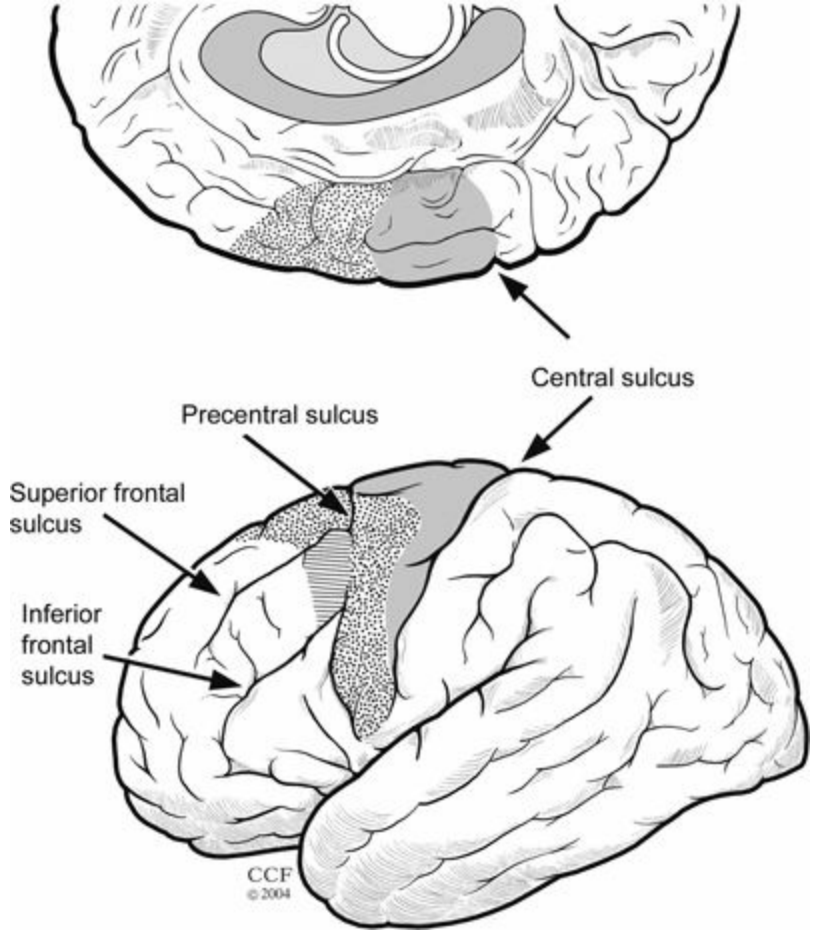


Figure 11.1. Mesial and lateral aspects of the left hemisphere: schematic representation of the three motor areas and their approximate relationship to the surface hemispheric anatomy. The shaded area corresponds to the primary motor cortex (Brodmann area 4). The stippled area illustrates the supplementary sensorimotor cortex on the mesial aspect. On the lateral view, the stippled area represents the premotor cortex. Also note the approximate location of the frontal eye field (hatched area).

The prefrontal and orbitofrontal cortices, as well as the dorsolateral and mesial frontal cortices anterior to the SSMA, are not considered part of the motor cortex. The term prefrontal cortex is used to define the extensive part of the frontal lobe that lies anterior to the motor and premotor zones (12). Modern anatomic and physiologic studies in humans and primates challenge the traditional division of motor areas (13). For example, part of the cingulate cortex, which was previously linked to the limbic system, is now considered as a fourth main motor area, the so-called cingulate motor area (14,15).

Activation studies using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) allude to the complex organization of the motor system. The breadth of cortical and subcortical areas activated with even the simplest movements attests to the wide distribution and extent of interconnected neural networks underlying motor control (14). Observed movements presuppose a series of parallel or sequential processes involving the selection, planning, preparation, and initiation of action (14,16).

Efferent and Afferent Connections

The familiar hierarchical model of motor control is based on the four levels of spinal cord, brainstem, PMA, and PreMC SSMA. This concept has influenced our understanding of the various motor manifestations of seizures (17). Motor commands are organized hierarchically from the most automatic (e.g., deep tendon reflexes) to the least (e.g., skilled and precise voluntary movements). Each level of motor control retains a somatotopic organization and receives peripheral sensory

information that is used to modify the motor output at that level (18). The cerebral cortex exerts its motor control by way of the corticospinal and corticobulbar pathways. The cortex also modulates the action of motor neurons in the brainstem and spinal cord indirectly through its influence on the brain's various descending systems.

To this day, limited direct information exists about specific neuronal connections between functional brain regions of the human cortex (19). Our knowledge of detailed connectivities is derived from invasive tracer studies in primates. Recent imaging advances are now permitting noninvasive studies of neuronal connections in humans, using the techniques of diffusion tensor imaging (DTI) and functional connectivity MRI (fcMRI)—the latter technique aims to identify highly correlative BOLD signal changes present in different regions of the cortex during the resting state or during specific tasks (20). Importantly, cortical regions identified by fcMRI may reside at a considerable distance from each other. Optogenetic techniques now also allow further in vivo mapping of interactions of motor and premotor areas in animal models (21).

Brainstem Motor Efferents

The brainstem gives rise to several descending motor pathways, which are divided into ventromedial and dorsolateral groups (22,23). The ventromedial system sends fibers through the ventral columns of the spinal cord and terminates predominantly in the medial part of the ventral horn, which contains the motor nuclei controlling proximal limb and axial muscle groups. In contrast, the dorsolateral system descends in the lateral part of the spinal cord and terminates on the lateral motor cell complex, which innervates more distal limb muscles (24). Thus, the dorsolateral motor system places its emphasis on muscles devoted to fine motor control.

Motor Cortex Efferents

The axons that project from layer V of the cortex to the spinal cord run together in the corticospinal tract (a massive bundle of fibers containing approximately 1 million axons). About one-third of corticospinal and corticobulbar fibers arise from the PMA. Another third originate from the SSMA and PreMC, and the rest have their origin in the parietal lobe (arising mainly from the somatosensory cortex of the postcentral gyrus) (25). The corticospinal fibers together with the corticobulbar fibers run through the posterior limb of the internal capsule to reach the ventral portion of the brainstem and send collaterals to the striatum, thalamus, red nucleus, and other brainstem nuclei (26). Many of these relationships can now be visualized noninvasively using combined fMRI and DTI techniques (Fig. 11.2). In the brainstem, the corticobulbar fibers terminate bilaterally in cranial nerve motor nuclei (either directly via a monosynaptic route or indirectly), with the exception of motor neurons innervating the lower face, which receive mostly contralateral corticobulbar input. About three-fourths of the corticospinal fibers cross the midline in the pyramidal decussation at the junction of the medulla and spinal cord and descend in the spinal cord as the lateral corticospinal tract (19). Uncrossed fibers descend as the ventral corticospinal tract. The lateral and ventral divisions of the corticospinal tract terminate in approximately the same regions of spinal gray matter along with corresponding brainstem-originating pathways. The majority of corticospinal tract terminals project on spinal interneurons. An estimated 5% of the fibers synapse directly on (both alpha and gamma) motor neurons (27).

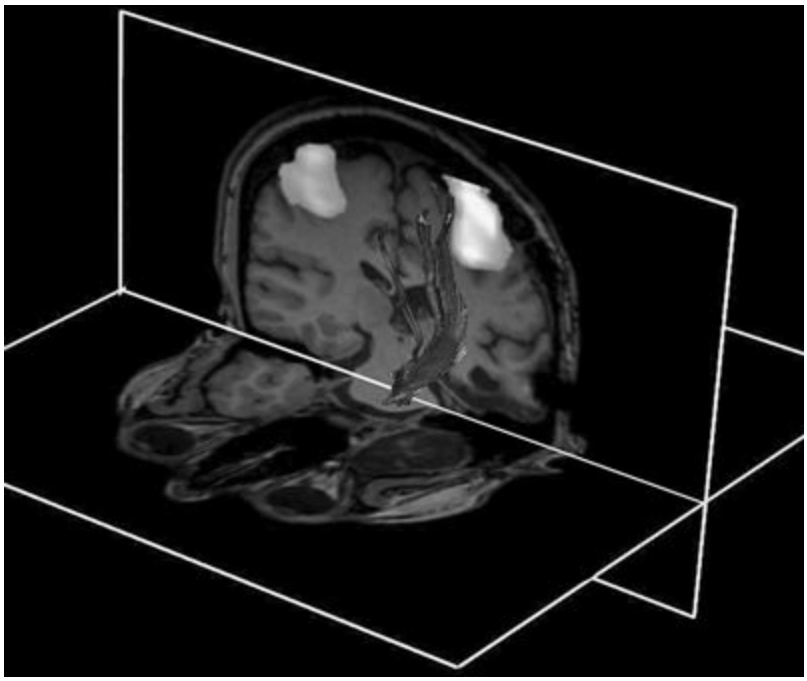


Figure 11.2. Combination of DTI, fMRI, and anatomic imaging demonstrating relationship of the left corticospinal tract to the motor regions using a finger-tapping paradigm. The fMRI and anatomic images are displayed as cut planes, with 3D superimposition of a surface representation of DTI tracks. A seed region for deterministic tracking is placed in the central pons—from this structure, the tracks ascend superiorly through the internal capsule and corona radiata to terminate in pericentral cortex. Note the expected close approximation of central tracks to the hand area.

These anatomic arrangements of descending tracts underlie the contralateral and/or bilateral motor manifestations of focal seizures arising from the motor cortex (17).

Motor Cortex Afferents

The major cortical inputs to the motor areas of cortex are from the prefrontal and parietal association areas (18). These are focused mainly on the PreMC and the SSMA, whereas the PMA receives a large input from the primary somatosensory cortex (28). In addition, the PMA receives direct and indirect inputs from the PreMC and the SSMA. In particular, the SSMA projects bilaterally to the primary motor cortex in a somatotopically organized manner. Other corticocortical inputs arrive from the opposite hemisphere through the corpus callosum (Fig. 11.3), which interconnects heterotopic as well as homologous areas of the two hemispheres (29,30). The major subcortical input to the motor cortical areas comes from the thalamus, where separate nuclei convey modulating inputs from the basal ganglia and the cerebellum (28).

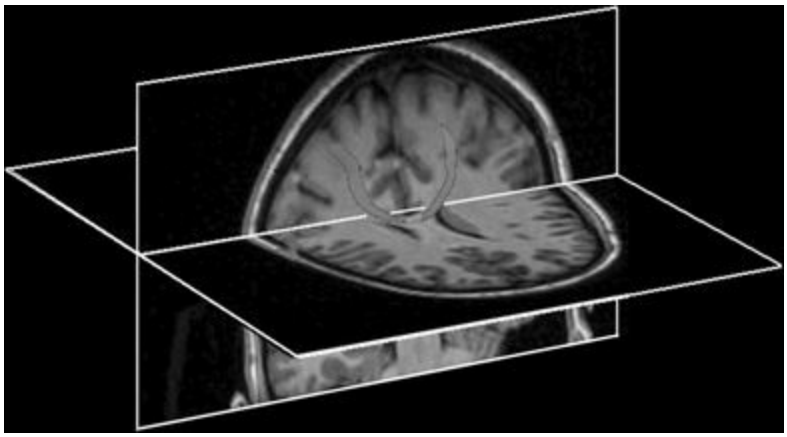


Figure 11.3. Example of corticocortical connectivity using probabilistic tractography from high-resolution DTI images. One seed region is placed in one motor area, and the target region is placed in the contralateral motor area. Computed tracts course across the corpus callosum as expected. The tracts are displayed as a red 3D overlay on black and white anatomic cut planes.

Stimulation Studies

In clinical practice, insights into the functional anatomy of the motor cortex and other eloquent brain cortical areas are afforded by direct cortical stimulation. At the same time, electrical stimulation of the human cortex provides an experimental model that can be used to reproduce the effects of cortical activation after an ictal discharge (31). Several groups use cortical stimulation to trigger habitual auras and/or seizures in an attempt to better delineate the ictal onset zone before epilepsy surgery.

In general, the observed clinical response is assumed to arise from cortex below the stimulated electrode or from the region between two closely spaced electrodes, given that the current density drops off rapidly with increasing distance from the tissue underlying the stimulated electrode (32,33). Electrical stimulation can elicit "positive" responses (such as localized movements resulting from activation of the PMA or SSMA cortex) or "negative" responses (such as inhibition of motor activity). The latter becomes apparent only if the patient engages in specific tasks during stimulation. In areas such as the supplementary motor cortex, both positive responses in the form of bilateral motor movements and negative responses such as speech arrest can be demonstrated. The area of stimulation gives rise to distinctive patterns of motor activation of the PMA, SSMA, or premotor regions. Overlapping clinical manifestations are commonly observed as a result of the highly developed interconnectivity between these regions (34).

Negative motor responses interfere with a person's ability to perform a voluntary movement or sustain a voluntary contraction when cortical stimulation is applied (35). The patient is unaware of the effects of stimulation unless asked to perform the specific function integrated by the stimulated cortical region. In a systematic review of 42 patients who had subdural electrodes over the perirolandic area, the Cleveland Clinic group observed negative motor responses over both hemispheres, when stimulating the agranular cortex immediately in front of the primary and supplementary face areas (35). To distinguish the two negative motor areas, investigators proposed the terms primary negative motor area (PNMA, in regard to the region of the inferior frontal gyrus immediately in front of the face PMA) and supplementary negative motor area (SNMA, in reference to the mesial portion of the superior frontal gyrus immediately in front of the face SSMA). Other investigators have been able to confirm and extend these observations using similar techniques of direct cortical stimulation with subdural electrodes, and have concluded that negative motor areas are in fact widely distributed throughout the perirolandic region and within the PreMC (36). These areas are considered a part of the cortical inhibitory motor system, the epileptic activation of which may give rise to **focal inhibitory motor seizures** (also referred to by some authors as "akinetic" seizures). Such seizures can be easily overlooked because patients may remain unaware of their weakness and/or inability to execute specific movements, unless they are carefully examined.

The effects of functional localization and effects of electrical stimulation in the three broad motor areas are briefly discussed below.

Primary Motor Area

The PMA resides in the anterior wall of the central sulcus (see Fig. 11.1) and corresponds to Brodmann area 4. On the basis of cytoarchitectonic criteria, area 4 is recognized primarily by the

presence of Betz cells (giant pyramidal cells) in cortical layer V and the absence of a granular layer IV (37). The central sulcus marks the border between the agranular motor cortex and the granular somatosensory cortex (38).

Radiographically, the central sulcus appears as a prominent, almost always continuous, sulcus, which extends from the mesial aspect (near the brain's apex) along an oblique coronal trajectory toward (and near to) the sylvian fissure. The superior and inferior aspects of the central sulcus are terminated by the paracentral lobule and subcentral gyrus, respectively, which effectively appear as a joining of the pre- and postcentral gyri. The radiographic identification of the central sulcus is often critical to the interpretation of imaging studies and planning surgical procedures, as it provides a central landmark from which other topologies can be located. There are several characteristic features identifying the central sulcus, three of which are shown in the cartoon of Figure 11.4 and on the T1-weighted MRI images of Figure 11.5. Most easily identified is the so-called hand knob, which assumes the form of an upside-down omega ("Ω") on axial images (39). Formed by a relative gyral hypertrophy corresponding to the PMA of the hand, the "hand knob" appears to project posteriorly from the precentral gyrus into the contour of the central sulcus. Due to anatomic variation, this feature sometimes assumes the shape of a horizontal epsilon ("ε"), rather than the inverted omega (39). Another confirmatory feature of the "hand knob" on the sagittal plane is that it appears as if forming a backward "hook" (see Fig. 11.5), but this appearance is less reliable than is the characteristic axial morphology. A second helpful landmark is the topology of the superior central gyrus, which is easily seen running along an anterior–posterior direction along the medial frontal lobe and whose posterior margin is the precentral gyrus. Identification of the precentral gyrus is further aided by demarcation of the pre- and postcentral sulci. Lastly, axial images nicely portray the pars marginalis, which is the ascending ramus arising from the posterior cingulate sulcus. The left and right ascending rami appear on axial images as bilaterally paired paramedian features that together form the shape of a "bracket" or "smile" (40). This characteristic appearance is often preserved over multiple axial slices and can be used to identify the central sulcus and differentiate it from the adjacent postcentral sulcus.

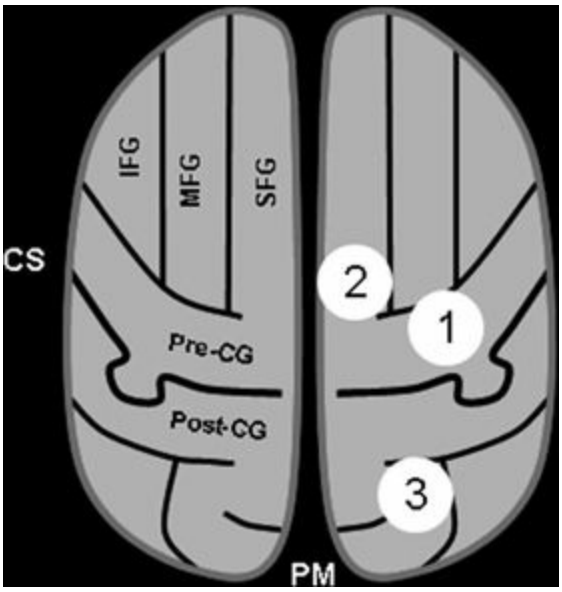


Figure 11.4. Key features for identifying the sensorimotor cortex. The essential step is identification of the central sulcus (CS), which separates the precentral gyrus anteriorly (motor cortex) from the postcentral gyrus posteriorly (sensory cortex). This schematic of an axial section illustrates three classic features that aid in the identification of the CS. (1) the "hand knob" is a posterior protuberance of the precentral gyrus, which corresponds to relative "hypertrophy" of the primary hand motor area. The shape of the sulcus in this area is often described as that of an upside-down omega ("Ω"). (2) The anterior–posterior orientation of the superior frontal gyrus is often easily identified, as it aligns along a paramedian plane. While the anterior margin of the SFG extends to the frontal poles, the posterior

margin merges with the precentral gyrus, such that the most posterior margin often appears as the central sulcus. (3) Posterior to the medial aspect of the central sulcus is the pars marginalis, which often has a slight concavity—when pairing together, the left and right pars marginalis assume the characteristic appearance that resembles a "smile" or "bracket," which can be seen on multiple axial sections, making identification easy. (IFG, inferior frontal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; Pre-CG, precentral gyrus; post-CG, postcentral gyrus; CS, central sulcus; PM, pars marginalis.)

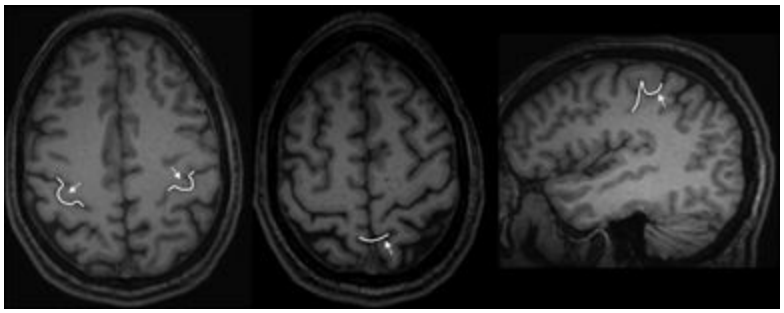


Figure 11.5. MRI examples of the landmark features described in Figure 11.4, which help locate the central sulcus. Shown as overlaid white line segments are the "omega" of the hand knob (**left** image) and the pars marginalis "smile" (**middle image**). The **middle** image also demonstrates the architecture of the superior frontal gyrus terminating posteriorly in the precentral gyrus. The **right** image displays the backward "hook" as described in the text—this feature is appreciated on sagittal images passing through the hand knob.

The somatotopic organization of the PMA was elucidated by the pioneering work of Krause (9), Penfield, Jasper, and Rasmussen (41,42), and others (Fig. 11.6). In this region of the PMA, simple movements were elicited with the lowest intensity of electrical stimulation (43). The resulting motor maps show an orderly arrangement with the tongue and lips near the sylvian fissure and the thumb, digits, arm, and trunk represented successively along the central sulcus, ending with the leg, foot, and toes on the mesial surface. The somatotopic organization of the motor cortex is not fixed and can be altered during motor learning or after injury (44). The layout of the motor homunculus is topographically similar to that of the somatosensory homunculus, which resides immediately behind the PMA. Contemporary noninvasive methods, such as BOLD imaging fMRI, nicely confirm and recapitulate the classic homunculus (see Fig. 11.6). Output of the PMA is directed to the corticospinal and corticobulbar tracts, as well as to the SSMA and homologous areas in the opposite hemisphere via the corpus callosum (45).

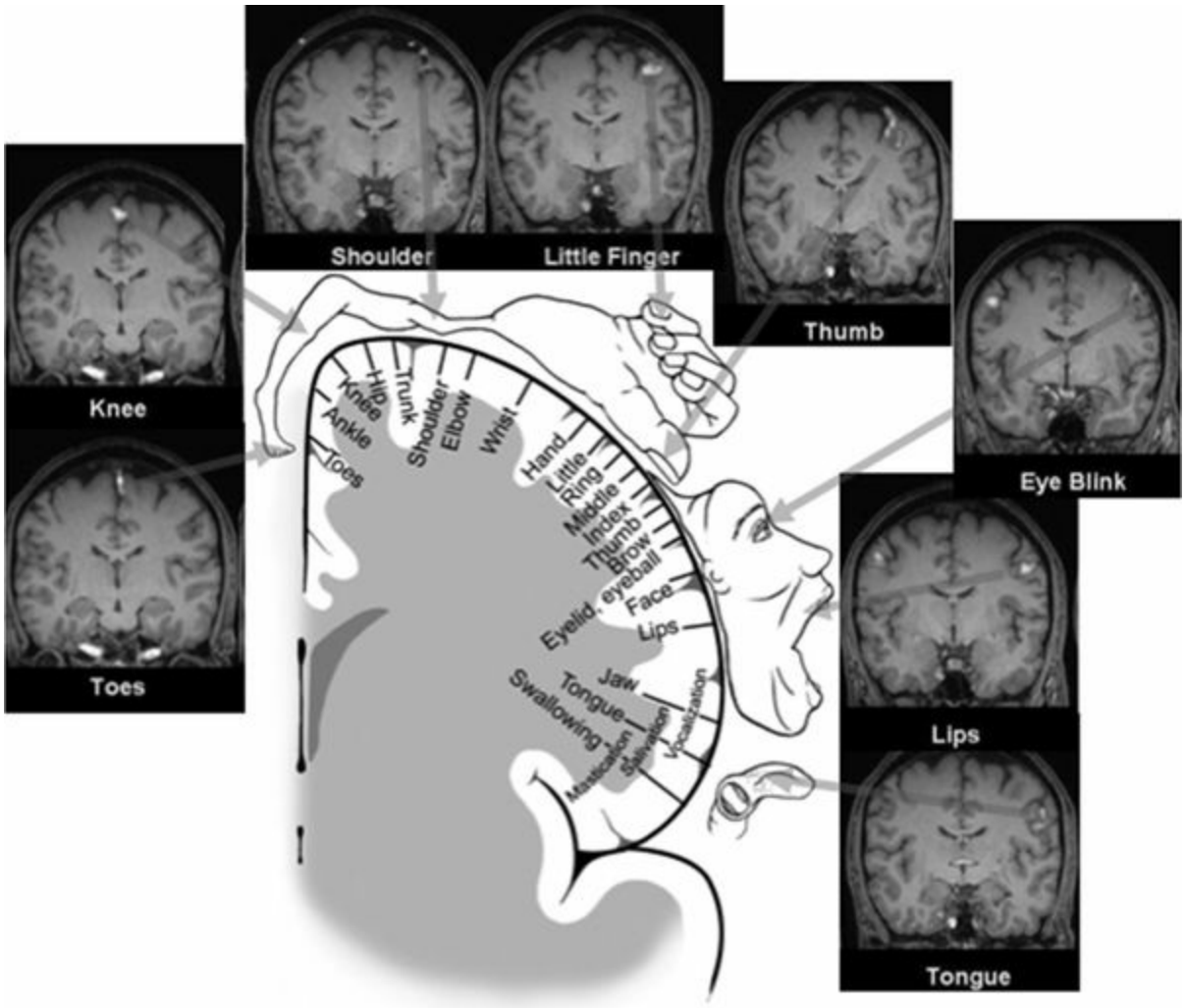


Figure 11.6. The motor homunculus after Penfield and Rasmussen depicting the somatotopic arrangement of the primary motor cortex (PMA) (with the tongue and lips near the sylvian fissure and the thumb, fingers, arm, and trunk represented successively along the precentral gyrus ending with the leg, foot, and toes on the mesial surface) occupies the center of this figure. Muscle groups involved in fine movements feature a disproportionately large representation. Surrounding this schematic representation of the motor homunculus are corresponding images of fMRI activation of the primary motor cortex obtained with eight different motor tasks—the fMRI images nicely recapitulate the classic motor homunculus. Images are provided in coronal oblique reformatted planes that are roughly parallel to the motor strip. Significant activity is shown as color overlay. The toe, knee, shoulder, and finger tasks employed flexion/extension or tapping at a rate of about 2 per second, using the right-sided limb only. The eye blink, lip (pursing), and tongue (pressing against palate) tasks were bilateral motions performed at a similar rate. Right lower extremity movements are clearly localized along the left superomedial cortical surfaces, with right upper extremity movements localized along left superolateral cortical surfaces. Note bilateral motions from the eyes, lips, and tongue show corresponding bilateral activation. (Adapted from Penfield W, Rasmussen T. The Cerebral Cortex of Man—A Clinical Study of Localization of Function. New York : The MacMillan Company; 1950, with permission.)

Stimulation Studies

In the PMA, single stimuli typically elicit single clonic movements of the contralateral somatic muscles represented by the area of the motor homunculus being stimulated. High-frequency (50 to 60 Hz) stimulus series result in slower, tonic contralateral motor responses (46). Intraoperative application of electrical stimulation mapping under local or general anesthesia provides the most direct and easy way to localize the perirolandic cortex in most adults (47). When local anesthesia is used, motor responses are usually evoked with currents of 2 to 4 mA. Sensory responses are elicited with stimulation of the postcentral gyrus, often at slightly lower thresholds (48). The threshold for eliciting a motor response in humans is lowest in the PMA. Electrical cortical stimulation studies

uncover the individual variability in the topographic organization of sensorimotor maps in humans with structurally normal anatomy (49). The importance of direct cortical stimulation studies in patients with lesions and/or epileptogenic foci encroaching on the sensorimotor cortex cannot be overemphasized (50). Furthermore, bilateral probabilistic map has proven to become a useful tool to map and anticipate cortical epicenters of human brain functions, including motor and language areas (51).

Supplementary Sensorimotor Area

The SSMA is a distinct anatomic region located on the mesial surface of the superior frontal gyrus and its adjacent dorsal convexity (52). The cerebral cortex of the SSMA corresponds to the mesial portion of area 6 of Brodmann cytoarchitectonic map of the brain (41,53) (see Fig. 11.1). Phylogenetically, the SSMA may be viewed as older motor cortex derived from the anterior cingulate periarchicortical limbic system (54). Similar to the primary motor cortex, the SSMA is referred to as agranular cortex, because the internal granular layer (layer IV) is not prominent. In contrast to area 4, area 6 does not contain Betz cells (53). The medial precentral sulcus defines the border between the PMA for the foot and the posterior limit of the SSMA (13,55). No clear cytoarchitectonic or anatomic boundary separates the SSMA from the adjacent PreMC (56).

The macaque and human mesial area 6 (SSMA) is further subdivided into pre-SSMA (rostrally) and SSMA proper (caudally) on the basis of comparable cytoarchitectonic and transmitter receptor studies (38). Studies in primates suggest that the pre-SSMA holds a hierarchically higher role in motor control. The functional properties of the SSMA subdivisions have not been detailed in humans (57). The border between the pre-SSMA and SSMA proper corresponds to the vertical anterior commissure line (VAC line, i.e., the vertical line passing through the anterior commissure and perpendicular to the AC–PC line, which connects the anterior and posterior commissures) (Fig. 11.7). The border between SSMA proper and PMA corresponds approximately to the VPC line (i.e., the vertical line that traverses the posterior commissure and is perpendicular to the AC–PC line) (58).

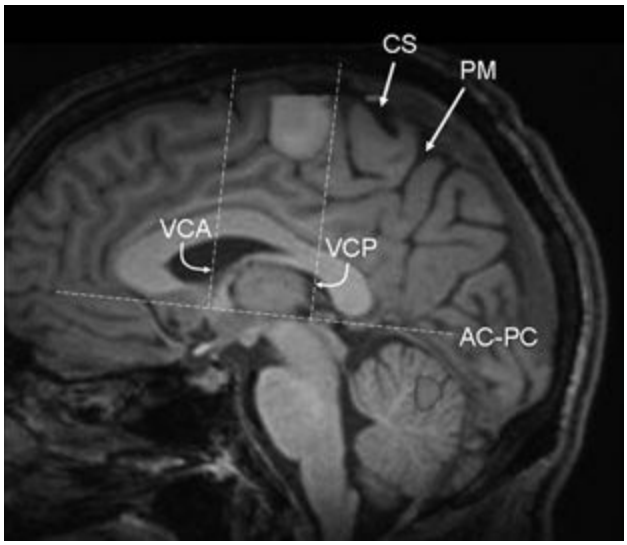


Figure 11.7. Functional MRI using a finger-tapping paradigm (paramedian sagittal plane) shows activation of the supplementary sensorimotor area (SSMA), which lies within the paracentral lobule and is located anteriorly to medial margin of the central sulcus. In addition, cerebellar activation is also present. Note the anatomical relationships of the SSMA to the AC–PC line, as described in the paragraph on Supplementary Motor Area, above. The border between the pre-SSMA anteriorly and SSMA proper corresponds to the VAC line, and the border between SSMA proper and PMA posteriorly corresponds approximately to the VPC line. AC–PC refers to

the line that connects the anterior and posterior commissures, VAC (or VCA as depicted above) refers to the vertical line passing through the anterior commissure and perpendicular to the AC–PC line, VPC (or VCP as depicted above) refers to the vertical line that traverses the posterior commissure and is perpendicular to the AC–PC line. (CS, central sulcus; PM, pars marginalis.)

Stimulation Studies

More than 70 years ago, Foerster was the first to describe motor responses in humans elicited by electrical stimulation of the mesial aspect of the superior frontal gyrus anterior to the primary motor representation of the lower extremity (2). Systematic study of this region with electrical stimulation was carried out at the Montreal Neurological Institute (MNI) during the intraoperative evaluation of patients with intractable focal epilepsy preceding surgical resection (59).

This was the first group to use the term supplementary motor area (SMA). Direct intraoperative electrical stimulation of the SMA produced vocalization, speech arrest, postural movements of all extremities, inhibition of voluntary movements, paresthesias, and autonomic changes. The rich repertoire of combined or postural movements included the so-called fencing posture, a term coined by the MNI group to describe the classical stimulation-induced postural response that consists of elevation of the contralateral arm with the head and eyes turned toward the raised hand (41). The Montreal studies demonstrated that both positive (such as bilateral motor movements) and negative responses (such as speech arrest) could be elicited by stimulating this region. The intraoperative study of the mesial interhemispheric surface carries significant limitations, because of the tedious and potentially dangerous surgical approach (in proximity to the superior sagittal sinus and its cerebral bridging veins), the restricted amount of time, and the relative difficulty in recognizing the specific gyral landmarks during surgery in this region.

With the advent of subdural electrodes, the Cleveland Clinic series of extraoperative stimulation studies showed that positive motor responses were not restricted to the mesial aspect of the superior frontal gyrus, but could also be elicited from its dorsal convexity, the lower half of the paracentral lobule, and the precuneus (60). The same group confirmed the presence of sensory symptoms that were elicited along with the positive motor responses after stimulation of the SMA and coined the term SSMA instead of SMA.

Using depth electrodes, Talairach and Bancaud (61) were the first to describe a somatotopic organization within the SSMA. The Yale group confirmed the presence of somatotopic distribution in the SSMA, where the face, upper extremity, and lower extremity responses are oriented in a rostrocaudal direction, with the lower extremities represented posteriorly, head and face most anteriorly, and the upper extremities between these two regions (62). Likewise, studies of movement-related potentials (MRPs) using subdural electrodes implanted over the SSMA region demonstrated that MRPs for different types of movements (finger, foot, tongue, vocalization, etc.) also have a somatotopic distribution within the SSMA, which is consistent with the organization defined by electrical stimulation (63–65). Notably, fMRI studies using motor activation paradigms, such as finger tapping, for example, demonstrate strong activations of the SSMA in addition to the primary motor cortex (see Fig. 11.7).

Premotor Cortex

Fulton coined the term PreMC in 1935 to describe the third major component of motor cortex (66). This area encompasses the more loosely defined agranular cortex of the lateral frontal convexity rostral to the PMA (11,23), which corresponds to the lateral portion of Brodmann area 6 (see Fig.

11.1). It is difficult to define the anterior border of the agranular PreMC in humans, where a broad zone of progressive transition exists between area 6 and the granular cortex of Brodmann frontal area 9 (67). In the macaque, the PreMC is further subdivided into a dorsal portion on the dorsolateral convexity and a ventral portion on the ventrolateral convexity (11). Despite the lack of direct correlation between microstructure and function in humans, the two subdivisions of the premotor area are considered to have homologous counterparts in the human brain. The motor and premotor cortices, as well as the frontal eye fields (FEFs) and the anterior cingulate cortex of area 24, have reciprocal connections with the SSMA (53). Anatomic labeling experiments in the macaque have demonstrated that the more anterior dorsal PreMC projects to the spinal cord, challenging the notion that the PreMC, unlike the PMA and SSMA, lacks prominent corticospinal connections (23,68,69).

According to the classic schema, the PreMC is responsible for the preparation and organization of movements (56). Several recent studies show that the PreMC also plays a central role in nonmotor attentional and receptive domains. Therefore, our current understanding suggests a dual PreMC function pertaining to motor and cognitive behaviors (70).

Stimulation Studies

On the basis of early electrical stimulation studies of the monkey brain (71), the agranular lateral PreMC (area 6) has been subdivided into a rostral section (6aβ or 6r) and a caudal section (6aα or 6c). Recent quantitative architectonic and neurotransmitter studies have corroborated the presence of similar topographic boundaries in the human brain (38,67). The rostral subdivision covers the anterior part of the precentral gyrus, and its caudal counterpart resides in the posterior part of the superior and middle frontal gyri, in front of the precentral sulcus (72).

Eye movements can be electrically induced from a large area of the human dorsolateral frontal cortex and the precentral gyrus. These stimulation-elicited responses have been attributed to electrical interference with the human homolog of the monkey FEF (73). Electrical stimulation studies in humans have confirmed the functional location of the eye movement sites anterior to the motor representation of the arm and face (73,74). However, some ambiguity exists as regards the exact location of the human FEF within this rather extensive oculomotor region. The divergence is largely caused by the methodologic differences of neuroimaging and electrical cortical stimulation studies.

The electrically defined human FEF is located in the posterior end of the middle frontal gyrus (see Fig. 11.1) immediately anterior to the precentral sulcus (and in proximity to the superior frontal sulcus). Electrical cortical stimulation of this area produces constant oculomotor responses characterized by low stimulation thresholds (73). Conversely, neuroimaging studies of cerebral blood flow (CBF) changes suggest that the homologous region in humans lies posterior to the electrically defined FEF. Indeed, the CBF-defined FEF is located between the central and precentral sulci in front of the primary hand representation, suggesting that the eye movement field lies in Brodmann area 6 (i.e., in a PreMC region homologous to the ventral PreMC) (75,76). More recently, corticocortically evoked potentials have been used to evaluate connections between the premotor and motor cortex in humans implanted with subdural electrodes (77).

FOCAL MOTOR SEIZURES

Focal seizure is the term proposed by the Task Force of the International League Against Epilepsy (ILAE) to describe seizures in which the initial activation involves a limited number of neurons in

part of one hemisphere (78). The terms localization- related or partial seizures have been used to describe the same seizure type. However, the more recently proposed diagnostic scheme of the ILAE Task Force prefers the less ambiguous term focal to partial or localization-related seizures (79).

Motor phenomena constitute the main clinical manifestations of motor seizures. As a rule, consciousness is retained in the majority of seizures arising from discrete motor regions. It is possible, however, for an ictal discharge to remain localized and still produce alteration of consciousness. Furthermore, certain motor manifestations and a patient's anxious reaction to the seizure symptoms may prevent the patient from responding appropriately during seizures. It may, therefore, be difficult to ascertain the level of consciousness in several patients with focal motor seizures. In the past, the presence or absence of altered awareness was used to dichotomize seizures of focal onset into "simple partial" and "complex partial." It is now proposed to move away from this dichotomy, which seems to have "lost its meaningful precision" (79).

Subsequently, the ILAE provided a glossary of descriptive terminology to describe ictal semiology (80). Ictal motor phenomena may be subdivided into **elementary motor manifestations** (such as tonic, clonic, dystonic, versive) and **automatisms**. Automatisms consist of a more or less coordinated, repetitive motor activity (such as oroalimentary, manual or pedal, vocal or verbal, hyperkinetic or hypokinetic) (80). Somatotopic modifiers may be added to describe the body part producing motor activity during seizures.

Another recent seizure classification is based on the clinical symptomatology and is independent of electroencephalographic (EEG), neuroimaging, and historical information (81). This classification uses terms such as focal clonic, focal tonic, or versive, and evolution during the seizure is indicated by arrows. For example, left-hand somatosensory aura → left arm clonic seizure → left versive seizure.

Clinical Semiology

This section reviews the elementary motor phenomena resulting from a variety of focal motor seizures. These seizures typically present with clonic or tonic manifestations. Hyperkinetic manifestations are usually attributed to seizures arising from (or spreading to) the frontal lobe. Other motor automatisms seen with focal seizures (such as oroalimentary, mimetic, or gestural automatisms) are reviewed elsewhere.

In a population-based study conducted in Denmark of 1054 patients with epilepsy who were between the age of 16 and 66 years, 18% had "simple partial" seizures (82). Mauguiere and Courjon examined the presenting seizure type in a large series of 8938 patients with seizures admitted to a single hospital over a 10-year period. They found that 1158 patients (12.9%) had focal tonic or clonic seizures without march (the most common presentation of focal seizures in this series); 582 patients (6.5%) presented with hemitonic or clonic seizures; 461 (5.2%) had adversive seizures; and only 199 (2.2%) had jacksonian seizures (83). Perirolandic epileptogenic lesions often involve both the precentral and postcentral gyri, giving rise to both motor and sensory phenomena. In one video–EEG study of 14 patients with a total of 87 "simple partial" seizures, sensory phenomena were observed in approximately one-third of patients exhibiting focal motor seizures (84).

Postictally, patients may experience a transient functional deficit, such as localized paresis (Todd paralysis), which may last for minutes or hours (up to 48 hours or longer). This interesting clinical phenomenon of "postepileptic paresis" is the signature of a focal seizure and bears the name of Dr. Bentley Todd, who first described it in the mid-19th century (85). Todd paralysis is believed to result

from persistent focal dysfunction of the involved epileptogenic region. Postictal Todd paralysis is a clinical sign of substantial value in lateralizing the hemisphere of seizure onset (86).

Clonic Seizures

Clonic seizures consist of repeated, short contractions of various muscle groups characterized by rhythmic jerking or twitching movements (87). These movements recur at regular intervals of <1 to 2 seconds. Most clonic seizures are brief and last for <1 or 2 minutes. During this period, clonic movements may remain restricted to one region or spread in a jacksonian manner. The majority of focal motor seizures tend to involve the hand and face, although any body part may potentially be affected (88). Such predilection is attributed to the large cortical representation of the hand and face area. The typical manifestation of a localized discharge within the precentral gyrus is clonic twitching of specific contralateral muscle groups, as determined by their proportionate somatotopic representation.

The clonic movements are usually limited to the corresponding area of the body, but may spread during the attack. Such spread (e.g., from the muscles of the face to the ipsilateral hand or arm) is known as the "jacksonian march." During these "jacksonian attacks," motor symptoms travel slowly from one territory to another, typically following the order of the corresponding somatotopic representation. The term jacksonian seizures was proposed by Charcot in 1887 to describe the characteristic march seen with this particular subtype of clonic seizures (89). The continued use of the term serves to remind us of Hughlings Jackson's astute clinical observations, which provided the basis for his revolutionary principles of functional localization long before the era of EEG and neuroimaging correlations (90). In his own words:

> "The part of the body where the convulsion begins indicates the part of the brain where the discharge begins and where the discharging lesion is situated. But from the focus discharging primarily the discharge spreads laterally to the adjacent "healthy" foci. One focus after the other is seized by the radiating waves of impulses. The march of the attack, the order in which the different parts of the body become involved, reveals the arrangement of the corresponding foci in the precentral convolution." (2)

The march usually starts from a distal body region (such as the thumb, fingers, great toe, mouth, or eyelids) and spreads toward a more proximal part. Jackson astutely described three variants: (i) "fits starting in the hand (most often in the thumb or both)," (ii) "fits starting in one side of the face (most often near the mouth)," and (iii) "fits starting in the foot (nearly always in the great toe)" (3). Typically, consciousness remains intact, and secondary generalization of jacksonian seizures is uncommon. At times, the march may skip some areas, a phenomenon that may be related to different seizure thresholds within the symptomatogenic region. Holowach et al. reviewed 60 jacksonian seizures in children and found that the majority (25 out of 60) began in the face (8 in the periocular and 5 in the perioral region), 17 in the hand, 7 in the arm, 2 in the shoulder, and 9 in the leg and foot (91).

Lastly, the term hemiconvulsions refers to unilateral clonic seizures (i.e., clonic activity affecting one side of the body). Prolonged unilateral convulsions followed by the onset of hemiparesis are described in the childhood syndrome of hemiconvulsion–hemiplegia–epilepsy.

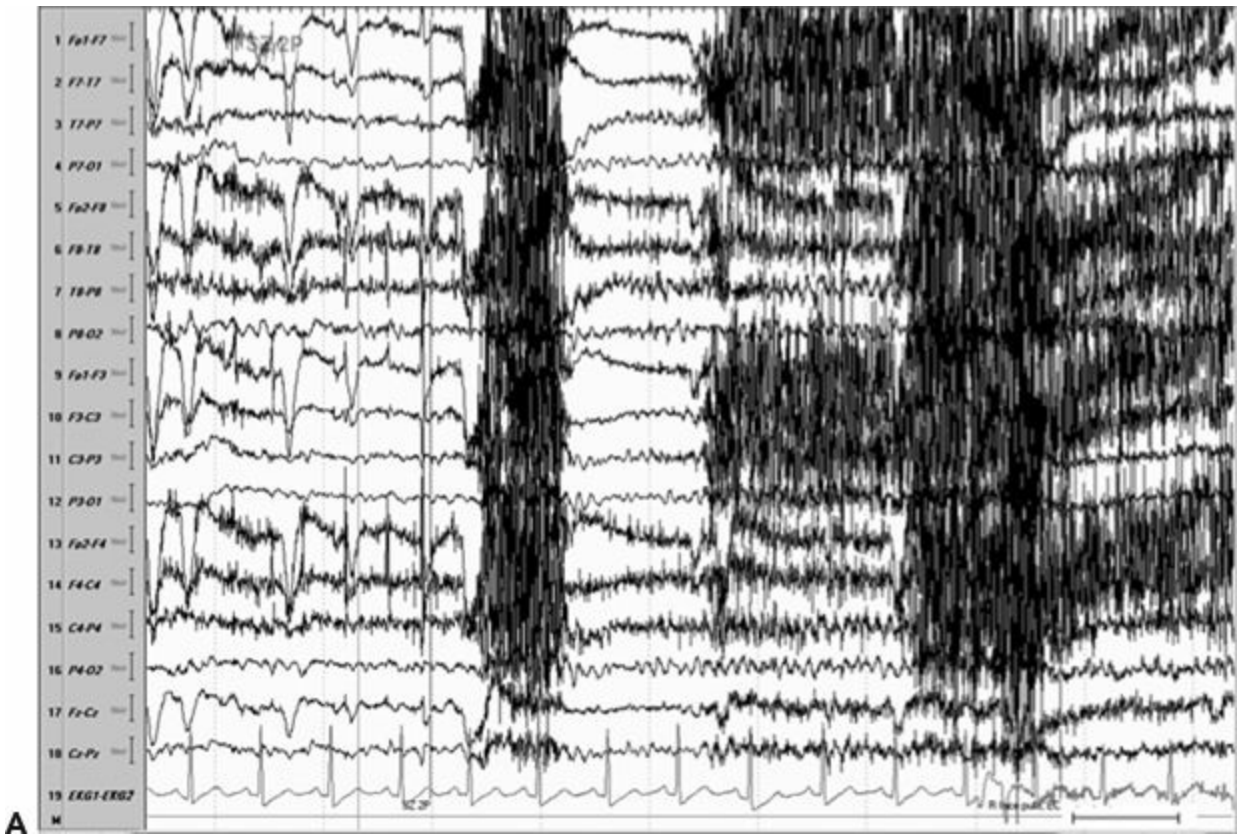
Myoclonus and Myoclonic Seizures

Many types of myoclonic phenomena (e.g., myoclonus caused by spinal cord disease or essential myoclonus) do not have an epileptic origin and need to be differentiated from (focal) myoclonic

seizures. Typically, myoclonic jerks are arrhythmic compared with clonic motor activity. Notable exceptions discussed under the broad definition of myoclonus include the more rhythmic motoric manifestations of epilepsia partialis continua (see below, paragraph on Epilepsia Partialis Continua) and the nonepileptic segmental myoclonus or palatal myoclonus (also called palatal tremor) (92).

Epileptic myoclonus is typically accompanied by an EEG correlate of spike- or multispike-and-wave complexes (93,94). Polygraphic recordings combining EEG with electromyography (EMG) of affected muscles may be necessary to unmask the relationship or the epileptic EEG activity to the myoclonic jerk. Video recordings can be helpful, but cannot replace polygraphy in ambiguous cases. The term myoclonic seizure is reserved for epileptic seizures, whose main components are single or repeated epileptic myoclonias (95). Gastaut (96) distinguished epileptic myoclonic events into generalized, segmental, and focal, according to whether the seizures affected the entire body, one or more limbs, ipsilateral body parts/segments, or only one part of a single limb, respectively.

Although an accurate distinction may oftentimes prove difficult, some authors do not consider epileptic myoclonus as part of focal motor seizures (94). Others view focal cortical myoclonus as one manifestation of focal motor seizures, given that myoclonus in this instance results from a hypersynchronous discharge arising from a distinct population of cortical cells within the PMA and/or premotor areas (97). Focal cortical myoclonus has been described in patients with focal lesions involving the motor cortex, such as tumors, trauma, cortical dysplasia, or vascular lesions (Fig. 11.8). In a report of four children with perirolandic cortical dysplasia presenting with focal cortical myoclonus, the authors observed that localization of the recorded epileptiform discharges correlated with the body part affected by the myoclonus (C3 electrode in two patients whose myoclonus involved predominantly the right upper extremity, C3–T7 electrodes in one patient with myoclonus affecting the face, and Cz electrode in the other patient with focal myoclonus of the left leg) (98).



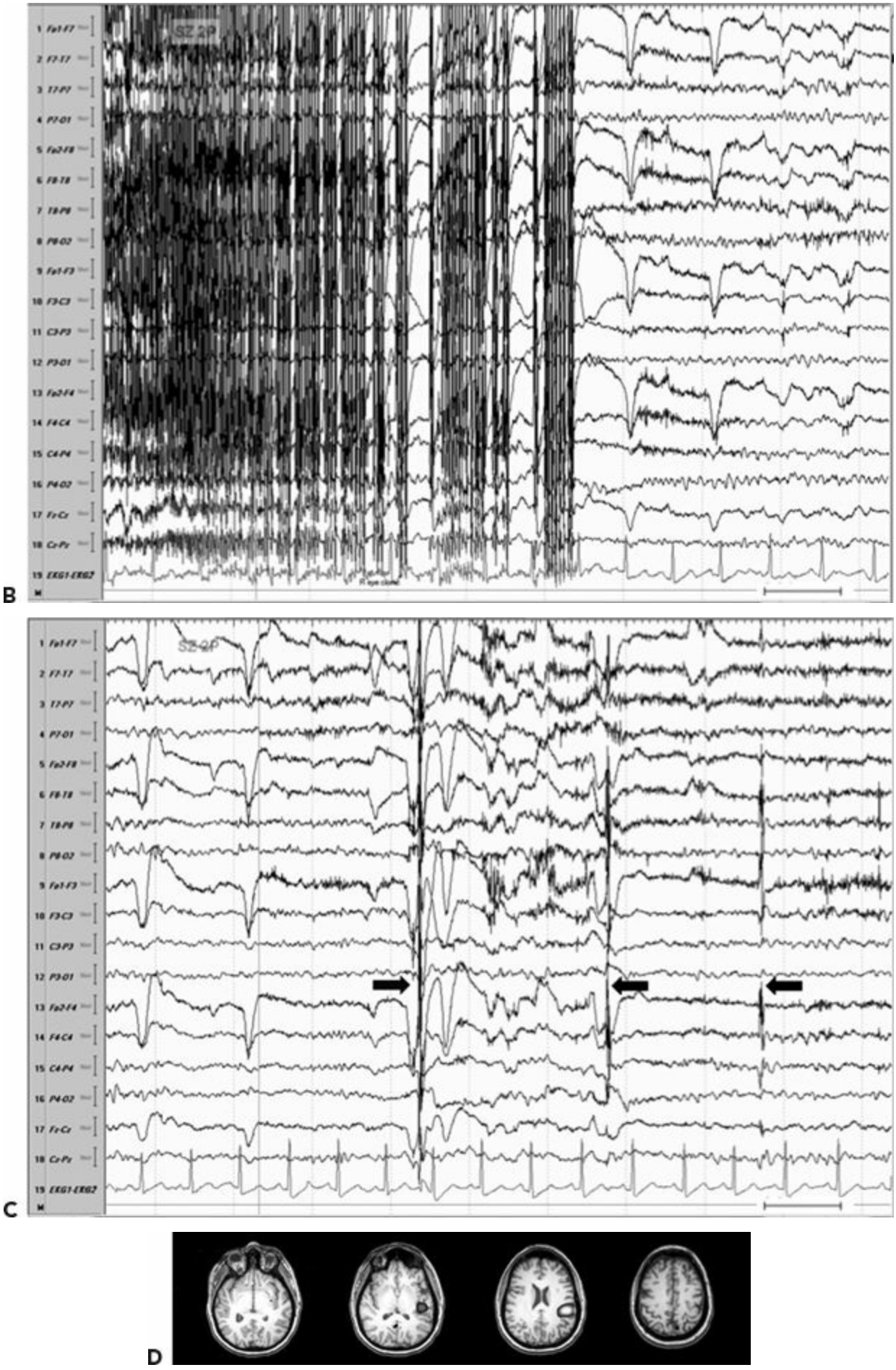


Figure 11.8. Consecutive scalp electroencephalogram tracings (**A** to **C**, longitudinal bipolar montage) during a typical stereotyped event do not disclose a definite evolving ictal pattern, in a 39-year-old patient with exquisitely focal motor seizures since childhood. In the last 3 years, she has been experiencing daily very brief seizures involving the muscles of the lower face on the right side without alteration of awareness. There is no history of jacksonian march or secondarily generalized tonic–clonic seizures. Interictal EEG is normal. Although EEG activity is predominantly obscured by the presence of high- voltage myogenic artifact, the sequence of motor

manifestations can be discerned from the appearance of this same artifact. **A:**Clinical onset in the middle of this 10-second page punctuated by tonic contraction of the right facial musculature with involuntary right eye closure and deviation of the jaw toward the right, associated with voluntary reactive tensing of the entire face, as evidenced by the widespread and asymmetric "tonic muscle artifact." **B:** Clinical evolution with a brief cluster of repetitive focal myoclonic seizures involving the right side of the lower face, as evidenced by the corresponding repetitive, nonrhythmic, and almost instantaneous muscle artifact. Because of its very high voltage, the artifact appears widespread on this printed page. Digital reformatting confirms that the myogenic artifact is in fact picked up predominantly by the right-sided EEG electrodes, which are adjacent and susceptible to the contracting ipsilateral facial muscles. **C:**After the end of this motor sequence, the patient experiences three isolated, less intense, but otherwise identical muscle jerks in the span of 5 seconds, which are associated with myogenic artifact of relatively lower voltage (arrows) interrupting the otherwise normal awake EEG recording. Note that in this instance, the terminal muscle jerk is indeed associated with myogenic artifact primarily involving the right-sided derivations. **D:**Subtraction ictal SPECT (single-photon emission computed tomography) study coregistered to the patient's MRI, as depicted in these selected axial images, revealed a small, discrete, and isolated area of hyperperfusion in the left precentral region, ventral to the expected location of the hand motor area. The patient's MRI was normal except for a small, questionable, but concordant (based on clinical semiology, EEG, and ictal SPECT findings) area of faint signal increase in the depth of the left precentral sulcus at the level of the middle frontal gyrus. Surgical pathology revealed a balloon-cell cortical dysplasia. The location of the lesion (in the depth of the sulcus) and the exquisitely focal nature of the patient's habitual seizures likely account for the lack of interictal and ictal EEG abnormalities in this case.

Finally, the paradoxical term negative myoclonus is reserved for cases of sudden, brief relaxations in tonic muscle contraction (92). Negative myoclonus (which also encompasses the phenomenon of asterixis typically seen in toxic–metabolic encephalopathies) is a nonspecific manifestation and can be associated with a variety of neurologic disorders. Epileptic negative myoclonus can be either unilateral or bilateral and can be seen in relationship with a number of heterogeneous epilepsies ranging from the benign idiopathic epilepsies to severe epileptic encephalopathies (99).

Tonic Seizures

Tonic seizures consist of sustained muscle contractions that usually last for more than 5 to 10 seconds and result in posturing of the limbs or whole body (100). From the standpoint of clinical semiology, tonic seizures can be described according to the distribution and symmetry of tonic contractions with involvement of the axial (neck, trunk, and pelvis) and limb musculature. Generalized tonic seizures involve axial and limb muscles in a symmetric and synchronous fashion. Unequal or asynchronous contraction of muscle groups involving both sides of the body results in bilateral asymmetric tonic seizures. Contraction restricted to a portion of the body on one side only gives rise to focal tonic seizures (101).

In contrast to focal clonic seizures, which represent epileptic activation of a restricted region of the precentral gyrus, tonic motor seizures may implicate a wider area of motor cortex including the SSMA and the PreMC (17,102). Even though focal tonic seizures are attributed to activation of Brodmann area 6 (and the mesial frontal region in particular), some overlap in symptomatology occurs, with ictal involvement of the premotor and/or PMAs (103).

In a video–EEG study of 481 consecutive patients with focal epilepsy—evaluated at two tertiary epilepsy centers over a period of 4 years—a total of 123 patients were observed to have tonic seizure manifestations during at least one of their video–EEG recorded seizures. The vast majority of these patients had extratemporal epilepsy. Tonic seizures more frequently involved both sides of the body (76% bilateral vs. 24% unilateral). Importantly, when seen at the beginning of the seizure evolution, tonic seizures were more frequently associated with frontal lobe epilepsy as compared to epilepsy arising from the posterior neocortex. Furthermore, auras were more likely to precede tonic seizures originating from the parietooccipital regions and were less frequently reported in frontal

lobe epilepsy (104).

Stimulation of the SSMA elicits bilateral, asymmetric tonic contractions affecting primarily the more proximal muscles. Less frequently, focal tonic contractions may be seen. The symptomatogenic zone is less clear in cases of symmetric, bilateral tonic seizures. However, these seizures are believed to be generated by simultaneous bilateral activation of Brodmann area 6, rostral to the precentral region, in both hemispheres (31). It is also possible that generalized tonic seizures result from direct activation of brainstem reticular-activating systems (105,106). The fact that slow-wave and rapid eye movement (REM) sleep, as well as decreased levels of vigilance, appear to facilitate some tonic seizures, for example, in patients with Lennox–Gastaut syndrome, further implicates the brainstem in the generation of these phenomena (107). It becomes evident that different types of tonic seizures utilize different neuroanatomical pathways, which is hardly surprising given that tonic seizures may be a common clinical manifestation resulting from a variety of different pathophysiologies underlying symptomatic and less frequently idiopathic epilepsies.

Nonepileptic focal tonic symptoms can result from subcortical pathology (e.g., spinal cord or brainstem dysfunction in the case of compression or multiple sclerosis). In addition, paroxysmal tonic phenomena may be seen as part of certain movement disorders (such as paroxysmal choreoathetosis or spasmodic torticollis) or other nonepileptic paroxysmal disorders (e.g., in the setting of convulsive syncope) (101).

Oculocephalic Deviation and Versive Seizures

Foerster and Penfield first described versive seizures in 1930. The seizures consist of a sustained, unnatural turning of the eyes and head to one side, as a result of a predominantly tonic contraction of head and eye muscles (108). Although consciousness is often lost by the time a patient experiences version, occasionally, patients may be aware of the forced, involuntary head and eye deviation (45,109).

As discussed, cortical stimulation studies have confirmed the functional location of eye movement sites in proximity to the primary motor representation of the arm and face (74). On stimulating this region, Rasmussen and Penfield (110) observed that the more anterior points were responsible for contralateral rotation. Stimulation of more posterior points (closer to the central sulcus) elicited contralateral, ipsilateral, or upward eye movements. Head rotation was usually seen in conjunction with contralateral eye rotation.

The lateralizing significance of oculocephalic deviation has met with controversy. Indeed, a number of authors use the terms head turning and head version interchangeably (111–113). This lexical ambiguity prompted Wyllie et al. (108) to restrict the term version to “unquestionably forced, involuntary head and eye deviation to one side resulting in sustained unnatural positioning of the head and eyes.” In this important study, the authors reviewed retrospectively all lateral head and eye movements observed during 74 seizures in 37 patients and classified as “nonversive” any mild, unsustained, wandering, or seemingly voluntary head and eye movements. Visual analysis of video recordings was performed without prior knowledge of EEG findings. By adhering to the strict definition of “version,” the authors showed that the presence of a contralateral versive head and eye movement provides reliable lateralizing information (especially when this movement precedes secondary generalization) (108). On the other hand, one should be cautious about interpreting the direction of eye and head turning, if the seizure does not become secondarily generalized (114,115).

Version may result from seizures originating from various locations and spreading to the PreMC.

A noteworthy clinical observation is that extratemporal seizures give rise to version earlier in the seizure (within 18 seconds from seizure onset), compared with seizures of temporal lobe origin (in which version is usually seen after 18 seconds or later) (114).

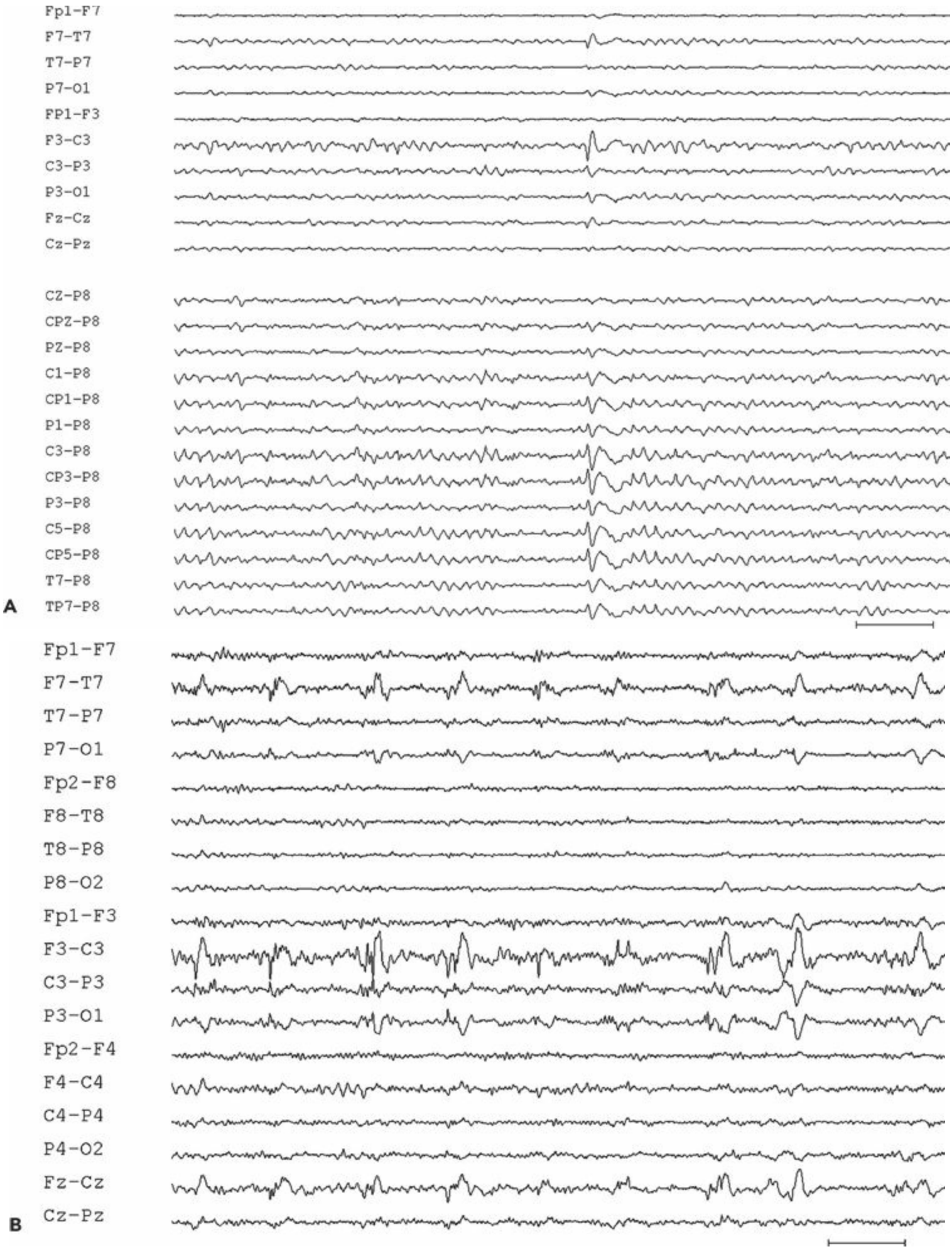
Seizures Manifested by Vocalization or Arrest of Vocalization

Several types of utterances can occur during epileptic seizures. A prolonged continuous or interrupted vocalization may occur in seizures involving the SSMA or lower PMA on either hemisphere (61). Vocalization, when it occurs as part of SSMA seizures, tends to be more sustained (116). Penfield and Jasper produced such phonatory phenomena in humans by stimulating the SSMA or the PMA below the lip or tongue area (41). Finally, the so-called epileptic cry is frequently seen at the onset of generalized tonic–clonic seizures.

Speech arrest, defined as inability to speak during a seizure despite conscious attempts by the patient (45), may result from involvement of the PMA (117) or SSMA in either the dominant or the nondominant hemisphere. Electrical cortical stimulation studies suggest that the speech arrest observed in cases of SSMA stimulation represents a negative motor response (resulting from inhibition of tongue movement) (118).

EEG Findings

The ability of scalp EEG to detect interictal activity depends on the extent of the irritative zone and the orientation of the dipole. Special techniques may be required to demonstrate epileptiform activity in patients with focal seizures. Sleep recordings, for example, have been reported to increase the yield of interictal epileptiform abnormalities (119–121). Special electrodes (such as sphenoidal, anterior temporal, or ear electrodes) and closely spaced additional scalp electrodes (Fig. 11.9A) may help to distinguish temporal from frontal foci and determine whether the electrical field of a midline sharp wave is higher over the left or right hemisphere (122–124).


Fp1-F7
F7-T7
T7-P7
P7-O1
FP1-F3
F3-C3
C3-P3
P3-O1
Fz-Cz
Cz-Pz
CZ-P8
CPZ-P8
PZ-P8
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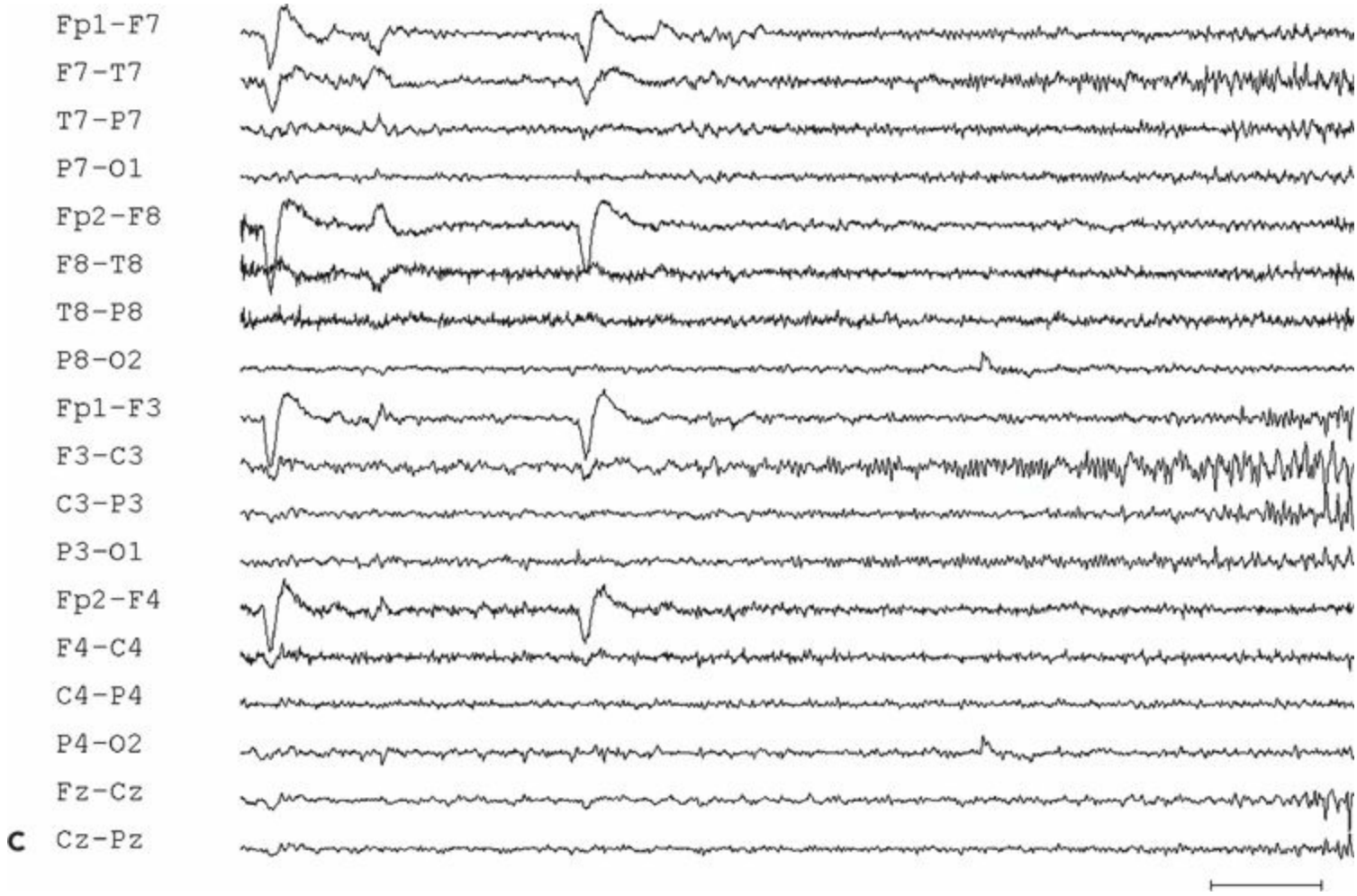


Figure 11.9. Scalp-EEG tracings (**A**, **B**, and **C**) from a 41-year-old patient with intractable left perirolandic epilepsy of unknown etiology since age 11 years. He presented with daily focal motor seizures involving the right leg and shoulder sometimes preceded by a somatosensory aura (tingling sensation in the right foot) and rare secondarily generalized tonic–clonic seizures. **A:**Interictal left centroparietal sharp wave as seen on a longitudinal bipolar (upper part) and referential montage (lower part). The P8 reference derivation of the sharp wave shows maximum negativity at electrode CP3. The addition of closely spaced surface electrodes (placed according to the 10–10 electrode placement system) provides for a more accurate distribution map. In this instance, the potential amplitude at electrode C5 is 85% and at electrodes C3 and CP3 is 83% of the amplitude recorded at the maximally involved electrode CP3. **B:** Periodic epileptiform discharge-like (PLED-like) pattern of left centroparietal sharp waves and polyspikes. This interictal finding was present during the first 24 hours of admission for acute exacerbation of his habitual focal motor seizures. **C:**The ictal onset is punctuated by the appearance of evolving low- to high-amplitude paroxysmal fast activity arising from the left centroparietal region.

Small epileptogenic foci may be entirely missed with interictal (and even ictal) surface EEG recordings (see Fig. 11.8). On the other hand, interictal epileptiform abnormalities may have a misleadingly widespread appearance because of the large distance and intervening cortical area that separates the epileptogenic zone from the scalp EEG electrodes (125).

Random EEG tracings in patients with focal epilepsy may not show evidence of focal epileptiform activity. In a case series of 19 patients with refractory frontal lobe epilepsy, Salanova and associates reported absence of interictal sharp waves in 7 of 19 (37%) patients (126). Secondary bilaterally synchronous discharges may be seen in up to two-thirds of patients with frontal lobe epilepsy (127). EEG interpretation should take into account the possibility of "secondary bilateral synchrony," a term introduced by Tükel and Jasper to describe the bilateral discharges seen in patients with parasagittal epileptogenic lesions (128).

Ictal recordings may show regional seizure patterns (Fig. 11.9C) or may have limited localizing or lateralizing value. As a rule, the patterns are more widespread and more difficult to lateralize compared with those seen with seizures of temporal lobe origin. Studies show that ictal EEG may be

nonlocalizing in more than half of patients with frontal lobe epilepsy (126,129). False localization may occur with an erroneous temporal ictal pattern on surface EEG as a result of underlying frontolimbic connections (125).

Particular EEG patterns may sometimes be seen in relationship to the corresponding seizure type: generalized tonic seizures, for example, may be associated with ictal EEG activity, which consists of repetitive rhythmic spiking of variable frequency (8 to 25 Hz, or faster) and amplitude (130). More recently, investigators have been able to ascertain the presence of gamma rhythms in the frequency range of 50 to 100 Hz associated with generalized tonic seizures during scalp EEG recordings in patients with Lennox–Gastaut syndrome (131).

Invasive recordings using subdural electrodes in frontal lobe epilepsies may only show evidence for a focal onset in a relatively small number of patients; often, a more diffuse "regional" pattern may be seen (126,132). This, of course, depends on the nature, location, extent, and connectivity of the underlying epileptogenic substrate and its relationship to the recording electrodes. In a careful invasive study of patients presenting with circumscribed focal clonic seizures, investigators observed that these seizures were always associated with a localized polyspike-and-wave intracranial ictal EEG pattern involving the subdural electrodes overlying the PMA, while neighboring subdural electrodes not overlying the precentral gyrus showed various other ictal patterns (133). Such ictal patterns associated with focal clonic seizures may occasionally be discernible by scalp EEG recordings.

EPILEPSIA PARTIALIS CONTINUA

Status epilepticus can be broadly divided into status epilepticus with motor or without motor phenomena (134). Subcategories of motor status epilepticus include generalized and secondarily generalized status, as well as focal motor status epilepticus. The latter is characterized by repetitive typical somatomotor seizures with or without jacksonian march originating from the perirolandic region. This condition may occur at the onset or during the course of epilepsies manifesting with focal motor seizures. Consciousness is usually preserved, and cerebral function of the uninvolved cortex remains intact. A variety of motor phenomena may be observed in the context of focal motor status ranging from overt to more subtle motor manifestations, such as epileptic nystagmus, for example, which may be seen in patients with oculoclonic status epilepticus (135,136).

Epilepsia partialis continua of Kojevnikov (EPC or partial continuous epilepsy) constitutes one form of focal motor status epilepticus, characterized by localized unremitting myoclonus. The condition was first described by Kojevnikov in 1895 as a disorder of persistent localized motor seizures (137). In published literature, EPC has been referred to as "Kojevnikov," "Kojewnikow," or "Kozhevnikov" syndrome.

Clinical Semiology

EPC has been regarded by some as "the semiologic epitome of a focal seizure" (138), as it usually involves a restricted area of the motor cortex of one hemisphere and presents with clinically localized motor manifestations. EPC is defined by the occurrence of almost continuous and rhythmic or semirhythmic muscular contractions (myoclonic jerks) that remain localized to a limited area on one side of the body and persist for hours, days, or even years (139,140). The definition has undergone several revisions in the past, reflecting differences of opinion among various authors. In

1989, the ILAE Commission defined EPC as a specific form of continuous somatomotor seizures involving the Rolandic cortex (141). Any muscle group may be involved, but distal musculature is more commonly affected. The myoclonic jerks may appear isolated or in clusters, with a regular or irregular occurrence at a frequency of 1 to 2 per second. In general, unilateral involvement with synchronous activation of agonists and antagonists is observed. The jerks are predominantly seen involving the muscles of the upper half of the body. In a study of 151 patients presenting with EPC, the authors observed that during its course, the disease involved the head in 16% of patients, the head and upper limb in 14%, the upper limb only in 40%, the trunk in 5%, the lower extremity in 14%, and the whole side of the body in 11% (142).

By definition, the jerks are spontaneous, although they may be aggravated by physical activity, psychic exertion, and/or sensory stimuli (143). In most cases, the jerks may be reduced in amplitude but persist during sleep (144,145). Other seizure types (such as jacksonian or generalized seizures) and a variety of neurologic deficits may be seen in these patients depending on the underlying etiology.

The pathophysiology of EPC is not well understood. It has been postulated that the absence of seizure propagation is associated with the specific anatomical location of the epileptic focus within a neocortical area of sufficiently preserved inhibition. Virtually, all authors today agree that involvement of the PMA is indispensable for the generation and sustainment of EPC (146). Bancaud and coworkers divided EPC into two broad categories based on the presence (type 2) or absence (type 1) of a progressive brain lesion (139): Type 1 was associated with a regional nonprogressive lesion in the sensorimotor cortex, whereas type 2 was typically seen in the setting of Rasmussen syndrome.

EPC may develop at any age. The usual etiology of EPC is a focal lesion involving the cortex (principally the sensorimotor cortex) that results from stroke, trauma, infection, metastasis, or primary tumor. A hypoxic, metabolic, or septic encephalopathy may predispose patients with a preexisting focal lesion to develop EPC. All patients presenting with EPC should be carefully evaluated for an underlying lesion that may be amenable to curative resective surgery. In one series, EPC was caused by a variety of different pathologens, including inflammatory and immune-mediated (52%), metabolic (13.7%), structural brain abnormalities (11.8%), cryptogenic (7.8%), vascular (5.9%), dual (5.9%), and postoperative (2%) causes (147). EPC is, of course, a common manifestation of Rasmussen syndrome (seen in almost 50% of cases) (148). Despite its focal expression, EPC in Rasmussen syndrome may be associated with MRI and EEG evidence of more diffuse hemispheric abnormalities. In the UK series of 36 patients from ages 1 to 84 years, who presented with EPC over the period of 1 year, the commonest isolated etiology was Rasmussen syndrome in seven (19%; five were children), followed by stroke in five (14%). In seven patients, the cause of their presentation remained undetermined (140). EPC and its variants have also been reported in the setting of multiple sclerosis (149), human immunodeficiency virus infection (150,151), Creutzfeldt–Jakob disease (152), and other neurodegenerative diseases such as mitochondrial disorders (153,154) or Alpers syndrome (155).

Focal motor seizures or EPC, or both, may be the presenting feature of nonketotic hyperglycemia or may occur as a later complication, especially in the presence of an underlying focal cerebral lesion (156). Hyperglycemia, hyponatremia, mild hyperosmolarity, and lack of ketoacidosis were found to contribute to the development of EPC predominantly in areas of preexisting focal cerebral damage in 21 patients with evidence of nonketotic hyperglycemia (157). One should note, however, that EPC has also been reported in the setting of ketotic hyperglycemia (140,158). Depending on the etiology,

EPC may be an early or late feature in the course of the underlying disease and may be seen either in isolation or in association with other seizure types (159). Similar to EPC, focal somatomotor status may reflect an underlying focal brain lesion (secondary to a vascular, neoplastic, traumatic, or infectious etiology) or may present in the context of toxic–metabolic abnormalities. In patients without preexisting epilepsy, the onset of focal motor status may signify underlying "asymptomatic" ischemia or interterritorial cerebral infarction (infarction in watershed territories).

Subcortical or spinal myoclonus and certain forms of tremor and other extrapyramidal movement disorders should be considered in the differential diagnosis of EPC. Clinical differentiation is often challenging, and special neurophysiologic examinations may be necessary (159,160).

EEG Findings

The conventional scalp EEG may be unrevealing or misleadingly normal. There may be very few or no paroxysmal abnormalities; and the background rhythm may be normal. In some cases, time-locked EEG events preceding the EPC-associated myoclonic jerks can be detected by back averaging. In addition, special stereoencephalographic or electrocorticographic recordings may prove helpful in resolving the underlying spike focus.

In other cases, irregular 0.5- to 3-Hz slowing may be seen in the frontocentral region along with reduction of the beta activity in the same area (45), but there are no characteristic EEG findings to aid in the diagnosis of EPC. In a study of 32 cases, the most common EEG finding was regional spiking (144). Other abnormalities included bursts of sharp waves or spike-and-wave discharges and unilateral or bilateral runs of abnormal rhythms. In a study of 21 adults presenting with EPC, the authors found EEGs to be abnormal in all but one patient. Each patient underwent at least two EEGs in the course of the disease; consequently more than one pattern was seen in some patients. The most common EEG finding was the presence of unilateral lateralized and/or localized spike or sharp wave discharges in ten patients (48%). Other lateralized abnormalities ranged from periodic lateralized epileptiform discharges (PLEDs) in three, paroxysmal slow-wave activity in two, and lateralized continuous slow activity in four patients. Four patients exhibited diffuse, continuous slow activity, one showed paroxysmal generalized slow-wave activity, and one patient had periodic generalized epileptiform discharges (161). In this study, only seven patients (33%) were found to have epileptiform discharges during EPC that correlated to the myoclonic jerks.

On rare occasions, PLEDs and PLED-like patterns that are time locked to the jerks are observed in the course of EPC (162). PLEDs are commonly viewed as a transient interictal pattern (see Fig. 11.9B), which usually disappears within a few days, but may last as long as 3 months or longer (163). PLEDs can occur in a variety of structural and metabolic disorders usually of acute or subacute nature (164,165). It is important to note that depending on the clinical scenario, there are occasions when PLEDs in fact represent an ictal EEG pattern (166). Furthermore, one should not overlook the common occurrence of seizures in association to the presence of PLEDs on EEG recordings—seizures have been reported to occur with a frequency ranging from 58% to 100% in some studies (164). The most common seizure type seen in the presence of PLEDs is focal motor seizures affecting the contralateral body (167), often presenting as status epilepticus or as repetitive focal motor seizures (164,167,168).

In Rasmussen encephalitis, it is important to identify and document MRI evidence of progressive atrophy, which usually involves only one hemisphere. An abnormal EEG with progressive regional or lateralized slowing and ipsilateral regional or multiregional spiking is the rule. In a case report of an

11-year-old girl with Rasmussen syndrome, and a 5-month history of EPC, fluorodeoxyglucose positron emission tomography (FDG-PET) studies demonstrated an area of hypermetabolism in the right central cortex and ipsilateral thalamus. A congruent sharp wave focus was present in the same region on scalp EEG recordings. Using simultaneously recorded EMG of the left tibialis anterior muscle, the authors demonstrated regular jerks, time locked with the right central sharp waves (169). With time, the EEG abnormalities of Rasmussen encephalitis may become bilateral or more widespread, multiregional, or synchronous suggesting progression of a more diffuse process than indicated by the clinical manifestation of EPC.

SUPPLEMENTARY SENSORIMOTOR SEIZURES

Clinical Semiology

Seizures arising from the SSMA are of brief duration, usually lasting only 10 to 40 seconds. Rapid onset of asymmetric tonic posturing involving one or more extremities is characteristically observed (52,170). While it is common for both sides of the body to be affected simultaneously, unilateral tonic motor activity may occur (171). The typical seizure is frequently referred to as a bilateral asymmetric tonic seizure.

Speech arrest and vocalization are common. Somatosensory symptoms, such as numbness, tingling, or pressure sensation, may precede the phase of tonic posturing (41); these body sensations are not well localized in contradistinction to somatosensory symptoms that result from epileptic activation of the postcentral gyrus (172). Common descriptions include a feeling of tension, pulling, or heaviness in an extremity or a sense that the extremity is "about to move" (173). In addition, the sensation of either an urge to perform a movement or an anticipation that some movement is about to occur has been reported in response to electrical stimulation (62). Although consciousness is usually preserved, patients may not be able to respond verbally during the tonic phase. Toward the end of the seizure, a few rhythmic clonic movements of the extremities may be observed (173). Postictal confusion is absent in the majority of SSMA seizures.

Asymmetric involvement of the upper extremities usually manifests with abduction at the shoulders, flexion of one elbow, and extension of the other upper extremity. As a rule, the lower extremities are also involved in the tonic posturing, with abduction at the hips and flexion or extension at the knees (52). Even patients, in whom tonic posturing appears to be unilateral, have bilaterally increased (or decreased) tone (34).

In their original report and illustrations of "somatic sensory seizures" arising from the SSMA, Penfield and Jasper (41) described head turning to the side of the flexed upper extremity. They observed that the head and eyes appear as if looking toward the flexed and raised arm with the patient adopting the so-called fencing posture—a motor response reminiscent of the asymmetric tonic neck reflex (34). Ajmone-Marsan and Ralston (174) subsequently coined the term "M2e" to describe the abduction and elevation of the contralateral arm with external rotation at the shoulder and slight flexion at the elbow. The patient's head and eyes deviate as if looking at the raised arm, while both lower extremities remain extended or slightly flexed at the hips and knees.

In contrast to these early reports, further analysis of SSMA seizures showed that assumption of the classic "fencing" or "M2e" posture is not common (103,175). Among the less common motor manifestations, coarse movements of the tonic postured extremities may be observed (176). If present,

vocalization may be prominent during the tonic phase reflecting the tonic involvement of the diaphragm and laryngeal muscles, which contract against semiclosed vocal cords (173).

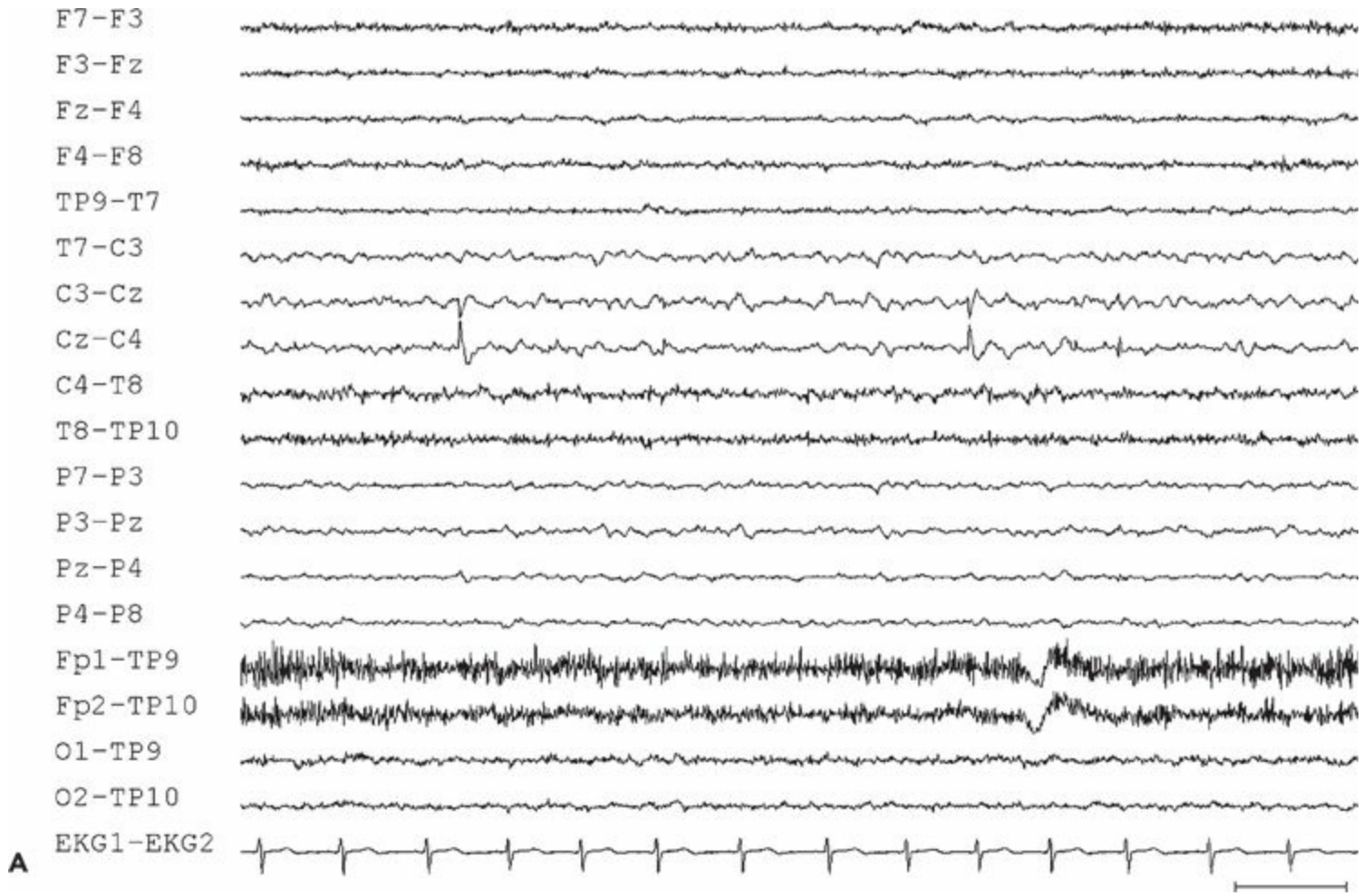
Ictal activity may spread to involve the PMA of the face on the dorsolateral convexity, resulting in unilateral clonic movements or contralateral head version. Secondary generalization may lead to a generalized tonic–clonic seizure. Clonic movements can be seen toward the end of the tonic seizure (173). Unusual hyperkinetic automatisms (involving the ipsilateral upper extremity) have been described with seizures involving the SSMA (177). Finally, writhing movements may be seen as some patients attempt to move around or sit up during the tonic seizure.

SSMA seizures may be frequent (up to 5 to 10 per day) and can occur in clusters. They tend to occur predominantly during sleep (172,178). In a systematic review of their relationship with sleep, almost two-thirds of a total of 322 SSMA seizures in 24 patients occurred during sleep, almost exclusively during non–rapid eye movement (NREM) sleep stages I and II—as demonstrated by video–EEG recordings (179).

It should be emphasized that only a minority of patients with seizures displaying the clinical features of SSMA activation ("SSMA seizures") actually have "SSMA epilepsy" (180). In most cases, the SSMA functions as the symptomatogenic zone: the observed seizures reflect the expression of ictal discharges originating from clinically silent regions that have anatomical or functional proximity to the SSMA, such as the basal frontal regions, the dorsolateral convexity of the frontal lobe, and the mesial parietal regions (52). This important point is illustrated by a recent stereo-EEG study of 14 patients with intractable focal epilepsy presenting with SSMA seizure semiology. Invasive EEG recordings showed evidence of seizure origin within the SSMA region in only six (43%) patients. The eight remaining patients were found to have diffuse unilateral or bilateral seizure onset. The authors concluded that SSMA semiology is suggestive of early involvement of this region, but is by no means a reliable indicator that the SSMA itself contains the seizure focus (181). Consequently, the SSMA itself may not need to be sacrificed in patients presenting with intractable SSMA seizures. Moreover, unless the location of the epileptogenic focus/generator has been carefully defined, resection of the SSMA may not be associated with a favorable postoperative outcome (182). Furthermore, the clinical picture of SSMA seizures with involvement of all four extremities and simultaneous preservation of awareness may be misleading, and it is not unusual for patients with this type of paroxysmal activity to be misdiagnosed as having psychogenic nonepileptic seizures (116). Of note, stereo-EEG (SEEG) studies now also suggest involvement of the SMA in startle seizures. Three patients with startle seizures became seizure free after epilepsy surgery in the SMA (183). In these patients resection was guided by SEEG suggesting prominent but not exclusive involvement of the SMA in startle seizures (183).

EEG Findings

Interictal sharp waves, when present, are usually found at the midline, maximum at the vertex, or just adjacent to the midline in the frontocentral region (Fig. 11.10A). Only 50% of 16 patients with supplementary sensorimotor seizures, who underwent evaluation with subdural electrodes, had shown scalp EEG evidence of midline frontocentral interictal epileptiform activity (184).


F7-F3
F3-Fz
Fz-F4
F4-F8
TP9-T7
T7-C3
C3-Cz
Cz-C4
C4-T8
T8-TP10
P7-P3
P3-Pz
Pz-P4
P4-P8
Fp1-TP9
Fp2-TP10
O1-TP9
O2-TP10
EKG1-EKG2
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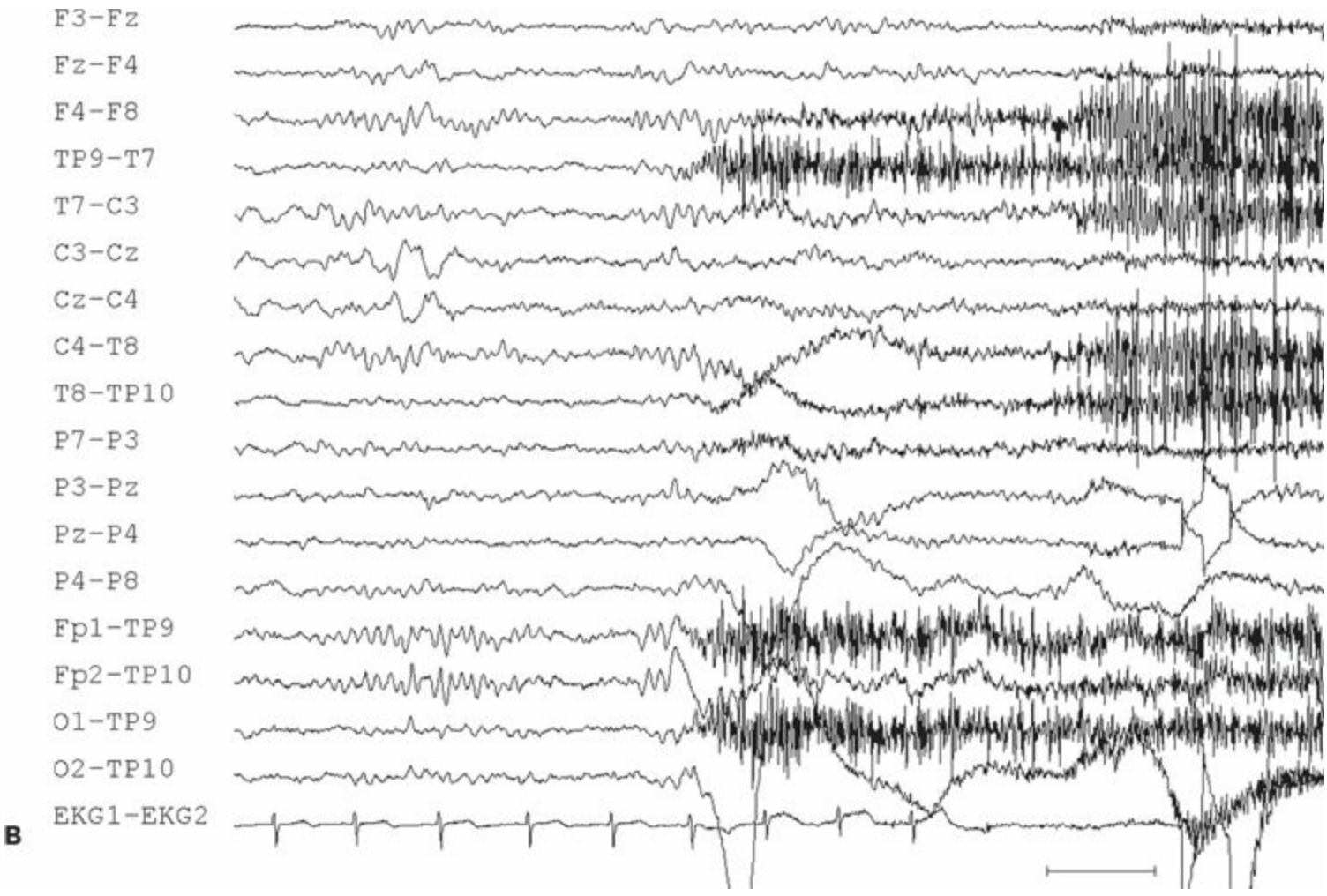
F3-Fz
Fz-F4
F4-F8
TP9-T7
T7-C3
C3-Cz
Cz-C4
C4-T8
T8-TP10
P7-P3
P3-Pz
Pz-P4
P4-P8
Fp1-TP9
Fp2-TP10
O1-TP9
O2-TP10
EKG1-EKG2
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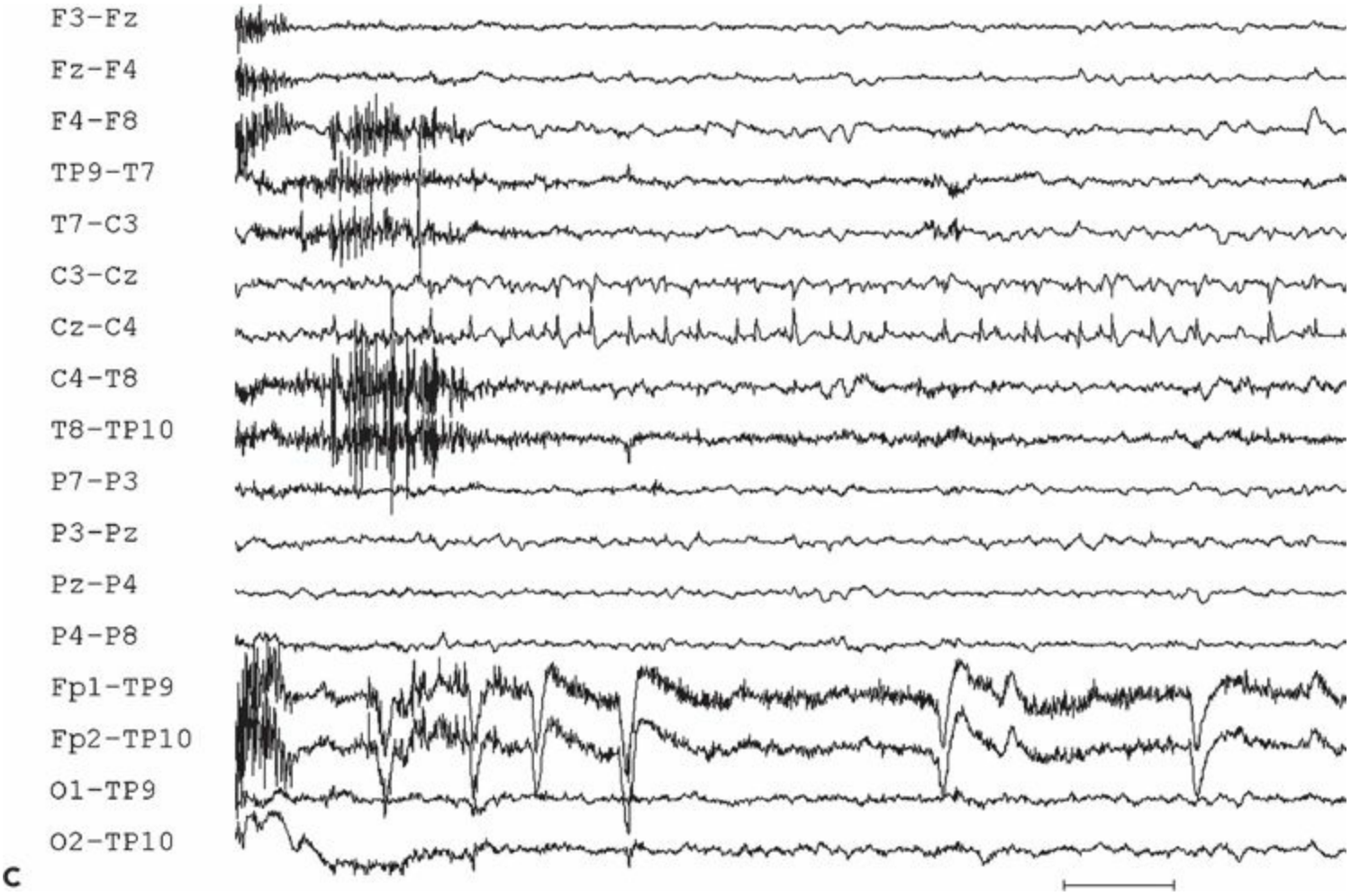

Figure 11.10. Interictal (**A**) and ictal (**B** and **C**) scalp electroencephalogram tracings with a transverse bipolar montage from a 12-year-old girl with left SSMA epilepsy. Bilateral asymmetric tonic seizures arising from sleep and wakefulness were captured during video–electroencephalograph evaluation. **A:**This awake recording shows sharp waves at the vertex (virtually confined to the Cz electrode). Note that the potential amplitude is slightly higher on the left (C3) than on the right (C4) central electrode. **B:**Clinical onset of typical seizure occurring out of sleep coincides with the appearance of bilateral myogenic artifact. Scalp EEG does not reveal a clear ictal pattern at the time of clinical onset. **C:** Rhythmic, repetitive sharp waves are present at the vertex within 15 seconds of clinical onset.

It is important to distinguish midline interictal epileptiform discharges from vertex sharp transients of sleep. This distinction may not be possible, when sharp waves are seen only during sleep. The presence of prominent after-going slow waves, occurrence of polyspikes, and/or consistently asymmetric distribution of the electrical field may raise the suspicion of epileptiform activity (184,185). In general, normal sleep-related transients display a symmetric field pattern, whereas midline sharp waves may be asymmetric. Appearance of the same midline sharp waves or spikes during wakefulness (see Fig. 11.10A) will lead to the correct diagnosis of underlying epilepsy.

During seizures originating from the SSMA (Fig. 11.10B), the EEG is frequently obscured by prominent EMG artifact owing to the associated tonic activity and the midline location of the ictal EEG discharges. However, careful review of the vertex region with the appropriate (usually transverse bipolar) montage and use of closely spaced parasagittal scalp electrodes may reveal the ictal EEG pattern despite considerable EMG artifact. Frequently, an initial high-amplitude slow transient or sharp wave may be seen at the vertex followed by midline low-amplitude fast activity or an electrodecremental pattern (173,185). These early changes are often followed by the development of high-amplitude rhythmic slowing distributed bilaterally in the frontocentral regions. Ictal activity

may remain restricted to the vertex (Fig. 11.10C) or have a more widespread distribution. In general, the lateralizing value of such ictal EEG changes is rather limited. Moreover, paradoxical, erroneous scalp-EEG lateralization is possible, when the generator of sharp waves is situated in the interhemispheric fissure producing a transverse or oblique dipole orientation (186). Lastly, a small percentage of patients with SSMA seizures will have no identifiable scalp EEG change during the ictus.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of focal motor seizures includes nonepileptic myoclonus (187) or tonic spasms (188,189), psychogenic nonepileptic seizures, complex motor stereotypies/tics (190), and other paroxysmal movement disorders such as paroxysmal choreoathetosis (191) and tremor (192).

As mentioned, the absence of abnormalities on outpatient EEGs does not exclude the possibility of focal motor seizures. When available, home videotape recordings can provide valuable diagnostic information by capturing the episodes in question. Otherwise, prolonged inpatient video–EEG monitoring may be necessary. Patients who present with infrequent attacks of unclear etiology pose considerable diagnostic challenges, given the low diagnostic yield of prolonged EEG recordings. Ambulatory EEGs are not particularly helpful in this setting, especially if no ictal EEG patterns are seen during the paroxysmal behavior.

Seizures arising from the frontal lobe can be bizarre (such as seizures characterized by prominent thrashing movements and preserved consciousness) and may be misdiagnosed as nonepileptic seizures of psychogenic origin. The reverse can also be true. Saygi et al. (193) compared the ictal manifestations of 63 frontal lobe seizures in 11 patients with the clinical features of 29 psychogenic seizures in 12 patients. The authors did not find any single clinical criterion that would sufficiently differentiate these two groups. Seizure characteristics favoring an epileptic diagnosis included younger age at onset, stereotyped patterns of movements, turning to a prone position during seizures, shorter duration of seizures, nocturnal occurrence, and the presence of MRI and EEG abnormalities. In another study, which only compared the clinical features of SSMA and nonepileptic seizures, the duration of SSMA seizures was much shorter than that of psychogenic events (116). None of the SSMA seizures lasted longer than 38 seconds, whereas psychogenic seizures had a mean duration of 173 seconds. In addition, SSMA seizures occurred predominantly out of sleep, whereas psychogenic seizures usually occurred from the waking state.

Epileptic motor seizures may manifest themselves at any time of the day or night. However, a number of epilepsy syndromes (including SSMA epilepsy, frontal lobe epilepsy, benign focal epilepsy of childhood, generalized epilepsy, and autosomal dominant nocturnal frontal lobe epilepsy [ADNFLE]) tend to manifest with seizures occurring predominantly during sleep. In addition, sleep-related paroxysmal motor phenomena can be seen with various sleep disorders (including NREM arousal disorders, REM behavior disorder of sleep, and sleep–wake transition disorder). The differential diagnosis of such nocturnal paroxysmal events is broad and often challenging, given the frequently poor clinical description and overlap of clinical manifestations (194).

It is not understood why certain seizure types occur preferentially during sleep (195). In a study of patients with intractable focal epilepsy, continuous video EEG and polysomnography were used to compare sleeping–waking distribution of seizures and quality of sleep organization in 15 patients with frontal lobe epilepsy and 15 patients with temporal lobe epilepsy (196). The authors demonstrated that seizures of frontal lobe origin occurred more frequently during the night compared

with seizures arising from the temporal lobe in this group of patients with pharmacoresistant epilepsy.

More recently, ADNFLE has been identified as a distinctive clinical syndrome (197,198). The disorder is characterized by clusters of brief nocturnal motor seizures with hyperkinetic or tonic manifestations. Stereotyped attacks are frequently seen in individual family members despite the significant intrafamilial variation. Interictal EEGs are frequently normal, and the diagnosis is established on a clinical basis. Seizures usually begin in childhood and may persist throughout life, although the overall seizure frequency tends to decrease over time (197). A strong linkage with the neuronal nicotinic acetylcholine receptor has been established in the years following initial description of this syndrome (199,200).

Several case reports highlight the unusual occurrence of repetitive involuntary movements in the setting of transient cerebral ischemia (the so-called limb-shaking transient ischemic attacks or "limb-shaking TIAs") that may be mistaken for focal motor seizures (201–203). These episodic attacks are often precipitated by standing up or walking and seem to involve only the limbs (hand–arm alone or hand–arm and ipsilateral leg) without spreading to the facial or truncal musculature (201,204). The need to recognize these paroxysmal positive motor manifestations as a sign of severe contralateral carotid occlusive disease is emphasized (201,202).

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CHAPTER 12 FOCAL SEIZURES WITH IMPAIRED CONSCIOUSNESS

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Awareness and responsiveness are the two sides of the coin characterizing a clinically applicable definition of consciousness as proposed by the International Classification of Epileptic Seizures (ICES) (1). These two concepts are intimately related, but it is important to recognize that they are essentially distinct: while consciousness as a whole is clearly impaired in epilepsy patients, who are completely unresponsive during their spells and are later amnestic of their events, the question is a bit more controversial in other cases. For example, we know now that up to 10% of patients with right temporal lobe epilepsies may be fully responsive and interactive during focal seizures associated with automatisms and yet not be able postictally to recall any of the events that occurred during the seizure (2,3). Conversely, some patients may not obey any commands during a seizure but do recall when interviewed postictally all the commands and instructions given during the ictus. This may be seen with several possible scenarios including ictal aphasia, inability to perform voluntary movements secondary to stimulation of negative motor areas, or diversion of attention by a hallucinated experience (4). These examples illustrate the conceptual complexity of assessing consciousness in relation to epileptic seizures and highlight the practical importance of a thorough seizure and postseizure interview while patients are being evaluated in epilepsy clinics and video-EEG monitoring units. Recently, some epilepsy centers have even proposed the use of a standardized "consciousness inventory" to assess the level and content of ictal consciousness (5,6). For the purposes of this chapter, we used the term "focal epilepsy with impaired consciousness" to refer to focal epilepsies where either responsiveness or awareness/recall is disturbed during the ictal period.

Another issue that needs to be spelled out prior to proceeding with this discussion of epilepsy and consciousness would be a clear definition and distinction of the following terms: "complex partial seizure," "dialeptic seizure," and "automotor seizure." The ICES defined "complex partial" as any seizure consisting of a lapse of consciousness and minimum motor activity if the ictal EEG shows focal epileptiform activity. A seizure with exactly the same symptomatology or "semiology" would be classified as an "absence seizure" if the ictal EEG shows generalized spike–wave complexes. The terms complex partial and absence referred therefore to electroclinical complexes where both clinical semiology and knowledge of the ictal EEG patterns—information that is not necessarily always available in an initial outpatient evaluation—are required for an accurate definition. Furthermore, the broad umbrella of "complex partial" seizures encompassed various seizure types that have little in common, except a focal onset. For example, partial seizures arising from the perirolandic region or supplementary motor area may involve impairment of consciousness but are very different from complex partial seizures arising from the mesial temporal lobe with an aura of déjà vu, staring, unresponsiveness, and stereotyped oroalimentary and hand automatisms. These issues lead to the proposition of a five-tier classification system that distinguishes the seizure characteristics (including semiologic features and frequency) of a given patient from the epilepsy

characteristics (including etiology, associated neurologic deficits, and location of the epilepsy, as determined through various diagnostic modalities including EEG and imaging) (7). In this semiologic classification, a seizure is defined solely based on its clinical characteristics. A "dialeptic" (from the Greek word "dialeptin" meaning "to stand still," "to interrupt," or "to pass out") seizure is one with impairment of consciousness as the predominant feature. An "automotor" seizure would be one with predominant automatisms regardless of whether consciousness was impaired or not.

More recently, the International League Against Epilepsy's (ILAE) Commission on Classification and Terminology has eliminated the distinction between "complex partial" and "simple partial" seizures, retaining a single classification of "focal seizures." In this framework, impaired consciousness is equated with other seizure descriptors in its value for performing an accurate seizure characterization and classification (8). This proposal has been controversial as many value the traditional and historical implications of the term "complex partial" seizure (9–12). In this chapter, we use the general term of focal seizures with impaired consciousness, as well as the more specific terms of dialeptic and automotor seizures when a distinction between the two is needed.

In the following sections, we first provide a brief historical overview and briefly discuss features that allow differentiation of focal from generalized seizures causing an impairment of awareness. Then, we focus on characterizing the localizing value of focal seizures with impaired consciousness and discuss lateralizing features that may help in further defining the epileptogenic focus. We then describe typical electroencephalographic findings and conclude with a section on the proposed mechanisms of impaired consciousness in partial epilepsy.

HISTORICAL BACKGROUND

Although descriptions of seizures with loss of consciousness and automatisms suggesting focal origin date to the days of Hippocrates, Galen, and Areatus. Hughlings Jackson first suggested their origin in the temporal lobe and called them "uncinate fits" (13). The introduction of the EEG in 1929 made it possible to identify the characteristic interictal and ictal features of these seizures. In 1937, Gibbs and Lennox proposed the term "psychomotor epilepsy" to describe a characteristic EEG pattern of temporal lobe seizures accompanied by mental, emotional, motor, and autonomic phenomena (14). Gibbs, Gibbs, and Lennox also noted interictal sharp waves in the temporal regions in patients with this seizure type. Penfield and Kristiansen (15) and Penfield and Jasper (16) observed that some patients with seizures and loss of consciousness had extratemporal sharp waves. Jasper et al. first pointed out that the localization of the EEG ictal discharge was more important than its actual pattern and that this pattern originated from "deep within the temporal lobes, near the midline" (17).

The early work of investigators at the Montreal Neurological Institute in Canada and in Paris, France, contributed immensely to our understanding of various types of epilepsy, including temporal and extratemporal, and used information from multiple techniques: scalp recordings, invasive recordings from depth electrodes and intraoperative corticography, and cortical stimulation studies (15,16,18,19). Ajmone-Marsan et al. (20–22) used chemical activation with pentylenetetrazol to study partial seizures from various locations. The Paris group (23) published a number of papers on frontal lobe epilepsy. Tharp (24) was the first to identify seizures with loss of consciousness arising from the orbitofrontal regions.

Early work on the symptomatology of focal seizures with impaired consciousness was based on eyewitness descriptions by family members, nurses, or physicians (18,22). Some studies employed cine film and analyzed photographs taken at 3 per second (20). The introduction of videotape

technology provided an inexpensive and effective way to easily record and play back seizures as often as needed, resulting in a better grasp of phenomenology. The observations of Delgado-Escueta, Theodore, Williamson, Quesney, Bancaud, and others vastly improved our understanding of focal seizures with impaired consciousness (25–30). Crucial insights were provided by Gastaut, who proposed the first ICES in 1970 (31).

In his 1983 monograph, Electroclinical Features of the Psychomotor Seizure, Wieser (32) described the order of symptom onsets and symptom clusters and attempted to correlate these clusters with electrographic activity recorded with depth electrodes. Maldonado et al. (33) also examined the sequences of symptoms in hippocampal–amygdalar–onset seizures. Using methods similar to those of Wieser, Kotagal examined temporal lobe psychomotor seizures in patients who were seizure free after temporal lobectomy (34). Similar methods also have been used to study frontal lobe seizures (35,36).

FOCAL VERSUS GENERALIZED SEIZURES WITH IMPAIRMENT OF CONSCIOUSNESS

Focal seizures with impairment of consciousness can present with or without an aura. The auras last from a few seconds to as long as 1 to 2 minutes before consciousness is actually lost. Impairment of consciousness is maximal initially. Partial recovery later in the seizure may allow the patient to look at an observer walking into the room or interact in some other way with the environment (34). Most of these seizures with automatisms last longer than 30 seconds—up to 1 to 2 minutes (sometimes as long as 10 minutes). Very few are briefer than 10 seconds, which helps to distinguish them clinically from typical absence seizures characterized by 3-Hz spike–wave complexes (29).

Blinking has been described more often in generalized absence as opposed to focal seizures with impaired consciousness. Automotor activity is not restricted to focal seizures, and subtle automatisms may be seen in typical absence (generalized) epilepsy (1). So, a clear distinction between dialeptic seizures seen in the setting of frontal or temporal lobe epilepsy from those in absence epilepsy may not be possible without obtaining an electrophysiologic confirmation and recording an ictal EEG (1).

LOCALIZING VALUE OF FOCAL SEIZURES WITH IMPAIRMENT OF CONSCIOUSNESS

Research during the past two decades has advanced our understanding of the symptomatology of focal seizures with impairment of consciousness arising from various locations (28,34). Most of these seizures arise in the temporal lobe; however, in at least 10% to 30% of patients evaluated in epilepsy surgery programs, the origin is extratemporal and most commonly in the frontal lobe (1).

Escueta et al. (29), described three types of complex partial seizures. Type I (24% to 30% of mesial temporal lobe seizures) begins with a motionless stare or behavioral arrest (phase 1) quickly followed by a period of unresponsiveness and stereotyped automatisms (phase 2) evolving to a final phase of a “clouded state” and semipurposeful reactive automatisms. Type II events are uncommon and similar to type I events except that phase I is absent. Type III complex partial seizures, previously called temporal lobe syncope, begin with a drop attack, followed by confusion, amnesia, and gradual return of composure (29). The localizing value of the motionless stare was believed to indicate mesial temporal lobe epilepsy (29). However, behavioral arrest is also seen in 20% of patients with

frontal lobe epilepsy (37). Types II and III are thought to be of extratemporal origin (38,39).

Different components of consciousness may be impaired depending on the location of the ictal seizure pattern. Frontal lobe seizures are more likely to manifest with loss of orientation behavior and expressive speech; left temporal lobe seizures lead to impairments of memory and expressive and receptive speech; and right temporal lobe seizures rarely involve impairment of consciousness (39).

Seizures of Frontal Lobe Origin

Seizures arising from the frontal lobes occur in up to 30% of patients with focal epilepsy and represent the second most common focal type after temporal lobe seizures (26). In 50% of patients with frontal lobe epilepsy, seizures are accompanied by loss of consciousness. Seizures with loss of consciousness can arise from various locations within the frontal lobe (except from the rolandic strip) (24,35,36,40). Semiologic features include occurrence in clusters, occurrence many times a day, occurrence for brief duration (lasting about 30 seconds with a sudden onset), and minimal postictal confusion. Bizarre attacks with prominent motor automatisms involving the lower extremities (pedaling or bicycling movements), sexual automatisms, and prominent vocalizations are common, and the seizures are remarkably stereotyped for each patient (35,36,38). Identification of seizure onset within the frontal lobe by semiology alone and differentiation of mesial temporal lobe epilepsy and frontal lobe epilepsy may be misleading and difficult; however, analysis of the earliest signs and symptoms, as well as their order of appearance, may allow this distinction in onset (35). Clonic seizures frequently arise from the frontal convexity, tonic seizures from the supplementary motor area, and automotor seizures from the orbitofrontal region (41). Seizures with "motor agitation" and hypermotor features are more likely to arise from the orbitofrontal and frontopolar regions, as opposed to seizures with oroalimentary automatisms, gesturing, fumbling, and looking around, which are more suggestive of a temporal lobe focus (35). In a surgical series of patients with intractable frontal lobe epilepsy, 14 of 26 patients had history of complex partial status epilepticus (41).

The unique symptomatology of supplementary motor seizures includes an onset with abrupt tonic extension of the limbs that is often bilateral but may be asymmetric and is accompanied by nonpurposeful movements of uninvolved limbs and vocalizations. Typically, these occur out of sleep and recur many times a night. Because of their bizarre symptomatology, they are sometimes mistaken for nonepileptic seizures. Consciousness is often preserved in supplementary motor area seizures, and postictally, baseline mentation returns quickly.

Cingulate gyrus seizures may also vary in semiology. Seizures arising from the anterior portion of the cingulate present with predominantly motor manifestations such as bilateral asymmetric tonic seizures, hypermotor seizures, and complex motor seizures, while posterior cingulate cortex epilepsies tend to predominantly have alterations of consciousness (dialeptic seizures) and automatisms of the distal portions of the limbs (automotor seizures) as the main clinical manifestations.

Orbitofrontal seizures manifest prominent autonomic phenomena, with flushing, mydriasis, vocalizations, and automatisms. The vocalizations may consist of unintelligible screaming or loud expletives of words or short sentences. Patients also may get up and run around the room.

Quesney et al. (30) reported that seizures of the anterolateral dorsal convexity may manifest with auras such as dizziness, epigastric sensation, or fear in 50% of patients; behavioral arrest in 20%; and speech arrest in 30%. One-third of the patients exhibited sniffing, chewing or swallowing, laughing, crying, hand automatisms, or kicking. A tendency to partial motor activity in the form of

tonic or clonic movements contralateral to the side of the focus was also noted. Bancaud et al. described speech arrest, visual hallucinations, illusions, and forced thinking in some patients during seizures of dorsolateral frontal origin. These patients may also show contralateral tonic eye and head deviation or asymmetric tonic posturing of the limbs before contralateral clonic activity or secondary generalization. Other patients may have autonomic symptoms such as pallor, flushing, tachycardia, mydriasis, or apnea (26).

Seizures of Temporal Lobe Origin

Approximately 40% to 80% of patients with temporal lobe epilepsy have seizures with stereotyped automatisms. In fact, seizures with predominantly oral and manual automatisms in addition to few other motor manifestations (excluding focal clonic activity and version) are highly suggestive of a temporal lobe origin (28–30,34). Secondary generalization occurs in approximately 60% of temporal lobe seizures (34). Postictally, gradual recovery follows several minutes of confusion; however, patients may carry out automatic behavior, such as getting up, walking about, or running, of which they have no memory. Attempts to restrain them may only aggravate matters. Violence, invariably nondirected, may be seen during this period. The patient is usually amnestic for the seizure but may be able to recall the aura. A few patients may exhibit retrograde amnesia for several minutes before the seizure.

In young children, focal seizures of temporal lobe onset are characterized predominantly by behavioral arrest with unresponsiveness (42); automatisms are usually oroalimentary, whereas discrete manual and gestural automatisms tend to occur in children older than age 5 or 6 years. In younger children, symmetric motor phenomena of the limbs, postures similar to frontal lobe seizures in adults, and head nodding as in infantile spasms were typical (43). Because it is impossible to test for consciousness in infants, focal seizures with impairment of consciousness may manifest as hypomotor seizures with none or only few automatisms. In very young infants, these may also occasionally be accompanied by central apnea (44).

Seizures of Parietal Lobe Origin

Like seizures of occipital lobe onset, focal seizures from the parietal lobe may manifest with loss of consciousness and automatisms when they spread to involve the temporal lobe. Initial sensorimotor phenomena may point to onset in the parietal lobe, as do vestibular hallucinations such as vertigo, described in seizures beginning near the angular gyrus. Language dysfunction may occur in seizures arising from the dominant hemisphere. Also described in parietal lobe complex partial seizures have been auras including epigastric sensations, formed visual hallucinations, behavioral arrest, and panic attacks (45,46). In a study of 40 patients with parietal lobe epilepsy as established by standard presurgical evaluation, including MRI, fluorodeoxyglucose–positron emission tomography, ictal single-photon emission tomography (SPECT), and scalp video-EEG monitoring, with additional intracranial EEG monitoring in selected cases, 27 patients experienced at least one type of aura. The most common auras were somatosensory (13 patients), followed by affective, vertiginous, and visual auras. Seizures had diverse manifestations. Eighteen patients showed simple motor seizure, followed by automotor seizure and dialeptic seizure (46).

A limiting factor in many studies of seizure symptomatology is that relatively few reported patients with extratemporal focal seizures with impaired consciousness become seizure free after

cortical resection, casting some doubt on the localization of the epileptic focus.

Seizures of Occipital Lobe Origin

The following features suggest the occipital lobe as the origin of a focal seizure with impaired consciousness: (i) Visual auras, usually of elementary sensations such as white or colored flashing lights, are often in the part of the visual field corresponding to the focus; the visual phenomena may remain stationary or move across the visual field. (ii) Ictal blindness in the form of a whiteout or blackout may be reported. (iii) Version of the eyes and head to the opposite side is common and is a reliable lateralizing sign; patients may report a sensation of eye pulling to the opposite side even in the absence of eye deviation. (iv) Rapid, forced blinking and oculoclonic activity also may be seen (47–49). Other symptoms may result from spread to the temporal or parietal lobes (49). Suprasylvian spread to the mesial or parietal cortex produces symptomatology similar to that in supplementary motor seizures, whereas spread to the lateral parietal convexity gives rise to sensorimotor phenomena. Spread to the lateral temporal cortex followed by involvement of the mesial structures may produce formed visual hallucinations, followed by automatisms and loss of consciousness. Direct spread to the mesial temporal cortex may mimic mesial temporal epilepsy. The visual auras may be the only clue to recognizing the occipital lobe onset of these seizures; however, the patient may not recall them because of retrograde amnesia if the aura was fleeting or if the seizure is no longer preceded by the aura as it was in the past (47).

In a study of 42 patients with occipital lobe epilepsy, 73% experienced visual auras frequently followed by loss of consciousness possibly as a consequence of ictal spread into the frontotemporal region. Vomiting is more common in benign than in symptomatic occipital lobe seizures and may also represent ictal spread to the temporal lobes (50).

Seizures of Insular Lobe Origin

The insula, also called the “fifth lobe” of the brain, lying under the frontal, parietal, and temporal opercula and covered by middle cerebral artery branches and corresponding veins. Seizures arising from the insula can masquerade as frontal, temporal, or parietal lobe seizures. Seizures arising from the mesial temporal lobe and orbitofrontal cortex often spread to the insula and vice versa. Electrical stimulation of the anterior insular produces viscerosensitive phenomena, whereas posterior insular stimulation results in somatosensory or auditory phenomena (51). Insular origin is suspected when seizures begin with viscerosensitive phenomena (nausea, vomiting, changes in gastric motility, salivation, or gustatory symptoms), motor symptoms (sense of throat constriction, early motor manifestation including tonic, hypermotor, or generalized tonic–clonic movements), and/or sensory phenomena (numbness, tightness, vibration, pain, receptive aphasia, auditory, or vertiginous symptoms) (52,53).

In the absence of a insular lesion seen on MRI, functional imaging (PET, SPECT), and magnetoencephalography, intracranial monitoring is needed for confirming the localization. This is typically done using stereotactically placed depth (SEEG) electrodes. If localization is confirmed, focal resection may be offered, though there is some risk of postoperative deficits such as dysphasia or paresis due to the proximity to blood vessels in this region.

LATERALIZING FEATURES ASSOCIATED WITH

FOCAL SEIZURES WITH IMPAIRED CONSCIOUSNESS

The focal seizures with impaired consciousness and automatisms—or automotor seizures—are the commonest type of seizures observed in video-EEG monitoring units. The number of clinical symptoms per seizure and the duration of the seizures are usually higher than in other motor seizures, especially when observed in relation to temporal lobe epilepsy, allowing for a rich spectrum of lateralizing semiologic findings (54). The following section reviews some of the most salient lateralizing signs potentially seen in this context.

Dystonic Limb Posturing

Unilateral dystonic posturing defined as forced, unnatural, unilateral (or predominantly unilateral) posturing of an arm or leg—in flexion or extension, proximal or distal, or usually with a rotatory component—is probably the most reliable lateralizing sign in temporal lobe automotor seizures (54–56). It could be easily distinguished from tonic posturing, in which there is only extension or flexion without accompanying rotation or assumption of unnatural postures. It occurs contralateral to the epileptogenic zone in about 90% of temporal and extratemporal seizures. When occurring in conjunction with unilateral automatisms of the opposite limb and head turning, it also has an excellent localizing value suggesting a mesial temporal lobe onset (54). It likely reflects direct or indirect basal ganglion activation, in addition to widespread subcortical and cortical involvement of different neural networks, as suggested by associated PET and SPECT changes and invasive EEG recordings (54–57).

Head Version

Classically, a versive head movement is defined as a tonic, unnatural, and forced lateral gyratory head movement, as opposed to head turning or deviation where more natural and unforced head gyratory movements occur. While the lateralizing value of simple head turning or deviation is questionable at best, classical head version strongly lateralizes the seizure onset to the contralateral side in >90% of the cases, especially when it occurs with conjugate eye version and shortly precedes secondary generalization (within <10 seconds) (54,56,58). It occurs in both temporal (about 35% of cases) and extratemporal (20% to 60%) seizures and may be caused by seizure spread to the premotor areas (Brodmann areas 6 and 8) (54).

A careful evaluation of the ictal head movements is also important in determining the lateralizing value of "whole body" versive activity, or gyratory seizures (GSs) defined as a rotation around the body axis during a seizure for at least 180 degrees. In a video-EEG series (59), this occurred more often in frontal lobe epilepsy (4/47 patients) versus temporal lobe epilepsy (8/169 patients). The direction of rotation lateralized seizure onset depending on the seizure evolution: (i) GSs starting with a forced version of the head ensuing into a body rotation lateralized seizure onset zone contralateral to the direction of rotation. (ii) In GSs without a preceding gyratory forced head version, the direction of rotation was toward the side of seizure onset.

Postictal Todd Palsy

Although the occurrence of postictal hemiparesis (Todd palsy) is a very rare occurrence (<1% of seizures), it is a very reliable lateralizing sign suggesting an epileptogenic focus in the contralateral hemisphere. It has, however, also been described in generalized epilepsies and after seizures without focal motor features or secondary generalization (60).

Automatisms

The broad term of "automatisms" refers to stereotyped complex behavior seen during seizures. Gastaut and Broughton (61) listed five subclasses of automatisms: alimentary, mimetic, gestural, ambulatory, and verbal. This list does not include stereotyped bicycling or pedaling movements or sexual automatisms.

Oroalimentary automatisms such as lip smacking, chewing, swallowing, and other tongue movements tend to occur early in the seizure, often with hand automatisms, and may be elicited by electrical stimulation of the amygdala (26). They may occur without loss of consciousness in temporal lobe seizures when the ictal discharge is confined to the amygdala and anterior hippocampus (2). A complex automatism such as singing has been described (62). As such, oroalimentary automatisms have no lateralizing value. Preserved responsiveness during automatisms does, however, lateralize to the nondominant hemisphere: while most automatisms are usually accompanied by impaired consciousness and subsequent amnesia, Ebner et al. (2) found that 10% of patients with right temporal lobe epilepsy had automatisms with preservation of consciousness; this was never observed in those with left temporal lobe epilepsy. Other researchers have made similar observations (54).

Hand automatisms, also referred to as simple discrete movements by Maldonado et al. (33) or bimanual automatisms, are rapid, repetitive, pill-rolling movements of the fingers or fumbling, grasping movements in which the patient may pull at sheets and manipulate any object within reach. Searching movements may also be seen. Some authors believed that unilateral automatisms had a lateralizing value (54). In our experience, they did not, unless accompanied by tonic/dystonic posturing in the opposite limb. In these patients, the seizures may begin with bilateral hand automatisms that are interrupted by dystonic posturing on one side while the automatisms continue on the other side (ipsilateral to the ictal discharge) (55) (Table 12.1).

Table 12.1 Frequency and Reliability of Various Lateralizing Signs Seen in Focal Seizures with Impaired Consciousness

Sign	Frequency	Lateralizing value
Postictal palsy (50)	<1% of patients	Contralateral in 100% of patients
Unilateral dystonic limb posturing (45,47,53)	15%–70% of FLE or TLE patients	Contralateral in >90% of the cases
Head version (29,48)	35% of TLE patients, 20%–60% of FLE patients	Contralateral in >90% of the cases
Unilateral tonic posturing (46)	15%–20% of TLE patients, 50% of FLE patients	Contralateral in 40%–90% of the cases
Unilateral immobile limb (46)	5%–28% of TLE patients	Contralateral in most cases
Unilateral eye blinking (54)	0.8%–1.5% of patients	Ipsilateral in 80% of patients
Postictal nose wiping (55)	50%–85% of mesial TLE patients, 10%–33% of FLE patients	Ipsilateral in 70%–90% of TLE patients, nonlateralizing in FLE patients

FLE, frontal lobe epilepsy; TLE, temporal lobe epilepsy

Like oroalimentary automatisms, the hand automatisms suggest onset from the mesial temporal

region. In extratemporal seizures with unilateral tonic posturing, thrashing to-and-fro movements, which are more proximal and not discrete, are sometimes seen in the opposite limb.

Eye blinking or fluttering may be observed. Although usually symmetric, unilateral blinking has been reported ipsilateral to the seizure focus (63). A mechanism similar to unilateral hand automatisms may be operative, but this has not been documented. Rapid, forced eye blinking when the seizure begins is thought to indicate occipital lobe onset (63). Seizures arising from the occipital region may produce version of the eyes to the opposite side (54).

Truncal or body movements may be seen, usually in the middle or late third of the seizure, when the patient attempts to sit up, turn over, or get out of bed (34).

Bicycling or pedaling movements of the legs are more commonly observed in focal seizures with impaired consciousness arising from the mesial frontal and orbitofrontal regions (30) than in temporal lobe seizures. They are sometimes seen in temporal lobe seizures but probably reflect spread of the ictal discharge to the mesial frontal cortex.

Mimetic automatisms, with changes in facial expression, grimacing, smiling, or pouting, are common in focal seizures with impaired consciousness (54). Crying has been noted in focal seizures with impaired consciousness arising from the nondominant temporal lobe (54).

Sexual or genital automatisms such as pelvic or truncal thrusting, masturbatory activity, or grabbing or fondling of the genitals are relatively uncommon during focal seizures with impaired consciousness. However, they have been reported in focal seizures with impaired consciousness of frontal lobe origin, as well as in those arising from the temporal lobes (54). Leutmezer et al. (64) postulate that discrete genital automatisms such as fondling or grabbing the genitals are seen in temporal lobe seizures, whereas hypermotoric sexual automatisms such as pelvic or truncal thrusting usually occur in frontal lobe seizures.

So, in summary, although various types of automatisms may have a useful localizing value, it is mainly unilateral distal limb automatisms with contralateral dystonia that is useful as a lateralizing sign.

Postictal Nose Wiping

Nose wiping or rubbing that occurs within 60 seconds of the seizure end has good localizing and lateralizing value: it occurs in 50% to 85% of temporal lobe epilepsy patients but in only 10% to 33% of extratemporal epilepsy patients. It is performed with the hand ipsilateral to the epileptogenic focus in 75% to 90% of the cases when seen in the context of a temporal lobe automotor seizure but has no lateralizing value when seen with an extratemporal seizure. Postulated mechanisms leading to its occurrence include ictal activation of the amygdala with subsequent olfactory hallucinations, or increased nasal secretions, and postictal contralateral hand movement abnormalities or neglect (54,65).

ELECTROENCEPHALOGRAPHIC FINDINGS

Interictal Electroencephalography

Most focal seizures with impaired consciousness and automatisms arise from the anterior temporal regions of one side or the other. Temporal intermittent rhythmic delta activity is found in up to 28% of patients evaluated for temporal lobe epilepsy as opposed to only 0.3% of the general population and

is therefore felt to be significantly predictive of temporal lobe epilepsy. Bitemporal sharp-wave foci are noted in 25% to 33% of patients and may be independent or synchronous. Mesial temporal spikes may not be well seen at the surface, and intermittent rhythmic slowing may be the only clue to deep-seated spikes (66). On a single routine EEG recording, 30% to 40% of patients may have normal interictal findings; activating techniques can reduce this to approximately 10% (67).

At the scalp, the field of mesial temporal spikes is often maximal at the anterior temporal electrodes (T_1 or T_2, FT_9 or FT_{10}). When nasopharyngeal or sphenoidal electrodes are used (especially in prolonged monitoring), the amplitude of the spike is usually maximal at these electrodes, consistent with their origin in the amygdalar–hippocampal region (Fig. 12.1).

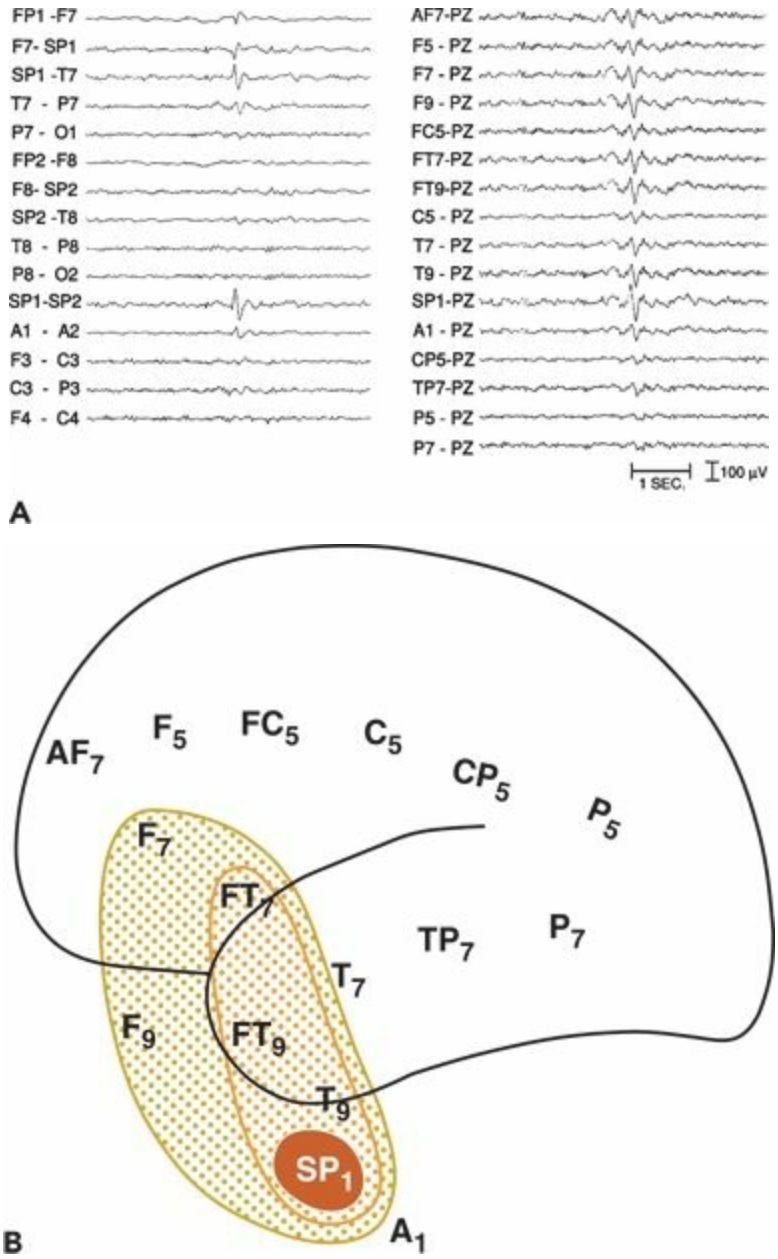

Figure 12.1. Left mesial temporal lobe. Interictal sharp-wave focus **(left)**. **A** and **B:**Distribution of the field of an interictal spike from a patient with temporal lobe epilepsy. The spike amplitude is maximal at SP_1 (measured on referential recordings); >90% at T_9, FT_9, and FT_7 electrodes; and >70% at F_7 and F_9.

Less frequently, sharp-wave foci are seen in the midtemporal or posterior temporal region. Interictal foci may be mapped according to amplitude, and the relative frequency of various sharp-wave foci may be taken into account during monitoring of epilepsy surgery candidates. A fair degree

of correlation is present between the predominant spike focus and side of ictal onset [63% in Wieser et al. (68) series of 133 patients]. Hyperventilation may activate focal temporal slowing or spikes and may provoke a clinical seizure.

In 10% to 30% of patients with focal seizures with impaired consciousness, an extratemporal focus is seen, usually in the frontal lobes (Fig. 12.2). In some patients with mesial frontal foci, the interictal discharge may take the form of a bifrontal spike-and-wave discharge.

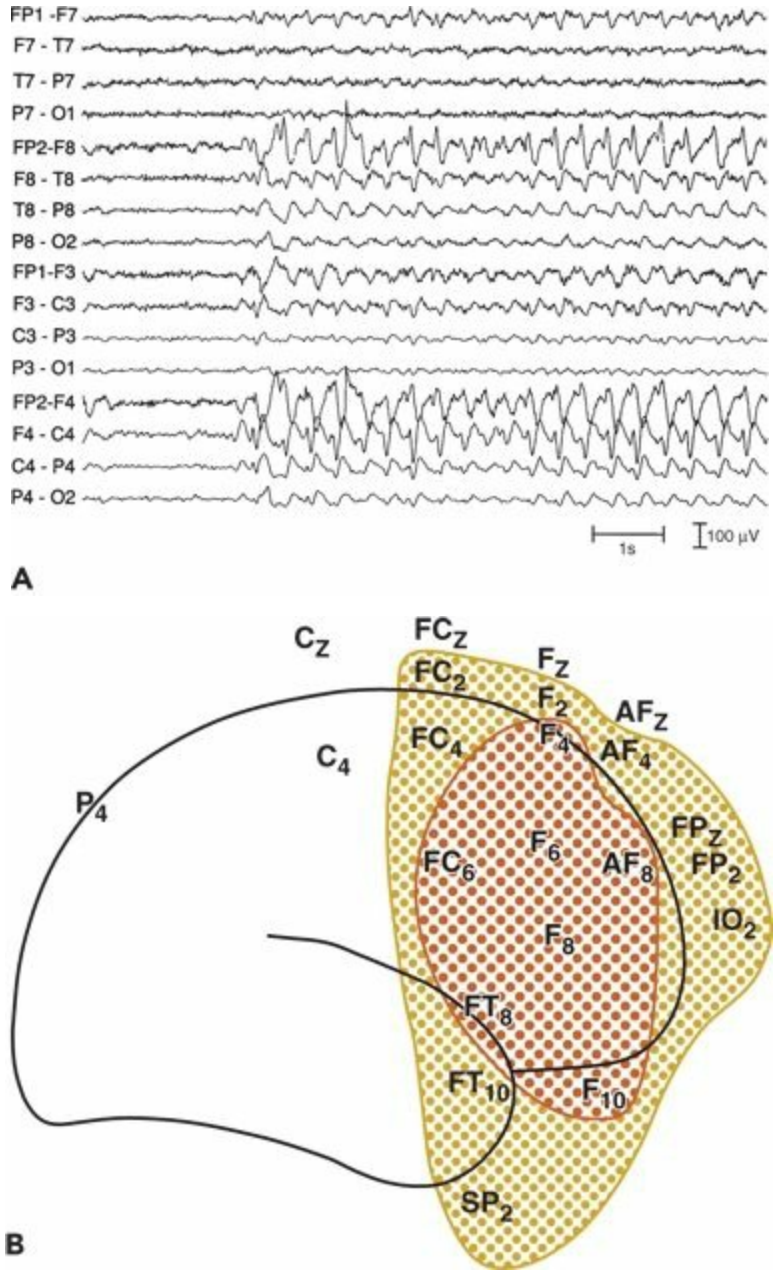

Figure 12.2. Run of focal spike-and-wave discharge in the right frontal lobe with no clinical signs **(left)** and right frontal lobe, interictal spikes **(right)**. **A** and **B:**Distribution of the field of interictal spikes occurring in runs from a patient with frontal lobe complex partial seizures. The field is widespread, involving most of the right frontal convexity.

Care should be taken to exclude nonepileptiform sharp transients such as benign epileptiform transients of sleep or small sharp spikes, wicket spikes, and 14- and 6-Hz spikes. Evidence suggests that when benign epileptiform transients of sleep occur in epileptic individuals, they do so frequently and in runs (69). Transients resembling benign epileptiform transients of sleep sometimes are found to be maximal at the sphenoidal electrode; such discharges should be interpreted cautiously.

Ictal Electroencephalography

Although interictal EEGs may show normal findings in some patients with focal seizures with impaired consciousness, ictal changes are seen in 95% of patients (except during isolated auras) (70). In frontal lobe seizures from the mesial frontal or orbitofrontal cortex, ictal and interictal activities may not be reflected at the surface or are often masked by electromyographic and movement artifacts (Fig. 12.3).

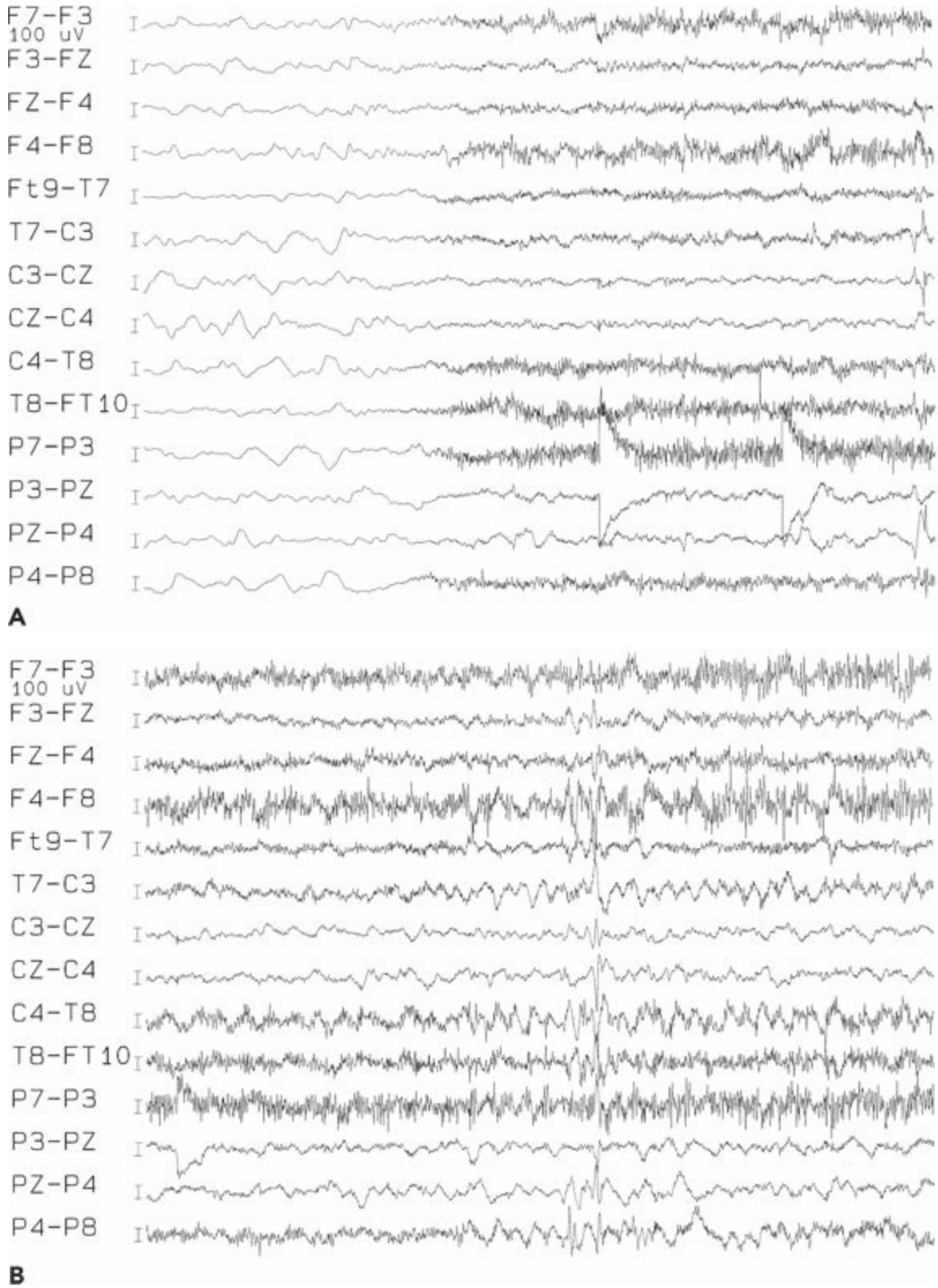

Figure 12.3. A and **B:** Ictal onset of a frontal lobe complex partial seizure arising out of sleep, beginning with low-amplitude fast rhythms, followed by rhythmic slowing near the vertex. The electroencephalographic seizure pattern cannot be lateralized.

An electrodecremental pattern is seen at the onset of a focal seizure with impaired consciousness in about two-thirds of patients. It is usually quite diffuse (perhaps owing to an associated arousal); if focal or accompanied by low-voltage fast activity, it has lateralizing significance. The low-voltage fast activity, best seen with depth electrodes, may appear only as flattening at the surface. Alternatively, diffuse bitemporal slowing, higher on one side, may occur (70,71).

Approximately 50% to 70% of patients with temporal lobe epilepsy exhibit a so-called prototype pattern (71) consisting of a 5- to 7-Hz rhythmic θ discharge in the temporal regions, maximum at the sphenoidal electrode (Fig. 12.4). This pattern may appear as the first visible EEG change or follow diffuse or lateralized slowing in the δ range (often within 30 seconds of clinical onset). Depth electrode studies have shown this pattern to have 80% accuracy in localizing the onset to the ipsilateral mesial temporal structures (72). Postictal slowing is also helpful in lateralization. In patients with unitemporal interictal spikes, the lateralizing value of the ictal data was excellent (70). Seizure rhythms at ictal onset confined to the sphenoidal electrode are often seen in patients with mesial temporal lobe epilepsy as opposed to those with non–temporal lobe epilepsy. Use of coronal transverse montages incorporating the sphenoidal electrodes may permit earlier identification of seizure onset (70).

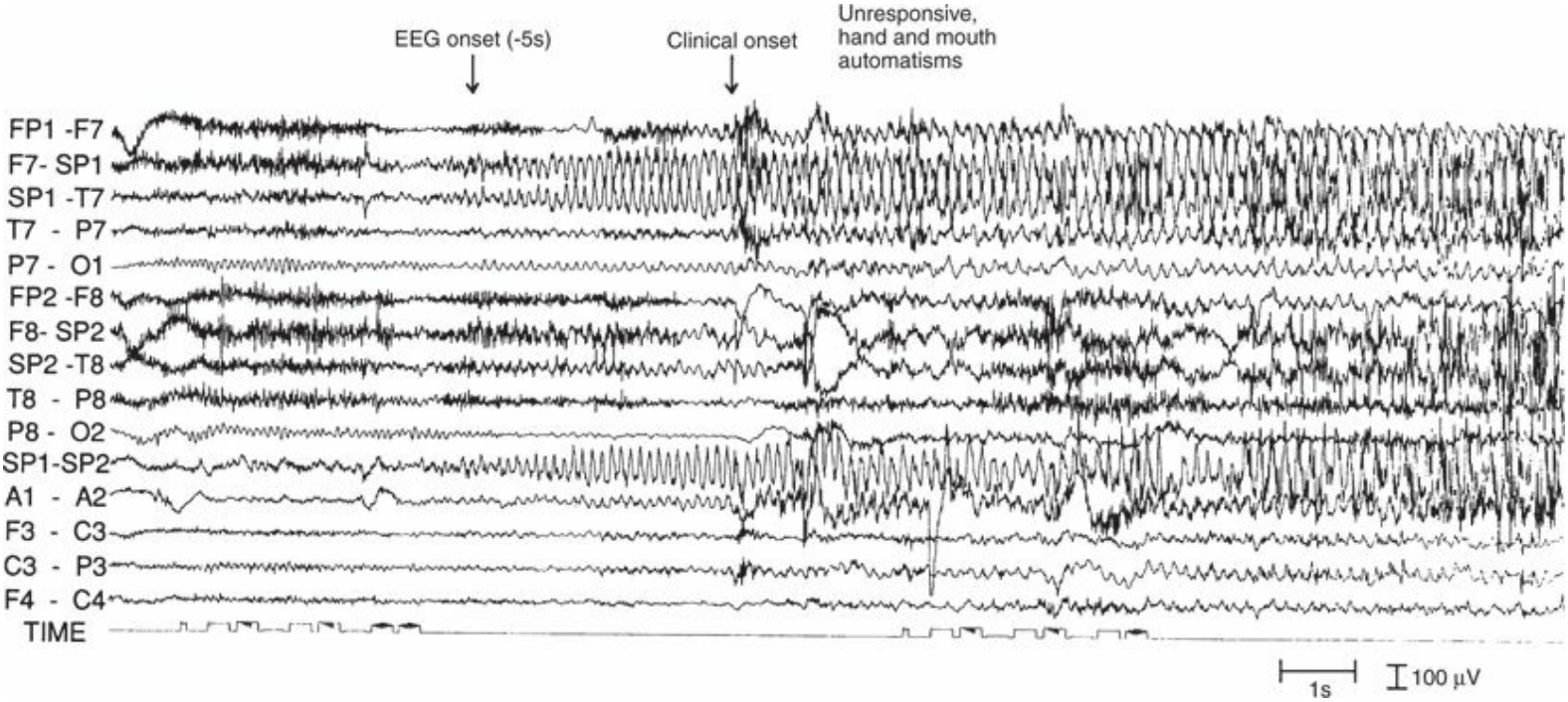

Figure 12.4. Ictal onset of a complex partial seizure (same patient as in Fig. 12.1). A brief electrodecremental response in the left temporal region is followed by the buildup of a rhythmic 5- and 6-Hz theta pattern, maximal at the left sphenoidal electrode. The electroencephalographic changes preceded the clinical onset by 5 seconds.

Although previous reports described false lateralization on the basis of scalp EEG, subsequent systematic studies have shown this to be infrequent except in the presence of a structural lesion that may mask or attenuate the amplitude of the ictal discharge on that side (70). Although lateralization from scalp EEG is usually satisfactory, localization within a lobe is sometimes incorrect, because seizures from an extratemporal site may spread to the temporal lobe and produce similar EEG patterns. The ictal discharge may then propagate to the rest of the hemisphere, or it may propagate bilaterally. Spread to the opposite temporal lobe is common. With some frontal lobe seizures, scalp ictal changes are difficult to appreciate because of electromyographic and movement artifacts. Occasionally, a generalized spike-and-wave discharge with a mesial frontal focus is seen (70).

PATHOPHYSIOLOGY OF IMPAIRED CONSCIOUSNESS IN FOCAL SEIZURES

Gloor believed in 1986 that while a "satisfactory explanation of consciousness . . . may never be possible . . . there are, however, aspects of conscious experience such as perception, cognition, memory, affect, and voluntary motility that are open to neurobiologic research" (4). Since that time, and because of multiple "neurobiologic research" attempts, significant advances have been made in the understanding of altered consciousness in the setting of focal seizures, and various mechanisms have been proposed.

Epileptic Activation of Subcortical Structures, Mainly the Thalamus and Upper Brainstem

Close connections exist between the prefrontal cortex and the nonspecific thalamic nucleus and the midline region of the intralaminar thalamic complex. Since epileptiform discharges arising from various regions within the frontal lobe—including the intermediate frontal region, orbitofrontal region, and cingulate gyrus—may elicit dialeptic seizures, and generalized discharges can be seen with epileptic activation of the mesial frontal lobe (secondary bilateral synchrony), it has been proposed that rapid epileptic spread from all of those frontal regions to the reticular formation is actually responsible for the impaired consciousness observed in frontal lobe epilepsy (1).

In temporal lobe epilepsy, a similar mechanism with additional spread to the upper brainstem structures has been suggested based on ictal SPECT perfusion studies (73) and supported by intracranial recordings demonstrating the more prominent occurrence of bilateral frontoparietal slow waves in seizures with impaired consciousness as opposed to "simple partial" seizures (74). The complete loss of consciousness seen in generalized seizures has been attributed to the involvement of both cortical and subcortical structures with epileptic activity (75). As such, the bilateral involvement of the thalamus and upper brainstem occurring early in generalized epilepsy or as a late spread phenomenon from the mesial temporal structures can selectively impair the frontoparietal association cortices and default mode networks, leading to loss of awareness (76).

Epileptic Activation of the Limbic System

Invasive EEG recordings have shown that ictal discharges in the mesial temporal lobes may be associated with the dialeptic symptomatology (1). In a recent study of 134 patients with focal seizures with impaired consciousness, Heo et al. found that interictal epileptiform discharges (IEDs) localized primarily to the temporal region and were more frequently detected in patients who were unaware of their seizures (94%) than in those who were aware (55%). Bilateral independent IEDs were found more frequently in the unawareness group than in the awareness group (48% vs. 13%). The bilateral presence of lesions was also more frequent in the unawareness group than in the awareness group (16.1% vs. 4.9%). The authors concluded that complete loss of consciousness was caused by rapid spread of ictal discharges to the contralateral hemisphere in association with bilateral independent IEDs and bilateral presence of lesions (77).

Epileptic Disturbance of the Normal Balance Between Excitation and Inhibition of Various Cortical/Subcortical Networks

Some authors suggest that arrest of activity during a seizure may be the result of either interference with the normal activity of the primary motor cortex or epileptic activation of the negative motor areas during frontal lobe involvement, or both (1). Abnormal increased activity in frontoparietal association cortex and related subcortical structures is associated with loss of consciousness in generalized seizures. Abnormal decreased activity in these same networks may cause loss of consciousness in focal seizures with impaired consciousness. Thus, abnormally increased or decreased activity in the same networks can cause loss of consciousness. Information flow during normal conscious processing may require a dynamic balance between these two extremes of excitation and inhibition (78,79).

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CHAPTER 13 AUTONOMIC SEIZURES, AUTONOMIC EFFECTS OF SEIZURES, AND SUDEP

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INTRODUCTION

Autonomic changes are frequently seen in both focal and generalized seizures during the preictal, ictal, and postictal phases (1–6). While all aspects of autonomic function can be affected, cardiac and pulmonary changes that may contribute to sudden unexplained death in epilepsy (SUDEP) have been most robustly explored. Ictal ECG or polygraphic recordings are crucial in detecting and further evaluating these autonomic symptoms and signs. Although intriguing, the relationship between profound cardiorespiratory symptoms and SUDEP has not been clearly established.

AUTONOMIC SEIZURES

In 2007, an international consortium proposed that an "autonomic seizure" be defined as "an epileptic seizure characterized by altered autonomic function of any type at seizure onset or in which manifestations consistent with altered autonomic function are prominent (qualitatively dominant or clinically important) even if not present at seizure onset" (7). "Autonomic status epilepticus" was defined as "an autonomic seizure that lasts more than 30 minutes or a series of such seizures over a 30-minute period without full recovery between seizures."

A diverse number of autonomic signs have been described with seizures. These are summarized in Table 13.1. There is evidence that the autonomic effects of seizures may be different in children than in adults (7,8), and autonomic ictal disturbances are very frequent in seizures in neonates and infants. The types of epilepsies associated with autonomic seizures vary somewhat based on age (Table 13.2) and need to be distinguished from nonepileptic conditions with prominent autonomic features (Table 13.3).

Table 13.1 Autonomic Signs and Symptoms That May Be Seen with Seizures

Cardiovascular changes
Palpitations/chest pain, sinus tachycardia, cardiac arrhythmias, bradycardia, asystole, chest pain, increase (or decrease) of blood pressure

Gastrointestinal
Emesis (nausea, retching, vomiting), epigastric auras, spitting, hunger, borborygmi, diarrhea; fecal incontinence

Genitourinary and sexual
Urinary incontinence, increase of intravesicular pressure, erotic feelings and genital sensations, erection, orgasm

Pupillary
Mydriasis, miosis, hippus

Respiratory
Apnea, hyperventilation, coughing, sighing, increased bronchial secretion, nocturnal acute laryngospasm, respiratory arrest, neurogenic pulmonary edema, postictal nose wiping

Thermoregulatory
Fever

Vasomotor, pilomotor, and secretory
Flushing, pallor, cyanosis, hyperhidrosis, piloerection, sweating, lacrimation, hypersalivation

Others
Cephalic auras

Table 13.2 Autonomic Epilepsies Presenting at Specific Ages

Age range	Epilepsies with prominent autonomic features
Neonate/infant	*Neonatal seizures*—often prominent autonomic features (apnea, tachycardia) with minimal motor changes *Migrating partial seizures of infancy*—apnea, cyanosis, flushing, diaphoresis often with focal clonic activity *Dravet syndrome*—prolonged hemiconvulsive seizures often triggered by hyperthermia *Temporal lobe epilepsy*—staring, ictal emesis, apnea
Child	*Panayiotopoulos syndrome*—ictal emesis, tachycardia, mydriasis *Rolandic epilepsy*—ictal hypersalivation *Temporal lobe epilepsy*
Adolescent/adult	*Temporal lobe epilepsy*—staring with emesis, nausea, changes in heart rate, abdominal rising, piloerection, pupillary abnormalities
All ages	*Epilepsy associated with specific genetic conditions*—Angelman, 18q–, Rett, protocadherin 19

Table 13.3 Nonepileptic Conditions with Prominent Autonomic Features by Age Group at Presentation

Age range	Nonepileptic conditions
Neonate/infant	*Gastroesophageal reflux*—apnea, bradycardia, pallor, hypotonia
	Sandifer syndrome—dystonic posturing, flushing, bradycardia, apnea
	Breath holding—apnea, cyanosis, pallor, bradycardia
	Inborn errors of metabolism—apnea, emesis
	Familial dysautonomia—paroxysmal attacks of vomiting, increased heart rate, blood pressure, sweating, drooling, and flushing
Child	*Breath holding*
	Inborn errors of metabolism
	Infantile gratification behavior—flushing, diaphoresis, tachycardia
	Benign paroxysmal vertigo—nausea, pallor
	Cyclic vomiting syndrome—recurrent episodes of emesis, particularly nocturnal
	Parasomnia—flushing, tachycardia, diaphoresis
	Syncope—pallor, hypotension, bradycardia, diaphoresis, nausea
	Anxiety/panic attack—hyperventilation, tachycardia, hypertension, diaphoresis, nausea and vomiting
Adolescent/adult	*Syncope*
	Anxiety/panic attack
	Postural orthostatic tachycardia syndrome—tachycardia, light-headedness, pallor
All ages	*Migraine*—headache, flushing, emesis, pallor

The pathophysiology of autonomic changes with seizures most likely involves direct excitation or inhibition of the neocortical and limbic cortices involved at seizure onset and their propagation to structures that constitute the central autonomic network (1,9). This network involves an extensive neural circuitry that extends from the forebrain to the brain stem and includes the insular cortex, amygdala, hypothalamus, periaqueductal gray matter, parabrachial complex, nucleus of the tractus solitaries, and ventrolateral medulla. Through this circuitry, autonomic, visceromotor, neuroendocrine, pain, and behavioral responses are controlled. Inputs to the central autonomic network are multiple including viscerosensory inputs relayed through the nucleus of the tractus solitaries and humoral inputs relayed through the circumventricular organs. Higher-order autonomic control is mediated by the prefrontal and insular cortices and amygdala. Electrical stimulation of these regions results in various autonomic signs. Stimulation of the right anterior insular cortex is

reported to elicit tachycardia and pressor responses, whereas bradycardia and depressor responses are reported to occur with left anterior insular stimulation. Stimulation of the medial prefrontal cortex results in changes in blood pressure, heart rate, and gastrointestinal motility. The amygdala and bed nucleus of the stria terminalis are responsible for integrated autonomic and motor responses to emotion.

Children appear to be particularly vulnerable to autonomic seizures and, in particular, ictal emesis. In adults, ictal vomiting is rare and is usually seen later in a seizure once consciousness is impaired and after onset of other temporal lobe symptoms. Conversely, ictal vomiting in children is common and usually seen at seizure onset with intact consciousness and without preceding focal cortical symptoms. It has been suggested that there is a maturation-related susceptibility for the central autonomic network, with children being more vulnerable to emetic disturbances (10). Furthermore, in children, central autonomic networks may have a lower threshold to epileptogenic activation than those producing focal cortical semiology. Regardless of the localization of onset of ictal discharge, the lower threshold autonomic centers may be activated initially, with consequent autonomic manifestations. Other higher threshold cortical regions that produce focal semiology such as motor, sensory, or other symptoms are only activated later and if the ictal discharge reaches a certain threshold.

Specific Epilepsies and Seizures with Prominent Autonomic Features

Neonatal Seizures

Seizures are among the most common neurologic disorders in neonates, with an incidence of 1 to 3 per 1000 live births. Most seizures in neonates are reflective of underlying brain pathology, although the list of potential etiologies is diverse. Seizures in the newborn are usually focal and often have subtle semiology with eye deviation, staring, blinking, nystagmus, mouthing, or chewing. Autonomic features are also very common, including apnea, abnormal respiratory patterns, hiccups, tachycardia, and/or hypertension (11). Profound ictal apnea may be the only manifestation of neonatal seizures arising from either the temporal or the occipital regions (12,13), although associated heart rate changes are rare in ictal apnea (14). The cause of the frequent association between neonatal seizures and autonomic features has not been well studied; however, connections between the posterior limbic cortex, the temporal lobe, and the midbrain respiratory centers have been postulated (13).

Epilepsy of Infancy with Migrating Focal Seizures

This rare but devastating syndrome presents in three distinct phases (15). In the first few weeks to months of life, focal motor seizures, which evolve to bilateral convulsive events, occur. Autonomic features are very common and include apnea, flushing, and cyanosis. The second phase is seen between 1 and 12 months and is characterized by a marked increase in seizure frequency, often to a point where seizures are nearly continuous. Prominent ictal autonomic features persist. The EEG at this time shows the typical migrating and multifocal pattern of ictal epileptiform discharges. During the third phase, which typically is seen between 1 and 5 years of age, the frequency of seizures markedly reduces, although clusters can still occur during intercurrent illnesses. The etiology of many cases is unknown, although a variety of genetic causes have been reported, including SCN1A and

KCNT1 mutations. Therapy is challenging, with some response reported with bromides, a combination of stiripentol and clonazepam, levetiracetam, or rufinamide (16). Two patients with profound ictal apnea and bilateral temporal involvement experienced significant improvement with addition of acetazolamide (17), possibly due to either cessation of bitemporal seizures or induction of metabolic acidosis that resulted in stimulation of central chemoreceptors.

Dravet Syndrome

Dravet syndrome is a devastating epilepsy syndrome that begins in the first 18 months of life with recurrent prolonged seizures, which are intractable to medical therapy. Initial seizures are often hemiconvulsive or evolving to bilateral convulsive activity. By age 2 years, other seizure types including myoclonic jerks, absences, focal seizures, and drop attacks emerge. Focal seizures with prominent autonomic features occur in over half of patients, with pallor, cyanosis, respiratory changes, and drooling, often associated with eye deviation, myoclonus, or focal motor activity. A significant provoking factor for seizures is hyperthermia due to intercurrent illness, postimmunization fever, physical exercise, warm baths, or elevated ambient temperatures. While caregivers frequently report disturbed body temperature regulation, red or bluish hands/feet, alteration in sweating, pupillary dilation, facial or chest flushing, tachycardia at rest, or slow gastric emptying, few studies have carefully evaluated autonomic function in these children.

Approximately 80% of children have a demonstrable mutation in the SCN1A gene. The risk of SUDEP in this cohort is high, with an approximate annual incidence of 0.6% (18) . SCN1A is primarily a neuronal gene; however, several studies have shown that the product of this gene, Nav1.1, is present in the heart in several animal species. It appears important in normal activity of the sinoatrial node, control of heart rate, and heart rate variability (19). A small number of studies have suggested a relative predominance of adrenergic tone in Dravet syndrome, as evidenced by reduced heart rate variability, and P-, QT-, and QTc wave dispersion (20, 21). Such changes may predispose to an increased risk of tachyarrhythmias and possibly explain the higher risk of SUDEP, although further studies are needed.

Panayiotopoulos Syndrome

Autonomic seizures and autonomic status epilepticus are core features of Panayiotopoulos syndrome, a common electroclinical syndrome that affects preschool or early school-aged children (7). Seizures frequently arise from sleep with a collection of autonomic symptoms and mainly emesis, with or without vomiting, tachycardia, syncope-like manifestations, unilateral eye deviation, and progressive altered awareness, which may progress to hemiconvulsions.

EEG studies in children with Panayiotopoulos syndrome typically reveal multiple foci, often with an occipital predominance. Using magnetoencephalography, Saito et al. noted that younger patients had spikes in the calcarine, parietooccipital, or rolandic regions, as opposed to older children in whom frontal foci were seen (22). These results are in keeping with a maturation-related cortical hyperactivity in this syndrome, which may result in activation of the lower-threshold central autonomic network.

Benign Epilepsy with Centrotemporal Spikes

Benign epilepsy with centrotemporal spikes is the most common focal epilepsy seen in children and

typically presents with diurnal focal seizures affecting the ipsilateral lower face and occasional ipsilateral upper extremity and/or nocturnal generalized seizures. One of the characteristic clinical features is profound ictal hypersalivation, which is usually seen with ipsilateral lower facial motor activity and dysarthria. Rarely, this syndrome may present with prolonged hypersalivation and oromotor and speech disturbances suggestive of an anterior opercular syndrome.

Temporal Lobe Epilepsy

Temporal lobe epilepsy often presents with autonomic features, particularly in children. "Abdominal epilepsy" may be seen, characterized by periumbilical, colicky abdominal pain, often accompanied by headache, dizziness, syncope, temporary loss of vision, and impaired consciousness. The duration of abdominal pain is typically no longer than 15 minutes and may be associated with sweating, borborygmi, salivation, and flatus.

Rarely, profound apnea attacks may be the sole manifestation of temporal lobe epilepsy, and this is most commonly seen in preschool children and infants. However, a case of SUDEP in a 30-year-old woman with temporal lobe epilepsy, who had previously documented ictal apnea, suggests that this autonomic disturbance may be a significant risk factor for SUDEP (23). Ictal apnea appears most likely with spread of temporal lobe epilepsy to the contralateral hemisphere (24).

The most common autonomic change seen in temporal lobe epilepsy is ictal tachycardia, which is present in up to 98% of childhood temporal lobe seizures. Ictal bradycardia is less frequent, and while it may be due to activation of the left temporal and insular cortex, a careful study found that it does not have consistent lateralization but rather appears after seizure activity becomes bilateral (25). Cardiac pacing should be considered in cases of ictal asystole.

Autonomic features suggestive of specific lateralization in temporal lobe seizures include both abdominal auras with vomiting and orgasmic auras, which both lateralize to the nondominant temporal lobe. Other symptoms that are not specific to lateralization and that may also be seen with nontemporal foci include postictal cough, flushing, pallor, sweating, piloerection, mydriasis, and miosis.

Epilepsy Associated with Specific Genetic Conditions

Ictal apnea appears to be particularly common in many epilepsies due to specific genetic conditions including protocadherin 19 mutations, 18q− syndrome, 1p36 deletion syndrome, and trisomy 18. Accurate diagnosis of the underlying etiology of autonomic symptoms in these genetic disorders can be quite challenging, as many have autonomic disturbances unrelated to seizures as well. Girls with Rett syndrome typically have peripheral vasomotor disturbances and breathing dysfunction. Additionally, cardiac testing has shown an exaggerated increase in heart rate response to breath holding and prolonged QTc suggestive of cardiorespiratory dysregulation. In 18q−, breathing abnormalities including hyperventilation or apnea crises are common. Video-EEG monitoring may be needed to determine if such symptoms have epileptiform correlate.

SUDDEN UNEXPECTED DEATH IN EPILEPSY

SUDEP is the most important direct epilepsy-related cause of death. It is defined as a sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death in a patient with epilepsy. This may or may not occur in the setting of an epileptic seizure and excludes deaths

resulting from status epilepticus. If the above criteria are met and an autopsy is performed, revealing no toxicologic or anatomical cause of death, the death is termed "definite SUDEP." "Probable SUDEP" is diagnosed if the above criteria are met, but an autopsy is not performed. When no autopsy is performed, insufficient evidence relating to the cause of death exists, and SUDEP cannot be excluded, a diagnosis of "possible SUDEP" can be made.

SUDEP has an estimated incidence of 1.8 per 1000 patient-years (26). However, higher incidences (3 to 9/1000 patient-years) have been reported with intractable epilepsy (27). While SUDEP is rarer in the pediatric population, it is still estimated to be between 1 and 2 per 10,000 patient-years (28).

Based on previous studies, the most consistently identified risk factor for SUDEP is poorly controlled generalized tonic–clonic seizures (29–33). Other, less-robust risk factors include antiepileptic drug polytherapy, developmental delay/intellectual disability, nocturnal seizures, young age at seizure onset, and longer duration of epilepsy (29–33). The use of specific drugs such as carbamazepine or lamotrigine has been suggested as potential risk factor however, recent careful studies have refuted these findings (34,35).

Prevention of SUDEP should involve increased efforts to decrease the frequency of generalized tonic–clonic seizures. Furthermore, supervision at night may be associated with a decreased risk of SUDEP (29).

SUDEP AND PERI-ICTAL AUTONOMIC DYSFUNCTION

While the exact pathophysiology of SUDEP has yet to be fully elucidated, ictally mediated autonomic dysfunction is most likely responsible. Such dysfunction may involve cardiac disturbances, including peri-ictal tachycardia, bradycardia, asystole, repolarization (QTc) anomalies, and reduced heart rate variability. Potentially fatal decreases in cerebral oxygenation could also result from peri-ictal hypoxemia and respiratory suppression. Recently, the contribution of postictal generalized EEG suppression to SUDEP has been studied. Through retrospective review of electrophysiologic data from people who later died of SUDEP and prospective studies of those at greatest risk, we continue to learn more about the mechanisms responsible for sudden death.

Peri-Ictal Tachycardia

Given its high prevalence, there is great interest in the potential role of peri-ictal tachycardia in SUDEP. Peri-ictal tachycardia (often defined as a heart rate greater than the 98th percentile for age) is the most commonly observed seizure-related autonomic disturbance, occurring during and/or after a majority of recorded seizures (36). Based on stimulation of the human insular cortex, Oppenheimer et al. (37) hypothesized that tachycardia is more likely to result from seizures lateralizing to the right hemisphere. However, peri-ictal tachycardia has more consistently been documented in association with mesial temporal lobe onset and seizure generalization (36).

Some studies of patients who later died of SUDEP suggest a link between peri-ictal tachycardia and resulting death. When comparing maximal ictal heart rates in patients who later died of definite/probable SUDEP to controls with refractory focal-onset seizures, significantly higher values were found in the SUDEP group (38). In addition, significant postmortem fibrotic changes in the deep and subendocardial myocardium have been detected in SUDEP cases versus controls, which could be

the result of myocardial ischemia from repetitive seizures (39). Sympathetic overactivity may be responsible for such tachycardia and cause transient dilatation of ventricular walls and left ventricular dysfunction. If such stress-induced cardiomyopathy was severe enough to diminish cardiac output, oxygen supply during periods of significant stress might be compromised enough to result in death.

Peri-Ictal Bradycardia and Asystole

Although less frequent than peri-ictal tachycardia, bradycardia and asystole are known autonomic manifestations of seizures. Peri-ictal bradycardia (heart rate less than the 2nd percentile for age) has been documented in 2% to 4% of monitored seizures (36,40). Although the cortical stimulation studies performed by Oppenheimer et al. (37) suggested that bradycardia resulted from left hemispheric epileptiform activity, this has not been consistently supported by subsequent research. Rather, significant decreases in heart rate are more likely to be observed when epileptiform activity is present bilaterally on scalp EEG (25). Peri-ictal asystole (or the absence of a detectable heartbeat for ≥4 seconds) is even rarer, occurring in <0.5% of recorded seizures. Given that some cases of SUDEP have involved an ECG showing bradycardia progressing to asystole, there is significant interest in how such autonomic changes may contribute to sudden death. If true, clinicians could theoretically reduce the risk of SUDEP by advising pacemaker implantation. However, studies documenting earlier seizure cessation in cases of ictal asystole argue against the sole contribution of bradycardia/asystole to SUDEP (41).

Peri-Ictal Cardiac Repolarization (QTc) Abnormalities

A potential cause of lethal cardiac arrhythmias could be peri-ictal QT interval changes. Lengthening of the QT interval may result in torsades de pointes, a form of ventricular tachycardia. Clinically significant QTc prolongation is not rare in the peri-ictal period, occurring in 4.8% to 16.2% of seizures (36). Shortening of the QT interval can also be potentially lethal, facilitating a reentrant ventricular tachycardia. Clinically significant QTc shortening has been observed in 3.8% to 4.8% of seizures (36).

The potential link between cardiac repolarization abnormalities and SUDEP has been strengthened by studies invoking shared genetic mutations. Cardiac depolarization/repolarization anomalies have been documented in two SUDEP victims. One had an SCN5A-encoded cardiac Nav1.5 sodium channel mutation; another had a RYR2-encoded cardiac ryanodine receptor/calcium release channel mutation (42,43). However, only one case of ventricular fibrillation progressing to asystole and death following a monitored focal dyscognitive seizure has been cited (44). Therefore, caution must be utilized when attempting to link all cases of SUDEP to cardiac depolarization/repolarization anomalies.

Heart Rate Variability

Decreases in heart rate variability, which have been associated with an increased risk of sudden cardiac death (45), have been documented in people with epilepsy, including those with chronic temporal lobe epilepsy (46) and Dravet syndrome (21). The decrease in heart rate variability is likely secondary to seizure-related reductions in cardiac sympathetic innervation. Cardiac ^{123}I-metaiodobenzylguanidine uptake, a quantifiable measure of cardiac sympathetic regulation, has been

shown to be reduced in people with chronic temporal lobe epilepsy versus healthy controls (47). Such changes may increase cardiac sensitivity to adrenergic stimulation, increasing the risk of catecholamine-induced arrhythmias and death.

Peri-Ictal Hypoxemia and Apnea

Peri-ictal hypoxemia has been documented using digital pulse oximetry in 25% to 33% of seizures in both adults and children (36,40,48). It is felt that such hypoxemia is likely a consequence of seizure-related hypoventilation. Up to 50% of seizures may be marked by central apnea, with 9% marked by mixed or obstructive apnea (48). This is supported by concurrent rises in end-tidal CO_2 during monitored seizures (48). Such hypoventilation/apnea may be secondary to disruption of brain stem respiratory centers by repetitive seizure discharges. Other potential causes of peri-ictal hypoxemia include a seizure-induced right-to-left shunt and neurogenic pulmonary edema (10).

The role of peri-ictal hypoxemia in SUDEP has been suggested by both postmortem and electrophysiologic studies. Moderate to severe pulmonary edema has been documented in a majority of SUDEP cases at autopsy. Up to 80% of witnessed SUDEP cases have been characterized by respiratory difficulty (49). While attempting to define the role of hypoxemia/apnea in SUDEP, researchers have drawn parallels to sudden infant death syndrome. This is particularly true with regard to dysfunction of the rostral medulla and its centers controlling respiration and gasping (10). Given that such centers are modulated by 5-hydroxytryptamine (serotonin) and norepinephrine, pharmacologic manipulation of these receptors may theoretically reduce the risk of SUDEP. This has been demonstrated in the DBA/2 mouse model of SUDEP, where administration of fluoxetine significantly reduced the risk of respiratory arrest after seizures (50). In humans, only a single small retrospective study has shown a reduced occurrence of ictal hypoxemia during focal-onset seizures without secondary generalization in those taking selective serotonin reuptake inhibitors (51). Therefore, further investigation is needed before clinicians can confidently prescribe such medications to reduce the risk of hypoxemia-related sudden death.

Postictal Generalized EEG Suppression

An area of increasing interest in SUDEP-related research is postictal generalized EEG suppression. This phenomenon is marked by the absence of electroencephalographic activity as measured by scalp EEG viewed at ≤10 mV amplitude. In a retrospective study of 10 patients who later died of SUDEP versus 30 controls, it was shown that postictal generalized EEG suppression was significantly longer in the SUDEP group. The odds of dying from SUDEP were increased when suppression duration was >50 seconds and quadrupled when the duration was >80 seconds (52). It is hypothesized that postictal generalized EEG suppression may result in sudden unexpected death via inhibition of brain stem respiratory centers and resulting apnea. In adults, lower mean oxygen saturation nadirs, longer desaturations, and lower end tidal CO_2 measurements have been documented in seizures marked by postictal generalized EEG suppression (53). It is possible that the cortical neuronal inhibition suggested by suppression on scalp EEG extends to deeper subcortical and brain stem structures, interfering with respiratory drive (52). This phenomenon, especially if part of a vicious cycle of events including reduced activity of pulmonary stretch receptors, increased carotid chemoreceptor sensitivity, and asystole, could result in sudden death. Another possibility is that postictal generalized EEG suppression may reflect the severity of seizure-related intrinsic pulmonary dysfunction. This is

supported by the lack of a significant difference in apnea duration in seizures with and without this finding (53).

CONCLUSIONS

Autonomic changes are common in the peri-ictal period and likely result from direct excitation or inhibition of neocortical and limbic cortices. This may occur at seizure onset or from the propagation of epileptiform activity to structures that constitute the central autonomic network. Children are particularly susceptible to autonomic seizures, possibly secondary to a maturation-related susceptibility of the central autonomic network. This may explain why greater numbers of specific epilepsy syndromes and seizures with prominent autonomic features are documented in the neonatal through early childhood periods versus adulthood. Peri-ictal autonomic changes are of particular interest to clinicians given their proposed association with SUDEP. Peri-ictal tachycardia, bradycardia/asystole, cardiac repolarization (QTc) abnormalities, reduced heart rate variability, hypoxemia/apnea, and postictal generalized EEG suppression have all been theorized to play pivotal roles in the pathophysiology of sudden unexpected death. However, given that each of these phenomena occur vastly more frequently than SUDEP, it is likely one alone is not enough to result in sudden death. Rather, SUDEP may result from several precipitating factors coming together in a "perfect storm" during the peri-ictal period. In identifying patients at greatest risk for SUDEP, it may ultimately prove more useful to look at the concurrence of multiple autonomic events rather than any single disturbance. Only then may it be possible to accurately stratify risk and devise appropriate preventative measures for this devastating condition.

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CHAPTER 14 GENERALIZED MOTOR SEIZURES

WILLIAM O. TATUM IV

INTRODUCTION

Generalized seizures may be subdivided into motor and nonmotor seizures (Fig. 14.1). Generalized motor seizures (GMS) are often referred to as convulsive seizures (1). In the revised terminology and classification of the International League Against Epilepsy (ILAE), generalized convulsive seizures arise within and rapidly engage bilaterally distributed cortical, subcortical, and brainstem networks of the brain (1). GMS, which occur in approximately one-half of patients with epilepsy, are among the most common of all the seizure types encountered in children and adults (2). These clinically visible events have an adverse effect upon the quality of life (3), and even infrequent seizures influence driving, employment, psychosocial enhancement, and cognition independent of the adverse effects that may be incurred by medical treatment (4).

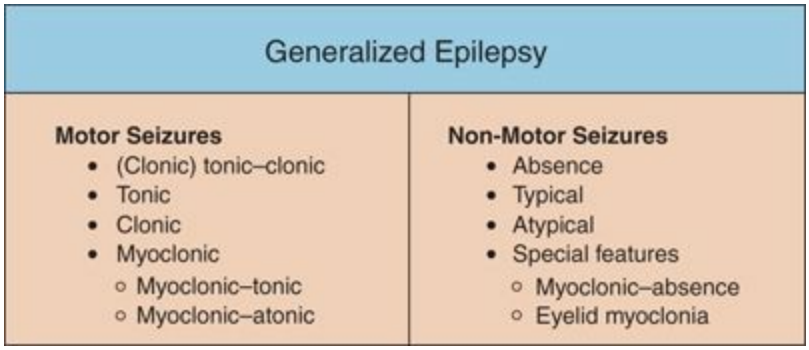


Figure 14.1. Generalized epilepsy subdivided into convulsive (motor) and nonconvulsive (nonmotor) seizures. (Adapted from Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia. 2010;51(4):676–685.)

GMS may be observed in several different epilepsy syndromes and are associated with various etiologies, including a structural–metabolic (symptomatic), genetic (idiopathic), or unknown (cryptogenic) cause (5). While an inherited pattern is frequently assumed to reflect a genetic cause for GMS, family histories are often absent because complex genetic patterns and de novo mutations are common and are therefore not identified in pedigrees. A genetic component in patients with GMS does not preclude a progressive or structural–metabolic component (i.e., Lafora disease and laforin gene mutation EPM2A/B). Neither does a primary genetic pathogenesis exclude the possibility of a concomitant structural–metabolic cause (Fig. 14.2). Combinations of GMS semiologies and EEG may permit identification of a specific epilepsy syndrome that influences treatment and ultimately prognosis (early myoclonic encephalopathy). This chapter focuses on the electroclinical features of generalized tonic–clonic (GTC), tonic, clonic, and myoclonic seizures.

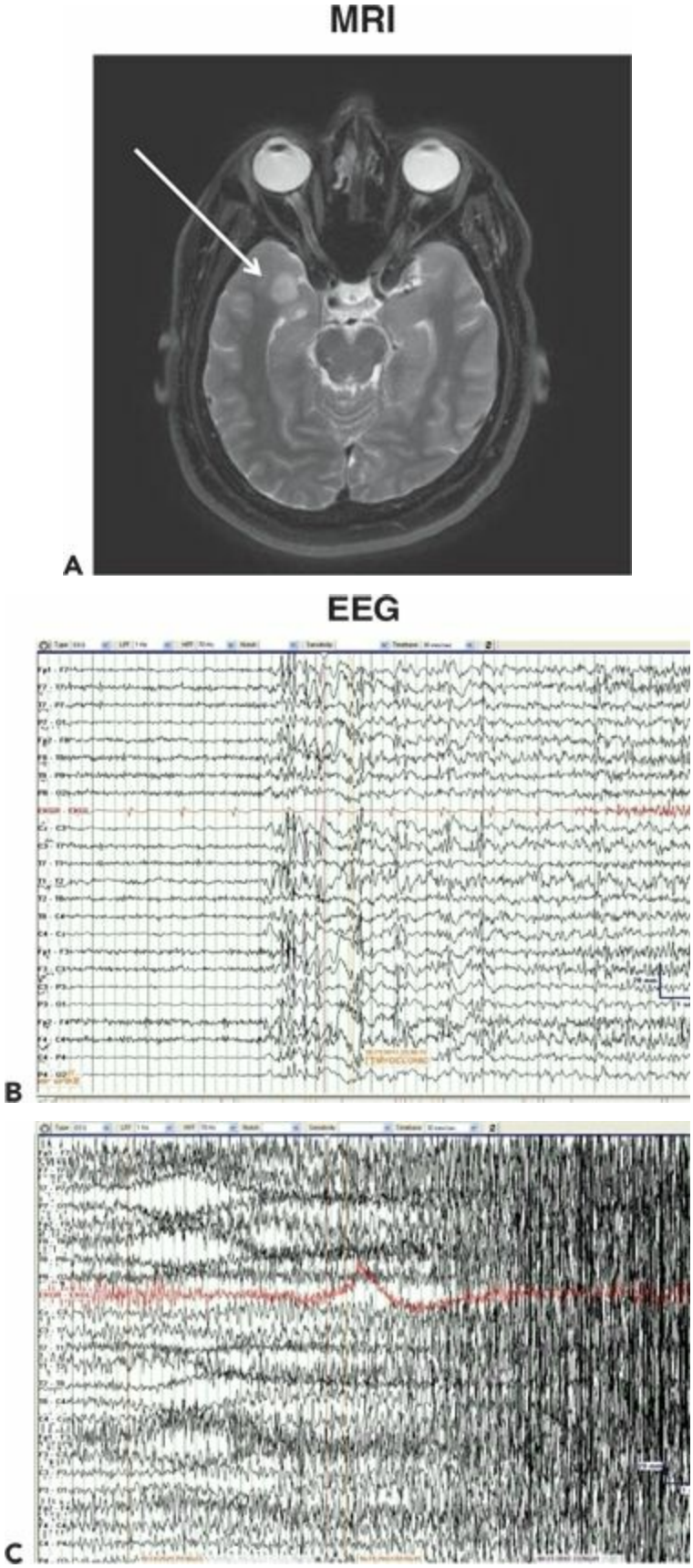


Figure 14.2. A 28-year-old Middle Eastern male was referred for epilepsy surgery. Recurrent GTC seizures were uncontrolled despite ASDs. **A:** MRI brain demonstrated a right temporal lobe lesion (arrow). **B and C:** Historical review suggested myoclonus beginning in adolescence. Video–EEG clearly demonstrated electroclinical myoclonic and GTC seizures confirming JME.

TYPES OF GMS

Generalized Tonic–Clonic

Descriptive terminology used by the ILAE defines a GTC seizure as one with a "tonic followed by a clonic phase" (6). Commonly known as a "grand mal," major motor seizure, or convulsion, the GTC is the most feared of all seizure types by patients, families, and observers. There is a multiplicity of brain disorders that produce GTC seizures. GTC seizures are the most common GMS occurring in 20% to 25% of adults with epilepsy. GTC seizures are rare in neonates and in infants younger than 2 years of age due to the immaturity and lack of organization of the developing brain that is typified by variable neuronal excitability, imperfect myelination, and incomplete interhemispheric connections (7). GTC seizures may occur as a first or solitary seizure and as the sole or mixed manifestation of an epilepsy syndrome. Adult-onset genetic generalized epilepsy (GGE) with GTC seizures may occur in 13.4% to 34.8% of hospitalized patients; however, most appear within the first 2 decades of life (8). In elderly patients, the onset is usually focal and then evolves to a bilateral GTC seizure. Public perception that all patients with epilepsy manifest "grand mal" seizures perpetuates misconception and stigma for patients with epilepsy (3).

Semiology

A GTC seizure has an initial tonic phase followed by a clonic motor phase that is characterized by rhythmic jerking and may result from a generalized or a focal-onset seizure. When the propagation to both hemispheres is rapid and involves the motor cortex, the clinical semiology of a focal seizure evolving to a bilateral convulsion ("secondarily" generalized) may be difficult to separate from a ("primary") GTC seizure that is associated with GGE. Myoclonic jerks may precede a GTC seizure during a myoclonic–tonic–clonic seizure to suggest a GGE such as juvenile myoclonic epilepsy (JME).

A prodrome is a nonictal warning composed of vague nonspecific symptoms that may occur prior to a GTC seizure. It can last from 5 minutes to a day before a seizure and often involve subtle changes in mood, cognition, and headache (9) though it may involve a variety of premonitory sensory, motor, autonomic, or psychic symptoms. As previously noted, motor signs in a GTC seizure involve an initial tonic phase and sudden loss of consciousness (5). Muscular rigidity occurs first with brief flexion followed by more prolonged tonic extension. The brief phase of flexion begins in the axial musculature and subsequently affects the limbs prior to more prolonged tonic extension lasting approximately 15 to 30 seconds. The tonic contraction is most intense in the axial musculature. When muscle contraction occurs in the thorax and abdomen, air is forced through the larynx to produce an "epileptic cry," respiratory stridor, or moan (10). In this phase, an apparent opisthotonic posture with the arms extended and fingers either extended or clenched in a fist is seen (5). The wrists are flexed or extended, and the forearms are pronated, while the legs are extended at the hips, knees, and ankles (Fig. 14.3). During tonic muscular contraction, respiration is inhibited and cyanosis may be evident. The ensuing clonic phase lasts about 30 to 45 seconds and involves initially a centrally spreading tremulousness (5,10). Phasic reduction in muscle tone intermittently occurs to create the generalized clonic jerking (10). Audible respiratory grunting may be heard that wanes in a decrescendo fashion, and the seizure ceases after 1 to 2 minutes (10). The tongue may be bitten, and urinary incontinence may be evident. Most tongue bites associated with GTC seizures have a predisposition for the posterolateral tongue or cheek region (5,10). Hypersalivation also occurs and, with the vascularity of the tongue, may produce copious amounts of blood-tinged sputum (5). Autonomic features include pupillary dilation, tachycardia, and blood pressure elevation (10). Diaphoresis is present during and

after the episode. Following the seizure, hypoventilation is encountered, which may be in the form of stridor with respiratory compromise or aspiration if the airway is not protected. There is marked individual variability between GTC seizures and between seizures in the same individual (5,10). Additionally, focal and lateralizing signs commonly occur in GTC seizures of patients with GGE and do not necessarily imply a focal onset (11).

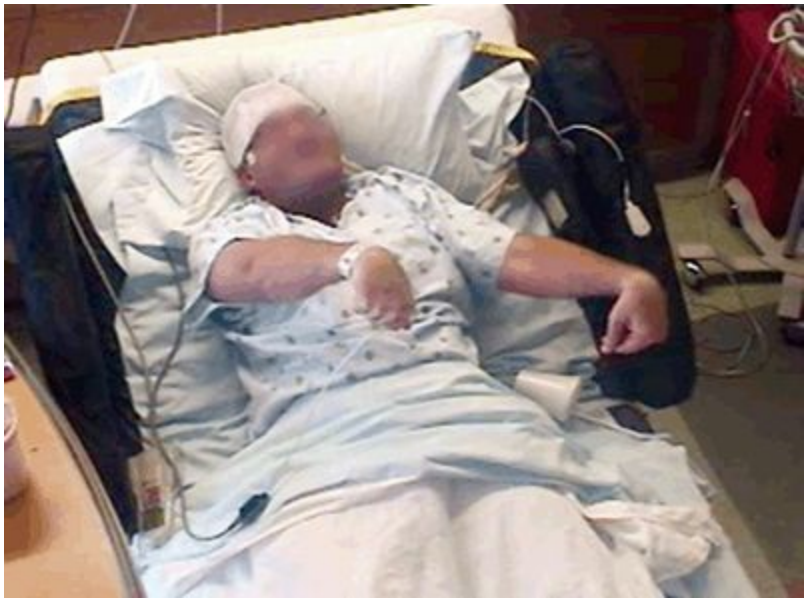


Figure 14.3. Generalized tonic extensor posturing preceding the clonic phase in a 32-year-old patient experiencing recurrent GTC seizures. Note the forearm pronation, wrist flexion, and partial finger extension.

The postictal state is initially composed of a flaccid unresponsive state of variable duration usually with recovery in 10 to 30 minutes. Confusion, disorientation, somnolence, headache, personality and mood changes, and myalgias may resolve over the next 24 hours. During this time, there is a notable loss of postural tone, unconscious state, and loss of deep tendon reflexes on examination. Ictal hypoventilation and subsequent postictal apnea may contribute to the development of cardiac arrhythmias (Fig. 14.4) (12). During the immediate postictal phase, there is nonspecific relaxation of the urinary sphincter resulting in urinary incontinence. Postictal agitation, confusion, and disorientation are common and characteristic. A postictal migraine-like headache, nausea, and vomiting may occur. Following a seizure, the postictal serum prolactin and creatine kinase may rise, though they have limited sensitivity and specificity as a biomarker for a GTC seizure (13).

Figure 14.4. Cardiac telemetry after GTC seizure. Note the initial premature ventricular beats (white arrows) prior to reestablishing a normal sinus rhythm (yellow arrow).

Electrophysiology

The waking interictal EEG background of patients with GTC seizures associated with GGE is typically normal. Focal features may occur when comorbid conditions are present. Preceding interictal epileptiform discharges (IEDs) in the preseizure period may be seen prior to onset of clinical symptoms (14). Bursts of intermittent rhythmic theta and delta activity is more commonly observed in patients and family members in GGE (15,16). Generalized spike and waves (GSW) usually indicate a GGE when interspike frequencies are 3 Hz or greater in patients with GTC seizures (Fig. 14.5) (5,15–17). Morphology and synchrony may exhibit significant intra- and interindividual variability over long periods of time (11,15). Focal IEDs or focal slowing usually suggests localization-related epilepsy; however, asymmetric discharges may be seen (especially during NREM sleep) in GGE that falsely suggest focal seizures (5,11). Secondary bilateral synchrony may give the false appearance of GSW; however, secondary bilateral synchrony is distinguished from GSW by the presence of persistent focal IED, a distinct morphologic difference between the focal or lateralized and the generalized discharge and the appearance of a consistent "lead" prior to the onset of the generalized epileptiform discharge (ED) (11,18). GTC seizures associated with encephalopathic generalized epilepsy (EGE) have slow background activity, voltage asymmetries, and intermixed focal or generalized theta and delta slowing in the EEG that may be continuous or intermittent, rhythmic, or polymorphic depending upon the degree of encephalopathy (5,7,19).

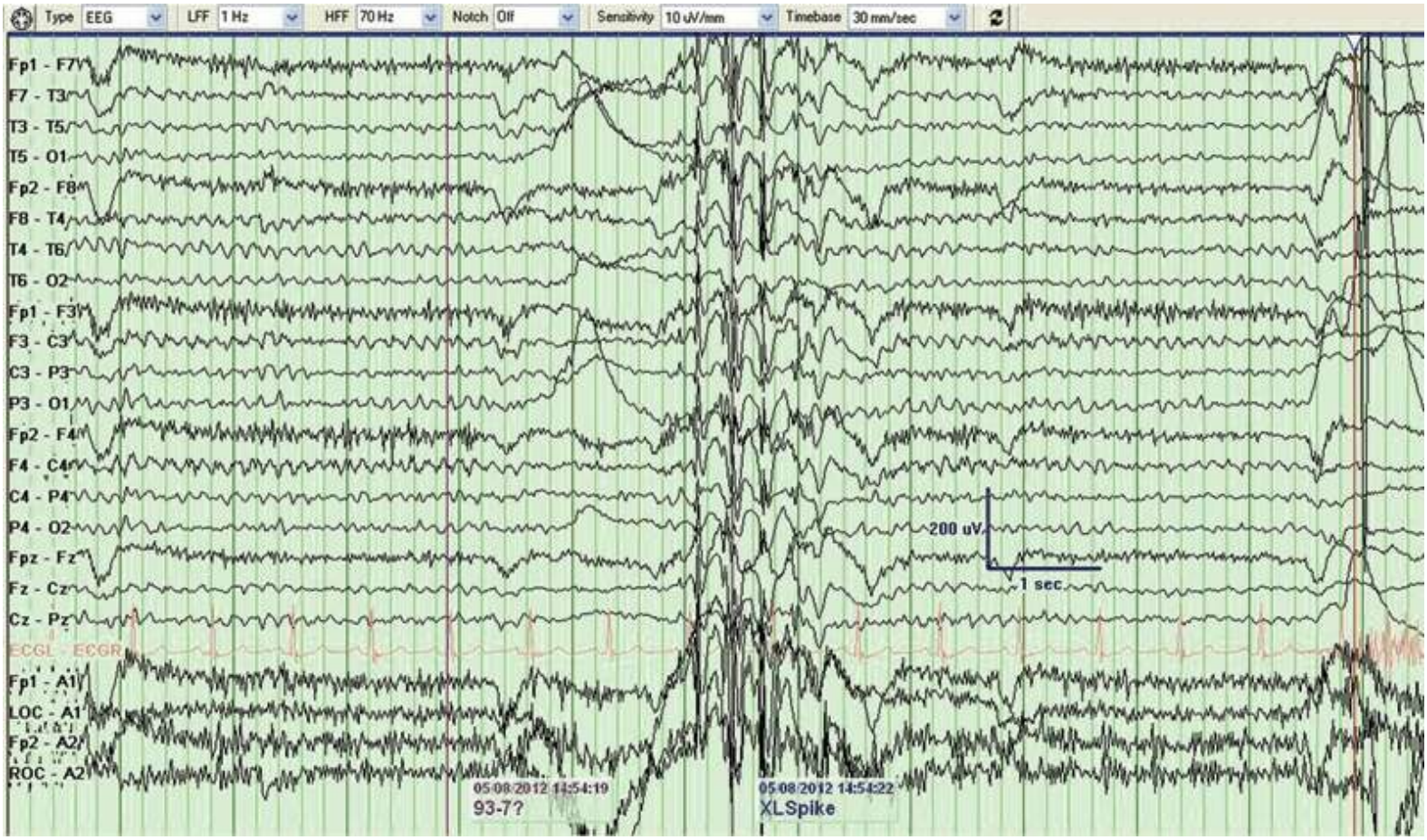


Figure 14.5. EEG with a 1-second burst of 3-Hz generalized spike-and-wave in second 6 in a patient with GTC seizures on awakening. Note: 3-Hz generalized spike-and-wave suggests a "primary" GMS, though it may be infrequently seen as a "secondary" bilateral synchronous discharge on focal origin.

The ictal EEG during a GTC seizure has generalized frontally predominant fast rhythmic spikes during the tonic phase. A 10-Hz discharge followed by a brief attenuation or low-voltage fast activity at a frequency of approximately 20 Hz is seen. Gastaut described the 10-Hz rhythm as the "epileptic recruiting rhythm," which progressively increases in amplitude (Fig. 14.6) (19). Following the tonic phase, the frequency of the ongoing ictal activity decreases as amplitude increases in association with repetitive clonic jerks. During the clonic phase, the initial fast rhythm becomes fragmented by rhythmic slow waves. Intermittent polyspikes are apparent and accompany the clonic jerk with a decreasing slow-wave frequency during the relaxation period (5,10). The postictal phase reveals immediate suppression of the background that evolves to diffuse slowing that gradually returns to the baseline background. During the postictal phase, a nonlocalized GTC seizure may demonstrate focal or lateralizing features that suggest the event was a focal-onset seizure that rapidly evolved to a bilateral convulsion.

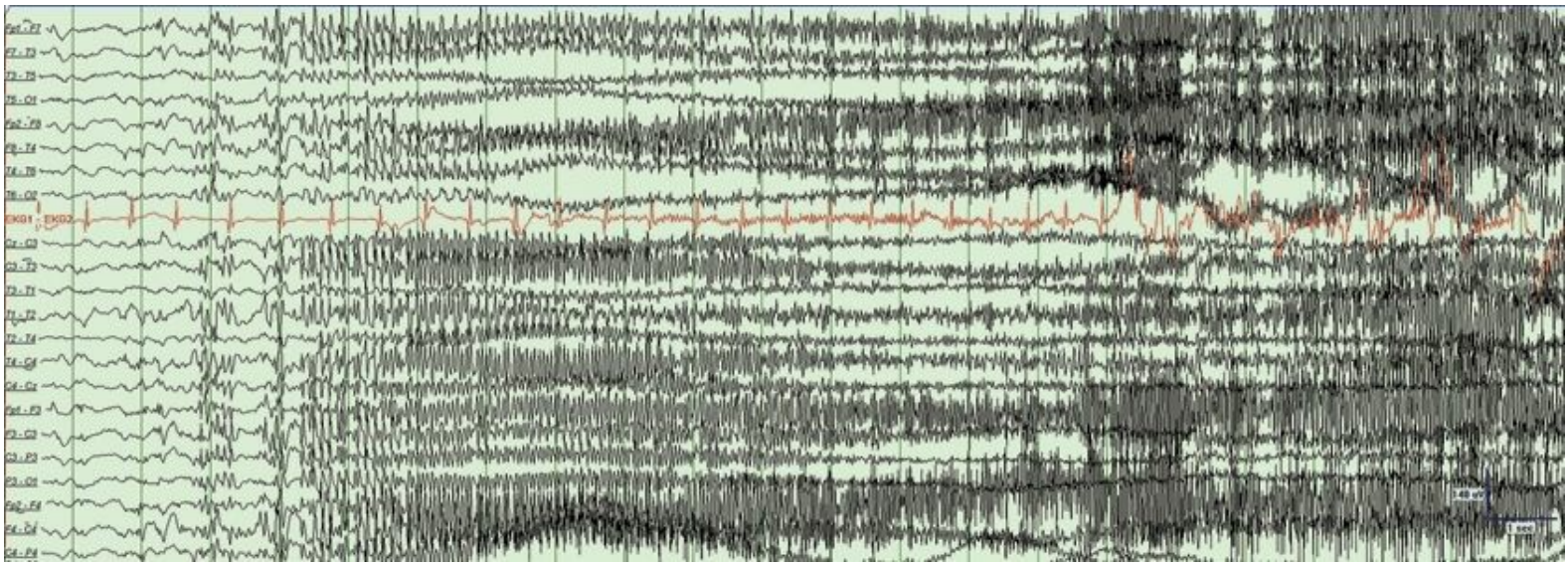


Figure 14.6. EEG during a GTC seizure in a patient with GGE. Notice the generalized onset and evolution during the seizure. (From Tatum WO. Handbook of EEG Interpretation. 2nd ed. New York: Demos Medical Publishing; 2014:135 [reprinted with permission from Demos Medical Publishing].)

Clinical Correlation

Diagnosis is usually not difficult. The aftereffects can include trauma to the head, tongue, and mouth; vertebral compression fracture; posterior shoulder dislocation; aspiration pneumonia; neurogenic pulmonary edema; and cardiac arrhythmia (5,10,20). Sudden unexplained death in epilepsy (SUDEP) may occur following a GTC due to postictal centrally mediated alteration in cardiorespiratory function (20). Some "convulsions" (i.e., benign neonatal familial convulsions) reflect terminology that is actually a misnomer since GTC seizures in infancy are more likely to be focal tonic–clonic seizures due to brain hyperexcitability with or without a genetic basis (16). GGE with sporadic GTC seizures may be self-limiting and express a single seizure semiology (5,16). Other syndromes with GTC seizures persist throughout life (epilepsy with GTC seizures on awakening). Some GGE epilepsy syndromes (JME and juvenile absence epilepsy) have mixed GMS, and some reflect combinations (epilepsy with myoclonic absences) (16,17). New-onset GTC seizures in adulthood likely have a focal onset (Video 14.1) though focal and lateralizing electroclinical signs in patients with GGE should receive consideration (11).

Many physiologic nonepileptic mimics of GTC seizures may occur. In early childhood, breath-holding spells can mimic epileptic GTC seizures. In adulthood, convulsive syncope, metabolic disturbances (electrolyte imbalance), drugs (i.e., bupropion and tramadol), and substance abuse (i.e., cocaine and alcohol) are important causes to consider. Similarly, acute symptomatic seizures within 7 days of a systemic or brain insult does not equate to posttraumatic epilepsy. However, psychogenic nonepileptic seizures exist as a leading cause in the differential diagnosis of GTC and GMS and are best addressed by video-EEG monitoring (21).

Generalized Tonic

A generalized tonic seizure (GTS) is a generalized motor seizure that is composed of generalized tonic muscular contraction with a loss of consciousness. A GTS occurs when the electroclinical onset arises simultaneously from both hemispheres (6,22,23). From infancy to adulthood, GTS may occur. Tonic seizures typically reflect the symptomatic nature of an underlying brain condition or disease

process (22,23) affecting the cerebral cortex in patients with an EGE (see Chapter 20). Despite the apparent homogeneous classification of seizure semiology, various underlying pathophysiologic mechanisms occur. GTS typically occurs with varying degrees of cognitive dysfunction and mental retardation. They are the most characteristic seizure type in the Lennox–Gastaut syndrome (LGS). GTS may present as either the initial or the primary manifestation of this syndrome (22). The prevalence of GTS is inadequately represented given the discrepancy between observed clinical seizure incidence and subclinical seizures noted during polygraphic recording (23). Tonic seizures often have an unknown etiology, although congenital brain malformation, hypoxic–ischemic encephalopathy, and central nervous system infections are the symptomatic causes most often found. Mental retardation is less common when tonic seizures begin later in childhood or in adulthood and is associated with a poor prognosis for seizure control and normal development with seizure onset before the age of 2 years (22–24).

Semiology

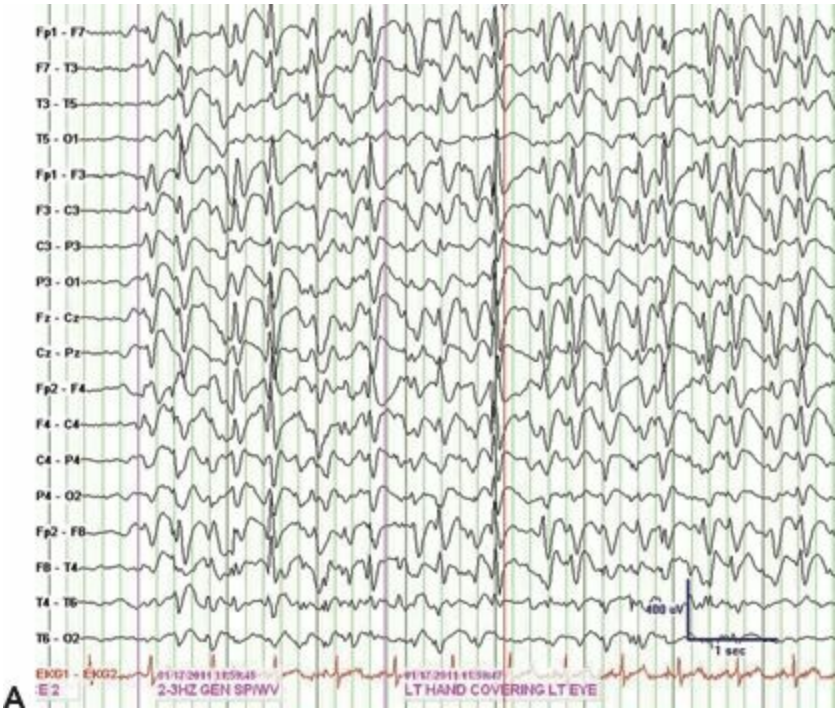
GTS may be very brief and appear nonconvulsive. When they are brief or associated with atonic seizures, the semiology may be difficult to differentiate. Video-EEG analysis of drop attacks with the patient in the standing position demonstrates that the first manifestations of GTS occur with either tonic flexion at the hips or propulsive or retropulsive falls (24). This is in contrast to atonic seizures that begin with flexion at the waist and knees, followed by additional knee buckling leading to a fall straight downward (24,25). Taxonomy has included (i) tonic axial seizures with abrupt tonic muscular contraction and rigidity of the neck, facial, and masticatory muscles; (ii) global tonic seizures involving widespread contraction of the axial and appendicular musculature (Video 14.2); and (iii) tonic axorhizomelic seizures as an intermediate form with contraction of the upper limb muscles and deltoid muscles that leads to elevation of the shoulders. Focal seizures with asymmetrical tonic posturing are referred to as tonic postural seizures. Short tonic seizures have high-amplitude, rapid muscular contractions that involve mainly the axis of the body and trunk, maximal in the neck and shoulder girdle, and last only 500 to 800 ms with forward positioning that resembles epileptic spasms (25). When tonic posturing is observed in patients with epileptic spasms, the term tonic spasms describes this drug-resistant seizure type (26). Prolonged tonic seizures may occur with a vibratory component that resembles a GTC seizure (24,26), although GTS are much briefer, averaging 10 to 15 seconds (27).

Tonic seizures may vary from a short, upward deviation of the eyeballs with or without nystagmoid eye movements to more intense generalized symmetrical or asymmetrical tonic stiffening, loss of consciousness, falls, and repeated injury (19,28). Falls from tonic seizures may be forward or backward depending on whether the axial and lower limb musculature is fixed in flexion or (less frequently) in extension. GTS and atonic seizures are referred to as drop attacks, though GTS are associated with falls less consistently than atonic seizures because the leg muscles are often not involved or have an increased extensor tone to maintain an upright posture (23). Scars on the forehead and occipital regions may reflect injury patterns associated with propulsive or retropulsive seizures. Contraction of the respiratory and abdominal muscles may create a high-pitched cry or a period of hypopnea. Seizure intensities may vary among patients and individuals, and combined seizure types may also occur (29). The duration of tonic seizures is several seconds to a minute, although most last for 5 to 20 seconds. Tonic seizures are most frequent during stages I and II of non–rapid eye movement (NREM) sleep (22–24,30). Autonomic features may include respiratory, heart

rate, or blood pressure increases; pupillary dilation; and facial flushing (22). Postictal features demonstrate a variable degree of cognitive and motor recovery, with the depth of the postictal state usually proportional to the seizure intensity (22,23). In patients with LGS, GTS may appear "subclinical" without detailed clinical testing and EEG (31). Tonic status epilepticus is not uncommon and may occur in 54% to 97% of patients with a brief initial tonic component (22).

Electrophysiology

The interictal EEG in patients with GTS is dependent on the specific epileptic syndrome and may change in adulthood (32). In most patients with GTS associated with EGE, a diffusely slow background with multifocal spikes and sharp waves (Figure 14.7b) is present on the EEG reflecting a diffuse structural injury of the brain (22). In patients with LGS beginning before the age of 5 years, generalized slow spike-and-wave complexes (Figure 14.7a) may not appear until the onset of epilepsy is well established (19,22–24,27). Epileptic spasms may have a similar semiology to GTS seizures though the EEG has the characteristic interictal pattern of hypsarrhythmia and an ictal pattern of an electrodecremental response (25,26).



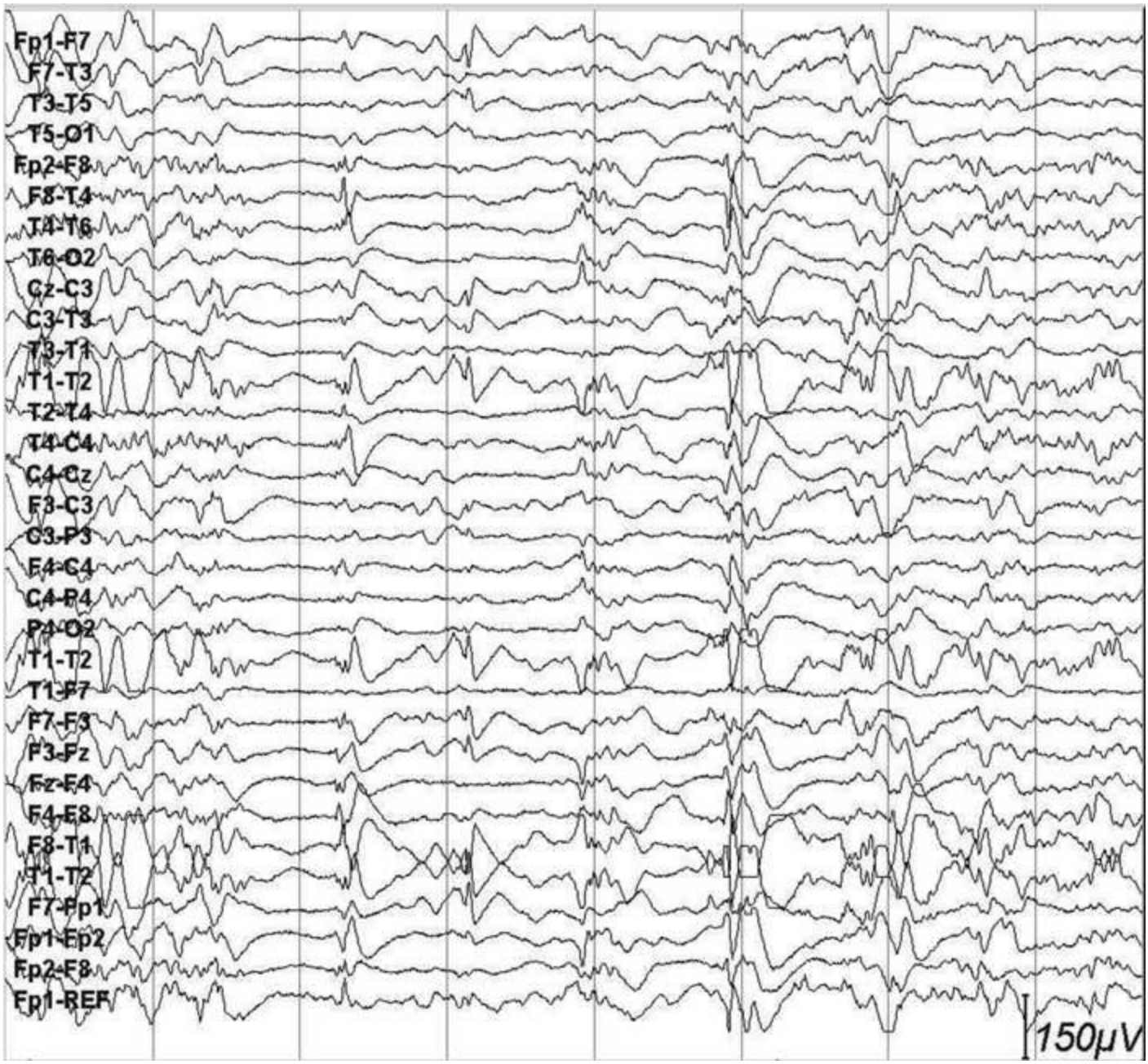


Figure 14.7. (**A**) Slow spike-and-waves and (**B**) multifocal independent spike discharges in two patients with GMS and mixed tonic, tonic–clonic, and myoclonic seizures. (From Tatum WO. Handbook of EEG Interpretation. 2nd ed. New York: Demos Medical Publishing; 2014:135 [reprinted with permission from Demos Medical Publishing].)

The ictal EEG manifestations of GTS associated with EGE are variable. Generalized paroxysmal fast activity (GPFA), generalized background attenuation, low-amplitude rhythmic fast activity of 15 to 25 Hz that progressively increases to 50 to 100 μV, and an initial attenuation followed by the rhythmic fast activity of 10 to 15 Hz that is high amplitude from the seizure onset are common features of GTS on EEG (33). Commonly, generalized frontally predominant initial attenuation of background activity that is associated with desynchronization precedes the appearance of bilateral 10 to 25 Hz spikes with voltages up to >100 μV (34). Attenuation in the EEG reflects a generalized desynchronization with or without rhythmic ictal fast activity. GPFA often appears as the electrographic counterpart of tonic seizures during slow-wave sleep and consists of diffuse, repetitive, medium- to high-amplitude spike discharges that usually have clinical semiologies with increased muscular tone (19,23). The pattern of GPFA on the EEG is a 10-Hz burst of bilateral fast activity that occurs frequently during NREM sleep, disappearing in REM sleep. Bursts of GPFA are identical to the discharges seen with GTS but may have subtle clinical signs such as brief apnea or

mild muscular contraction that is best seen on electromyography (Fig. 14.8). GPFA is not pathognomonic for LGS since extratemporal focal seizures may also manifest similar bursts. A mixture of clinical and EEG patterns seen with GTS may also be associated with other types of GMS (Fig. 14.9) (23,29). Fast ictal spike discharges have been noted in the centromedian nuclei of the thalamus bilaterally with invasive electrodes that correlate with the onset of tonic seizures during concomitant scalp EEG change (35). Rhythmic and morphologically distinct ictal theta and delta have been described in patients with tonic status epilepticus and LGS (36).

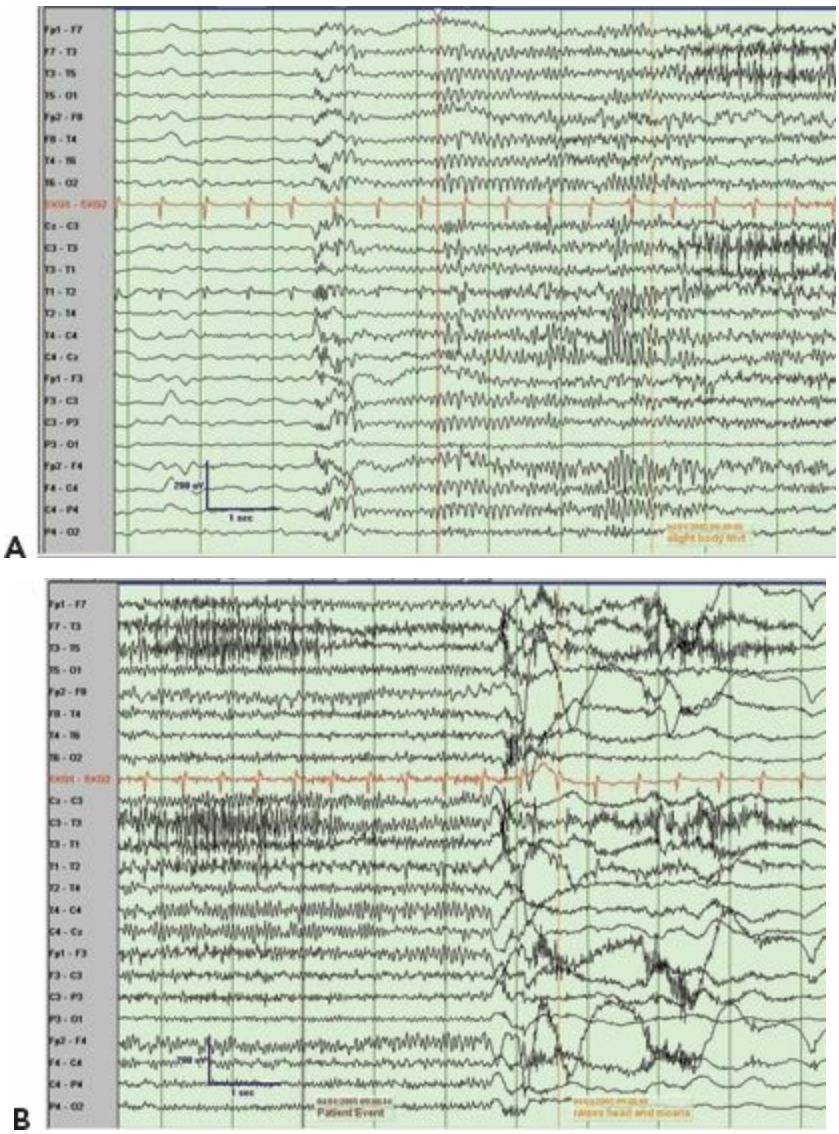


Figure 14.8. EEG of a GTS from sleep. Note the initial generalized polyspike followed by 10-Hz activity **(A)** accompanying a subtle GTS and the minimal myogenic artifact 3.5 seconds following onset **(B)** but the significant postictal slowing.

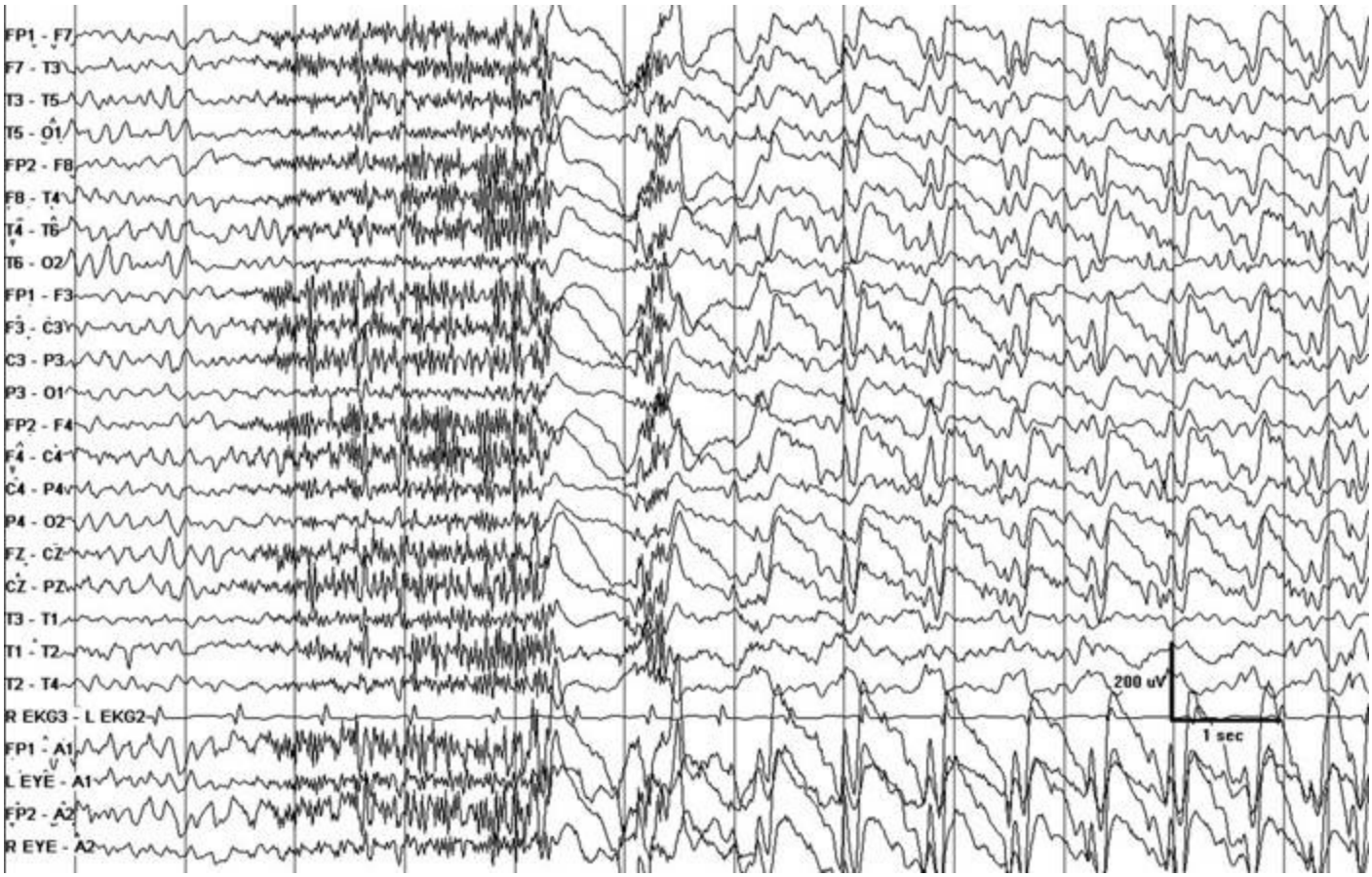


Figure 14.9. EEG demonstrating a burst of polyspikes at the onset (tonic component) that precedes a burst of generalized slow spike and waves (atonic component) during a drop attack.

Tonic postural seizures associated with localization-related epilepsy often have interictal midline spikes in the scalp EEG when they are detected (37). Ictal discharges may arise from an epileptogenic zone in the frontal cortex that is remote from the scalp EEG and be unrevealing. A regional, low-amplitude, high-frequency rhythmic ictal fast frequency discharges (33) or subtle diffuse attenuation of the background may be apparent in some patients (38).

Clinical Correlation

Tonic seizures frequently coexist with mental retardation, an abnormal EEG, and a poor response to therapy. The implication of GTS is based on the clinical history and disease course. GTS represents one of the cardinal seizure types in LGS (22,23,30). Although GTS are characteristic of LGS affecting 74% and 90% of patients (22), they may be virtually absent in other EGEs (i.e., severe myoclonic epilepsy of infancy). Tonic seizures are the most common cause of a sudden fall (drop attacks) in children with LGS (38) and a major cause of morbidity and mortality, often necessitating the use of a protective helmet (22). When seizures are present during neonatal development, GTS represent one of the earliest clinically identifiable semiologies (39). Early infantile epileptic encephalopathy is an EGE that is also characterized by frequent tonic seizures. West syndrome and epileptic spasms are a unique form of GTS, which occurs with a sudden flexion or extension followed by tonic contraction for seconds without clonic jerking. Although epileptic spasms have a semiology that is similar to GTS, spasms are more rapid in onset (lasting for 1 to 2 seconds), occur in clusters, and have hypsarrhythmia on the interictal EEG.

Seizures may appear to possess a generalized semiology even though they have a focal onset.

Secondarily, GTS with asymmetrical tonic abduction and elevation of the arms may mimic tonic seizures in patients with EGE. When tonic postural seizures occur, they are often frequent, nocturnal, and associated with other focal semiologies and episodes of recurrent status epilepticus, given their predisposition to arise from the frontal cortex (40).

Nonepileptic tonic or opisthotonic posturing should also be considered when painful tonic spasms or posturing occur, even though treatment may include antiseizure drugs (ASDs). Nonepileptic tonic posturing is readily differentiated from epileptic tonic seizures by normal interictal and ictal EEG. Video-EEG monitoring has improved our identification, classification, and quantification of patients with GTS in pharmaceutical research and surgical selection.

Generalized Myoclonic Seizures (GMCSs)

A GMCS is a brief generalized motor seizure resulting in a lightning-like jerk. Myoclonus is a brief, sudden, involuntary, shock-like muscular contraction of the body that results in a movement that may be either epileptic or nonepileptic. Nonepileptic myoclonic jerks may be activated during intentional movement (action myoclonus) or occur spontaneously in the face of other neurologic conditions (i.e., spinal cord and cerebellar dysfunction). A GMCS has an electroclinical correlation with myoclonus and an ictal ED on EEG in a patient with epilepsy. A GMCS may occur predominately upon awakening or during transition to sleep. Cortical reflex myoclonus is a term that reflects a motor movement resulting from focal region of brain dysfunction in epilepsy with the clinical manifestations reflecting the area of the brain responsible for motor activation. Reticular reflex myoclonus, on the other hand, may occur with generalized epilepsy but originates in the subcortical structures and brainstem. Myoclonic seizure may occur either as part of a GGE syndrome or as a feature of EGE though rarely as a feature of localization-related epilepsy.

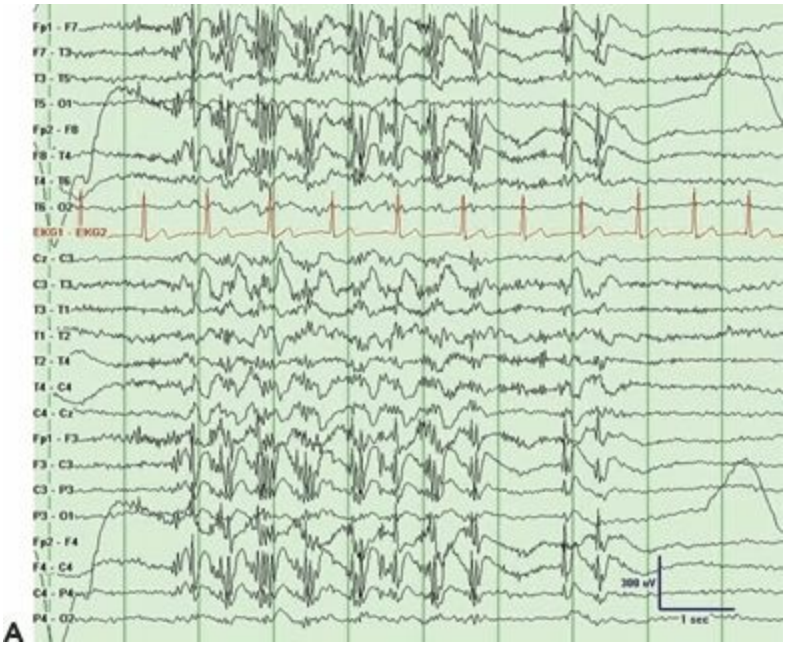
Semiology

GMCSs are characterized by brief, sudden, involuntary muscle contractions involving different combinations of the head, trunk, and limbs (Video 14.3). They are often generalized, but may also be limited to the face and axial musculature (41). They usually occur without detectable loss of consciousness (41). GMCS may be regular or irregular, symmetrical or asymmetrical, and synchronous or asynchronous. They may be isolated or rapidly repetitive. Myoclonic jerks may occur as a positive or negative motor movement, manifesting extra movement or a sudden loss of movement and postural tone (41). Massive epileptic myoclonus implies that a bilateral jerk is large enough to create a fall. Focal seizures with tonic posturing may occasionally mimic myoclonic seizures, though the presence of a relative asymmetry or sustained increase in motor tone should help distinguish this semiology. Seizure combination with myoclonic seizures (myoclonic–tonic, myoclonic–atonic) have been recognized by the new ILAE classification (1). GMCS may occur as part of another seizure type (i.e., epilepsy with myoclonic absence seizures). Myoclonic status epilepticus typically occurs in patients with EGE and occurs less frequently during sleep (42).

Electrophysiology

In general, myoclonic jerks have a high-amplitude, bisynchronous, diffuse spike-and-wave or polyspike-and-wave discharge as their electrophysiologic correlate despite interictal– ictal and syndromic differences (Fig. 14.10). A very brief latency between short bursts of synchronized

electromyographic potentials in both agonist and antagonist muscles and that of the corresponding spikes occur. The spikes are time-locked events that are coupled with the myoclonic jerks that follow. By using back-averaging techniques, latencies are found to occur between 21 and 80 ms (43). When a myoclonic jerk is generated by subcortical structures, a generalized IED follows the first electromyographic sign of myoclonus though a primary epileptogenic mechanism has been controversial (43,44). Negative myoclonus, if due to a lapse of tone, can be seen only during antigravity posture and is coupled with either the slow-wave or the second positive component of a polyspike-and-wave discharge (41,43). Myoclonic seizures have semiologies with an electromyographic pattern, demonstrating a brief synchronous potential of <50 ms that is seen simultaneously in the involved muscle groups (41). During the myoclonic jerks, medium- to high-amplitude repetitive 16-Hz spikes are seen on the surface of the scalp EEG (44). Recordings from thalamic nuclei during myoclonic seizures demonstrate subcortical slow polyspike-and-wave discharges that lead the seizures recorded on the scalp surface in patients with LGS (35). Myoclonic jerks may appear to represent brief GTS but instead are single muscular contractions that last <200 ms, while GTS are more intense and sustained lasting for seconds in duration (22), although they may be associated with a myoclonic (or atonic) component (35). The EEG is critical in defining benign syndromes with GSW (i.e., benign myoclonic epilepsy of infancy) from more malignant epilepsies associated with GMCS and burst suppression (early myoclonic encephalopathy). Giant visual evoked potentials appearing as occipital high-amplitude polyphasic spikes may be observed during intermittent photic stimulation at low repetition rates of <3 Hz in some patients with progressive myoclonus epilepsy (45,46). Focal myoclonias are suspected to be derived from a hyperexcitable cortex responsible for motor activation. Electrographic secondary bilateral synchrony is common in patients with myoclonic jerks and extratemporal focal seizures. Generalized IEDs may show a brief delay in interhemispheric representation as a function of coherence and phase analysis (45).



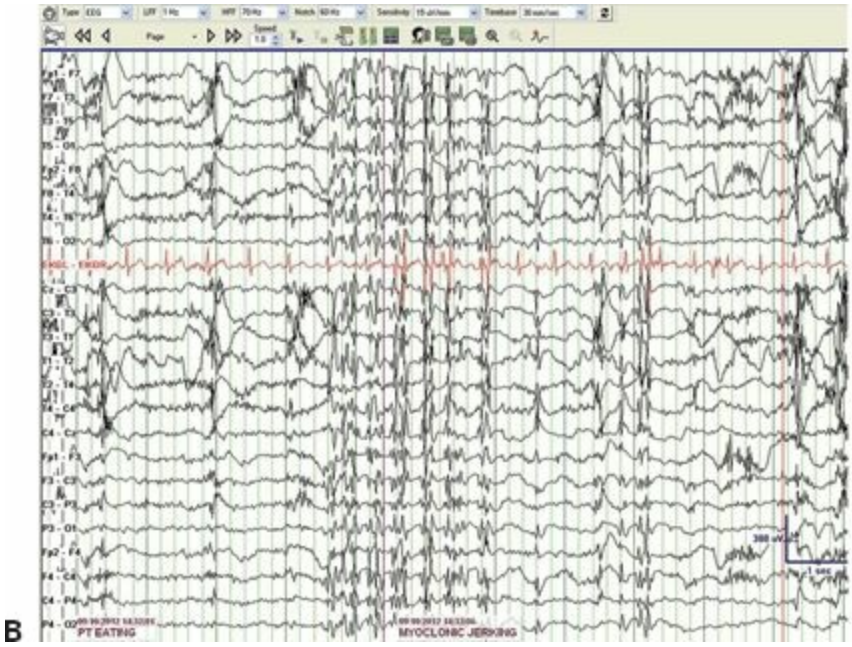


Figure 14.10. Generalized polyspike-and-waves in two patients with myoclonic seizures: (**A**) with JME and (**B**) with progressive myoclonus epilepsy (adult-onset neuronal ceroid lipofuscinosis). Note the waveform similarity despite differences in the interictal (**A**) and ictal state (**B**) and clinical impact of these two syndromes.

Clinical Correlation

Myoclonic seizures are clinically heterogeneous and are associated with many different types of epilepsies and epilepsy syndromes from early infancy into adulthood. Myoclonic seizures may be associated with GGE syndromes (Chapter 17), EGE syndromes (Chapter 20), and mimic epileptic spasms (Chapter 16). There can be semiologic difficulty with distinguishing GMCS from GTS-associated drop attacks. GMCSs and GTC seizures in patients with normal cognition suggest JME, whereas GMCS mixed with other seizure types and mental retardation suggest one of the EGE. Causes of GMCS vary greatly from genetic to acquired causes (45,46). The associated features help to define the epilepsy syndrome rather than the semiology. In JME, the presence of myoclonus preceding GTC seizures helps distinguish a GGE relationship (44). In other epilepsies, GMCSs may also occur with deleterious consequences (epilepsy with myoclonic astatic seizures) to complicate classification between GGE and EGE or as a combined seizure type (epilepsy with myoclonic astatic seizures) (43,44,47). Patients with GGE infrequently manifest drug- resistant myoclonic seizures though it is frequently noted in the setting of developmental delay (44).

A structural–metabolic (or unknown) etiology is often found when myoclonic seizures begin before the age of 4 years (43). Febrile seizures and subsequent GMCS often herald a malignant epilepsy during infancy and early childhood (early myoclonic encephalopathy and Dravet syndrome) (43). Myoclonic seizures may be distinguished by the associated background EEG features such as hypsarrhythmia in spasms and burst suppression in early myoclonic encephalopathy. This is in contrast to the EEG of GGE and GMCS that is typically associated with generalized polyspikes. The progressive myoclonic epilepsies (see Chapter 19) with cognitive deterioration and abnormal neurologic signs are a rare, but extremely debilitating and progressive, heterogeneous subgroup of EGE with myoclonic seizures as the hallmark of the conditions (46).

Generalized Clonic Seizures (GCSs)

A GCS is a convulsive seizure that involves bilateral rhythmic or semirhythmic contractions of a

group of muscles in the body. The absence of a tonic component serves to distinguish it from a GTC seizure. However, electrical brain stimulation of the primary motor cortex in humans elicits repetitive clonic muscle contractions and, with subdural recordings, has demonstrated a brief tonic component prior to clonic jerking (48). Clonic seizures are most frequently observed in very young children. GCSs are more common than GTC seizures during the neonatal period due to the immature myelination of the brain that occurs at this age (49). GCS are more likely to occur in children with other GMS types such as GTC and myoclonic seizures. GCS seizures frequently occur in patients with focal epilepsy, especially in the frontal lobe. Frontal lobe epilepsy with or without impaired consciousness may also occur with axial clonic jerks (i.e., anterior frontopolar region) and focal clonic jerks (i.e., opercular and dorsolateral) and may also manifest bilateral clonic jerking that is symmetric or asymmetric (Video 14.4).

Semiology

Clonic seizures are often asymmetrical and consist of a brief onset and offset (33). The clonic jerking of a GCS seizure has a decrescendo frequency of repetitive clonic jerks that maintain the same level of intensity despite declining frequency (33,50). GCS may involve a discrete group of muscles preferentially, though the arms, neck, and facial muscles are most commonly involved. The clonic jerking is more sustained and rhythmic than the single lightning-like jerks that occur with myoclonic seizures and without a prominent tonic phase seen with GTC seizures. When clonic seizures are generalized, they are associated with impairment of consciousness. The duration of the seizures varies, and when prolonged, generalized clonic status epilepticus may occur. GCS may also appear multifocal with clonic movements that appear to migrate over the body or even from limb to limb with variable impairment of consciousness (3,49,50). The presence of autonomic features and significant postictal state is atypical for a GCS (33,50). When it occurs, the postictal phase is usually brief. Other GMS may be coupled with a clonic phase (i.e., clonic–tonic–clonic seizure). GCSs may be slow to propagate and may yield focal clonic jerking that exhibits a "jacksonian march" as the propagation of electrical activity spreads from one region of the brain to adjacent areas recruiting the face, arm, and leg musculature that is innervated by the contralateral neocortex. Clonic status epilepticus may occur and is relatively rare in adults and much more common in infants (49,50).

Electrophysiology

The interictal EEG in patients with GCS may offer nonspecific clues to the etiology. Background abnormalities are much more likely to predict the presence of seizures. Spike- and polyspike-and-wave discharges may be present (Fig. 14.11) (49). In the neonatal period, there is less diagnostic specificity when seizures occur (33,50). GCS are often accompanied by a generalized 10-Hz rhythm that is intermixed with slow waves of variable frequency (50). However, GCS may have an overlap with the EEG such that no changes are detectable (or interpretable due to artifact) on scalp EEG when a focal seizure originates in a distant or small portion of cortex (Fig. 14.12). In one series that analyzed the electroclinical spectrum of approximately 100 infantile seizures, 6/69 manifested GCS (49). The ictal EEG consisted of diffuse repetitive EDs that have been reported to be frontal or occipital predominant (49). Seizure termination may be poorly defined with alternating ictal and background rhythms gradually leading to resolution (33,49,50). For those with abrupt seizure termination, return of background activity or diffuse attenuation or slowing was noted. In adults, focal clonic seizures are associated with a polyspike-and-wave pattern in the EEG of the primary motor

area. Compound muscle action potentials occurring simultaneously in agonist and antagonist muscles followed the polyspikes in the intracranial EEG with a latency of 17 to 50 ms in 1 study, with the muscle contractions occurring during the slow waves (48). Clonic status epilepticus may follow another form of status (i.e., myoclonic status epilepticus) and appear with variable EEG ictal patterns commonly associated with rhythmic bilateral bursts of high-amplitude delta activity with intermixed spikes and polyspikes.

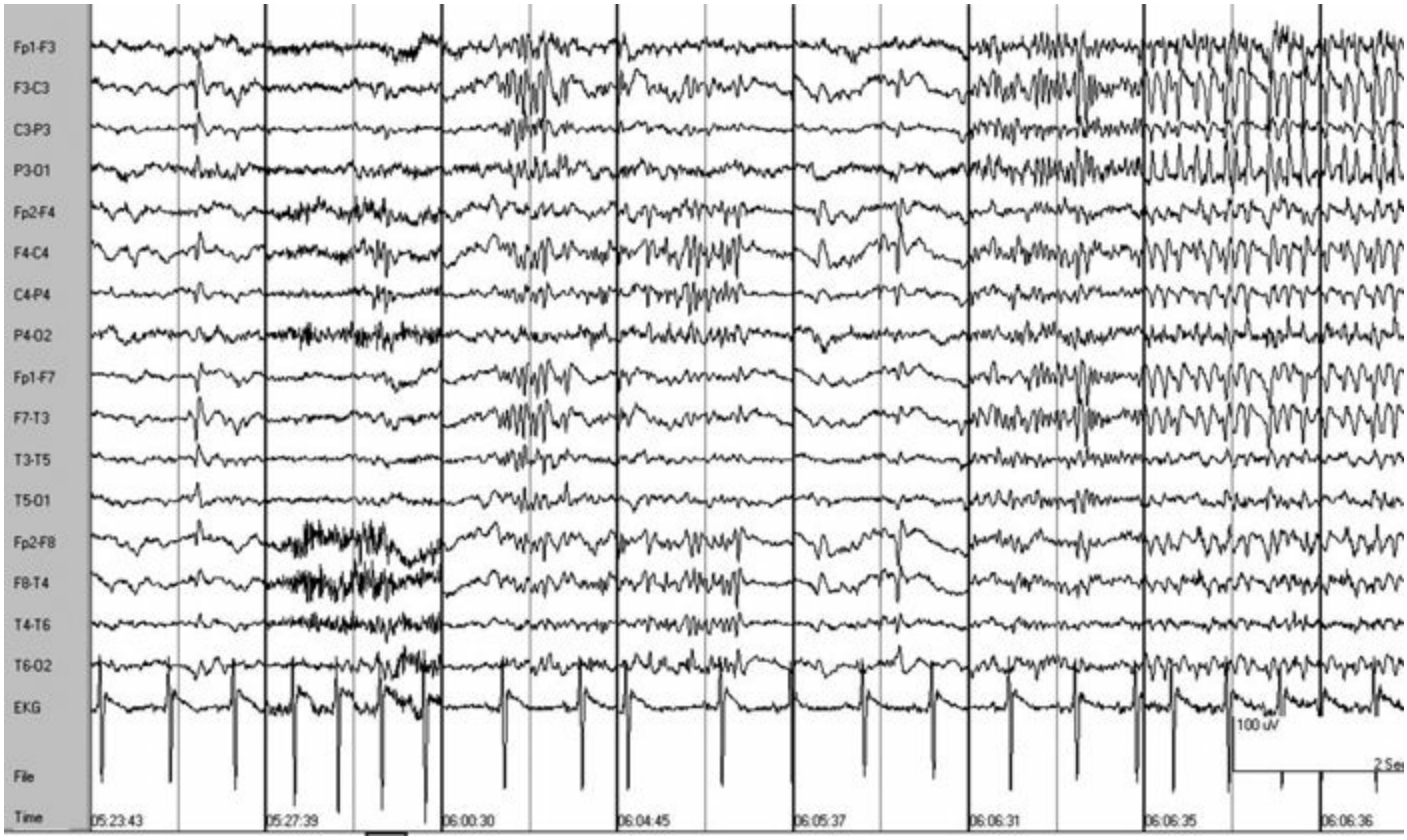


Figure 14.11. Ambulatory EEG with 2-second segments of lateralized spikes (seconds 1 and 5), lateralized bursts of polyspikes (seconds 3 and 4), GPFA (second 6), and diffuse polyspikes (second 7) in a patient with EGE and mixed seizure types including GMS.

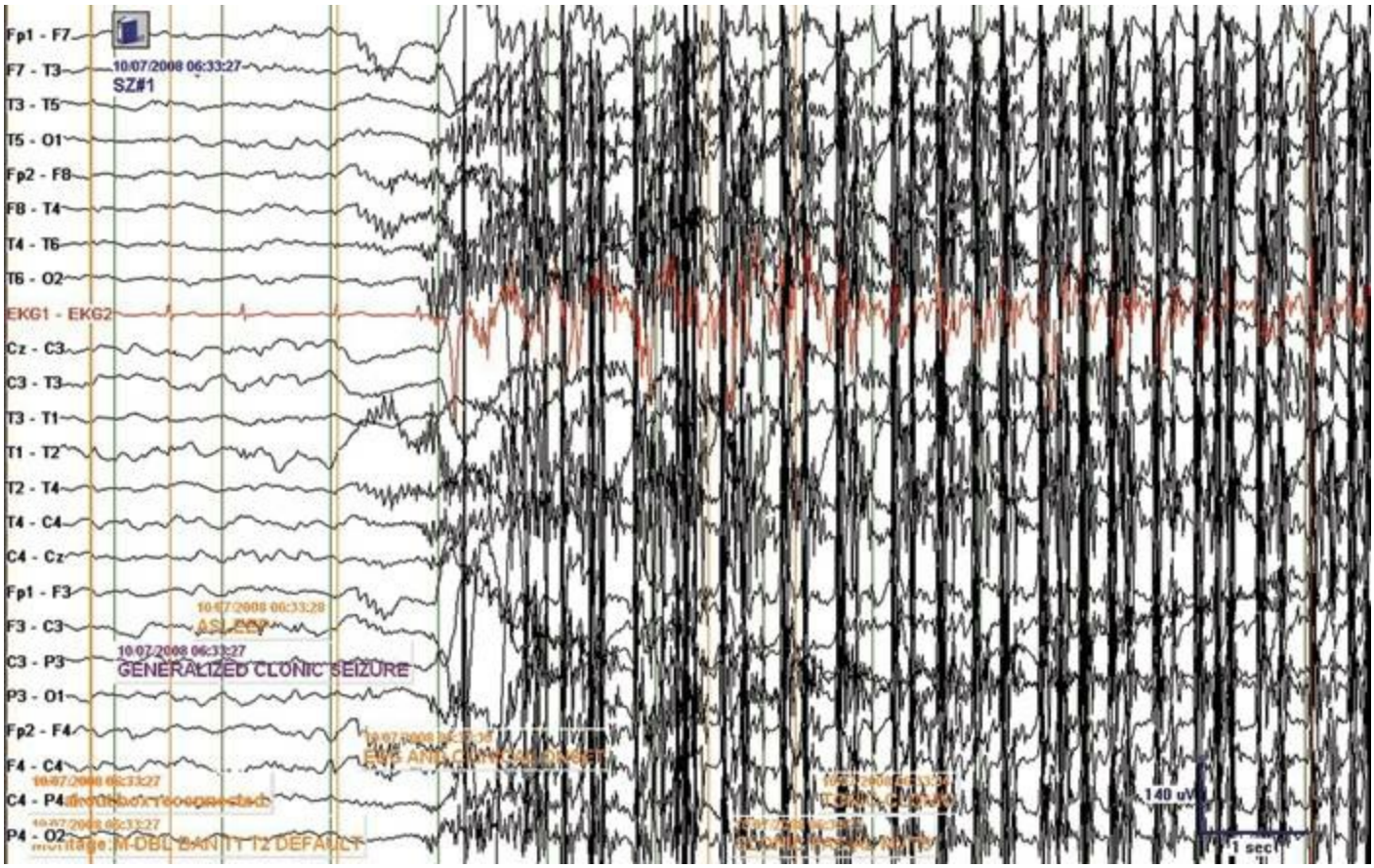


Figure 14.12. GCS in a 14-year-old with mental retardation and long-standing drug-resistant GMS. Note the phasic myogenic artifact at the start and throughout the seizure with mild increase in frequency but without change in the apparent amplitude.

Clinical Correlation

When ictal activity involves the primary motor cortex, clonic convulsions of the body can occur (48,50,51). GCS are usually noted in the neonatal or early infantile period (49). They are not characteristic of any particular epileptic syndrome, but an underlying structural–metabolic etiology is more likely with GCS than with GTS (50). GCS are typically focal- onset seizures in the adult, though in the neonate and infant are more likely to appear bilateral, despite a focal onset. Benign neonatal convulsions may demonstrate frequently repeated clonic (or apneic) seizures that occur about the fifth day of life (aka fifth day fits); however, no etiology or concomitant structural–metabolic component is typically found. When inherited in an autosomal dominant fashion, benign neonatal familial convulsions reveal a family history of similar GCS. Other more malignant epilepsies (Dravet syndrome) may have normal development during the first year of life until developing a generalized or unilateral febrile clonic seizure that heralds the onset of this devastating epilepsy syndrome. Nonepileptic clonic jerks may be seen in convulsive syncope and breath-holding spells, as well as in the recovery phase of patients who experience cataplexy, and are important mimics of clonic seizures that require a different approach to management (50).

Pathophysiology

The pathophysiologic basis for GMS is incompletely understood (19,25,33,41). Some of the key neural connections that are involved with GMS have been elucidated with brain stimulation and from epilepsy surgery patients. In addition, a genetic basis for many of the individuals that possess these seizure types is common and is continuing to unfold (47,50). A heterogenous group of structural

pathologies underlie similar ictal semiologies that are associated with GMS, but despite the vast differences in neuroanatomical substrates, the end result is a generalized motor seizure that bears a similar alteration in motor behavior.

The GTC seizures associated with GGE arise from corticoreticular and thalamocortical pathways, though the precise mechanisms for initiation, propagation, and termination are not fully understood (52). GGE with GTC seizures have been associated with gene mutations involving ion channels, including the sodium channel (SCN1A and SCN1B), calcium channel (CACNA1H), and chloride channel (CLCN2) (16,53). Animal models (e.g., genetically epilepsy-prone rat that when exposed to audiogenic kindling can have seizures that mimic a GTC seizure) have implicated brainstem structures (lateral geniculate body, ascending paths through anterior thalamus and mamillary bodies, and the substantia nigra and locus caeruleus) in the pathogenesis of generalized seizures (54). The spread of hyperexcitability to subcortical, thalamic, brainstem, and spinal cord structures corresponds with the tonic phase of the seizure. Following this, an inhibitory impulse at the level of the thalamus interrupts the tonic phase creating the discontinuous bursts of electrical activity that are manifest clinically as repetitive clonic jerks. GTC seizures that begin from a focal onset have received more extensive evaluation than those that occur in association with the GGE (55).

The pathophysiology of GTS suggests recruitment of the subcortical and the corticoreticular system, which connects the frontal attention areas to the pontine reticular formation and is normally responsible for postural tone and orienting behavior (25,56). A subcortical–cortical polysynaptic connection seems plausible given the clinical observation that corpus callosotomy has a beneficial effect in patients with GTS (22,23). A heterogeneous combination of several seizure types may also coexist, yet share a single epileptogenic symptomatic substrate (22,24,30). Tonic postural (focal) seizures usually arise from the contralateral mesial frontal or parietal cortex from a structural basis or, less frequently, through genetic means (i.e., autosomal dominant frontal lobe epilepsy). The maximal electroshock animal model produces generalized tonic extensor rigidity during electrical stimulation that serves as a mimic of human focal seizures (57). Other animal models demonstrate that an intact brainstem is required to produce a tonic seizure and that it is not solely dependent on intact frontal cortex (58). The reticular formation within the upper midbrainstem is probably involved, given that electrical stimulation will reproduce similar behaviors and lesions in that area suppress them (57). In humans, MRI has demonstrated altered anatomic architecture near the red nucleus of the brainstem in patients with GTS, providing further support for brainstem involvement (59). Limiting extrapyramidal motor inhibition with tonic spasms as a release phenomenon has also been postulated (25). The GABA–chloride ionophore complex appears to play a role in the development of GTS (22,23).

GMCSs are hypothesized to be produced by both cortical and subcortical generators that involve the thalamocortical and reticular projections (43). Because of the wide variety of mechanisms associated with the clinical expression of myoclonic seizures, no single pathology has been identified (41). In patients with EGE, a wide range of pathologic substrates may exist, although frontal lobe abnormalities may favor a predisposition (45). A genetic propensity for the existence of a structural lesion underscores the best-described pathophysiologic mechanisms for myoclonic seizures, with various modes of inheritance observed. For example, the progressive myoclonus epilepsy syndromes have isolated gene loci involved in the majority of the disorders (46). Myoclonic seizures associated with X-linked inheritance, chromosomal abnormalities, mutant mitochondrial DNA, ion channelopathies, and defects of neurotransmitter systems form part of the wide variety of the genetic influences that have been reported (41,45,46).

In GCS similar to GTC, the motor neocortical structures are implicated in the hypersynchronous cortical neuronal discharges associated with seizures (48–51). Hemiclonic seizures (sometimes alternating) may occur (i.e., Dravet syndrome) though, commonly, GCS appear as GMS if they arise from a region adjacent to the motor strip and exhibit rapid propagation either through the corpus callosum or the rostral brainstem (48,51). The pathogenetic mechanism for clonic contractions noted with these seizures is unclear (49,51).

TREATMENT

Many ASD trials conducted are based upon the epilepsy syndrome classification (i.e., partial epilepsy) as opposed to individual seizure type. Over 30% of patients with GGEs and GTC seizures may be refractory to treatment (60). If the patient is not controlled on a newer ASD, it may be useful to try valproate (VPA) at maximal doses even if it has been used earlier at conventional levels. When large-scale randomized clinical trials compared ASDs concentrating on individual seizure types (complex partial and secondarily generalized seizures), no significant differences were seen with older ASDs in the efficacy of GTC seizures (61). A follow-up Veterans Affairs cooperative study comparing VPA and carbamazepine (CBZ) demonstrated no difference in the efficacy of GTC seizures, despite smaller studies suggesting the superiority of VPA in the treatment of GTC seizures (62). Large pragmatic ASD drug trials incorporating the newer ASDs were evaluated in 2 large studies in the United Kingdom: the Standard and New Antiepileptic Drugs (SANAD) trials. One arm (Arm B) of the study evaluated patients with generalized epilepsy and found that VPA was better tolerated than topiramate and more effective than lamotrigine (63). VPA has demonstrated noninferiority in multiple trials assessing GTC seizures and is considered a first-line treatment (64). In addition, lamotrigine (LTG), topiramate (TPM), levetiracetam (LEV) and possibly zonisamide (ZNS), barbiturates, and benzodiazepines are ASDs effective in GTC seizures with a broad spectrum of activity.

GTS are a clinical marker for medical intractability in patients with epilepsy (22,23). VPA is a useful ASD with an intravenous preparation available for replacement therapy and rapid loading. VPA and LTG may demonstrate synergy in patients with GTS in combination. Patients with LGS who have GTS may respond to CBZ; however, it can aggravate myoclonic and atypical absence seizures. LTG, TPM, ZNS, and LEV are ASDs that may be useful in patients with mixed seizures that include GTS. Rufinamide and clobazam are newer ASD treatment options that are useful in the treatment of patients with mixed seizure types that include GTS (65). Phenytoin (PHT) is an effective treatment for patients with tonic status epilepticus (22,40). Tonic seizures have occurred paradoxically from IV benzodiazepine administration (22). Resective surgery may be an effective option for patients with tonic seizures in whom a focal structural lesion is responsible for the seizures (65,66), though it is rarely efficacious when mixed seizure types associated with EGE exist (66,67). Corpus callosal section is an effective palliative treatment for most patients with drop attacks due to GTS (68). Vagus nerve stimulation (VNS) is a less invasive adjunctive treatment that may be useful (67). Stimulation of the anterior nucleus of the thalamus may be promising for patients with GTS given the pathophysiology involving subcortical structures (22). The modified Atkins diet that is high in fat and low in carbohydrates may also be beneficial for patients GTS (69).

Myoclonic seizures are usually responsive to VPA in the majority of cases, though the teratogenic potential for the female population has limited use during the child-bearing years. VPA resistance or unusual presentations of medical illness with myoclonic seizures may occur with seizures of frontal

lobe origin. LEV is probably the most commonly used alternative to VPA and is effective against GTC seizures as well. VPA, LEV, LTG, TPM, ZNS, and clonazepam may all be effective ASDs in the treatment of patients with myoclonic seizures (64). LTG has been used as an initial treatment approach in female patients due to teratogenic concerns though caution is advised because of the possibility of aggravating myoclonic seizures (63). PHT, CBZ, gabapentin, tiagabine, pregabalin, and vigabatrin may aggravate GMCS and should be avoided (70). Other less commonly used agents include acetazolamide, piracetam, and stiripentol (22,70). The ketogenic diet should be considered if ASDs are ineffective for myoclonic seizures though exacerbation of behavioral problems and metabolic acidosis should be considered (especially with TPM and ZNS) (69,70). VNS may also be a useful adjunct in patients with myoclonic seizures with a broad spectrum of activity (67).

Early use of phenobarbital in the neonatal period for clonic seizures is tempered by the limited evidence for its efficacy and the results from animal studies that raise concern for deleterious effects during early development (50,70). Benzodiazepines and PHT have also been considered one of the first-line therapies when clonic seizures occur in the neonatal and early childhood period (49,70). ASD use in adolescence and adulthood for GCS should have broad spectrum of activity when other seizure types are encountered though a primary focal onset should be considered and surgical evaluation excluded for those with a lesion on brain MRI (48,51).

VPA may be useful in many patients with GMS though idiosyncratic risks with VPA treatment are increased in those <2 years of age, treated with polytherapy, and patients with inborn errors of metabolism (70). People with myoclonic epilepsy with ragged red fibers (MERRF) should avoid VPA due to the potential for reduction in the cellular uptake of carnitine and metabolic dysfunction that may result in hepatic failure. Felbamate has demonstrated a broad spectrum of activity though its use is limited by adverse effects. Combinations of ASD (i.e., VPA and LTG) may also provide a synergistic result (71). Implications of genetic mechanisms suggest avoiding sodium channel blockers in certain epilepsies (i.e., Dravet syndrome due to SCN1A mutation). Overall factors predicting a favorable health-related quality of life in newly diagnosed epilepsy with any of the GMS have included the number of ASDs, the presence of a comorbid behavior or cognitive problem, parental depression, and family functioning and demands (72). Active interventions, including education, information on consulting services, seizure tracking cards, and reminders to take ASDs, aid compliance and reduce GTC seizures (73). Children, as well as adults, with both focal and GMS seizures may respond favorably to VNS not only for seizures but for mood disorders (level C) (67). VNS has been recommended prior to corpus callosotomy by some and may facilitate ASD reduction improving over time (67). Children with swallowing problems and GMS should be monitored closely for potential aspiration. Corpus callosotomy is the surgical procedure of choice for disabling GMS when resection is not feasible though it renders few patients seizure-free (66). Generalized tonic and GTC seizures are often improved with up to 80% reduction, whereas myoclonic seizures and focal seizures are not (66). A palliative benefit is noted in most patients, and an improved response to ASD therapy may follow sectioning (66).

SUMMARY

GMS are the sentinel of epilepsy by virtue of their convulsive nature. Video–EEG monitoring is the gold standard for identifying nonepileptic mimics and classification. Many causes exist though pathogenic mechanisms remain largely unknown. The most frequently encountered GMS are GTC seizures involving most age groups and epilepsy syndromes. SUDEP is a real outcome for patients

with drug-resistant GMS most likely to occur in patients with GTC seizures (20). Counseling patients about lifestyle management to ensure safety is an important goal to guide realistic expectations of outcome. Broad-spectrum ASDs are the mainstay of medical therapy for patients with GMS and unclassified epilepsy. Newer ASDs (65), evolving pharmacogenomics (16), dietary manipulation (69), emerging surgical techniques, and new forms of neurostimulation may provide new hope to patients when GMS are uncontrolled (72).

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CHAPTER 15 ABSENCE SEIZURES

EMILY ROBBINS AND DENNIS J. DLUGOS

BACKGROUND

An absence seizure is characterized by a sudden interruption of activity, followed by a blank stare and possible upward rotation of the eyes. The event lasts a few seconds to half a minute and ends with a sudden return to activity (1). Absence seizures can be typical or atypical, and can occur as part of at least five epileptic syndromes, including childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), myoclonic absence epilepsy (MAE), and Lennox–Gastaut syndrome (LGS). CAE is common, accounting for 10% to 17% of all childhood epilepsy, and is slightly more common in girls than boys (2–4).

"Typical" and "atypical" absence seizures are sometimes considered two distinct seizures types. Yet, it is important to recognize that they exist along a continuum with a significant amount of overlap in patient characteristics, seizure semiology, and EEG features (Table 15.1). The clearest distinguishing features between typical and atypical absence seizures are the presence of any associated neurodevelopmental disabilities in the patient: Patients with typical absence seizures are at an increased risk for attention deficit hyperactivity disorder (ADHD), learning differences, and mood disorders (5), while patients with atypical absence seizures usually have overt developmental delay and intellectual disability (6).

Table 15.1 Features of Typical and Atypical Absences Seizures

Features	Typical absence	Atypical absence
Development	Normal; increased risk ADHD/ learning difficulties/mood disorders	Delayed → Intellectual disability
Seizure onset	Abrupt	Insidious
Seizure duration	~10 s	>10 s
Provoked by HV	Very likely	Less likely
Postictal period	Absent or brief	Present
Associations	Automatisms	Changes in tone
Ictal EEG	3 Hz per second spike-and-wave	Heterogenous; <2.5 Hz per second spike-and-wave
Interictal EEG	Usually normal or short GSW bursts	Abnormal: background slowing, disorganization, focal epileptiform abnormalities

TYPICAL ABSENCE SEIZURES

Clinical Features

Typical absence seizures last an average of 10 seconds, are usually provoked by hyperventilation, and postictal confusion is either absent or very brief (7,8). The International League Against Epilepsy (ILAE) classification recognizes seven subforms of typical absences (2):

- Absence with impaired consciousness only
- Absence with mild clonic components
- Absence with atonic components
- Absence with tonic components
- Absence with automatisms
- Absence with autonomic phenomenon

Most patients exhibit a mix of these subforms. In the majority of absence seizures, the first clinical sign is arrest of activity, but other initial signs include eyelid movements, eye opening, altered awareness, or automatisms. As the seizure evolves, other clinical signs may develop. In a clinical and EEG study including 339 typical absence seizures in 47 children, the first clinical sign occurred at an average of 1 second into the seizure (SD 1.29, range 0 to 9 seconds), and included arrest of activity (46%), eyelid movement (28%), eye opening (19%), altered awareness (7%), or automatisms (4%) (9). Most children who were engaged in an activity prior to the episode had an arrest of activity, though 8% continued their activity. If awake with eyes initially closed, the eyes opened in 59% of all the seizures and in at least one seizure in 95% of children. Some children opened their eyes at the beginning of the seizure and others a few seconds into the seizure. Staring was seen in 78% of children who had their eyes open. The direction of the eye stare tended to be consistent in an individual child, but varied among children. Consistent myoclonic movements involving muscles of the head, face, trunk, and limbs were seen in four children. Automatisms were seen in 41% of seizures and were mostly oral (72%). The child was unaware of the automatisms in 75% of cases and partially aware in 20%. Response testing revealed that 75% were completely unaware, with no response to testing and no memory of the events, during at least part of the seizure, and an additional 20% were partially unaware.

In untreated patients, absence seizures are frequent and are quickly documented on routine EEG testing, with most seizures occurring within 10 minutes of EEG recording, and more than 90% of seizures occurring before or during a trial of hyperventilation (8).

TYPICAL ABSENCE SEIZURES

EEG Features

Absence seizures are characterized electrographically by bilateral, synchronous, symmetric spike-and-wave discharges at a frequency of approximately 3 Hz, a finding first published in 1935 by Frederic Gibbs and William Lennox (10) (Fig. 15.1).

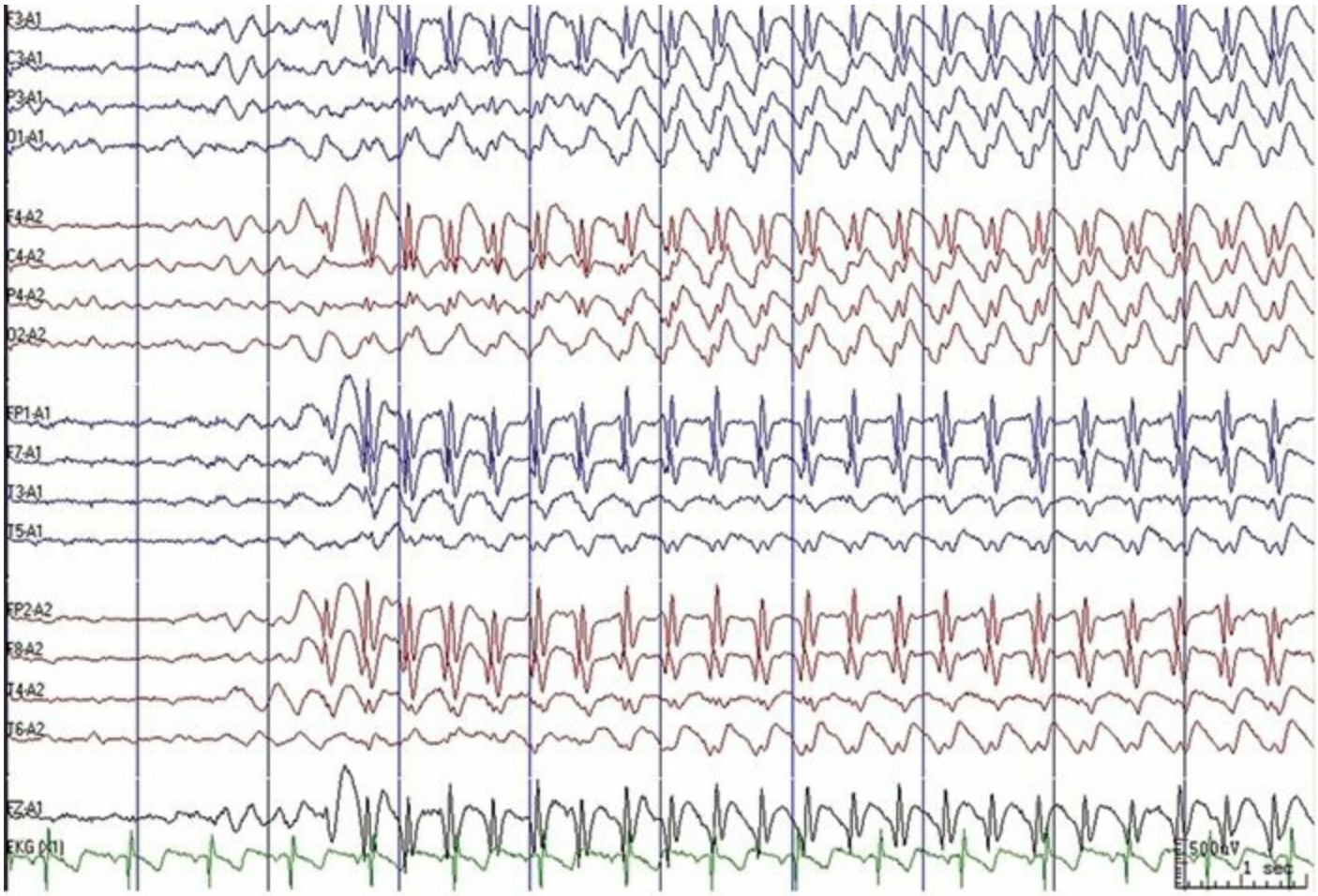

Figure 15.1. EEG during hyperventilation showing generalized, 3 Hz spike-and-wave discharge. Use of an ipsilateral ear reference montage often provides a clear display of spike-and-wave morphology.

In a recent randomized clinical trial of newly diagnosed patients with CAE (5,8,11), the median time to first seizure across 440 patients on a pre-treatment EEG was 6.0 minutes (range 0 to 59 minutes). The median number of seizures per 1-hour study EEG was 5 (range 1 to 60), and the median seizure duration was 10.8 seconds (range 3.3 to 77.6 seconds). The median duration of shortest seizure per EEG was 7.5 seconds (range 3 to 77.6 seconds), whereas the median longest seizure per EEG was 14.9 seconds (range 3.6 to 105.3 seconds). At least one seizure lasting 20 seconds or longer was noted in 29% of subjects (129/440).

Generalized spike wave (GSW) frequency at seizure onset is typically 3 Hz, with a range of 2.7 to 4.0 Hz. Toward the end of the discharge, the frequency often slows and the spikes become less obvious or disappear. The electrical field of the GSW burst is maximally negative at the bifrontal or frontopolar electrodes. Within a sample of 721 GSW bursts reviewed by three EEG readers for morphologic characteristics, 84% (604/721) of bursts contained single spike-and-wave discharges at onset, 3% (21/721) contained polyspike-and-wave discharges at onset, and consensus on spike morphology could not be reached with 13% of bursts (96/721) (8). Since only 3% of bursts contained definite polyspikes and 13% of bursts contained unclear spike morphology, usually because of inconsistent morphology based on electrode location or montage, GSW morphology may not be a reliable and reproducible variable to consider when evaluating EEG features and treatment response, later evolution of other seizure types, or outcome.

EEG variations may be present in typical absence seizures. The ictal onset can be asymmetric for about 0.5 seconds prior to generalization on scalp EEG. While most bursts are frontally predominant at onset, some are predominant in the occipital regions. Unilateral discharges are very rare in

untreated patients, but can be seen occasionally once treatment is begun. Fragments of GSW bursts are also seen, and are especially common after treatment is begun. Photoparoxysmal response is uncommon in typical absence seizures, seen in only 1% to 15% of patients (8,12).

The interictal EEG in most children with CAE is usually normal, unless short fragments of GSW bursts are present. Rhythmic posterior bilateral delta activity, ranging from 2.5 to 4 Hz, is seen in 21% to 32% of patients (8,9); frontal intermittent rhythmic delta activity in 4.5%; focal sharp waves (distinct from fragments of GSW) in 2.5%; and focal slowing in 0.7% (8). During sleep, GSW bursts become more irregular in frequency and morphology, with polyspike and wave discharges seen in 40% of children (9).

ATYPICAL ABSENCE SEIZURES

Clinical Features

Patients with atypical absence seizures often have a structural or metabolic (remote symptomatic) etiology for their epilepsy, and baseline rates of developmental delay and intellectual disability are as high as 95% (6). Since typical and atypical absence seizures can both include complex automatisms, incontinence, and changes in tone (13), a classification of atypical absence seizures should not be based on seizure semiology alone, but rather on a combination of patient factors, ictal semiology, and EEG features. In general, atypical absence seizures have a more insidious onset and offset, are longer in duration, include hypertonic or atonic components, and are less likely provoked by hyperventilation than typical absence seizures (2,6).

EEG Features

Typical and atypical absences share many similar clinical and EEG features, and should be considered as a part of the same continuum (14). Patients with atypical absence seizures have a more heterogeneous ictal recording, often with unclear ictal onset and offset, asymmetric spike-wave discharges, GSW frequencies of 2.5 Hz or less, and are less likely to activate with hyperventilation (2,6). Ictal duration can be unusually brief (<3 seconds) or long (>60 seconds). Interictal abnormalities often include background slowing and disorganization, focal or multi-focal slowing, focal or multi-focal sharp waves, and fragmentary and asymmetric spike-and-slow-wave complexes (2,6).

EPILEPSY SYNDROMES

Typical absence seizures are a core feature of at least five epilepsy syndromes: CAE, JAE, JME, MAE, and LGS.

CAE is defined by frequent daily absence seizures in normal school age children with EEG showing bilateral, synchronous, symmetric, approximate 3-Hz spike wave discharges, superimposed on a normal EEG background (2,5).

JAE occurs in older children, with onset between ages 8 and 16 with a peak age between 10 and 12 years (15,16). The syndrome includes absence, generalized tonic clonic seizures (GTCs) and myoclonic seizures and typically requires long-term treatment. The absences in JAE can be frequent, although usually less frequent than CAE, and are typically not triggered by hyperventilation (2,5,17).

In JME, absence seizures occur in about one-third of patients and are usually infrequent and not associated with automatisms, making an accurate absence seizure count challenging to obtain. They generally respond well to treatment, although long-term treatment is usually required (2,17). The overlap between JAE, JME, and primary GTCs upon awakening can be substantial, but the presence of myoclonic seizures should prompt careful consideration of a diagnosis of JME.

Atypical absence seizures are seen in MAE and LGS. Both syndromes occur in children with associated neurodevelopmental disabilities and other seizure types. Absences in MAE are often associated with rhythmic myoclonic jerks, and are treatment-resistant (2,17). In LGS, tonic and atonic seizures, plus atypical absence seizures, are the core seizure types. Absence seizures in LGS are challenging to monitor, since clinical signs can be subtle and the children typically have coexistent cognitive and behavioral disabilities.

Eyelid myoclonia with absences (Jeavons syndrome) includes typical absence seizures with the usual ictal signature of approximate 3 Hz GSW and episodes of rapid eye flutter with retention of awareness (eyelid myoclonia). In Jeavons syndrome, the eyelid myoclonia typically correlates with GSW or polyspike and wave discharges on EEG. Some patients with absence seizures have paroxysmal eyelid movements with no ictal change on scalp EEG other than eye flutter artifact. This condition can be easily confused with Jeavons syndrome, and differentiation between the two requires EEG. However, neither the ictal eyelid myoclonia of Jeavons syndrome nor the paroxysmal eyelid movements sometimes associated with absence seizures typically respond to treatment with antiepileptic drugs (18–20).

Absence status epilepticus, which can involve typical or atypical absence seizures, is defined as prolonged absence seizures lasting more than half an hour, with continuous impairment of consciousness and generalized discharges of 1 to 4 Hz spikes or polyspikes and slow waves on the EEG. Absence status can be a seemingly unprovoked exacerbation of an underlying seizure disorder or may be associated with inappropriate antiepileptic drug choice, drug intoxication, drug withdrawal, or electrolyte disturbance (21). Once absence status is successfully treated or stops spontaneously, the patient typically returns to baseline without deleterious effects, as long as injuries are avoided.

Pathogenesis

Absence seizures are provoked by an abnormal thalamo-cortical circuitry that activates abnormal oscillatory rhythms, which then generate 3 Hz spike-and-wave discharges (22). The cellular mechanism involves low-current T-type calcium channels, which are blocked by ethosuximide (ESM) (17). $GABA_B$ receptors appears to play a role in the generation of absence seizures as suggested by the observation that $GABA_B$ receptor agonists worsen and $GABA_B$ receptor antagonists suppress absences (22).

Genetic factors play an important role in the pathogenesis of typical absence seizures, as suggested by a high concordance rate among twins (23). Mutations in genes that encode $GABA_A$ receptor (24), voltage-gated chloride channels (25), and T-type calcium channels (26) have been identified. However, the vast majority of patients with absence seizures do not have an identifiable genetic cause at this time.

About 10% of patients with early-onset absence epilepsy, defined as onset age before 4 years of age, have glucose transporter 1 (GLUT1) deficiency caused by a mutation in SLC2A1. GLUT1 is a protein that facilitates the transport of glucose across the blood–brain barrier (27,28). GLUT1

deficiency can be diagnosed by gene testing or by the presence of hypoglycorrhachia (fasting CSF glucose <2.2, CSF/plasma glucose ratio <0.45) (27). This diagnosis is important because seizures caused by GLUT1 deficiency can be treated with the ketogenetic diet. SCL2A1 mutations do not appear to play a major role in absence epilepsies beginning after the age of four (28).

Differential Diagnosis

Absence seizures may be confused with normal daydreaming, inattentiveness associated with ADHD, tics with eye blinking or facial movements, or focal seizures with impairment of awareness. However, in a child with absence seizures, a careful history will usually reveal stereotypic episodes of arrest of activity, decreased responsiveness, associated ocular, facial or extremity automatisms, and a quick return to baseline. Isolated staring episodes without other features are almost never absence seizures, but rather reflect normal behavior or inattentive ADHD. Clinical signs suggesting that the staring episodes are nonepileptic include: the events do not interrupt play; the events were first noticed by a professional such as a teacher, rather than a parent; and the staring child is responsive to touch or "interruptible" by other external stimuli (Table 15.2). Each of these features has close to 80% specificity for suggesting nonepileptic staring episodes. Twitches of the arms or legs, incontinence, or upward eye movement are more likely to be seen in epileptic seizures (29).

Table 15.2 Clinical Signs Suggesting that Staring Episodes are Nonepileptic. Specificity is the Percentage of Children without Epilepsy who are Correctly Identified as Not Having Epilepsy

Clinical sign	Specificity for nonepileptic staring episode (%)
Do not interrupt play	~80
First noticed by professional, not parent	~80
Staring interruptible by stimuli (touch, sound)	~80

Diagnostic Evaluation

For most children, routine EEG will confirm the diagnosis of untreated absence seizures within 10 minutes, if a trial of hyperventilation is performed early in the EEG recording (8). In the CAE treatment trial, only 6% of patients required more than 30 minutes of EEG recording to confirm the diagnosis, and 92% of patients had seizures before or during the first trial of hyperventilation (8). Once treatment has been initiated, treatment response should be assessed by clinical history, office-based trials of hyperventilation, and routine EEG, since approximately 30% of patients who are seizure-free by parent-teacher report have seizures on a 1-hour EEG recording (12).

Treatment

Based on the results of the CAE treatment trial, published in 2010, ESM has class I evidence as the optimal initial treatment for CAE (5). This double-blind, randomized, controlled trial enrolled 453 children with newly diagnosed and untreated CAE, who were randomly assigned to treatment with

ethosuximide (ESM, n = 156), lamotrigine (LTG, n = 149), or valproic acid (VPA, n = 148). The primary outcome measure was freedom-from-failure (FFF), defined as no clinical or electrographic seizures at 16 to 20 weeks of therapy and no treatment-limiting adverse effects. The FFF rates for ESM and VPA were similar (53% and 58%, respectively, P = 0.35) and were higher than the FFF rate for LTG (29%, P < 0.001 when compared to both ESM and VPA). Discontinuation rates due to adverse events were not significantly different between the three drugs. However, post-treatment attentional dysfunction was more common with VPA than with ESM (49% and 33%, respectively, P = 0.03). The study concluded that while ESM and VPA were more effective than LTG in the treatment of CAE, ESM is the optimal initial treatment for CAE as it was associated with fewer adverse attentional effects.

At 12 months of follow-up, ESM and VPA remained superior to LTG, but the VPA group experienced higher rates of drug discontinuation and attentional dysfunction. VPA-associated weight gain also became apparent at 12 months follow-up (12). Across all three treatment groups, only 37% of all subjects continued on their first medication at 12 months. FFF rates for ESM and VPA were similar (45% and 44%, respectively, P = 0.82) and were higher than LTG (21%, P < 0.001 when compared to both ESM and VPA). Almost two-thirds of the 125 subjects with treatment failure due to lack of seizure control were in the LTG group. The largest subgroup (42%) of the 115 subjects discontinuing due to adverse events was in the VPA group. The previously reported higher rate of attentional dysfunction seen at 16 to 20 weeks in the VPA group compared with the ESM or LTG groups persisted at 12 months (P < 0.01).

Strikingly, even the best initial monotherapy fails in 55% of children with CAE over the first 12 months (12). Overall, ESM provides the best, though still very suboptimal, combination of efficacy and tolerability, and does not worsen inattention. VPA is as effective as ESM for seizure control, but has higher rates of adverse effects and worsens inattention. LTG is not as effective in controlling seizures, but is well-tolerated and does not worsen inattention. If ESM fails, then either VPA or LTG are possible second-line choices depending on seizure burden, attentional difficulties, body mass index, and other factors. If all three drugs fail in monotherapy, then combination therapy can be considered (17), although high-quality evidence to support its use is lacking.

Other medication treatment options for CAE, either alone or in combination, based on case series and case reports, include zonisamide (30); benzodiazepines, particularly clonazepam (16); acetazolamide (13); levetiracetam (31); or felbamate (32). Ketogenic diet (33), vagus nerve stimulation (34), and amantadine (35) have also been reported in small case series to have efficacy in some patients with treatment-resistant absence seizures.

Importantly, carbamazepine, vigabatrin, and tiagabine are contraindicted in the treatment of absence seizures, since these agents have been reported to worsen absence seizures and precipitate absence status epilepticus (7,21,36).

Prognosis

Seizure Outcomes

In the CAE treatment trial, longer pre-treatment seizure duration was associated with better drug response outcome at 16 to 20 weeks. Children whose shortest seizure lasted longer than 7.5 seconds had better response to initial treatment than those with briefer seizures. However, patients with any seizures longer than 20 seconds were more likely to display attentional difficulties (8). These

findings underscore the complex relationship between seizures and inattention in CAE.

Reported long-term remission rates for absence seizures in CAE range from 56% to 84% (33,37). In small series, factors associated with persistent seizures past puberty include onset after 8 years of age, GTCs at the time of absence seizures, myoclonic jerks, eyelid or perioral myoclonia, family history of GTCs, absence status, and background slowing on EEG (38,39). Focal interictal spikes have not been shown to be related to outcome (40).

A retrospective cohort study of 115 patients found that age of onset $\geq$8 years and family history of GTCs in patients with CAE predict development of GTCs, but polyspike and wave discharges do not. It is possible that CAE with GTCs is a distinctive syndrome from CAE without GTCs (41).

One retrospective chart review of 119 patients found that typical absence seizures are more likely to respond to the initial antiepileptic drug compared to atypical absences, but the remission at 2 years is similar in the two groups (14).

There are few outcome studies of JAE. GTCs are seen in 47% to 95% of patients, and remission rates range from 37% to 62% (15,39,42,43). Some studies (15,42) have found that myoclonus and GTCs are associated with persistent seizures, but other studies have not confirmed this finding (39). Another case series of CAE and JAE found that patients who responded to initial AED therapy were more likely to achieve remission and not progress to JME (38).

Psychosocial Outcome

CAE is often described as a benign epilepsy, with few associated cognitive and behavioral challenges. However, there is a growing evidence suggesting that the psychosocial impact of CAE is grossly underestimated and the need for early detection and treatment of comorbid cognitive and psychological difficulties (37,44,45). In the CAE treatment trial, baseline rates of inattention were 30% to 42%, inattention did not improve even with successful seizure treatment, and VPA worsened inattention. This finding dismisses the notion that successful treatment of seizures also improves comorbid inattention in CAE.

Children with CAE, when compared to matched controls, also have increased risk of cognitive deficits (25% of CAE children), linguistic deficits (43%), psychiatric diagnoses (61%), particularly ADHD and anxiety disorders, and clinically relevant scores (30%) on a child behavior checklist. Only 23% of the patients in this study had interventions directed at these co-morbid conditions (44).

Long-term outcome is also very concerning. A population- based study from Nova Scotia found that young adults with a history of typical absence seizures had greater psychosocial difficulties later in life compared to children with a non-CNS chronic disease (juvenile rheumatoid arthritis). Findings are summarized in Table 15.3. On every measure, young adults with a history in CAE fared worse than young adults with JRA (37). Most patients in this study had entered remission of their seizures and, while persistence of seizures predicted even worse psychosocial outcomes, remission of seizures did not ensure favorable psychosocial outcome (37).

Table 15.3 Psychosocial Outcome of Patients with CAE Compared with JRA in their Mid-20s

	CAE patients (%)	JRA patients (%)	Odds ratio (CI)
Not a high school graduate	36	14	3.7 (1.3–10.4)
Special classes	16	3	5.7 (1.1–40.5)
Repeated a grade before diagnosis	20	3	7.6 (1.4–52.8)
Ever considered a behavior problem	41	10	6.4 (2.2–19.9)
Unplanned pregnancy	34	3	19.3 (2.3–426.1)
Psychiatric or emotional problems	54	31	2.6 (1.1–5.9)
Unskilled laborer	53	16	5.9 (1.6–24.0)
Manager or professional	0	29	Undefined
Not employed in area of training	50	14	5.7 (1.2–33.9)

Adapted from Wirrell EC, Camfield CS, Camfield PR, et al. Long-term psychosocial outcome in typical absence epilepsy. Sometimes a wolf in sheeps' clothing. *Arch Pediatr Adolesc Med.* 1997;151(2):152–158.

Whether early recognition and management of the many nonictal manifestations associated with typical absence seizures will improve long-term psychosocial outcome is unknown, but it is clear that successful seizure control with tolerable side effects—only achieved in <50% of children—should not be the sole therapeutic goal. Atypical absence seizures have long been noted to be associated with significant neurodevelopmental comorbidities. It is now clear that the nonictal manifestations associated with typical absence seizures also demand early recognition and intervention.

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CHAPTER 16 EPILEPTIC SPASMS

KELLY G. KNUPP AND INGRID TUXHORN

Infantile spasms (IS) were first described in 1841 by James West in a letter to the Lancet titled "On a particular form of infantile convulsions" after he had observed these events in his own son (1). He described a "peculiar seizure disorder," which was later named West syndrome in his honor, that manifested with axial spasms (brief extension or flexion of the arms and legs typically associated with a drop of the head) occurring in clusters and failure of normal development. With the clinical application of electroencephalography (EEG) approximately 100 years later by Gibbs in the 1950s, the triad of West syndrome as an epileptic encephalopathy of infancy manifesting with spasms, psychomotor retardation, and hypsarrhythmia as a specific electroencephalographic signature was completely described (2). Hypsarrhythmia, as further described in the chapter, is a chaotic EEG pattern of high amplitude with multifocal spike–wave discharges.

An epileptic spasm (ES) is a brief bilateral arm and leg stiffening lasting 1 to 2 seconds in duration. An ES can be an isolated event or, more typically, occur in a cluster. It is a pervasive seizure type occurring in a number of epilepsy syndromes of infancy and childhood such as the West syndrome, Ohtahara syndrome or early epileptic encephalopathy with burst suppression, and Lennox–Gastaut syndrome (LGS). However, older children and even adults may have seizures that are semiologically similar to IS, so that the general term epileptic spasms may be more encompassing and appropriate (3). Similarly, the etiologies are quite varied, and although the prognosis is frequently guarded and often grave, a small proportion of children may show complete recovery without sequelae.

Historically, ES has evolved from a syndrome diagnosis to a seizure type as well as from a generalized seizure to its current classification of "unknown" seizure type. ESs manifesting in infancy were considered to be a generalized seizure type in the past classification framework of the International League Against Epilepsy (ILAE), when IS were placed among the generalized seizure disorders in the first 1970 classification schema. In the 1981 revision schema, IS were not featured, while in the 1989 epilepsy classification update, IS were reintroduced as an age-related generalized seizure type and epilepsy. In the 2001 and 2006 ILAE task force reports on epileptic syndromes, the concept of epileptic encephalopathies was introduced for the first time and specific age-related features were further characterized. Of the eight epileptic encephalopathies featured, early myoclonic encephalopathy, Ohtahara syndrome, and West syndrome are invariably associated with IS or ES as a leading seizure type, while Dravet syndrome and LGS only variably so (4). With the recent extensive use of video-EEG monitoring, it has become more obvious that ES, particularly in infancy, may be a feature of a generalized as well as a focal epilepsy and is due to varied etiologies and pathologies that may include metabolic and structural brain disease. Therefore, it is important to emphasize that IS and ES are not a diagnosis but an age-related seizure type seen in a number of epilepsy syndromes. This is an important consideration for appropriate medical or surgical management that significantly impacts on the short- and long-term prognosis. In the most recent report of the ILAE Commission on Classification and Terminology in 2010, ESs are listed as "unknown, insufficient evidence to

characterize as focal, generalized, or both" recognizing the various etiologies that can be associated with this seizure type (5).

EPIDEMIOLOGY

Epidemiologic studies from various countries show an incidence of ES of approximately 2 to 5 per 10,000 live births worldwide (6–10), with an estimated lifetime prevalence by age 10 years of 1.5 to 2 per 10,000 children (7,11). The lower prevalence rates most likely are a result of the associated mortality, evolution of ES into other seizure types, and incomplete determination in population-based studies of older children (12). A genetic predisposition may exist as ES have been reported in both monozygotic and dizygotic twins (13,14). Boys appear to be affected in 60% of cases, but in some studies, sex differences are inconsistent (6,9,15).

CLINICAL SEMIOLOGY OF ES

ES are seizures usually associated with a severe developmental epilepsy syndrome with onset in the first year of life, peaking between 3 and 10 months of age (16).

ES are brief axial movements with extension or flexion of the arms and legs that frequently appear in clusters. The seizure starts with a phasic contraction that lasts for <2 seconds, followed by an ensuing tonic contraction for 2 to 10 seconds, although only the phasic contraction may be present (17). Sometimes called tonic spasms, prolonged muscle or tonic contractions are seen in intractable cases (17). The three types of spasms—flexion, extension, and mixed—are classified by the type of contraction. In flexion spasms, the trunk, arms, legs, and head flex. In extension spasms, the back arches and arms and legs extend, while mixed spasms combine extension of the legs and flexion of the neck, trunk, and arms. Mixed spasms are the most common type, accounting for 42% of all ES. Flexion spasms account for 35% and extensor spasms comprise only 23% of all ES (17). Many children have more than one type, even in the same cluster, often influenced by position (18). If the trunk remains vertical, the resemblance is to a flexion spasm; if the patient is horizontal, what looks like an extension spasm is seen (19). The contractions themselves also may vary in intensity, and ES can range from only a subtle head drop, upward eye deviation, or shoulder shrug, which usually occurs at the beginning of an episode, building up to more marked muscle contractions (18,20). Videotelemetry with electromyography (EMG) of ES has shown that the first activated muscle can vary in the same patient between different clusters or even from spasm to spasm within the same cluster, while the EEG shows no variation of the patterns. Even if the same muscle were initially activated with every spasm, the ensuing sequence or pattern of muscle involvement may differ within the same cluster (21).

The initial spasms, at the onset of the epilepsy, are usually mild before they become more characteristic and full-blown, as described above, which may produce a delay in diagnosis. This subtlety also can occur when spasms resolve, leading to need to clarify with EEG true treatment response.

Complex rotation of the eyes, deviation, or nystagmoid movements may occur in two-thirds of all ES (17). Eye movements may be independent of the spasm or may precede its development by weeks, which may result in delayed diagnosis of the epileptic nature, or occur as part of the motor features associated with the spasm (20). In addition, abnormal eye movements may suggest altered consciousness, but decreased responsiveness may follow ES or occur independently as a second

seizure type. Between spasms, most children cry, although this is probably not an ictal phenomenon but may be a result of surprise or pain (17). Up to 60% of all patients have respiratory pauses during the spasm, while pulse changes occur less often. Some spasms are induced by sound or touch, rarely by photic stimulation (22).

Rarely, one arm or leg is more extended or the head deviates to one side. Spasms are usually asymmetric on the side contralateral to a unilateral lesion such as hemimegalencephaly. Symmetric spasms and a symptomatic etiology usually indicate diffuse lesions such as in Down syndrome or neurofibromatosis (23); however, some children with focal or unilateral lesions may have only symmetric spasms (22,23). Recently, videotelemetry has allowed more frequent detection of asymmetric spasms. These patients may either have consistently asymmetric spasms or alternate between asymmetric or symmetric spasms.

Spasms may be intermixed with other seizure types in one-third to one-half of patients (24–26). The muscle contraction in spasms is faster than that in tonic seizures but slower than that in myoclonic seizures (27,28). Tonic seizures can occur simultaneously with or precede spasms and may be difficult to differentiate, requiring videotelemetry to define the seizure type. Tonic seizures last longer than spasms and lack the initial phasic component. Both may be generated by a similar mechanism or have a similar origin such as the brainstem (17).

Asymmetry of eye movements and head, neck, and limb jerks during the spasms is often documented by video-EEG recording implying a focal component. Focal seizures may occur before, during, or after a spasm and frequently precede a cluster of spasms (19).

There is frequently a diurnal variation of spasm frequency. Most spasms occur on awakening or after feeding, less often during sleep, and typical clusters last <1 to 5 minutes (17). Clusters typically consist of 3 to 20 spasms and occur several times a day, although single spasms may also occur (12). The spasms decrease in intensity at the end of longer clusters; however, the number and type of spasms may vary markedly from week to week with less day-to-day variation (17,29).

Focal seizures suggest a symptomatic cortical lesion, and a symptomatic etiology is likely if the focal seizure precedes the spasms (30). Focal seizures may precede the spasms or appear to induce the appearance of spasms. Such spasms are usually asymmetric with the predominant side conforming to that of the preceding focal seizure.

The effects of brain maturation on seizure semiology have been recently studied in children with well-defined “pure cultures” of temporal and extratemporal lobe focal epilepsy (31). It has been shown that axial or bilateral motor components comprising brief ES (depending on the patient’s age) frequently appear in an age-dependent fashion in young children with well-localized temporal lobe seizure onset (31). The more typical behavioral, psychomotor-type semiology only invariably manifests after 4 years of age while there is an inverse linear correlation of the motor ES components with age, and very young children may only manifest with ES. Only later does the semiology transition from the ES seizure type to the more adult focal dyscognitive seizure type. The semiology of temporal lobe epilepsy may, therefore, mimic generalized epilepsy with ES in the very young child or infant. Animal studies in immature rats, investigating the ontogenetic expression of drug-induced limbic seizures, have shown a similar age- dependent phenomenology in addition to high after-discharge thresholds that suggest a relative resistance of the immature limbic system to synchronization, so that extratemporal and possibly subcortical neuronal networks primarily contribute to the seizure semiology and not to the limbic system (32).

ASSOCIATED NEUROLOGIC FINDINGS

Psychomotor development may be normal or abnormal prior to onset of ES and reflects the etiology and presence of an underlying brain injury.

Abnormal neurologic findings on presentation of ES are quite frequent and may include motor impairments including tetraparesis, diplegia, hemiplegia, ataxia, athetosis, as well as blindness, deafness, and microcephaly. These findings have been described in 30% to 89% of patients and may be considered a prognostic factor for underlying brain injury as 85% to 90% of this group will eventually have developmental delay (11,15,33,34). Other studies have documented mental retardation in 75% and cerebral palsy in 50% of patients (11,25,26,35–37). Children with ES of unknown etiology are frequently neurologically normal prior to the onset of ES. Deterioration and loss of acquired milestones including head control, reaching for objects, and visual tracking may be affected. Loss of visual tracking may reflect the degree of epileptic encephalopathy present and appears to be a neurologic risk factor for poor prognosis of psychomotor development (38).

ETIOLOGY

A variety of disorders can cause ESs, with the etiology driving management, prognosis, and overall outcome. Preexisting brain damage has been demonstrated in 60% to 90% of cases reflecting pre-, peri-, or postnatal brain injury that may usually be determined by history and clinical neurologic examination. Children with a known etiology account for 70% to 80% of all cases and generally have a poorer prognosis than those with unknown etiology (9,26,39–41). Those with a structural etiology usually have more focality on neurologic examination, a history of focal seizures evolving into spasms, or lateralization on EEG (42).

Prenatal causes include congenital malformation, congenital infections, neurocutaneous disorders, chromosomal abnormalities, metabolic disorders, and congenital syndromes. Prenatal etiologies account for 30% to 45%, perhaps as many as 50%, of all cases (24,37,43,44). Tuberous sclerosis may be found as a cause in 10% to 30% of patients whose spasms are the result of a prenatal etiology (6,25,43,44). There is some radiologic evidence that a larger tuber burden is more likely to produce spasms rather than focal seizures, but this may also reflect an age-specific seizure manifestation (45). Although focal seizures are most common with focal cortical dysplasia (FCD), ES can occur (46); positron emission tomography (PET) scans may help to identify these patients (47). Occipital lesions are associated with earlier onset of ES than are frontal lesions (48). Neurofibromatosis type I has been associated with spasms, but these children usually have a better prognosis than other symptomatic etiologies (49). Chromosomal abnormalities, most commonly Down syndrome (44,50), represent approximately 13% of prenatal etiologies; these children usually do not have a poor prognosis compared to other symptomatic cases (51,52). There may be dual etiologies in this group of patients such as hypoxia (53).

Perinatal causes account for 14% to 25% of spasms but may be decreasing in frequency (54), perhaps because of a lowered incidence of neonatal hypoglycemia (55). Perinatal causes include hypoxic–ischemic encephalopathy and hypoglycemia. The difference may be relative, however, and reflect an increased survival in low birth weight infants rather than a true decrease in perinatal causes. Hypoxic–ischemic encephalopathy often involves severe neonatal electroencephalographic findings such as markedly or maximally depressed backgrounds in the first week of life (56). In children with cerebral palsy, deep white matter injuries are not associated with West syndrome;

therefore, spasms are less likely in premature infants (55). Spasms associated with periventricular leukomalacia typically have an EEG with hypsarrhythmia and an EEG prior to ES onset often demonstrates irregular polyspike and wave discharges that are located more posteriorly than anteriorly (28,57).

Postnatal causes include meningoencephalitis and other types of infections, stroke and trauma, hypoxic–ischemic insult such as near drowning and cardiac arrest, and tumors.

Besides the above-mentioned acquired brain injuries, cerebral malformations may account for up to 30% of cases and may include the various neurocutaneous syndromes (e.g., tuberous sclerosis complex, TSC), Aicardi syndrome, polymicrogyria, lissencephaly, hemimegalencephaly, schizencephaly, and FCD.

In addition, rare inborn errors of metabolism may manifest with infantile seizures and encephalopathy resembling ES. These conditions include Menkes disease, phenylketonuria and tetrahydrobiopterin deficiency, and mitochondrial diseases.

When the underlying cause cannot be identified, spasms are classified as unknown; in the past, this category accounted for up to 50% of cases. However, with increasing recognition of genetic etiologies and the advent of magnetic resonance imaging (MRI), only 10% to 15% of cases are still unknown (29,58–61). In fact, some imaging studies that were normal early in life may later demonstrate lesions on MRI after normal myelination has progressed (62). This time window in the first and second year of life may require serial imaging to detect the underlying pathology that will usually turn out to be type 1 FCD. ^{18}FDG-PET may also increase the likelihood for finding a malformation of cortical development not visualized with MRI scan in some cryptogenic patients.

Patients for whom a diagnosis is not established (unknown etiology), and previously identified as idiopathic, often are products of a normal pregnancy and birth, with normal development prior to the onset of spasms and normal findings on physical examination. The spasms begin abruptly without a background of previous focal seizures. Results of neuroimaging and laboratory evaluations are frequently normal. These patients have been shown to have higher levels of CSF corticotropin, serum progesterone, CSF GABA, and CSF nerve growth factor (63), which may reflect brain damage from the spasms or that stress hormones may play a role in the pathogenesis of spasms.

Although most children with spasms have no family history, 7% to 17% may have a positive history of febrile seizures, which may reach an incidence of up to 40% in unknown cases (25). Autosomal dominant inheritance is found in patients with TSC and neurofibromatosis type I presenting as ES. Sex-linked dominant inheritance may be seen in incontinentia pigmenti, double cortex syndrome, and lissencephaly. Some families have been reported with an X-linked transmission that has been mapped to regions Xp11.4-Xpter and Xp21.3-Xp22.1 and that also is associated with mental retardation (64). One of these loci is implicated in neuroaxonal processing (radixin, RDXP2) (65). ARX gene mutations were subsequently located in this same region at Xp22.13 (66–68). Chromosomal translocations may also be implicated in Down syndrome presenting with ES.

INTERICTAL AND ICTAL EEG

ES are commonly associated with the characteristic interictal EEG pattern termed hypsarrhythmia, which translates from the Greek as high-amplitude irregular waves. This pathognomonic electrographic pattern consists of random high-voltage slow waves and spikes that may vary from moment to moment in localization, amplitude, and duration (20). As early as 1952, Gibbs and Gibbs noted that the abnormality was almost continuous and represents a highly abnormal, chaotically

disorganized EEG pattern signaling the grave prognosis of a severe epileptic encephalopathy. The spike discharges are usually multifocal, independently arising from multiple regions of the brain. Rarely, the spike discharges may generalize, but it is not common to have rhythmic, repetitive, and synchronously organized runs of spike discharge patterns that resemble the petit mal variant or slow spike–wave EEG phenotype. Synchrony may significantly increase with age, while increasing asynchrony may occur with advancing sleep stages. On serial EEG recordings, fluctuation and a waxing and waning of the basic pattern may be seen (69–71). The interictal pattern may vary with some aspects being determined by the underlying pathology, some by the type of epilepsy syndrome, but also by age, sleep stages, and a variable combination of these (Figs. 16.1–16.6).

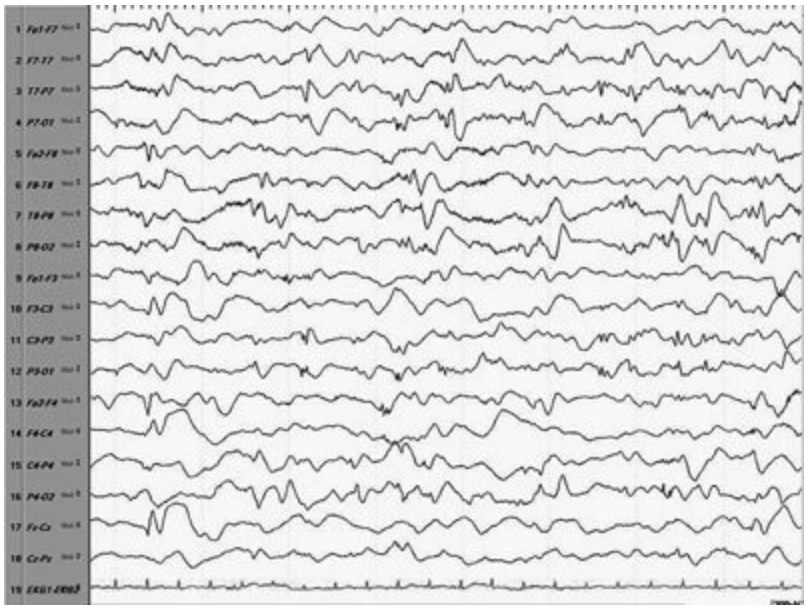

Figure 16.1. EEG showing classic hypsarrhythmia consisting of high-amplitude polymorphic delta waves and multiregional spike waves.

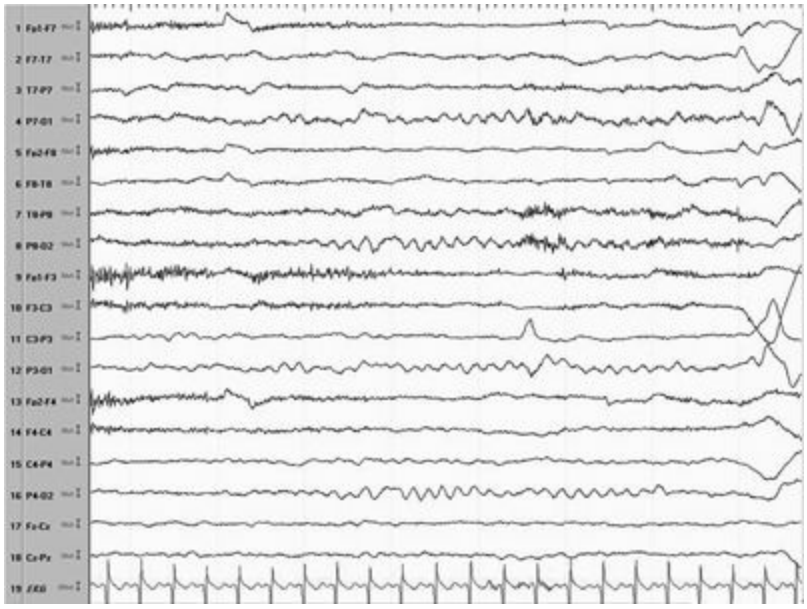

Figure 16.2. EEG of a patient in Figure 16.1 shows normal background and resolution of hypsarrhythmia within 4 weeks on ACTH.

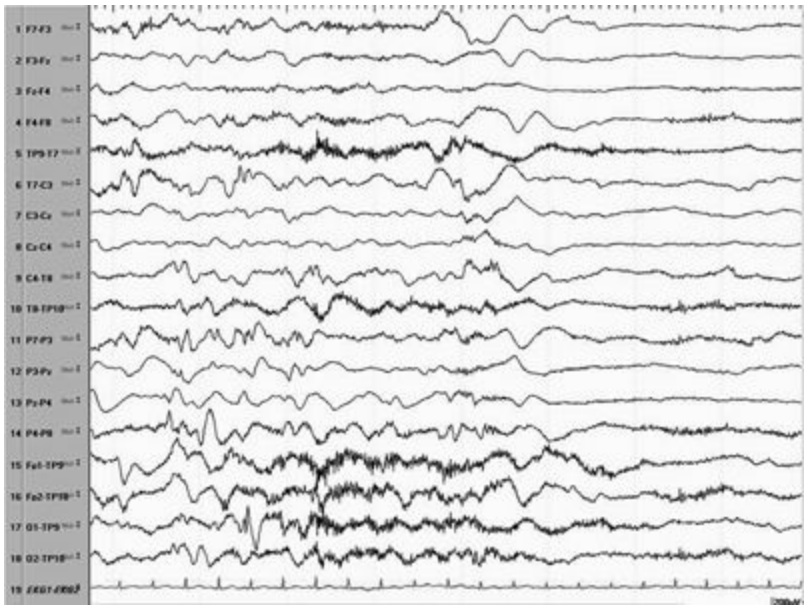

Figure 16.3. Electrodecremental pattern associated with an IS preceded by a broad central slow wave.

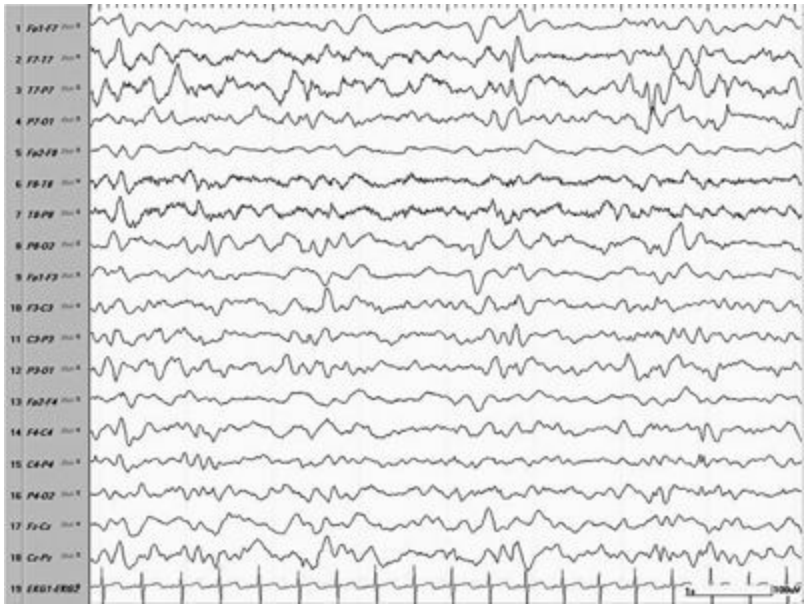

Figure 16.4. EEG showing a modified hypsarrhythmia pattern consisting of more lateralized high-amplitude multifocal spikes over the left hemisphere, suggesting a structural lesion.

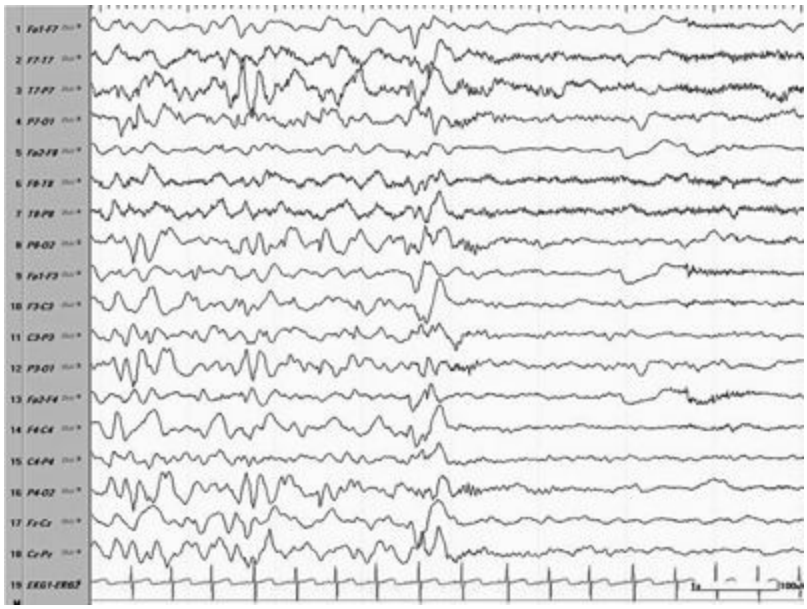

Figure 16.5. EEG showing an ictal change associated with an ES in the form of a generalized wave followed by an electrodecremental pattern.

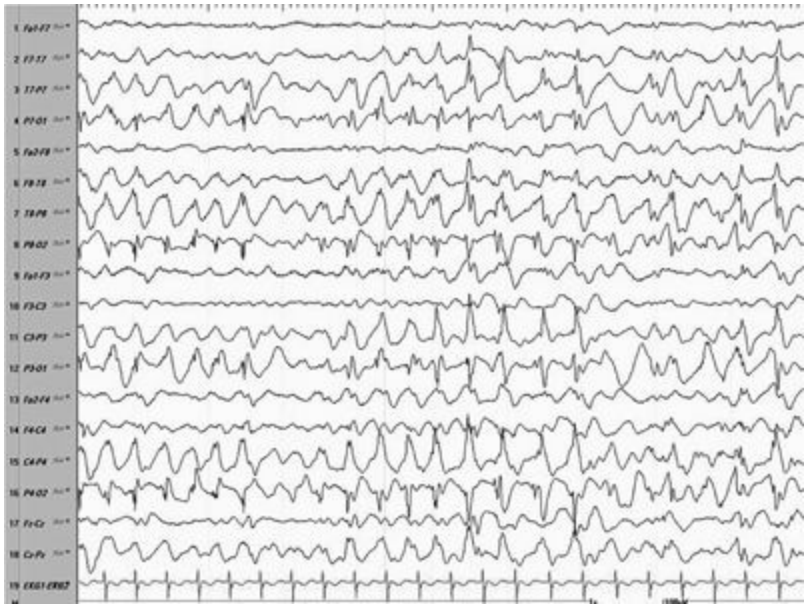

Figure 16.6. Modified hypsarrhythmia in an older child with more synchronized posterior hypersynchronous activity.

Rarely, the interictal EEG may be normal early in the onset of ES and should, therefore, be repeated serially at close intervals if there is a high index of suspicion for the diagnosis of ES (17). By the same token, ES caused by a localized cortical pathology involving a single lobe or hemisphere may not be associated with hypsarrhythmia, and focal slow-wave activity or a persistently interictal spike focus localizing to one brain region even in the presence of multifocal spikes may point to focal epileptiform pathology such as cortical dysplasia, porencephaly, or a developmental tumor. Hypsarrhythmia may precede the presentation of ES and be found incidentally with routine EEG surveillance or patterns that evolve into hypsarrhythmia may be present prior to evolution of ES that may allow early detection of infants who are at risk for ES (72–74).

The background activity never approaches normal frequencies or amplitudes and is characteristically of high voltage (500 to 1000 mV), disorganized, and asynchronous with a waxing and waning quality (2).

The sleep–wake cycle has a significant effect on the manifestation of the pattern of hypsarrhythmia. During non–rapid eye movement (REM) sleep, there may be fragmentation of the hypsarrhythmic pattern, while by the end of REM sleep or during arousal from sleep, near-normal activity may occur; this "pseudonormalization" may also immediately precede a cluster of spasms (75,76). Long-term monitoring has disclosed variable patterns throughout the day, with more hypsarrhythmia noted in slow-wave sleep and less in REM sleep (22). Fast-wave bursts were seen during REM sleep in 35% of patients with spasms, sometimes occurring periodically until clinical spasms appeared and the patient awakens (21). Spasms may start subclinically in REM sleep (76).

Any variation in the characteristic hypsarrhythmic pattern as described above has been termed modified hypsarrhythmia and includes background synchronization, very focal features, voltage asymmetries, generalized background burst suppression, and slow waves without spikes (17). In an analysis of pretreatment electroencephalograms, the modified pattern occurred in up to 36 (69%) of 53 patients with spasms; cortical dysplasia was associated with hemihypsarrhythmia or burst suppression (77).

Regarding the role of the EEG as a prognostic tool, a burst–suppression pattern, as seen in children with Ohtahara syndrome, suggests a poor prognosis; a lower-voltage EEG may indicate a better outcome (77), as may preservation of hypsarrhythmia between spasms (28,54), faster background activity, and absence of postictal electrodecremental responses (as described in the following paragraph). However, children with more typical features of hypsarrhythmia such as disorganization, slowing, high-amplitude, spike, and electrodecremental discharges independent of seizures, absent normal sleep architecture, burst suppression, hemihypsarrhythmia, occipital hypsarrhythmia, interhemispheric asymmetry, and interhemispheric synchronization may predict a more severe developmental and epilepsy seizure prognosis (77). In late-onset ES, a more organized electroencephalographic background predicts better development while persistent hypsarrhythmia and a disorganized background may be a risk factor for poorer prognosis (78).

The most common ictal discharge that has been described consists of an initial multiphasic, high-amplitude slow wave, sometimes of positive polarity or less frequently a de novo low-amplitude, brief, fast frequency discharge (19,28). The generalized positive slow waves are followed by attenuation or an electrodecremental response, observed mainly at PZ (parietal midline), FZ/PZ, or FZ (frontal midline) with some variable degree of laterality (17,23). Because the decremental activity follows the slow wave and clinical spasm, it most likely is a postictal phenomenon (19,28), and the slow wave corresponds to the actual ES. An electrodecremental response can also be seen in the absence of a clinical seizure (12). Slow-sharp and slow-wave complexes, although less frequent with spasms, differ from the elongated appearance of those in myoclonic seizures (28). Diffuse attenuation, generalized spike wave, paroxysmal fast activity or fast frequencies, and slow wave are also associated with ES. There is no correlation between the semiology of the spasms and the different ictal patterns. The ictal pattern usually is brief, only lasting for approximately 1 second, while longer patterns are usually also associated with behavioral arrest (22). EMG shows that the axial muscles contract earlier than the limb muscles and the head earlier than the arms (23). A review of the EEG and behavioral changes before and between the spasms suggests that a cluster of spasms may represent a single sustained ictal event rather than brief, repetitive seizures (79). Pseudonormalization and high-amplitude slowing may precede the spasms and are associated with decreased activity and interaction (76), while subclinical discharges without clinical manifestations are also possible at the end of a spasm cluster; however, surface EMG may confirm subclinical contractions without actual perceptible movement on video-EEG during the subclinical discharges

(28).

Fast activity is often associated with tonic spasms with sustained tonic muscle contraction and may be more common in asymmetric spasms, suggesting a cortical onset for spasms (76,78,80–82). Fast activity can also fade during repeated spasms or in partial seizures that occur with spasms (83).

CURRENT MODELS AND THEORIES OF THE PATHOPHYSIOLOGY OF ES

Several promising animal models to study the pathophysiology of ES have recently emerged. However, an ideal model that recapitulates every aspect of human ES does not yet exist. The ideal model would develop ES at the appropriate age and possess an EEG background similar to hypsarrhythmia; the extensor or flexor spasms would occur in clusters and have an associated slow wave followed by an electrodecrement, and the response to currently available medications would mimic that seen in humans. Some of the issues are interspecies differences in brain development and the lack of comparative developmental biomarkers across the species for variable seizure phenotypes and EEG signatures. However, each model will hopefully add another piece to the puzzle to give a clearer picture that will potentially translate experimental findings into clinically useful therapies. Several different models have been recently reviewed: (i) the corticotropin-releasing hormone (CRH) model examining the role of stress and response to adrenocorticotropic hormone (ACTH) in the developing brain; (ii) the N-methyl-D-aspartic acid model examining cryptogenic IS; (iii) the tetrodotoxin model examining hyperexcitability provoked by a decrease of neuronal activity; (iv) the multiple hit model examining cortical and subcortical lesions mimicking symptomatic IS; (v) the aristaless gene (ARX) mutation models, a genetic knockout model and a knockin model that recapitulates human mutations of ARX with an IS and MR phenotype and may prove the hypothesis that a deficiency of cortical interneuronal GABAergic inhibition (interneuonopathy) underlies developmental epileptic encephalopathies; and lastly (vi), the Down syndrome model, Ts65Dn Mouse model, that suggests that $GABA_B$ receptor alterations (agonists) may be a spasm-provoking mechanism (84,85).

From a recent human tissue study of four infants with FCD and IS treated with surgical resection, $GABA_A$ receptor abnormalities have been described using a novel technique of electrophysiologic recording after oocyte membrane injection from cortical brain tissue of these infants. Characterization of the cortical $GABA_A$ receptor properties demonstrated unaltered intrinsic physiology but altered neuromodulation to neurosteroids and zinc, which parallels the response of IS to ACTH (86).

Current theories on the generation of ES are that they represent a nonspecific age-dependent reaction of the immature brain to injury involving subcortical structures that acts diffusely on the cortex, leading to the hypsarrhythmic electroencephalogram pattern and the generalized spasms (12). Individual case reports have described abnormalities in the pons and involvement of the serotonergic, noradrenergic, or cholinergic neurons in the brainstem nuclei to support this assumption (87–89). Brainstem origin has also been postulated on the basis of abnormalities in brainstem auditory-evoked responses in patients with spasms and disruptions of REM sleep (90–92). In addition, ES and hypsarrhythmia have been noted in children with severe cortical injury or absence of cortex, supporting this theory. Because hypsarrhythmia occurs mainly during sleep and the brainstem controls sleep cycles, this sleep association again suggests that the brainstem plays a role in the manifestations of ES (92,93).

The frequent intermixture of focal seizures with generalized or asymmetric spasms suggests a cortical–subcortical interaction, a hypothesis supported by the effectiveness of cortical resection in controlling generalized ES (19). In other words, the cortical lesion interacts with developing brainstem pathways, causing motor spasms that are similar to startle or cortical reflex myoclonus (83,94).

Further supporting the brainstem hypothesis are results of PET scans in patients with ES showing hypermetabolism of the lenticular nuclei (95). That serotonergic ([^{11}C]-methyl-L-tryptophan) and α-aminobutyric acid (GABA)-ergic ([^{11}C]-flumazenil) tracers may be more effective than FDG-PET in defining a focus in patients with ES also suggests brainstem involvement, because the raphe–cortical or striatal projections use serotonin as a neurotransmitter, and these pathways cause the diffuse hypsarrhythmic patterns on EEG (41). On ictal single photon emission computed tomography (CT) studies, both subcortical and cortical structures were activated (96).

The response to corticotropin suggests involvement of the hypothalamus and pituitary–adrenal axis. Baram has proposed that a nonspecific stressor releases the proconvulsant CRH, which may be the final common pathway for the multitude of etiologies of ES (97). CRH causes severe seizures and death in neurons associated with learning and memory, and its effects are especially important in infants because CRH receptors are most abundant during the early developmental period (98). To support the hypothesis that corticotropin inhibits the release and production of CRH through a negative feedback mechanism, Nagamitsu et al. (99) measured CSF levels of β-endorphin (also derived from a common precursor of corticotropin), corticotropin, and CRH (which releases both corticotropin and β-endorphin) in 20 patients with spasms. The CSF levels of β-endorphin and corticotropin were lower than in controls, as was the CRH level, although not significantly. Riikonen (63) observed that CSF corticotropin levels were higher in infants with cryptogenic than symptomatic spasms.

Because ES typically begin at the time when the first immunizations are administered, the question has been whether the association is causative or coincidental. Numerous anecdotal reports have noted the appearance of ES within a few hours to a few days after a diphtheria, pertussis, tetanus vaccination, although all controlled studies to date have failed to demonstrate any association (100–102). Some proposed immunologic mechanisms have been based on antibodies to brain tissue in blood samples from patients with ES (103,104), or increased numbers of activated B and T cells in the blood (83), or increased levels of HLA-DRw52 antigen (34). Calcium-mediated mechanisms have been postulated, but further studies are needed to substantiate this (105). mTOR pathways have also been implicated in TSC patients as well as children with cortical dysplasia and hemimegencephaly (106).

DIFFERENTIAL DIAGNOSIS AND EVALUATION

The true epileptic nature of spasms may be easily missed in the beginning and considered to be colic, gastroesophageal reflux, or paroxysmal crying (16). Other paroxysmal disorders that may mimic ES include benign myoclonus of infancy in which the interictal and ictal EEGs are normal, including in sleep; hyperekplexia, in which the jerks may be triggered by touching the nose; Sandifer syndrome due to gastroesophageal reflux, paroxysmal tonic upward gaze, jactatio capitis, spasmus nutans, breath-holding spells, and infantile gratification behavior (16).

West syndrome is the classic epileptic encephalopathy of infancy associated with ES and is characterized by a triad of ES, hypsarrhythmia, and developmental failure or regression. Over the

years, salaam seizures, jackknife seizures, axial spasms, periodic spasms, and serial spasms have been used as synonyms for ES.

The age of onset is typically between 4 and 8 months (17), but ES can occur as early as 2 weeks or as late as 18 months of age (12,107) and, rarely, can begin in adulthood. In some studies (107), late-onset spasms may be cryptogenic or associated with cortical dysplasia, hypoxic–ischemic encephalopathy, or genetic anomalies and were refractory to medications (17). Late-onset spasms may be intermixed with atonic, tonic, partial, myoclonic, or generalized tonic–clonic seizures or atypical absences. The characteristic spasms generally resolve spontaneously or evolve to other generalized seizure types or focal seizures but may persist as ES in 15% to 23% of patients beyond 3 to 7 years of age (35,36).

Watanabe has suggested that a subset of the cryptogenic group may be truly an "idiopathic" form of West syndrome (54). These patients have normal development, and the spasms usually remit after a short period. Developmental regression and focal interictal EEG abnormalities are usually not present; symmetric hypsarrhythmia reappears between each spasm in a cluster; and a family history of seizures is common. This group may represent from approximately half to 80% of the cryptogenic cases (25,97), referred to as "unknown" in the updated classification.

West syndrome may eventually evolve into LGS in many children ranging from 3% to 54% in various studies (108,109). Tonic seizures usually coexist with and are more marked during this stage of the syndrome. Seizure clustering is seen more frequently in West syndrome, but less frequently in LGS (23). Clusters of ES will usually become single spasms in LGS in parallel, with the changed interictal pattern from hypsarrhythmia to a generalized slow spike-and-wave pattern at 1 to 2.5 Hz (94).

The epileptic encephalopathy associated with ES needs to be differentiated from more benign epilepsy syndromes, particularly benign familial infantile convulsions (BFIC) and benign myoclonic epilepsy of infancy (BMEI) (110–112). A firm diagnosis is necessary before initiation of therapy because many common medications (specifically corticotropin and vigabatrin [VBG]) carry a higher risk of morbidity or mortality than most commonly used anticonvulsants. Like IS, the seizures associated with BFIC and BMEI present in the first year of life. The seizures of BFIC are usually focal, but the EEG may be normal (111). Myoclonic seizures in BMEI can occur in clusters. The EEG may be normal or show generalized spike-and-wave discharges but not the hypsarrhythmia or multifocal independent spike discharges typically seen in West syndrome. Because patients with ES may not display the distinguishing EEG abnormalities early in the disease, a normal or mildly abnormal record does not rule out West syndrome in the early disease stage, and follow-up EEG studies are essential for clarification. A pattern of normal development prior to seizure onset and continued normal development after seizures start is highly suggestive of benign epilepsy syndromes and not an epileptic encephalopathy with IS. In contrast, children experiencing IS may or may not be normal at seizure onset but will invariably demonstrate either developmental regression or failure to achieve developmental milestones in a timely fashion.

As with all forms of epilepsy, the evaluation begins with the history and physical/neurologic examination. The skin should be examined for evidence of neurocutaneous disorders and the fundi for a cherry-red macula suggestive of a storage or mitochondrial disorder or for chorioretinitis indicating possible transplacental infection. In one study, nearly half of all of the etiologic diagnoses were established or suspected by the historical and physical data. Many diagnoses, however, require confirmatory MRI, and once imaging is complete, approximately 70% of patients will have a confirmed etiologic diagnosis (113). In many cases, expensive and time-consuming laboratory studies

can be avoided. In the remaining 30% of cases, an etiology will be established for no more than one-third, leaving about 10% of cases in which a diagnosis is determined by results of lumbar puncture or metabolic or genetic testing. A more recent prospect study found etiologies in 61% of children, 33% had no etiology, and 6% were not fully evaluated. (61)

Neuroimaging

Much of the decrease in unknown cases is a result of the advances in MRI techniques of the past 10 to 15 years. Comparing etiologic categories of IS, Riikonen noted that identification of brain malformations increased from 10% between 1960 and 1977 to nearly 35% between 1977 and 1991 (114). Imaging should be considered essential to the evaluation. MRI is preferred to CT scanning because of the greater sensitivity for brain malformations and is not associated with the risk of radiation exposure. CT, however, can show subtle calcifications caused by transplacental infections. In a study of 86 patients with IS, MRI assigned 91% to a symptomatic etiology, most commonly hypoxic–ischemic encephalopathy (30%) (115) characterized by diffuse atrophy and thinning of the corpus callosum. Delayed myelination in 27% of patients did not appear to be associated with any specific etiology (Table 16.1).

Table 16.1 Magnetic Resonance Imaging Findings Implying a Genetic Etiology

Abnormality	Possible genetic association
Lissencephaly	
▪ Posterior predominant lissencephaly or Miller–Dieker syndrome	*LIS1* gene on chromosome 17
▪ Anterior predominant lissencephaly or band heterotopia	*DCX* gene on X chromosome
▪ Lissencephaly with cerebellar hypoplasia	*RELN* gene
Cortical tubers, periventricular nodules	Tuberous sclerosis; *TSC1* or *TSC2* mutations; 75%–85% are spontaneous mutations; parents should be evaluated
Perisylvian polymicrogyria	Some are familial; multiple associations X-linked recessive X-linked dominant Autosomal recessive 22q11.2 deletions
Cerebral calcifications	Transplacental infections
Loss of cerebral white matter	Pyruvate carboxylase deficiency
Hypoplasia of corpus callosum	Nonketotic hyperglycemia

Some MRI abnormalities suggest specific etiologies, many genetically based, which may require further evaluation. Genetic etiologies including Rett syndrome due to various mutations in the MECP2 gene, atypical Rett syndrome due to CDKL5 mutations, and X-linked ARX homeobox gene mutations need to also be considered in the etiologic diagnosis and diagnosed with chromosomal microarrays and specific mutational studies. Additional genetic and metabolic etiologies are continuing to be added to this list as our understanding of the genetic contributions to ES advances (116). Additional associated genetic diagnoses to consider include STXBP1, SCN2A, FOXG1, PCDH19, SLC2A1,

ALDH7A1, and POLG. The number of identified genes is growing, and therefore, a complete list is not possible. Improved genetic technology now allows large gene panels to be performed earlier leading to increased genetic diagnosis.

Metabolic Studies

Metabolic studies are indicated to identify more than 50 disorders associated with infantile seizures (117–119). A trial of folinic acid is warranted (120), as is a 100-mg intravenous pyridoxine bolus to exclude pyridoxine-dependent seizures. It is important to remember that further testing is required to completely exclude this diagnosis. Complete blood count, electrolytes (looking for an anion gap), and glucose determinations are appropriate. Measurements of uric acid, transaminases, lactate, pyruvate, ammonia, urine organic acids, and serum amino acids will identify the vast majority of inborn errors of metabolism linked to ES. In the past, phenylketonuria was a relatively common inborn error identified by testing that has been nearly eliminated by neonatal screening. Nevertheless, such screening is not routine in all countries, and measurement of urine amino acid levels will detect phenylketonuria and maple syrup urine disease, as well as other, rarer, metabolic diseases. Zellweger syndrome and neonatal adrenoleukodystrophy are other rare causes of ES that can be diagnosed with the serum very–long-chain fatty acid test (Table 16.2).

Table 16.2 Etiologies of Infantile Spasms Due to Specific Etiologies That May Respond to Specific Therapies

Symptomatic IS	Therapy
Pyridoxine-dependent seizures	Pyridoxine[a]
Phenylketonuria	Diet[a]
Maple syrup urine disease	Diet[a]
Glucose transporter defect	Ketogenic diet
Tumor	Surgery to remove tumor[b]
Arteriovenous malformation	Surgery to treat the malformation[b]
Sturge–Weber syndrome	Early surgery if medications fail[a]
Tuberous sclerosis	Vigabatrin, possible surgery if medications fail[a]
Biotinidase deficiency	Biotin[a]
Menkes disease	Copper histidinate[a]
Hyperammonemia disorders	Possible diet, depending on the disorder[a]
Nonketotic hyperglycinuria	Benzoate[a]
Cortical dysplasias	Possible cortical resection if medications fail[b]
Focal cortical dysplasia	Surgery if medications fail
Hemimegalencephaly	Surgery if medications fail

[a]Symptomatic with a specific therapy and a genetic etiology.
[b]Symptomatic with a specific therapy without an identified genetic etiology.

Lumbar Puncture

A few very rare disorders, such as nonketotic hyperglycinemia, may be detected only by study of the CSF (121). In addition to routine evaluations for glucose, protein, and cells, the CSF should be assessed for amino acids plus lactate and pyruvate to detect possible mitochondrial disorders. CSF

neurotransmitters are needed if cerebral folate deficiency is considered as an etiology, and CSF glucose will allow one to discern glucose transporter defects.

PHARMACOLOGIC TREATMENT

Recovery is only considered to have occurred when both the ES and the EEG abnormality of hypsarrhythmia have responded to treatment and ceased. More than 100 years after James West's initial description of IS, the effectiveness of steroids was first recognized and to date only two medications have class 1 evidence of efficacy: corticotropin and VBG (122,123). Corticotropin and, as of 2009, vigabatrin are approved by the Food and Drug Administration for use in the United States. In addition, some patients respond to valproic acid, lamotrigine, high-dose pyridoxine, topiramate, and zonisamide, while most conventional antiepileptic drugs are ineffective. Some drugs such as carbamazepine or oxcarbazepine may even worsen the seizures, which should be considered when IS are associated with focal features.

Corticotropin and Steroids

The effectiveness of corticotropin and steroids underscores how ES differ from all other epilepsy syndromes. In 1958, Sorel et al. (122) administered 4 to 10 IU/day of corticotropin to seven patients, four of whom responded within a few days while therapy failed in only one patient. In the 45 years since that report, efficacy has been repeatedly confirmed, but agreement is still lacking on the most appropriate dose and duration of treatment. Dosing is complicated by the existence of natural and synthetic forms of corticotropin. Studies of the synthetic product generally used much lower doses than studies of the natural product. It is estimated that 1 IU of synthetic corticotropin is equivalent to 40 IU of natural corticotropin. The synthetic version is used primarily in Japan where a low dose is 0.2 IU/kg/day and a high dose is 1 IU/kg/day. Even with the low dose, 75% of patients responded in one study (124). In contrast, natural corticotropin at doses up to 150 IU/m^2 body surface area/day succeeded in 14 of 15 patients; 5 later had relapses for a long-term response rate of 60% (125). A review of seven studies did not confirm a better response with 150 IU/m^2/day and 40 IU/m^2/day being a common dose (36). The overall long-term response rate ranged from 53% to 91%. Current dosing recommendations are now on the package insert.

Despite its effectiveness for ES, no medication carries a higher potential for significant side effects. Most children develop a Cushing syndrome with obesity, plethora, hypertension, and intense irritability. All patients are at risk for arterial hypertension, electrolyte imbalance, gastric ulcer, growth retardation, cardiomyopathy, or immunosuppression with increased risk of infection. In one study, the risk of serious side effects was 43% with 160 IU/m^2/day; the incidence was lower with lower doses (126). Death from infection and cardiomyopathy has ranged from 2% to 5% in some series. Sepsis, tuberculosis, meningoencephalitis, and protracted cytomegalovirus infection have been reported. Corticotropin exacerbates the seizures in a few infants, and treatment for more than a few weeks leads to steroid insufficiency if the drug is stopped abruptly (127). Parents must be fully informed of the associated morbidity and mortality risks (reported at approximately 2% to 5%) before the therapy begins, and these must be balanced against the virtual certainty of mental retardation if the spasms are not rapidly controlled. Careful follow-up with regular measurements of blood pressure, electrolytes, and urinalysis is mandatory. The current risk-to-benefit assessment favors corticotropin, but if another, less hazardous medication proves to be as effective; it would be

the drug of choice.

There are few comparative trials of the efficacy of steroids and ACTH but one double-blind trial showed that a 2-week trial of high-dose ACTH was superior to 2 weeks of prednisone, while another found no difference with either compound (128). In addition, some patients may respond to one drug but not the other. Following response to steroids or corticotropin, the relapse rate is high and variably reported between 33% and 56% (35). Relapses usually occur within the first 2 months following the end of treatment, but a second course may give a remission and response in up to 75% of patients (36). Recovery of mental function has been reported between 14% and 58%, particularly in patients with a cryptogenic etiology (125).

Vigabatrin

This drug has been reported to be effective in the treatment of ES of all etiologies, and in patients with TSC, it was superior to steroids (129). In 1991, 29 of 68 patients with medically refractory ES achieved complete resolution with VGB as add-on therapy, as did 12 of 14 patients who had TSC (130). VGB also might be effective in Down syndrome (131).

Since 1997, several controlled trials have been reported. Vigevano and Cilio (132) administered either corticotropin 10 IU/day or VGB 100 to 150 mg/kg/day to children with newly diagnosed IS. Eleven of twenty-three VGB patients responded (one late relapse) compared to 14 of 19 corticotropin patients (six late relapses). Vigabatrin was more effective in patients with TSC or cerebral malformations; corticotropin was more effective in patients with perinatal hypoxic–ischemic encephalopathy. There was no difference in cryptogenic cases. Appleton and colleagues (133) used VGB or placebo for 5 days, followed by open-label VGB. Seven of twenty patients in the VGB group were seizure free at the end of 5 days, as were 2 of 20 in the placebo group. For 14 days, Elterman et al. (134) treated 75 patients with 18 to 36 mg/kg/day (low dose) and 67 patients with 100 to 148 mg/kg/day (high dose) of VGB. Eight low-dose patients and 24 high-dose patients achieved complete control. In a study involving underlying TSC, all 11 patients treated with VGB responded, compared with only 5 of 11 patients treated with hydrocortisone (135). An American Academy of Neurology practice parameter published in 2012 stated that VGB "may be useful for short-term treatment of IS" (136).

VGB appears to be well tolerated. The reports of hypotonia, somnolence, or insomnia (137) are expected in a drug that enhances GABA activity. Constriction of peripheral visual fields, which substantially limits the drug's use, was not reported until 1997 (138) and now affects from 15% to 50% of patients. In one report (139), constriction occurred in more than 90% of patients who had been taking VGB for a mean of 8.5 years. Foveal function also may be impaired (140). Most studies have suggested that the constriction is not reversible; however, 8 of 12 patients who underwent full withdrawal improved significantly; none of the 12 who continued taking the drug did so (138). The problem is mild enough that most patients are unaware of the disturbance, which becomes apparent only on perimetric studies.

Unfortunately, visual fields are virtually impossible to evaluate in very young children, many with cortical visual impairment and visual inattention unrelated to VGB therapy. Given the catastrophic nature of IS, visual field constriction may be an acceptable price for seizure control and improved opportunity for normal development (139).

VGB has also been reported to be associated with MRI T2 signal abnormalities in the deep grey nuclei (141–143). These characteristic changes involve the basal ganglia, thalamus, dentate nucleus,

brainstem, and cerebellum. Restricted diffusion may also be seen with diffusion-weighted imaging and apparent diffusion coefficient maps. Changes appear to resolve with discontinuation of medication, reduction of dose and while medication has continued. Age and dose of VGB appear to risk factors for MRI changes. No clear clinical changes have been associated with reported MRI changes. It is thought that this likely correlates to intramyelinic edema that has been seen in animal models (144,145).

Valproic Acid

Before the availability of VGB around the world, single reports of seizure response to valproic acid were reported with tolerable side effects. In a 1981 report, valproic acid produced an "excellent" response in 4 of 18 patients treated with 20 mg/kg/day (146). A year later, 7 of 19 patients achieved good control (11 had also been treated with corticotropin) (147). Seizures were controlled in 11 of 22 patients treated with up to 100 mg/kg/day for 4 weeks (148). Other patients later responded but also received dexamethasone or carbamazepine, so the effect of valproic acid was less clear. Prospective randomized studies of efficacy against IS are lacking. Because liver failure is a risk in children younger than 2 years of age (149), although none of the reported patients were affected, valproic acid should be used cautiously and probably not as a first line of therapy for IS, particularly if metabolic etiologies have not been excluded (150).

Pyridoxine

A trial of 100 mg of pyridoxine intravenously is appropriate for patients with an unclear etiologic diagnosis because pyridoxine (vitamin B_6) dependence can be a rare but highly treatable cause of ES (151). Seizures caused by pyridoxine-dependent epilepsy typically cease immediately following intravenous administration of vitamin B_6 but may take several days. As early as 1968, however, it has been known that long-term oral administration of high doses of pyridoxine has been effective against non–pyridoxine-dependent seizures (152). In 1993, 5 of 17 patients treated with 100 to 300 mg/kg/day responded within 4 weeks—most within 1 week (153). In Japan, high-dose vitamin B_6 has been the drug of choice (153,154), with reported response rates of 10% to 30%. Loss of appetite, irritability, and vomiting are modest compared with the side effects of corticotropin or VGB, but there may be a high risk of gastric hemorrhage. Pyridoxine is not used as frequently outside of Japan, but given its relatively low-risk profile, a 1- to 2-week trial of 100 to 400 mg may be reasonable before or in addition to other therapies.

Nitrazepam

One of the earliest nonsteroid treatments for IS, the benzodiazepines succeed only occasionally but may be useful if more effective therapies have failed (155–157). Nitrazepam administered to 24 children controlled IS in 11, but hypotonia was reported as a significant side effect (158). A multicenter, randomized comparison of corticotropin and nitrazepam demonstrated no statistical difference between the two medications in significantly reducing spasms (159). Side effects with corticotropin were more severe, leading to discontinuation in six patients. Many reports noted an increase in oral secretions and a higher incidence of aspiration and pneumonia with nitrazepam. Several deaths occurred in one series (160). The incidence of mortality was 3.98 deaths per 100

patient-years when young epilepsy patients were taking nitrazepam and 0.26 deaths per 100 patient-years if the medication had been discontinued (161).

Other Antiepileptic Drugs

None of the new anticonvulsants have enough evidence of efficacy to permit a recommendation. The Japanese experience suggests that zonisamide may be effective in about one-third of patients (162), but controlled and comparison trials are lacking. Five of twenty-five patients had a complete clinical and electrographic response to doses ranging from 8 to 32 mg/kg/day; most responses occurred in 1 to 2 weeks (163). Zonisamide was well tolerated, but 20% of the patients in one study experienced anorexia and one patient lost weight (164). If the more than 30% efficacy figures hold up in controlled studies, zonisamide could become a first-line therapy.

Topiramate up to 25 mg/kg/day was effective in 5 of 11 patients with intractable ES (165). In another study, seizures decreased in 43% of 14 patients but worsened in 29%; no patient became seizure free (166). A prospective study with topiramate in doses up to 8 mg/kg/day found that 10 of 40 patients with new-onset ES responded to topiramate measured by seizure freedom (167). Before reports of aplastic anemia, three of four patients with medically intractable IS responded to felbamate as add-on therapy (168). Because aplastic anemia has not been noted in prepubertal patients, felbamate may be as safe as some other drugs and could be recommended if other medications have failed.

Anecdotal evidence, but no prospective controlled trials, supports the efficacy of lamotrigine. One report noted that 25 of 30 patients became seizure free (169). The usual dose is 6 to 10 mg/kg/day; however, three patients in whom VGB and corticotropin had failed responded to <1 mg/kg/day (169). Use of a low dose is important because rash, the major side effect, depends to some extent on how rapidly the dose is increased. The usual recommendation is a slow rise over 2 months to the minimum expected therapeutic dose. Given the need to control IS as soon as possible, this 2-month requirement decreases the therapeutic value of lamotrigine. If the very low dose is effective, however, lamotrigine becomes a fallback drug (170).

KETOGENIC DIET

The ketogenic diet is a decades-old therapy enjoying a resurgence of interest and widespread application. Two retrospective reports of 40 children suggest control of spasms in 20% to 35% of patients with otherwise intractable disease (171,172). An additional retrospective review of initial treatment of ES with ketogenic diet found seizure freedom within 1 month in 8 of 13 infants (62%) although compared to 18 of 20 treated with ACTH (90%). There was a longer lag in improvement of EEG with ketogenic diet (173). A prospective study for treatment of refractory ES found response rates of 35% at 1 month and 25% at 3 months, although additional medication had been added by 3 months (174). Children younger than 1 year of age can achieve ketosis and may benefit from the diet. Despite generally good tolerability, renal stones, gastritis, hyperlipidemia, and gastroesophageal reflux may occur. More recently, there has been a report of 40% seizure freedom (n = 19) with Modified Atkins Diet (175). This option may be more tolerable to some families.

INTRAVENOUS IMMUNOGLOBULIN

High-dose intravenous immunoglobulin (IVIG) is another effective nonantiepileptic drug therapy that may be effective in a variety of seizure disorders, especially when associated with an epileptic encephalopathy. All six children with unknown ES, but only one of five symptomatic patients, achieved complete remission (176). IVIG may also improve juvenile spasms, which are electrically and clinically similar to IS but occurring in older children (177). Doses range from 100 to 200 mg/kg administered every 2 to 3 weeks to 400 mg/kg/day for 5 consecutive days. Actual efficacy is unclear, however, and the most appropriate doses and duration have not been determined.

SURGICAL MANAGEMENT

Removal of an epileptogenic cortical lesion may be highly effective in treating IS and hypsarrhythmia. Patients with single lesions including tumors, FCD, porencephaly, hemimegalencephaly, and catastrophic epilepsy are ideal surgical candidates who should be selected early for surgery as there is compelling evidence that earlier surgery and shorter duration of epilepsy predict improved cognitive outcome (178).

A history of focal seizures that preceded or accompanied IS, cortical disturbances on MRI, or localized EEG abnormalities that suggest a cortical defect should prompt referral to a pediatric epilepsy surgery center (179).

COURSE AND PROGNOSIS

Prognostic features are overall difficult to assess. Signs of brain injury usually preclude complete recovery even in cases where seizure remission is achieved. In cryptogenic cases without evidence of brain lesions, the best outcome appears to be predictable in patients who do not lose visual eye contact (38). Although IS are self-limited and approximately 6% to 15% will recover spontaneously after a few weeks or months, control of epilepsy is difficult to predict in the individual case.

However, ES are a seizure type that are generally associated with a severe epileptic encephalopathy and carry a grave prognosis associated with significant morbidity and also mortality. Intractable epilepsy, mental retardation, and autism are possible consequences of ES. Mortality is increased in the acute short term due to treatment complications and neurologic morbidity underlying various etiologies. In addition, the long-term mortality may be high: a 25- to 35-year follow-up of 214 patients demonstrated that 31% died, many in the first 3 years of life (36,180). Eight of the 24 deaths by age 3 years were a consequence of complications of corticotropin therapy. The most common cause of death overall was infection. Of the 147 survivors, 25 (17%) had an intelligence quotient (IQ) of 85 or higher; 11 others (7%) were in the dull- normal range with IQs of 68 to 84; and 45% were retarded. Overall outcome is driven by the underlying etiology and seizure control. While some etiologies, such as severe hypoxic– ischemic encephalopathy and lissencephaly, will lead to death or mental retardation regardless of whether IS develop, children with cryptogenic spasms or spasms caused by FCD may have a normal or near-normal developmental outcome if the second factor, seizure control, is achieved. Accurate diagnosis and appropriate medical or surgical management need to be the gold standard in these cases to reduce the severe cognitive sequelae of this epileptic encephalopathy.

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SECTION B EPILEPSY CONDITIONS: DIAGNOSIS AND TREATMENT

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CHAPTER 17 PRESUMED GENETIC AND BENIGN FOCAL EPILEPSIES OF CHILDHOOD

ELAINE C. WIRRELL, CAROL S. CAMFIELD, AND PETER R. CAMFIELD

The idiopathic focal epilepsies (IFEs) of childhood account for 10% to 20% of all pediatric epilepsies and are characterized by the following features (1,2):

- Age-dependent occurrence, with specific peak ages for each subtype.
- Absence of significant structural lesions on neuroimaging.
- Normal neurologic status without prior neurologic insult.
- Favorable long-term outcome, with remission occurring prior to adolescence in most children.
- Genetic predisposition.
- Specific semiology: Most seizures are focal motor or sensory with dyscognitive features, although focal dyscognitive and focal evolving to bilateral convulsive seizures also may be seen; nocturnal occurrence is common, and frequency is usually low.
- Rapid response to antiepileptic medication in the majority.
- Specific electroencephalographic (EEG) features: Spikes of distinctive morphology and variable location superimposed on a normal background, with occasional multifocal sharp waves or brief bursts of generalized spike–wave; epileptiform discharges are often activated by sleep.

Table 17.1 summarizes the core/classic features of the presumed genetic and benign focal epilepsies of childhood.

Table 17.1 Benign Focal Epilepsy Syndromes

Syndrome	Age of presentation	Clinical features	EEG features	Prognosis
Benign epilepsy with centrotemporal spikes	Range, 3–13 y Peak, 7–8 y	Diurnal or nocturnal simple partial seizures affecting the lower face with numbness, clonic activity, drooling, and/or dysarthria, nocturnal generalized seizures	High-voltage centrotemporal spikes with horizontal dipole, activated with sleep; normal background	Remission by adolescence
Panayiotopoulos syndrome	Range, 2–8 y Peak, 5 y	Nocturnal seizures with tonic eye deviation, nausea, and vomiting; often prolonged	High-amplitude, repetitive, occipital, centrotemporal, or parietal spike and wave, with fixation-off sensitivity EEG may be normal or nonspecific	Remission within 1–2 y after onset
Late-onset benign occipital epilepsy (Gastaut type)	Range, 3–16 y Peak, 8 y	Brief diurnal seizures with elementary visual hallucinations, often with migraine-like, postictal headache	As above	Five percent suffer recurrent seizures in adulthood
Benign epilepsy in infancy	Range, 3–10 mo Peak, 4–6 mo	Clusters of seizures with motion arrest, decreased responsiveness, staring, simple automatisms, mild convulsive movements with possible secondary generalization	Normal- or low-voltage rolandic or vertex spikes in sleep	Remission by age 2 y
Benign familial infantile seizures	First days to months of life	Focal-onset seizures that may evolve to bilateral convulsive seizures. May have coexisting neurologic disorders Inherited in autosomal dominant manner	Benign familial infantile or neonatal–infantile seizures—interictal EEG often normal; ictal EEG shows fast activity in posterior head regions Benign familial neonatal seizures—interictal EEG may be normal or show rolandic discharges	Usually excellent with ultimate remission. Rare cases can result in epileptic encephalopathy
Autosomal dominant frontal lobe epilepsy	Teens to adulthood	Nocturnal seizures with hypermotor semiology	Normal or frontal spikes	Usually easily controlled with medication
Familial temporal lobe epilepsy	Usually second or third decade	Lateral: focal seizures with elementary auditory auras, aphasic seizures, often with progression to bilaterally convulsive seizures Mesial: autonomic aura, déjà vu, then may progress to focal dyscognitive seizure	Temporal spikes	Most respond well to antiepileptic medication
Possible benign focal epilepsy syndromes				
Benign partial epilepsy in adolescence	Range, adolescence Peak, 13–14 y	Motor or sensory symptoms, often with jacksonian march; auditory, olfactory, or gustatory symptoms never seen	Normal or nonspecific epileptiform discharge	Infrequent seizures that usually abate after a brief period

Benign frontal epilepsy	Range, 4–8 y	Head version ±trunk turning; fencing posture, sometimes followed by truncal, bipedal, or pelvic movements	Unilateral or bilateral frontal or posterior–frontal spikes	May persist into adulthood
Benign partial epilepsy in infancy with midline spikes and waves during sleep	Range, 4 mo–2 y	Cyanosis and motion arrest, at times with stiffening	Low-voltage, fast spike followed by higher bell-shaped slow wave over midline region in sleep	Remission by age 2–3 y
Benign partial epilepsy with extreme somatosensory-evoked potentials	Range, 4–6 y	Diurnal partial motor seizures with head and body version	High-voltage spikes in parietal and parasagittal regions evoked by tapping of the feet	Resolution by adolescence
Benign partial epilepsy with affective symptoms	Range, 2–9 y	Brief episodes with sudden fear, screaming, autonomic disturbance, automatisms, and altered awareness	Rolandic-like spikes in the frontotemporal and parietotemporal regions in wakefulness and sleep	Remission within 1–2 y

mo, months; y, years.

BENIGN EPILEPSY WITH CENTROTEMPORAL SPIKES

In 1958, Nayrac and Beaussart (3) described the clinical symptoms of benign childhood epilepsy with centrotemporal spikes (BECTS), and its excellent prognosis was recognized early on. In distinction to other focal epilepsies, rolandic spikes were reported to be unrelated to structural pathology (4) and, at times, observed without clinical seizures (5). Although BECTS is easily recognized in its "pure" form, atypical features are common and may make a confident diagnosis difficult.

Epidemiology

BECTS accounts for 6% to 10% of all childhood epilepsies. Onset is between 3 and 13 years, with a peak at 7 to 8 years and with resolution by age 16 (6). Boys are more commonly affected (7).

Genetics

The clinical genetics of BECTS is not clearly understood. Early work suggested an autosomal dominant inheritance of centrotemporal spikes (8,9); however, no causal gene has been found. Additionally, while such spikes are characteristically seen in BECTS, they are not pathognomonic and are also present in more complex epilepsy syndromes and autism spectrum disorders. In a study of 18 twin pairs, where one twin had classic BECTS, all 18 were discordant, suggesting that noninherited factors are important in development of epilepsy (10). In a genetic study of 53 probands with BECTS, 9.8% of the first-degree, 3% of the second-degree, and 1.5% of the third-degree relatives had a history of seizures, although epilepsy types were heterogeneous (11). Of affected first-degree relatives, 38% had febrile seizures, 19% BECTS, and 10% epilepsy–aphasia spectrum disorder. Thus, while BECTS does have a genetic component consistent with complex inheritance,

acquired or environmental factors are likely necessary for expression of the seizure disorder. Furthermore, BECTS likely represents the mild end of an epilepsy–aphasia spectrum, with rare severe forms including Landau–Kleffner or continuous spike–wave in sleep.

Pathophysiology

BECTS most likely represents a "hereditary impairment in brain maturation" (12). Mechanisms might include "pruning" of axonal branches and synaptic connections that are more abundant in early childhood or the developmental regulation of voltage-dependent ion channels.

Clinical Manifestations

Seizures typically occur either shortly after falling asleep or before awakening. However, 15% have seizures in both sleep and wakefulness and 20% to 30% in the waking state alone (7,13). The classic semiology involves the lower face unilaterally with paresthesias of the tongue, lips, gum, and cheek; clonic or tonic activity of the face, lips, and tongue; dysarthria; and drooling. Very young children commonly present with hemiconvulsions instead of the typical facial seizure (13). Rarely, partial motor seizures may change sides without becoming generalized (13). Evolution to bilateral convulsive seizures is common during sleep.

Seizures often occur in clusters, followed by long seizure- free intervals. Single seizures are seen in 13% to 21% (14,15). Frequent seizures are uncommon (6%) and usually seen in those with onset before 3 years of age (15). There is no known correlation between severity of the EEG abnormality, seizure frequency, and final outcome (13). Postictal Todd's paresis occurs in 7% to 16% and may suggest focal onset in patients who present with a generalized nocturnal seizure (16).

Most seizures are brief; however, status epilepticus has been described (16). Temporary oromotor and speech disturbances with intermittent facial twitching suggestive of functional impairment in the anterior opercular region and correlating with nearly continuous spike discharge in the perisylvian region may persist for weeks and may not respond well to antiepileptic therapy (17). Steroids, however, may be of benefit in this setting (17).

BECTS can rarely evolve along the epilepsy–aphasia spectrum either to Landau–Kleffner, with progressive language deterioration and auditory agnosia, or to continuous spike–wave in sleep. Additionally, evolution to "atypical benign partial epilepsy" or "pseudo–Lennox" syndrome, with atonic, atypical absence, and myoclonic seizures, nonconvulsive status epilepticus, and cognitive and behavioral disturbances, has been reported (18). With this syndrome, sleep EEGs show nearly continuous, bilaterally synchronous anterior spike-and-wave activity, and although ultimate seizure remission occurs, many children are left with varying degrees of intellectual disability.

The medical history of BECTS is usually uneventful, although 6% to10% experience neonatal difficulties and up to 16% have antecedent febrile seizures (13). Comorbid migraine is also more prevalent (19).

EEG Manifestations

The characteristic EEG findings are high-amplitude diphasic spikes or sharp waves with prominent aftercoming slow waves (Fig. 17.1). Spikes have a characteristic horizontal, anterior–posterior dipole, with maximal negativity in centrotemporal (inferior rolandic) and with positivity in frontal regions (20). They frequently cluster and are markedly activated in drowsiness and non–rapid eye

movement sleep (Fig. 17.2). The focus is unilateral in 60% of cases, bilateral in 40%, and may be synchronous or asynchronous (13). While the location is usually centrotemporal, a study of children with typical BECTS undergoing 24-hour EEGs showed that 21% had a single focus outside the centrotemporal area and half lacked a horizontal dipole (21). Follow-up recordings showed shifts in foci both toward and away from the centrotemporal area. Additionally, cases with both generalized spike-and-wave discharge and centrotemporal spikes in the same EEG have been reported (22). Usually, the background is normal, although mild slowing has been observed (16). With remission, spikes disappear first from the waking record and later from the sleep recording (13). Few reports of recorded rolandic seizures exist (Fig. 17.3), but two unique features are noted (13,23). Ictal spike-and-wave discharges may show dipole reversal, with electropositivity in the centrotemporal region and negativity in the frontal area; postictal slowing is not seen.

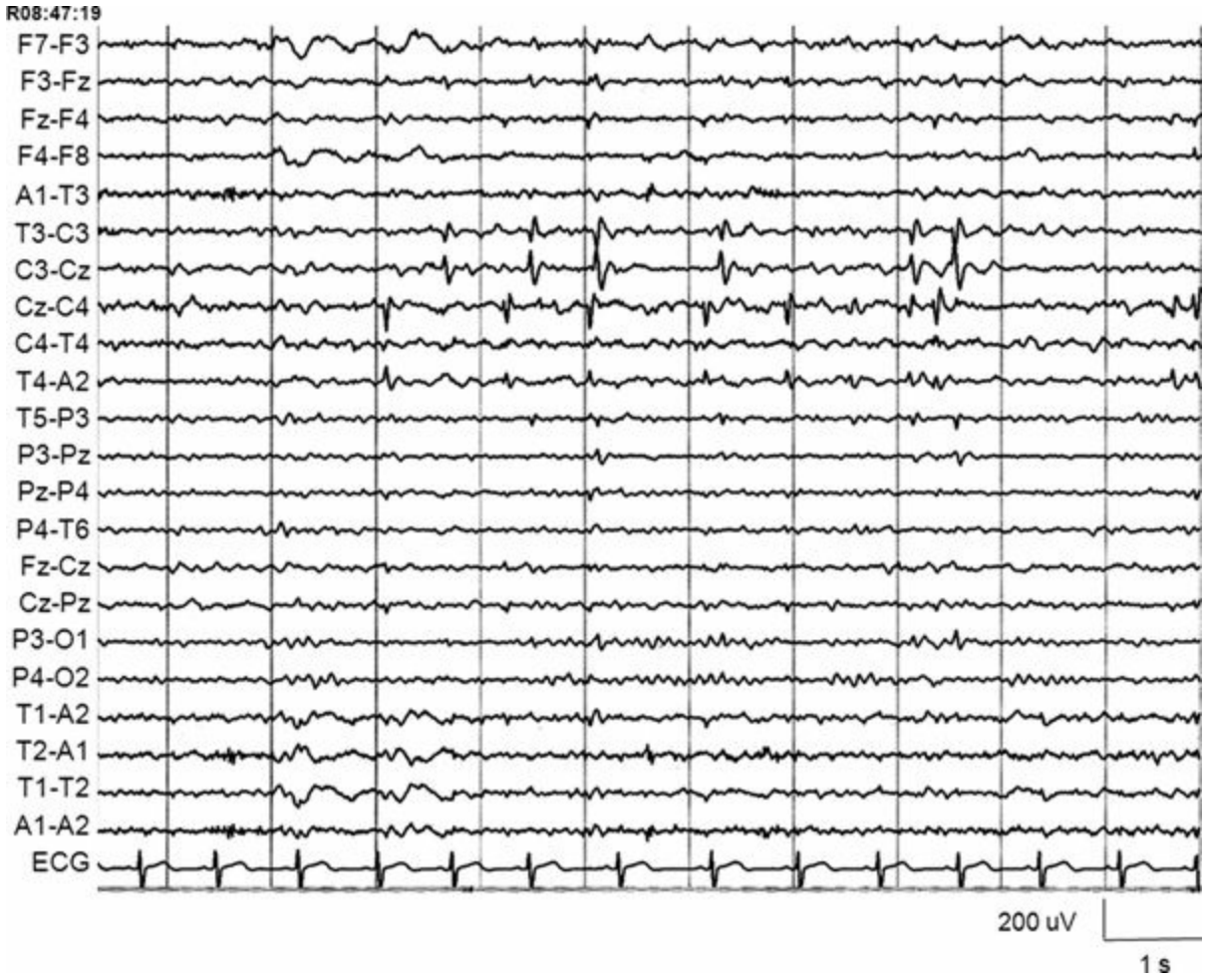


Figure 17.1. Typical rolandic spikes at C3 and C4-T4.

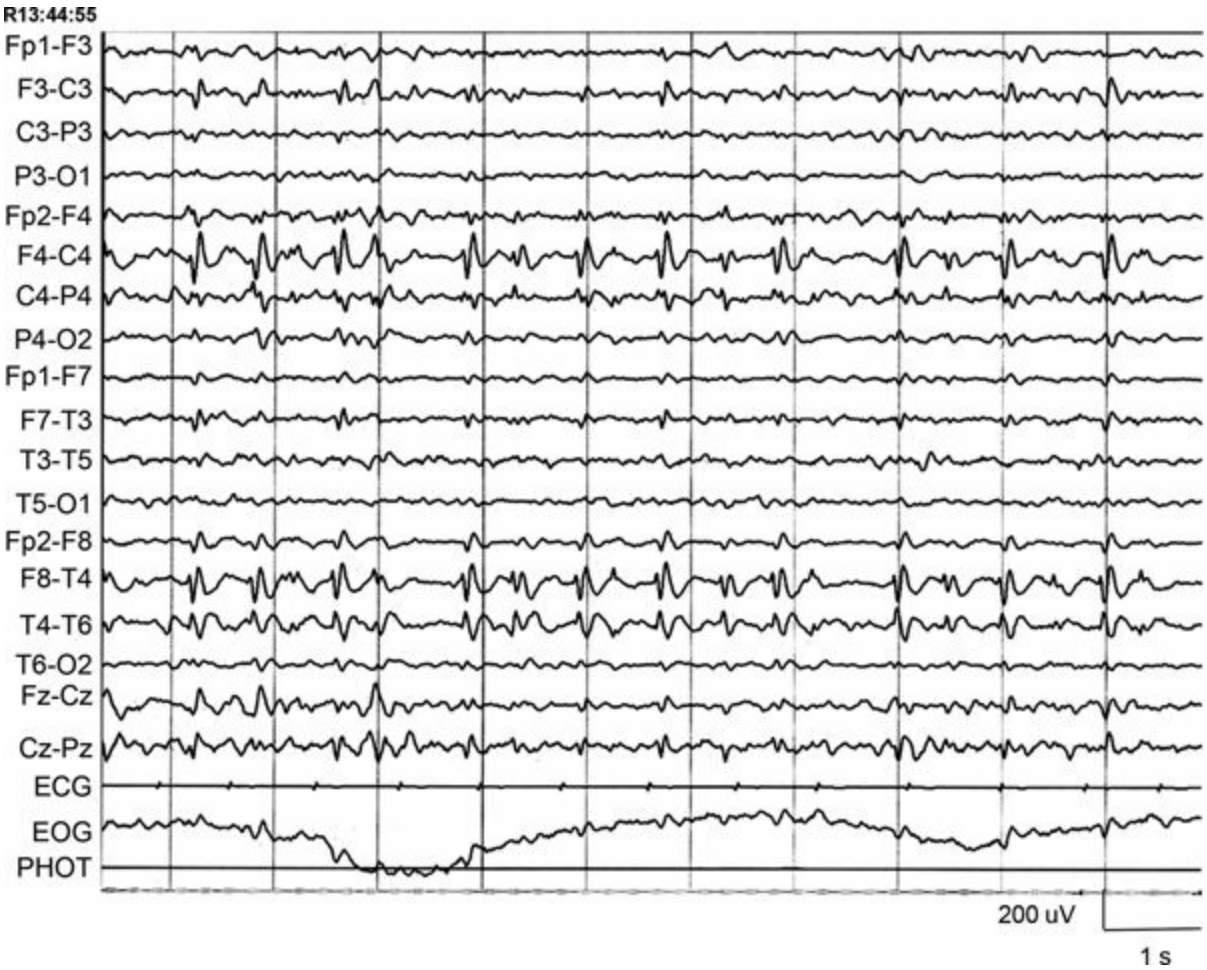
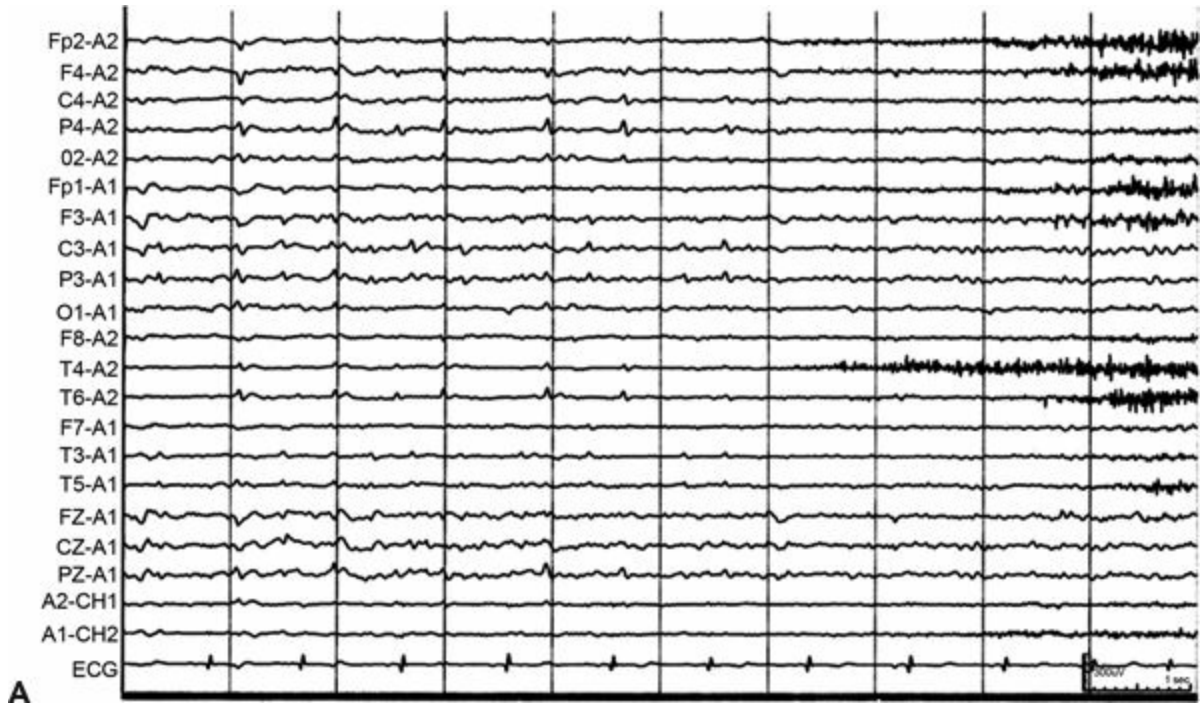


Figure 17.2. Marked activation of rolandic spikes with sleep.



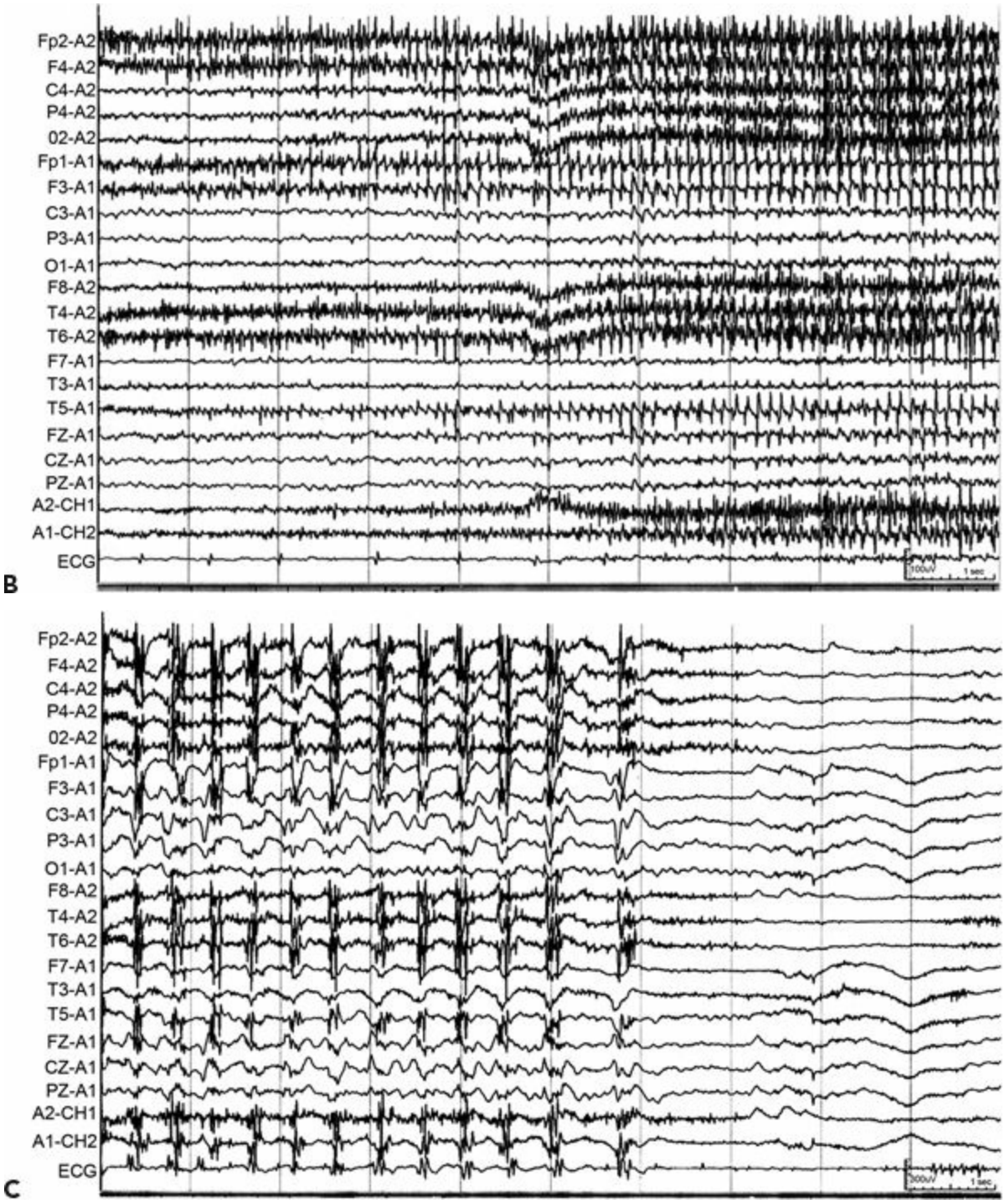


Figure 17.3. Recorded rolandic seizure. **A:** Start of seizure; note onset of rhythmic activity at C3/P3. **B:** Ten seconds later. **C:** End of seizure. (Courtesy of Mary Connolly, Children's Hospital and University of British Columbia.)

Typical rolandic discharges are seen in 0.7% of EEG recordings during wakefulness in children without a history of seizures (24). The percentage of children with rolandic sharp waves who develop clinically apparent seizures is unclear, although it is probably <10%, on the basis of reported incidences of BECTS and of rolandic EEG discharge in normal children. Therefore, rolandic discharges should be considered an incidental finding in children with spells or seizures whose semiology is not suggestive of BECTS. Rolandic spikes have also been reported in children with brain tumors, cortical dysplasia, fragile X syndrome, and Rett syndrome.

Neuropsychological Aspects

Some children with BECTS have abnormal cognitive and behavior maturation, with impaired

attention, executive function, and language (23), and both structural as well as functional causes for these impairments have been suggested. Structural brain changes in regions critical for motor processing and executive function have been shown (25). Bilateral putamen and left caudate hypertrophy were noted at initial diagnosis, and such changes appeared developmentally adaptive, with improved cognitive performance on tests of executive function seen in those with greater putaminal volumes. Functional MRI studies have also suggested that reorganization of language (particularly anterior language regions) occurs in more bilateral or right-hemispheric networks as a compensatory strategy to stabilize language performance (26). However, neurocognitive deficits may also be functionally related to epileptiform discharges, as they correlate with the amount and location of interictal spike discharge and, like the seizures and discharges, resolve over time (27).

Investigations

If the clinical history and EEG suggest BECTS and the child is neurologically and developmentally intact, no further investigations are required. An MRI scan should be considered in patients with atypical features. Several studies have shown MRI abnormalities including hippocampal asymmetry, white matter abnormalities, or developmental lesions in a minority of cases (28,29). However, the presence of such lesions does not alter the benign course of BECTS.

Treatment

Children with BECTS achieve remission regardless of antiepileptic drug therapy. We are unaware of any peer-reviewed reports of children with BECTS dying of sudden unexpected death in epilepsy or sustaining brain injury from a seizure. A no-medication strategy is reasonable for the majority of children who have infrequent, nocturnal, focal seizures. If recurrent generalized or diurnal seizures occur, or if they are sufficiently disturbing to the child or the family, treatment is generally started.

Only sulthiame and gabapentin have been studied in randomized, placebo-controlled trials. On the basis of case series and a recent meta-analysis of 794 children (30), antiepileptic drugs prescribed for focal seizures have equivalent efficacy, with 50% to 65% having no further seizures once medication is started. Gabapentin tended to be more effective than placebo in a study of 220 children although the results did not reach statistical significance (31). Sulthiame significantly improves the EEG and decreases clinical seizures. In a randomized, double-blind trial comparing sulthiame to placebo in 66 children, 81% taking sulthiame completed 6 months of therapy with no further seizures or adverse events, compared with only 29% taking placebo ($P < 0.00002$) (32). Of 25 children remaining on sulthiame at 6 months, 10 (40%) had a normal EEG, compared with only 1 of 10 (10%) in the placebo group.

Rarely, antiepileptic drugs may aggravate BECTS, resulting in evolution to continuous spike and wave during slow sleep with neuropsychological deterioration. Such deterioration has been reported with carbamazepine, phenobarbital, and lamotrigine.

Prognosis

The long-term prognosis of BECTS is excellent, even if seizures are initially frequent and troublesome. In a meta-analysis, 50% of patients were in remission at age 6 years, 92% at age 12 years, and 99.8% at age 18 years (Fig. 17.4) (30). Remission occurs sooner in children who are older at onset and in those with sporadic seizures or seizure clusters (14). Conversely, short intervals

between the initial seizures and younger age at onset predict higher seizure frequency. Although learning and behavior problems may be seen in the acute phase, long-term psychosocial outcome is excellent (33), with no increase in psychiatric problems or personality problems, and excellent occupational status.

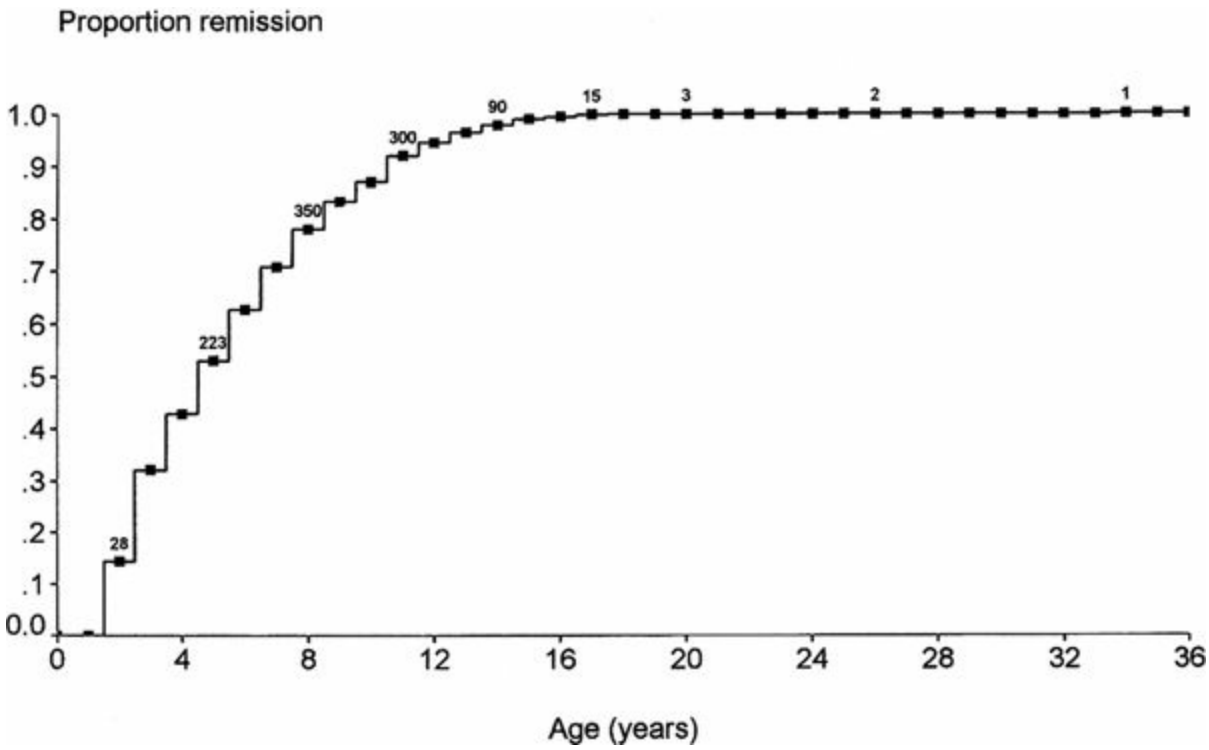


Figure 17.4. Remission of BECTS by age. Numbers in the figure represent the number of patients in the analysis. (From Bouma PAD, Bovenkerk AC, Westendorp RGJ, et al. The course of benign partial epilepsy of childhood with centrotemporal spikes: a meta-analysis. Neurology. 1997;48:430–437.)

PANAYIOTOPOULOS SYNDROME (EARLY ONSET BENIGN OCCIPITAL EPILEPSY)

Gibbs and Gibbs were the first to recognize that some children with occipital epilepsy had a benign course (34). Two syndromes are identified—early onset (Panayiotopoulos syndrome or PS), which is a clearly delineated syndrome based on over 500 published cases (35), and late onset (Gastaut type), which is much less well defined.

Epidemiology

PS accounts for 1% to 2% of children with focal epilepsy (36,37), about one-third the incidence of BECTS. The peak age of onset is 5 years (range, 3 to 8 years) with a female preponderance.

Genetics

Approximately 10% of PS patients have a first-degree relative with epilepsy (37–39), and 5% to 17% has a history of febrile seizures. In a study of 16 probands with PS including 7 twins, Taylor found that monozygotic twin pairs did not show a higher concordance rate than dizygotic twin pairs, suggesting that nonconventional genetic influences or environmental factors play a major role (39).

Rarely, SCN1A mutations may be found in atypical PS if the seizures have a very early age of onset and are frequent (40).

Pathophysiology

It is speculated that PS is the result of a combination of multifocal cortical hyperexcitability and an unstable autonomic nervous system (41). If the cortical region exceeds a critical epileptogenic level, the autonomic nervous system is first activated and then becomes involved in cortical/subcortical self-sustaining oscillations. These temporarily synchronize with resultant focal cortical symptoms.

Clinical Manifestations

Children with PS are typically otherwise normal. Seizures are nearly always nocturnal and present with autonomic symptoms especially nausea, retching, and vomiting (36,38). Other autonomic symptoms may include pallor, urinary or fecal incontinence, hypersalivation, mydriasis, miosis, coughing, respiratory or cardiac irregularities, or even syncope (42). Tonic eye deviation is common while other ictal visual symptoms, such as visual hallucinations, affect <10% (38). Consciousness may be impaired, and seizures can evolve to hemi- or generalized convulsions. Seizures last frequently longer than 30 minutes—one-third of patients develop focal status epilepticus (35,36). Seizure frequency varies, and one-third of patients experience only a single event (36,38,39). Rarely, PS evolves atypically with the appearance of many seizure types including absences, atonic seizures, and intellectual deterioration (36).

EEG Manifestations

The interictal EEG in PS shows spikes in variable locations that often shift foci on subsequent recordings. Spike location is variable and does not always involve the occipital regions—an equal number of cases show centrotemporal/parietal foci, and discharges are primarily multifocal, high-voltage, frequent, and increased in sleep (38). Occasionally, EEGs can be normal or show irregular, generalized spike–wave discharge (36).

Magnetoencephalography shows dipole clusters along the parietooccipital, calcarine, and rolandic fissures, and a superficial rather than deep dipole source location of the occipital spikes suggests a benign disorder rather than symptomatic occipital epilepsy (43). Sometimes, runs of repetitive occipital spikes and sharp waves are seen (Fig. 17.5) (36).

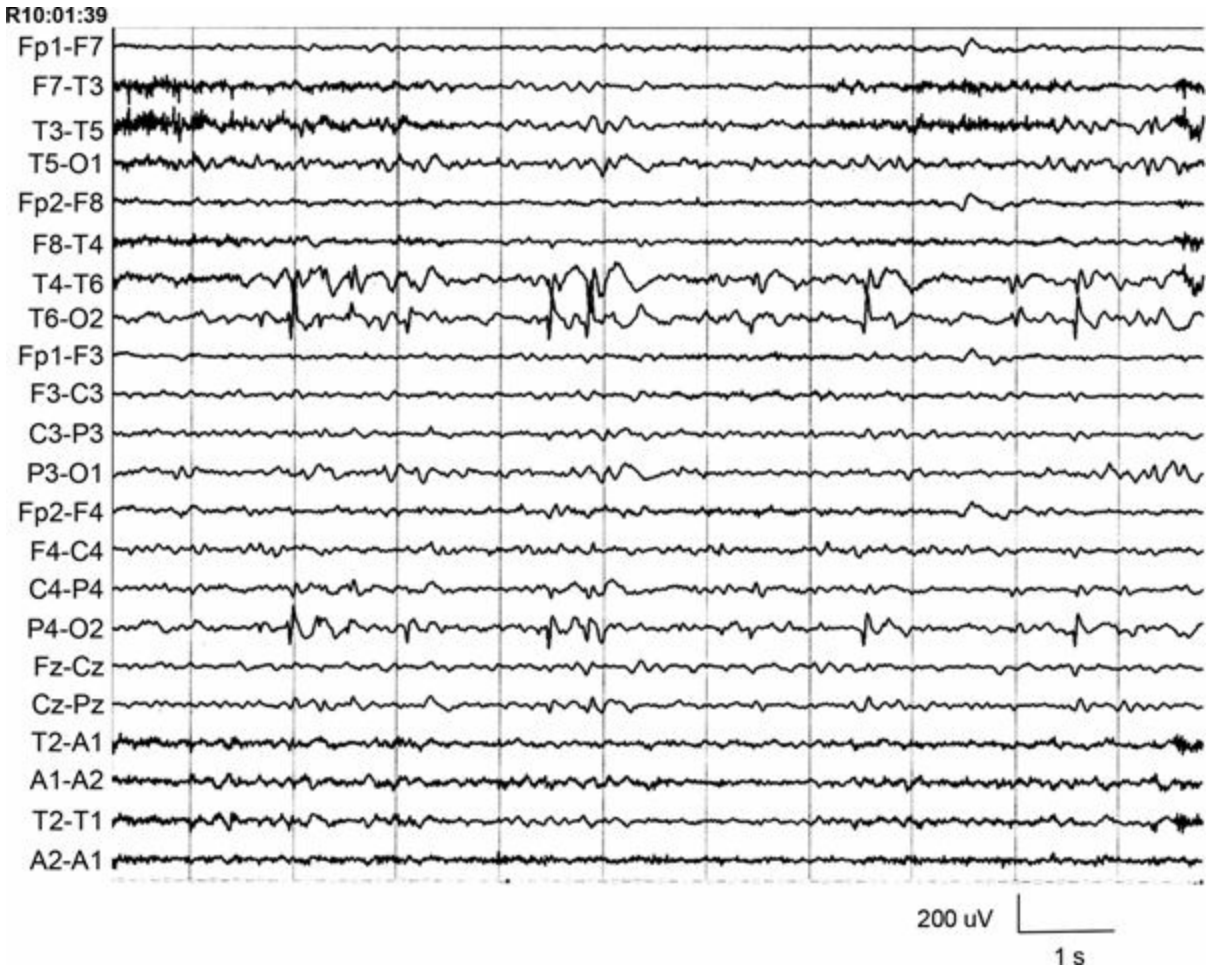


Figure 17.5. Posterior temporal–occipital spikes in a 4-year-old girl who presented with a 65-minute seizure consisting of focal eye deviation and retching.

The ictal EEG shows rhythmic theta or delta activity with intermixed spikes that usually start posteriorly, although anterior onset has been reported (35,36). Some studies suggest that, in rare cases, PS may evolve to continuous spike–wave in slow-wave sleep.

Neuropsychology

Specchio (36) evaluated 17 cases of PS after their first seizure compared with age- and sex-matched controls and found no differences between verbal and performance IQ scores on the Wechsler Intelligence Scale-Revised. This study supports the generally accepted clinical dictum that most children with PS have no cognitive deficits.

Investigations

Imaging is not required with a typical clinical history of PS and an EEG showing occipital paroxysms with fixation-off sensitivity. MRI should be considered if the EEG or clinical picture is atypical.

Treatment

Most children with PS have infrequent seizures and do not require antiepileptic drug treatment. Intermittent use of benzodiazepines could be considered for the child with prolonged events. No particular antiepileptic drug has been shown to be superior (35), although carbamazepine is most

frequently prescribed. Spikes may persist for several years after clinical remission.

Prognosis

In PS, remission of active epilepsy occurs 1 to 2 years from onset. As in BECTS, even those with many seizures usually achieve long-term remission.

LATE-ONSET (GASTAUT TYPE) BENIGN OCCIPITAL EPILEPSY

Late-onset BOE is a rarer and less distinct electroclinical syndrome that begins in mid- to late childhood, with a peak age of 8 years (range, 3 to 16 years); both sexes are equally affected (44). The diagnosis of late-onset BOE should be made cautiously, as the semiology may also be seen with lesional occipital epilepsy, and the prognosis is not always benign (44).

Clinical Manifestations

Late-onset BOE manifests as frequent (>15) diurnal, brief, visual seizures consisting of elementary visual hallucinations or brief amaurosis, which may result in brief but total blindness (44). Typically, hallucinations consist of moving, multicolored, circular patterns, which can multiply during the seizure, and more complex hallucinations (faces or figures) or visual illusions (i.e., micropsia or palinopsia) are rare. Sensory illusions of ocular movement or pain, tonic eye and head deviation, or eyelid closure may coexist. Consciousness is typically intact unless there is secondary generalization. There is a complex relationship with migraine. Headache may precede the seizure or occur at the onset (45), and postictal headache, indistinguishable from migraine, is seen in 25% to 50% of cases. Helpful features to distinguish late-onset BOE from the visual aura of migraine is that the latter evolves more slowly (over 10 to 20 minutes rather than 1 to 3 minutes) and tends to be achromatic and linear rather than multicolored and circular (46).

EEG Manifestations

Runs of occipital spikes are characteristic, and extraoccipital spikes are uncommon (44). The spikes may show “fixation-off sensitivity,” that is, they attenuate with eye opening and are induced by elimination of central vision by eye closure, darkness, or vision through +10 spherical lenses (Fig 17.6) (47). However, this finding does not reliably distinguish lesional from benign occipital epilepsies. The ictal EEG in late-onset BOE shows fast rhythms appearing in the occipital lobe at the onset of visual symptoms.

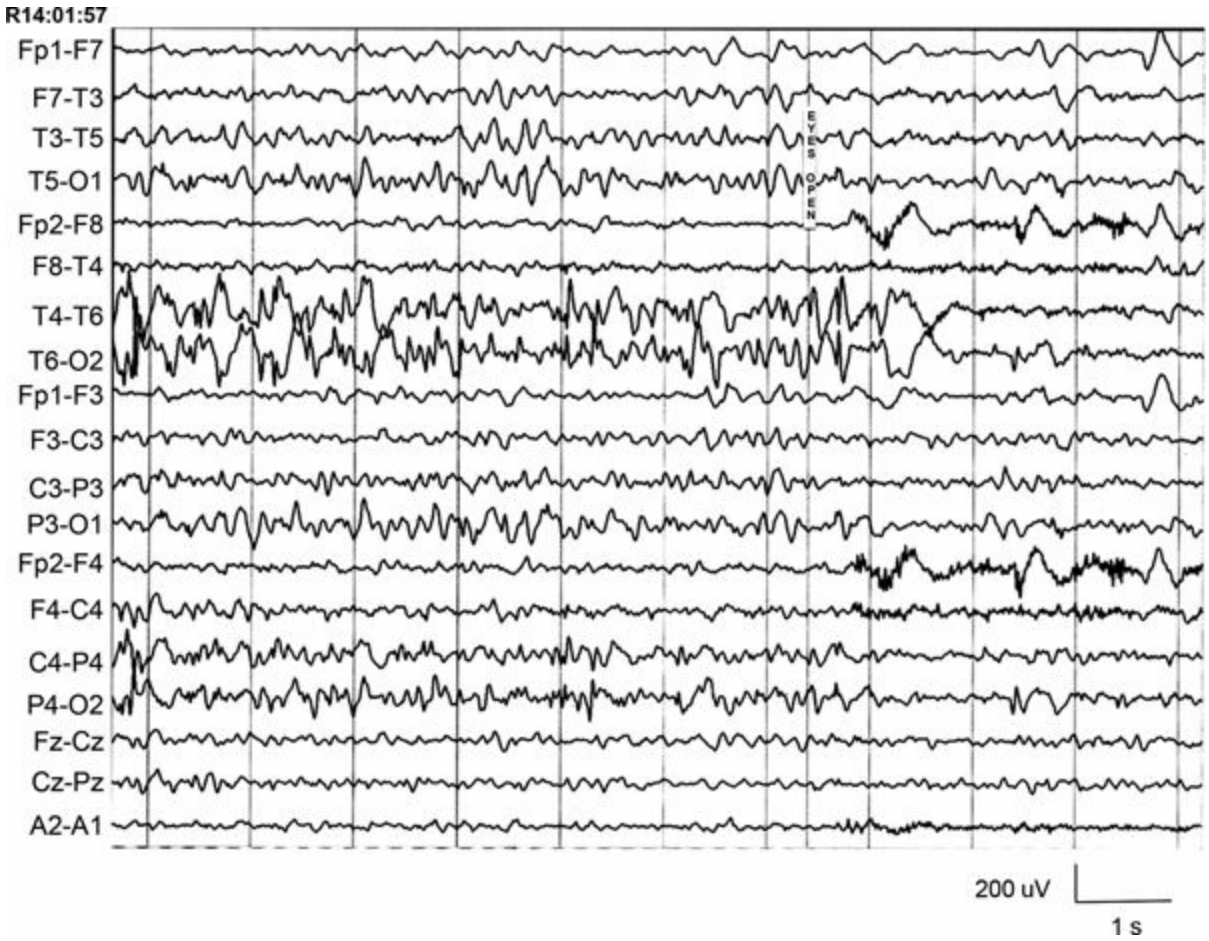


Figure 17.6. Prominent fixation-off sensitivity with eye closure in the same 4-year-old girl.

Investigations

MRI should usually be obtained because lesional occipital lobe epilepsy due to such etiologies as cortical dysplasia, mitochondrial disease, Lafora disease, or celiac disease may mimic Gastaut-type BOE.

Treatment

Most cases require treatment, as seizures are more frequent, although only 60% of 63 patients reported by Gastaut achieved complete seizure control (44).

Prognosis

The prognosis is less clear in late-onset BOE, although Gastaut reported that 5% of his 63 cases had recurrent seizures into adulthood (44).

BENIGN FOCAL EPILEPSIES IN INFANCY

Several variants of benign focal epilepsy in infancy have been described (48), and the ILAE currently recognizes both benign epilepsy in infancy (BEI) and benign familial infantile epilepsy. Clear distinction between each of these syndromes can be challenging, and further progress in genetics may improve our understanding of many of these entities.

Benign Epilepsy in Infancy

Watanabe proposed this disorder in 1987 (49,50) and described two forms: one with focal dyscognitive seizures alone and another with focal evolving to bilateral convulsive seizures. BEI represents approximately 7% to 29% of all epilepsies in the first 2 years of life (51,52). Both reports noted that the form with secondarily generalized seizures was slightly more common, accounting for 64% to 73% of all BPEI cases. Peak age at onset is 4 to 6 months, with a range of 3 to 10 months.

Developmentally normal infants typically present with clusters of seizures consisting of motion arrest, decreased responsiveness, staring, simple automatisms, and mild convulsive movements, with possible evolution to bilateral convulsive activity. Neuroimaging is normal. The interictal EEG is usually normal, but infants may show low-voltage rolandic and vertex spikes in sleep (53). Ictal recordings in infants with focal dyscognitive seizures alone demonstrate an EEG seizure pattern that is maximal in the temporal–occipital regions. In patients with bilateral convulsive semiology, EEG seizures are located in the central–parietal–occipital region. Seizures are easily controlled with antiepileptic drugs, and remission occurs in 91% within 4 months and in all children by age 2 years (52).

To determine how accurately BEI can be diagnosed in infancy, Okumura et al. (54) followed up 39 children who were believed to have the syndrome after 5 years. Eighty-five percent of cases had achieved remission, were no longer treated with antiepileptic drugs, and were developmentally normal. However, the diagnosis appeared incorrect in the remaining 15%, who had recurrent seizures after 2 years and/or showed developmental delay, emphasizing the need for close follow-up of these children.

Benign Familial Infantile Seizures and Other Benign Familial Neonatal and Infantile Epilepsies

Infants with benign familial infantile seizures (BFIS) are developmentally normal and present with clusters of focal seizures between 4 and 8 months of age, consisting of psychomotor arrest, cyanosis, head or eye deviation, tonic contraction, and bilateral clonic jerks (48). This condition is autosomal dominantly inherited, and other neurologic disorders including paroxysmal choreoathetosis and familial hemiplegic migraine may also coexist. The interictal EEG is normal, and ictal studies show fast activity in the parietooccipital region.

Benign familial neonatal–infantile seizures are also autosomal dominant and present between 2 days and 7 months. Clinical seizures manifest with focal motor manifestations that evolve to bilateral convulsive seizures. Interictal EEG may be normal or show posterior discharges.

Benign familial neonatal seizures present between days 2 and 28 of life with focal-onset seizures. The interictal EEG is typically normal. However, focal discharges may be seen, particularly in the rolandic region.

Seizures in the familial focal infantile epilepsies typically respond well to antiepileptic medication and resolve by early childhood. Several genes have now been identified that lead to familial seizures in the first year of life. Age at onset and comorbid neurologic symptoms can provide clues to the most likely gene, with benign familial neonatal seizures predominantly involving KCNQ2 and, less commonly, KCNQ3, with benign familial neonatal–infantile seizures involving either KCNQ2 or SCN2A, and with BFIS most often involving PRRT2 (often with coexisting paroxysmal choreoathetosis). However, SCN2A, KCNQ2, and KCNQ3 may also result in BFIS. Very rarely,

KCNQ2 mutations may lead to a severe epileptic encephalopathy with medically intractable epilepsy and profound neurologic disability.

Benign Focal Epilepsy in Infancy with Midline Spikes and Waves During Sleep

In this syndrome, neurologically and developmentally normal children present with brief sporadic seizures consisting of cyanosis, staring, motion arrest, and stiffening between 4 and 30 months of age (48). Seizures cluster in 31% of cases. Automatisms or lateralizing signs are rare, and secondary generalization has not been reported. A family history of epilepsy is present in 47% of cases. The EEG shows a low-voltage, fast spike followed by a higher bell-shaped slow wave over the midline region during sleep only, which spreads to the central or, less commonly, to the temporal region. Outcome is excellent—seizures resolve by 2 to 3 years of age, and many cases do not require antiepileptic drug treatment.

AUTOSOMAL DOMINANT FRONTAL LOBE EPILEPSY

This syndrome presents in adolescence or young adulthood with nocturnal seizures of frontal lobe semiology that present out of sleep. Typically, seizures are frequent and often hypermotor, with moaning, rocking, grabbing, or extension and abduction of the arms. The interictal EEG may be normal or show frontal spikes, and ictal recordings show fast, bifrontal discharge. Mutations in CHRNA4, CHRNB2, and CHRNA2 are causative, and functional studies suggest these mutations result in activation of a potassium channel (KCNT1) in the central nervous system. Most patients respond favorable to carbamazepine with good seizure control. Although remission may occur, for many patients this disorder is lifelong.

FAMILIAL TEMPORAL LOBE EPILEPSY

Autosomal dominant lateral TLE, also known as autosomal dominant partial epilepsy with auditory features, is associated with mutations in the leucine-rich, glioma-inactivated 1 (LGI1) gene in approximately 50% of families (55). Median age at onset is in late adolescence (range 1 to 60 years), and the focal seizures have prominent elementary auditory auras. Aphasic seizures are seen in 17% of cases and secondarily generalized seizures in 90%. Neuroimaging is usually normal, and the clinical course is benign, with most patients achieving good control with antiepileptic medications. In a review of 100 individuals from 20 families, Crompton et al. (56) characterized the clinical features of familial mesial TLE, which they propose is inherited in a polygenic (rather than autosomal dominant) manner. Median age at seizure onset was 15 years (range 3 to 46 years), antecedent febrile seizures were seen in 9.8%, and nearly all patients had normal neuroimaging. Seizure semiology is characterized by déjà vu, fear, and nausea, with evolution to focal seizures with or without loss of awareness. Most patients had a relatively benign course with good response to medication.

OTHER POSSIBLE BENIGN FOCAL EPILEPSY

SYNDROMES

Other syndromes that have not been completely described to know whether they stand the test of time as a benign focal epilepsy of childhood are of interest but not placed in this chapter (Table 17.1). These include benign frontal epilepsy, benign partial epilepsy with extreme somatosensory evoked potentials, benign partial epilepsy with affective symptoms, and benign partial epilepsy of adolescence.

SUMMARY

The IFEs of childhood account for a significant proportion of seizure disorders in pediatric patients. In its classic form, BECTS is easily recognizable, occurring in neurologically normal children and having a distinct semiology and EEG pattern. PS, with characteristic ictal semiology, also lends itself to a confident diagnosis. Such is not the case for the other IFEs or for BECTS or early-onset BOE with atypical clinical or electrographic features. These diagnoses may be made definitively only in retrospect.

Minor cognitive changes during the active period of epilepsy occur in some children with IFE but also appear to remit with time. Many children with IFEs, however, will not require antiepileptic drugs, as most have infrequent seizures. Recognition of these benign epilepsy syndromes is important for appropriate counseling of the child and family.

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CHAPTER 18 IDIOPATHIC GENERALIZED EPILEPSY SYNDROMES OF CHILDHOOD AND ADOLESCENCE

STEPHEN HANTUS

Idiopathic generalized epilepsy (IGE) represents 20% of all epilepsies. The diagnosis is often made in childhood or adolescence and may become self-limited or persist into adulthood. With proper diagnosis and medical management, these epilepsy syndromes are controlled with medications in 80% of cases. Diagnosis is important as certain medications can aggravate these epilepsies and lead to increased seizures and pseudointractability. Proper medication management is often able to allow patients to live an otherwise unaffected life, although persistent social and psychological problems are reported in some studies (1,2).

IGEs are defined by the International League Against Epilepsy (ILAE) as an epilepsy that arises spontaneously, with no associated structural lesion or neurologic sign or symptom, and is of presumed genetic origin (3,4). IGEs are a group of epilepsies that give rise to three types of seizures that occur in various combinations depending on the syndrome.

TYPICAL ABSENCE SEIZURES

These seizures are clinically characterized by unresponsiveness of short duration (5 to 15 seconds) with abrupt onset and termination. Patients are unresponsive during the seizures and have no memory of these brief events. Occasionally, there is associated eye fluttering or automatisms. There is little or no postictal confusion or disorientation associated with this seizure type. Electroencephalogram (EEG) demonstrates the typical 3-Hz spike-and-wave complexes that are often most prominent during hyperventilation.

MYOCLONIC SEIZURES

This is a seizure type characterized by brief jerks (10 to 100 ms on average) that occur sporadically and often involve the upper extremities bilaterally as well as the trunk. They are often described as “shock-like” muscle contractions and occur most frequently in the morning. Patients typically deny any alteration in consciousness during these jerks and have no associated postictal confusion or disorientation. Jerks may be minor causing barely perceptible movements up to larger jerks that result in dropping objects or falling. EEG demonstrates generalized polyspike discharges prior to the muscle jerk of the myoclonic seizure, which is often apparent on scalp EEG but is at times only appreciated with back averaging of EEG data.

GENERALIZED TONIC–CLONIC SEIZURES

These seizures typically last 1 to 3 minutes and are associated with loss of consciousness and a muscular convulsion. The tonic phase lasts for 10 to 45 seconds and may involve bilateral arm stiffening and often a vocalization. This is followed by a clonic phase with rhythmic jerking of various muscle groups. There is often an extensive postictal period of confusion and disorientation that may last from 5 minutes to several hours. EEG during these seizures shows generalized spike-and-wave discharges that evolve in frequency and amplitude.

IDIOPATHIC GENERALIZED EPILEPSY SYNDROMES

IGE syndromes are best viewed as a spectrum of disorders with these three seizure types expressed in variable amounts as different clinical phenotypes. These syndromes often have overlapping genetic etiologies as well. It is most important to distinguish the focal/localization-related epilepsies from the generalized epilepsies because the treatment and prognosis are very different. The risk of intractability is much higher in focal epilepsies, and the drugs that treat focal epilepsy can exacerbate IGE. The following section describes the diagnostic criteria of the IGE syndromes and what is known about their etiology and prognosis.

CHILDHOOD ABSENCE EPILEPSY

Childhood absence epilepsy (CAE) is a widely recognized syndrome with absence seizures as the only manifestation in many patients, while generalized tonic–clonic (GTC) seizures can also occur in up to 40%, although GTC seizures are more common in the juvenile form (5,6).

Epidemiology

CAE has been estimated to comprise 2% to 8% of epilepsy in the total population but appears to be heavily age dependent. Studies of childhood cohorts (0- to 15-year age group) estimate 13% to 18%, with a smaller proportion of 3% to 6% in patients in the older than 15-year age group. Large epidemiologic studies in Europe and the United States have shown an incidence of 6 to 8 per 100,000 in the 0- to 15-year age group (7). There has been a female predominance noted in several studies (5,8).

Clinical Features

CAE characteristically begins between the ages of 4 and 8 years with absence seizures, but the age of onset can vary between ages 2 to 10 years (9). The absence seizures are often provoked by having the patient hyperventilate in the office, effective in up to 98% of patients. A smaller number of patients (16% noted in one study) are found to be photosensitive (10). In addition to the typical abrupt loss of consciousness and quick recovery of a typical absence, automatisms, transient loss of tone, fluttering of the eyelids, and brief myoclonic jerks are also common. Seizures typically last from 5 to 15 seconds and without medications may occur hundreds of times per day. Patients with CAE have been noted to have cognitive, linguistic, and psychiatric comorbidities (11). In the study by Caplan et al.

(11), one-fourth of patients had subtle cognitive difficulties, almost half had linguistic deficits, and approximately 67% had a psychiatric diagnosis with attention deficit hyperactivity disorder and anxiety being most common. There is some indication that treatment with medications can improve some neurocognitive skills (e.g., visual memory), and the results are dependent on seizure control (12). Although it is a defining characteristic that patients with CAE (and IGEs in general) have normal intelligence, recent studies have emphasized that untreated behavioral and psychiatric problems are common (11,13).

IGEs are also by definition not related to a structural or anatomic cause, and normal imaging with magnetic resonance imaging (MRI) is the most common clinical finding. However, there are some volumetric studies that suggest that the anterior half to the thalamus is larger in patients with absence epilepsy, suggesting a possible structural correlate (14). This finding was not present in patients with other seizure types (GTC seizures).

EEG

The EEG in CAE shows monomorphic high-voltage generalized spike-and-slow-wave complexes at 3 Hz (2.5 to 4.0 Hz). These spike-and-wave complexes may occur interictally or as an ictal pattern depending on the duration and responsiveness of the patient. The typical length of an ictal event is 5 to 15 seconds and may begin with 3.0-to 3.5-Hz spike-and-wave complexes that may slow to 2.5- to 3.0-Hz discharges. Responsiveness is typically tested during the SWC discharges to assess whether the event is considered a seizure or interictal discharge. The background EEG is typically normal. In up to 50% of patients, bursts of rhythmic slowing lasting 2 to 4 seconds can be seen in the occipital leads. A small study suggested that occipital intermittent rhythmic delta activity indicated a good prognosis for response to medication in typical absence epilepsy (15).

Generalized epilepsies have been considered to arise from the bilateral, global neocortex by definition but have been noted to have a frontal predominance on EEG. The use of dense array EEG (256 channels) and software to superimpose the electrical signals over the patients MRI has suggested that there are discrete areas that are activated during an absence seizure (16,17). Dense array EEG suggests a corticothalamic circuit involving the medial frontal and orbitofrontal cortex maximally.

Genetics

Classic family studies have suggested that one-third of patients with CAE have a family history of epilepsy and siblings of affected individuals have an approximately 10% chance of suffering seizures (18). The essential genetic nature of IGE is demonstrated in twin studies that show an 81% concordance among monozygotic twins, while dizygotic twins are only 26% concordant for epilepsy (19). The genetics of CAE is a complex pattern with most patients having multiple genetic factors likely contributing to their epilepsy and rare cases with a monogenetic etiology reported (20). Most of the genes that have been identified are subunits of ion channels, with some exceptions. Identified mutations have been shown in the γ-aminobutyric acid receptor γ2 (GABRG2), γ-aminobutyric acid receptor α1 (GABRA1), γ-aminobutyric acid receptor β3 (GABRB3), chloride channel receptor 2 (CLCN2), the calcium channel voltage-dependent, T-type α1H subunit (CACNA1H) genes, and γ3 subunit of neuronal voltage-gated calcium channel (21). A study that examined gene expression in monozygotic twins that were discordant for epilepsy identified altered expression of early growth

response 1 (EGR 1) and reticulocalbin 2 (RCN 2), suggesting a role for these proteins in CAE (22).

Treatment

Medical treatment has been shown to suppress absence seizures in more than 80% of patients. Studies that have compared ethosuximide, valproate, and lamotrigine were not able to establish a difference in efficacy and are all considered first-line medications (23). Ethosuximide does not protect against GTC seizures and has neurotoxic and gastrointestinal side effects that limit its use. Valproate is effective as a broad-spectrum agent treating absence, GTC seizures, and myoclonic seizures. Valproate use is limited due to side effects of weight gain and potential teratogenicity. Lamotrigine is effective in treating absence, has fewer cognitive side effects, and is the preferred medication for females due to the lower rate of teratogenicity as compared to valproate (23). Levetiracetam and zonisamide have been shown to decrease absence seizures by 50% to 60% in small studies and are considered second-line medications (24,25). Refractory absence epilepsy occurs in 5% to 20% of cases (5). Treatment with an inappropriate antiepileptic drug (AED) is a frequent cause of "pseudointractability," as some drugs have been shown to exacerbate absences (26,27). Carbamazepine is the most frequent cause of worsening seizures and has been associated with absence status epilepticus (26). Phenytoin, tiagabine, vigabatrin, and oxcarbazepine have also been shown to cause a paradoxical increase in seizures in patients with absence epilepsy. Combinations of medications, particularly with valproate, have been shown to be more effective than single medications alone (27).

The decision to stop therapy is often difficult. A minimum seizure-free interval of 2 years is typically recommended before withdrawal of medication. However, each case must be evaluated individually in terms of the attitude of the patient and the family, participation in sports, occupation, and driving an automobile. The EEG findings may help guide the decision, but the presence of occasional brief epileptiform discharges should not preclude drug withdrawal in the seizure-free patient (28).

Prognosis

CAE is one of the relatively benign childhood epilepsies, but not all patients become seizure free. Approximately 50% of patients with CAE will have a spontaneous remission by the age of 10 to 12 years, with a range of 21% to 89% remission (29). In patients with absence seizures only, the seizure-free rate is approximately 80%, while patients with GTC seizures and absence were only 30% seizure free (29). Early institution of effective therapy is believed to improve prognosis in terms of the later development of tonic–clonic seizures and relapse of absences. A Dutch study with long-term follow-up (12 to 17 years) indicated that seizure freedom in the first 6 months of treatment predicted outcome, while EEG and baseline characteristics did not impact outcome (30).

JUVENILE ABSENCE EPILEPSY

Juvenile absence epilepsy (JAE) has a number of features that are clinically distinct from those of the other absence epilepsies and has been recognized as a separate syndrome (3,4). JAE has later age at onset with fewer seizures on average and is more often associated with GTCs. It is often diagnosed retrospectively after a GTC seizure occurs or other associated features are noted.

Epidemiology

There are no definitive epidemiologic studies for JAE, but large studies of absence epilepsy have shown a peak at age 6 to 7 years (consistent with the peak ages of the onset of CAE) and another around age 12 (7). Several cohort studies have estimated that JAE comprises 0.2% to 3.0% of childhood epilepsies. Juvenile myoclonic epilepsy (JME) has a prevalence of 0.1 per 100,000 persons in the general population, which is much less common than CAE (7,31).

Clinical Features

Most cases begin during or near puberty, with a range of 10 to 17 years and an average onset at age 12 (7,31). The absences are less frequent than those of CAE and occur once per day or several per week (as compared to the 100 per day often seen in CAE). The absences of JAE have been described in various clinical reports as resulting in less severe loss of consciousness, having a retropulsive component (backward motion of the eyes), and lasting longer than CAE at approximately 10 to 60 seconds (8,32). GTC seizures have been reported in 47% to 80% of patients with JAE and frequently occur upon awakening (8,31). Myoclonic jerks are less frequent and occur in 10% to 15% of patients and illustrate the clinical overlap with some features of JME (8).

EEG

JAE is associated with generalized spike-and-wave discharges that occur typically at 3 to 4 Hz, which is slightly faster than CAE. They have also been reported to be slightly less rhythmic and less organized than the spike-and-wave complexes seen in CAE. Photosensitivity is rare but appears to be more common in females and in the juvenile form (33,34). The interictal background activity is normal.

Genetics

The genetic origin of JAE remains largely undiscovered at this point. It is known from twin studies that genetics play a large role in JAE (35) and that patients with JAE have a family history of epilepsy in 29% to 35% of cases (8,31). Sander et al. reported that the kainate-selective glutamate receptor gene (GRIK1) is a susceptibility gene for developing JAE (36). The chloride channel ClCN2 has also been implicated in CAE, and JME is also thought to play a role in JAE (37).

Treatment

Valproate has been the historically most effective treatment choice. It treats the absences and also treats the possible associated GTC seizures and/or myoclonic jerks. However, due to the side effects of weight gain and teratogenicity, it is generally used with caution in young females. Lamotrigine has also been shown to be an effective choice, treating absence seizures as well as GTC seizures. If myoclonus is present, then treatment with levetiracetam may be an alternative to valproate. Due to the frequent occurrence of GTC seizures with JAE, ethosuximide is not recommended as first-line medication. Education about avoiding sleep deprivation and alcohol consumption is also important in adolescent patients.

Prognosis

The response of JAE to pharmacologic therapy is typically very good. Valproate alone has been shown to treat over 80% of cases. However, the seizure-free rates tend to be less than in patients with CAE (8). Patients with GTC seizures tended to have a worse prognosis (8).

JUVENILE MYOCLONIC EPILEPSY

JME is a well-known IGE syndrome that involves adolescents. JME often goes undiagnosed until a GTC seizure occurs, because myoclonic jerks are often ignored or attributed to morning clumsiness. Increased awareness by clinicians and the availability of video-EEG has helped make this diagnosis more expedient.

Epidemiology

The incidence of JME has been estimated to be 1 per 100,000 persons, with a prevalence of 0.1 to 0.2 per 100,000. The frequency of JME in large cohorts has been estimated to be 5% to 10% of all epilepsies and 18% of IGEs (7). Certain populations or family groups have been reported to have a higher incidence of JME such as Saudi Arabia and sections of India (38,39).

Clinical Features

The age of onset for JME is typically 12 to 18 years, with a peak onset at age 15, but can manifest in all age groups (40). The clinical presentation of JME is typically a GTC seizure that occurs in the morning after a night of sleep deprivation and/or alcohol consumption in an otherwise healthy individual. A detailed history will often reveal whole-body jerks that occur mostly in the morning and result in spilling drinks, dropping objects, and/or brief spells of unresponsiveness that have occurred for several months prior to the GTC seizure. Patients with JME will most frequently have myoclonic seizures (100%), with 87% to 95% having GTC seizures and 10% to 33% having absence seizures (41,42).

Myoclonic seizures are brief jerks that affect the neck, shoulders, arms, or legs. The jerks are more frequent in the upper than in the lower extremities and are typically bilateral and symmetric, but on occasion may be unilateral (43). Asymmetric myoclonic seizures may delay the diagnosis of JME, and video-EEG should be used to make the definitive diagnosis (43). Myoclonic jerks of the upper extremities can often cause patients to drop objects and can interfere with morning activities such as eating breakfast, brushing teeth, or applying cosmetics. The jerks can be single or repetitive and often involve extensor muscles. Falling to the floor is uncommon, but falls may occur when patients are in an awkward position and are surprised by the jerk. The amplitude of the jerk is variable but is typically not forceful or massive, and recovery is immediate with no loss of consciousness. Some patients report electric shock type feelings only, with no physical signs of the myoclonic seizure. The relatively mild myoclonic seizures in JME are in contrast to the myoclonic seizures in Lennox–Gastaut syndrome and some progressive myoclonic epilepsies, which are massive and propel patients to the ground with great force.

GTC seizures in JME are often described as clonic–tonic–clonic due to the several repetitive myoclonic jerks that often precede a GTC seizure. The patient has no loss of awareness during the myoclonic jerks, and this serves as a warning to some patients to get to a safe place seconds prior to

a GTC seizure (41). Consciousness is abruptly lost with the onset of the GTC seizure, with tonic extension of the head, face, neck, trunk, and extremities. The tonic phase lasts for 10 to 30 seconds and leads to the final phase of clonic trunk and limb jerks. Patients often emit a high-pitched "ictal cry" during the initial tonic phase. Due to the forceful contraction of many agonist and antagonist muscles simultaneously, patients are often very sore and tired after the seizure. Tongue and/or lip biting and loss of urinary or bowel continence is common. After the seizure, confusion and disorientation typically take 5 to 30 minutes to resolve. Patients typically have no memory of the event.

Absence seizures in JME are less common, occurring in 10% to 33% of patients and tend to be relatively infrequent, of short duration, and not associated with automatisms. In a prospective video-EEG study of JME patients, 16 of 42 (31.9%) were found to have absence seizures (44). When the seizures occurred prior to the age of 10, the patient would stop activities, not answer questions, and stare without postictal symptoms and without memory of the event. When the seizures occurred after the age of 10, the manifestations were usually less severe and consisted of subjective instant loss of contact and concentration or of brief impairment of concentration revealed by testing only (44).

Precipitating factors are commonly reported in patients with JME. Myoclonic and GTC seizures occur most often in the morning or upon awakening (42). Studies of cortical excitability with transcranial magnetic stimulation suggest an increase in cortical excitability/loss of intracortical inhibition in the early morning hours with drug-naive JME patients (45). Sleep deprivation, fatigue, alcohol use, photic stimulation (video games, strobe lights), and menstruation have also been shown to precipitate seizures in patients with JME (41,46). Patients should be counseled to maintain good sleep hygiene and to avoid excessive alcohol consumption since these precipitants can contribute to poor seizure control despite good AED management.

The neurologic exam in JME patients is generally normal, although some neuropsychological tests have suggested cognitive dysfunction with deficits in executive function and expressive language consistent with frontal lobe dysfunction (47,48). The neuroimaging studies in patients with JME typically do not reveal the etiology for the epilepsy but may show nonspecific abnormalities or subtle changes in cortical volumes (49). A quantitative voxel-based MRI study has shown increased cortical gray matter in the medial frontal lobes in 40% of patients with JME (50). FDG-PET and proton MRS studies have also shown metabolic frontal lobe dysfunction in JME patients (51,52). However, not all studies have been able to duplicate the frontal dysfunction in JME patients, demonstrating the pathophysiologic diversity of this condition (53).

EEG

The interictal EEG in JME is abnormal in 50% to 85% of untreated patients, while only 5% to 10% of patients treated with AEDs will have an abnormal EEG (42,54). The characteristic EEG pattern of JME consists of discharges of diffuse bilateral, symmetric, and synchronous 4- to 6-Hz polyspike-and-wave complexes (Fig. 18.1). These discharges may be accentuated over the frontocentral regions. The interictal complexes usually have two or more higher-voltage (150 to 300 μV) surface negative spikes that are maximum in the anterior head regions. Focal abnormalities have been reported in up to 30% of cases (42). Response to photic stimulation with myoclonic seizures or epileptiform discharges after 12- to 16-Hz stimulation is common and occurs in 30% to 50% of cases of JME (34,42). Dense array EEG studies have contested the "generalized" nature of the interictal discharges in JME and have suggested that they are localized to a thalamocortical network that

involves the medial orbitofrontal cortex and anterior basal–medial temporal lobes maximally (55).

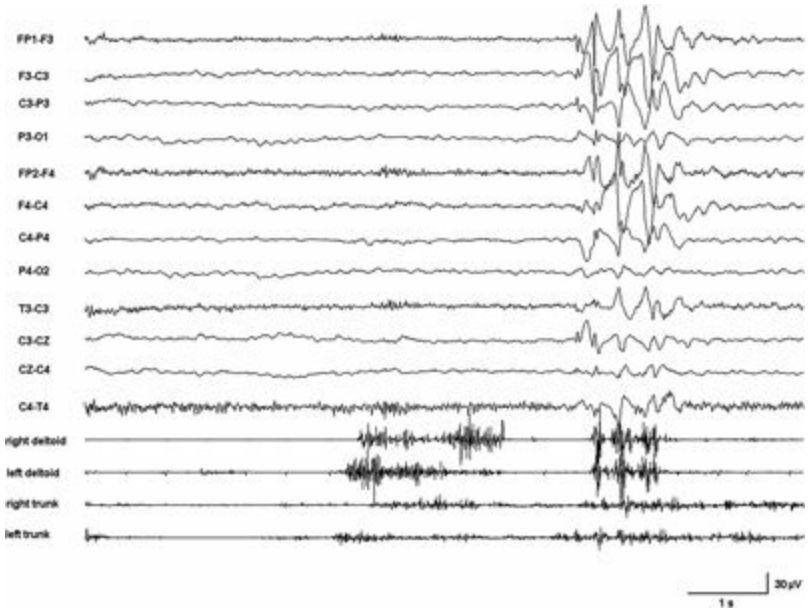

Figure 18.1. Interictal 4- to 6-Hz polyspike-and-wave discharge of frontocentral predominance in JME. No clinical changes were seen, and the patient could recall a word given during the discharge.

Genetics

The genetic nature of JME has been well established and is likely complex and polygenic in most patients, though some rare monogenic forms are being identified. About 40% of patients with JME report a positive family history for epilepsy (56). Genetics studies to date suggest that JME is a heterogeneous condition with multiple different mutations and susceptibility loci that have different modes of inheritance and possible mechanisms of action (21). Autosomal recessive, autosomal dominant, and complex polygenic models have been proposed in different family pedigrees (21). Analysis of JME families has identified linkages to multiple chromosomal loci that may contain genes that are causative or increase the susceptibility for developing JME. Chromosomal locations that demonstrate increased susceptibility in JME families include 6p12-p11 (EFHC1), 6p21 (BRD2/RING3), 15q13-14 (Cx-36), 5q34 (GABRA1), 2q22-23 (CACNB4), 1p36.33 (GABRD), 3q21.1 (CASR), 18q21 (ME2), 19q13 (SCN1B), and Xp11.4-11.3 (EFHC2) (20,21,57–60). Several studies have also identified mutations that are rare but appear to be causative in selected families. Mutations have been identified in EFHC1/Myoclonin1, CLCN2, GABRA1, and CACNB4 (57). In addition, single nucleotide polymorphism susceptibility alleles have been identified in the bromodomain- containing protein 2 (BRD2) and connexin 36 (Cx-36) (61–63).

EFHC1/Myoclonin1

Studies of multiple families of JME have implicated the 6p12-p11 region as a susceptibility focus, and the potential gene was referred to as EJM1. Mutational analysis was able to narrow this locus to the candidate gene EFHC1, which encodes for the protein Myoclonin1 (64). Proposed mechanisms of action for EFHC1/Myoclonin1 include promoting apoptosis, regulating R-type calcium currents, cell cycle regulation, and neuronal migration (64–66). Animal studies have shown that mice deficient in EFHC1 have spontaneous myoclonus and increased seizure susceptibility (67). Mutations of EFHC1/Myoclonin1 have been reported in 9% of JME patients in Mexico and Honduras and 3% of

JME patients in Japan, which is more frequent than any other identified mutations in JME thus far (66).

CLCN2

Mutations of the CLCN2 chloride channels were found in three families of JME patients (37). The proposed mechanism was a reduction in chloride channel activity and increased neuronal excitability. The mutations were detected in patients with JME and also some apparently unaffected family members as well but not in a control population (68). The authors concluded that CLCN2 mutations may act as susceptibility factors for epilepsy among other unknown genetic alterations (68).

GABRA1

Studies of a large French–Canadian family with JME led to the discovery of a mutation in the α1 subunit of the γ-aminobutyric acid receptor subtype A (GABRA1). Studies in vitro suggested a loss of gamma-aminobutyric acid (GABA)-activated currents in receptors containing the mutant subunit (69). Expression of the mutant protein revealed a misfolded protein with impaired insertion into the plasma membrane (70). The proposed mechanism of action is a loss of inhibitory signals due to the defective GABA receptors and subsequent increased cortical excitability (69).

CACNB4

A female patient diagnosed with JME was found to have a mutation in the calcium channel β4 subunit (CACNB4) and her daughter with the same mutation had epilepsy with 3-Hz spike-and-wave complexes (71). A father and son with absence and GTC seizures have also been identified. The proposed mode of inheritance is autosomal dominant. This mutation is thought to impair the channel function by shifting the voltage dependence of activation and inactivation. Additional mutations of the same subunit were associated with epilepsy and episodic ataxia (71).

It should be noted that although progress in identifying a few of the genes involved in JME is beginning to emerge, the vast majority of genes and combinations of genes that are involved are yet to be discovered (20,21). While the clinical presentation in JME is fairly homogenous, the pathogenesis appears to be complex and diverse (41).

Treatment

Appropriate management of a patient with JME requires consideration of multiple factors including AED selection, avoiding precipitating factors, and anticipating special considerations that might impact their care (pregnancy, driving, behavioral issues). Response to medical therapy is generally good, with 60% to 80% seizure-free rate on medications. However, noncompliance and lifestyle choices that involve sleep deprivation, alcohol use, and other precipitants often lead to breakthrough seizures. AED selection is also critical as some AEDs can exacerbate JME and lead to a pseudointractable state (26,32). Quality of life dramatically improves if a patient is able to reach seizure freedom, which can lead to driving, employment, and a higher likelihood of social success. In addition to an appropriate AED choice, patients should be counseled to obtain adequate sleep, avoid alcohol, and wear polarized sunglasses if their seizures are sensitive to photic stimulation.

Valproate

Valproic acid is the treatment of choice for JME as it effectively treats absence, myoclonic, and GTC seizures in 86% to 90% of patients (72,73). A recent large, unblinded, randomized, controlled study of patients with IGE treated with Standard and New Antiepileptic Drugs (SANAD) suggested that valproate was preferred to lamotrigine due to better control of seizures and preferred over topiramate due to lower rates of discontinuation due to side effects (74). Valproate is associated with a number of side effects that can sometimes limit its use or warrant reconsideration, including weight gain, hair loss, tremor, and teratogenicity. Weight gain is a frequent reason for discontinuing valproate, with 50% to 70% of patients gaining more than 4 kg (75). The standard dosing of valproate is 20 to 30 mg/kg/day, but patients with JME often respond to low doses, such as 500 mg/day (76). Valproate at low doses (below 1000 mg/day) and with extended-release preparations has significantly less side effects and is often well tolerated.

Lamotrigine

Lamotrigine is a useful alternative for patients with JME, especially when valproate alone is not effective or not well tolerated. In a retrospective cohort study, no difference in seizure control was found between valproate monotherapy and lamotrigine monotherapy, and the authors concluded that lamotrigine was an acceptable alternative to valproate (77). When compared in a randomized, controlled trial (SANAD), valproate had better efficacy in terms of seizure control than lamotrigine (74). There have also been some reports of exacerbation of myoclonic seizures with lamotrigine (78). In a study using lamotrigine as an add-on agent in treatment-resistant generalized epilepsy, 80% of patients had a >50% reduction in seizure frequency and 25% became seizure free (75). In an open-label study of lamotrigine monotherapy in patients who had failed valproate, there was no significant change in their underlying seizures, but 67% of patients reported improvement in their global clinical status on lamotrigine and 76% of patients rated lamotrigine as better tolerated than valproate (79). The major side effect of lamotrigine reported was a rash, which in some patients can be severe. An allergic skin reaction occurs in approximately 10% of patients with severe rash (such as Steven–Johnson syndrome) occurring in 0.3% of adults and 1% of children (80). The lamotrigine-associated rash may be more severe when combined with valproic acid (80). Lamotrigine is well tolerated and effective as an adjunctive therapy for JME, but concerns over decreased seizure control compared to valproate and exacerbation of myoclonic seizures in some patients limit its use as a monotherapy.

Topiramate

Topiramate is another possible adjunctive or alternative therapy to valproate, but there are limited data on application in patients with JME. In double-blind, placebo-controlled studies of topiramate, 73% of patients in the JME subgroup had a >50% reduction in primary GTC seizures and 16% became seizure free (81). In a randomized open-label comparison, topiramate and valproate had similar rates of seizure freedom (67% and 57%, respectively), and in both treatment groups, 11% of patients stopped the medication due to adverse effects (82). In the SANAD study, topiramate had similar efficacy to valproate but was associated with more side effects (74). Typical side effects with topiramate include cognitive dysfunction, anomia, weight loss, and nephrolithiasis.

Levetiracetam

A number of studies have shown the efficacy of levetiracetam as an adjunctive therapy for IGE, and its features of no known drug interactions and overall good tolerability have made this drug a useful asset. Using a retrospective design, Kumar (83) reported 25 IGE patients treated with levetiracetam and found that 68% of patients had some improvement in their seizures and 16% became seizure free. In an open-label study, Kraus et al. (84) studied 55 patients with GTC, myoclonic, and absence seizures and found that 76% had a >50% reduction in seizures and 40% became seizure free. These authors also found that 15% of patients discontinued levetiracetam due to adverse events (with sedation being the most common). In a multicenter, double-blind, placebo-controlled study, Berkovic et al. examined 164 patients with IGE. They reported that 72.2% of patients had a >50% reduction in seizures, with 34% of patients seizure free from GTC seizures and 24% seizure free from all seizure types (85). Levetiracetam was well tolerated in this study, and only 1.3% of patients discontinued therapy due to adverse events. A randomized, double-blind, placebo-controlled, multicenter trial by Noachtar et al. addressed the effects of levetiracetam on myoclonic seizures (86). They examined 120 patients and found that 58.3% of patients with myoclonic seizures had a >50% seizure reduction within days/week. The rate of myoclonic seizure freedom was 25%, and seizure freedom from all seizure types was seen in 21%. Levetiracetam has been shown to be efficacious as an adjunctive therapy in JME for all seizure types including myoclonic seizures. Adverse events of somnolence, headache, and irritability are relatively rare in 1% to 15% of patients.

Zonisamide

There have been relatively few studies on the efficacy of zonisamide in IGE and JME, but initial data have shown efficacy as an adjunctive agent for multiple seizure types, including JME. Zonisamide has been available in Japan since 1989, and much of the data derive from the Japanese experience. In a prospective postmarketing survey, Yamauchi et al. (87) reported that 78% of patients with IGE and 50% of patients with myoclonic seizures had a >50% seizure reduction with zonisamide. Yagi reported on pooled zonisamide efficacy data of 1008 patients collected from controlled and uncontrolled phase II and phase III studies and found 59% of GTC seizures, 62% of absence seizures, and 43% of myoclonic seizures were reduced by >50% (88). In a small retrospective open-label study, Kothare et al. reported that 80% of patients with JME had a >50% reduction in seizures on zonisamide monotherapy (89). They also reported seizure freedom in 69% of GTC seizures, 62% of myoclonic seizures, and 38% of absence seizures. Preliminary data suggest that zonisamide is efficacious as an adjunctive medication for JME, but further data from randomized, controlled trials will help delineate this. The advantages of zonisamide are once-daily dosing. Common side effects include weight loss, cognitive problems, and nephrolithiasis.

A number of medications have been reported to exacerbate JME, especially myoclonic seizures (26). The most common medications causing seizure aggravation are carbamazepine and oxcarbazepine. Phenytoin, gabapentin, and vigabatrin may also exacerbate seizures in JME or do not have efficacy.

Special Considerations of Treating JME in Pregnancy

Childbearing-age women represent 25% of patients treated for epilepsy, and the possibility of pregnancy often influences AED selection (90). While all of the AEDs have some risk of teratogenicity, valproate has the highest risk, especially when given in doses >1000 mg/day (6% to 11% chance of birth defects) (91). This is balanced by the evidence that valproate is the clinically

most effective medication to prevent seizures based on the SANAD study (74). Lamotrigine has been the best studied of the newer medications in pregnancy, has been followed in multiple pregnancy registries, and has a reported 2.7% risk of major congenital malformations (92,93). However, the actual risk of birth defects with lamotrigine is unclear since pregnancy induces the clearance of this drug by up to 94%, and this decrease in drug levels is not accounted for in the pregnancy registries (94). There has also been increased seizure frequency in mothers taking lamotrigine during pregnancy (94). There has been some indication of a dose-responsive risk of birth defects with lamotrigine, with an increased malformation rate in patients taking more than 200 mg/day, reported in the UK pregnancy registry but not in the International Lamotrigine Pregnancy registry (92,93). There is little information on other medications in JME during pregnancy such as topiramate, zonisamide, levetiracetam, and clobazam. Monotherapy in general had less risk of malformations (3.7%) than does polytherapy (6.0%) regardless of AEDs involved (93). There is some evidence that exposure to AEDs during pregnancy can affect the cognitive development of the fetus, with valproate associated with worse cognitive outcomes (91,95). In the Neurodevelopmental Effects of Antiepileptic Drugs study, children exposed to valproate had a lower intelligence quotient on average by 9 points compared to patients exposed to lamotrigine (95). The effect of valproate was dose dependent and was not observed at dosages below 800 mg/day.

A cautious and informed approach is needed when treating female patients in their childbearing years. Valproate is generally considered the most efficacious drug at suppressing the seizures in JME and is a reasonable choice if doses of <800 to 1000 mg/day can be used. Lamotrigine has shown fewer incidences of birth defects and potential cognitive problems but has fewer efficacies in preventing maternal seizures, and increased seizure frequency has been reported (94), in particular exacerbation of myoclonic seizures. Young women with JME should not be discouraged from having children in general, as >90% of women have normal pregnancies. However, placement on monotherapy and preconceptual planning should be encouraged to reduce the risk of fetal malformations and potential cognitive delays.

Prognosis

The prognosis for JME is generally considered excellent as the majority of patients can be treated successfully with AEDs. Seizure-freedom rates of 60% to 90% have been reported. It has been noted that while response to medication is good, patients tend to have breakthrough seizures due to noncompliance, sleep deprivation, alcohol use, or other precipitants. Achieving seizure freedom often involves lifestyle modifications as well as compliance with AEDs. Multiple studies in the past have suggested that JME is often a lifelong condition (96). Delgado-Escueta and Enrile-Bacsal have reported a 90% relapse rate with withdrawal of medications in the past. However, a more recent longitudinal study followed patients with JME for 25 years and found that 48% had voluntarily stopped their medications, 17% were without seizures on no medication, and 13% had myoclonus only, also without medication (1). It should also be noted that 36% of patients followed in the study had an episode of convulsive status epilepticus and 13% had medically intractable seizures. While a small percentage of patients with JME could likely come off medications at some time interval as suggested in the study, determining who will remain seizure free and who will continue to have seizures is less clear.

EPILEPSY WITH GENERALIZED TONIC–CLONIC SEIZURES ONLY

Epilepsy with GTC seizures only has recently been described by the ILAE in their most recent proposed diagnostic scheme for people with epileptic seizures and epilepsy as a separate syndrome (3). It includes "epilepsy with GTC seizures on awakening," which was previously described as a separate syndrome. The diagnosis of this syndrome can be challenging as many IGEs as well as focal epilepsies have some component of GTC seizures.

Epidemiology

There is limited information on the epidemiology of patients presenting with GTC seizures only. In a population-based study, epilepsy with grand mal upon awakening was reported as a major feature in 23% of generalized epilepsies (97). A population-based study in France reported an incidence of 1.8 per 100,000 people (97).

Clinical Features

The peak age of onset is at 15 with an age range between 5 and 50 years (7). Neurologic exam and imaging is normal, and other tests except for the EEG do not reveal any other neurologic abnormalities.

The predominant seizure type is GTC. Absence seizures and myoclonic seizures are seen less frequently. Seizures are mainly provoked by alcohol and sleep deprivation and can also be brought out by photic stimulation. Seizures tend to worsen with age. Wolf reported GTC seizures on awakening in 17% to 53%, during wakefulness in 23% to 36%, during sleep in 27% to 44%, and not related to wake or sleep patterns in 13% to 26% of patients (98). In the subcategory of GTC seizures on awakening, GTC seizures occur in more than 90% within 1 to 2 hours after awakening or at the end of the day (during relaxation), with only rare myoclonic or dialeptic seizures. Unterberger et al. compared epilepsy with GTC seizures on awakening and randomly occurring GTC seizures and found that patients with early morning seizures had a longer duration of epilepsy, a higher relapse rate, and a stronger relationship to seizure provoking factors (99).

EEG

Interictal features on EEG consist of generalized epileptiform discharges presenting either as generalized 4- to 5-Hz spike-and-wave complexes or as generalized polyspikes. Discharges can be seen bilaterally with occasional asynchrony or asymmetry of bursts.

Ictal EEG is characterized by generalized fast rhythmic spiking, with a bifrontal maximum during the tonic phase of a GTC seizure. EEG activity is frequently obscured by tonic or clonic muscle artifact. Spiking can be asymmetric and asynchronous. This activity slows down and evolves into discontinuous repetitive generalized bursts of generalized (poly) spikes and waves intermingled with rhythmic slow waves. Clonic jerks start approximately at a spike frequency of 4 Hz. Postictally, electrical activity is reduced and can occasionally appear silent (<10 μV) for a brief period and is usually followed by irregular diffuse slowing.

Genetics

Patients with epilepsy with GTC seizures only frequently have a positive family history of epilepsy. Most recently, different mutations in unrelated families of the chloride channel-2 gene (CLCN2) on chromosome 3q26-qter have been found to be associated with GTC seizures on awakening (37). Interestingly, CAE, JAE, and JME were also found in families with this mutation (37).

Treatment

Monotherapy with lamotrigine or valproate is recommended, with valproate having higher efficacy and lamotrigine fewer side effects (74). Other options include topiramate, levetiracetam, and zonisamide. If the maximum tolerated dose does not reduce seizure frequency, an alternative medication should be tried. In case of monotherapy failure, combination therapy of lamotrigine and valproate may be effective (100). Gabapentin is not helpful, and tiagabine and vigabatrin may exacerbate seizures in some cases (26). Additionally, the prevention of precipitating factors of seizures such as sleep deprivation and alcohol intake drug treatment is beneficial.

Prognosis

The prognosis of patients with GTC seizures only is very good and usually better than in patients with focal epilepsy and secondary generalized seizures (101). Up to 95% of patients with GTC seizures of unknown origin will have a continuous 5-year seizure-free period within 20 years after epilepsy onset (101). Twenty-one percent of patients who have been seizure free for 5 years or longer relapse within a 20-year observation period (101). Frequency of GTC seizure at the time of diagnosis predicts outcome and remission (102). Failure to remit within 2 years of diagnosis reduces the chance of remission in the following years (103).

GENERALIZED EPILEPSY WITH FEBRILE SEIZURES PLUS (GEFS+)

Generalized epilepsy with febrile seizures plus (GEFS+) is a heterogeneous disorder with some features of an IGE. Generalized epilepsy seizure types as well as febrile seizures, focal seizures, and progressive epilepsy syndromes such as Dravet syndrome have been described (104,105). There is an underlying genetic basis for this disorder with four genes identified thus far, but the clinical features of GEFS+ are divergent from typical IGE in some patients. GEFS+ illustrates the complexity of epilepsy syndromes with multiple different phenotypes arising from the same mutation and different mutations giving rise to clinically similar phenotypes, all-in-one syndrome.

Epidemiology

The epidemiology of GEFS+ has not been studied in a large epidemiologic study, and the incidence/prevalence is unknown. It has been speculated that GEFS+ is a common childhood syndrome, and detailing this will be a challenge given the clinical heterogeneity that has been attributed to this syndrome thus far (106).

Clinical Features

Most patients with GEFS+ present with febrile seizures in the typical ages between 3 months and 6 years, then continue to either have additional febrile seizures outside of this age range or begin having afebrile seizures as well (104,105). Seizures can persist into late adolescence or longer and may remit in the early teenage years. A history of febrile seizures in other family members is crucial to the diagnosis.

Febrile seizures begin approximately at the age of 1 year, slightly earlier than in the average infant with febrile seizures. Onset of afebrile seizures may overlap with febrile seizures or may occur after a seizure-free interval between febrile and afebrile seizures.

Neurologic exam is normal in the majority of patients described but may also show cognitive impairment and developmental abnormalities (104,106,107).

Clinical seizures consist of febrile seizures in association with afebrile seizures presenting as GTC seizures or dialeptic seizures (absences). Other seizure types of myoclonic–astatic, atonic, tonic, and complex partial seizures have also been described (104,106,107). Seizures usually persist beyond 6 years of age until adolescence or longer.

EEG

The syndrome lacks a clear electroclinical pattern, and interictal EEG can be normal. However, interictal epileptiform discharges frequently consist of irregular generalized spike and waves or polyspikes with infrequent 2- to 3-Hz generalized spike-and-wave complexes (104). Due to variable clinical presentations, interictal EEG may also present with focal epileptiform discharges, for example, in the frontal, temporal, and occipital regions (108).

Genetics

Mode of inheritance has been described as autosomal dominant with incomplete penetrance in a number of family pedigrees (104–108).

Five genes have been associated with GEFS+ thus far, three genes encode for a sodium channel subunit and two encode for $GABA_A$ receptor subunit. SCN1A encodes the α1 subunit of the neuronal voltage-gated sodium channel and was implicated in GEFS+ by identified mutations (109). It is suspected to increase excitability by decreasing the inactivation of the channel. SCN1B, which encodes the β1 subunit of the neuronal voltage-gated sodium channel, has also been found to be mutated in families with GEFS+ (110). This mutation is suspected to interfere with the modulation of the gating of the sodium channel leading to neuronal hyperexcitability. SCN2A has also been implicated by a missense mutation in a patient with GEFS+ (111). The γ-2 subunit of the $GABA_A$ receptor (GABRG2) has also been shown to be mutated in patients with the clinical phenotype of GEFS+ at that benzodiazepine-binding site (112). The mutation is predicted to reduce the flow through the channel, decreasing its inhibitory effect.

Treatment

The decision to treat pharmacologically should be made based on seizure frequency and severity of afebrile seizures. Clinical presentation and individual seizure types should determine the treatment approach and selection of AED if applicable. Due to paucity of reported cases, only little information

on the efficacy of specific pharmacologic treatments is available. Gerard et al. report pharmacologic treatment in 6 out of 15 affected individuals "with success and seizure control in most" after analysis of a multigeneration pedigree of GEFS+ patients in France (113). Interestingly, in one family with a mutation in the GABRG2 gene (GEFS+ type 3), decreased benzodiazepine sensitivity has been reported (114).

Prognosis

The prognosis is usually very good but is dependent on the variable clinical phenotypes associated with GEFS+. Spontaneous remission occurs frequently in the early teenage years (10 to 12 years) (112). However, seizures can persist, and several other epilepsy syndromes can develop (CAE, JME, myoclonic–astatic epilepsy, focal epilepsy) (112,115).

IDIOPATHIC GENERALIZED EPILEPSY SYNDROMES AS PART OF THE GENERALIZED EPILEPSY SPECTRUM

Overall, there are many similarities among the above-described types of IGE syndromes. According to Janz (2), 4.6% of cases of CAE evolve into JME when patients reach the usual age of JME onset. A population-based study of 81 children with CAE found that 15% had progressed to JME 9 to 25 years after seizure onset (116). In this study, the development of GTC or myoclonic seizures in a patient with CAE receiving AEDs made the progression to JME very likely (116). Syndromes manifest with the same seizure types, have similar EEG changes, may evolve into one another, and have overlapping genetic origins. Neurologic exams as well as imaging studies are typically normal. Therefore, IGEs may be viewed as a continuous spectrum of conditions, representing common clinical presentations, and overlapping and complex genetic etiologies.

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CHAPTER 19 PROGRESSIVE AND INFANTILE MYOCLONIC EPILEPSIES

BERND AXEL NEUBAUER, ANDREAS HAHN, AND INGRID TUXHORN

Myoclonus is characterized by brief, shock-like jerks that may be generalized, confined to larger or smaller muscle groups, or restricted even to a single muscle. It is termed epileptic when occurring in combination with cortical epileptiform discharges. Electromyographic (EMG) bursts lasting 10 to 100 ms may be preceded by discharges (spikes or polyspikes in general) that are easily visible on surface electroencephalography (EEG) (Fig. 19.1) or that are only detectable when jerk-locked back averaging or other sophisticated techniques are applied. Epileptic negative myoclonus is defined as an interruption of tonic muscular activity for <500 ms without evidence of antecedent myoclonia (Fig. 19.2). The term clonic means the rhythmic repetition of a myoclonic jerk, mainly at a rate of 2 to 3 seconds. Myoclonic seizures predominantly affect limb, axial, neck, and shoulder muscles, and less frequently facial and extraocular muscles. Rarely, myoclonic seizures occur in series and evolve into a myoclonic status epilepticus, with or without complete loss of consciousness. In most epilepsy syndromes with myoclonic seizures as the cardinal feature, additional seizure types occur at lesser frequency. Mostly, these other seizure types include generalized tonic–clonic seizures (GTCS), generalized clonic seizures, atonic seizures, absence seizures, and atypical absences (1).

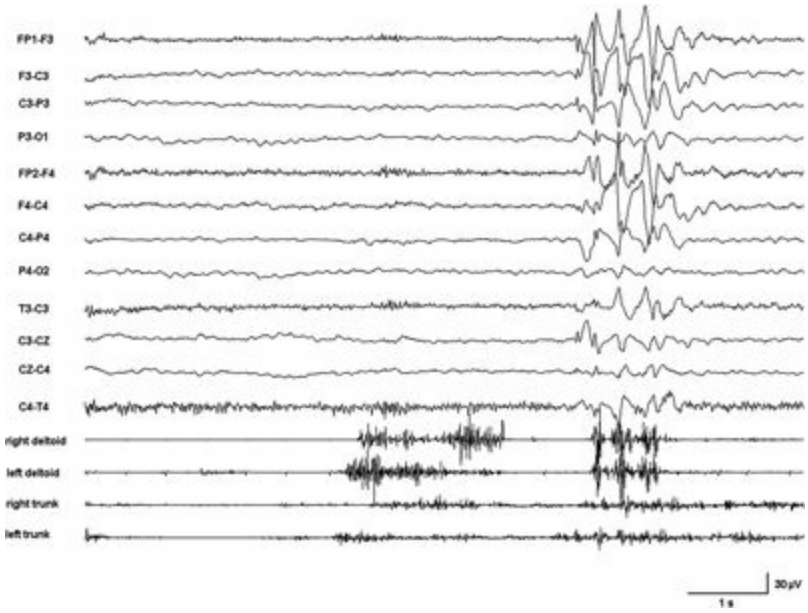

Figure 19.1. EEG–EMG recording with surface electrodes in a 3-year-old boy with MAE (Doose syndrome). Three brief and symmetric myoclonic jerks each time-locked to single generalized single spike–wave discharges are recorded from both deltoid muscles.

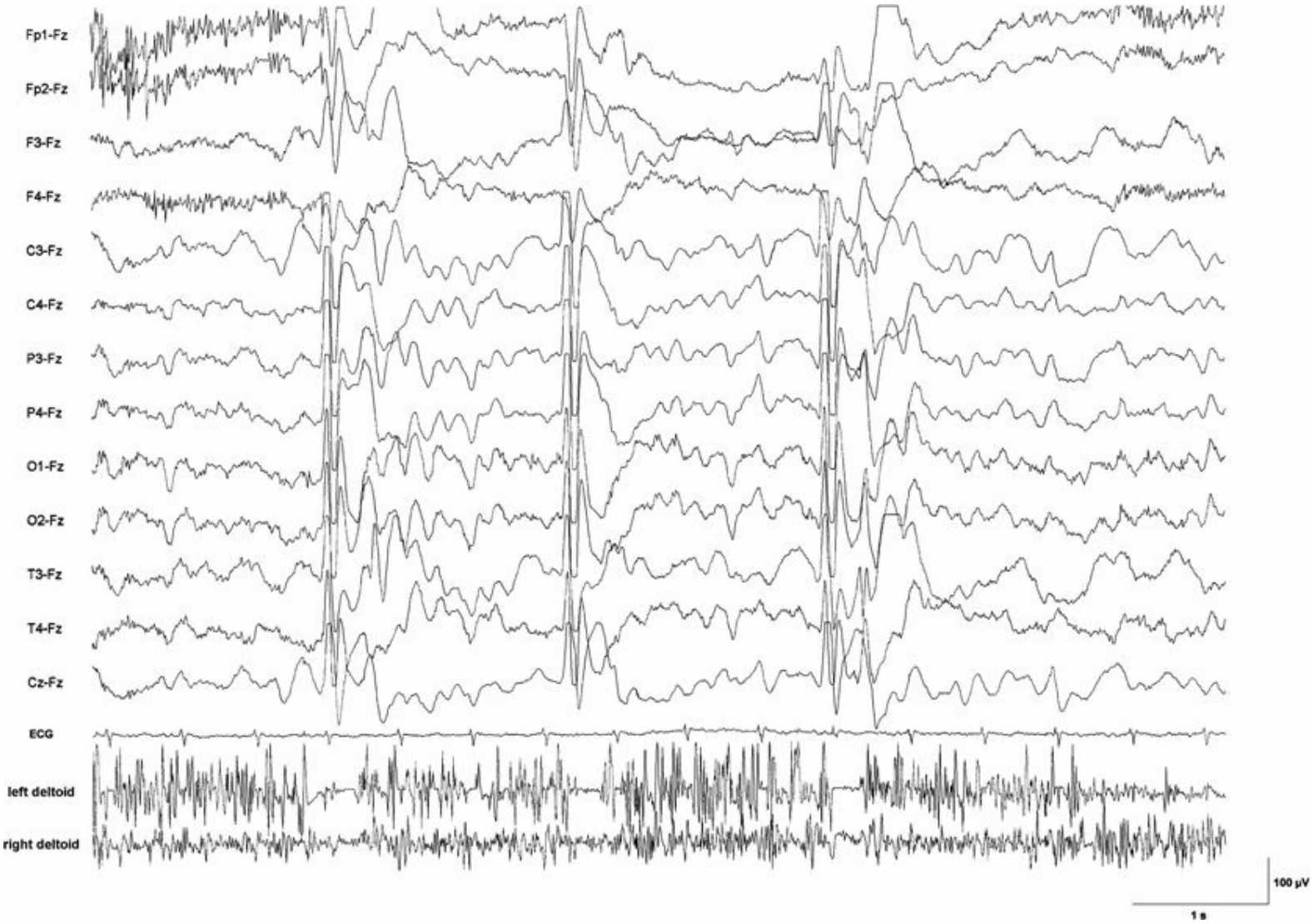

Figure 19.2. EEG–EMG recording with surface electrodes in a 6-year-old boy with epileptic negative myoclonus due to lesion-related epilepsy. Silent periods in the EMG from the deltoid muscles lasting between 100 and 150 ms are time-locked to a generalized sharp slow-wave complex. Clinically, each brief EMG pause was associated with nodding of the head and sinking of the arms during sustained muscle contraction.

ETIOLOGY

Myoclonic epilepsies are predominantly genetic in origin. In terms of classification, they may be grouped as genetic epilepsies (e.g., benign myoclonic epilepsy in infancy [BMEI]), epileptic encephalopathies (e.g., Dravet syndrome), or progressive myoclonic epilepsies (e.g., Unverricht–Lundborg disease).

BMEI usually presents in normally developed children, and in the majority of cases, antiepileptic treatment may be weaned after some years of active epilepsy. Behavioral and cognitive prognosis is good in the majority of cases. Familial cases are extremely rare, with the exception of one case identified in the context of a generalized epilepsy with febrile seizures plus (GEFS+) family (2) and a family with three affected children (3). However, a positive family history for febrile seizures or idiopathic epilepsies was repeatedly reported (4). Altogether, classification as a genetic generalized epilepsy syndrome seems unequivocal. The etiology is most likely oligogenic or complex (several genes and possibly environmental factors involved).

Myoclonic astatic epilepsy (MAE) or Doose syndrome, initially described by Doose et al. (5), was reported to be an idiopathic generalized epilepsy syndrome. The separation of this syndrome

from a group of epilepsies that were formerly classified as symptomatic (many of them as Lennox–Gastaut syndrome) was only reluctantly accepted. This is mirrored by the fact that MAE was classified among the "cryptogenic or symptomatic generalized epilepsies and syndromes" for many years. Now it is recognized that the initial description of Doose et al. included cases that, from today's point of view, might also be diagnosed as benign myoclonic and severe myoclonic epilepsies, but the current classification scheme now accepts Doose syndrome as a genetic epilepsy syndrome (6). As with BMEI, familial cases are exceptional, but retrospective studies demonstrated positive family histories for febrile seizures and idiopathic epilepsy syndromes at a clearly elevated rate (7). Although in single cases genetic defects in the genes (mostly SCN1A) known to be involved in GEFS+ families were reported, the majority of patients do not carry an identifiable defect in these genes (8).

Severe myoclonic epilepsy of infancy (SMEI) or Dravet syndrome from one point of view may be classified as an idiopathic genetic disorder, since children are healthy and normally developed until onset of the epilepsy, and there is a clear genetic cause (usually a SCN1A defect) in the majority of cases. The syndrome may even be observed in GEFS+ families (9). However, Dravet syndrome is a devastating disorder with an extremely severe course in most patients; hence, it was declared an epileptic encephalopathy (6).

Progressive myoclonus epilepsies (PME) are defined as neurometabolic or neurodegenerative diseases with myoclonias and myoclonic seizures as dominating clinical features. Frequently, myoclonic seizures represent the initial clinical symptom. These disorders are in general progressive; however, course varies from moderately mild (e.g., Unverricht–Lundborg) to rapidly progressive and fatal (e.g., neuronal ceroid lipofuscinoses [NCL] type 2). PME follow a monogenic, mostly autosomal recessive mode of inheritance (10). Some diseases such as Rett-like syndrome (CDKL-5 defects) are usually not regarded as "classic" PME but may at certain stages and in individual patients show the typical symptomatology and course of a PME. These disorders, which frequently manifest during infancy or early childhood, may be summarized as progressive encephalopathies with myoclonic seizures (Table 19.1).

Table 19.1 Progressive Myoclonic Epilepsies and Progressive Encephalopathies with Myoclonic Seizures

- *With manifestation during neonatal period/early infancy*
  - Pyridoxine-dependent/pyridoxal phosphate–dependent epilepsy/folinic acid–responsive seizures
  - Nonketotic hyperglycinemia
  - Sulphite oxidase deficiency/molybdenum cofactor deficit
  - X-linked cyclin-dependent kinase-like 5 (*CDKL5*) encephalopathy
  - X-linked myoclonic epilepsy with spasticity and intellectual disability associated with mutations in the *ARX* gene
  - Others (e.g., aminoacidopathies, organic acidurias, deficits of β-oxidation of fatty acids, CDG syndrome variants, GABA-transaminase deficiency, Zellweger syndrome/other peroxisomal disorders, urea cycle deficits)
- *With manifestation during late infancy/early childhood*
  - Glucose transporter (GLUT-1) deficiency (De Vivo disease)
  - Early infantile neuronal ceroid lipofuscinosis (*CLN 1*)
  - Late infantile neuronal ceroid lipofuscinosis (*CLN 2*)
  - Holocarboxylase synthetase deficiency/biotinidase deficiency
  - Disorders with 5-MTHF depletion in CFS (e.g., FOLR1 mutation)
  - Progressive myoclonic epilepsy with mutation in KCDT7
  - Childhood spinal muscular atrophy with progressive myoclonic epilepsy (ASAH1)
  - Others (e.g., glutathione peroxidase deficiency, methylenetetrahydrofolate reductase deficiency, hereditary anomalies in serine synthesis, Menkes disease, mitochondrial disorders, GM2 gangliosidosis, succinic semialdehyde dehydrogenase deficiency)
- *With manifestation during late childhood/adolescence*
  - Juvenile neuronal ceroid lipofuscinosis (*CLN3*)
  - Adult neuronal ceroid lipofuscinosis (*CNL 4*)
  - Neuronal ceroid lipofuscinosis variants (*CLN 3, CLN 5, CLN 6*)
  - Myoclonic epilepsy with ragged red fibers
  - Unverricht–Lundborg disease
  - Lafora disease
  - Sialidosis types I and II
  - Galactosialidosis
  - Neuroserpinosis
  - Dentato-rubro-pallido-luysian atrophy
  - Juvenile form of Huntington disease
  - Gaucher disease (type III)
  - Action myoclonus–renal failure syndrome
  - Leukoencephalopathy with vanishing white matter
  - Progressive ataxia–myoclonic epilepsy with mutation in PRICKLE1 gene
  - North Sea progressive myoclonus epilepsy (GOSR2)
  - Progressive myoclonic epilepsy with mutation in COL6A2

BENIGN MYOCLONIC EPILEPSY IN INFANCY

Definition and Epidemiology

BMEI is a rare epilepsy syndrome. Its classic description was done by Dravet and Bureau (11). Altogether about 110 cases have been reported, and it is estimated that BMEI accounts for <1% of childhood epilepsies (12). BMEI is mainly recognized in Europe (France, Italy), and it may be suspected that in cases with rare myoclonic seizures or seizures that respond quickly to therapy, correct classification may not be applied, thereby underestimating its real prevalence. Some cases may overlap with MAE (Doose syndrome). In one patient who was initially diagnosed with BMEI, later a SLC2A1 (glucose transporter-1) defect was established (4).

Symptomatology

Onset is mostly between 4 months and 3 years but may extend up to the 5 years. Febrile seizures antecedent to myoclonic seizures are reported in about 30% of cases. In the beginning, myoclonic seizures are often rare and brief, involving predominantly the upper limbs. But intensity and frequency of the seizures increase often early during course. In the largest series reported, polygraphic video–EEG recordings revealed that myoclonic seizures consisted of axial jerks with head drop, elevation and extension of both arms, flexion of the legs, and upward gaze. Myoclonic seizures may vary in intensity ranging from simple head nods to severe falls, when generalized. Seizures may occur repetitively but usually only in short trains lasting 1 to 3 seconds. Usually they are symmetrical, but rarely may be unilateral. In about a third of patients, they are triggered by stimuli-like noise, startle, or photic stimulation. Drowsiness is also known to provoke myoclonic seizures (4).

EEG

Background activity is normal. Myoclonic jerks are associated with generalized spike–waves and polyspike–waves. Ictal spikes last for 1 to 3 seconds. Most, if not all, myoclonic seizures are associated with discharges on the surface EEG. EEG discharges are generalized with a frontocentral accentuation. After the myoclonia, there may be a short atonia that may result in a drop, that is, a myoclonic astatic seizure. Focal abnormalities, usually spike–waves in sleep recordings, were reported in some patients (4). Its significance is unknown.

Treatment and Prognosis

Valproic acid is the drug of first choice and is usually the only drug needed to control the seizures in the majority of cases. Some authors recommend high plasma levels at the start of treatment (up to 100 mg/L) (13). Ethosuximide, benzodiazepines, and phenobarbital were also effective in the few cases reported who did not receive valproic acid. Altogether there seems to be no specific difference in treatment compared to MAE. Untreated cases continue with pure myoclonic seizures even if the epilepsy lasts for years. Developmental delay and behavioral disturbances are reported in a substantial number of patients. Precise numbers vary substantially between different series, ranging from 0% to 86% (14). A rate of 20% to 30% seems acceptable. This renders the term “benign” questionable and makes it difficult to differentiate cases with frequent generalized myoclonic seizures and evolving developmental delay from patients with MAE. Bureau and Dravet are convinced that mental prognosis depends on early diagnosis and successful treatment (4). However, there are no

controlled studies with antiepileptic drugs (AED) on record, and there are no good data on required treatment duration. By definition, myoclonic seizures will disappear eventually in all cases. Most reported children older than 6 years were already weaned off medication without seizure relapse. But in some patients, generalized tonic–clonic seizures (GTCS) occurred when valproate treatment was stopped. While a subgroup with overt reflex seizures appears to be very easily controlled by AED, cases with marked photosensitivity may be more difficult to control (4).

MYOCLONIC ASTATIC EPILEPSY/DOOSE SYNDROME

DEFINITION AND EPIDEMIOLOGY

The prominent genetic etiology together with the characteristic seizure symptomatology dominated by myoclonic and myoclonic astatic seizures led Doose et al. (5) to delineate MAE as an idiopathic (today: genetic) generalized epilepsy syndrome of its own right. MAE, as a rule, occurs in children with an uneventful history. The epilepsy starts in 94% during the first 5 years of age and accounts for 1% to 2% of all childhood epilepsies (15). Doose et al. reported that in about 20%, the seizures have their onset during the first year of life (7,16). Today, many authors feel that onset before the second year of life is exceptional. The age of peak presentation is 3 years (17). Like most other myoclonic epilepsies of early childhood, it affects more boys than girls. The sex ratio is about 2.7/1 (16). If the inclusion criteria include all children older than 1 year, this ratio might even reach 3/1 (17).

Symptomatology

In about 60% of cases, the epilepsy starts with febrile or afebrile GTCS. Alternating grand mal (i.e., hemi–grand mal, unilateral seizures) is a possible presentation. Some days or short weeks later, myoclonic and/or myoclonic–astatic seizures set in abundance, frequently in combination with brief absences. At first, this occurs predominantly after awakening. Tonic axial seizures may manifest during long-term course, frequently occurring during sleep. Myoclonic seizures consist of symmetric, mostly generalized jerks, accentuated in the arms and the shoulders, and are frequently associated with a simultaneous flexion of the head. The intensity of these seizures is variable and ranges from violent myoclonic jerks with sudden falls to abortive forms merely presenting as short irregular twitches of the face. Myoclonic–astatic seizures are characterized by a loss of muscle tone preceded by a (short) myoclonia. In polygraphic recordings, the loss of muscle tone corresponds to a silent period in the EMG that is paralleled by the slow wave in the EEG following the spikes or polyspikes of the myoclonus. Myoclonic seizures with and without discernable myotonia frequently occur together. The initial myoclonia and the subsequent myotonia equally contribute to the characteristic myoclonic astatic seizure (18–20). Absences are seen in more than half of the children with MAE. Myoclonic and astatic seizures, when they come in series, are frequently accompanied by absences often combined with myoclonic jerks. A unique type of nonconvulsive status epilepticus (“status of minor seizures”) is a rather specific finding observed in 36% (5,7,18) to 95% (17) of MAE patients. The characteristic clinical picture is a somnolent, stuporous child with subtle myoclonic seizures, frequently involving the face and the extremities. The child is unresponsive, drools, has a slurred speech, or is even aphasic. This status may continue for days if not interrupted by adequate means.

EEG

Background activity is of special interest in MAE. In cases starting with GTCS, the EEG may stay entirely normal for weeks. However, almost in all instances, a rhythmic, parietally accentuated 4- to 7-Hz activity develops early in the course. This rhythmic slowing of background activity was frequently questioned and falsely attributed to drowsiness. In patients with MAE (and other idiopathic generalized epilepsies of early childhood with myoclonic seizures), it represents a constant trait that is not related to the state of vigilance. This has been documented by EEG recordings of children who were kept attentive by displaying cartoons and so on (20). During the early stages, spikes, irregular spikes, and polyspikes may well be absent and appear only after some delay starting during sleep. If myoclonic seizures dominate the course at a given time, the EEG shows short paroxysms of irregular spikes and polyspikes. In children with astatic and myoclonic astatic seizures, 2- to 3-Hz spikes and waves appear. As the epilepsy progresses, typical absence patterns may appear. During a status of myoclonic–astatic seizures, the EEG displays continuous spike–waves with interposed slow waves. Especially in younger children, an irregular polymorphous hypersynchronous activity, sometimes resembling hypsarrhythmia may be recorded. During nocturnal tonic seizures, typical 10- to 15-Hz spike series can be observed. In distinction to the tonic seizures observed in Lennox–Gastaut syndrome, the EEG onset is generalized in MAE.

Therapy and Prognosis

Revised treatment standards over the last years have significantly improved outcome and prognosis (21). Valproic acid is still the drug of first choice. If efforts fail to achieve complete remission, the decision which drug to use next depends on the predominating seizure type. If absences prevail, ethosuximide should be commenced as the next step. If GTCS represent the leading semiology, bromide is frequently the most effective drug, even superior to phenobarbital or primidone (22). Lamotrigine may be effective but is also known to provoke myoclonic seizures in generalized myoclonic epilepsies. It therefore may represent a valuable option but has to be used with caution (23). Basing on the broad mechanism of action, topiramate is an additional possibility. However, no data on its effectiveness in MAE are yet available. Carbamazepine, phenytoin, and vigabatrin should be avoided, for they frequently provoke seizure exacerbation (17,24,25). In cases with refractory nonconvulsive status epilepticus adrenocorticotropic hormone (ACTH) or high-dose steroid pulse therapy may be alternatives to be considered (24). Zonisamide is effective in myoclonic epilepsies of different etiology (26). Levetiracetam may be used successfully in myoclonic epilepsies; however, it may also aggravate seizures (27). Ketogenic diet is a further possibility that was reported as effective (28).

Already from the early descriptions of the disorder, it becomes clear that outcome is highly variable. The spectrum ranges from complete remission (frequently obtained within the first 3 years) and totally normal intellectual development to therapy resistant epilepsy with severe cognitive disability (5,21,24,29). Over the years, however, therapeutic possibilities constantly improved, and the danger of seizure and epilepsy aggravation by carbamazepine and phenytoin was more and more recognized. In a series of 81 patients with MAE, 68% became eventually seizure free. In this retrospective Japanese series, ACTH, ethosuximide, and ketogenic diet proved especially effective (21). Repetitive nonconvulsive status epilepticus (“status of minor seizures”) and nocturnal tonic seizures were frequently associated with an unfavorable prognosis (16,21). This is, however, not unequivocal (17).

SEVERE MYOCLONIC EPILEPSY OF INFANCY/DRAVET SYNDROME

Definition and Epidemiology

This electroclinical syndrome was delineated by Dravet (30) in 1978 and soon was labeled SMEI. Later, it was recognized that in a substantial number of cases, myoclonic seizures and single other features may be lacking, and still the epilepsy will take the same course. This led to the proposal to rename the epilepsy to Dravet syndrome, which is now recognized as an epileptic encephalopathy (6). In order to include cases that seemed to belong to the same entity but lacked single features of classic SMEI, recently the term "borderline SMEI" (SMEB) was introduced. Different variants of what is now called SMEB were earlier recognized independently by different authors, such as "intractable childhood epilepsy with GCTS," "severe idiopathic epilepsy of infancy with generalized tonic–clonic convulsions," "severe polymorphic epilepsy of infants," and even a few others (8).

The rate of cases with Dravet syndrome seems to augment constantly as the syndrome may be diagnosed increasingly frequently by SCN1A (α subunit of the neuronal type I sodium channel) gene analysis (31,32). This unique opportunity has sharpened the diagnostic view of the medical community. After one has succeeded in diagnosing a few cases, it frequently becomes an experience of pattern recognition. Therefore, the formerly calculated incidence of 1/40,000 may be an underestimate (33). It is of note that many epileptic vaccine encephalopathies in which an immunization-provoked fever triggered the epilepsy were retrospectively identified as having a SCN1A mutation (34).

Symptomatology

The disease most frequently starts with febrile seizures within the first year of life, in an up to then healthy child. These seizures may initially be indiscernible from regular febrile seizures but frequently become prolonged. Fever, infections without fever, vaccinations, hot baths, or even only hot weather may trigger recurrent seizures. These may occur generalized or unilateral affecting different sides of the body on different occasions (i.e., alternating hemi–grand mal, unilateral seizures, hemiclonic convulsions). The tendency to suffer temperature-sensitive seizures seems to persist over many years. In the series of Dravet et al. (33), short, single myoclonias were noted by some parents before onset of febrile seizures. Even though approximately 70% of cases begin with generalized or unilateral febrile seizures, focal seizures may occur already early in the course, but this is not the rule. Febrile seizures typically occur repeatedly within the first year of life and are frequently the dominating manifestation of the epilepsy in the first 9 months of age. Later, afebrile generalized seizures add to the febrile seizures and are soon followed by myoclonic seizures and atypical absences (33).

Dravet et al. (33) define "steady-state seizures" as those that prevail in many cases throughout the course. The authors recognize 10 different seizure types:

1. "GTCS" are basically identical to those encountered in idiopathic generalized epilepsy syndromes.
2. "Hemiclonic convulsions" are frequent in the first 3 years of life, and then they become

rare. Postictal hemiparesis is a frequent feature. If they—by chance—reoccur on a specific side of the body, they may falsely be taken for focal seizures.

3. "Falsely generalized seizures" clinically appear like GTCS. On polygraphic recordings, this seizure can be resolved as bilateral asymmetric tonic contractions of different muscle groups.
4. "Unstable seizures" are clinically related to "falsely generalized seizures" with concomitant focal EEG discharges that change their origin between and during seizures.
5. Myoclonic seizures predominantly affect the axial muscles and may range from mild to severe, from simple head nodding to violent thrashes involving the entire body. Severe myoclonic seizures may result in falls and injuries. Repeated twitching of the head is a third observed type. These seizures may precede generalized tonic–clonic convulsions. Interictal myoclonias (without concomitant epileptic discharges on surface EEG) are a frequent feature, mainly observed in periods with high seizure frequency (roughly 70% of cases). Myoclonic seizures may abate over time.
6. Atypical absences may appear at any age during course; however, mostly after the first year of life. In our view, absences are not always "atypical" because regular 3-Hz spike slow-wave absences may be recorded. Absences may range from pure impairment of consciousness to absences with intermixed myoclonic seizures. Duration varies between 3 and 10 seconds in most cases.
7. Simple and complex focal seizures, frequently associated with strong autonomic reactions such as pallor, cyanosis, and sweating, are detectable in about two-thirds of cases. They may start already within the first year of life, but usually begin later. Adversive seizures and clonic seizures frequently in combination are typical manifestations.
8. Tonic seizures are rare in this syndrome. They seem to resemble those seen in Lennox–Gastaut syndrome, often with a myoclonic component.
9. Obtundation states are episodes of reduced attention (drowsy states). They occur in more than one-third of children. Usually, they are associated with erratic myoclonias involving the limbs or the face. These drowsy states may continue for hours or even days. In the EEG, dysrhythmic slow waves intermingled with spikes and sharp waves are characteristic. This state may evolve from an overt seizure or end in one.
10. A status of generalized tonic–clonic convulsions may occur without warning. Frequently fever, infection, or even photic stimulation may act provocative. If the status is then falsely treated by phenytoin (a sodium channel blocker), it may have an unfavorable outcome.

Besides intractable epilepsy, a variable degree of developmental delay (usually severe) characterizes the course. Children frequently develop an ill-defined moderately severe ataxia (60% to 70%) and mild pyramidal signs. Usually, ataxia is not disabling, will not prevent from walking, and will attenuate over the years. Besides fever, infection, and hot weather conditions, seizures may also be triggered by (hot) water immersion, joyful mood (e.g., birthday party), or physical exercise. Hyperkinetic behavior, especially at times of high seizure frequency, and autistic features are frequent findings. In general, the more severe the epilepsy, the more marked will be the developmental and behavioral problems. Death is reported in about 10% of larger historic series. Causes were mixed, ranging from status epilepticus to drowning, sudden unexplained death in epilepsy, and accidents (33).

EEG

In the first 1 or 2 years of life, the interictal EEG is frequently normal. Photosensitivity may be found in about 40% of cases. Over time, the background activity deteriorates. As reported by Doose, a rhythmic theta activity with accentuation over the central channels and independent of vigilance develops (20) (Fig. 19.3). Generalized regular and irregular spike–waves as well as multifocal spikes and sharp waves may evolve during the course. In unilateral seizures, lateralized spike–wave or slow spike–wave activity with intermittent irregular spike–wave is observed. In "falsely generalized seizures," an initial amplitude reduction and spike–wave and slow spike–wave activity with changing asymmetry are observed. In unstable seizures, the epileptic EEG activity is similar but migrates from one brain region to another during the same seizure. In myoclonic seizures, spike–wave and polyspike–wave discharges occur simultaneously with the myoclonias. Absences are accompanied by irregular 2.5 to 3.5 generalized spike–wave discharges lasting mostly 3 to 10 seconds. Obtundation states (nonconvulsive status epilepticus) are characterized by generalized spike–wave and slow spike–wave discharges with intermixed fast and slow activities (30).

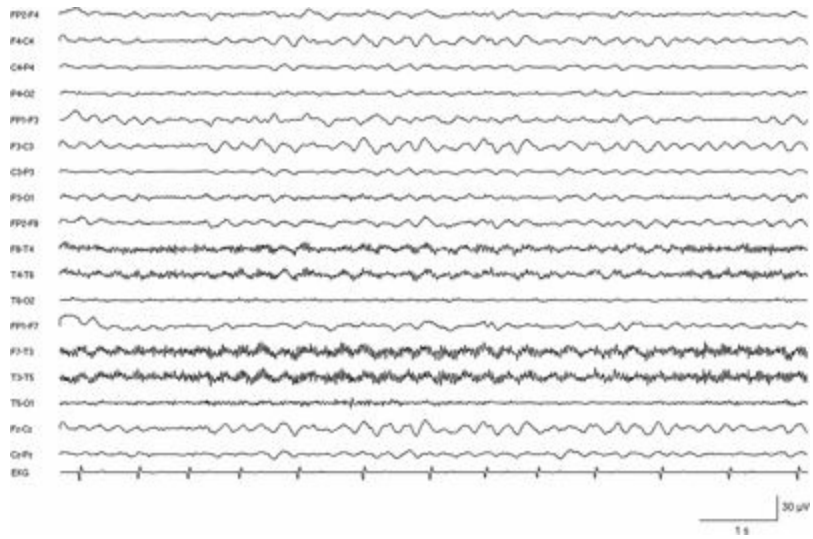

Figure 19.3. EEG recording in a severely retarded 14-year-old girl with SMEI showing persistent rhythmic slowing of background activity.

Treatment and Prognosis

Maybe the most important therapy option is to avoid provocative AED. In most cases of Dravet syndrome, SCN1A, the major sodium channel of inhibitory interneurons is reduced in activity or function to as low as 50% of normal. Application of sodium channel blockers (e.g., carbamazepine, oxcarbazepine, phenytoin, lamotrigine) may further aggravate this defect, resulting in seizure provocation up to status epilepticus. Head-to-head studies are impossible to conduct; however, retrospective analyses and clinical observation show that several agents are effective. Frequently, in the first 2 years of life, valproic acid is commenced. The next step would be to add either clobazam or topiramate, or successively both (35). If generalized tonic–clonic (especially fever- or infection-triggered) seizures and status still prevail, bromides (potassium bromide) may be of great help (22). From our point of view, bromides are possibly the most powerful drugs available for children with Dravet syndrome. Its potency in this syndrome should not be underestimated, but however, bromides predominantly control only GTCS. Children already treated with valproate and clobazam had a 70%

seizure reduction under added stiripentol. The reduction of clonic and tonic–clonic seizures was most marked (36). Other drugs used with partial success are zonisamide, phenobarbital, and chloral hydrate. In addition, the ketogenic diet was reported to be successful (37,38). In children with a severe course, implantation of a permanent IV line (e.g., Port-a-Cath) is helpful to prevent or shorten repeated status epilepticus by rapidly administering phenobarbital and benzodiazepines.

Prognosis is dismal in basically all patients who bear the diagnosis of Dravet syndrome by right. Developmental delay usually becomes evident during the second or third year of life. Complete seizure freedom is not a realistic option. However, in some cases, reasonable results may be obtained by antiepileptic (combination) therapy. There are cases in the borderland (SMEB) who come closer to the clinical spectrum of GEFS+ and who may respond better to therapy.

Genetics and Molecular Diagnostics

Family history was formerly reported to be frequently positive for febrile convulsions and idiopathic epilepsy syndromes. However, a recent study could not reproduce these findings (39). By far, the most cases of Dravet syndrome are caused by defects in the SCN1A gene. In cases diagnosed by applying strict inclusion criteria (SMEI), heterozygous SCN1A mutations may be detected in up to 80% of cases (40). Other genes like SCN1B, SCN2A, and GABRG2 were detected in single patients or families with Dravet syndrome, but quantitatively do not play a significant role. About 95% of SCN1A mutations detected in Dravet syndrome patients appear de novo. The remaining 5% that are inherited are usually connected with milder epilepsy phenotypes resembling the GEFS+ spectrum. This is consistent with a mostly negative family history. SCN1A mutations are distributed over the entire gene. Truncating mutations are found in about 50% of SMEI patients. The remaining are mostly missense mutations loosely clustering at the ion pore positions of the channel protein. Splice site mutations and heterozygous deletions ranging from single exons to the entire gene are rare. Borderland patients (SMEB) also frequently show SCN1A mutations, but to a lesser degree (60% to 70%).

The spectrum of epilepsies associated with the SCN1A gene, however, is broader than Dravet syndrome (SMEI and SMEB) and GEFS+. It also covers some less well-defined infantile epileptic encephalopathies. All of them start within the first year of life and are therapy resistant. These are denoted “cryptogenic generalized epilepsy,” “cryptogenic focal epilepsy,” and “severe infantile multifocal epilepsy” (40).

Selection criteria to maximize chances of a SCN1A mutation detection are given in Table 19.2 (31). If four or more criteria are fulfilled, detection chances are about 70% or higher, using a combination of DNA sequencing and exon quantification assay (e.g., MLPA (multiplex ligation dependent probe amplification)).

Table 19.2 Common Features Recognized in Children with SCN1A Mutations that may be Used as a Guidance in Order to Estimate Chances of Detection in Mutational Analysis

1. Normal development prior to start of epilepsy (~99% of reported cases)
2. Onset of febrile or afebrile GTCS within the first year of life (~96% of reported cases)
3. Unilateral motor seizures (~73% of reported cases)
4. Myoclonic seizures (~75% of reported cases)
5. Temperature sensitivity (~74% of reported cases)
6. Therapy resistance, continuous seizures to adulthood (~89% of reported cases)
7. Development of mostly mild to moderate ataxia (~70% of reported cases)
8. Mental decline (~92% of reported cases)

From Ebach K, Joos H, Doose H, et al. SCN1A mutation analysis in myoclonic astatic epilepsy and severe idiopathic generalized epilepsy of infancy with generalized tonic–clonic seizures. *Neuropediatrics.* 2005;36(3):210–213.

In girls with Dravet (like) syndrome, PCDH19 defects are an important differential diagnosis and may be detected in about 15% of SCN1A-negative females. Juberg and Hellman (41) reported in 1971 on a syndrome named "epilepsy and mental retardation limited to females." The publication was not really reflected for many years, because it reported a by then mostly unknown exceptional mode of inheritance, namely "X-linked dominant with male sparing." Later the syndrome was rediscovered and defined in more detail by Dibbens et al. (42). Salient features are (41–43):

1. Only females affected
2. Epilepsy as a frequent phenotype (90%)
3. Seizure onset mostly in the second year of life (6 to 36 months)
4. GTCS, clonic seizures, myoclonic seizures, absences, unilateral seizures, focal seizures, febrile seizures
5. Seizures may remit spontaneously (mean 12 years)
6. Low intelligence in about 70% of cases
7. Developmental regression in about 50% of cases
8. Behavioral comorbidities are frequent (obsessive–compulsive, attention deficits, etc.)
9. Several reports of sudden unexpected death in epilepsy
10. No specific EEG pattern

PROGRESSIVE MYOCLONUS EPILEPSIES

Unverricht–Lundborg disease, Lafora disease, myoclonic epilepsy with ragged red fibers (MERRF), NCL, sialidosis, and dentato-rubro-pallido-luysian atrophy (DRPLA) are the archetypes of this disease group. Other disorders with variable phenotypes may—in some of the affected—take the course of a PME (see Table 19.1). PME are rare and comprise <1% of epilepsies. In their early course, some of them may be difficult to differentiate from idiopathic generalized epilepsies. Precise personal and family history and a thorough clinical and neurologic examination are pertinent to obtain diagnostic clues at an early stage (44). Extremely enlarged somatosensory evoked (Fig. 19.4) or

visually evoked potentials induced by flashlight, an enhanced long-latency reflex in response to electric stimuli referred to as C-reflex, and an abnormal reaction to paired pulse transcranial magnetic stimulation all reflecting increased cortical excitation or decreased cortical inhibition may be diagnostically helpful neurophysiologic findings. Examination of the eye background is also important, since this may reveal optic atrophy, a cherry red spot or retinitis pigmentosa.

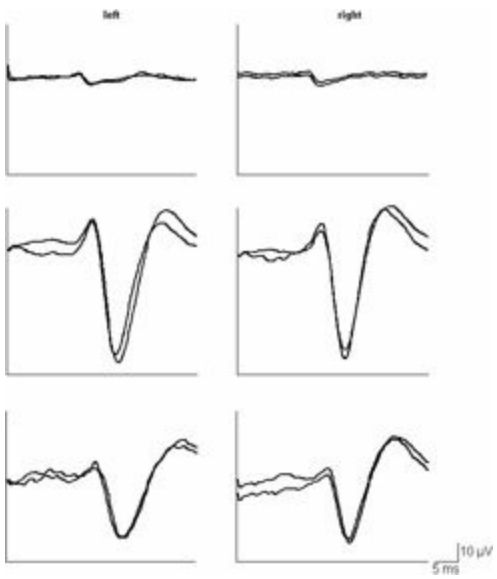

Figure 19.4. Somatosensory evoked potentials (SEPs) in a 13-year-old boy with progressive myoclonus epilepsy (PME) and in a healthy male of same age **(top)**. Giant SEPs are recorded in the patient with PME reflecting extreme cortical hyperexitability to sensory stimuli **(middle)**. Notice the substantial reduction of the SEP amplitude during treatment with levetiracetam **(bottom)**.

UNVERRICHT–LUNDBORG DISEASE

This disease clusters in Finland and in Mediterranean countries, where the prevalence reaches up to 1/20,000. The age of onset ranges from 6 to 18 years. The disorder is characterized by stimulus-sensitive myoclonus, elicited by passive joint movement, startle, and light. Myoclonus becomes more and more severe, until finally patients are wheelchair dependent. Ataxia, intention tremor, and dysarthria develop. Generalized tonic–clonic convulsions are the presenting sign in 50% of cases. Absences are also observed. Epilepsy is usually easy to control. Mental decline occurs late and is frequently mild. In the beginning, the EEG is indiscernible from idiopathic generalized epilepsy. Over time, background activity deteriorates, and frequent spikes and polyspikes are seen. Photosensitivity is a constant feature (Fig. 19.5). Reduced cortical inhibition results in giant somatosensory potentials. The disease stabilizes over time and the affected survive to old age (45).

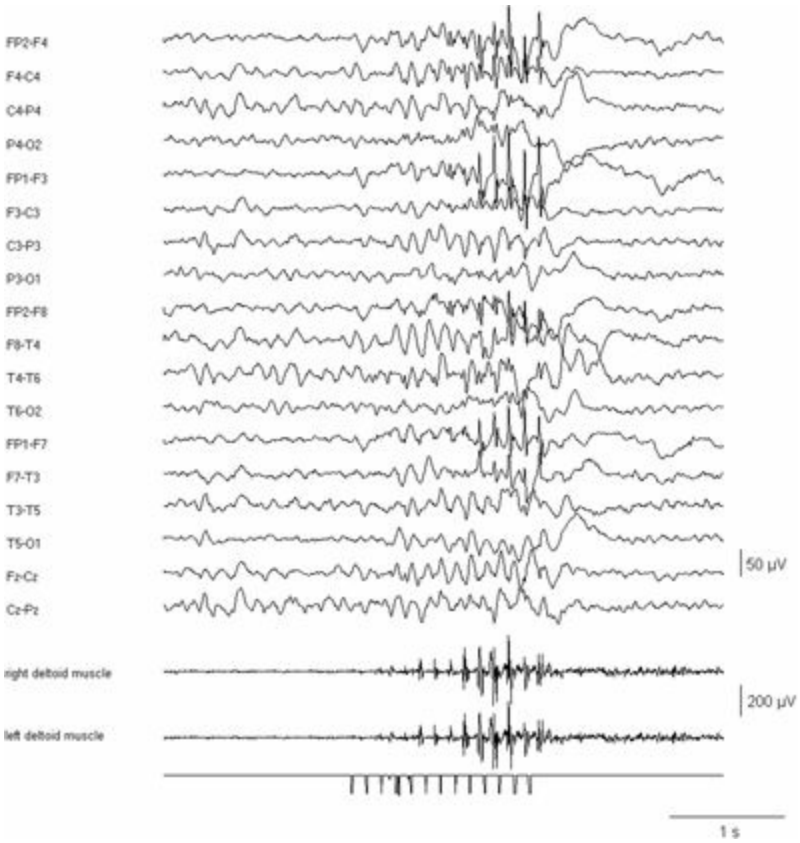

Figure 19.5. Marked photosensitivity at low stimulation rate associated with myoclonic jerks in a 15-year-old girl with Unverricht–Lundborg disease.

Recessive mutations in cystatin B (CSTB, EPM1), a protease inhibitor, are causative for the disease. The disease mechanism is still to be elucidated, but recent research suggests that CSTB is important to defend cerebellar neurons from oxidative stress (46). The most common mutation is an expanded dodecamer repeat in the untranslated 5′ promotor region. Point mutations within the gene are much rarer (44,45).

Valproate and add on clobazam are effective to control seizures and ameliorate myoclonus. Myoclonus responds to piracetam and possibly to levetiracetam. Other agents and vagus nerve stimulation have been used with success in some patients. Phenytoin is strictly to be avoided, for it aggravates the disease (45).

Lafora Disease

Lafora body disease is an autosomal recessively inherited generalized polyglucosan storage disorder that takes a rapidly progressive course. It is characterized by epilepsy, stimulus-sensitive myoclonus, blindness, and mental deterioration. Mutations in the EPM2A gene (laforin) cause about 60% of cases, and mutations in EPM2B gene (malin) are found in about 35% of patients. Polyglucosan inclusion bodies may be detected in (e.g., axillary) sweat glands by biopsy. How polyglucosan inclusion bodies accumulate is still not entirely understood. The disorder is most prevalent in the Mediterranean countries (46).

The disease starts with seizures in normally developed children between 6 and 19 years. Febrile seizures may precede, and initially it may be difficult to differentiate the presentation from juvenile myoclonic epilepsy. Visual seizures, absences, generalized tonic–clonic seizures, and astatic seizures are characteristic. Myoclonus is usually mild at the beginning but becomes disabling over time.

Patients usually die within one decade after onset of the symptoms, frequently in status epilepticus. The EEG is normal at the beginning, but later background activity deteriorates with interposed generalized spikes, polyspikes, and occipital sharp slow waves (Fig. 19.6). Therapy of epilepsy and myoclonus is unspecific (44,46,47).

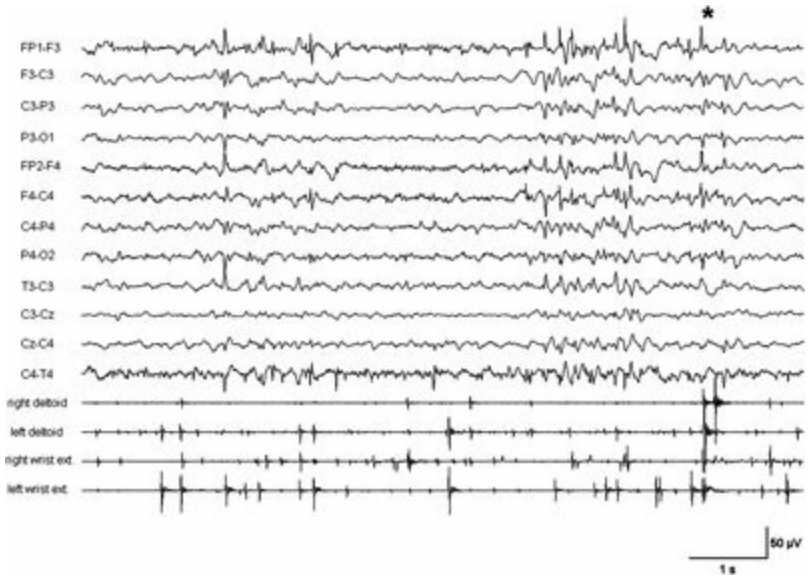

Figure 19.6. EEG–EMG recording in a 14-year-old girl affected by Lafora body disease. Numerous predominantly multifocal and asynchronous positive myoclonic jerks of short duration (50 to 100 ms) and varying intensity are recorded from different muscles. Note that only one myoclonic jerk is associated with a spike–wave discharge in the EEG (asterisk).

Myoclonic Epilepsy with Ragged Red Fibers

MERRF is one of the more common forms of PME (44,48). It may be sporadic or familial. Some cases show a clear maternal mode of inheritance while others are sporadic or autosomal inherited. In approximately 90% of cases, three point mutations of the tRNALys gene may be revealed (8344A>G, 8356T>C, and 8363G>A). In adults, ragged red fibers representing aggregates of abnormal mitochondria are detectable in 90% of cases. In children, these numbers are much smaller. Cytochrome C oxidase-negative fibers in muscle biopsy are a further characteristic finding. The syndrome is clinically variable as patients may carry different proportions of defective mitochondria in single tissues ("heteroplasmia"). Typical manifestations include generalized epilepsy, myoclonus, and ataxia. The onset may range from childhood to young adulthood with remarkable intrafamilial variation. The disease may present insidiously or set in as a metabolic crisis. Optional additional features are cognitive impairment, spasticity, myopathy, deafness, failure to thrive, lipomas, neuropathy, optic atrophy, cardiomyopathy, external ophthalmoplegia, and diabetes. MERRF may clinically overlap with MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke like episodes). In full-blown cases, the EEG is grossly abnormal, but unspecific. It may show background slowing with rhythmic delta activity, bilateral synchronous spike–waves, irregular spike–waves, and occipital spikes and sharp waves. Many patients are photosensitive and also show a photomyoclonic response. In MRI, signal intensity changes may be seen in the basal ganglia (Fig. 19.7). Cortical atrophy may be present early or will ensue over time. There are no approved therapies. Valproate may result in metabolic crisis and hepatic failure, probably because it reduces the cellular uptake of carnitine. However, many patients who were erroneously treated did well with valproate for many years. L-carnitine supplementation may be indicated, but its effectiveness is unproven (44,48).

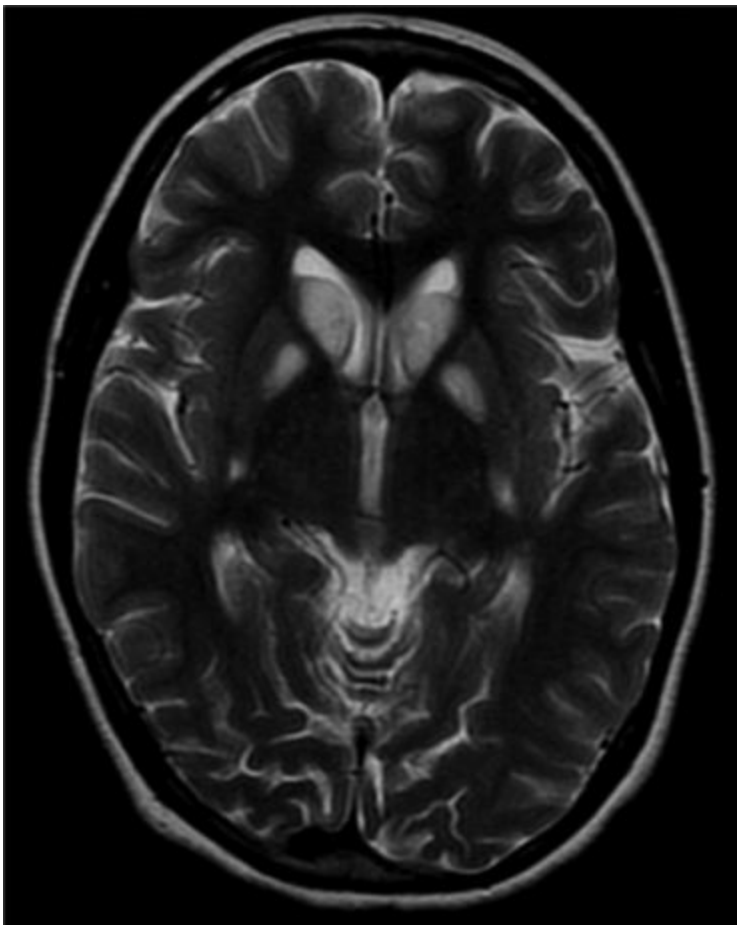

Figure 19.7. T2-weighted MRI in an 8-year-old girl with MERRF demonstrating bilateral signal hyperintensities of the caudate nuclei.

Neuronal Ceroid Lipofuscinoses

NCL constitute the most frequent neurodegenerative disorder in children. The majority of them are inherited in an autosomal recessive manner. Epileptic seizures, progressive psychomotor decline, visual failure, and early death are the characteristic clinical features. Abnormal amounts of lipopigments are stored in the lysosomes of neurons and other cells. Until now, eight genes have been identified (CLN1, CLN2, CLN3, CLN5, CLN6, CLN7, CLN8, and CLN10). Two further genes are predicted to exist but still await identification (CLN4, CLN9). Despite large efforts during the last years, the pathomechanisms underlying protein dysfunction remain still elusive (49). MRI reveals progressive cerebral and cerebellar atrophy with signal hyperintensities observed in the white matter on T2-weighted images. Muscle, skin, conjunctival, rectal, or brain biopsies show inclusions of different shapes, depending on the specific type of NCL. The most relevant form in childhood is the "late infantile variant" (NCL type 2, Jansky–Bielschowsky disease). The disease starts at 2 to 4 years. Generalized tonic–clonic convulsions, astatic seizures, and atypical absences are characteristic. Developmental regression is recognized shortly after onset of the epilepsy while spasticity and ataxia follow early on. Loss of vision occurs at 4 to 6 years, and patients die about 5 years after onset of first symptoms. EEG frequently shows massive background slowing from the beginning of the epilepsy. Slowing is pronounced over the occipital regions. Generalized irregular spike–waves are present. The characteristic EEG response to low frequency photic stimulation (1 to 3 Hz) may not be present at the beginning of the seizures. Visual evoked potentials lack cortical inhibition and have greatly increased amplitude ("giant visual potentials"). Curvilinear bodies may be detected by skin biopsy or buffy coat (Fig. 19.8). The causative enzyme is tripeptidyl peptidase 1

(TPP1). A multitude of mutations have been detected in the encoding gene. Enzyme activity can be measured even from dried blood spots (44,50).

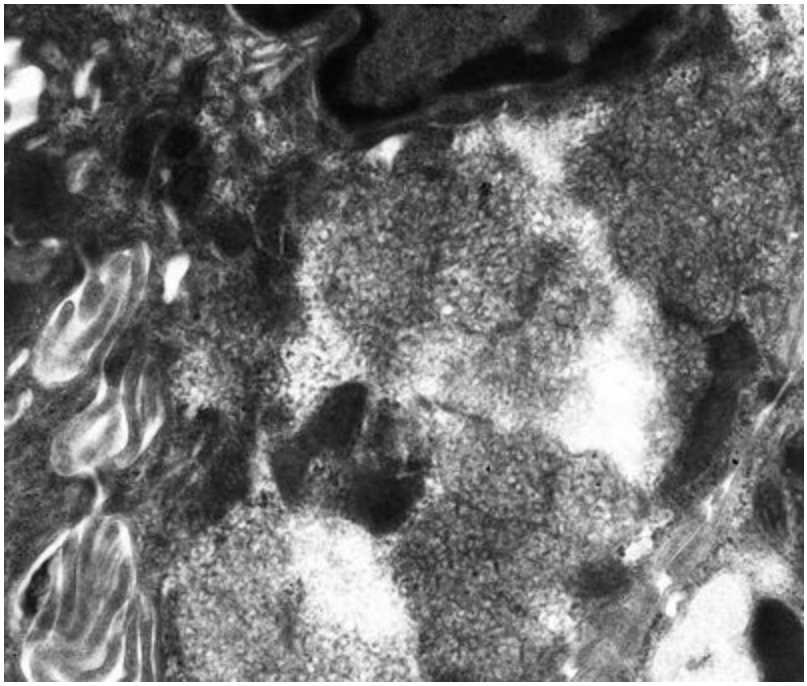

Figure 19.8. Electron microscopic image of a skin biopsy from a 3-year-old boy with NCL type 2 showing curvilinear inclusion bodies. (Courtesy of Dr. Anne Schänzer, Institute of Neuropathology, Giessen, Germany.)

There are several other rare variants of the late infantile type, which are mostly restricted to certain ethnic groups. Among those are the "late infantile finish variant" (NCL type 5), the "late infantile variant" (NCL type 6), and the "Turkish variant late infantile form" (NCL type 7) (44,50).

Juvenile NCL (NCL type 3, Batten disease, Spielmeyer–Vogt–Sjögren disease), the most common variant, presents with loss of vision before the onset of epilepsy. Generalized tonic–clonic convulsions are frequent. Myoclonus remains subtle. Disease onset is at 4 to 7 years of age. Behavioral problems and psychotic symptoms are prevalent. Later, dementia and extrapyramidal signs will develop. The course is relentless. Death occurs within 5 to 10 years after onset. The causative gene is identified, but its function remains unknown. Multiple gene defects are on record. The most common one is a deletion of exons 7 and 8. In skin biopsy, a "fingerprint" pattern is detectable, and lymphocytes may show vacuoles reflecting enlarged lysosomes. Some rare patients show defects in the CLN1 gene (44).

The adult type (NCL type 4 or Kuf disease) is a rare autosomal dominant disorder that may begin in adolescence or adulthood. Dementia, ataxia, and later myoclonus and seizures will develop. Vision remains intact. Most patients die within 10 years. EEG shows background slowing and generalized spike–wave discharges. Photosensitivity at low frequencies (1 to 3 Hz) may be present. Visual evoked potentials remain normal while somatosensory potentials are enlarged. There is no known gene (50).

Sialidoses

Sialidosis type 1 (cherry red spot myoclonus syndrome) is an autosomal recessive disorder caused by a deficiency of neuraminidase A (51). Sialylated oligosaccharides are detectable in urine. Multiple gene defects of the gene Neu1 are on record. Truncating mutations are most common. Action and

intention tremor and generalized tonic–clonic convulsions start in adolescence or early adulthood. Visual impairment is mild or even absent, and cognitive decline occurs during course. Spasticity, ataxia, and a painful sensory peripheral neuropathy may be observed. There is no hepatomegaly or skeletal dysplasia. Vacuolated Kupffer cells are hallmarks in histology. EEG shows few epileptic discharges and a low-amplitude fast background activity. Myoclonic attacks are paralleled by central 10 to 20 Hz activity. Somatosensory potentials are enlarged, and visual evoked potentials are reduced in amplitude (44,51).

Sialidosis type II is also caused by neuraminidase deficiency but runs a more severe course than type I. Affected patients show dysostosis multiplex, hepatosplenomegaly, mental deterioration, corneal clouding, and a Hurler-like phenotype. Onset ranges from the neonatal period to adolescence. EEG features are similar to sialidosis type 1 (44,51).

Dentato-Rubro-Pallido-Luysian Atrophy

DRPLA is a rare autosomal dominant repeat extension disorder with the highest prevalence in Japan. The disease is variable with three different main phenotypes recognized. General symptoms include epilepsy, extrapyramidal symptomatology, myoclonus, and dementia (52). One form presents as a PME, one as a pseudo-Huntington disease, and one as the ataxo-choreoathetoid form. The PME form has its onset before 20 years of age. Seizures, myoclonus, and mental deterioration are characteristic. EEG shows a normal background activity, spike–waves, and frequently photosensitivity (44,52).

Other Rare Types of Progressive Myoclonus Epilepsies

Gaucher disease is caused by a deficiency of the lysosomal enzyme glucocerebrosidase, which cleaves glucose from cerebroside. The subacute neuronopathic form of the disease (type III) may manifest as a typical PME. Hepatomegaly, splenomegaly, thrombopenia, anemia, and osseus symptoms such as osteopenia, pain, and deformations are systemic signs of the disease. Myoclonus, myoclonic seizures, and GCTS may occur in adolescents and young adults. Typically, the EEG shows generalized spike–waves and marked photosensitivity. Beneath a mild mental decline, supranuclear horizontal ophthalmoplegia, ataxia, dystonia, and spasticity are additional, but inconstant neurologic symptoms. Enzyme replacement therapy is available for Gaucher disease and has been shown to prevent or reverse systemic signs, but its value in improving the neurologic manifestations of the disease has not yet been demonstrated (53).

Huntington disease may manifest as early as during the first decade of life. Such children may suffer from severe dystonia and rapidly progressive myoclonus epilepsy. Since the disorder is caused by an autosomal dominant trinucleotide “CAG” (Cytosine, Adenine, and Guanine) repeat expansion in the so-called Huntingtin gene, careful anamnesis should identify at least one other near relative with Huntington disease (44).

The clinical and electroencephalographic findings in patients with Galactosialidosis are similar to those observed in subjects affected by sialidosis type II. But in divergence from sialidosis type I and II, there is a combined deficiency of sialidase and β-galactosidase due to a primary defect in protective protein/cathepsin A. Three subtypes are recognized: the early infantile type, the late infantile type, and the juvenile/adult type (54).

The list of neurometabolic disorders that, in single cases, may present as a PME is even longer, and some authors also mention neuroaxonal dystrophy, pantothenate kinase associated

neurodegeneration (neurodegeneration with brain iron accumulation, Hallervorden-Spatz disease), and GM2 gangliosidosis. In virtually all cases, other clinical symptoms, besides myoclonic seizures, will aid diagnostic efforts.

PROGRESSIVE ENCEPHALOPATHIES WITH MYOCLONIC SEIZURES

Vitamin B_6 (pyridoxine) is present in various dietary products. The phosphorylated active form pyridoxal phosphate is required as a cofactor to glutamic acid decarboxylase that catalyzes the conversion of glutamate to the inhibitory neurotransmitter GABA (γ-amino-butyric acid). Pyridoxine-dependent epilepsy is a rare autosomal recessive disorder (55). Typically, first seizures occur within hours after birth and are not sufficiently controlled by conventional antiepileptic medication. Impressively, seizures resolve within minutes and the EEG normalizes within hours after intravenous administration of 50 to 100 mg pyridoxine. Affected infants show hyperexitability with marked agitation, irritability, hypervigilance, and startle responses to touch and sounds. Usually, various seizure types are observed including myoclonic, partial clonic, and generalized clonic seizures. Lifelong pyridoxine medication is necessary, but even in early treated subjects, mental retardation seems not to be uncommon. Besides this classic type, an increasing number of patients with otherwise therapy- resistant myoclonic, focal clonic, partial motor, generalized tonic–clonic, and complex partial seizures, beginning beyond the neonatal period is been reported. ALHD7A1 encoding for antiquitin, which is the α-aminoadipic acid semialdehyde dehydrogenase in the pipecolic acid pathway of lysine catabolism, has been identified as the causative gene. Deficiency of the encoded enzyme results in accumulation of Δ^1-piperidine-6-carboxylate that reacts with pyridoxal phosphate, thereby causing inactivation of the latter (56).

Some patients presenting with intractable epilepsy during the neonatal period did not respond to administration of vitamin B_6, but their seizures ceased when they were treated with pyridoxal phosphate (pyridoxal phosphate–dependent epilepsy). Because of CSF abnormalities indicating a reduction of intracellular pyridoxal phosphate in patients in whom pyridoxal phosphate stopped the seizures where pyridoxine had failed, Mills et al. (57) sequenced the pyridox(am)ine 5′-phosphate oxidase (PNPO) gene and found homozygous missense, splice site, and stop codon mutations in five affected infants. Except for one, all patients died within the neonatal period. Whether mutations of the PNPO gene also contribute to less severe forms of pyridoxal phosphate–dependent seizures remains to be elucidated.

Several patients with otherwise intractable neonatal seizures responding to treatment with folinic acid had also been described. Most patients presented with myoclonic or clonic seizures, apneas, and irritability within the first 5 days of life. An autosomal recessively inherited abnormality of folate metabolism has been postulated, but no specific defect could be identified. Recent research revealed that folinic acid–responsive seizures are identical to pyridoxine-dependent epilepsy (58). However, it has been recommended to treat all patients affected by α-aminoadipic semialdehyde dehydrogenase deficiency with pyridoxine, folinic acid, and a low lysine diet (58).

Biotin is a water-soluble vitamin that is an indispensable coenzyme for four important carboxylases. There are two autosomal recessive defects of biotin metabolism, holocarboxylase synthetase deficiency and biotinidase deficiency, which result in multiple carboxylase deficiency and which can be effectively treated with pharmacologic doses of biotin (59). While the very rare

holocarboxylase synthetase deficiency manifests during the neonatal period, the first signs of biotinidase deficiency emerge by 3 to 6 months or even later. Frequently, therapy-resistant myoclonic or tonic seizures are the initial symptoms. Erythematous or seborrheic skin lesions beginning around the mouth, conjunctivitis, and alopecia are important diagnostics that are present in about 70% of cases. Without biotin treatment, irreversible neurologic damage including psychomotor retardation, ataxia, optic atrophy, and deafness can occur (59).

In addition, myoclonic seizures may represent a prominent symptom in a variety of other metabolic encephalopathies presenting during infancy or early childhood (see Table 19.1).

RECENTLY RECOGNIZED TYPES OF PROGRESSIVE MYOCLONUS EPILEPSIES AND PROGRESSIVE MYOCLONIC ENCEPHALOPATHIES

Leukoencephalopathy with vanishing white matter is caused by mutations in genes encoding for the subunits of the eukaryotic subscription factor 2B (eIF2B). Although epileptic seizures are frequent in affected infants and children, the disease is usually not linked to PME. But recently, Jansen et al. (60) reported on a young adult showing symptoms that justified the diagnosis of PME and who was found to have a homozygous mutation in EIF2B5 after other causes underlying PME had been ruled out.

Action myoclonus-renal failure syndrome is a rare autosomal recessive disorder first reported in the French-Canadian population. Recently, it has been shown that the disease is caused by mutations in the SCARB2/LIMP2 gene encoding for the lysosomal membrane protein SCARB2. Severe focal glomerulosclerosis and PME associated with accumulation of storage material in the brain are the clinicopathologic hallmarks of the disease. An increasingly disabling action myoclonus and cerebellar features emerge during the second or third decade of life. Proteinuria progressing to renal failure may occur before or after the onset of neurologic symptoms (61). Polyneuropathy and dilated cardiomyopathy represent further potential features of the disease (62).

Familial encephalopathy with neuroserpin inclusion bodies is a very rare disease that has been identified as a cause of PME (63). The disorder may manifest as early as during the second or third decade and may take a rapidly progressive course. It is transmitted in an autosomal dominant mode and caused by heterozygous point mutations in the SERPIN1 gene. Neuroserpin belongs to the superfamily of SERPIN (serine proteinase inhibitor), but its exact function in the CNS is still not clear. Mutated neuroserpin accumulates in neuronal inclusions (Collins bodies) throughout the gray matter of the cerebral cortex and in certain subcortical nuclei (63,64) but is not detected in muscle, skin, and rectal biopsies (64).

GLUT-1 deficiency that was first described by de Vivo in 1991 is caused by a defect in the facilitative glucose transporter GLUT1. Impaired glucose transport across brain tissue barriers is reflected by hypoglycorrhachia and results in an epileptic encephalopathy with developmental delay and motor disorders. Usually, patients present with seizures during infancy. Among other seizure types, myoclonic seizures, myoclonias, and prolonged absence seizures with myoclonias can be observed. In some subjects, seizure frequency is increased, and the EEG is more abnormal during fasting than shortly after a meal. In most patients, motor and mental development is substantially delayed, and microcephaly evolves in a substantial number. Typically, CSF glucose levels are <0.33

g/L, and glucose CSF/blood ratios are lower than 0.35. But the diagnosis may be missed if lumbar puncture is not performed after a sufficient period of fasting. EEG findings are variable and compromise multifocal or generalized paroxysmal abnormalities and slowing of background activity. Epileptic seizures do not respond well to anticonvulsants but usually cease when commencing a ketogenic diet. The phenotype of GLUT-I deficiency has been expanded during the last years, and now encompasses older children with exertion-induced dystonia, and patients with seizures and EEG findings, resembling those seen in myoclonic–astatic epilepsy or other types of idiopathic generalized epilepsies with early onset (65).

X-linked cyclin-dependent kinase-like 5 encephalopathy is caused by mutations in the CDKL5 gene. The phenotype is reminiscent of the Hanefeld variant of Rett syndrome. As in girls with Rett syndrome, patients are severely mentally retarded, have autistic features, no purposeful hand use, and demonstrate the characteristic stereotypic hand movements. While classic Rett syndrome is caused by mutations in the gene encoding for methyl CpG binding protein 2 (MECP2), the product of the CDKL5 gene has been shown to be involved in the activation of MECP2. Typically, frequent brief tonic and tonic–clonic seizures start within the first 3 months of life. From 6 months to 3 years, infantile spasms intermixed with short tonic seizures are the dominating seizure types, while profound psychomotor retardation and severe muscular hypotonia become evident. In some subjects, seizures may respond to anticonvulsant therapy, whereas in others, the occurrence of myoclonias and myoclonic seizures heralds the terminal stage of epilepsy (66).

Mutations of the human Aristaless-related homeobox (ARX) gene are associated with a variety of pathologic conditions including X-linked syndromic and nonsyndromic mental retardation, dystonia, and X-linked lissencephaly with abnormal genitalia. Polyamine tract expansions of the ARX gene are the commonly observed genetic defect in subjects with X-linked infantile spasms, whereas longer expansions have been detected in two males with early infantile epileptic encephalopathy with suppression-burst pattern (Ohtahara syndrome) (67). In addition, Scheffer et al. described a family with six affected boys over two generations who had a missense mutation in the ARX gene. Since all boys had myoclonic seizures as the dominating seizure type, spasticity, and profound mental retardation, the authors termed the disorder X-linked myoclonic epilepsy with spasticity and intellectual disability (68).

Several unrelated, genetically determined disorders with reduced 5-methyltetrahydrofolate (5-MTHF) levels in the CSF have been delineated during the last years. If 5-MTHF depletion goes unnoticed or is left untreated, regression of psychomotor development, progressive ataxia, and myoclonic epilepsy in conjunction with abnormal brain myelination are characteristic features (69).

Mutations in the potassium channel–related gene KCTD7 have been described in patients with PME from different ethnicities. Usually, a difficult to treat myoclonic epilepsy starts within the second year of life. In the beginning, seizures and EEG findings resemble closely those observed in MAE. But progressive loss of mental and motor skills becomes apparent within 2 years after onset of first symptoms. Lack of storage material in skin biopsy and normal eye background helps to distinguish this peculiar type of PME from NCL forms manifesting in late infancy or early childhood (70).

Childhood spinal muscular atrophy associated with PME (SMA-PME) has been recognized as a specific entity. Recently, exome sequencing in three unrelated families revealed homozygous missense mutations in the ASAH1 gene, encoding the enzyme acid ceramidase. While enzyme activities <10% seem to result in classical Farber disease, an infantile, rapidly progressive lysosomal storage disorder characterized by subcutaneous lipogranulomata, joint pain, and

hoarseness of the voice, higher residual activity appears to result in SMA-PME (71).

In patients with PME out of three families originating from the Middle East, a homozygous mutation in the PRICKLE1 gene has been identified, encoding a protein in the noncanonical WNT signaling pathway. Patients affected by this type of Progressive myoclonus Epilepsy-Ataxia syndrome usually present with symptoms similar to those seen in Unverricht–Lundborg disease. In most cases, ataxia is the initial symptom, while seizures start between 5 and 10 years of age. Cognitive decline is mild or even absent, whereas myoclonus affecting limb, bulbar, and occasionally facial muscles worsens. Impaired upward gaze represents a peculiar neurologic feature (72).

A single homozygous mutation in the Golgi SNAP receptor complex 2 gene (GOSR2) has been reported in 12 patients with a peculiar type of PME. Since all patients stem from countries bounding the North Sea, the term "North Sea" progressive myoclonus epilepsy has been coined. Affected individuals develop ataxia by an average age of 2 years, followed by onset of various seizure types 3 to 5 years later. Scoliosis emerging during adolescence and moderately elevated CK values are characteristic features of the disorder. The EEG showed generalized spike–waves with occipital predominance and photosensitivity in all cases. The course of disease is progressive, and all affected individuals became wheelchair bound at a mean age of 13 years (73).

PME in conjunction with a homozygous COL6A2 mutation has been recently reported in a consanguineous Iranian family. While COL6A2 was shown to be expressed in the cerebral cortex, its pathogenic role in epilepsy pathogenesis is elusive (74).

MANAGEMENT OF PROGRESSIVE MYOCLONIC EPILEPSIES

Therapy is mainly symptomatic. Seizures and myoclonus may be treated with valproic acid, benzodiazepines, levetiracetam, zonisamide, and phenobarbital. Myoclonus may respond well to a high dose of piracetam. Phenytoin, carbamazepine, oxcarbazepine, gabapentin, tiagabine, and vigabatrin may aggravate myoclonus. In Unverricht–Lundborg disease, phenytoin is strictly contraindicated. Acetylcysteine has been shown to be effective in a mouse model of Unverricht–Lundborg disease. Lamotrigine may aggravate or attenuate myoclonus. Therefore, it should be tested with caution. In mitochondrial disorders (MERRF, MELAS), valproic acid should be avoided. Vagus nerve stimulation may offer help when other therapeutic options are lacking (10,44).

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CHAPTER 20 ENCEPHALOPATHIC GENERALIZED EPILEPSY AND LENNOX–GASTAUT SYNDROME

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Encephalopathic generalized epilepsy (EGE) constitutes a heterogeneous group of conditions associated with cognitive dysfunction, multiple seizure types, and epileptiform abnormalities on the EEG. Patients with EGE often require more thorough reassessment in the clinical practice of epileptology due to frequent, refractory seizures requiring care as well as due to related comorbidities. The Lennox–Gastaut syndrome (LGS) is the prototypic EGE. Patients with LGS have a unique electroclinical profile characterized by frequent uncontrolled seizures, mental retardation (MR), and the presence of slow spike-and-wave (SSW) on the interictal electroencephalogram (EEG). The EEG was initially used to help classify the epileptic encephalopathies in 1945, when William Lennox noted that unlike those patients with the 3-Hz generalized spike-and-waves (GSW), the "petit mal variant" with SSW often occurred in brain-injured patients with no clinical accompaniment during the discharge and a poor prognosis. Under the direction of Henri Gastaut, Charlotte Dravet detailed the clinical profile that included cognitive impairment and multiple seizure types, and emphasized the interictal features of SSW on the EEG while awake and generalized paroxysmal fast activity (GPFA) during sleep (1). Subsequently, Doose et al. (2) noted a lack of homogeneity in patients with SSW including a group of patients with a clinical picture dominated by myoclonic and atonic seizures with a variable and sometimes more favorable prognosis, which was attributed to a subset of patients with myoclonic astatic epilepsy (MAE). In 1982, Jean Aicardi described atypical benign partial epilepsy of childhood with continuous SSW in sleep. This condition was termed the "pseudo-Lennox–Gastaut" syndrome due to the electroclinical features that included multiple seizure types and frequent association with falls (3). Other EGEs include early-onset infantile epileptic encephalopathies (Ohtahara syndrome and early myoclonic encephalopathy [EME]) and epileptic spasms (please see Chapter 16). In particular, Ohtahara syndrome, West syndrome (WS), and LGS may manifest from similar etiologic causes as an age-related expression of EGE.

EGE may manifest as drug-resistant epilepsy with multiple seizure types, arrested psychomotor development, and behavioral disorders but occur without SSW. Patients with epilepsy and multiple independent spike foci (MISF) may be clinically similar to LGS but manifest a nonprogressive course without SSW on the EEG (4). Other patients with encephalopathy and epilepsy may have SSW on EEG due to secondary bilateral synchrony (SBS) and a predominance of focal seizures with rapid secondarily generalized motor seizures that mimic the electroclinical presentation associated with EGE to suggest LGS (5). This chapter explores the spectrum of clinical features that are critical for diagnosis and treatment in patients with EGE and LGS.

LENNOX–GASTAUT SYNDROME

The LGS is the prototypic EGE and represents a common devastating epilepsy syndrome that typically begins within the second and sixth year of life. LGS accounts for approximately 1% to 4% of all childhood epilepsies (1,6). It is an epilepsy syndrome that is characteristically refractory to antiseizure drugs (ASDs). Some authors have used the term LGS to identify any severe epilepsy syndrome of childhood with MR that includes different types of seizures with drop attacks or injury and refractory to ASD treatment (1). Additionally, LGS has been applied to any severe childhood epilepsy that is associated with SSW on the EEG (7). In this chapter, we exclude the latter two broader interpretations and only describe patients presenting with the typical clinical triad of LGS:

1. Multiple mixed seizure types including tonic, atonic, and atypical absence with a high seizure frequency, often with a history of status epilepticus (SE).
2. Impaired intellectual function or behavior disturbance.
3. Interictal EEG demonstrating an abnormal diffusely slow background with SSW while awake. There may also be frequent MISF and bursts of GPFA during sleep.

When all the components are present, the diagnosis is clear. Unfortunately, all of the features of LGS may not be present at the time of presentation.

DEMOGRAPHICS

Population-based studies demonstrate that EGE is not uncommon, representing approximately 11.6% of all childhood epilepsies in one study (8). In one group of patients with EGE, LGS was the final diagnosis in 20%, while 16% had WS, 11% had myoclonic astatic (Doose) syndrome, and 3% had Dravet syndrome (8). However, more than 40% could not be classified into a recognizable syndrome (8). In a southeastern metropolitan city of the United States, the incidence of LGS at age 10 years was 0.26 per 1000 children or approximating 4% of all childhood epilepsy (6).

PATHOPHYSIOLOGY

There are a variety of pathophysiologies that underlie both EGE and the LGS. EGE and the LGS are usually subdivided into structural–metabolic (symptomatic) and unknown (cryptogenic) forms. The majority of patients with LGS have a demonstrable etiology identified. A symptomatic cause for LGS accounts for approximately 70% of the cases (9,10). Most causes are present within the first year of life though the electroclinical syndrome may be identified later. The reason for the commonality of this constellation of multiple seizure types, MR, and SSW on EEG is unclear. The various etiologies include hypoxic–ischemic encephalopathy, stroke and intracerebral hemorrhage, perinatal meningoencephalitis, traumatic brain injury, brain tumors, vascular malformations, and malformations of cortical development (9). In LGS due to unknown cause, patients may have normal development prior to the onset. In a cohort of patients with LGS and an unknown (cryptogenic) etiology living in Atlanta, Georgia, this subgroup represented 44% of LGS patients (6). Conversely, 39% of the children with LGS had preceding ES (11). There is a low incidence of inheritance in LGS due to structural–metabolic causes with a family history present in <10% of patients (1,10,12).

CLINICAL COURSE

The clinical presentation varies depending on whether the etiology has a symptomatic basis or an unknown etiology (7). In symptomatic cases, the syndrome is most readily diagnosed after the patient has evolved from another type of epilepsy such as WS. Most known causes are present in the first year of life (1). The initial presentation in very young children with unknown etiology usually consists of atonic seizures manifesting as head drops (7). Cognitive deterioration may precede the onset of recurrent seizures (13). In older children, drop attacks (tonic and atonic seizures) and behavioral disturbances are more common (7). Infrequently, the onset of the clinical triad of LGS may develop during adolescence (12).

The natural history of LGS usually involves progressive intellectual deterioration as well as frequent seizures and episodes of SE. There can be periods of remission, but they are brief. Seizures persist despite ASDs in the majority, with <10% experiencing remission (6,8).

Individual Seizure Types

The seizure types that define LGS are tonic seizures, atonic, and atypical absences, and different seizure types typically coexist. Myoclonic, clonic, focal, and generalized tonic–clonic (GTC) seizures may also occur as the initial seizure type, particularly in symptomatic LGS.

Tonic seizures are the most common and characteristic seizure type that is seen in LGS, differentiating it from other epileptic encephalopathies. Polygraphic recording with video demonstrates tonic seizures in over 75% of patients (12). Tonic seizures manifest as a paroxysmal increase in muscle tone that may result in a drop attack or may be quite subtle and often goes undetected without video-EEG (1,10,12). The ictal EEG of tonic seizures classically reflects the abrupt onset of low-voltage 15- to 25-Hz ictal generalized fast activity, voltage attenuation, or rhythmic high-amplitude 10- to 15-Hz activity seizure onset (1). Atonic seizures clinically present with a sudden loss of postural tone that occurs without warning, and like tonic seizures, may result in falling. They can be subtle and may only manifest with a simple head nod or involve the axial musculature resulting in a fall. Atonic seizures are a common seizure type that occurs in patients with LGS; however, the majority of epileptic falls in LGS result from tonic seizures (1). The ictal EEG correlate for atonic seizures is most often a burst of generalized spike- or polyspike-and-wave discharges. Atypical absence seizures are seen in more than 75% of LGS patients (12). Atypical absences are characterized by a transitory fixed stare with brief loss of consciousness. Seizures are often delayed up to 1 second after the onset is noted on EEG and may last <30 seconds but are usually longer than typical absence seizures. Patients may continue purposeful activity during atypical absences, and the seizure may be difficult to recognize with the associated comorbid cognitive dysfunction. Unlike typical absences, these seizures are not precipitated by hyperventilation or intermittent photic stimulation. The EEG correlate of atypical absence seizures consists of generalized SSW with a repetition rate of 1.5 to 2.5 Hz that is similar to the interictal SSW pattern, but usually more regular and of higher amplitude (1). Myoclonic seizures are not specific for LGS or the EGE and may also occur in the other generalized epilepsies (e.g., juvenile myoclonic epilepsy). They are seen in approximately 30% of patients diagnosed with LGS (12). When patients demonstrate prominent myoclonus with additional mixed seizure types, a myoclonic variant of LGS has been described that may be associated with a better prognosis (10). Ictal EEG demonstrates bursts of polyspike-and-waves during the episodes of myoclonus (1).

Status Epilepticus

At least half of LGS patients will experience episodes of SE, and while nonconvulsive SE often occurs, any of the seizure types present in LGS may result in SE (14). There is concern that many of the cases of SE are precipitated by overtreatment with hypnotic/sedative ASDs including the barbiturates and benzodiazepines (1). Tonic status and atypical absence SE are most common. Tonic SE can be life threatening because of accompanying autonomic symptoms such as apnea and bronchial hypersecretion that may lead to respiratory compromise (10). Commonly, mixed episodes of SE may present with features of both tonic seizures and atypical absence seizures lasting as long as several days (1). Atypical absence seizures that result in nonconvulsive SE as well as tonic seizures that result in convulsive SE can occur and can be refractory to treatment (14). Atypical absence SE manifesting as impairment of consciousness can be difficult to recognize in LGS patients who are often cognitively delayed at baseline (14). Symptoms may appear as confusion, lethargy, or behavioral changes that defy recognition as a seizure. The EEG during SE may not appear to be distinctly different than the interictal EEG with bursts and runs of SSW. However, during SE, the SSW may appear more persistent and regular as compared to baseline recordings in the same patient (14).

COGNITIVE ASPECTS OF EGE

MR is a component of EGE and one criteria of the classic triad found in patients with LGS. However, MR is not seen in all patients. Up to 10% of patients remain in the normal IQ range although most still demonstrate some degree of slow mental processing (6). Symptomatic patients generally are delayed prior to the onset of LGS, and they often have marked cognitive delay. Symptomatic cases of LGS were found to have a 72% risk of severe MR, while cases without a known cause had only a 22% risk (12). When a known cause is not present in patients with LGS, most do not have developmental delay at the onset (12). It remains unclear if the underlying EGE syndrome and associated MR are progressive, independent of the effect of uncontrolled seizures (7). Further complicating are the effects that may result from ASD polytherapy that is often utilized.

Morbidity and Mortality

A high incidence of injuries is associated with drop attacks (predominantly tonic and atonic seizures). Tonic seizures are the most common cause of falls in children with LGS and a major cause of morbidity, and repeated injury is often encountered (15). Seizures that result in drop attacks often necessitate the use of a protective helmet to prevent head injury during the course of a fall. Other facial and dental injuries are also common. Beyond the frequent injuries from breakthrough seizures, behavioral and cognitive problems often lead to overtreatment with medication that can compromise balance and gait and lead to and worsening of gait, with an iatrogenically induced component of morbidity. Mortality is often associated with accidental injury and is estimated up to 10% over a 10-year follow-up period (15).

EEG

LGS is characterized by the presence of diffusely slow background and SSW on the interictal EEG during the awake state. The presence of SSW is one of the cardinal features in the diagnosis of LGS

(Fig. 20.1). There is controversy about including GPFA as one of the criteria for diagnosis (1,10). The SSW pattern of LGS consists of a spike (20 to 70 ms) or more commonly a sharp wave (70 to 200 ms) that is followed by an after-going surface electronegative slow wave of 350 to 400 ms in duration (16). The SSW discharges are not always symmetrical and may be lateralized to one hemisphere. Photic stimulation, hyperventilation, and sleep do not activate the SSW in LGS like they do in other generalized epilepsy syndromes. Occasionally, the frequency of SSW can approximate 3 Hz though usually a frequency of 1.5 to 2.5 Hz is seen. When the SSW is present only during sleep, then atypical benign partial epilepsy with continuous spike-and-wave of sleep should be considered. In addition, Landau–Kleffner syndrome (with electrical SE in sleep) and the syndrome of continuous spike-and-waves of slow sleep may also manifests SSW on EEG during sleep, though distinct electroclinical differences assist in the syndromic differentiation from LGS.

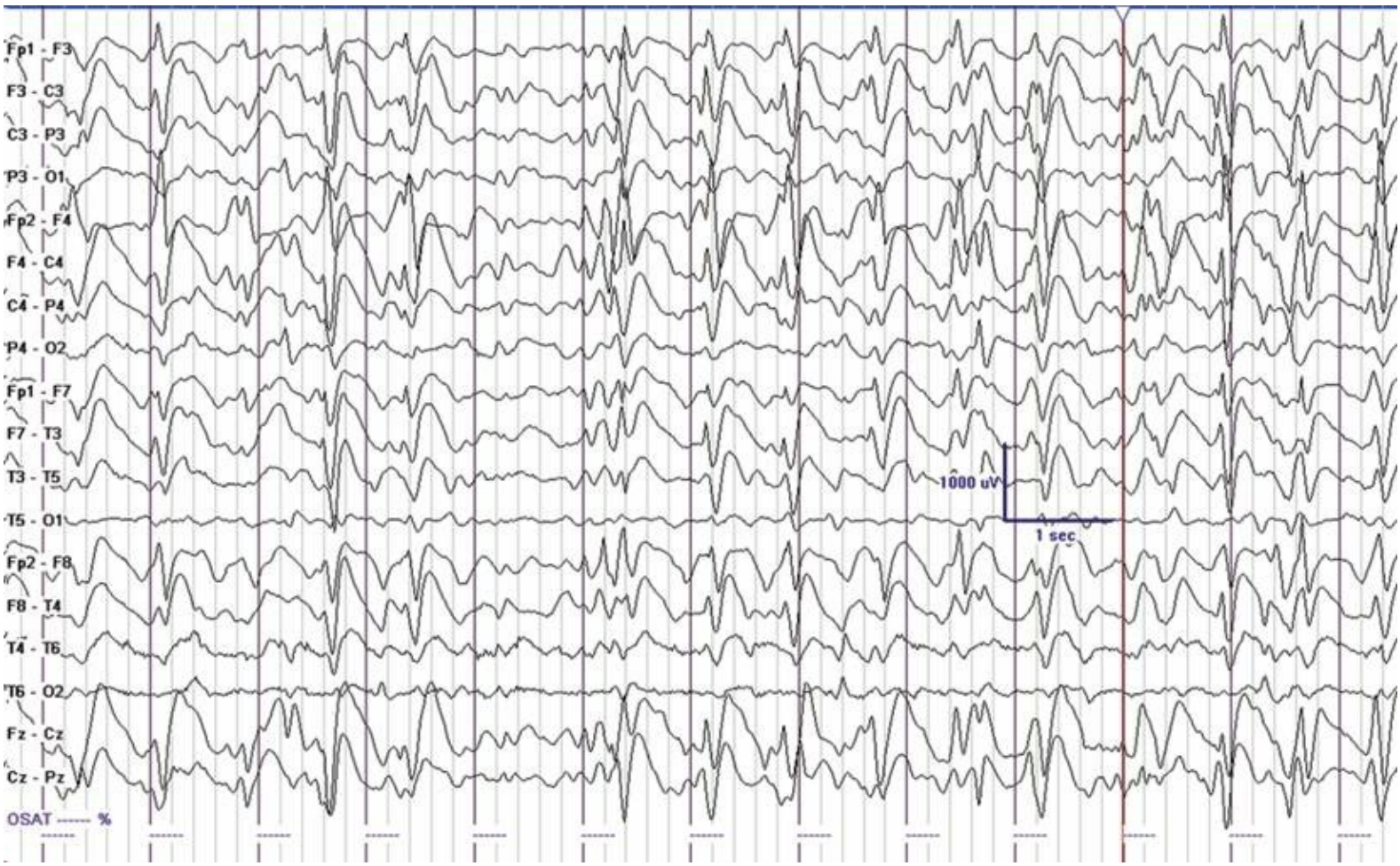

Figure 20.1. Diffuse slow spike-and-wave complexes on interictal EEG in a 7-year-old with LGS.

The finding of SSW on the EEG is an ominous finding. Drug-resistant generalized epilepsy is present in most patients with SSW (16). In one unselected group of patients with SSW on EEG, a >95% likelihood of manifesting seizures was predicted, with a >60% chance of having multiple seizure types, and a 70% chance of having difficult to control seizures (16).

It has been noted that children with interictal SSW discharges had underlying diffuse structural brain injury and subsequently a poor prognosis (16). Antecedent conditions associated with LGS almost always involve the cerebral cortex (1). Bilateral frontal lesions and diffuse dysplastic lesions of the cortex are commonly implicated. Interestingly, patients with Aicardi syndrome do not have LGS, suggesting that presence of the corpus callosum may be important (10). Lissencephaly is rarely

associated with LGS (10). GPFA and tonic seizures are important because they help differentiate LGS from other epileptic encephalopathies that may have a better prognosis. The electrographic pattern of GPFA is a 10-Hz burst of bilateral fast activity that occurs during non–rapid eye movement sleep (Fig. 20.2). These bursts are generally brief and may appear frequently during sleep and disappear during rapid eye movement sleep (10). They are identical to the discharges seen with tonic seizures but may have minimal clinical signs such as brief apnea or mild axial tonic features that are best illustrated on electromyography. GPFA is not pathognomonic for LGS since it may also occur in localization-related epilepsy with focal seizures that arise from extratemporal (often frontal lobe) origins. Patients with EGE, tonic seizures as the predominant seizure type, and GPFA on EEG had a worse prognosis than did patients presenting with predominantly atypical absence, myoclonic or atonic seizures (17).

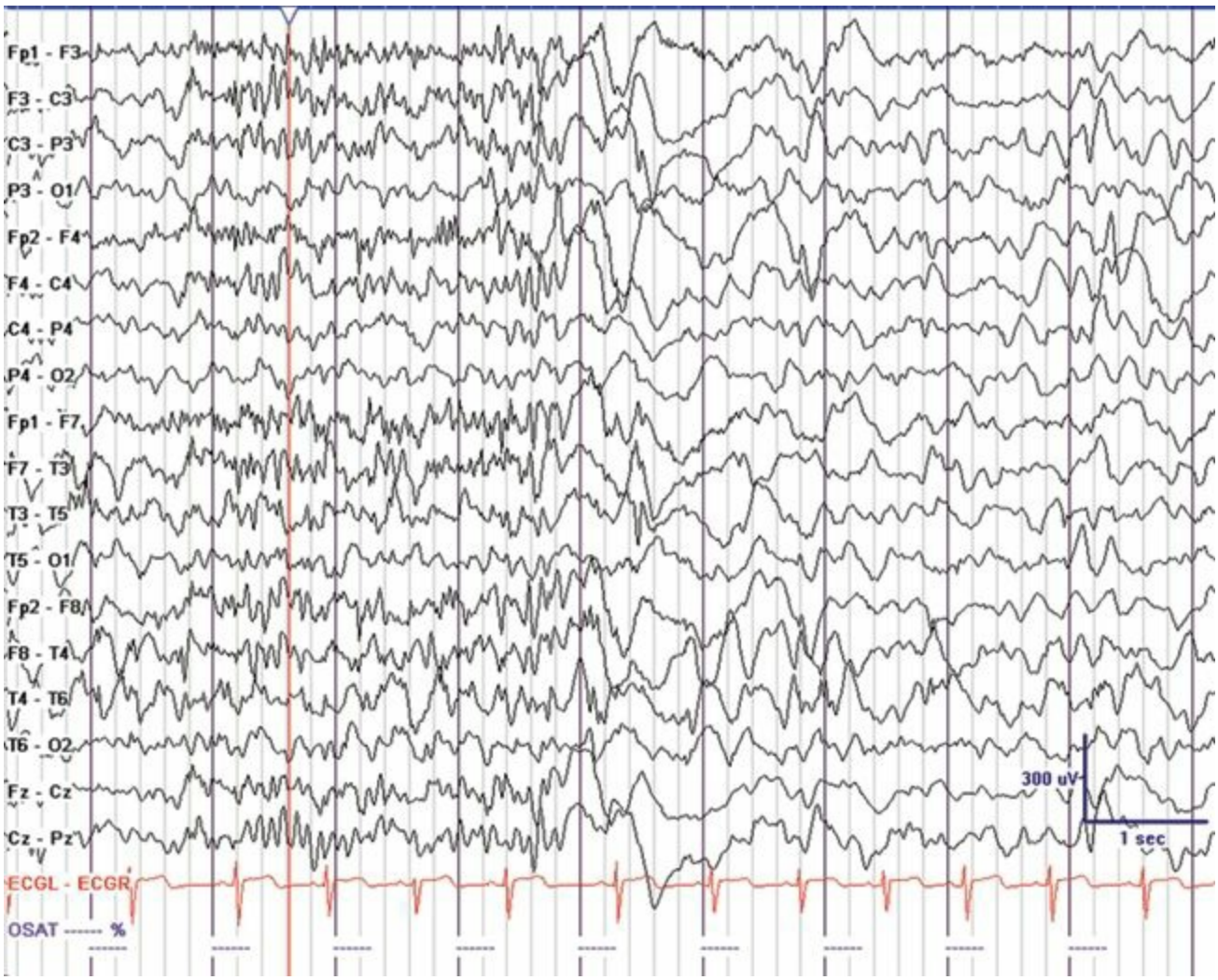

Figure 20.2. GPFA in a 4-year-old with EGE and mixed seizures. Tonic seizures were noted in sleep with eye opening, mild axial stiffening, and apnea. (Courtesy of Joseph Casadonte, MD.)

DIFFERENTIAL DIAGNOSIS

Most of the epileptic encephalopathies evolve over the first few years after the clinical presentation. In contrast to LGS, certain epileptic encephalopathies, such as severe myoclonic epilepsy of infancy (SMEI) (aka Dravet syndrome) and epilepsy with MISF, rarely have SSW (4,18). If SSW are intermixed with 3-Hz or faster GSW, then genetic generalized epilepsy should be considered, especially in patients with normal mental status. If there are predominantly SSW during sleep, and

focal interictal electrical discharges while awake, then atypical benign partial epilepsy with continuous SSW of sleep is an important differential diagnosis. Focal abnormalities on neuroimaging, EEG, clinical semiology, and physical examination may suggest localization-related epilepsy with focal seizures and SBS on EEG when intermixed features are encountered that are not state specific. This is particularly important as resective surgery in localization-related epilepsy may be a treatment option when patient have focal seizures in the setting of bilateral EEG abnormalities or SBS. The most difficult diagnostic distinction is between MAE and LGS (Table 20.1).

Table 20.1 Summary of the Encephalopathic Generalized Epilepsy Syndromes and Clinical Features

Syndrome vs. clinical features	Lennox–Gastaut syndrome (4,10,14)	Myoclonic-astatic epilepsy (2,14,19)	Severe myoclonic epilepsy of infancy (10,18,20)	Epilepsy with MISF (4,21)	Localization-related epilepsy with secondary bilateral synchrony (22,23)	Landau–Kleffner syndrome and atypical benign partial epilepsy with CSWS (3,10)
Clinical seizure types	Atypical absence (75%), tonic–atonic seizures (75%), myoclonic (30%), partial (15%), and GTC (7%) seizures	Myoclonic, myoclonic-astatic seizures, partial seizures rare	Febrile seizures followed by afebrile U/L clonic and GTC seizures. Later myoclonic, atypical absence, and complex partial.	GTC, tonic, partial, myoclonic, atypical absence, and atonic seizures	Partial, atypical absence, and GTC seizures	Partial seizures, clusters of atonic and myoclonic seizures in ABPE with CSWS. LKS with associated auditory agnosia.
MRI	Normal or nonspecific abnormal	Normal	Normal	Normal or abnormal	Normal or abnormal	Usually normal
Interictal EEG pattern	Awake = SSW Asleep = GPFA Background with diffuse slowing often multifocal spikes	GSW, often mixture of SSW and fast (>3 Hz) GSW	Multifocal and generalized spikes; PPR in 40%	Multifocal spikes	Frontal or bifrontal predominant GSW often 3 Hz or <3 Hz	Focal temporal predominant spikes; SSW during sleep
Course	Often severe mental retardation	50% with resolution of seizures in 3 y and 50% with normal IQ	Mental retardation, persistent seizures	Variable	Variable	Possible good outcome if steroid responsive
Prognosis	Progressive deterioration despite broad spectrum AEDs	Often stabilizes with AEDs after the first 3 y, often dramatic response to ketogenic diet	Progressive deterioration initially followed by a static phase	Static	Static; may respond to surgical intervention	Variable; may respond to steroid therapy

GTC, generalized tonic–clonic; U/L, unilateral; PPR, photoparoxysmal response; GPFA, generalized paroxysmal fast activity; GSW, generalized spike-and-waves; SSW, slow spike-and-waves; AED, antiepileptic drugs; CSWS, continous spike and wave during slow wave sleep; LKS, Landau Kleffner Syndrome.

West Syndrome

WS is present in 2 to 5 per 100,000 children and consists of a triad that includes ES, developmental arrest, and a unique EEG abnormality referred to as hypsarrhythmia (see Chapter 16) (Fig. 20.3). Hypsarrhythmia is an interictal chaotic, very high-voltage, asynchronous background with intermixed multifocal spikes and sharp waves that is associated with ES. Hypsarrhythmia in the setting of WS may precede LGS and may later on evolve into a SSW pattern (see Chapter 17) (see Fig. 20.3). A history of ES may occur in up to 40% of children with LGS though variable EEG patterns may be evident (1,6,8,9). Parallel associations among ES, MISF, and LGS exist. For example, patients with Down syndrome may have ES and hypsarrhythmia on the EEG that transition to EGE with MISF or to LGS in approximately 5% of patients (24). The onset of WS is usually between 4 and 7 months of age including 90% that are associated with neurologic abnormalities from underlying structural, genetic, or inborn errors of metabolism present (25).

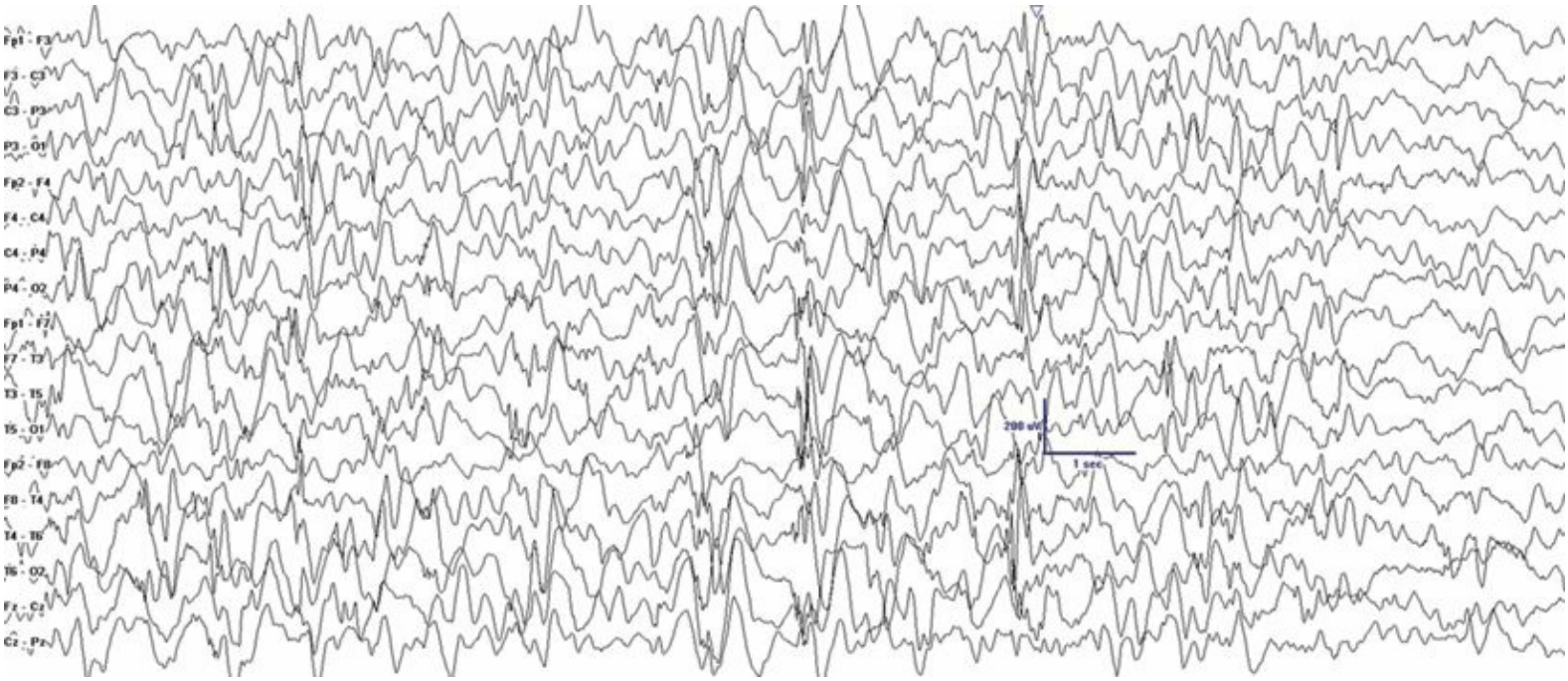

Figure 20.3. Hypsarrhythmia depicted on ictal EEG in a 7-month-old with new-onset epileptic spasms. A 2-week course of ACTH was followed by resolution of hypsarrhythmia and spasms.

Myoclonic Astatic Epilepsy

MAE was first described by Doose as a childhood EGE syndrome characterized by seizure types that are similar to those seen with LGS including atypical absence, myoclonic, atonic, tonic, and tonic–clonic seizures (2). In contrast to LGS, MAE has more prominent myoclonic seizures and less prominent tonic seizures early in the course of the condition. Focal seizures are rare. MAE usually presents between 7 months and 6 years of age. The characteristic massive myoclonic seizures are brief symmetrical jerks involving the neck, shoulders, and arms followed by an abrupt loss of muscle tone that usually results in a fall (astatic seizure). Patients with MAE may also present with pure atonic seizures, atypical absence, GTC seizures, or with episodes of nonconvulsive SE. Most patients are neurologically normal at onset, and there is a family history of epilepsy in 40% of patients (2). The ictal EEG shows spike- or polyspike-and-wave discharges at a frequency of 2 to 4 Hz. The interictal EEG may be normal. When it is abnormal, it may show brief bursts of 3-Hz GSW, 4- to 7-Hz parietal theta, and 4-Hz occipital slowing consistently blocked by eye opening (Fig. 20.4) (26). In contrast to the uniformly poor prognosis of LGS, seizures are controlled in at least half of the patients with MAE within 3 years, and more than 50% of patients will have a normal IQ in this subgroup (14). Valproic acid (VPA), lamotrigine (LTG), and ethosuximide have been generally used for treatment (14). Carbamazepine, phenytoin, and vigabatrin may worsen minor motor seizures. Many centers now consider the ketogenic diet (KD) after failure of one to two drugs or even as a first-line therapy because of its often superior seizure control in this syndrome (20).

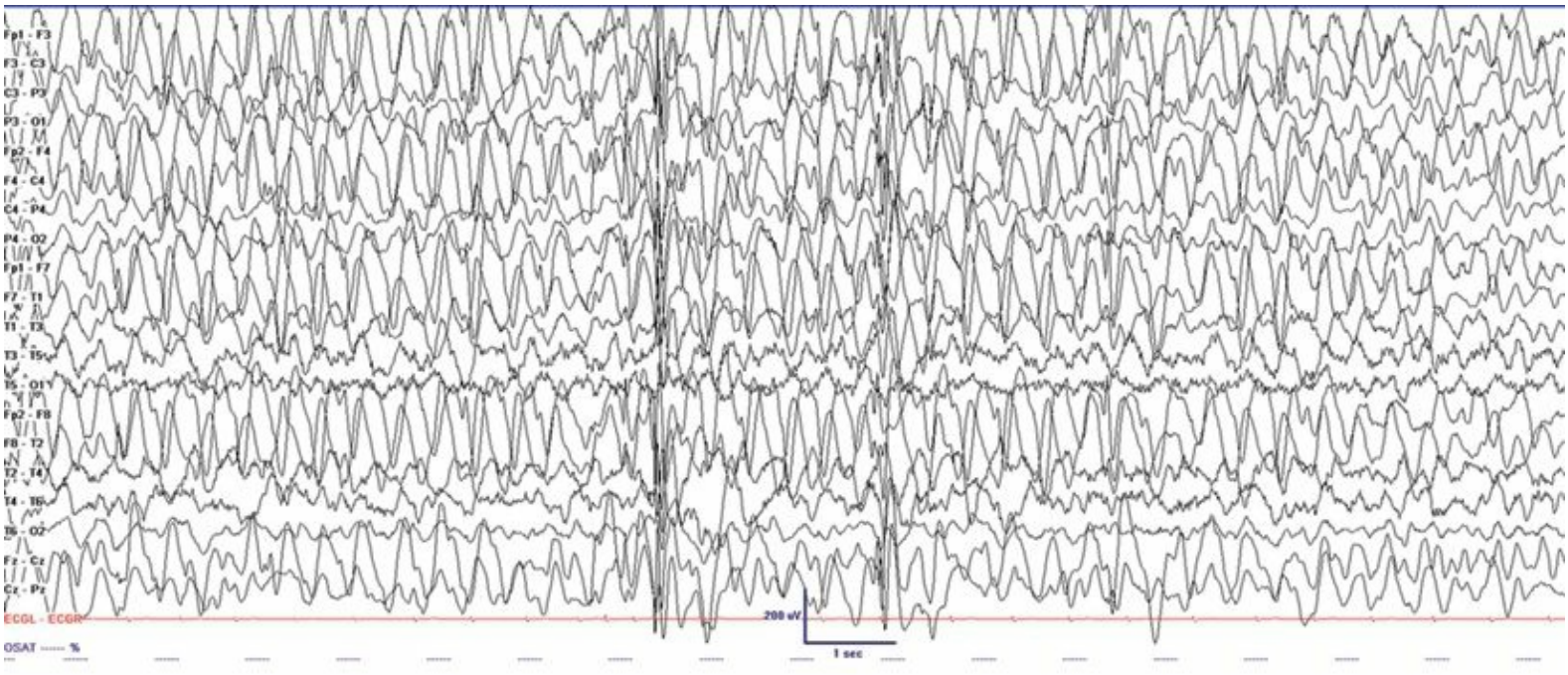

Figure 20.4. Generalized spike-and-wave at varying frequencies in a 2-year-old patient with MAE. Treatment with KD normalized the EEG.

Dravet Syndrome

SMEI also known as Dravet syndrome is a childhood epileptic encephalopathy that usually presents with prolonged febrile seizures during the first year of life. Febrile hemiclonic or GTC seizures are common presentations (18). During the second and third years of life, myoclonic seizures and atypical absences subsequently appear. The myoclonic seizures may be massive and associated with falls. Tonic–clonic and focal seizures are also common. Tonic seizures are rare, and when present, they are infrequent. The EEG is often initially normal but may show SSW as an ictal correlate during atypical absence seizures. Over time, focal abnormalities may develop in addition to generalized spike- and polyspike-and-wave discharges that are usually associated with myoclonic seizures. Stimulus-provoked seizures can occur, particularly light or stress induced, and therefore testing for photosensitivity may be useful (18). Although the myoclonic seizures may resolve, other seizure types persist, and there is progressive cognitive deterioration and overall poor developmental prognosis, with ongoing difficult-to-control seizures. After age 5 years, GTC seizures with nocturnal predominance are usually the predominant seizure type. Behavioral disorders are common. Ataxia is frequently seen, and adolescents may develop a peculiar crouched gait (18). As genetic techniques have improved, patients have shown SCN1A mutations in approximately 70% to 80% of Dravet patients, with 95% of these mutations occurring de novo (27). There is a wide spectrum of epilepsies associated with mutations of SCN1A including generalized epilepsy with febrile seizures plus (GEF+). SCN1A mutations are estimated to cause 7% of severe epilepsies in children under the age of 3 years. The mutation is suspected to cause dysfunction of interneurons involved in the inhibitory circuit of the brain (18). Mortality in SMEI is estimated to be 15% by age 20. SUDEP is well described in this disease (18). Treatment is difficult, and VPA, levetiracetam (LEV), zonisamide (ZNS), topiramate (TPM), and clobazam (CLB) are often used. Stiripentol, in conjunction with VPA and/or CLB, has been shown to be helpful in reducing frequency of seizures (28). A Dravet-like phenotype with a better prognosis is also seen in patients with mutations of protocadherin 19 (PCDH19) in females (29).

Early-Onset Epileptic Encephalopathies

Early infantile epileptic encephalopathy (EIEE) or Ohtahara syndrome accounts for only 0.2% of the early childhood epilepsies. It presents with drug-resistant tonic epileptic spasms, burst suppression on EEG, and has an overall poor prognosis. Seizure onset is within the first 3 months of life and asymmetric tonic seizures and focal seizures occur in approximately one-third of patients. EIEE often evolves to WS between 3 and 6 months of age and subsequently into LGS between 1 and 3 years of age (30). The cause is often symptomatic, and a high mortality rate is encountered in infancy. It generally is associated with malformations of cortical development. Another early epileptic encephalopathy is EME. It presents in the first month with vigorous myoclonias and multifocal seizures. Both EIEE and EME patients later in the course of development manifest tonic seizures and with a burst suppression pattern on EEG. Differences between the two entities include tonic seizures as the main type of seizures in EIEE, in addition to an earlier onset, and the presence of burst suppression in both the awake and sleep state (30). The similarity of the EEG patterns has led authors to question whether EIEE and EME are separate entities (22). DNA sequencing has led to identification of genes that can help define a genetic basis for some of the early-onset epileptic encephalopathies (EIEE, EME, and WS).

Atypical Benign Partial Epilepsy with Continuous Spike-and-Wave of Sleep

This syndrome presents with developmental stagnation or regression and includes features of EGE and localization- related epilepsy. Due to developmental decline and often medical intractability during the acute stage when presenting with continuous spike-and-wave in slow sleep, it has also been termed “pseudo-LGS” (10). Atypical benign partial epilepsy with continuous spike-and-waves in sleep may present with clusters of myoclonic and atonic seizures but not tonic seizures between 2 and 6 years of age. The seizures cluster lasting 2 to 4 weeks and then are separated by seizure-free periods (3). This differentiates this syndrome from LGS where tonic seizures are common and remissions do not occur. The EEG shows diffuse SSW discharges during sleep (Fig. 20.5). Central spikes are usually prominent in this syndrome similar to other forms of more benign focal epilepsy. Remission occurs before age 15, but patients may be left with a permanent cognitive impairment (3).

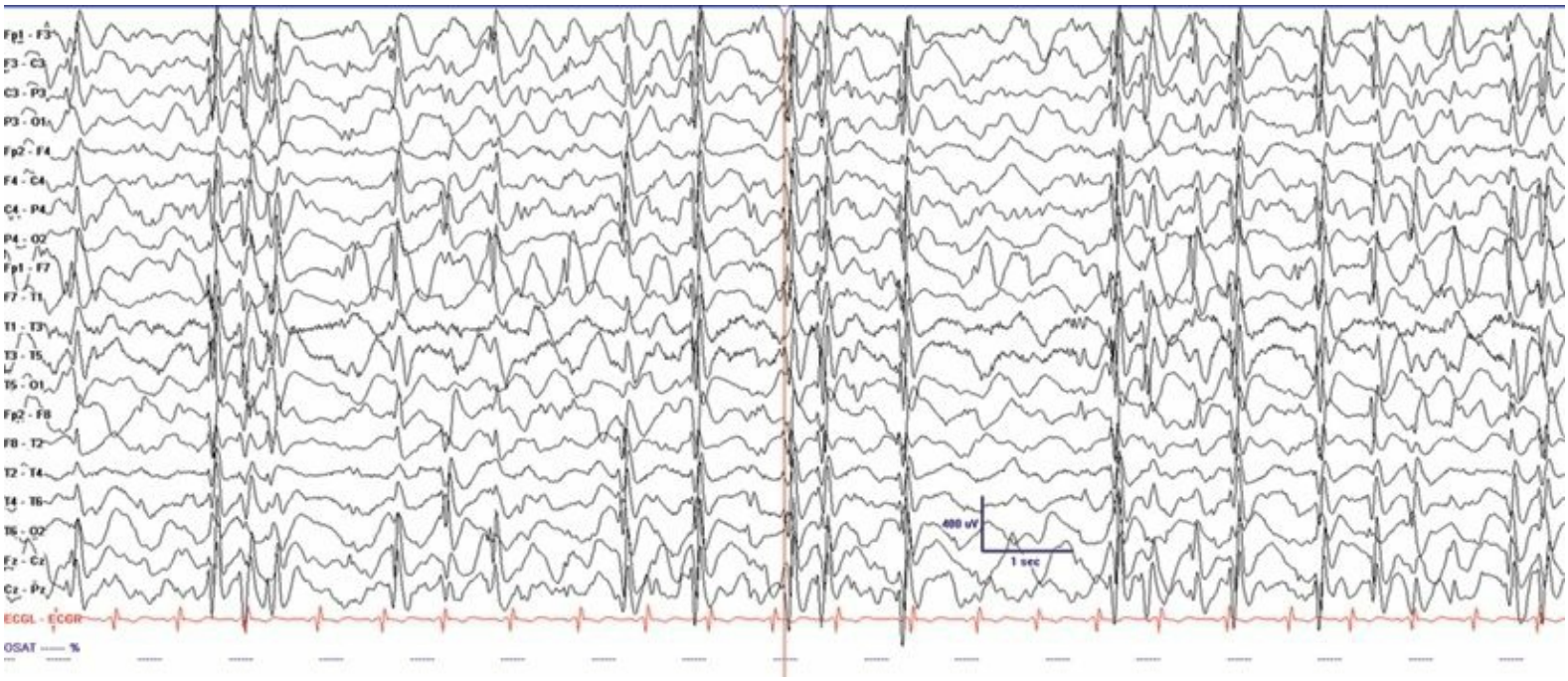

Figure 20.5. Electrical SE in slow-wave sleep in a 7-year-old child with Landau–Kleffner syndrome.

Localization-Related Epilepsy with Secondary Bilateral Synchrony

Focal epilepsy with SBS is usually present when there is a focal EEG spike that leads into a generalized discharge resembling SSW. Because of the limitations of surface scalp EEG recordings, there may be variability in the presence of a preceding focal discharge before the generalized burst in seen. Characterization of the discharges shows that they tend to have a frontal predominance at 2 to 2.5 Hz. The interval between the focal discharge and the onset of the generalized discharge is very brief but is greater than the mean callosal transmission time and may further decrease in duration as the discharge continues (5). Since the primary focus may not be discernable on routine EEG, it may mimic a generalized discharge. Foci in the frontal lobes are most often associated with this phenomenon, but this fast spread of an initially focal discharge can also be seen elsewhere along the midline of the brain (21). Furthermore, clinical seizures associated with this phenomenon may imitate absence seizures further providing a challenge to differentiate a generalized from focal seizure.

Severe Epilepsy with Multiple Independent Spike Foci

EGE with MISF has been proposed as an independent entity (31) that is clinically related to LGS due to associated MR and drug-resistant seizures. Three or more epileptic foci are present with at least one in each hemisphere. In patients with this EEG finding, more than 50% of patients had more than one type of seizure and 50% were having daily seizures (4). This is particularly true for patients presenting with spikes at least every 10 seconds (4). When EGE with MISF is present, a variety of seizures including GTC, focal, tonic, myoclonic, atypical absence, and atonic seizures may be seen. It has extensive overlap with the other epileptic encephalopathies and may frequently transition in an age-dependent fashion to other epilepsies including LGS, EIEE, and WS (31). It may also be seen in up to 20% of symptomatic LGS patients as they age, but rarely in those without a structural–metabolic basis (32). Like LGS, EGE with MISF may be seen in patients with extensive bilateral cerebral pathology and manifests as severe drug-resistant epilepsy. When the EEG features of MISF are present, a more variable prognosis with a larger potential for normal cognitive development is

present, and up to one-third of patients may be developmentally normal (4).

Genetic Syndromes Causing EGE

Angelman syndrome (AS) is characterized by severe developmental delay, absent speech, paroxysms of laughter, a puppet- like gait with ataxia, and jerky movements (also referred to as "happy puppet syndrome" in the past although some consider this term now obsolete), in addition to other distinctive clinical features. Patients with AS also have intractable epilepsy and EEG characteristics that may be confused with LGS (33). Seizure types that may be observed include atypical absence, myoclonic, clonic, and complex partial seizures. Characteristic EEG findings are diffuse, bilateral, frontally predominant, high-amplitude delta waves with a notched or triphasic-like slow waves that mimic SSW complexes. The notched appearance of the sharp waves superimpose upon the slower delta activity. The frequency may be 2 to 2.5 Hz and is maximal in the prefrontal derivations, similar to the SSW seen in LGS (Fig. 20.6). Due to the notched appearance of sharp waves, the findings have also been referred to as "ill-defined slow spike-and-wave" (33). The 10-Hz GPFA seen in LGS is not seen in AS (33).

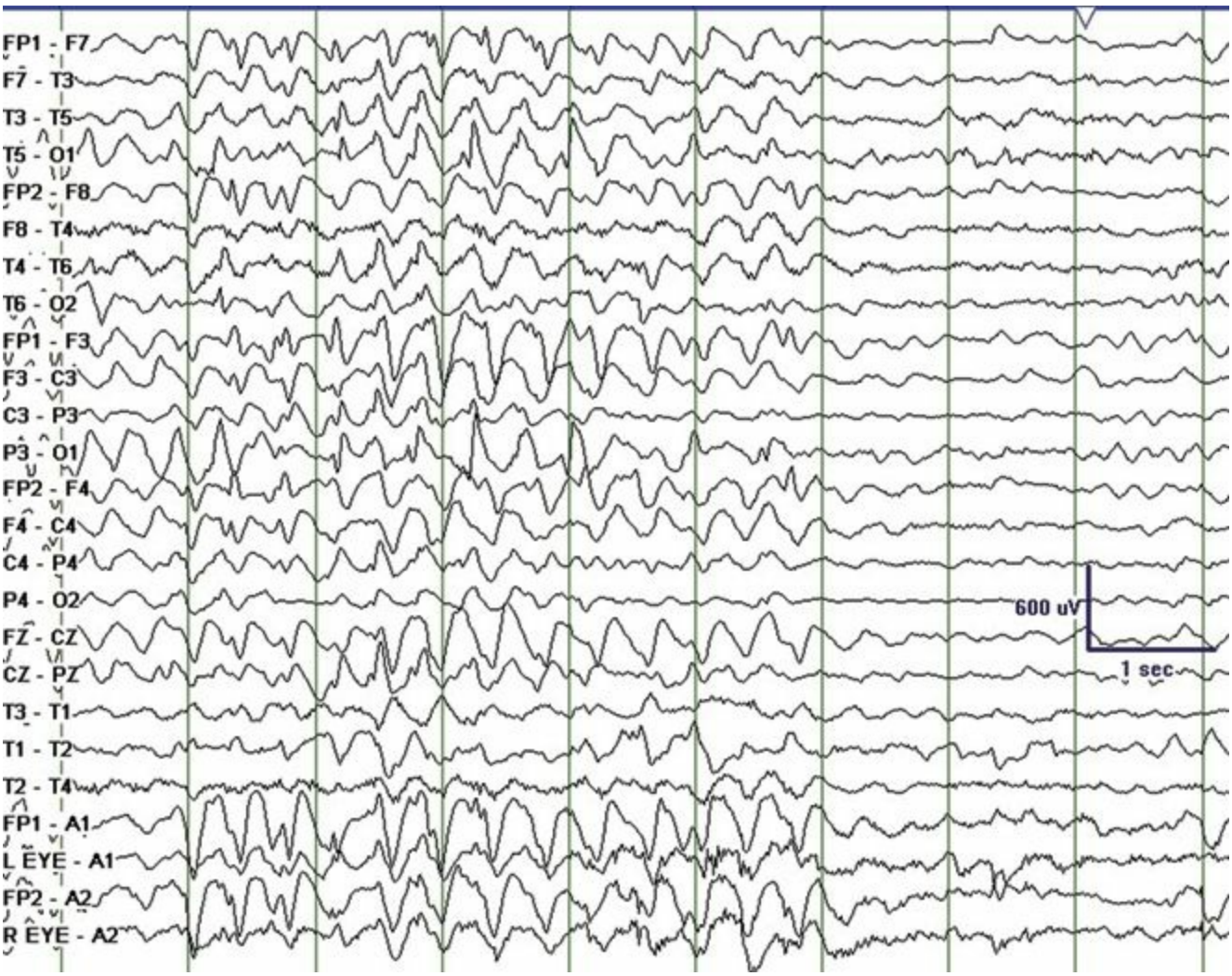

Figure 20.6. "Ill-defined" slow spike-and-wave on interictal EEG in a 4-year-old patient with Angelman syndrome.(Courtesy of Maria Gieron-Korthals, MD.)

Rett syndrome is encountered between 6 months and 3 years of age and occurs only in females. Epilepsy in typical Rett syndrome usually presents after age 3 years (34). Rett syndrome is

characterized by initial normal development followed by cognitive regression, autistic features, microcephaly, ataxia, and hand-wringing movements in addition to multiple seizure types that include absence, myoclonic, and atonic seizures mimicking LGS. The EEG may show progressively worsening slowing of the background activity with needle-like central spikes that are activated by somatosensory stimulation. A unique feature includes a 4- to 6-Hz rhythmic theta pattern maximal centrally (35). Rett Syndrome may also present with SSW (Fig. 20.7). Paroxysmal nonepileptic events are common in patients with Rett syndrome, and video EEG can be helpful to distinguish epileptic and nonepileptic events. There are atypical variants in which epilepsy often presents in infancy without initial normal development. In typical Rett syndrome, there is an associated mutation in the MECP2 gene at Xp28.2 in 93% of cases. In atypical variants, MECP2 mutations are responsible for 50% to 70%. Other causes include MECP2 duplications, CDKL5 mutations, and FOXG1 mutations (34).

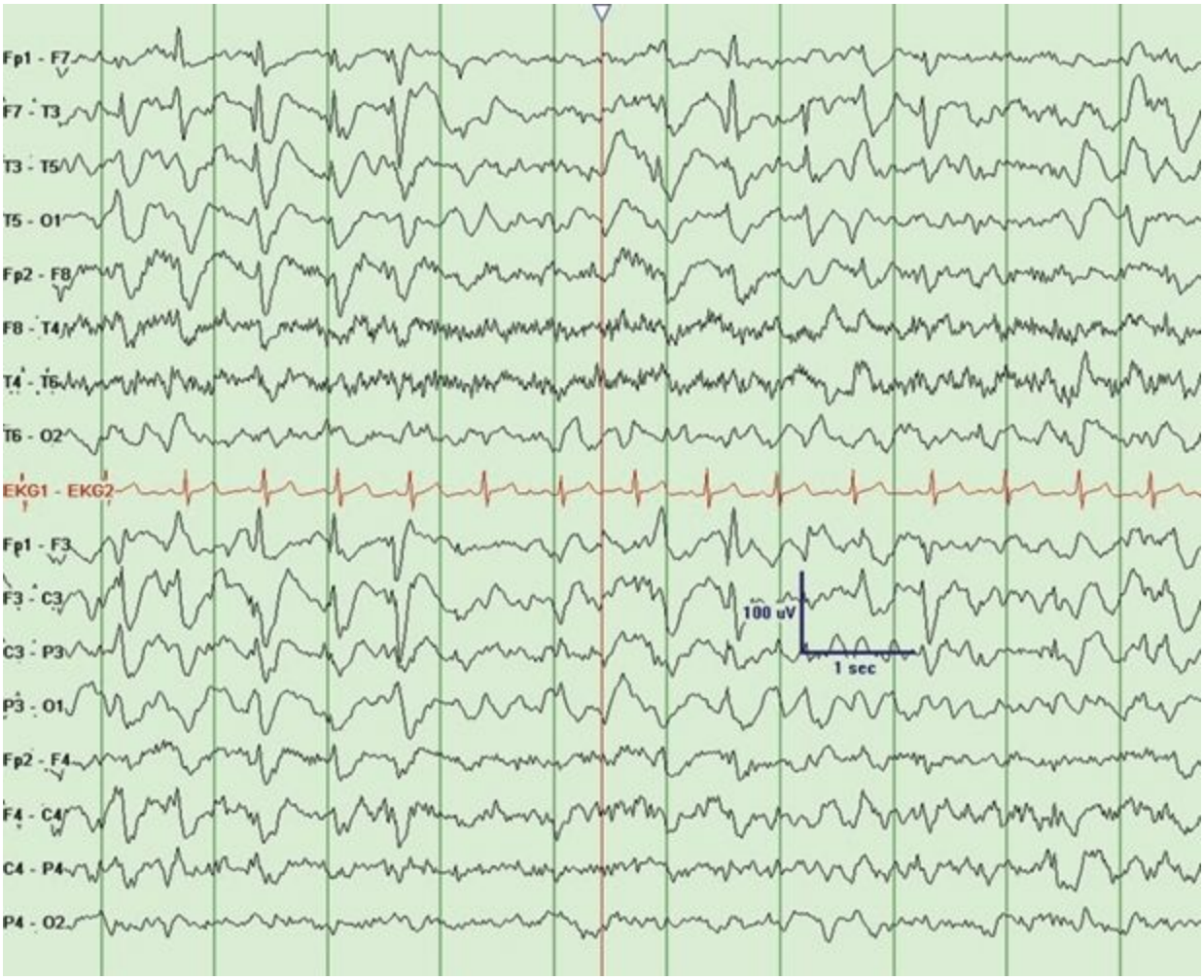

Figure 20.7. Slow spike-and-wave in an 8-year-old child with Rett syndrome.(Courtesy of Selim R. Benbadis, MD.)

There are also chromosomal abnormalities that cause LGS and EGE. Genetic testing is important in all epilepsies where the etiology is uncertain, especially when dysmorphic features are present. Ring chromosome syndromes, including ring 14 and 20, often include epileptic seizures. In addition, inverted duplicated 15 syndrome (IDIC 15), Wolf–Hirschhorn syndrome, Down syndrome (trisomy 21), and a chromosomal abnormality associated with DEL 1p36 are associated with cognitive deficits and epilepsy. Ring chromosome 20 may present with minimal dysmorphic features, normal initial development, and with developmental regression after the onset of epilepsy. The lack of clear dysmorphic features can detract from the consideration of a chromosomal alteration (36).

DIAGNOSTIC EVALUATION

High-resolution neuroimaging is essential to detect the many diverse structural lesions that may cause EGE and LGS potentially impacting the diagnosis and treatment. It is helpful to have specific neuroimaging protocols that are designed to detect neuronal migration disorders in this group that might further implicate an underlying pathophysiology for diagnosis as well as identifying a potentially surgically remediable lesion. PET scans of the brain obtained in patients with LGS (37) have yielded variable findings and may reflect the varying etiologies. However, FDG-PET brain scans have proven useful during the workup for resective epilepsy surgery when focal seizures with SBS mimicking an EGE are the disabling seizure type. EEG is the cornerstone to the diagnosis in patients with epileptic encephalopathies. Hypsarrhythmia, SSW, GPFA, MISF, and interictal disturbances of the waking background are notorious features seen in patients with EGE and LGS. Video-EEG monitoring may differentiate and classify the ictal electroclinical behavior for medical and nonmedical treatment options.

Patients with an obvious cause for EGE may need a less extensive evaluation. In patients with an early-onset epileptic encephalopathy, evaluations are directed to exclude potentially treatable causes. Metabolic etiologies should address metabolic derangements including the aminoacidopathies, urea cycle defects, organic acidopathies, mitochondrial disorders, and neurotransmitter disorders. Genetic testing should be performed when epileptic encephalopathies are encountered especially when dysmorphic features or congenital abnormalities are present. An analysis with fluorescein in situ hybridization using regional-specific probes or CGH chromosomal microarrays should be considered if routine karyotyping is unrevealing and a chromosomal syndrome is suspected since not all deletions and translocations are readily identifiable. Epilepsy gene panels that are now commercially available utilizing large panels of gene probes may assist in directing a specific diagnosis.

TREATMENT

The treatment of patients with EGE and LGS includes efforts at managing the underlying cause of the associated cognitive or behavioral dysfunction, attempting to control seizures, and providing support for the family or caretakers involved with their care. ASDs are the mainstay of therapy for patients with EGE and LGS despite the characteristic drug resistance. The challenge for the clinician is often to optimize quality of life for the patient and caretakers while weighing seizure reduction against side effects and overuse of ASDs. The multiple seizure types associated with LGS often require broad-spectrum AEDs singly or in combinations. VPA, LTG, and TPM are the most widely used agents and have proven useful in LGS (10,38,39). FBM has been shown to have a significant effect on both seizure reduction as well as demonstrating a favorable neurocognitive profile; however, its use is limited by serious side effects including the occurrence of hepatic failure and aplastic anemia (40). Two newer ASDs CLB and rufinamide were recently approved for the treatment of LGS (41,42). Many other medications have purported benefit including LEV, ZNS, and clonazepam (CLZ) though these may require more evidence to demonstrate consistent efficacy. Clobazam may be preferable to CLZ given the lower likelihood of sedation. Benzodiazepines in particular may evoke sedation and provoke atypical absence seizures and tonic SE. Oversedation from ASDs may paradoxically worsen seizure control, hamper development, and limit functional skills as much as intermittent seizures. In clinical practice, simplifying ASDs may surprisingly improve seizure control and functionality (1).

Intravenous immunoglobulin has previously been used successfully in patients with LGS (19). Corticosteroids and ACTH may be effective early in the treatment of cryptogenic LGS though steroids usually have a limited role due to the high rates of relapse following discontinuation though they may be used in pulse doses for episodes of nonconvulsive SE (10).

NONMEDICAL THERAPIES

The KD is a specialized high-fat, low-carbohydrate diet that may be useful for EGE and LGS. It may be particularly helpful in decreasing the number of atonic seizures and should be considered an option when medical therapy is ineffective (see Chapter 70). The use of the KD and a reduction in the number of AEDs may be useful not only for seizure frequency but also for functionality. There is some evidence that adults with refractory epilepsy may benefit from the diet even when less restrictions are used (such as the modified Atkins diet) (43).

Surgical options are usually palliative, with corpus callosotomy and vagus nerve stimulation (VNS) most frequently utilized (see Chapter 71). Corpus callosotomy is a surgical procedure that disconnects the anterior two-thirds to three-fourths of the cerebral hemispheres to prevent seizure propagation and eliminate the risk of falls and injury by reducing spread of generalized seizures (see Chapter 88). Sectioning the anterior portion of the corpus callosum is effective in 50% to 75% of cases while complete callosotomy may reach 80% to 90% reduction of drop attacks associated with generalized tonic and atonic seizures (44).

VNS can be helpful in LGS although it may be as effective as in focal seizures (45). In a study of LGS and Lennox-like syndrome patients at one center, 24 consecutive patients subjected to callosotomy were compared to 20 consecutive patients implanted with VNS (23). In this study, callosotomy was found to be more effective in decreasing the frequency of atonic seizures while VNS was more effective in decreasing the frequency of myoclonic seizures (23). There were similar decreases in GTC and atypical absence seizures and no effect of either intervention on tonic seizures (23). In the past, resective surgery has been thought to provide no clear benefit to patients with LGS, based on the hypothesis that tonic seizures are often due to bilateral cortical dysfunction. However, LGS has been shown to be associated with focal lesions (46) and hypothalamic hamartomas (47) prompting considerations for resective surgery. A recent series reported that 24 of 39 carefully selected patients with LGS had a successful outcome following surgical resection (48). Newer techniques may advance surgery in this difficult population in the future.

PROGNOSIS

The prognosis of the EGEs and of LGS overall is poor. Few patients lead independent lives as an adult as a result of daily seizures, cognitive, or behavioral abnormalities. Refractory seizures are the rule, and normal intellectual function rarely occurs (8). An onset before age 3 is more likely to be associated with MR with the majority of individuals requiring special classes or sheltered workshop environments. Some patients show deterioration of previously established function especially when seizures are frequent (32). Though tonic seizures may persist, the SSW pattern may resolve and rarely newer types of seizure semiologies will evolve to dominate the clinical profile such as focal seizures. Approximately half of symptomatic LGS and one-third with unknown causes lose the complete electroclinical complement of characteristics for LGS evolving into another form of EGE, epilepsy with MISF or LRE (32). Patients with an early age of onset, frequent disabling seizures,

repeated episodes of SE, and a preceding history of IS associated with WS have a relatively worse prognosis for normal cognitive development (1). Patients with LGS followed for a mean of 35.7 years showed that the main seizure type in patients as adults was tonic seizures during sleep. Other types of seizures were less common. The EEG in the awake state showed a gradual normalization with improved background activity and less epileptic abnormalities during the awake state and persistence of subtle tonic seizures and associated generalized PFA during sleep. Unfortunately, most adult patients remained moderately or severely mentally retarded despite the improvement in seizure activity and EEG abnormalities (49). More than 75% of patients with EGE and LGS survive for over 20 years, and therefore, preparation of the patient and families for adult living arrangements such as group homes and appropriate vocational opportunities needs to be an ongoing part of care of adolescent patients. In addition, the need for guardianship and future medical care should be discussed.

CONCLUSION

There are few patients as challenging to care for as those with LGS and EGE. Seizures are usually resistant to treatment, and the overall prognosis for normal cognitive development is poor. It is crucial to distinguish patients with EGE from those with LRE who may possess a surgically remediable condition or those with a more favorable prognosis such as MAE. Similarly, identifying refractory epilepsies with a genetic component such as AS, Rett syndrome, and those epilepsies associated with a SCN1A mutation are important when considering treatment and to provide genetic counseling. In EGE, the benefit of treatment with ASDs with respect to the goal of seizure reduction must be realistically balanced with the risks of overmedication. When ASDs are ineffective and injury is recurrent, alternative therapies such as KD, VNS, and corpus callosotomy should also be considered. Last but not least, support for caretakers and families of patients with EGE and LGS is crucial as refractory seizures that cause injury create considerable anguish for caretakers and family alike, and protective measures should be considered at home and also at school. While protective helmets may help prevent injury, they stigmatize patients with uncontrolled seizures and an effort should be made to seek the least intrusive methods to balance safety with psychosocial development.

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CHAPTER 21 CONTINUOUS SPIKE-AND-WAVE DURING SLEEP INCLUDING LANDAU–KLEFFNER SYNDROME

IVÁN SÁNCHEZ FERNÁNDEZ AND TOBIAS LODDENKEMPER

INTRODUCTION

Continuous spike-and-wave during sleep (CSWS) is an epileptic encephalopathy characterized by three defining features: (i) seizures, (ii) an electroencephalographic (EEG) pattern of almost continuous spiking during non–rapid eye movement (non-REM) sleep termed "electrical status epilepticus in sleep" (ESES), and (iii) global and severe regression in most or all developmental domains (1–4). The aim of this chapter is to summarize the main characteristics of CSWS, Landau–Kleffner syndrome (LKS), and related syndromes and to suggest an approach to treatment. In this review, we consider CSWS, LKS, and the "benign" pediatric focal epilepsy syndromes ("benign" epilepsy of childhood with centrotemporal spikes, Panayiotopoulos syndrome, and Gastaut-type late-onset childhood occipital epilepsy) as related entities in the context of a broader "seizure susceptibility syndrome."

CONTINUOUS SPIKE-AND-WAVE DURING SLEEP

Use of Terminology

"ESES" and "CSWS" have been used in the literature as interchangeable terms to refer to either the EEG pattern of almost continuous spiking during non-REM sleep or the electroclinical syndrome of epileptic encephalopathy with global regression. A survey on the use of CSWS/ESES terminology among neurologists and epileptologists in North America demonstrated a very heterogeneous understanding of terms, concepts, and defining features (5). In this chapter, we use the term "ESES" when referring to the EEG pattern and the term "CSWS" when referring to the epileptic encephalopathy. We have arbitrarily adopted this use of terminology for consistency with the International League Against Epilepsy classifications, but we acknowledge that the future development of a universally agreed upon terminology is critical to the advancement in the understanding of this syndrome.

Epidemiology

CSWS is an age-related epileptic encephalopathy that occurs only in children and adolescents. CSWS is more common in males (6–8). The prevalence of CSWS ranges from 0.2% to 7% depending on the study setting and inclusion criteria (7,9–12). In tertiary pediatric epilepsy centers, prevalence is

approximately 0.2% to 0.6% (10,12), and in epilepsy surgery series, it is found in 1.3% to 2% (9,11) of patients. These figures may include a considerable referral bias, and the prevalence of CSWS in less specialized settings may actually be lower. However, recognition of the ESES pattern requires an EEG with sufficient sleep, and therefore, CSWS could also be underdiagnosed. The EEG pattern of ESES may be even more frequent than previously thought as suggested by a retrospective review of 1497 overnight EEG recordings that identified 102 children (7%) with ESES, although these patients had different clinical presentations (7).

Electroclinical Presentation

Clinical Characteristics

In addition to ESES, seizures, and regression, children with an underlying structural brain lesion may have additional clinical characteristics such as focal neurologic findings associated with their brain lesion.

Overview and Clinical Stages.

Both normally developing children and children with developmental delays can develop CSWS. Clinical characteristics of CSWS usually follow sequential stages and an age-related timeline. There are three major clinical events in the evolution of CSWS: seizure onset, developmental regression, and seizure freedom. These clinical events delineate four stages of the disease: dormant, prodromal, acute, and residual (Fig. 21.1) (13).

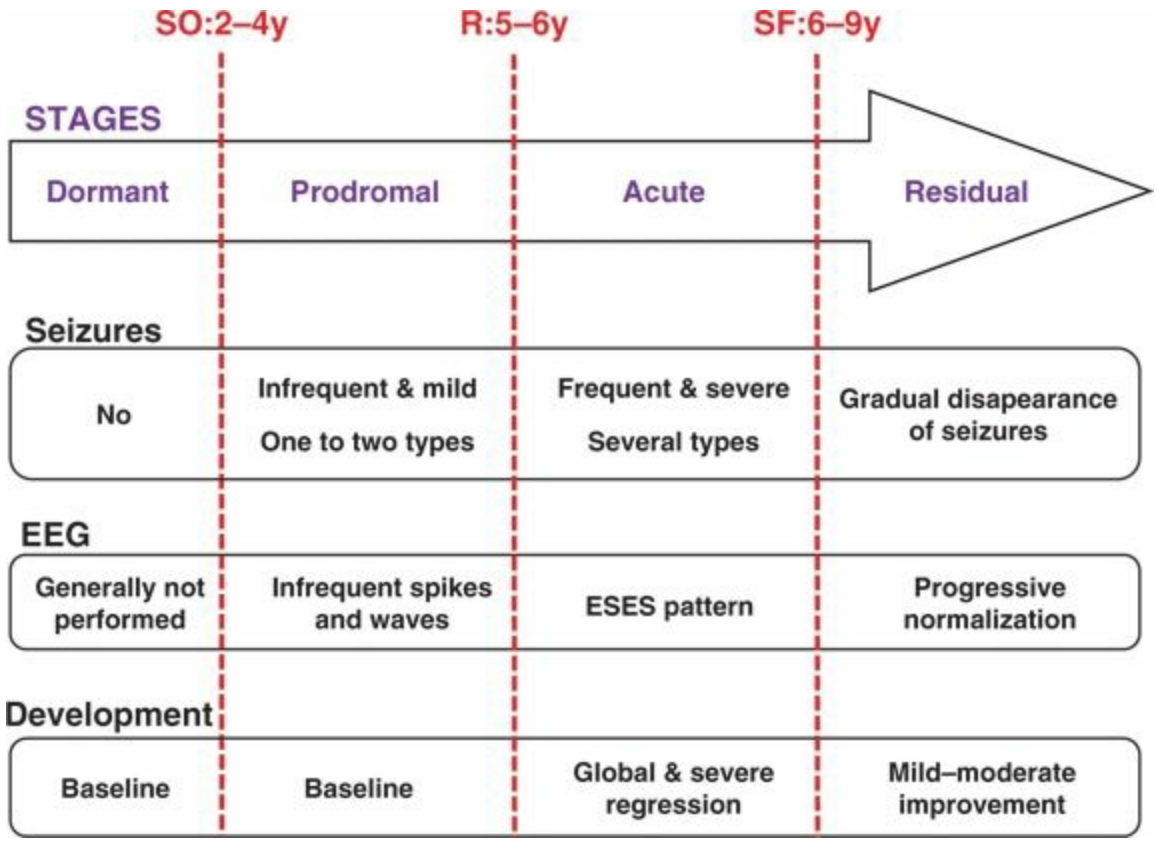

Figure 21.1. Graphic representation of continuous spike-and-wave during sleep evolution over time. The age of clinical events varies in individual patients but tends to peak at approximately the displayed ages. EEG, electroencephalogram; R, regression; SF, seizure freedom; SO, seizure onset; y, years.) (Modified from Sánchez Fernández I, Loddenkemper T, Peters JM, et al. Electrical status

epilepticus in sleep: clinical presentation and pathophysiology. Pediatr Neurol. 2012;47(6):390–410.)

Seizures are the most common presenting sign in CSWS. The age at seizure onset is typically between 2 and 4 years with a bimodal distribution. Seizure onset clusters at around 2 years of age in patients with underlying structural brain lesions and at around 4 years of age in patients with CSWS of unknown etiology (2). During the prodromal stage, seizures are infrequent and relatively easy to control, and development is not severely affected. Seizures typically occur years before the ESES pattern is recognized on EEG. Therefore, recognition of CSWS during the prodromal stage does not typically occur.

Subacute worsening involving seizures, developmental regression, and worsening of EEG abnormalities occurs at approximately 5 to 6 years of age. This subacute regression heralds the acute stage. During the acute stage, seizures become more frequent and difficult to control, patients suffer a global and severe developmental regression, and almost continuous spiking during non-REM sleep appears on the EEG. CSWS is typically diagnosed during this acute stage. After a variable number of years, seizures tend to resolve spontaneously with a peak time of seizure freedom at approximately 6 to 9 years of age (2).

In the residual stage that follows seizure freedom, there is a gradual normalization of the EEG pattern and mild-to-moderate cognitive improvement, although severe residual cognitive impairments often remain (2,4).

Seizures.

During the prodromal stage, seizures typically occur out of sleep (3). Seizures are infrequent and most patients have only one seizure type. Seizure types during this prodromal stage include focal or unilateral motor seizures, focal dyscognitive seizures, absence seizures, and generalized tonic–clonic seizures. During the acute stage, most patients manifest several seizures of several different types per day, and seizures are often difficult to control (2,4,14). Unilateral seizures become rare, atonic and bilateral motor seizures appear, and atypical absence seizures increase in frequency. Absence seizures may also evolve into absence status epilepticus (2,4). The lack of tonic seizures is a typical feature of CSWS and permits differentiation from patients with Lennox–Gastaut syndrome (2,4).

Development.

Developmental regression in CSWS involves a wide spectrum of behavioral, cognitive, language, social, and motor milestones in varying but often severe degrees. Regression includes a decrease in overall intelligence, learning disorders, memory problems, and attention span (1,4,15,16). Language regresses in the form of a subacute and progressive aphasic disorder with spontaneous fluctuations over time. Behavior becomes disruptive, and behavioral manifestations include hyperactivity, impulsivity, and even aggression. Deterioration of fine and gross motor skills as well as loss of social skills add to the severe functional deterioration.

EEG Characteristics

Evolution of the EEG Characteristics.

The EEG hallmark of CSWS is ESES, a pattern of almost continuous spike-and-wave that occupies most or all of the EEG tracing during non-REM sleep (2–4). However, the ESES pattern is typically

preceded by earlier and milder EEG abnormalities. In the few patients who underwent an EEG during the dormant stage, mild EEG abnormalities and infrequent epileptiform discharges have been detected. During the prodromal stage, epileptiform discharges are rare and occur essentially only during sleep. This pattern worsens progressively, and epileptiform discharges become also abundant during wakefulness, with additional marked potentiation of epileptiform discharges in the transition from wakefulness to sleep. A clinical presentation with almost continuous spike-and-wave during non-REM sleep is typical during the acute stage (Fig. 21.2).

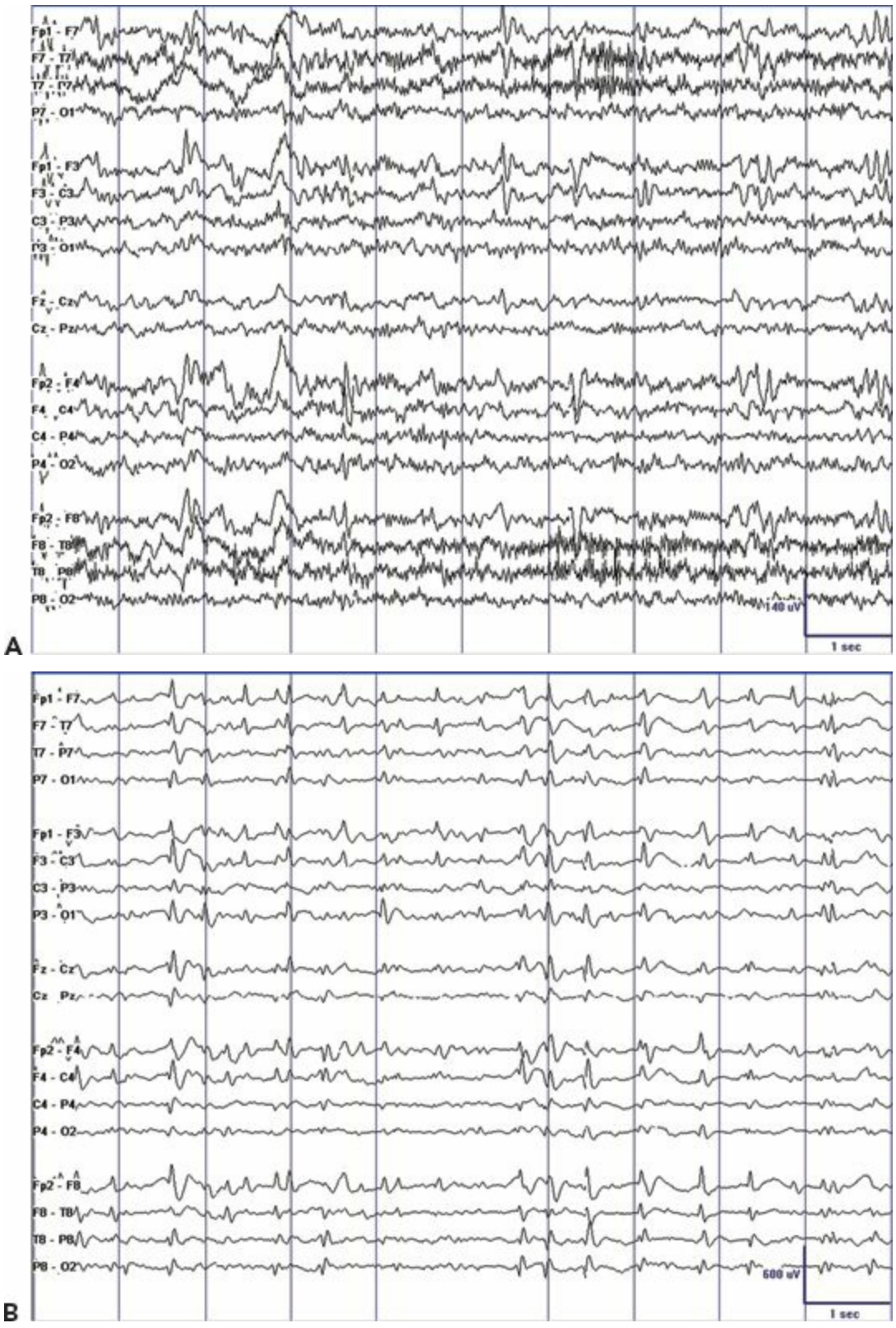

Figure 21.2. EEG tracings illustrating the dramatic sleep potentiation of epileptiform activity in the transition from wakefulness to sleep. **A:** During wakefulness, infrequent and relatively low-amplitude spikes occur in the setting of a normal background. **B:** During

non-REM sleep, almost continuous spike-and-wave replace the normal sleep graphoelements of non-REM sleep. Also note the difference in voltage.

Classical Definition of the ESES Pattern.

The EEG pattern of ESES is classically defined by the presence of generalized bilateral and symmetric 1.5- to 3-Hz spike–waves that occupy at least 85% of the EEG tracing during non-REM sleep (4,17). The originally proposed cutoff value of 85% has largely been followed in the literature. However, the definition of the International League Against Epilepsy does not include a specific threshold percentage and only requires that spike-and-wave be "continuous" and "diffuse" (18). Consequently, there have been authors who used lower cutoff values (6,7,19,20) or did not consider a specific threshold (14). Further, the percentages of epileptiform activity vary over time in the same patient (13). Therefore, a more flexible criterion such as "a dramatic activation of epileptiform discharges by sleep" may be considered in the definition of ESES in the future (1).

Quantification of Epileptiform Activity.

The classical quantification of epileptiform activity in ESES is the spike–wave index, expressed as a percentage of slow sleep occupied by spike–waves (3,4). Most authors refer to this percentage without defining the method or the EEG segment considered for calculation. Quantification of epileptiform activity in ESES can be assessed as the percentage of 1-second bins with at least one spike-and-wave in each second (13,21) or as the total number of spike–waves per unit of time (13). Another difficulty in the reproducibility of methods for quantification of epileptiform activity is that there is no consensus regarding the specific portion of the EEG tracing used for the calculation of epileptiform activity: Some authors use whole-night sleep recordings, and others use selected segments of non-REM sleep (5). Different timings of EEG assessment with respect to sleep and circadian phases as well as different methods of quantification may result in considerable variation in percentages among studies. Efforts are under way to create a better defined and reproducible method of epileptiform activity quantification.

Lateralization of Epileptiform Activity.

The first descriptions of the ESES EEG pattern required bilateral, symmetric, or diffuse EEG manifestations (17,18). However, markedly asymmetric, bilateral, or even more focal examples of ESES have been published, and series that compared the clinical features of patients with generalized versus those with more focal ESES did not find marked differences in clinical presentation (7,14,22).

Criteria for ESES.

Based on the above considerations, three essential features emerge when describing the EEG pattern of ESES: (i) a marked activation or potentiation of epileptiform discharges in the transition from wakefulness to sleep, (ii) leading to a (near)-continuous pattern of slow spike-and-wave, and (iii) that occupy a "significant proportion" of the non-REM sleep EEG tracing with a cutoff value ranging from 25% to 85% in the literature (2).

Age of ESES in the EEG.

The age at detection of the ESES pattern depends both on the definition of this pattern as well as on the frequency of routine, prolonged, or overnight EEG recordings with sufficient periods of sleep

captured in the EEG tracing. With these limitations in mind, the ESES pattern appears at approximately 4 to 8 years of age and remits at around 8 to 9 years of age, broadly coinciding in time with the acute stage of CSWS (2).

Pathophysiology and Etiology

The cause of CSWS and the pathophysiologic mechanisms that lead to age-specific clinical and EEG abnormalities are unknown. The ESES pattern is thought to be related to a disruption of the physiologic corticothalamocortical circuitry, which may also be involved in the generation of sleep spindles (23). When structural or functional insults disrupt this circuitry, physiologic sleep spindles may be replaced by generalized spike-and-wave, and, in some cases, evolve to ESES.

It is currently unknown to what extent this EEG pattern is causal in developmental regression seen in CSWS and whether effective treatment of ESES improves developmental prognosis in patients with CSWS. Early developmental structural brain lesions have been identified as one important etiology in CSWS, with genetic predisposition possibly playing an additional role.

Early Developmental Lesions

Several case reports and small case series have found an association between CSWS and malformations of cortical development (24) and with early vascular lesions that involve the thalamus and basal ganglia (25–27). Larger studies also support the hypothesis that insults to the developing brain are associated with the development of the ESES pattern on EEG and with CSWS. In a series that studied 32 patients with prenatal or perinatal thalamic lesions, a dramatic sleep potentiation of epileptiform activity occurred in 29 cases (90.6%) (28). In a series of 67 patients with ESES and neuroimaging, 33 patients (49.3%) presented with early developmental lesions, with no information on thalamic involvement (7). In another series, 18 of 44 (41%) patients with ESES had structural lesions of the brain, but no details on thalamic involvement were available (29). In a series of 14 survivors of neonatal thalamic hemorrhage secondary to cerebral sinovenous thrombosis, 7 (50%) had sleep potentiation of epileptiform activity (30). In another series of 100 patients with ESES, 48 (48%) had early developmental lesions and 14 of these demonstrated thalamic involvement (31). In this series, patients with ESES were compared with a control group of patients with epilepsy but without ESES (31). Patients with ESES had a higher frequency of early developmental lesions (48% vs. 19%, odds ratio = 3.9, 95% CI: 1.71 to 8.9) and a higher frequency of thalamic lesions (14% vs. 2%, odds ratio = 7.49, 95% CI: 0.95 to 58.76) than did patients with epilepsy without ESES (31). In all of the above-mentioned series, the lesion occurred typically perinatally or early in life, with a predominance of vascular etiology in all series (Fig. 21.3). Taken together, these studies demonstrate that vascular brain lesions affecting the thalamus early during brain development are common in patients with ESES and may potentially play a causal role. However, these series also indicate that in more than half of patients, the cause cannot be attributed to a macroscopic structural brain abnormality. In those cases, a similar functional disruption of the corticothalamocortical neuronal networks without macroscopic correlate on MRI may play a role.

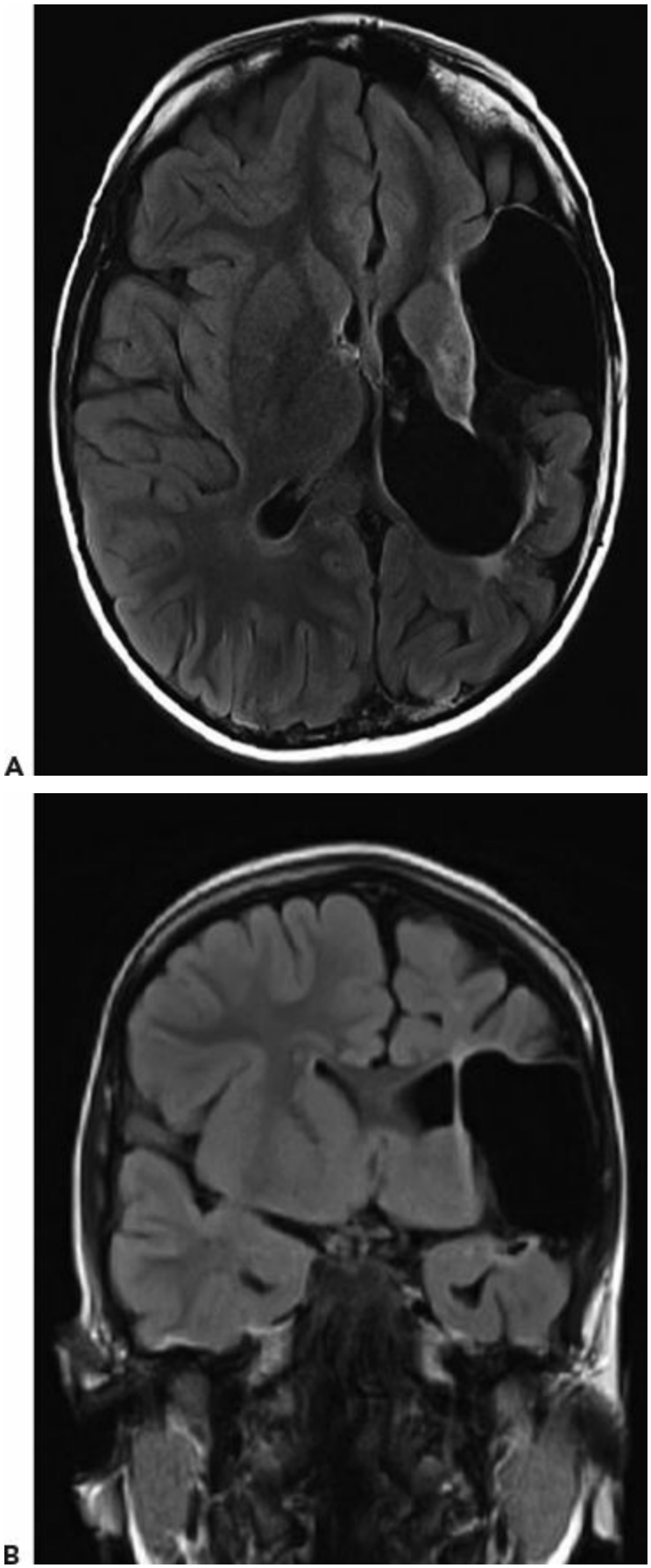

Figure 21.3. Early developmental lesion in a patient with CSWS. An extensive cystic encephalomalacia affects the left hemisphere in the distribution of the left middle cerebral artery. The patient suffered a perinatal stroke. **A:** Axial view, T2-weighted FLAIR MRI. **B:** Coronal view, T2-weighted FLAIR MRI.

Evolution into CSWS from Other Epileptic Syndromes

"Benign" pediatric focal epilepsy syndromes ("benign" epilepsy of childhood with centrotemporal spikes, Panayiotopoulos syndrome, and Gastaut-type late-onset childhood occipital epilepsy) share some common features with CSWS and LKS:

1. Age-related evolution
2. Epileptiform discharges that are of disproportionate severity in comparison with the associated clinical features
3. Sleep potentiation of epileptiform activity
4. Persistence of epileptiform discharges for years after seizure freedom.
5. Because of these similarities, it has been proposed that "benign" pediatric focal epileptic syndromes may represent a milder variation within this electroclinical spectrum.

A shared pathophysiology with different severities could potentially account for the electroclinical continuum of CSWS, LKS, and "benign" focal pediatric epilepsy syndromes. Furthermore, a genetically determined disruption of brain maturation during the first years of life may lead to hyperexcitable neuronal networks in selected cases, while other insults may also play a role. The location of the disrupted and hence hyperexcitable network then translates into different clinical features: the lower rolandic cortex that represents the face and the oropharynx could lead to the clinical features of "benign" epilepsy with centrotemporal spikes, the central autonomic neuronal networks could manifest their discharges as Panayiotopoulos syndrome, the occipital lobe that represents the cortical visual system could express their abnormalities as Gastaut-type late-onset childhood occipital epilepsy, and the involvement of the language cortex could manifest as LKS (32,33). More severe disruptions of neuronal networks as seen due to larger early developmental lesions could lead to CSWS (23,28,31). This framework of a common "seizure susceptibility syndrome" suggests that most affected children (>90%) manifest only with epileptiform discharges without clinical correlate, around 9% may present with benign pediatric focal epileptic syndromes, and in <1% of children, frequent and difficult-to-control seizures and severe neuropsychological regression may occur (33).

Frequently, patients present with electroclinical characteristics that are intermediate between the different syndromes. Further, patients with CSWS often initially present with "benign" pediatric focal epilepsy syndromes or other forms of epilepsy that later evolve into CSWS (14,34).

Genetic Predisposition

Genetic factors have been implicated in selected cases of CSWS and familial antecedents of seizures (including febrile seizures) are found in approximately 10% to 15% of the cases (4,32). A growing number of case reports and small series describe associations with copy number variations and different mutations in several chromosomes (Table 21.1). To date, the causal role of these heterogeneous genetic factors in CSWS is largely undefined. Some of these genetic variants may not be associated with CSWS per se, but with different neurologic conditions that result in the final common pathway of ESES and/or CSWS. Recently, heterozygous mutations in GRIN2A (codifying for the NMDA receptor) have been found in 27 of 359 (7.5%) patients with "seizure susceptibility syndrome" and appear to be specifically correlated with its pathophysiology (33).

Table 21.1 Genetic Factors That Have Been Described in Association with CSWS or with ESES

Study	Type of study	Association
Case reports (1995) (35)	Case series	CSWS occurred in two monozygotic twins
Praline et al. (2006) (36)	Case series	Two siblings with ESES and different clinical presentation
Verhoeven et al. (2012) (37)	Case report	One patient with CSWS and dysmorphic features carried a de novo 8q12.3q13.2 microdeletion
Coutelier et al. (2008) (38)	Case report	One patient with CSWS carried a G392R mutation in neuroserpin of probable pathogenic significance (the mutation led to a progressive neurodegenerative disease and CSWS)
Nakayama et al. (2012) (39)	Case series	Two patients with CSWS and dysmorphic features carried an unbalanced translocation between 8p and 9p
Giorda et al. (2009) (40) and Broli et al. (2011) (41)	Case series	Five patients with CSWS carried a Xp11.22-p11.23 duplication
Kevelam et al. (2012) (19)	Case series	Two patients with CSWS carried copy number variations in CHRNA7 and PCYT1B genes of probable pathogenic significance
Mefford et al. (2011) (42)	Case series	One patient with CSWS carried a copy number variant in the DOK5 gene of uncertain pathogenic significance
Reutlinger et al. (2010) (43)	Case series	Three patients with ESES and different clinical presentations and dysmorphic features carried a deletion in 16p13.2p13.13
Atkins et al. (2011) (44)	Case series	One patient with ESES (not further details on clinical presentation) carried a partial trisomy 13/21
Van Harssel et al. (2013) (45)	Case series and review of other series	Patients with PCDH19 mutations presented different features of ESES

CSWS, continuous spike-and-wave during sleep; ESES, electrical status epilepticus in sleep.
Modified from Sánchez Fernández I, Chapman KE, Peters JM, et al. Continuous spikes and waves during sleep: electroclinical presentation and suggestions for management. *Epilepsy Res Treat.* 2013;2013:583531.

Treatment

Treatment for CSWS is based on case reports and small uncontrolled series. Comparison of treatment strategies between different series is challenging because of heterogeneous patient populations, different drug doses, frequent polytherapy, variable durations of treatment, different measures of outcome, and naturally occurring fluctuations in severity over time. We will review the characteristics of different treatment options and then provide general suggestions for management.

Benzodiazepines

Benzodiazepines have demonstrated efficacy in reducing epileptiform activity. Transitory resolution of the ESES pattern was observed after the administration of clonazepam (6,8). However, the shorter half-life of diazepam may have contributed to a more frequent use in CSWS. In a series of four patients with CSWS refractory to valproate and ethosuximide, a short cycle of high-dose oral or rectal diazepam (0.5 to 1 mg/kg/day for 6 to 7 days) showed short-term efficacy in two patients (6). In a series of 15 patients with CSWS, all patients responded to high-dose rectal diazepam (46). High-dose oral diazepam (0.75 to 1 mg/kg/day for 3 weeks) was also efficacious in 3 out of 8 (37.5%) patients, but the response was temporary (14). In 29 patients with ESES and different clinical presentations, the mean epileptiform activity decreased from 77% to 41% after nocturnal administration of 1 mg/kg of oral diazepam (47). This reduction in epileptiform activity persisted for several months (48), but whether this reduction in epileptiform activity is accompanied by a sustained improvement in clinical neuropsychological features remains to be proven. Other series showed that 9 of 10 patients did not respond to valproate and benzodiazepines, and 3 patients experienced

adverse behavioral side effects (16). Adverse effects of high-dose diazepam treatment are generally considered mild and self-limited (46,47), but severe behavioral disinhibition that at times necessitates discontinuation have also been described in a few children (1,48). Small series suggest that the benzodiazepine derivative clobazam is also successful in the treatment of CSWS (30) and deserves further study.

Conventional Antiepileptic Drugs

The most commonly used antiepileptic drugs for CSWS include valproate, ethosuximide, and levetiracetam (49). In a series of 15 patients with CSWS treated with high-dose valproate alone or with valproate and ethosuximide, 10 cases (67%) responded with long-term control of their epilepsy and partial recovery of cognitive function (6). In a separate study, the combination of valproate and ethosuximide was effective in two additional patients (50). In contrast, other series did not report similar improvements after treatment with comparable medication regimens. Valproate was not effective in a series of 28 patients (14). Valproate and benzodiazepines did not lead to any improvement in seven patients and were associated with adverse behavioral reactions in three children (16). Levetiracetam was effective in several case series and also in the only placebo-controlled double-blind crossover study in patients with ESES. In this cross-over study of 18 patients, levetiracetam reduced epileptiform activity from a spike index of 56 to 37, although 3 other patients discontinued treatment because of negative cognitive side effects (51). Other drugs with some effectiveness in small series include sulthiame (14,52) and lamotrigine (24,53). Most clinicians avoid phenytoin, phenobarbital, and, especially, carbamazepine and oxcarbazepine because these drugs have been associated with exacerbation of epileptiform discharges in patients with ESES (53,54). In particular, carbamazepine and oxcarbazepine have been associated in some patients with "benign" focal epilepsies of childhood with deterioration and transformation into CSWS, although a clear causal effect has not been demonstrated (7,55).

Corticosteroids

Corticosteroids lead to improvement or even resolution of ESES in selected cases of CSWS. In a series of 44 children with ESES and clinical presentations of variable severity, prolonged corticosteroid treatment (hydrocortisone 5 mg/kg/day during the first month, 4 mg/kg/day during the second month, 3 mg/kg/day during the third month, and 2 mg/kg/day during the next 9 months followed by slow withdrawal for a total treatment duration of 21 months) led to reductions of seizures or neuropsychological improvement in 34 of 44 (77.3%) cases, with 34 patients achieving complete control of seizures and normalization of EEG abnormalities in 21 patients. The long-term remission rate was 45% (29). Inclusion of milder clinical presentations in this series may make it difficult to compare the results of this study with the results of other CSWS series that included patients with more prominent global cognitive deterioration (29). In a different study, 11 of 17 patients with CSWS responded to different corticosteroids (prednisone, methylprednisolone, or adrenocorticotropic hormone) (14). The intramuscular administration of 0.001 to 0.04 mg/kg/day of adrenocorticotropic hormone was reported to be effective in one of four patients (6). Although generally regarded effective, the side effects of corticosteroids frequently limit their long-term use.

Immune Modulation Therapy

Very limited data are available on intravenous immunoglobulins, but some series report a response to treatment in a few cases. Variable outcome results, high cost, and risks of complications associated with immunoglobulins may have prevented widespread use in the treatment of CSWS to date (14,56).

Surgery

Selected patients with CSWS may benefit from surgical treatment. In CSWS, the ESES pattern and the seizures tend to spontaneously resolve with time, and therefore, ESES as a sole indication for epilepsy surgery is debated (24). However, in patients with severe developmental regression, a well-defined structural lesion and ongoing intractable seizures, epilepsy surgery may be a very effective treatment for seizures and epileptiform activity, with some improvement in developmental regression (11). Potential surgical interventions include multiple subpial transections (MSTs), focal resective surgery of the epileptogenic zone, hemispherectomy, and corpus callosotomy. MST consists of multiple small superficial parallel cuts in the cortex that theoretically sever only the local corticocortical connections in an attempt to disrupt local horizontal epileptic circuitry without altering the vertical neural columns and their function. MSTs led to recovery of age- appropriate speech in 7 of 14 patients with ESES and acquired aphasia (57) whereas other series report less prominent language improvement (58,59). Two patients with CSWS secondary to neonatal stroke markedly improved after hemispherectomy (60). In another study, two patients with CSWS secondary to early developmental lesions in the thalamus became seizure free after a hemispherectomy in one and after an extensive corticectomy around a large porencephalic cyst in the other (28). Additionally, 13 patients with CSWS secondary to different early developmental lesions underwent various surgical procedures including anterior callosotomy (6 patients), complete callosotomy (3 patients), hemispherectomy (2 patients), and lobar resection (2 patients). Subjects achieved an overall improvement in seizure control and EEG features in most cases (15). Improvements after surgery included resolution of ESES, seizure freedom or improved seizure control, and improvements in cognitive function, with varying results among patients. Data on the long-term neurocognitive outcome of surgically managed CSWS patients are not available.

Suggestions for Management

The current literature does not permit the development of an evidence-based management approach to CSWS (Fig. 21.4). In practice, most patients with CSWS were already on a standard antiepileptic drug (valproate, levetiracetam, etc.) after seizure onset and prior to the diagnosis of CSWS. Once patients enter the acute phase, standard antiepileptic drugs, corticosteroids, and benzodiazepines may be considered as first choices depending on the particular patient and the familiarity of the physician with these drugs. Several groups have reported the usefulness of benzodiazepines, and one protocol includes application of nocturnal diazepam 1 mg/kg up to 40 mg during the first night while monitoring vital signs in the hospital followed by 0.5 mg/kg (maximum: 20 mg) upon discharge and every following night for 1 to 3 months (47,48). For chronic CSWS management, and particularly for seizure control, standard antiepileptic drugs such as valproate, levetiracetam, and ethosuximide are frequently used. Polytherapy is often needed. Medication selection should be guided by presenting seizure types. Other options include treatment with corticosteroids or adrenocorticotropic hormone. Epilepsy surgery should be considered, especially in patients with an early unilateral developmental lesion, even when the epileptiform activity on EEG is generalized. For the acute control of very active nighttime epileptiform discharges, high-dose benzodiazepines have been used over a period of

a few months. While adequate control of seizures improves the quality of life of the patients and should be pursued, it is unknown how aggressively interictal epileptiform activity in relationship with neurocognitive regression should be treated. Only prospective studies that correlate the response to treatment of interictal epileptiform activity with the improvement in neurocognitive function will be able to answer that relevant question.

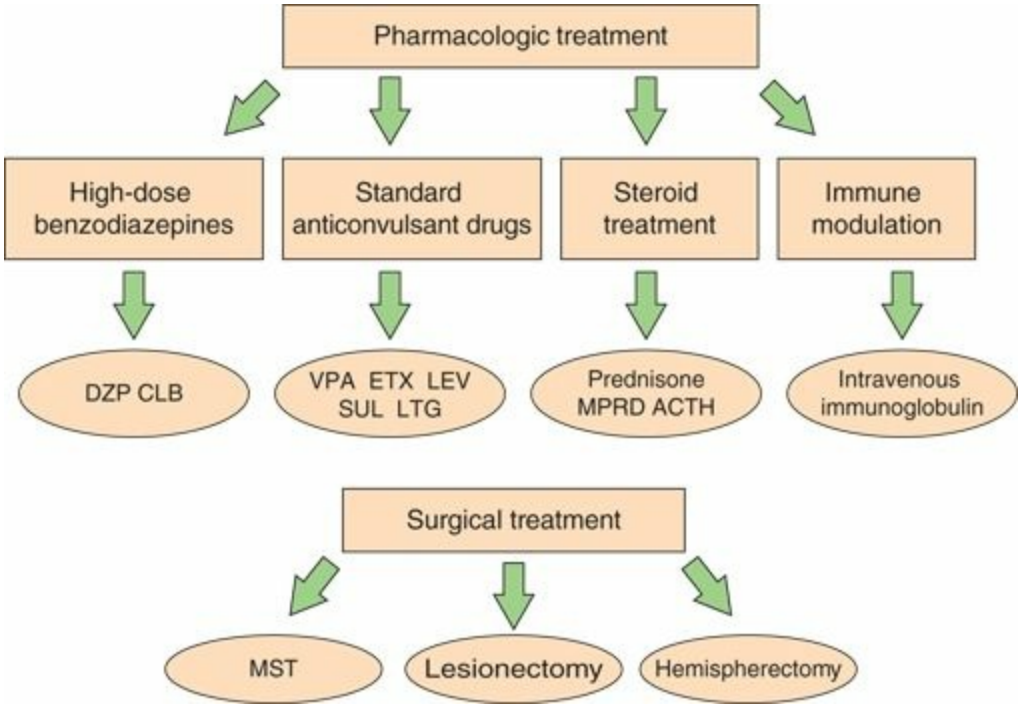

Figure 21.4. Options for the management of patients with CSWS. Options for chronic management are high-dose benzodiazepines, standard antiepileptic drugs in different combinations, and corticosteroids and immune-modulating agents. These options are considered first choice by different authors, although standard antiepileptic drugs are generally started prior to diagnosis of CSWS. Epilepsy surgery is reserved for a few selected refractory cases. ACTH, adrenocorticotropic hormone. (From Sánchez Fernández I, Chapman KE, Peters JM, et al. Continuous spikes and waves during sleep: electroclinical presentation and suggestions for management. Epilepsy Res Treat. 2013;2013:583531.)

Outcome

Important outcome variables in CSWS may be summarized in terms of clinical seizures, EEG, and neurocognition:

1 . Seizures. Clinical seizures usually resolve with age, and this age-related pattern is universal and independent of etiology, as illustrated by remissions in patients with a static structural brain lesion (24,28) and even in patients with a progressive neurodegenerative disorder (20).
2. EEG. ESES progressively resolves, and the physiologic sleep patterns frequently reappear around the same age as seizure freedom, although in some patients there is a prolonged period during which EEG abnormalities persist and can be very active even after seizure freedom (61).
3 . Development and cognitive function. A mild to moderate improvement in cognitive function is expected at the beginning of the residual stage. However, a functionally normal or near-normal outcome is very rare and at least 50% of patients remain impaired (1,4).

It is not currently known whether an effective treatment of CSWS modifies outcome (2). At a minimum, most clinicians elect to treat clinical seizures. Many will also attempt to target EEG features based on expert opinion and some studies in the literature that suggest improved cognition at times of improvement or resolution of EEG features (11,62). Despite these practices, it is important to note that to date, there is no clear evidence for or against treatment of interictal spiking patterns. It is a well-documented fact that interictal epileptiform activity disrupts cognitive processes in the short term (63,64). However, the effect of chronic epileptiform activity on cognition and the efficacy of treating epileptiform discharges for achieving better cognitive outcome remain to be clarified.

LANDAU–KLEFFNER SYNDROME

William Landau and Frank Kleffner originally described the syndrome of acquired epileptic aphasia in a series of five children in 1957 (65).

Epidemiology

LKS is an age-related epileptic encephalopathy that only occurs in children and adolescents. Some consider this clinical presentation a milder manifestation of CSWS with regression mainly in the language and at times behavioral domains. There is overlap with CSWS and distinctions are sometimes difficult to delineate. Therefore, there are limited epidemiologic data. LKS is a rare condition as illustrated by the fact that in a study of 440 epileptic children studied in an outpatient setting, only 1 (0.2%) had LKS (10). The peak age of onset is 3 to 6 years with boys affected twice as frequently as girls (2).

Electroclinical Presentation

The main characteristics of LKS can be summarized in terms of seizures, development, and EEG features.

Seizures

Seizures are infrequent and easy to treat. Approximately 20% to 30% of patients with LKS may not have any clinical seizures. The most common seizure type consists of focal motor seizures, and these occur mostly out of sleep (1,66).

Development

The most striking manifestation of LKS is the loss of language skills in children with previously normal to mildly delayed speech development. This regression typically manifests first as loss of receptive language in the form of a verbal auditory agnosia, frequently mimicking deafness. This is followed by loss of expressive language (67). The aphasia presents with subacute onset and progressive course with spontaneous fluctuations over time. Behavioral and cognitive deterioration can accompany the language regression with various degrees of severity.

EEG Features

Interictal epileptiform discharges tend to be maximal in the temporoparietal–occipital lobes. There is marked spread and potentiation of epileptiform activity during non-REM sleep. While epileptiform activity in CSWS is usually generalized with a bifrontal maximum, epileptiform discharges in LKS are typically unilateral or clearly lateralized (67).

Etiology

Structural lesions are very infrequent in LKS, and neuroimaging is not usually recommended (2). Copy number variations have been described in association with LKS, although their pathogenic significance is unclear (42).

Treatment

Seizures are easily controlled with antiepileptic drugs such as valproate, ethosuximide, clonazepam, or clobazam. Carbamazepine and oxcarbazepine are generally avoided because they have been associated with exacerbation of epileptiform discharges (54,68). Corticosteroids have been associated with improvement of the disease (29,69,70). Additionally, intravenous immunoglobulins have been successfully used in selected cases (71,72). The focus of epileptic discharges usually involves eloquent language cortex, and therefore, resective surgery is usually not an option. However, MSTs have been tried, with variable results (58,59,73).

Outcome

Seizures, when present, remit spontaneously, and the EEG pattern normalizes over time. Language improves to some degree after a variable number of years, but less than one-quarter of patients regain baseline language skills (74).

OUTLOOK

The development and validation of a common terminology and conceptualization of CSWS is critical to advance the field. A better understanding of the etiology and pathophysiology in cases with non-macroscopic lesions on MRI may unveil new treatment approaches. Finally, a most relevant question remains in CSWS: does a successful treatment of ESES improve developmental and cognitive features? The answer to this question may improve the management and eventually the outcome of patients with CSWS and many other epileptic patients with interictal and apparently subclinical discharges.

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CHAPTER 22 EPILEPSY WITH REFLEX SEIZURES

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DEFINITION AND CLASSIFICATION

Although seizures occur usually unexpectedly, at least 50% of patients recognize a general or more specific precipitating factor (1). Emotional stress and physical stress are by far the most recognized factors. Physical stress includes fever, sleep deprivation, hyperventilation, drug or alcohol withdrawal, menstruation, and physical exercise. Mental or emotional stress is less clearly demonstrable and can be due to either happy occasions (birthday, Santa Claus, etc.) or more negative experiences (problems at work, and major life events like death and divorce) (2).

Seizures provoked by the above-mentioned general factors alone are, however, not considered to be reflex seizures. The provoking factor needs to be specific. Usually, the triggers are brief and sudden like flashing lights, sudden noises, and tapping, provoking especially myoclonic jerks, although they can be more complex and gradual like reading, thinking, eating, bathing, drawing, gaming, and listening to music, with less sudden seizure expressions (temporal lobe type of seizures).

In most hospital-based studies, about 6% of epilepsy patients recognize specific factors as their only or predominant precipitant of seizures. In a survey of seizure-provoking factors in a community-based cohort of adolescent (>12 years) and adult epilepsy patients, a total of 47% reported at least one factor that could provoke their seizures. Of these subjects, seizures provoked by specific factors were mentioned to be evoked predominantly by flickering lights (sunlight, stroboscope light, TV, or video games) and sounds in 17% and 5%, respectively (3); thus, more than 8% of epilepsy patients mention reflex seizures.

Reflex seizures may be classified as occurring in generalized or in focal epilepsy syndromes (4). Reflex seizures that occur in patients who also have spontaneous seizures are generally listed as seizure types, for example, photosensitive seizures in patients with juvenile myoclonic epilepsy (JME). Reflex seizures can also be classified according to the seizure trigger. If the trigger is exceptionally specific or exotic, the epilepsy is even named after the provocative factor like mahjong epilepsy, telephone epilepsy, vacuum cleaner epilepsy, and tooth-brushing epilepsy (5–8). However, it is questionable whether it is useful to make such detailed subdivisions (9).

The use of the term reflex has been and still is controversial. Marshall Hall (10) first applied it to epilepsy in 1850; he differentiated seizures precipitated by peripheral stimuli (eccentric or reflex) from central causes. About a century later, in the 1960s, Servit, a neo-Pavlovian, stated that the genesis of epilepsy can be considered as a reflex mechanism (11). Arguing that no reflex arc is involved in reflex epilepsy, others proposed terms such as sensory precipitation (12,13) or stimulus-sensitive epilepsies with simple and complex forms (14).

The International League Against Epilepsy (ILAE) (15) describes in 1989 reflex epilepsies as "epilepsies characterized by specific modes of seizure precipitation." The classification proposal of

Engel from 2001 (16) redefines reflex epilepsy syndromes as "syndromes in which all epileptic seizures are precipitated by sensory stimuli." Apart from the fact that reflex epilepsies are characterized by seizures, specific syndromes among the reflex epilepsies have also been recognized: idiopathic photosensitive occipital lobe epilepsy (IPOE), other visual-sensitive epilepsies, primary reading epilepsy, language- induced epilepsy, seizures induced by thinking, eating epilepsy, and musicogenic epilepsy (16). At the same time, the ILAE task force published a glossary of descriptive terminology for ictal semiology (17). In this glossary, a provocative factor is described as "a transient and sporadic endogenous or exogenous element capable of augmenting seizure incidence in persons with chronic epilepsy and evoking seizures in susceptible individuals without epilepsy." This article therefore distinguishes between reactive seizures (due to illness, sleep loss, or emotional stress) and reflex seizures (objectively and consistently demonstrated to be evoked by a specific afferent stimulus or by an activity of the patient). Afferent stimuli can be elementary (i.e., unstructured [light flashes, startle, a monotone]) or elaborate (i.e., structured, [a symphony]). Activity may be elementary (e.g., motor [a movement]), elaborate (e.g., cognitive function [reading, chess playing]), or both (reading aloud).

The more recent ILAE report on classification and terminology (18) has mentioned only reflex epilepsies as an electroclinical syndrome or other epilepsies with a less specific age relationship; the fact that reflex seizures were not included at all has been criticized by Panayiotopoulos (19). As an advocate of the multifactorial Lennox theory of the epileptic threshold, Shorvon introduces in his etiologic classification (2011) a new, broader, category of epilepsy, namely "provoked epilepsy" that includes the reflex epilepsies (20). This provoked epilepsy is defined as an epilepsy in which a specific systemic or environmental factor is the predominant cause of the seizures and in which there are no gross causative neuroanatomic or neuropathologic changes. Thus, until today, the definition and classification of reflex seizures and reflex epilepsies remain a point of discussion and debate: is there really a dichotomy between reflex and spontaneous seizures and—if so—to what extent? (9,20,21).

Most epileptologists refer to reflex epilepsy when a certain stimulus regularly elicits a response in the form of abnormal, paroxysmal, electroencephalographic (EEG) activity associated with or without a clinical seizure. Although some investigators restrict the term reflex epilepsy to cases in which a certain stimulus always induces seizures (22), it may include cases in which typical spontaneous seizures occur without the trigger and in which triggers do not always induce a seizure (23).

In a recent inventory of definitions used in the literature between 2002 and 2012, it was demonstrated that few definitions were identical, and definitions of a particular type varied considerably with a wide range of components being referred to as part of reflex seizures (21). Consensus on terminology thus does not exist at this moment. Reflex seizures may not differ in semiology from those encountered in other forms of epilepsy, but understanding of the seizure trigger is important in the management of the patient and helps study mechanisms of epileptogenicity. Interesting in that respect is the documentation of a 57-year-old man with temporal lobe epilepsy, who had 40% of his seizures provoked by tooth brushing, looking at the toothbrush, or even thinking about the brush (24). In this case, a somewhat wider epileptogenic network seems to be involved than usually based on the broader range of triggers.

The term "epilepsy with reflex seizures," or perhaps provoked epilepsy as suggested by Shorvon (20), to underline the unmistakable interaction between the various general and specific factors, would better reflect clinical reality and more accurately describe cases with both reflex and

spontaneous attacks.

Reflex seizures have long fascinated epileptologists. Photosensitivity or better visual sensitivity, thus comprising all types of visual stimuli like TV screens, video games, and striped patterns, is mostly recognized and studied, while making up for 90% of all reflex epilepsy patients (25). After introducing the rather simple provocation method of intermittent photic stimulation (IPS) during an EEG in the early fifties, visual sensitivity has over the years been studied intensively both clinically and electroencephalographically. Apart from epileptic photosensitivity to flickering light and other visual stimuli, other cases of reflex epilepsy such as thinking- and reading-evoked seizures are rare and permit glimpses into the organization of cognitive function.

The identification of a patient with reflex epilepsy depends on the physician's awareness and on the observations of the patient and witnesses. The epileptogenic trigger must occur often enough in everyday life so that the patient suspects its relation to the resulting seizures. If the trigger is ubiquitous, however, the seizures appear to occur by chance or with no obvious antecedent. If longer stimulation is necessary like in reading and musicogenic epilepsy, detecting a relationship between the stimulus and seizure is much more difficult. Many different triggers have been recognized and studied (5–8).

This chapter reviews the neurophysiology of reflex epilepsy from available human and animal studies. We also discuss clinical features of reflex seizures classified by the triggering stimulus.

BASIC MECHANISMS OF REFLEX EPILEPSY

There are two types of reflex epilepsy animal models. In the first, irritative cortical lesions are created, and their activation by specific stimuli is studied. The second model type involves naturally occurring reflex epilepsies or seizures induced by specific sensory stimulation in genetically predisposed animals.

The first approach has been used since 1929, when Clementi (26) induced convulsions with IPS after applying strychnine to the visual cortex. This technique also demonstrated that strychninization of auditory (27), gustatory (28), and olfactory cortex (29) produced focal irritative lesions that may produce seizures with the appropriate afferent stimulus. EEG studies showed that the clinical seizures (chewing movements), which were induced by photic stimulation in rabbits with strychnine lesions of the visual cortex, resulted from rapid transmission of the epileptic discharge from the visual cortex to masticatory areas (30). The EEG spread of paroxysmal discharges from the visual cortex may also occur in fronto-rolandic areas during seizures (31). The ictal EEG spread was thought to represent corticocortical conduction (17,31), although later work with pentylenetetrazol also implicated thalamic relays (32) and demonstrated spread of the visual evoked potential to the brain stem reticular formation (33). Hunter and Ingvar (34) identified a subcortical pathway involving the thalamus and reticular system and an independent corticocortical system for spread of visual-evoked responses to the frontal lobe. In cats and monkeys, the fronto-rolandic region was also shown to receive spreading-evoked paroxysmal activity from auditory and other stimuli (35,36).

The second approach, the study of naturally occurring or induced reflex seizures in genetically susceptible animals, has been pursued in domestic fowl and chickens with photosensitivity (37,38), rodents susceptible to sound-induced convulsions (39), the E1 mouse sensitive to vestibular stimulation (40), and the Mongolian gerbil sensitive to a variety of stimuli (41,42).

The species in which the reflex seizures and EEG findings are quite similar to those in humans is the baboon Papio hamadryas papio, better known as Papio papio from Senegal (43), except that the

light-induced epileptic discharges in baboons occur in the fronto-rolandic area rather than in the occipital lobe (44). Additionally, there is a statistically significant association of spontaneous epileptiform discharges and seizures with photosensitivity (45,46). Like in humans, photosensitivity is maximal when the animals had their eyes closed during IPS or with chemically induced pupillary dilation (47). When the light source is closer (8 cm vs. 25 cm) and its surface area is larger (128 cm^2 vs. 8 cm^2), IPS is more likely to trigger epileptic discharges. However, unlike in humans, colors of shorter wavelengths, such as blue-green and dark green, are more effective in producing EEG afterdischarges than are colors of longer wavelengths, such as red.

EEG, visual evoked potentials, intracerebral recordings, lesions, and pharmacologic studies show that visual afferents are necessary to trigger fronto-rolandic light-induced epileptic discharges. The occipital lobe does not generate this abnormal activity but sends corticocortical visual afferents to hyperexcitable frontal cortex, which is responsible for the epileptiform activity (48). The interhemispheric synchronization of the light-induced paroxysmal EEG activity and seizures depends mainly on the corpus callosum and not on the brain stem. Brain stem reticular activation depends initially on frontal cortical mechanisms until a seizure is about to begin, at which point the cortex can no longer control reticular activation. The genetically determined hyperexcitability may be related to cortical biochemical abnormalities, involving regulation of extracellular calcium concentration (49,50) or an imbalance between excitatory and inhibitory neurotransmitter amino acids (51) similar to those described in feline generalized penicillin epilepsy and in human epilepsy (52).

In recent studies in members of the baboon subspecies Papio hamadryas anubis or Papio hamadryas cynocephalus or hybrids housed in the Southwest National Primate Research Center at the SFBR in San Antonio, photosensitive baboons demonstrated increased cerebral blood flow using functional PET in the right orbitofrontal and anterior cingulate region compared to nonepileptic nonhuman primate controls. There were significant activations in the parietal and motor cortices, but no activation of the occipital lobes. In the control animals, there was an expected activation of the striate and peristriate cortices and posterior cingulate gyrus. While the activations of the motor cortices were expected due to activation of discrete myoclonic seizures, the role of the frontal and parietal lobe activations in the photosensitive baboons was unclear. The absence of occipital activation and deactivation of the posterior cingulate gyrus suggested inhibition in these areas (53).

In human epileptic photosensitivity, generalized epileptiform activity and clinical seizures can be activated by the occipital trigger. Studies in photosensitive patients who are also sensitive to black and white striped patterns suggest that generalized seizures and EEG paroxysmal activity can occur in these subjects if normal excitation of the visual cortex involves a certain “critical mass” of cortical area with synchronization and subsequent spreading of excitation (54–57). Wilkins et al. (58) suggested that a similar mechanism involving recruitment of a critical mass of parietal rather than visual cortex is responsible for generalized seizures induced by thinking or by spatial tasks. Studies of reading epilepsy also suggest that increased task difficulty, complexity, or duration increase the chance of EEG or clinical activation (59,60).

Wieser (61) proposed a neurophysiologic model for critical mass, referring to the group 1 and group 2 epileptic neurons of the chronic experimental epileptic focus described by Wyler and Ward (62). Group 1 neurons produce abundant, spontaneous, high-frequency bursts of action potentials. Group 2 neurons have a variable interspike interval, and their spontaneous epileptic activity is less marked. Moreover, these properties are influenced by external stimuli that can promote or inhibit the incorporation of group 2 neurons into the effective quantity of epileptic tissue and thus trigger or inhibit a seizure. The stimuli effective in eliciting reflex seizures would act on this population of

neurons, recruiting them into the highly epileptic group 1 neuron pool to form the critical mass needed to produce epileptogenic EEG activity or clinical seizures. This mechanism can also explain conditioning (63) and deconditioning (64) of reflex epileptic responses. A further generalizing system must also be postulated to account for the seizures observed with photic or cognitive stimulation, analogous to the corticocortical pathways linking occipital cortex with fronto-rolandic cortex in Papio papio. A role for reticulothalamic structures has been suggested but seems unnecessary, at least in certain animal models in which corticocortical spread of evoked epileptic activity persists after mesencephalic and diencephalic ablation (34).

Patients and parents may report that emotion plays a fundamental role in seizure induction, and such an observation has been also described recently in a 9-year-old girl by Gilboa (65).

Gras et al. (66) emphasized the influence of emotional content in activating EEG spikes in a patient with reading epilepsy. An emotional component was also obvious in several cases of musicogenic and eating epilepsy. Similarly, Scollo-Lavizzari and Hess (67) showed that the mere sight, memory, or anticipation of releasing stimuli could elicit the same epileptiform EEG abnormalities and seizures as did the stimulus itself.

Fenwick (68) described psychogenic seizures as epileptic seizures generated by an action of mind, self-induced attacks (e.g., by thinking sad thoughts), and those unintentionally triggered by specific mental activity such as thinking. This use of the term psychogenic seizures, common in European epileptology, does not refer to nonepileptic events. Fenwick related seizure induction and inhibition in some individuals with or without typical reflex seizures to the neuronal excitation and inhibition accompanying mental activity. He also referred to the alumina cream model, with recruitment of group 2 neurons and evoked change in neuronal activity surrounding the seizure focus as factors in seizure occurrence, spread, and inhibition.

Wolf (69) believed that two pathophysiologic theories have arisen in the discussion of reflex epilepsies. For primary reading epilepsy, he observed that seizure evocation would depend on involvement of the multiple processes used for reading, an activity involving both hemispheres, with a functional rather than a topographic anatomy. “Maximal interactive neuronal performance is at least a facilitating factor,” (69) he wrote and suggested that the functional complexity of the epileptogenic tasks leads to seizure precipitation. He contrasted this with the suggestion described previously that the latency, dependence on task duration and complexity, and influence of nonspecific factors such as attention and arousal often observed in these seizures depend on the ad hoc recruitment of a critical mass of epileptogenic tissue to produce a clinical seizure or paroxysmal EEG activity in response to the different characteristics of an effective triggering stimulus. In seizures induced by reading, thinking, IPS, and striped patterns, the relatively localized trigger induces generalized or bilateral EEG abnormalities and seizures. The recruitment that produces these seizures, however, need not be confined to physically contiguous brain tissue or fixed neuronal links. Instead, it may depend on activity of a function-related network of both established and plastic links between brain regions, modified by the effects of factors such as arousal. These two approaches share much common ground.

Disorders of cortical development based on genetic predisposition may be present in some patients with reflex seizures: musicogenic reflex epilepsy was shown in a patient with Dravet syndrome (70).

Reportedly normal imaging may be misleading; subtle changes or dysplastic lesions may be missed without special magnetic resonance imaging (MRI) techniques or may only be found in a surgical pathology specimen (71–75).

Of special interest is also the case history of a 19-year-old male with thinking-induced seizures

that occurred exclusively during acute bacterial meningitis (76). SPECT and MRI studies in patients with eating epilepsy have shown lesions near the perisylvian region (77). Future fMRI and PET studies should elucidate the preferred networks of the reflex stimulus, although many individual (genetic) differences may exist.

SEIZURES INDUCED BY VISUAL TRIGGERS

Epilepsy with reflex seizures evoked by a variety of visual stimuli in daily life (78,79) is clearly the most common reflex epilepsy. Even epidemics have occurred: after a specific Pokemon cartoon TV transmission in Japan, studies have shown that about 1% of the viewers, mainly children, had provoked seizures (in about 75% it was the first seizure) and 10% had symptoms of headache, nausea, blurred vision, vertigo, etc. (80,81). In about 40% of these cases, photoparoxysmal EEG responses or photoparoxysmal responses (PPRs) were found.

Complaints of headache are found significantly more often in photosensitive patients (twice as often) and it is also a regular finding during a PPR (78,82). Headache can also be the sole manifestation of an epileptic event and remaining complaint after AED treatment (83), especially in families with both migraine and epilepsy (84). Conversely, if children and adolescents complain about headache and are diagnosed as having migraine with aura, a PPR is found in about 30% (85).

Following the Pokemon incident, subjects known to have visually induced seizures were examined whether color modulation could be an independent factor in human epileptic photosensitivity. Among photosensitive epilepsy patients sensitive to flash and pattern stimulation, 25 of 43 were sensitive to color stimulation, particularly at frequencies below 30 per second. Red was the most effective color, and red-blue was the most provocative alternating stimulus. They concluded that "color sensitivity follows two different mechanisms: one, dependent on color modulation, plays a role at lower frequencies (5 to 30 Hz). Another, dependent on single-color light- intensity modulation, correlates with white light sensitivity and is activated at higher frequencies." This also suggests a mechanism to explain observations that colored spectacles adapted to the patient's color sensitivity may be useful for treatment (86).

Of the several abnormal EEG responses described in the laboratory, IPS and especially evoked generalized paroxysmal epileptiform discharges (e.g., spikes, polyspikes, spike-and-wave complexes) are clearly linked to epilepsy in humans. About 5% of all patients with epilepsy show this response to IPS (78,87) and 1.4% of healthy schoolchildren. No follow-up studies have been performed in these children in order to know if clinical seizures did occur later in life.

Family studies indicate an autosomal dominant mode of inheritance of PPRs with age- and sex-dependent penetrance (88,89). Several molecular genetic studies in generalized epilepsy patients with a PPR have shown evidence for linkage to chromosomes 7q32; 16p13 (90) and to 6p21.2; 13q31.3 (91). Combination of both studies and additional samples from other European countries identified 16p13.3, 5q35.3, and 8q21.13, with replication of only 16p13.3 (92). Continued research is necessary taking EEG patterns and clinical information into account.

Photosensitivity occurs most frequently in adolescents and women, but studies of the epileptic response to IPS are complicated by differences in how IPS is performed. An expert panel has recommended a protocol for performing IPS and guidelines for interpreting the EEG responses (93,94). This is also shown in a review with video (55).

Sensitivity to IPS is often divided into three groups: patients with light-induced seizures only, patients with photosensitivity and other seizure types, and asymptomatic individuals with isolated

PPRs (nonepilepsy patients or family members of epilepsy patients). However, half of known photosensitive patients questioned immediately after stimulation, denied having had brief but clear-cut seizures induced by IPS and documented by video–EEG monitoring (95). In combination with the observation that patients can start having overt (light- induced) seizures several years after discovery of a PPR as seen in family studies, any subdivision should be taken as flexible as possible. Until now, no controlled studies have been performed on evolution of the various physiologic phenomena in combination with clinical data. A flexible system using all available information can be used as a temporary informative classification. The following working categories can be discerned (82):

1. Normal individuals (no history of epileptic seizures) with a PPR in the EEG
2. A first visually induced seizure in special circumstances (TV, stroboscopic lights, video games, etc.), with or without a PPR
3. Recurrent visually induced seizures, with or without a PPR
4. Spontaneous seizures and a PPR
5. Visually induced and spontaneous seizures, without a PPR
6. Visually induced and spontaneous seizures, with a PPR

Decision about treatment should, however, always be made on an individual level based on prevention of seizures as primary goal, rather than classification in a subgroup. Criteria like extent of sensitivity to visual stimuli (range of flash frequencies, size of patterns, reaction to TV/computer screens) and severity of seizures or complaints in combination with age and lifestyle are important.

For educational purposes, we discuss two commonly encountered discriminative clinical manifestations in more detail: (i) recurrent visually induced seizures and (ii) spontaneous seizures and a PPR. In reality and dependent on available EEG, clinical, and follow-up information data, there is an overlap. Although most patients are sensitive to various visual triggers (96), patients can similarly be roughly divided in those primarily sensitive to flicker (the majority) and those sensitive to pattern. A specific category of patients are the self-inducers; they use their sensitivity to visual stimuli to evoke PPRs. Self-induction is therefore described in a subsection.

Patients with Recurrent Visually Induced Seizures

According to Jeavons (97), 40% of photosensitive patients have generalized seizures provoked exclusively by a flickering light source, and television is the most common precipitating factor. Video games may also trigger these generalized seizures (96,98). Other typical environmental stimuli include discothèque (stroboscopic) lights and sunlight reflected from snow or the sea or interrupted by roadside structures or trees. Rotating helicopter rotors and tower-mounted wind turbines, which can reflect or break up light into flicker, also present risk (99,100).

In this category, female adolescents are typically overrepresented. Reviews of the topic have been provided by several authors (78,87,95,101). The seizures are generalized tonic–clonic in 84% of patients (102), absences in 6%, partial motor seizures (possibly asymmetric myoclonus in some cases) in 2.5%, and myoclonic seizures in 1.5% of patients. Subtle myoclonic seizures may go unnoticed until an obvious seizure occurs. The developmental and neurologic examinations are normal. The resting EEG may be normal in about one-half of patients, but spike-and-wave complexes may be seen with eye closure. IPS evokes a PPR in virtually all patients. Depending on the photic stimulus and on the patient's degree of photosensitivity, the clinical response ranges from subtle

eyelid myoclonus to a generalized tonic–clonic convulsion.

These photosensitive patients are typically conceptualized as having a variety of genetic generalized epilepsy, but cases occur in which EEG and clinical evidence favors the occipital lobe origin, as predicted by theoretical and animal models (103,104). IPS can also induce clear-cut partial seizures originating in the occipital lobe (105,106). As in more typical photosensitive subjects, environmental triggers include television and video games. Many of these patients have IPOE, a relatively benign, age-related syndrome without spontaneous seizures, although cases with occipital lesions have been reported, including patients with celiac disease. The clinical seizure pattern depends on the pattern of spread. The visual stimulus triggers initial visual symptoms that may be followed by versive movements and motor seizures; however, migraine-like symptoms of throbbing headache, nausea, and sometimes vomiting are common and can lead to delayed or incorrect diagnosis.

Since the seizures are provoked by visual stimuli, the best prevention is avoidance, or modification of the environmental light stimuli, such as increasing the distance from the television set, watching a small screen in a well-lighted room, using a remote control so that the set need not be approached, and monocular viewing or the use of polarized spectacles to block one eye, should provide protection (97,107). Colored spectacles may be useful in selected cases (108,109).

Drug treatment is needed if these measures are impractical or unsuccessful or if photosensitivity is severe. The drug of choice, in particular in male patients, is valproate. Valproate abolishes PPRs in 54% of patients and markedly reduces it in additional 24% (110). In females, preference goes to levetiracetam (95) and lamotrigine. Benzodiazepines such as clobazam (111) may be also useful. About one-fourth of patients lose their photosensitivity by 25 years (112). Because this resolution usually occurs only in the third decade, too early withdrawal of treatment may facilitate seizure recurrence; serial EEG recording to determine the photosensitivity range may be helpful in assessment and during follow-up (94,95).

Patients with Spontaneous Seizures and PPR

Jeavons and Harding (102) found that about one-third of their photosensitive patients with environmentally precipitated attacks also had spontaneous seizures. Spike-and-wave activity was common in the resting EEG patterns of patients with spontaneous seizures, and only 39% of patients had normal resting EEGs. PPRs may accompany idiopathic generalized epilepsies, especially JME, and is associated with onset in childhood and adolescence, normal intellectual development and neurologic examination, normal EEG background rhythm, and generally good response to treatment. Photosensitive benign myoclonic epilepsy may also begin in infancy, with a generally good prognosis though the events may be overlooked by the parents for some time before diagnosis (113). PPRs also may occur with severe myoclonic epilepsy of infancy or Dravet syndrome (114) or with diseases associated with progressive myoclonic epilepsy syndromes like Lafora body disease, Unverricht–Lundborg disease, and the neuronal ceroid lipofuscinoses (114). Photosensitivity is generally seen in eyelid myoclonia with absences (EMA) but not in benign occipital epilepsies of childhood of the Gastaut or Panayiotopoulos types despite the florid EEG abnormalities (114).

Seizures Induced by Patterns

Absences, myoclonus, or more rarely, tonic–clonic seizures may occur in response to epileptogenic

patterns. These are striped and include common objects such as the television screen at short distances, video games, curtains or wallpaper, escalator steps, and striped clothing. Pattern sensitivity is seen in about 70% of photosensitive patients tested with patterned IPS in the EEG laboratory, but sensitivity to stationary striped patterns affects only about 30% (56). However, clinical pattern sensitivity is not easily recognized: patients often may not make the association, the family may be unaware of it, and physicians may not inquire about it.

Wilkins et al. (55,57,115–117) studied the properties of epileptogenic patterns, isolating visual arc size, brightness, contrast, orientation, duty cycle, and sensitivity to movement and binocularity. They concluded that the seizures involve excitation and synchronization of a sufficiently large number of cells in the primary visual cortex with subsequent generalization. We can compare this with the previously described animal experiments and Wieser's theory. Pattern sensitivity optimally requires binocular viewing, and treatment may be aided by avoidance of environmental stimuli (admittedly often impractical) as well as by alternating occlusion of one eye with polarizing spectacles and increased distance from the television set. A high degree of pattern sensitivity requires antiepileptic drug treatment, as described for the predominantly flicker-sensitive patients.

Seizures Induced by Television and Other Electronic Screens

Television likely remains the most common environmental trigger of photosensitive seizures. A television screen produces flicker at the main frequencies, generating IPS at 60 Hz in North America and 50 Hz in Europe. Jeavons and Harding (102) found that photosensitivity was more common at the lower frequency, which partly explained the higher incidence of television-induced seizures in Europe as compared to North America. Television-induced seizures, however, are not related to alternating current (AC) frequency flicker alone. Wilkins et al. (116,117) described two types of television-sensitive patients: those sensitive to IPS at 50 Hz, who apparently were sensitive to whole-screen flicker even at distances >1 m from the screen, and patients not sensitive to the mains frequency flicker but who responded to the vibrating pattern of interleaved lines at half the AC frequency, which can be discerned only near the screen. They emphasized that increased distance from the screen decreased the ability to resolve the line pattern and that a small screen evoked less epileptiform activity than a large one. Binocular viewing was also needed to trigger attacks.

Not surprisingly, domestic video games using the home television screen viewed at close distances for long periods and sometimes under conditions of sleep deprivation and possible alcohol or nonmedical drug use can trigger seizures in predisposed individuals. Some individuals are not photosensitive and may have seizures by chance or induced by thinking or other factors. These events, however, have caused many patients with epilepsy to believe erroneously that they are at risk of seizures evoked by video games, and they need accurate information about their personal risk (118).

Not all seizures triggered by television and similar screens fit this pattern. Seizures can be triggered even at greater distances and by noninterlaced screens without flicker. Flashing or patterned screen content is implicated in such episodes including that from video games. Nevertheless, the 50/25-Hz frequency appears to be a powerful determinant of screen sensitivity, and in countries with 50-Hz AC, special 100-Hz television sets have been shown to reduce the risk of attacks (119). Other preventive measures include watching a small screen from afar in a well-lighted room, using a remote control to avoid approaching the set, and covering one eye and looking away if the picture flickers or if myoclonia occurs (120).

Broadcasting of certain forms of flashing or patterned screen content has been responsible for

outbreaks of photosensitive seizures, most notably in Japan where 685 people, mostly children and young adults with no history of epilepsy, were hospitalized after viewing a cartoon (121). The details of triggering factors in screen images have been summarized (122) and were used to develop broadcast standards in the United Kingdom and Japan, which now reduce this risk. Electronic filters have also been proposed (123). Modern displays, like liquid crystal, organic and polymer light-emitting diodes, and plasma-driven panels, all generate their light output in a different way, and it will probably depend on the size of the screen, the contrast, and the luminance as to whether these provoke seizures in photosensitive patients.

Further outbreaks are to be expected if viewers, especially mass audiences of adolescents, are exposed to such screen content when guidelines do not exist or are violated (124). The diversity in screens and programs combined with at random exposure to potentially epileptogenic triggers might make it much more difficult to recognize this form of photosensitivity.

Self-Induced Seizures

Reports of self-induced epileptic attacks using visual sensitivity antedated the discovery of the photoconvulsive EEG response (125). Regarded as rare, self-induction was reported particularly in mentally retarded children and adolescents, with a female preponderance (78,87,126,127). More recent information, however, shows that although some affected patients are mentally challenged, most patients have relatively normal or only mildly delayed development (128–130). When carefully sought, the syndrome is not rare; it was found in about 40% of photosensitive patients studied by Kasteleijn-Nolst Trenité et al. (128). The EEG usually shows spontaneous generalized spikes or spike-and-wave complexes, and about 75% of patients are sensitive to IPS. The self-induced seizures are usually myoclonic, especially with palpebral myoclonus, or absences, and some patients have EMA. Patients induce seizures with manoeuvers that cause flicker, such as waving a hand with fingers spread apart in front of their eyes or gazing at a vertically rolling television image. Monitoring (130,131) shows that these behaviors, once thought to be part of the seizure, precede the attacks and are responsible for inducing them. The compulsive nature of this behavior has been observed often and has been likened to self-stimulation (132) in experimental animals. Patients have reported intensely pleasant sensations and relief of stress with self-induced photosensitive absence seizures (129,130). Frank sexual arousal has been described (133,134). Patients are often unwilling to give up their seizures, and noncompliance with standard, well-tolerated antiepileptic drugs is common (128,129). Treatment is difficult, however, even in compliant patients (127). Drugs that suppress self-stimulation in animals, such as chlorpromazine and pimozide, may block the pleasurable response without affecting the response to IPS and have partially reduced or completely terminated self-induction (127,135). The effectiveness of valproate in reducing or abolishing photosensitivity has resulted in virtual disappearance of this form of self-induction, which is now encountered in patients for whom the drug has not been prescribed and in those with inadequate drug levels for any reason.

Quesney et al. (136) proposed a dopaminergic mechanism in human epileptic photosensitivity based on the transient abolition of photosensitivity with apomorphine, and bromocriptine and parenteral L-dopa have been reported to alleviate photosensitivity (137,138). Based on these findings, a candidate linkage study on the five dopamine receptor gene regions of DRD1 to DRD5 was performed in families with PPR, but none of these loci were found to be linked to the PPR (139).

In Dravet patients who self-induce, treatment with the serotonergic drug fenfluramine and the

voltage-gated calcium channel blocker verapamil has been effective (140,141). However, many patients appear not to want treatment for their self-induced attacks. Photosensitive patients may induce seizures with maneuvers that do not produce flicker. These attacks are similar to flicker-induced seizures, but the inducing behaviors are not. Pattern-sensitive patients may be irresistibly drawn to television screens, which they must approach closely to resolve the epileptogenic pattern of vibrating lines, or they may spend hours gazing through venetian blinds or at other sources of pattern stimulation. Those sensitive to eye closure have been observed to use forceful slow upward gaze with eyelid flutter (142,143) to induce paroxysmal EEG discharge and, at times, frank seizures. These patients are often children, who describe the responses as pleasant: "as nice as being hugged, but not as nice as eating pudding" (Kasteleijn, personal observation). We have noticed that these tonic eyeball movements are always associated with spike-and-wave activity in young individuals. As they mature, their movements may persist but no longer elicit epileptiform activity and can be likened to a tic learned in response to positive reinforcement. These observations and the compulsive seizure-inducing behavior of many such patients suggest that, as in flicker- induced seizures, the self-induced attacks provide pleasure or relieve stress. Experience suggests that treatment is similarly difficult (128). They must be distinguished from rare seizures occurring with eyes closed or with loss of central fixation. Panayiotopoulos et al. (144,145) studied these extensively and described the syndromes in which they occur.

SEIZURES INDUCED BY COMPLEX NONVISUAL ACTIVITY

Reflex epilepsy with nonvisual stimuli is rare though reflex seizures with JME are more common than previously thought (146,147). In a Brazilian study, the following triggers were found to be provocative in adult JME patients based on questionnaires: thinking and concentration (23%), praxis (20%), visual stimuli (15%), speaking in public (11%), reading (7%), calculating and writing (5%), music-related activities (5%), and drawing (3%).

Seizures may be classified as those with relatively simple somatosensory triggers (bathing, rubbing, etc.) and those triggered by complex activity, such as thinking, eating, listening to music, or gaming [for reviews, see Gastaut and Tassinari (142) and Striano et al. (148)]. There are clear differences between populations regarding prevalence of specific reflex stimuli: in India, eating and hot water bathing (pouring hot water on the head) are the most prevalent triggering factors (149), while in Caucasians, language-related stimuli like reading and writing are more common.

Seizures Induced by Thinking and Gaming

Wilkins et al. (58) introduced the term seizures induced by thinking to describe a patient who reported seizures induced by mental arithmetic but who proved also to be sensitive to tasks involving manipulation of spatial information with or without any motor activity. Other complex mental activities have been reported to trigger seizures, such as card games and board games, such as checkers (British, draughts), mahjong, go and Baduk games, or making complex decisions. A rather consistent electroclinical syndrome emerges, most succinctly called seizures induced by thinking, reviewed in Andermann et al. (150). EEG monitoring during detailed neuropsychological testing is not always performed, and this peculiar type of reflex epilepsy might thus be more common than originally estimated. Reading is not usually an effective trigger, and unlike reading epilepsy, most

patients also have apparently spontaneous attacks. The seizures are typically generalized myoclonus, absences, or tonic–clonic attacks, and the induced EEG abnormalities are almost always generalized spike-and-wave or polyspike-and-wave activity. Focal spiking is found in only about 10% of patients, and photosensitivity is seen in about 25%. Although numbers are small, most subjects are men. The mean age of onset is 15 years. Family histories of epilepsy are neither typical nor helpful in the diagnosis. Avoidance of triggering stimuli is practical only when activation is related to cards or other games, but drugs effective in idiopathic generalized epilepsies have been most useful. Epileptogenic tasks in these patients involve the processing of spatial information and possibly sequential decisions. The generalized seizures and EEG discharges may depend on initial involvement of parietal or, possibly, frontal cortex and subsequent generalization, much as pattern-sensitive seizures depend on initial activation of primary visual cortex. Recent studies provide more detail on the cerebral representation of calculation and spatial thought and document a bilateral functional network activated by such tasks (151). Similar results were found in a Korean study in 11 patients with seizures exclusively being experienced while playing Go–stop or Baduk games with one interesting difference: the mean age at onset was 53.7 years, and they had played the games without any problem for many years since adolescence (152).

Praxis-Induced Seizures

Japanese investigators (153) have described praxis-induced seizures as myoclonic seizures, absences, or generalized convulsions triggered by activities as in seizures induced by thinking but with the difference that precipitation depends on using a part of the body to perform the task (e.g., typing). Hand or finger movements without "action-programming activity" (defined as "higher mental activity requiring hand movement" and apparently synonymous with praxis) are not effective triggers (154). EEG responses consist of bisynchronous spike or polyspike-and-wave bursts at times predominant over centroparietal regions. Most subjects have JME; some had another idiopathic generalized epilepsy syndrome. None had clear-cut localization-related epilepsy. In its milder forms, such as the morning myoclonic jerk of the arm manipulating a utensil (M. Seino, personal communication, 1999), this phenomenon resembles cortical reflex myoclonus as part of a "continuum of epileptic activity centered on the sensorimotor cortex" (155). It also appears to be another manifestation of triggering of a generalized or bilateral epileptiform response by a local or functional trigger (156), in this case requiring participation of the rolandic region of one or both hemispheres, which may be regionally hyperexcitable in JME (157). The seizures of idiopathic generalized epilepsy may involve only selected thalamocortical networks (158), and this seems especially so in JME (159).

Seizures Induced by Reading

Bickford et al. (160), in 1956, first identified primary and secondary forms of reading epilepsy. The primary form consists of attacks triggered exclusively by reading, without spontaneous seizures. Age at onset is typically between 12 and 25 years. Patients report characteristic jaw jerks or clicks. If reading continues, a generalized convulsion may occur. Prolonged reading-induced partial seizures with ictal dyslexia, bilateral myoclonic seizures, and absences have been reported. The resting EEG pattern is normal, but during reading, abnormal paroxysmal activity is recorded, often consisting of sharp theta activity that may be generalized (142,160–163) or localized to either temporoparietal

region, especially on the dominant side (164,165). These abnormalities frequently are correlated with the jaw jerks, and monitoring also shows perioral reflex myoclonus similar to that seen in JME. Bilateral or asymmetric myoclonic attacks or jerks of the arms and head also similar to those of JME may also occur, with bilaterally synchronous spike-and-wave activity.

Patients with primary reading epilepsy are typically developmentally normal, with normal neurologic examinations. No structural lesions have been demonstrated. A family history of epilepsy is common, and familial reading epilepsy has been reported (165,166). Patients with secondary reading epilepsy also have spontaneous seizures without jaw jerking and often have an abnormal baseline EEG. Primary reading epilepsy was classified as an idiopathic, age-related, localization-related epilepsy, but its focal nature has recently been questioned (16,167). Attacks are induced by reading and may be reproduced easily in sensitive subjects. Functional MRI has shown (168) activations in most subjects in areas overlapping or adjacent to those physiologically activated during language and facial motor tasks, including subcortical structures as also noted by Archer et al. (169). Reading epilepsy seems to be an example of activation of a hyperexcitable network, which can produce seizures when sufficient critical mass is incorporated by adequate stimuli to produce a seizure, at times a seizure of apparently generalized epilepsy. We have noted that it may rely on both existing and reorganized functional links between brain regions and need not be confined to physically contiguous brain sites or established neuronal links.

The triggering stimulus in reading epilepsy is unknown, but several authors have speculated about the origin. Bickford et al. (160) proposed that normal sensory stimuli influenced some hyperexcitable cortical focus. Critchley et al. (164) emphasized several factors: the visual pattern of printed words, attention, proprioceptive input from jaw and extraocular muscles, and conditioning. Forster (64) theorized that the seizures were evoked by higher cognitive functions; however, patients with primary reading epilepsy are not photosensitive, deny other precipitating cognitive stimuli, and do not appear to have thinking-induced seizures. Patients with the latter almost always deny activation by reading. A recent detailed study in one patient showed that the alphabetical nature of written stimuli triggered his seizures (170). Another single patient with otherwise clear-cut primary reading epilepsy reported induction by card playing while drinking beer (171). Comprehension of the material being read is essential in some cases and irrelevant in others, suggesting that attention is not sufficient to precipitate seizures. Studies suggest that increased difficulty, complexity, or duration of a task increases the chance of EEG or clinical activation (59,60).

Functional imaging has shown that these seizures result from activation of parts of a speech and language network in both hemispheres (172), confirming that the hyperexcitable neuronal tissue forming the critical mass is not necessarily contiguous but is functionally linked, as discussed by Salek-Haddadi et al. (168), by Rémillard et al. (173), and by Safi et al. (170). A mechanism similar to that in pattern-sensitive epilepsy, in which generalized activity is activated by the occipital cortical stimuli, may operate in some cases of primary reading epilepsy in which bilateral myoclonic attacks or bilaterally synchronous epileptiform activity is triggered.

Primary reading epilepsy generally responds well to valproate, and benzodiazepines or lamotrigine is expected to be useful as well, but patients often decline treatment especially if they have only jaw jerks. Exquisite treatment response to levetiracetam was reported in two patients, one with primary and one with secondary reading epilepsy (174).

Language-Induced Epilepsy

Geschwind and Sherwin (175) described a patient whose seizures were induced by three components of language: speaking, reading, and writing. Some other cases have been reported since. Similar to those in primary reading epilepsy, the seizures consist of jaw jerks, with focal (161,176–178) or generalized (175) abnormal paroxysmal EEG activity during language tasks. In some patients, isolated components of language were the only effective seizure triggers. Writing (179,180), typing (132), listening to spoken language (181), and singing or recitation (182) have been reported as isolated triggers. Writing or speaking may activate patients with reading epilepsy (178,183), and exceptionally, reading epilepsy occurred in a patient who was also activated by card games (172). We consider activation by drawing (184) to be part of seizures induced by thinking, and other patients believed to have language-induced epilepsy may have thinking-induced seizures. This heterogeneity suggests that the definition of a language-induced epilepsy is not clear-cut. Cases may form part of relatively more stereotyped syndromes of reading epilepsy, whose definition should be broadened. Alternatively, Koutroumanidis et al. (172) suggested that primary reading epilepsy might be classified as a variant of a more broadly defined language-induced epilepsy. The association of reflex language-induced epilepsy and idiopathic generalized epilepsy was explored by Valenti et al. (184) and is of interest since some patients with reading epilepsy also seem to have an underlying generalized epilepsy.

Seizures Induced by Music

The rare musicogenic epilepsy consists of seizures provoked by hearing music. The music that triggers seizures is often remarkably specific in any one patient, and no consistent epileptogenic features of musical sound can be identified. A startle effect is not required. Many patients have spontaneous attacks as well. Some attacks can be provoked by music and by nonmusical sounds such as ringing or whirring noises from telephones or vacuum cleaners (6,7). In some patients, an effective musical stimulus often induces emotional and autonomic manifestations before the clinical seizure begins. Patients may report triggers with personal emotional significance. However, in some patients, the triggers have no particular connotations (185), while in others, they may (186). Triggers without particular emotional significance can induce the typical autonomic features before the clinical attack (187,188). Establishment of the seizure as a conditioned response has also been suggested (142,185,187,189), but this view is not generally accepted (190). A case with self-induction possibly motivated by emotional factors has been described (191). Musicogenic attacks may appear only in adulthood, often in the context of a preexisting symptomatic localization-related epilepsy. Many case reports antedate intensive monitoring and modern imaging, but the seizures appear to be simple or complex partial, and epileptiform EEG abnormalities are recorded focally from either temporal lobe but more frequently over the right side. Mesial temporal and lateral temporal seizure onsets have been documented (192).

The pathophysiology of musicogenic epilepsy is obscure. Studies in epileptic subjects not sensitive to music show that musical stimuli may have widespread effects on neuronal activity in human temporal lobes, extending well beyond the rather restricted primary auditory area (193); that different components of music have different effects, possibly with specialized lateralization and localization; and that the effects of music differ from those of speech (194,195). Components of musical stimuli such as melodic contour and perception of unfamiliar pitch patterns are processed by cortical subsystems rather than by a nonspecific music area of the brain (196–198). Functional imaging of musical perception has been reviewed (199). Wieser et al. (200) suggested a right

temporal predominance for musicogenic seizures. Right anterior and mesial hyperperfusion during ictal single- photon emission computed tomography has been documented (199,201), and later, detailed coregistration functional imaging supported a privileged role for right temporolimbic activation (202). Zifkin and Zatorre (203) note that more complex musical processing tasks activate more cortical and subcortical territory bilaterally, although with right hemisphere predominance. Hyperexcitable cortical areas could be stimulated to different degrees and extents by different musical stimuli in patients sensitive to these triggers. Gloor (204) suggested that responses to limbic stimulation in epileptic subjects depend on widespread neuronal matrices linked through connections that have become strengthened through repeated use of interest in considering the delay from seizure onset to the development of sensitivity to music and the extent of the networks involved in musical perception.

The extreme specificity of the stimulus in some patients and the delay from stimulus to seizure onset can be useful in preventing attacks, but these seizures usually occur in patients with partial seizures, and appropriate antiepileptic drugs are generally required. Intractable seizures should prompt evaluation for surgical treatment. Furthermore, in musicians, right temporal lobectomy can cause loss of musicality (205).

Seizures Induced by Eating

Boudouresques and Gastaut (206) first described eating epilepsy in four patients who experienced seizures after a heavy meal. Gastric distention may have been at least partly responsible for the attacks (207), but many such seizures occurred early in the meal and were unrelated to gastric distention (208,209). The clinical characteristics are usually stereotyped in individual patients, but there are few common features among patients. Some patients have seizures at the very sight or smell of food, whereas others have them only in the middle of a meal or shortly afterward. In some patients, the seizures may be associated with the emotional or autonomic components of eating; in others, they are associated with sensory afferents from the tongue or pharynx. These seizures have also been documented in young children, in whom they can be mistaken for gastroesophageal reflux (210).

Seizures with eating are almost always related to a symptomatic partial epilepsy. Cases in which the seizures were generalized from onset are exceptional (211). Rémillard et al. (173) suggested that seizures in patients with temporolimbic epilepsy are activated by eating from the beginning of their seizure disorder and continue to have most seizures with meals. In contrast, patients with localized extralimbic, usually postcentral, seizure onset develop reflex activation of seizures later in their course, with less constant triggering by eating and more prominent spontaneous seizures. These patients typically have more obvious lesions and findings on neurologic examination.

The mechanism of eating epilepsy is unclear. Several investigators suggest that interaction of limbic and extralimbic cortices (212) and contributions from subcortical structures, such as from the hypothalamus (67,206,213), are particularly important. Other proposed triggering mechanisms include a conditioned response, mastication (213), stimulation of the esophagus (214), and satisfaction of a basic drive (210). Rémillard et al. (173) suggested that seizures with extralimbic, suprasylvian onset, often involving obvious structural lesions, may be activated by specific thalamocortical afferents. Detailed studies of three male and three female patients with eating epilepsy in India showed ictal rhythmic slowing/fast activity in parietotemporal (n = 2) or frontotemporal (n = 4) regions with subsequent secondary generalization in three. Ictal and interictal SPECT imaging showed changes in frontal lobe (n = 1), anterior temporal lobe (n = 1), and

parietoinsular region (n = 1), suggesting that these areas are part of the ictal onset zone (77).

That obvious combinations of several stimuli are required in some cases (215,216) added to the circumstantial evidence favoring an interaction among cortical areas and diencephalic structures, which in other cases could involve less obvious combinations of stimuli. When the abnormal cortex is located in regions responding to proprioceptive and other sensory afferents (especially lingual, buccal, or pharyngeal) activated by the extensive sensory input generated by a complex behavior such as eating, patients may be more sensitive to the physical manipulation of food, texture, temperature, and chewing. They may also have seizures induced by activities such as brushing teeth. These patients have extralimbic seizure onset. This mechanism may be similar to that described for other proprioceptive or somatosensory-induced seizures (155). A similar mechanism, but with afferents recruiting hyperexcitable temporolimbic structures, may also operate in subjects with temporolimbic seizure onset, who may be more sensitive to gustatory, olfactory, affective, or emotional stimuli or to stimuli arising from more distal parts of the gut. Alerting stimuli have been reported to abolish attacks (217), providing further circumstantial evidence for the participation of an increasing cortical mass and of subcortical influences in some cases of reflex epilepsy.

The extraordinarily high frequency of seizures associated with meals in Sri Lanka (218) may be ascribed to the inclusion of all attacks occurring from 0.5 hours before to 0.5 hours after eating. This does not correspond to eating epilepsy as defined here.

Proprioceptive-Induced Seizures and Startle Epilepsy

Proprioceptive-induced seizures include those that appear to be evoked by active or passive movements. Gowers (219) first described seizures induced by movement in humans, and they have been characterized as movement-induced seizures. Studies in the monkey by Chauvel and Lamarche (220) suggest that proprioception is the most important trigger and that the term movement-induced seizures is incorrect. Spontaneous and reflex seizures were observed with a chronic alumina focus in the cortical foot area. Reflex motor attacks were triggered by active or passive movement of the contralateral limb and by tapping the hindlimb tendons. The stimuli activating proprioceptive afferents to a hyperexcitable cortical area triggered seizures. Seizures could not be elicited in the curarized animal. In humans, focal reflex or posture-induced seizures can be transiently observed in patients with nonketotic hyperglycemia, resolving only with metabolic correction. Interictal focal neurologic deficits are seen as evidence of underlying cortical dysfunction (216,221). Proprioceptive afferents, rather than the observed movements, are implicated in seizure precipitation in animal studies and probably in humans (222), although the case reported by Gabor (223) is a possible exception. Arseni et al. (224) and Oller-Daurella and Dini (225) have confirmed the epileptic nature of these attacks.

Startle epilepsy involves seizures induced by sudden and unexpected stimuli (226,227). Typically lateralized and tonic, the seizures are often associated with developmental delay; gross neurologic signs, such as hemiplegia; and cerebral lesions (228–230). Computed tomography scans often show unilateral or bilateral mesial frontal lesions (225); patients with normal scans have had dysplastic lesions identified on MRI (231). Electroencephalograms with depth electrodes have shown initial ictal discharge in the supplementary motor area (232) and mesial frontal cortex (233). These represent a symptomatic localization-related epilepsy and are often medically intractable. Most patients have other spontaneous seizures.

Proprioceptive-induced seizures can be confused with nonepileptic conditions. Clinical and EEG

findings should permit differentiation of startle epilepsy from startle disease or hyperekplexia and from other excessive startle disorders (234–236) and should exclude cataplexy and myoclonic epilepsy syndromes. Apparent movement-induced seizures without startle must be distinguished from paroxysmal kinesigenic choreoathetosis, in which movements are clearly tonic and choreoathetoid, consciousness is preserved, and the EEG pattern remains normal during attacks (seizures induced by somatosensory stimulation). Seizures may be induced by tapping or rubbing individual regions of the body (155). These are partial seizures, often with initial localized sensory symptoms and tonic features, and typically occur in patients with lesions involving postrolandic cortex. A well-defined trigger zone may be found, for example, in patients whose seizures are triggered by brushing the teeth (237). Drugs for partial seizures are needed, but the seizures may be intractable and require evaluation for surgery.

Reflex drop attacks elicited by walking (238) are seen rarely in patients with reflex interictal spikes evoked by percussion of the foot (239). We consider these to be a variety of seizures induced by proprioceptive stimulation. They are interesting because, unexpectedly, individuals with the interictal-evoked spikes do not usually have such attacks. This disorder probably represents a form of idiopathic localization-related epilepsy of childhood, distinct because of the parietal lobe involvement, though underlying dysplastic lesions cannot be excluded. Participation of a more elaborate network for motor programming cannot be excluded in some cases especially if the effective stimulus seems restricted to activities such as walking (240).

Touch-Evoked Seizures

Seizures can be evoked by simple touch (i.e., “tap” seizures), apparently unrelated to proprioceptive afferents (241,242), although startle may be important. These reflex-generalized myoclonic attacks and associated bilateral spike-and-wave EEG discharges occur without evidence of lateralized lesions; the family history may be positive (243). Seizures typically occur in normal infants and toddlers and can represent an idiopathic and relatively benign generalized myoclonic epilepsy syndrome rather than a progressive myoclonic encephalopathy (244,245). They usually respond to valproate, but prolonged treatment may not be needed.

Seizures Induced by Hot Water

Seizures triggered by immersion in hot water were first described in 1945 (246). The condition is rare in Japan, the Americas, and Europe but seems to be more common in India (247,248). Little EEG documentation is available, but the epileptic nature of these attacks has been confirmed in some patients (249,250). Indian patients are typically boys, with a mean age at onset of 13.4 years. Patients experience complex partial or generalized tonic–clonic seizures during ritual bathing when jugs of hot water are poured over the head. Startle and vasovagal events cannot be excluded in many cases nor can they be discounted in some North American, European, and Japanese reports. These cases typically involve younger children than in India, with complex partial seizures occurring as soon as the child is immersed in hot water; sensitivity often diminishes with time (251). A mechanism involving defective thermoregulation has been proposed, and some of the attacks may be a form of situation-related seizure with age-dependent occurrence similar to febrile convulsions (246). However, many Turkish subjects have interictal temporal EEG abnormalities and complex partial seizures (252); spontaneous seizures have been reported in most Turkish subjects if the reflex attacks

begin after early childhood (252).

Miscellaneous Reflex Seizures

Other unusual reflex stimuli have been described, usually as occasional clinical case reports but more recently with improved EEG and radiologic documentation. Vestibular stimuli have been reported to induce seizures. It is important to exclude startle effects with caloric stimulation, for example, and to take into account the time required for caloric stimulation to be effective (253).

Klass and Daly reported the extraordinary case of a child with generalized seizures self-induced by looking at his own hand. By 4 years of age, medications were withdrawn, and no further seizures, reflex or otherwise, occurred in 26 years of follow-up (254). The EEG was said to be normal. A similar case has been reported (64). Other remarkable reflex seizures are those provoked by micturition (255).

CONCLUSIONS

Reflex seizures and reflex epilepsy continue to challenge and puzzle neurologists and neurophysiologists. Intensive monitoring and advances in imaging have helped to clarify some of the mechanisms involved in these cases, which must represent some of nature's more complex experiments. Cortical and subcortical networks are involved.

Reflex seizures can occur with any epilepsy type, and although the stimulus might be very specific, the epilepsy phenotype is not. Treatment or better prevention of seizures is achieved in many patients primarily by avoidance (for example, no more disco visits) or modification (different TV set and vacuum cleaner; wearing blue lenses) of the specific stimulus or change in behavior (no more self-induction). If AEDs are nevertheless necessary to suppress seizures, drugs active in focal as well as generalized epilepsies have been found successful.

Continued progress in understanding the basic mechanisms of epilepsy through reflex seizures depends on the skill and imagination of neurologists and at least as much on their patients, for whom these studies are dedicated (256–262).

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CHAPTER 23 RASMUSSEN SYNDROME

FRANÇOIS DUBEAU

Rasmussen encephalitis (RE) is a sporadic, progressive, inflammatory disorder of childhood, associated with hemispheric atrophy, severe focal epilepsy, intellectual decline, and hemiparesis. Neuropathologic features described in the surgical specimens show characteristics of chronic inflammation such as perivascular and leptomeningeal lymphocytic infiltration, microglial nodules, astrocytosis, and neuronal degeneration. There are variants of this syndrome with regard to age at onset, staging, localization, progression, and outcome. Treatment options are limited. Antiepileptic drugs (AEDs) usually show no significant benefit. Immunotherapy trials (undertaken mostly after the 1990s) showed some improvement in symptoms and disease progression in a proportion of patients. Only hemispherectomy, or variants of functional hemispherectomy, seems to produce persistent relief of seizures and functional improvement.

The disorder was first described by Dr. Theodore Rasmussen in 1958, who, together with Jerzy Olszewski and Donald Lloyd-Smith, published the clinical and histopathologic features of three patients with focal seizures caused by chronic focal encephalitis (1). The original proband, FS, a 10-year-old boy, was referred in 1945 to Dr. Wilder Penfield by Dr. Edgar Fincher, chief of neurosurgery at Emory University in Atlanta, Georgia, because of intractable right-sided focal motor seizures starting at 6 years of age. FS developed a right hemiparesis and underwent, between 1941 and 1956, three surgical interventions (two at the Montreal Neurological Hospital and Institute [MNHI]) at 7, 10, and 21 years of age in an attempt to control the evolution of the disease. In the first chapter of the monograph on chronic encephalitis published by Dr. Frederick Andermann in 1991, Dr. Rasmussen reported a letter by Dr. Fincher to Dr. Penfield (dated 1956) urging him to consider a more extensive cortical excision and concluded, “I note in your discussion that you list the cause as unknown, but if this youngster doesn’t have a chronic low-grade encephalitic process which has likely, by now, burned itself out, I will buy you a new hat.” The last intervention was a left hemispherectomy performed by Dr. Rasmussen, and histology showed sparse perivascular inflammation and glial nodules. FS remained seizure free until his last follow-up at 51 years of age. He had a mild intellectual disability and a fixed right hemiplegia. He developed hydrocephalus as a late complication of the surgical procedure and required a shunt. Dr. Penfield, who was consulted in this case, remained skeptical of the postulate that the syndrome was a primary inflammatory disorder, and he raised most of the issues that continue to be debated: if it is an encephalitic process, would it not involve both hemispheres? Is the encephalitic process the result of recurrent seizures caused by a small focal lesion in one hemisphere? Why it is that epileptic seizures are destructive in one case and not in another? Dr. Rasmussen himself recognized that Fincher’s 1941 diagnosis of chronic encephalitis in FS’s case was made 14 years before case 2 of the original 1958 report (1). The story does not say, however, if Dr. Penfield had to provide his colleague and friend Dr. Fincher with a new hat (2).

This diagnosis, later recognized as “Rasmussen encephalitis (RE) or syndrome,” became the subject of extensive discussion in the literature, initially debating the best timing for surgery and best

surgical approaches and, more recently, the etiology and pathogenesis of this unusual and enigmatic disease (3). A large number of publications can now be found in the literature, and two international symposia were held in Montreal, first in 1988 and again in 2002. In 2004, a European Consensus Group proposed formal diagnostic criteria and therapeutic avenues for the management of RE patients (4). The obvious interest for this disease, which is usually described in children, was initially driven by the severity and inescapability of its course, which rapidly led to its description as a prototype of "catastrophic epilepsy." Physicians and scientists became interested by the unusual pathogenesis and evolution of the syndrome and are now trying to reconcile the apparent focal nature of the disease with the postulated viral and autoimmune etiologies that may or may not be mutually exclusive. This chapter reviews and updates a number of issues regarding RE, particularly the putative humoral and cellular immune mechanisms of the disease, the variability of the clinical presentations, and the indications and rationale of new medical therapies, such as immunomodulation and receptor-directed pharmacotherapy.

CLINICAL PRESENTATIONS

Typical Course

In the early stages of the disease, the major issue is diagnosis. A combination of characteristic clinical, electrophysiologic, and imaging findings aids in the diagnosis. The 48 patients studied at the MNHI were collected over a period of 30 years and consisted mostly of referrals from outside Canada. Although now easier to recognize, this disease remains rare. During the last two decades, no more than one to two new cases are identified at the MNHI per year. This is a small number compared to the 100 to 150 inpatients with intractable focal epilepsy due to other causes studied each year at the center. Typically, the disease starts in healthy children between 1 and 13 years (mean age, 6.8 years) with 80% developing seizures before the age of 10 years (5). There is no difference in incidence between the sexes. In approximately half the patients, a history of infectious or inflammatory episode was described 6 months prior to the onset of seizures.

The first sign of the disease is the development of seizures. They are usually partial or secondarily generalized tonic–clonic seizures; 20% of patients in the MNHI series presented with status epilepticus as the first manifestation. Early seizures could be polymorphic with variable semiology, but motor manifestations are almost always reported. Other variable semiology of seizures with somatosensory, autonomic, visual, and psychic features has been described (5,6). The seizures rapidly become refractory, with little response to AEDs. Epilepsia partialis continua (EPC) and other forms of focal seizures are particularly unresponsive to AEDs (7,8). A review of the AED therapy in 25 patients of the initial MNHI series revealed that no specific agent or combination therapy appeared to be more effective or less toxic than other regimens (7). Our experience with more recently approved AEDs in other patients with RE did not support improved effectiveness or tolerability for newer agents. Levetiracetam, topiramate, and even felbamate may theoretically have a role in the treatment of RE, because levetiracetam has efficacy in treating cortical myoclonus, and topiramate and felbamate have a direct effect on glutamate receptors and release of N-methyl-D-glutamine (NMDA).

A variety of seizure types develop over time. The most common are focal motor and EPC (in 56% of the patients), with scalp electroencephalogram (EEG) patterns suggesting perirolandic onset.

Secondarily, generalized motor seizures are also common in many patients, but these appear to be easier to control with AEDs. Other, less frequent types of motor seizures include Jacksonian march (12%), posturing (25%), or versive movements of the head and eyes (13%), suggesting involvement of the primary motor, premotor, and supplementary motor areas. Drop attacks, however, are rare. Focal seizures with somatosensory (22% of the patients), visual (16%), or auditory (2%) manifestations are less frequent and appear later in the course of the disease, suggesting that the epileptogenic process has migrated from frontocentral regions to more posterior cortical areas. Adult-onset variant (see below under: Clinical Variants of Rasmussen Encephalitis: Late-onset Adolescent and Adult Variants) is also characterized by different early and late features reflecting a progressive involvement of different brain structures from the temporal and frontal lobes to perisylvian and insular regions.

Oguni et al. (5) divided the progression of the disease into three stages: stage 1, from the onset of the seizures and before the development of a fixed hemiparesis (3 months to 10 years, mean duration, 2.8 years); stage 2, from the development of a fixed hemiparesis (occurring in all 48 patients) to the completion of neurologic deterioration, including intellectual decline (85%), visual (49%) and sensory (29%) cortical deficits, and speech problems (dysarthria 23%, dysphasia 19%) dependent or independent of the burden of seizure activity (2 months to 10 years, mean duration, 3.7 years); and stage 3, stabilization of the condition in which further progression no longer occurs, and even the seizures tend to decrease in severity and frequency.

Bien et al. (9) presented the clinical natural history of RE in parallel with the time course of brain destruction as measured by serial magnetic resonance imaging (MRI), in a series of 13 patients studied histologically. They separated the progression of the disease into prodromal (during this stage, patients had rare seizures and minimal neurologic deterioration), acute (a period of intense seizure occurrence, neurologic deterioration associated with the affected hemisphere and atrophy of one hemisphere), and residual (with a marked reduction in seizure frequency) stages comparable to the three stages presented by Oguni et al. However, Bien et al. distinguished two patterns of disease depending on the age at onset of the disorder: one with an earlier and more severe disorder starting during childhood (mean age at first seizure, 4.4 years; range, 1.6 to 6.4 years) and a second with a more protracted and milder course starting during adolescence or adult life (mean age at first seizure, 21.9 years; range, 6.4 to 40.9 years), the second pattern representing a now well-described variant of RE (see below).

The main two aspects of the clinical phenotype of RE consist of progressive functional neurologic decline and pharmacologically intractable epilepsy (3). The progressive neurologic deficit, usually fixed at one point in time, with a more severe decline in children compared to adolescents and adults, is caused by the chronic inflammatory process. The degree of the deficit may, however, be fluctuating due to seizure severity. The disease is also characterized by the epilepsy, usually but not necessarily severe, that persists throughout the evolution of the process.

Clinical Variants of Rasmussen Encephalitis

RE has been known for more than 50 years. After the initial description, it became clear that the disease is clinically heterogeneous despite the pathologic hallmark of chronic inflammation in the affected hemisphere. This heterogeneity may be explained by different etiologies (viral, viral-, and nonviral-mediated autoimmune disease), by different reactions of the host's immune system to exogenous or endogenous insults (age, genetic background, presence of another lesion, or "double

pathology"), and by the modulating effect of a variety of antiviral, immunosuppressant, and immunomodulatory agents, or receptor-directed pharmacotherapy used in variable combinations and durations to treat these patients. Atypical or unusual clinical features include early onset (usually younger than 2 years of age) with rapid progression of the disease; bilateral cerebral involvement; relatively late onset during adolescence or adult life with slow progression; atypical anatomic location of the initial brain MRI findings; focal and chronic protracted, subcortical, or even multifocal variants of RE; and double pathology.

Bilateral Hemispheric Involvement

Typically, the disease affects only one hemisphere, and most autopsy studies confirmed unilateral cerebral involvement (10). Over time, however, there may be some contralateral ventricular enlargement and cortical atrophy attributed either to the effect of recurrent seizures and secondary epileptogenesis or to wallerian degeneration (11). Patients with definite bilateral inflammatory involvement are exceptional and such involvement has been described in approximately 20 patients (12–18) including some with atypical or doubtful bilateral RE (given the lack of histologic confirmation of bilateral involvement). Bilateral disease tends to occur in children with early onset (before age 2 years) but was also described in the late-onset adolescent or adult forms. A small number had received high-dose steroids or an intrathecal antiviral agent, which suggested that early aggressive immunologic therapy may have predisposed them to contralateral spread of the disease. Thus, there seems to be an early-onset variant of RE in which there is an increased risk of bilateral disease, a more malignant course, and a high mortality. Bilateral RE may be related to immaturity of the immune system or to a possible adverse effect of immunotherapy.

Late-Onset Adolescent and Adult Variants

In the first edition of this book, we evaluated the proportion of late-onset RE to be approximately 10% of the total number of patients. A thorough review of the literature seems to confirm that the adolescent or adult variant is more common than initially thought. From 1960 to 2013, we identified at least 40 papers in which over 90 cases of late-onset RE are reported (9,12,19–37). In the MNHI series, 9 (16%) of 55 patients collected between 1945 and 2000 started to have seizures after the age of 12 years. The largest series, described by Hart et al. (21), included 13 adults and adolescents collected from five centers. In comparison with the childhood form, late-onset RE has a more variable evolution, a generally more insidious onset of focal neurologic defects and cognitive impairment, and an increased incidence of occipital involvement (23% in the series described by Hart et al. vs. 7% in children younger than 12 years old in the MNHI series). Hemiparesis and hemispheric atrophy are often late and may not be as severe when compared with the more typical childhood form. Occasionally, the outcome in late-onset RE is similar to or worse than in children, but because of the generally more benign and protracted course, early hemispherectomy seems less appropriate in this group of patients in whom neurologic deficits are usually less pronounced. Moreover, because of a lack of plasticity in adults, the decision for hemispherectomy is complicated because of potential risk of new irreversible postoperative deficits in the form of severe motor, visual, and speech and language (dominant hemisphere) impairment.

Focal and Chronic Protracted Variants

There are rare reports of patients with RE whose seizures were relatively well controlled with AEDs or focal resections, and in whom the neurologic status stabilized spontaneously (21,30,33,38). Rasmussen had already suggested the existence of a "nonprogressive focal form of encephalitis." With Aguilar, he reviewed 512 surgical specimens from 449 patients and found 32 cases with histologic evidence suggesting the presence of active encephalitis (19). Twelve demonstrated progressive neurologic deterioration compatible with RE, and 20 (4.4%) showed no or mild neurologic deterioration. In his review of patients who underwent temporal resections for intractable focal seizures, Laxer (38) found five patients (3.8% of a series of 160 patients) with what he thought was a benign, focal, nonprogressive form of RE. These patients (children or adults) with no evidence of progression are clinically indistinguishable from those with refractory seizures due to other causes, including mesial temporal sclerosis.

Delayed Seizure–Onset Variant

Bien et al. (39) described five children with RE and delayed seizure onset. All had slowly progressive hemiparesis, contralateral brain atrophy, and four had pathologic features characteristic of RE. Mean age at disease onset was 6.1 (4.8 to 7) years. Two children had seizures 0.5 and 0.6 years after disease onset and the other three were still seizure free at the time of the report (1.3 to 1.9 years after disease onset). Interestingly, the authors demonstrated that the progression of the hemiatrophy in these five patients was similar to the one observed in RE cases with seizures. These two studies reemphasized the fact that patients with RE may present a more insidious course, and the disease should be suspected in cases with new-onset progressive unilateral neurologic deficits.

Basal Ganglia Involvement

EPC and other types of focal motor seizures are a common finding in patients with RE. Chorea, athetosis, and dystonia were infrequently described and may have been overlooked because of the preponderance of the epileptic manifestations and of the hemiparesis. In 27 of the 48 patients of the MNHI series who had EPC, nine additionally had writhing or choreiform movements, and a diagnosis of Sydenham chorea was made in three of the patients early in the disease course (5). Matthews et al. (40) described a 10-year-old girl with a 1-year history of progressive right-sided hemiparesis, EPC, and secondary generalized seizures. MRI showed diffuse cortical and subcortical changes maximum in the perisylvian frontotemporoparietal area. At examination, she had choreic movements of the right arm and hand in addition to EPC. Tien et al. (41) were the first to describe atrophy of the caudate and putamen with abnormal high signals and severe left hemispheric atrophy in an 8.5-year-old girl with intractable focal motor seizures. They interpreted these findings as the result of gliosis and chronic brain damage. Topçu et al. (8) described a patient who developed hemidystonia as a result of involvement of the contralateral basal ganglia. The movement disorder appeared 3 years after the onset of seizures. A rather typical subsequent evolution suggested RE. The movement disorder started during intravenous immunoglobulin (IVIg) and interferon therapy and did not respond to anticholinergic drugs or to a frontal resection. Ben-Zeev et al. (42), Koehn and Zupanc (43), Frucht (24), Lascelles et al. (44), and, finally, Kinay et al. (31) each reported a case of RE whose clinical presentation was dominated by a hemidyskinesia, with EPC in three of those patients, and progressive hemiparesis. Two cases showed selective frontal cortical and caudate atrophy on MRI; one developed progressive left basal ganglia atrophy and later focal frontotemporoparietal atrophy; one had only pronounced right caudate, globus pallidus, and putamen atrophy; and one showed

progressive right frontoinsular and later diffuse hemispheric atrophy with also progressive atrophy of the right caudate head and putamen. In the case of Frucht, IVIg dramatically improved both the hyperkinetic movements and the EPC, but the effect was transient, suggesting a common neuroanatomic mechanism or humoral autoimmune process. In a series of 21 patients with RE, Bhatjiwale et al. (32) looked specifically at the involvement of the basal ganglia. Fifteen (71%) patients showed mild to severe basal ganglion involvement on imaging in three different patterns: predominantly cortical in six cases, predominantly basal ganglia in six cases, and both cortical and basal ganglia involvement in three cases. In five cases, the changes found in the basal ganglia were static, whereas in the others, there was steady progression. The caudate nucleus was generally more prominently involved, usually in association with frontal atrophy. Five cases also showed putaminal involvement, always with temporoinsular atrophy. Interestingly, two of the six patients with prominent basal ganglia involvement had dystonia as a presenting feature. The authors postulated that the disease may proceed from different foci, including cases where RE seems to start in the deep gray matter. Similar findings were recently described by the Italian Study Group on Rasmussen encephalitis (45), which found basal ganglia atrophy in 9 of 13 patients studied. They suggested that atrophy of the basal ganglia represents only secondary change because of disconnection from the affected overlying frontal and insular cortex.

Brainstem Variant

McDonald et al. (46) reported a 3-year-old boy with RE manifested by chronic brainstem encephalitis. After a prolonged febrile seizure associated with an acute varicella infection, he developed recurrent partial motor seizures, EPC, and left hemiparesis within a few weeks. After a few more weeks, signs of brainstem involvement appeared, repeated MRI showed increased signal in the pons, but a complete infectious and inflammatory evaluation, including brain biopsy, was negative. He died 14 months after the onset of his illness. Neuropathologic findings in the brainstem were typical of those found in RE. Bilateral mesial temporal sclerosis was also present. The authors proposed that this case represents a rare focal form of RE with primary involvement of the brainstem and hemiparesis and mesial temporal sclerosis resulting from seizure activity. This was an isolated case report in a complicated patient, and existence of this variant was then questionable. However, recently, a case of adult-onset RE was described with a relatively typical evolution with EPC, focal motor seizures, progressive impaired motor function of the right hemibody, and progressive atrophy of the left hemisphere maximal in the perisylvian regions (29). The diagnosis of RE was confirmed 2.5 years after onset by a brain biopsy, and the disease progressed in spite of IVIg. The patient rapidly became hemiplegic but also seizure free at about the same time. One year later, this patient was admitted because of swallowing problems, palatal paresis, and a flaccid dysarthria. MRI showed a progression of the left hemispheric atrophy and an increase in signal extending in the left mesencephalon and pons but sparing the medulla, without contrast enhancement. Authors suggested that the brainstem involvement represented a late relapse of disease activity involving the brainstem.

Multifocal Variant

Maeda et al. (47) described a 6-year-old girl with typical RE. One year following the onset of seizures, MRI-FLAIR (fluid- attenuated inversion recovery) sequences showed multiple high-signal-intensity areas in the right hemisphere, and a methionine-PET (positron emission tomography) performed at the same time exhibited multifocal methionine uptake areas concordant with the MRI

lesions, suggesting multiple independent sites of chronic inflammation. The authors proposed that the inflammatory process in RE may spread from multifocal lesions and not necessarily originate from localized temporal, insular, or frontocentral lesions, as usually described, before spreading across adjacent regions to the entire hemisphere.

Double Pathology

A small number of reports have documented coexisting brain pathologies with RE (10,35,48–51): tumors (anaplastic astrocytoma, ganglioglioma, anaplastic ependymoma), dysgenetic tissue or focal cortical dysplasia, multifocal perivasculitis, and cavernous angiomas with signs of vasculitis were described. Double pathology in RE supports the theory of focal disruption (trauma, infection, or other pathology) of the blood–brain barrier (BBB). This increased permeability of the BBB may provide access of antibodies produced by the host to neurons expressing the target receptor and production of focal inflammation (2). So far, however, only one case of double pathology provided reasonable support for this hypothesis (50). Strongly positive anti-GluR3 (glutamate receptor 3 subunit) antibodies were measured in one case of RE with concomitant cortical dysplasia in a 2.5-year-old girl with catastrophic epilepsy starting at age 2 years. She underwent a right, partial frontal lobectomy, plasmapheresis, and therapy with IVIg with a transient response, and, finally, a right functional hemispherectomy with good seizure control. GluR3 antibodies were measured serially throughout the course of her treatment and correlated with her clinical status. They were undetectable 1 year after her last surgery.

There are also reports of coexisting autoimmune diseases such as Parry-Romberg syndrome (52) or linear scleroderma (53) and systemic lupus erythematosus (25) with changes mimicking RE. A case of adult-onset RE associated with a typical narcolepsy syndrome in a previously healthy 40-year-old man was also reported (26). Over the course of a few months, the patient developed narcolepsy with confirmatory polysomnography, a HLA type DQB1*0602 and no detectable cerebrospinal fluid (CSF) hypocretin. Within 2 years, he developed refractory temporal lobe seizures. His brain MRI was initially normal and subsequently showed progressive T2 signal changes in the left temporal, insular and inferior frontal regions sparing the hypothalamus and brainstem. Pathology from a first partial temporal lobe resection was consistent with RE. Over the next 5 years, the patient remained refractory to antiepileptic medication but showed no progressive neurologic deficits or further MRI anomalies and still normal hypothalamus and brainstem. The authors suggested that these two co-occurring rare conditions could be explained by a common autoimmune process affecting the cortex and the hypothalamic hypocretin neurons. Also, the coexistence of a postviral acute disseminated encephalomyelitis progressing 6 months later to EPC with clinical and imaging features of a RE was described in a 15-year-old boy (54). Both disorders have an immunologic basis, and the authors again proposed that they represented manifestations of a common autoimmune disorder of the central nervous system (CNS). The association of RE and CNS granulomatous disease with mutations NOD2/CARD15 was described in a 12-year-old girl (55). The patient presented with typical clinical features of RE in addition to two sequential biopsies that also supported the two diagnosis. She was subsequently found to have three mutations in the NOD2/CARD15 gene. Family history was positive for a paternal uncle with Crohn disease and a paternal grandfather with inflammatory arthritis. Moreover, her clinical manifestations, the seizures and the hemiparesis, and the MRI lesions improved dramatically after she received infliximab, a TNF-α inhibitor. Finally, the association of RE and Behçet disease has been described in the same family (a son and his father,

respectively) suggesting a common genetic susceptibility to develop autoimmune conditions (31). Inflammatory changes suggestive of RE have also been observed in disorders with impaired immunity such as agammaglobulinemia (56) and multiple endocrinopathies, chronic mucocutaneous candidiasis, and impaired cellular immunity (57). The occurrence of two conditions presumably caused by impaired immunity in the same individual may strengthen the view that immune- mediated mechanisms are responsible for the development of RE.

Finally, the rare association of uveitis or choroiditis with typical features of RE has led to the speculation that a viral infection may have been responsible for both (58). In all cases, the ocular pathology was ipsilateral to the involved hemisphere that showed chronic encephalitis. It was hypothesized that a primary ocular infection, in particular a viral infection with herpes simplex virus, varicella-zoster virus, Epstein–Barr virus, cytomegalovirus, measles, or rubella, followed by vascular or neurotropic spread to the brain, was a possible mechanism for development of RE. Another patient with adult-onset RE presented with bilateral uveitis that occurred late (19 years after onset) in the course of the disease (34). Anti-GluR ε2 IgG and IgM antibodies were detected in her serum in association with the brain and ophthalmologic inflammatory processes. According to authors, the patient responded favorably to immunotherapy and interferon β-1b.

ELECTROENCEPHALOGRAPHY

Few studies specifically reported the EEG changes associated with RE (6,59) or tried to correlate the clinical and EEG features of the disease over time (6,59,60). So and Gloor (59) reported the scalp (339 studies) and perioperative (58 electrocorticograms) EEG findings in the MNHI series of 49 patients with RE. They summarized the EEG features as follows: (a) disturbance of background activity in all except one patient with more severe slowing and relative depression of background rhythms in the diseased hemisphere; polymorphic or rhythmic delta activity was found in all (more commonly bilateral with lateralized preponderance); (b) interictal epileptiform activity in 94% of patients, rarely focal (more commonly multifocal and lateralized to one hemisphere or bilateral independent, but strongly lateralized discharges with or without bilateral synchrony); (c) clinical or subclinical seizure onsets were variable and occasionally focal, but more often poorly localized, lateralized, bilateral, or even generalized; and (d) no clear electroclinical correlation apparent in many of the recorded clinical seizures, in particular in EPC. The electrographic lateralization of these abnormalities (focal slowing, progressive unilateral deterioration of background activity, ictal, and multifocal interictal hemispheric epileptiform activity) was sufficiently concordant with the clinical lateralization to provide essential information about the abnormal hemisphere in 90% of cases. These EEG features, indicative of a widespread destructive and epileptogenic process, in the specific clinical context of catastrophic epilepsy and worsening neurologic deficits involving one hemisphere, suggest the diagnosis of chronic encephalitis.

The evolution of the EEG was studied longitudinally in a small number of patients (6,59,60). The studies showed progression of the EEG abnormalities. At the onset of the disease, EEG abnormalities tended to be lateralized and nonspecific, with unilateral slowing of background activity. As the disease progressed, it tended to become bilateral and widespread, multifocal or synchronous, suggesting a more diffuse hemispheric process, but not always confined to one hemisphere. It is not clear if this late bilateralization of the EEG abnormalities represented functional interference, secondary epileptogenesis, or, much less likely, an inflammatory process directly involving the contralateral hemisphere.

Longaretti et al. (60) recently reviewed EEG in RE and focal cortical dysplasia (19 and 17 patients, respectively) for early indicators of either pathology. They found no specific EEG changes at diagnosis of epilepsy that help differentiating the two conditions. Interestingly, the EEG was even normal in the initial phase of RE (as for many dysgenetic cases), in 20% of the children at 3 months and in 12% at 6 months. They found, however, that lateralized slow-wave activity and the emergence of epileptiform activity over the unaffected hemisphere were both suggestive of RE as the condition evolves. Also, significant cognitive decline was observed more often in RE patients with independent epileptic activity in the unaffected hemisphere (none of those children presented with evidence of bilateral disease on imaging or during the course of the process), suggesting that RE has the potential to be an epileptic encephalopathy.

Finally, persistent ictal EEG discharges after a functional hemispherectomy suggest that the inflammatory process may continue even in a disconnected hemisphere (61).

IMAGING

Anatomic Imaging

Imaging studies, although not specific, are extremely important for the diagnosis of RE. Typically, they show progressive, lateralized atrophy coupled with localized or lateralized functional abnormalities (6,9,34,38,49,62–65). Brain magnetic resonance studies early in the course of the illness may be normal, rapidly followed by a combination of characteristic features that parallel the clinical and electrophysiologic deterioration, reflecting the nature of the pathologic process. Recent studies using serial MRIs in a relatively large number of patients with RE provided better insight into the early, progressive, and late gray and white matter changes expected in this disease: cortical swelling, atrophy of cortical gray matter and deep gray matter nuclei, particularly the caudate, a hyperintense signal in gray and white matter, and secondary changes (6,9,32,38,65). In the early phase of the disease, when the MRI still appears normal, a few studies demonstrated abnormalities of perfusion or metabolism by single photon emission computed tomography (SPECT) or PET, suggesting that these imaging procedures may aid in early identification of the disease and of the abnormal hemisphere (34,64,66–68). In some studies, PET was found to detect lesions sooner and depict their extent better than concomitant MRI (68). Rapidly on early magnetic resonance scans, however, the cortex shows focal hyperintense signals on T2 or FLAIR sequences (38) and may appear swollen. This can be explained by brain edema at the onset of inflammation (65) or, alternatively, by recurrent focal seizures. Bien et al (65) compared MR images with surgical specimens obtained from 10 RE patients. In those areas with increased signal, the number of T cells, microglial nodules, and GFAP-positive astrocytes was increased compared to areas showing more atrophy and no increased signal. They demonstrated that the densities of T cells, microglial nodules, and astrocytes were inversely correlated to disease duration. Very early signal change in the white matter (within 4 months) is also frequent, usually focal, with or without swelling (38). Later, progressive atrophy of the affected hemisphere occurs, reflecting the manner in which the disease spreads, and with most of the hemispheric volume loss occurring during the first 2 years (9,38,64). The cortical atrophy is initially temporal, frontoinsular, or frontocentral and, more rarely, parietooccipital, later spreading across the hemisphere. Basal ganglion involvement, mostly of the putamen and caudate, is also characteristic and may be a result of direct damage by the pathologic

process or secondary to changes caused by disconnection of the basal ganglia from the affected overlying frontocentral and insular cortices (32,38). MRI brain volumetry studies performed in a large series of patients with RE confirmed that the unaffected contralateral hemisphere also undergo progressive tissue loss although at a lower rate and with a much lesser magnitude compared to the affected hemisphere (11). Other secondary changes usually associated with severe hemispheric tissue loss are atrophy of the brainstem, particularly of the cerebral peduncle and pons, thinning of the corpus callosum, and atrophy of the contralateral cerebellar hemisphere (38). Gadolinium enhancement on MRI is rarely observed (38,49,64,65). Finally, the finding of calcifications is atypical and should raise doubts on the diagnosis of RE. The European consensus group suggested cranial CT to document or exclude calcifications (4).

Functional Imaging

Several studies, often case reports, have emphasized the utility of functional imaging such as PET, SPECT, and proton magnetic resonance spectroscopy (MRS) in the diagnosis and follow-up. Functional abnormalities may be useful in cases in which MRI is normal, usually at the onset of the disease, or when structural imaging fails to provide satisfactory localizing information. Combined anatomic and functional neuroimaging may serve to focus the diagnostic workup, hasten brain biopsy for definitive diagnosis, or define the appropriate surgical approach. It may be useful to follow the evolution of the disease or the result of treatment. Finally, functional studies may provide insight into the cortical reorganization of speech areas and of the motor and somatosensory cortices.

Fiorella et al. (64) reviewed 2-deoxy-2-[^{18}F]-fluoro-D-glucose PET (FDG-PET) and MRI studies of 11 patients with surgically proven RE. All had diffuse, unilateral cerebral hypometabolism on PET images, closely correlated with the distribution of cerebral atrophy on MRI. Even subtle diffuse atrophic changes were accompanied by marked decreases in cerebral glucose use that, according to the authors, increased diagnostic confidence and aided in the identification of the abnormal hemisphere. During ictal studies, patients had multiple foci of hypermetabolism, indicative of multifocal seizure activity within the affected hemisphere, and never showed such changes in the contralateral one. Similar findings had been reported in smaller series (38,66,69). Although MRI alone is generally sufficient to identify the affected hemisphere, FDG-PET confirms the findings in each case. Blood flow or perfusion studies using Oxygen-15 PET showed a similar correlation, with regions of perfusion change corresponding with structural MRI changes (66). Using a specific radioligand ([^{11}C](R)-PK11195) for peripheral benzodiazepine-binding sites on cells of mononuclear phagocyte lineage, Banati et al. (70) demonstrated in vivo the widespread activation of microglia in three patients, which is usually found by neuropathologic study. Also, a [^{11}C]methionine-PET demonstrated in a 6-year-old girl with RE multifocal uptake regions, which corresponded to high-signal-intensity areas described on FLAIR MR imaging and suggesting sites of underlying inflammation (47).

SPECT was used to study regional blood flow in a number of patients (8,45,60,67,69,71). The findings may be of some help and more sensitive than anatomic neuroimaging early in the disease but are nonspecific. As with FDG-PET, the regions of functional change usually correlate with anatomic abnormalities. Interictal SPECT scans reveal diminished perfusion in a large zone surrounding the epileptic area shown on EEG. This hypoperfusion may show some variability depending on fluctuation of the epileptic activity. Ictal studies often show zones of hyperperfusion representing likely areas of more intense seizure activity. MRS has been used in a number of patients with RE

(33,38,72–75). Localized proton MRS was described for the first time in two patients by Matthews et al. (40). They showed reduced N-acetylaspartate (NAA) concentrations—a compound exclusively found in neurons and their processes—in diseased areas in two patients, suggesting neuronal loss. In addition, MRS showed increased lactate in a patient with EPC, probably the result of excessive and repetitive seizure activity. These findings were confirmed by Peeling and Sutherland (72) and by Cendes et al. (73). Peeling and Sutherland also showed that the concentration of NAA in vitro (MRS on tissue obtained from surgical patients) was reduced in proportion to the severity and extent of the encephalitis. Cendes and colleagues did sequential studies at 1 year in three patients and demonstrated progression of the MRS changes. They noted that those changes were more widespread than the structural changes seen on anatomic MRI. Tegkul et al. (75) also did sequential NAA/Cr ratios in three patients with RE and demonstrated progressive reduction of the ratios related to the duration and progressive course of the disease. They measured interleukin-6 (a proinflammatory cytokine produced by astrocytes and microglial cells) response in their CSF and serum and found that the magnitude of the responses in the CSF was correlated with the severity of neuronal damage as measured by MRS. Overall, the studies using NAA indicate that MRS can identify and quantify neuronal damage and loss throughout the affected hemisphere, including areas that appear anatomically normal. In addition to NAA and lactate, other compounds measured included choline, creatine, myo-inositol, glutamine, and glutamate. Choline is usually elevated, which probably indicates demyelination and increased membrane turnover (67,73). Myo-inositol, a glial cell marker, was found to be elevated in a small number of patients (67,74), indicating glial proliferation or prominent gliotic activity. Hypothetically, myo-inositol signal should increase with the progression of the disease. Lactate was almost always elevated, and this increase probably results from ongoing or repetitive focal epileptic activity rather than from an inflammatory process itself (72,73). The largest peaks in lactate were usually detected in patients with EPC. Glutamine and glutamate levels were also elevated in two patients so far, a finding of interest considering the potential role of excitatory neurotransmitters in the disease (67).

ETIOLOGY AND PATHOGENESIS

The etiology and pathogenesis of RE remain unknown. Typical histologic findings reported in surgical or autopsy specimens are perivascular lymphocytic cuffing, proliferation of microglial nodules, neuronal loss, and gliosis in the affected hemisphere. The microglial nodules are associated with frequent nonspecific neuronophagia and occur particularly near perivascular cuffs of lymphocytes and monocytes. There is some evidence of spongiosis, but this is not as widespread as in the true spongiform encephalopathies. Lesions tend to extend in a confluent rather than a multifocal manner. Finally, the main inflammatory changes are found in the cortex, and their intensity is inversely correlated with disease duration, with slow progress toward a “burnt-out” stage (9,10,76). A neuropathology study of 45 hemispherectomies in RE patients (76) showed the multifocality (contradicting the previous impression of a centrifugal pattern of the cortical pathology) and heterogeneity of the pathologic changes in each patient, findings consistent with a progressive process of neuronal damage (at multiple times and in various sites). Pathologic changes ranged from early inflammation to extensive neuronal cell death and cavitation, and the presence of T lymphocytes and neuroglial reactions suggested an immune-mediated process involving the cerebral cortex and white matter. Three mechanisms or processes, not mutually exclusive, have been proposed to explain the initiation and unusual evolution of this rare clinical syndrome: first, viral infections directly inducing

central nervous system (CNS) injury; second, a viral-triggered autoimmune CNS process; and third, a primary autoimmune CNS process. It is also possible that RE has a noninflammatory origin and that the observed inflammation merely represents a response to injury or insult, possibly in the setting of a genetic predisposition.

The observation of the type of inflammatory process found within the lesions has led over the last few years to multifaceted approaches to uncover a possible infectious or immune- mediated (humoral or cellular) etiology. Epidemiologic studies have not identified a genetic, environmental (geographical or seasonal), or clustering effect and failed to demonstrate any association between exposure to various factors, including viruses, and the subsequent development of RE. In many cases, there is no apparent increase in preexistent febrile convulsions, or immediately preceding or associated infectious illness. Serologic studies to detect antecedent viral infection have been contradictory or inconclusive (12,77,78), the search for a pathogenic virus has so far mostly focused on the herpes virus family, and direct brain tissue analysis has also yielded inconsistent results (12,78,79). Expression of the interferon- induced MxA protein was test negative in several cases of RE also arguing against a viral etiology (80). The role of an infectious agent, and the viral hypothesis, in the causation of RE remains, at best, uncertain. It should be noted, however, that a few patients were reported to improve with antiviral therapy (15,81,82).

Systemic (38–41,44) and CSF compartment immune responses still fail to indicate clear evidence of either ongoing or deficient immune reactivity (83). A primary role for pathogenic antibodies in the etiology of RE was proposed after Rogers and colleagues (84) described rabbits immunized with fusion proteins containing a portion of the GluR3. Those animals developed intractable seizures, and, on histopathologic examination, their brains showed changes characteristic of RE with perivascular lymphocytic infiltrate and microglial nodules. The subsequent finding of autoantibodies to GluR3 in the sera of some affected patients with RE led to the definition of a GluR3 autoantibody hypothesis and allowed new speculation into its pathogenesis. GluR3 autoantibodies may cause damage to the brain, and eventually epilepsy, by excitotoxic mechanisms. In the animal model, GluR3 autoantibodies appear to activate the excitatory receptor that leads to massive influx of ions, neuronal cell death, local inflammation, and further disruption of the BBB, allowing entry of more autoantibodies (85). Another proposed mechanism suggests that GluR3 autoantibodies can cause damage by activating complement cascades that lead to neuronal cell death and inflammation (86). These hypotheses prompted a number of open-label therapeutic attempts to modulate the immune system of patients, especially by removing or annihilating the circulating pathogenic factors presumably responsible for the disease (84,86–88). Among cases with no detectable anti-GluR3 antibodies, several were also described to respond well to immunosuppressive treatments (2,20). Other reports in several patients showed no response to plasma exchange (20,87). Finally, more recent work shows that anti-GluR3 antibodies are not specific for RE but can be detected in other neurologic disorders, particularly in non-RE patients with catastrophic epilepsy. Since the sensitivity of detection is low for the RE population and the presence of GluR3 antibodies does not distinguish RE from other forms of epilepsy, the anti-GluR3 antibody test is not useful for a diagnosis of RE (89–93). In one study, GluR3 antibodies were found in the serum of 5/6 and CSF of 4/4 patients with RE and 12/71 patients with other epilepsies (94).

Some patients also harbored additional autoimmune antibodies (in serum of 5/6 patients with RE; e.g., anti-GAD, anticardiolipin, anti-dsDNA, anti-RNP, anti-SS-A). In another study, the same group (95) found elevated levels of GluR3B in the serum of two monozygotic twins, one with presumed RE and the other healthy. More interestingly, both twins also exhibited elevated titers of anti-dsDNA,

anti-GAD, anti-cardiolipin, anti-RNP, anti-SS-A, and anti-beta2GPI and elevated levels of different cytokines—the formers tended to be more elevated in RE twin and the latters more elevated in the healthy one. The reasons for these findings are unknown, but the authors speculated that they represented immune responses to a common injury leading in one to an immune or autoimmune epilepsy disorder. Whether GluR3 autoantibodies in severe forms of epilepsy are responsible for the seizures or whether they result from an underlying degenerative or inflammatory process is still unclear. Passive transfer of the disease into naive animals remains unsuccessful so far, and additional animal models of this illness are lacking.

Various other autoantibodies against neural molecules were described in RE: autoantibodies against munc-18 (96), neuronal acetylcholine receptor α7 subunit (93,97), glutamic acid decarboxylase (anti-GAD) (94), and NMDAAR2A to 2D, specifically GluR ε_2 (27,98), have been reported in some patients. Again, however, these autoantibodies could be detected in neurologic diseases other than RE, confirming that none of the described autoantibodies is specifically associated with this disease, and that a variety of autoantibodies to neuronal and synaptic structures can be found that may contribute to the inflammatory process, or represent an epiphenomenon of an activated immune system. Takahashi et al. (98) showed that GluR ε_2 were present only in patients with EPC (15 patients, including 10 with histologically proven or clinical RE, 3 with acute encephalitis/encephalopathy, and 2 with nonprogressive EPC), and antibodies were directed primarily against cytoplasmic epitopes, suggesting the involvement of T-cell–mediated autoimmunity. To summarize, it may very well be that the antibodies are related to epilepsy rather than specific for RE and are markers for neuronal damage rather than causative (99).

Reports indeed suggested that a T-cell–mediated inflammatory response may be another initiating or perpetuating mechanism in RE. Active inflammatory brain lesions contain large numbers of T lymphocytes. These are recruited early within the lesions, suggesting that a T-cell–dependent immune response contributes to the onset and evolution of the disease. Li et al. (100) analyzed T-cell receptor expression in the lesions of patients with RE and found that the local immune response includes restricted T-cell populations that are likely to have expanded from a small number of precursor T cells, responding themselves to discrete antigenic epitopes. However, the nature of the antigen that triggers such a response is unknown. Nevertheless, more recent work provides further credence to the hypothesis that a T-cell–mediated cytotoxic reaction ($CD8^+$ T-cell cytotoxicity) induces damage, correlating with activation of the granzyme B pathway, and apoptotic death of cortical neurons in RE (91). In an attempt to combine existing knowledge, these investigators (101–103) proposed a new scheme of pathogenesis: an initial unihemispheric focal event leading to BBB opening, the onset of a cytotoxic T-cell response and then spreading of the immune attack across the affected hemisphere. First, a focal event initiates the process (e.g., infection, trauma, immune-mediated brain damage, even focal seizure activity) and an immune reaction with antigen presentation in the CNS and entry of cytotoxic T lymphocytes into the CNS across the disrupted BBB. Second, activated cytotoxic T lymphocytes attack CNS neurons while the inflammatory process, together with the release of cytokines, causes a spread of the inflammatory reaction and recruitment of more activated cytotoxic T lymphocytes. Third, the generation of potentially antigenic fragments, including GluR3 and others to be identified, gives rise to autoantibodies (101) and may lead to an antibody-mediated "second wave of attack." More recently, the same investigators added to this scheme of pathogenesis that astrocytic apoptosis and loss are also features of RE (102). They suggested a specific attack by cytotoxic T lymphocytes responsible for astrocytic degeneration, which in turn would contribute to more neuronal

dysfunction and death.

CRITERIA FOR (EARLY) DIAGNOSIS

The clinical changes of RE are nonspecific, particularly at the beginning of the disease, and clearly at this stage, the major issue is diagnosis. We now have better diagnostic criteria that can lead to early diagnosis (Table 23.1) (3,4,9,12,45,64). The onset in a previously healthy child is of rapidly increasing frequency and severity of simple focal, usually motor, seizures often followed by postictal deficit. This, and a lack of evidence of anatomic abnormalities on early brain MRI, should raise suspicion regarding the diagnosis of RE. Further course and evaluation with scalp EEG showing unilateral findings with focal or regional slowing, deterioration of background activity, multifocal interictal epileptiform discharges, and seizure onset or EPC, particularly corresponding to the cortical motor area, are major neurophysiologic features in favor of RE. Early MRI characteristics include the association of focal white matter hyperintensity and cortical swelling with hyperintense signal, particularly in the insular and peri-insular regions. This is later followed by hemispheric atrophy that is usually predominant in the peri-insular and frontal regions and the head of the caudate nucleus contralateral to the clinical manifestations. Gadolinium enhancement is unusual in RE, and calcifications are not present. Functional imaging studies may reveal abnormalities before any visible structural changes. Typically, FDG-PET shows diffuse hemispheric glucose hypometabolism. SPECT shows unilateral interictal hypoperfusion and ictal multifocal areas of hyperperfusion confirming the lateralized hemispheric nature of the lesion and its extent. MRS may also help in the early detection of brain damage and shows a lateralized decrease in NAA intensity relative to creatine, suggesting neuronal loss or damage in one hemisphere. No laboratory test can support the diagnosis of RE. There is no consistent systemic and CSF response that may contribute to the diagnosis, and, in fact, the most common feature is the lack of cellular or protein response including oligoclonal bands in the CSF of patients with RE. Brain biopsy is often used as a diagnostic tool to confirm the diagnosis. However, histologic findings in RE are nonspecific chronic inflammatory changes that may be subtle enough to be missed by an inexperienced pathologist. Furthermore, the brain involvement may be patchy, and a normal biopsy, particularly when obtained from small stereotactic needles, does not rule out the diagnosis of RE. In some experienced centers, brain biopsy is not routinely done, and clinical evolution in association with scalp EEG and brain MRI are considered diagnostic of RE. Granata et al. (6) suggested that the association of refractory focal seizures with a predominant motor component and with contralateral focal EEG and neuroimaging changes could allow a diagnosis of RE 4 to 6 months after the appearance of the first symptoms.

Table 23.1 Criteria for (Early) Diagnosis of Rasmussen Encephalitis

Clinical	■ Refractory focal motor seizures rapidly increasing in frequency and severity, and often polymorphic ■ Epilepsia partialis continua ■ Unilateral cortical deficits: Motor, progressive hemiparesis, and cognitive deterioration
Electroencephalography	■ Focal or regional slow-wave activity contralateral to motor manifestations ■ Multifocal, usually lateralized, interictal, and ictal epileptiform discharges ■ Progressive, lateralized impoverishment of background activity
Imaging	■ *MRI*: focal cortical swelling with hyperintensity and white matter signal hyperintensity (T2/Flair hyperintense signal), insular cortical atrophy, atrophy of the head of caudate nucleus, and progressive gray and white matter atrophy, unilateral. No gadolinium enhancement and no calcifications on head CT ■ *PET*: unilateral, hemispheric, but during early stage may be restricted to frontal and temporal regions, glucose hypometabolism ■ *SPECT*: unilateral interictal hemispheric hypoperfusion and ictal multifocal hyperperfusion ■ *MRS*: unilateral reduced NAA, and increased lactate, choline, myoinositol, and glutamine/glutamate
Blood	■ None, except inconsistent finding of anti-GluR3 antibodies
Cerebrospinal fluid	■ None, except sometimes presence of oligoclonal bands and inconsistent elevated levels of anti-GluR3 antibodies
Histopathology	■ Activated microglial cells forming typically, but not necessarily, microglial nodules, perivascular lymphocytic infiltration, neuron degeneration, reactive astrogliosis, and spongy degeneration ■ Combination of active and remote, multifocal, intracortical and white matter lesions

CT, computed tomography; GluR3, glutamate receptor 3 subunit; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAA, *N*-acetylaspartate; PET, positron emission tomography; SPECT, single photon emission computed tomography.

The differential diagnosis is large and encompasses progressive, unilateral, neurologic disorders due to inflammatory or infectious processes, developmental, metabolic or degenerative diseases, and neoplastic, paraneoplastic, vascular, or even toxic neuropathogeneses (4). It includes focal cortical dysplasia and tuberous sclerosis, mitochondrial encephalopathy, such as mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, brain tumors, focal unihemispheric cerebral vasculitis, degenerative cortical gray matter diseases, and some forms of meningoencephalitis or disseminated encephalomyelitis. Although several diagnostic criteria have been proposed, especially for an early diagnosis of RE, the correct identification of patients with this disease remains a matter of experience, particularly if specific investigative or therapeutic interventions are considered. When a constellation of clinical and laboratory findings highlights the possibility of RE, close follow-up is necessary to assess progression of the disease and eventually confirm its diagnosis.

MEDICAL AND SURGICAL TREATMENTS

The typical evolution of RE is characterized by the development of intractable seizures, progressive neurologic deficits, and intellectual impairment. AEDs quite consistently fail to provide any significant improvement in seizures. This has led clinicians to try a variety of empiric treatments, including antiviral agents and immunomodulatory or immunosuppressive therapies. Surgery, and specifically hemispherectomy, appears to be successful in arresting the disease process. However, the ensuing neurologic deficits due to surgery usually lead to reluctance to carry out this procedure until significant hemiparesis or other functional deficits have already occurred. Apart from the surgical treatment, there is no established treatment for RE. However, with increased experience and knowledge on the pathogenesis of RE, very promising, therapeutic, options are available, and long-term immunotherapies have now a more rational basis for their use and clearer indications (3). These therapies should probably be considered at the early stages of the disease to halt its progression, in cases where surgery is not possible, for instance when important functional brain areas are involved or in severe bilateral or other unusual variants of RE.

Antiepileptic Drug Therapy

Guidelines for AED treatment in RE are difficult to define and have always been empirical. No AED, or any polytherapy regimen, has been proven to be superior (7), and the choice of the ideal AED rests on its clinical efficacy and side effect profile. Because of the nature of this disease, the danger of overtreatment is high. AED pharmacokinetics, toxicity, and interactions may be better determinants of AED selection and combination therapy. EPC is particularly difficult to treat, but AEDs can reduce the frequency and severity of other focal and secondarily generalized seizures. Since the author's original report on AED efficacy in RE, several new agents have been introduced. Drugs such as topiramate and felbamate that act on excitatory neurotransmitters or those that may affect cortically generated myoclonus, like levetiracetam in EPC, may have a more specific role in treatment. Improved tolerability and better pharmacokinetic profiles and interactions may argue in favor of the newer AEDs.

Antiviral Therapy

Most treatments directed at aborting the progression of the disease were based on the assumption that RE is either an infectious, viral, or an autoimmune disorder. Examples of antiviral treatments are scarce, and only three reports are published: two on the treatment of eight patients with ganciclovir (82), a potent anticytomegalovirus drug, and another on the treatment of a single patient with zidovudine (15). Although some improvement was documented in four of the nine patients, no further reports using antiviral agents in RE have been published; this treatment appeared to be effective only when given early in the course of the disease in three of them raising the possibility that the inaugural insult was maybe indeed viral (82).

Immune Therapy

Evidence implicating humoral and cellular immune responses in the pathophysiology of RE has led to various therapeutic initiatives. A number of case reports and small series suggesting potential therapeutic roles of immune-directed interventions have now been published. These include interferon, steroids, IVIg, plasmapheresis, selective immunoglobulin G immunoadsorption by protein A, and immunosuppression or immunomodulation with drugs such as cyclophosphamide, azathioprine, tacrolimus, rituximab, and even thalidomide. Rarely, such approaches have been associated with sustained cessation of seizure activity and arrest in the progression of the inflammatory process. In the majority of the cases, only transient or partial improvements because of immunomodulator or immunosuppressor use have been noted. Of potential importance is the observation that, to date, the more aggressive immune therapies have been deferred to later stages of the disease, where the burden of the disease is considered to outweigh the toxicity of these interventions. The challenge is to develop safe therapeutic protocols that can be tested in patients soon after the diagnosis and at a time when less damage has occurred and the process may have a better chance to respond to therapy. Eventually, regimens that strike the proper balance between safety and efficacy in typical RE could be applied to the more unusual variants (3).

Interferon-α

Intraventricular interferon-α has been tried in two children (80,81) with the rationale that interferons have both immunomodulating (enhancement of phagocytic activity of macrophages and augmentation of the cytotoxicity of target-specific lymphocytes) and antiviral activity (inhibition of viral replication in virus-infected cells). In both cases, improvement of the epileptic and neurologic syndrome was observed. Interferon β-1b has been used in a case of adult-onset RE, concomitantly or sequentially with steroids and immunosuppressants, and authors reported that treatment reduced seizure frequency, prevented exacerbation of other CNS symptoms, and slowed development of brain hemiatrophy (34).

Steroids

Relatively low- and high-dose steroid regimens were used either alone or in association with other agents such as IVIg. Initial reports were somewhat discouraging (56), but eventually, the use of high-dose intravenous (IV) boluses led to encouraging results. When applied during the first year of the disease, pulse IV steroids were effective in suppressing, at least temporarily, the inflammatory process (13,14,20). The proposed modes of action of steroids include an antiepileptic effect, an improvement of BBB function—and hence reduction of entry into the brain of potentially deleterious toxic or immune mediators—and a direct anti-inflammatory effect. Because of a less favorable

response and of the adverse effects of prolonged high-dose steroids, Hart et al. (13) suggested the use of IVIg as initial treatment followed by high-dose steroids, or both, to control seizures and improve the end point of the disease. Granata et al. (25) have proposed a protocol for administration of immunomodulatory treatments in children and adults with RE. Corticosteroids were given alone or in combination with plasmapheresis, IVIg, protein A Ig immunoadsorption, or cyclophosphamide with positive but time-limited clinical responses in 11 of 15 patients. The long-term efficacy of steroids in RE remains unknown, but there are reports supporting steroid use (13,14,25), specifically pulsed steroid courses to stop status epilepticus (13,25). Also, one has to weigh the risks of long-term steroid therapy and maybe more importantly of delaying unduly the most appropriate treatment for this severe condition, which, in the majority of the patients, remains on the long run surgery of the affected hemisphere.

Immunoglobulin

The use of IVIg in RE was first described by Walsh (104) in a 9-year-old child who received repeated infusions of IVIg over a period of several months with initial improvement but later followed by protracted deterioration and cessation of the treatment. Eight subsequent studies reported on the effect of IVIg, alone or in combination with other treatment modalities (13,20,22,23,25). These reports show similar results with initial benefit, but with a much less clear-cut, long-term effect. IVIg is usually much better tolerated than steroids. The basis for a potential therapeutic effect of immunoglobulin in RE is not known but may reflect the functions of natural antibodies in maintaining immune homeostasis in healthy people. Leach et al. (22) showed a delayed but more persistent response in two adults and suggested that IVIg is more effective in adults than in children. They also proposed that IVIg may have a disease-modifying effect. This phenomenon is probably real but, to date, no one has shown that the early use of immune therapy can modify the long-term course of RE. In a recent report (105), guidelines on the use of IVIg for neurologic conditions were presented by a Canadian expert panel. The expert panel stated that in view of the seriousness of potential adverse events and current lack of data surrounding their frequency and in view of the relatively high costs, IVIg should be prescribed only for appropriate clinical indications for which there is a known benefit. They identified five reports of IVIg use for RE and recommended that IVIg may be an option as a short-term, temporary measure for patients with RE.

Plasmapheresis and Selective IgG Immunoadsorption

Plasma exchange is used with the assumption that circulating factors, likely autoantibodies, are pathogenic in at least some patients (20,25,84,87,88). The majority of patients treated with apheresis showed repeated, and at times dramatic, but transient responses. Because of the lack of long-term efficacy, the complications, and the expense, plasmapheresis should probably be used as adjunctive therapy and may be especially useful in patients with acute deterioration, such as status epilepticus.

Immunosuppressive and Immunomodulation Therapy

Immunosuppressants are used in other autoimmune disorders and also in the prevention and treatment of transplant rejection. They act against the activation of T cells, which, in view of the recent findings of cytotoxic T-lymphocyte–mediated damage in RE, may lead to their acquiring a more prominent role in medical treatment.

Few studies reported on the use of cyclophosphamide in no more than half a dozen patients (20,25,87). It was proposed that intermittent cyclophosphamide may well replace steroid therapy because it is associated with less risk of systemic complications. The experience in this small number of patients is suggesting that neither acute nor chronic use of cyclophosphamide produces significant change on seizure frequency or disease progression.

Seven patients with RE were treated with oral tacrolimus (median follow-up, 25.4 months) with superior outcome regarding neurologic function and progression rate of atrophy but no better seizure outcome as compared to 12 untreated RE patients (106). There were no major side effects. A randomized prospective study comparing IVIG and tacrolimus in RE is currently underway (107).

Following demonstration of antibodies directed against brain tissue in RE and the real but modest effects on disease with immunomodulation (steroids, IVIg, apharesis, and immunosuppressants), a pilot study is now also ongoing with rituximab to directly target the B cells thought to be involved in the process (108). Recently, a single case report described a patient with RE that entered a seizure-free period after being treated with IgG immunoadsorption and intravenous rituximab (109). This suggests that rituximab, a monoclonal anti-CD20 that causes depletion of B cells, may also have an effect on T cells.

Thalidomide was used for the first time by Ravenscroft et al. (110) in a 7-year-old male with RE and high level of CSF tumor necrosis factor-α, leading to a dramatic and sustained clinical response. This prompted a second case report of a 13-year-old girl with very refractory RE since age 5 in whom thalidomide was administered because of a life-threatening condition (111). Prior to thalidomide administration, she received sequentially acyclovir, IVIg, IV and oral steroids, a partial left parasagittal frontoparietal resection, plasma exchanges, and cyclophosphamide. After thalidomide was started, she rapidly improved and during the following 3 years received oral thalidomide 300 mg/day (in addition to valproic acid, clonazepam, piracetam) with a significant and sustained reduction in the frequency and intensity of her seizures. She only developed moderate neutropenia attributed to the drug.

Other Nonsurgical or Semi-Invasive Approaches

Repetitive transcranial magnetic stimulation by reducing cortical excitability can suppress at least momentarily seizure activity and hence may be a useful noninvasive palliative tool in some cases; only one case has been reported (112) and clearly further explorations are needed. Two other patients with adolescent and adult-onset RE (both had brain biopsies) received transcranial direct current stimulation at 1- and 2-mA intensity for 60 minutes in four sessions over a period of 2 months. There were no complications. One patient showed a significant reduction in seizure frequency and the other became seizure free (at follow-up evaluations at 6 and 12 months), and both patients showed improvement in cognition and alertness (37). Finally, a single patient, also with an adult-onset RE, experienced a significant and persistent (over 2 years) reduction in seizure frequency (>50%) and improvement of her neurologic and cognitive condition after vagal nerve device implantation and vagal nerve stimulation (36).

Botulinum toxin was marginally used in attempts to control focal seizures or hyperkinetic movements in RE. To date, only two patients were reported with such treatment (113,114). Finally, to our knowledge, no patient with RE showed significant benefit from deep brain stimulation.

Surgery

The only effective surgical procedure seems to be the resection or disconnection of the affected hemisphere (63,115,116). Alternative procedures such as partial corticectomies, subpial transection, and callosal section have limited results and did not render patients seizure free (117–120). Kossoff et al. (116) demonstrated the benefits of hemispherectomy in children with RE. They showed that 91% of 46 children (mean age at surgery, 9.2 years) with severe RE who underwent hemispherectomy (in the majority hemidecortication) between 1975 and 2002 became seizure free (65%) or had nondisabling seizures (26%) that often did not require medications. Patients were walking independently, and all were talking at the time of their most recent follow-up, with relatively minor or moderate residual speech problems. Twenty-one patients had left-sided pathology (presumably involving the dominant hemisphere in most) with a mean age at surgery of 8.8 years.

Hemispherectomy, hemidecortication, functional hemispherectomy, or hemispherotomy have proven efficacy for control of seizures in patients with RE (3,25,63,115,116,121–126). The decision on how early in the course of the disease surgery should be undertaken depends on the certainty of the diagnosis, the severity and frequency of the seizures, and the impact on the psychosocial development of the patient. The natural evolution of the disease and the severity of the epilepsy often justify early intervention, even prior to maximal neurologic deficit. Finally, involvement of the dominant hemisphere by the disease process provides important observations on brain plasticity, especially on the shift of language (4,122,127). Recent reports looking at language outcomes after long-term RE, serial Amobarbital tests, functional MRI studies, and hemispherectomy illustrate the great plasticity of the child's brain and the ability of the nondominant hemisphere to take over some language function even at a relatively late age. The decision about such a radical procedure requires considerable time and thought, and the psychological preparation of the patients and their families is essential (3,63,128,129).

CONCLUSION AND FUTURE PERSPECTIVES

Rasmussen's encephalitis, although a rare disorder, is now much better delineated and understood by the wider clinical and scientific community. However, recognition of the disease in a naive patient to make an early diagnosis continues to be a challenge. Although confirmation of the clinical diagnosis of RE rests on pathologic findings, in vivo combinations of diagnostic approaches such as clinical course, scalp EEG findings, and high-resolution MRI suggest the diagnosis with a high degree of accuracy. The syndrome, however, appears more clinically heterogeneous than initially thought; localized, protracted, or slowly progressive forms of the disease have now been described suggesting that distinct pathophysiologic mechanisms may be at play. Evidence implicating immune responses in the pathophysiology of RE has accumulated involving both B- and T-cell–mediated processes, but the mechanisms by which the immune system is activated remain to be elucidated. The identification of autoantigens provides evidence that RE can be associated with an immune attack on synaptic antigens and impaired synaptic function leading to seizures and cell death. In addition, T-cell–mediated cytotoxicity may lead to neuronal damage and apoptotic death. Identification of the initiating event (possibly the antigen that triggered the autoimmune response) and of the sequence of immune responses occurring in the course of the disease will hopefully allow timely and specific short- or long-term immunotherapy. Patients with RE, however, usually present with rapid progression, and questions on the type and timing of surgical intervention are still being raised. Most patients will fare better with earlier surgery, and only hemispherectomy techniques can provide definitive and satisfactory results with good seizure, cognitive, and psychosocial outcome.

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CHAPTER 24 TEMPORAL LOBE EPILEPSIES

NORMAN K. SO

This chapter on temporal lobe epilepsies (TLEs), and the next on extratemporal epilepsies, present an updated appreciation of the many expressions and manifestations of focal epilepsy. Specifically, this chapter outlines the following:

- Familial and genetic TLEs (also see Chapter 4)
- Mesial temporal epilepsy with defined pathology (and bitemporal epilepsy)
- Other subcompartments of TLE and concept of temporal plus epilepsy
- Dual pathology in TLE (also see Chapter 26)
- Atypical manifestations of TLE and pseudotemporal epilepsy
- Unusual causes of TLE (also see Chapter 33)

FAMILIAL TEMPORAL LOBE EPILEPSIES

Traditional attention to family history revealed some large familial cohorts to show clinical features of TLE with a classical autosomal dominant pattern of inheritance. They account for a relatively small percentage of all patients with TLE. Gene localization or linkage has been successful in some forms. Diagnosis is not really possible other than by a careful family history as genetic testing is not usually indicated and unlikely to provide additional prognostic information.

The best characterized epilepsy syndrome is autosomal dominant lateral temporal epilepsy or autosomal dominant partial epilepsy with auditory features (ADPEAF). Patients describe prominent elementary or complex auditory aura (buzzing, ringing, altered sounds, voices, etc.) in isolation or evolving into complex partial seizures and secondarily generalized tonic–clonic seizures. Some patients report that sudden loud sounds can trigger a seizure. As genetic analysis in families proceed, other affected family members are found to show more variability in clinical expression, with some experiencing visual, cephalic, vertiginous, or psychic auras, and aphasic seizures (1,2). Age at onset ranges broadly from 2 to 60 years but is most common in teenage years. Overall seizure frequency is low and usually amenable to medical treatment. To date, MRI studies have not shown an abnormality. Genetic linkage was found to chromosome 10q, and point mutations or less commonly a microdeletion of the leucine-rich glioma inactivated 1 (LGI1) gene can be identified in 30% to 50% of families (2–5). This mutation of the LGI1 gene was found in a transgenic mice model to block postnatal retinogeniculate axon pruning producing defects in sensory axon remodeling (6). Autoantibodies to LGI1 are also recognized as a cause of limbic encephalitis, but the clinical manifestations in these patients are quite different.

Familial mesial temporal lobe epilepsy (FMTLE) is also recognized but is proving to be more complex and heterogeneous. Clinical recognition comes from taking a good family history. The

original concept of the condition comprised autosomal dominant inheritance with incomplete penetrance; prominent psychic (déjà vu, dreamy states, affective), abdominal, and other auras; less frequent complex partial or tonic–clonic seizures; and a relatively benign prognosis with relatively few disabling seizures and good response to medications (6). Families in earlier reports did not present with a history of febrile seizures, but later ones did, and in some patients, the two forms of seizures were associated (7). Seizure onset starts most commonly in late childhood to early adult life but has a broad range. FMTLE is now recognized as heterogeneous in its evolution and prognosis. Some families had normal MRIs, while others showed evidence of hippocampal atrophy and sclerosis (8,9). MRI evidence of hippocampal atrophy or signal change correlated with disease duration and refractoriness. Refractory patients with hippocampal disease benefited from surgical resection. Several candidate gene loci have been mapped in FMTLE, to chromosome 3q, 4q, 5q, 12q, and 18q, without much consistency in the different reports.

MESIAL TEMPORAL LOBE EPILEPSY WITH DEFINED PATHOLOGIES (AND BITEMPORAL EPILEPSY)

Most consider mesial TLE with mesial temporal sclerosis (MTS) a distinct entity, whether as a syndrome or a "constellation" in an ILAE proposal. Clinically, a history of a childhood cerebral insult is often found, most commonly that of an early convulsion in as many as 50% to 81%, which included febrile seizures (with complicated features in half) or status epilepticus (10,11). There remain many questions on the relationship between the early convulsive insult and later development of MTS, namely the degree of cause and effect, the role of a preexisting developmental predisposition, and also if later seizures contribute to progressive hippocampal damage. In the prospective FEBSTAT study of children who had febrile status epilepticus, acute hippocampal injury was detected by MRI in 11.5% within the first week, and developmental hippocampal abnormalities such as malrotation were found in 10.5% as compared to a rate of 2% in controls (12). Other recognized early-life risk factors for MTS include birth trauma, childhood cerebral infections, and head injury, while infarction in the vascular territory of the posterior cerebral artery can damage the hippocampus at any age. This still leaves a sizeable number of patients with mesial TLE and MTS, in whom no history of an insult or discernible etiology can be found. Seizures can begin in childhood or later, with a possible delay in diagnosis as early manifestations might be mistaken for childhood anxiety, stomach upset, or other behavior disorders. When they begin in childhood, early treatment is often successful leading to medication withdrawal after a few years, with seizures returning after a latent period in adolescent or adult life, either spontaneously or coinciding with menarche or other circumstances that might have lowered the seizure threshold. The disease is thereafter persistent, and a majority of patients end up with difficult-to-control or refractory epilepsy (13). Patients often experience abdominal, autonomic, emotional, or psychic auras, which can coexist as multiple sensations, while other special sensory (olfactory and gustatory) and somatosensory auras are also possible. Complex partial seizures with predominant dyscognitive/dialeptic features and oroalimentary and distal extremity automatisms are common. Some present with pure amnesic seizures. Certain semiological signs that have lateralizing value in mesial TLE include dystonic posturing of the hand (contralateral to the ictal discharge), unilateral eyelid quivering or blinking (ipsilateral), unilateral hand automatisms (ipsilateral), ictal and postictal dysphasia (dominant

hemisphere), and ictal responsive speech with automatisms (nondominant), among other less established lateralizing signs (see Chapter 12 in this volume). Progression to secondary generalized tonic–clonic seizures can occur, which together with falls, injuries, urinary incontinence, and inappropriate amnestic behaviors (like undressing) leads to social debility and morbidity. Ictal asystole can be another complication during these seizures. When the disease is refractory to medications, there is often a downhill course not only from seizure-related injuries but also in other cognitive and emotional domains. After many years, patients may lose the aura they used to have, exhibit more disabling seizures, suffer more injuries, report greater memory difficulty, and exhibit increased comorbid anxiety, depression, and altered personality.

Common EEG findings include intermittent slow waves over one or the other temporal region, with or without rhythmicity (14). Interictal epileptiform discharges are detected in 80% to 90% of patients (15), with a field topography showing maximal voltage at mesial (sphenoidal) or anterior basal temporal (rows 9 and 10 in the 10–10 nomenclature, as in FT9, FT10, T9, and T10) electrodes (16). Discharges when strictly unilateral almost always correlate with the side of seizure onset, but bilateral discharges are found in 30% to 40% or more. Discharges increase in frequency and topographical area in slow-wave sleep. An ictal pattern of sharply contoured rhythmic theta (>5 Hz) activity over one temporal region whether at onset, or emerging later within 30 seconds, if sustained, is found to correlate with the lobe of seizure onset. This pattern is, however, found in only about 50% to 60% of seizures in patients with verified mesial TLE, and other patterns, localizing or nonlocalizing, account for the remainder. This classic pattern, while most common in mesial TLE, is not pathognomonic and can be seen as a result of spread from another lobe.

The most common pathology in mesial TLE is that of MTS, which encompasses not just hippocampal atrophy and sclerosis with its subtypes (17) but also extensive changes in the entorhinal cortex (parahippocampal gyrus) and variable portions of the temporal lobe to the fornix. The pathology involves bilateral temporal structures in about 60% of autopsied cases (18,19). On structural MRI, this can be visualized, measured, and quantified as changes in signal, volume, and cortical thickness (20). There are further extensive functional alterations throughout the limbic system, unilaterally and often bilaterally as revealed by MRI techniques (spectroscopy, diffusions tensor imaging, tractography), and positron emission tomography. Furthermore, hippocampal atrophy and sclerosis may occur in the following settings: Febrile status epilepticus can cause acute injury in the hippocampus and the adjacent medial temporal structures. Additionally, preexisting hippocampal anomalies such as malrotation may predispose to febrile status. Furthermore, hippocampal atrophy can progress over time, and bilateral disease is common. There is secondary atrophy and cortical thinning in the entorhinal and temporal neocortex in disease of long duration. Some patients have such subtle pathology of the hippocampus that it cannot be detected by MRI and is only seen on pathologic studies.

Other pathologies in the mesial temporal region, which includes the amygdala, hippocampus, parahippocampal gyrus, basal temporal cortex as the fusiform gyrus, can present with a similar electroclinical picture. This arises from rapid recruitment of the temporal limbic system in the seizure network. The pathologies include all types of tumors particularly glioneuronal tumors such as ganglioglioma and dysembryoplastic neuroepithelial tumor; cavernous hemangioma and other arteriovenous malformations; focal cortical dysplasia; traumatic encephalomalacia; strokes; postencephalitic damage; and damage from other cerebral infections (abscess, neurocysticercosis) (21,22).

The treatment of mesial TLE deploys all options available. For patients with a defined pathology

or suspected pathology and medically refractory epilepsy, surgical resection provides the greatest chance of complete seizure control. In the process of presurgical evaluation, a proportion of patients with mesial TLE, in the range of 5% to 10%, are found to have independent seizures from each temporal lobe, or bitemporal epilepsy. As noted, bilateral MTS is common when assessed by MRI or pathology. One explanation of bilateral disease is that the original pathology or insult affected both temporal lobes. This seems understandable when the patient had a history of a complicated febrile seizure, status epilepticus, or encephalitis early in life. Rarely, the patient suffered separate pathologies affecting each temporal lobe, for instance childhood meningitis with MTS on one side and an acquired lesion like a tumor on the other. There are, however, still many cases in which we have a poor understanding of why there is bilateral epileptogenicity. They include patients who have no MRI abnormality. Secondary epileptogenesis had been proposed as a mechanism in bitemporal epilepsy, but its role remains unclear. Clinically, patients with bitemporal epilepsy often exhibit more severe disease in all aspects: increased seizure burden, cognitive complaints, and comorbidities. These patients are usually more prone to suffer postictal psychosis, and they are usually medically refractory. Additionally, these patients also pose a challenge during presurgical evaluations and not all patients may be candidates for surgical resection (23).

OTHER SUBCOMPARTMENTS OF TEMPORAL LOBE EPILEPSY AND CONCEPT OF TEMPORAL PLUS EPILEPSY

Several authors distinguish between mesial limbic TLE and lateral neocortical TLE (Fig. 24.1). Many papers were published comparing these two groups in their etiology, semiology, and electrophysiologic features (24–26). Mesial TLE seizures are more likely to show psychic and emotional auras, and complex partial seizures with unilateral hand dystonia. Seizures in lateral TLE are more likely to have auditory, visual and somatosensory aura, and early signs of contralateral motor involvement (clonic, tonic, versive). However, this dichotomization may be too rudimentary, and classic descriptions of the different compartments of TLE by the French school of Bancaud and Talairach in Paris, further elaborated in the 1963 monograph by Wieser (27), may serve as an even more detailed approach. The “temporobasal limbic” type fits in what is said of mesial TLE. The “temporal pole” subtype describes a seizure initiated in the temporal polar cortex or the amygdala. Clinical manifestations overlap with mesial TLE. However, there may be more prominent autonomic features of heart rate and respiratory alteration, and emotional manifestations such as fear and crying out loud. In the most extreme form, fearful vocalizations are followed by complex agitated movements, and these correlate with propagation of the ictal discharge to the orbito- and mesial frontal regions (28). The “temporal perisylvian” or “opercular” subtype seizures usually arise from the superior temporal gyrus, planum temporale, Heschl gyrus, and insula. An auditory aura is the most specific feature, but vertiginous, gustatory, and somatosensory auras are also suggestive. Somatic sensations are complex involving ipsilateral, contralateral, or bilateral segments, from activation of the second sensory area or insula. Profuse salivation may occur. In the dominant hemisphere, the patient may experience early conscious auditory agnosia or dysphasia. Further clinical manifestations are highly variable as the ictal discharge can first propagate into the frontal or parietal cortex or insula and rapidly to the contralateral hemisphere. With the “posterior neocortical” subtype, seizures arise from varying portions of the lateral or basal temporal neocortex extending to the parietal and

occipital lobes that constitute somatosensory or visual association cortices. Superiorly, it overlaps with "opercular" type in the presence of vertiginous and somatosensory aura. Inferiorly, ill-defined or complex visual aura may be reported. In the dominant hemisphere, conscious dysphasia may be appreciated. Subsequent spread to the temporal limbic network results in a seizure with a more mesial TLE flavor, but the spread can also be suprasylvian evoking contralateral motor manifestations with version. Scalp EEG in these nonmesial TLE subtypes can differ from that of mesial TLE. Interictal EEG discharges may show voltage maxima away from the mesial and basal temporal areas and instead over frontal, posterior temporal, or parietal areas. Complex polyspikes, and rhythmic or repetitive spikes in the EEG, are now recognized as suspect for underlying focal cortical dysplasia. Ictal EEG patterns are more often lateralized rather than well localized to one temporal region. Considerable overlap occurs though in the EEG of mesial and nonmesial TLE.

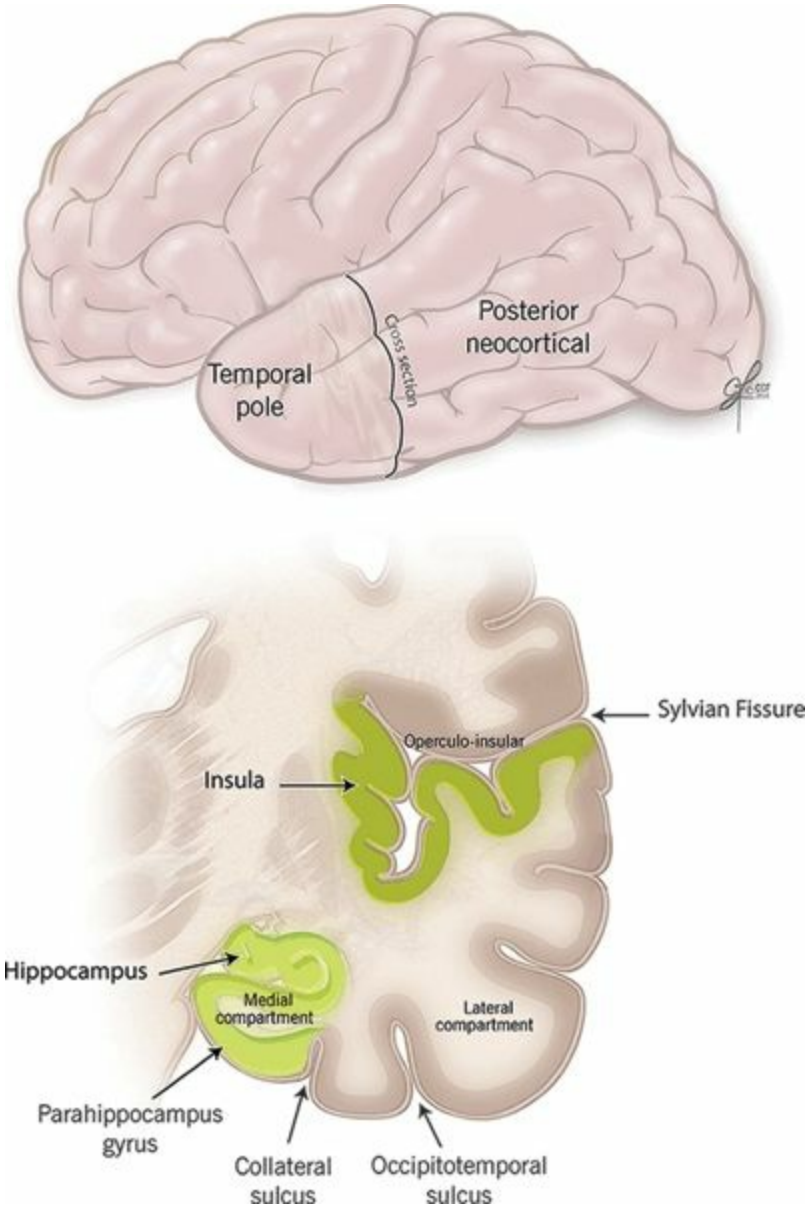


Figure 24.1. The different compartments of TLE. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2014. All Rights Reserved.)

The pathology of nonmesial TLE subtypes runs through the usual categories, including tumors, vascular malformations, and encephalomalacia secondary to stroke and head trauma. But in medically refractory patients who had epilepsy surgery, the most important pathology is that of focal cortical

dysplasia (29). As is discussed next, hippocampal sclerosis can coexist with another distinct pathology. The corresponding findings on imaging may be variable depending on the pathology. Many of the patients with nonmesial TLE who do not have an obvious lesion are called "MRI negative." PET scans can show temporal hypometabolism in these "MRI-negative" cases, and pathology of resection specimens frequently reveals subtle focal cortical dysplasia.

These subcompartments of TLE lead naturally to the "Temporal Plus" concept. In a series of 80 patients (30) investigated by stereo-EEG (SEEG), 22 (27.5%) were classified into the Temporal Plus category based on the topography of initial EEG seizure onset, of which 9 involved the inferior frontal cortex, 7 the suprasylvian opercular cortex, and 6 the temporoparietooccipital junction. Hippocampal sclerosis by MRI was found in 77% of these patients, and they were treated surgically by resection of the temporal lobe and the additional cortical areas identified. When contrasted with patients with TLE proper, differences are found in auras, seizure manifestations, and scalp EEG along the lines expected based on the nonmesial TLE subtypes discussed. What remains far from agreement is the frequency of occurrence of Temporal Plus. The Grenoble cohort gave a high estimate of 27.5% in suspected TLE. By contrast, in the first 100 SEEG implantations into all lobes at Cleveland Clinic (31), only 5% had simultaneous frontal and temporal onsets treated by combined resection of the orbital or inferior frontal cortex and temporal lobectomy. There were no cases of temporoinsular epilepsy, but there were examples of frontoinsular or operculoinsular epilepsy. The biologic or pathologic basis of "Temporal Plus" can only be speculated upon. When there is a combination of hippocampal sclerosis and epileptogenicity beyond the temporal lobe, the situation can be viewed as an example of dual pathology. In this setting, pathologies such as focal cortical dysplasia or traumatic encephalomalacia are not necessarily bound to anatomical lobar boundaries.

DUAL PATHOLOGY IN TEMPORAL LOBE EPILEPSY

The term has been used in different ways, leading to possible misconceptions if definitions are not stated at outset. Experimentally, it has been applied to the creation of a two "hit" model of epilepsy, for instance, first irradiating rodent pups in utero who are then subjected to a second insult in the postnatal period. From the pathologist's point of view, it means two separate definable pathologies. In practice, this usually means the presence of either hippocampal sclerosis or cortical dysplasia with another defined pathology (17,29). It is well known that cortical dysplasia is often associated with or contiguous to a neurodevelopmental tumor such as ganglioglioma and dysembryoplastic neuroepithelial tumor, wherever its location. Cortical dysplasia can present with hippocampal sclerosis in the same temporal lobe. The coexistence of focal cortical dysplasia with another pathology, be it tumor, hippocampal sclerosis, vascular malformation, or other, is now classified as FCD type III (29). Finally, dual pathology is also used to indicate the presence of two macroscopic and topographically separate structural abnormality detected by MRI.

Based on pathologic examinations, the presence of both hippocampal sclerosis and surrounding cortical dysplasia or other definition of malformation of cortical development occurs in 35% to 45% of temporal lobe resections (32,33). Others have defined one pathology, that of hippocampal sclerosis by imaging, and the other of cortical dysplasia by pathology in the resected specimen (34) and found that both coexist in 38%. Controversy abounds on what constitutes a true marker of a significant developmental abnormality in imaging studies of TLE. In one series of 30 patients with

MRI-visualized temporal lobe developmental malformation based on blurring or signal change (but only 4 confirmed by pathology), 65% had associated hippocampal sclerosis based on MRI visual analysis and 87% by volumetric analysis (35). However, the histopathologic correlation of gray–white blurring and white matter signal increase in the anterior temporal lobe is a matter of controversy. One study found increased heterotopic neurons in the white matter (36). Others could not confirm these findings but identified a correlation of anterior temporal white matter blurring on MRI with myelin loss, increased water content, and axon degeneration (37,38), which may serve as markers of more prolonged or severe disease.

When dual pathology is defined by macroscopic findings on MRI, the incidence appears to be about 15%. In 100 patients with MRI volumetric or histologic evidence of hippocampal sclerosis, malformations of cortical development were found in 15% (39). But of interest, many of the malformations were either bilateral or on the side contralateral to the diseased hippocampus. Separately, in 167 patients with macroscopic lesions, whether temporal or extratemporal, 15% had an atrophic hippocampus defined by abnormal volumetric ratio (40). Atrophy is more common in patients with porencephalic cyst (31%), malformation of cortical development (25%), and gliosis (23.5%) as compared to tumors (2%) or vascular malformations (9%). Interestingly, the side of hippocampal atrophy can be found opposite to the side of the lesion. A history of febrile seizures occurred more frequently in those with hippocampal atrophy.

The clinical questions relevant to dual pathology include how each contributes to the epileptogenic process, whether one is the cause and the other the effect, and if resection of both is required for lasting seizure control in those considered for epilepsy surgery. Cortical dysplasia next to a neurodevelopmental tumor is frequently epileptogenic or at least potentially epileptogenic. Thus, invasive EEG recordings typically show seizure onset from an area next to the tumor, and a lesionectomy without removal of the surrounding epileptogenic areas more often results in surgical failure to control seizures. When cortical dysplasia occurs with hippocampal sclerosis in the same temporal lobe, there are more seizure onsets from the neocortical structures, either simultaneous with the hippocampus or independently as studied by combined subdural and depth electrodes (41). For this type of dual pathology with hippocampal sclerosis and histologic cortical dysplasia in the same temporal lobe, there is no major difference in postsurgical seizure outcome as compared to patients with focal cortical dysplasia alone, at least when followed over a 2-year period (42,43), although longer-term follow-up is necessary to learn if this pathology predisposes to late recurrences. When dual pathology is defined by two macroscopic lesions, it makes sense to remove both if they are amenable to safe resection within the same temporal lobe. The principle of removing both lesions becomes less certain when the distance separating the two gets bigger and bigger, as for instance, when there is hippocampal sclerosis in the temporal lobe and a separate lesion in the frontal, parietal, or occipital lobe (Fig. 24.2). Some authors recommend removal of both pathologies, but the experience is based on very small numbers (44). It becomes even more challenging when the lesions are in opposite hemispheres, or when hippocampal sclerosis coexists with diffuse cortical malformations in both hemispheres. For the foreseeable future, such cases will require invasive EEG evaluation to guide surgical planning on an individual basis.

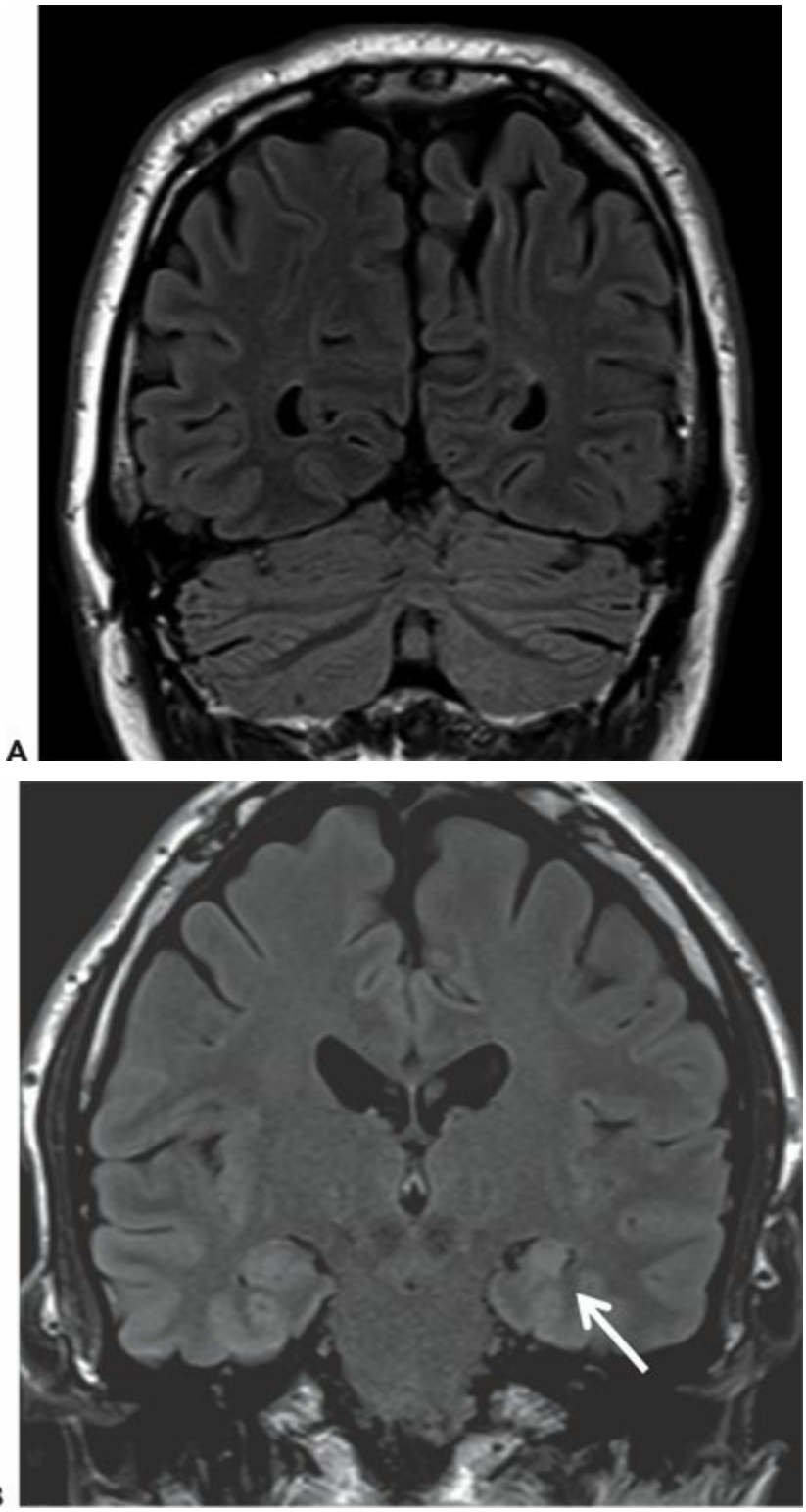
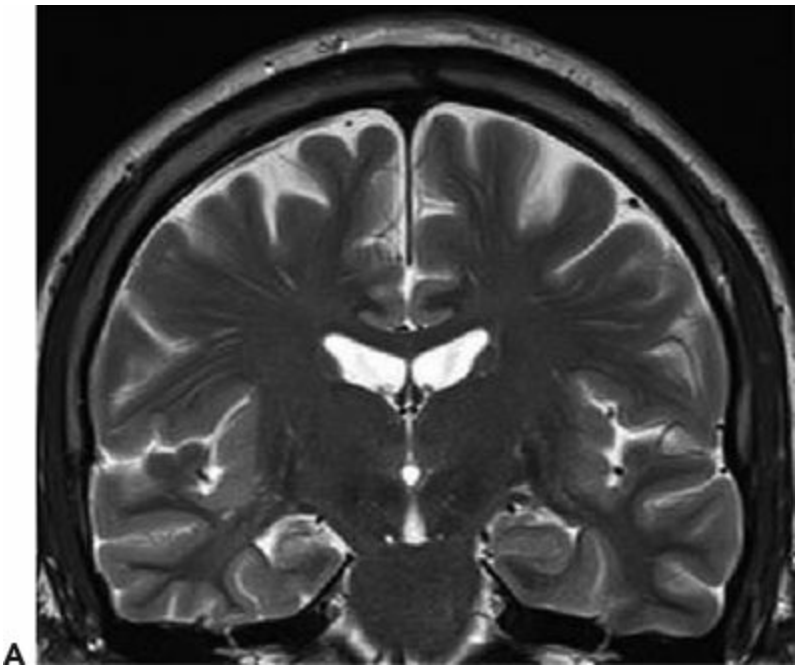


Figure 24.2. Case history: The patient had surgical correction of craniosynostosis as an infant. Seizure onset was at the age of 40 years. Early on, he had an aura of "being on the outside looking in," but later, his seizure semiology changed and the aura presented with light-headedness and dizziness. Seizures evolved into chewing and hand automatisms, with right facial tonic deviation, followed by progression into a generalized convulsion. Scalp EEG showed left (60%) and right (40%) temporal sharp waves, with scalp ictal EEG patterns lateralized to the left hemisphere. SEEG investigation showed seizures arising from the left hippocampus and entorhinal cortex. He underwent left anterior temporal lobectomy and became seizure free. **A:** Left mesial parietal encephalomalacia. **B:** Left hippocampal atrophy and sclerosis (arrow).

ATYPICAL MANIFESTATIONS OF TEMPORAL LOBE EPILEPSY AND PSEUDOTEMPORAL

The picture of TLE in childhood can be different, particularly due to modification by maturational factors. In the first few years of life, a child is unlikely to report auras but is likely to show behaviors in response to the experience, for instance by running to a parent for help. Early on, motor features can be rather nondescript with bilateral tonic or clonic limb movements or head nods (45). Seizures frequently manifest clinically with behavioral arrest and posturing or by a paucity of movements, a hypomotor seizure (46).

Other atypical manifestation include the coexistence of focal and generalized EEG discharges and seizures, exclusively generalized EEG discharge and seizures, and TLE looking like extratemporal epilepsy. In the latter, having an appreciation of the subcompartments of TLE and how seizures spread outside of the temporal lobe to other networks may help explain the extratemporal features. The coexistence of focal and generalized EEG features in patients with TLE is well known but the incidence unclear. In 101 patients who became seizure free after temporal resection (10), 38% had bilaterally synchronous spike–wave complexes as an interictal finding. This is surprisingly high as compared to 1% seen in the 67 TLE patients who were rendered seizure free after resection at a different center (15). Hypotheses to explain the coexistence of focal and generalized EEG features include an inherited trait of generalized epilepsy and other unknown synchronizing mechanisms producing bilateral generalized discharges, potentially in the setting of early developmental lesions. Less than 1% of patients truly express both clinical and EEG features of focal and generalized epilepsy, either chronologically with generalized seizures presenting earlier or concurrently (47). Even less frequent, generalized EEG discharges and seizures can be the only expression of surgically treated TLE (Fig. 24.3).



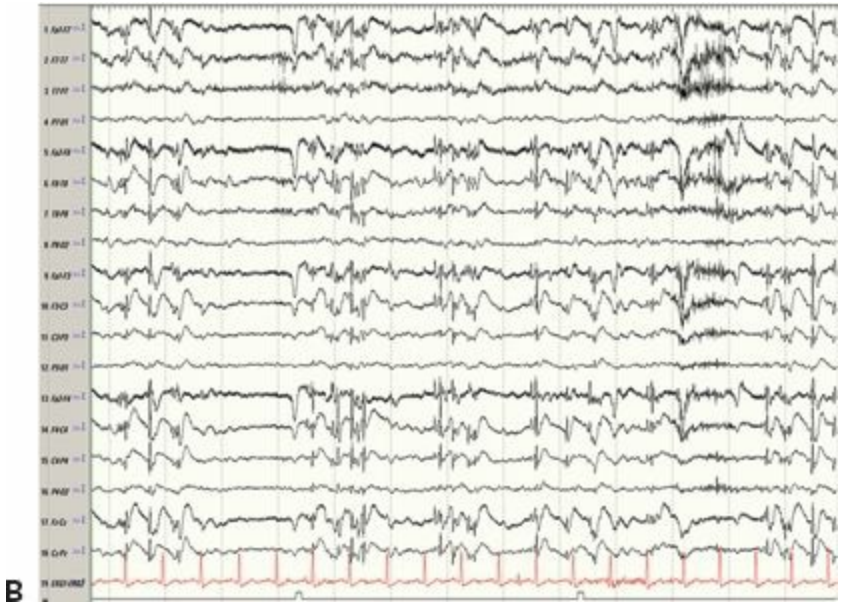


Figure 24.3. Case history: A 44-year-old man had febrile seizures twice at 2 years of age followed by afebrile seizures. Clinically, he had an aura of dizziness, and then either stared or entered a generalized tonic–clonic seizure. PET showed right temporal hypometabolism. Ictal SPECT (SISCOM) showed right temporal hyperperfusion. He has been seizure free after a right temporal lobectomy. **A:** Right hippocampal atrophy. **B:** Ictal EEG 6 minutes after initial onset. One minute later, the patient became unresponsive and entered a generalized tonic–clonic seizure.

It is also possible to mistake extratemporal epilepsy for TLE as encompassed by the term "pseudotemporal" epilepsy (48). The error is most commonly committed after a too cursory analysis of clinical semiology and scalp EEG findings. The eventual clues revealing seizures to arise from outside of the temporal lobe usually derive from the symptoms of the initial aura and imaging findings. Here, the temporal lobe acts as a "sink" to a propagated source, making the interictal and ictal EEGs, and part of the seizure evolution indistinguishable from that of TLE proper (49).

UNUSUAL CAUSES OF TEMPORAL LOBE EPILEPSY

A rare cause of TLE is an encephalocele or encephaloceles on the floor of the temporal fossa. They are most commonly found at the temporal tip near the ridge of the sphenoid bone. In earlier case reports, the pathology was often not suspected and only uncovered during surgery (50). The clinical and EEG manifestations are indistinguishable from mesial TLE, and therefore, these findings were previously regarded as MRI-negative TLE. But improvements in MR and CT imaging now nearly always permit preoperative diagnosis as long as the studies are done and looked at properly (51). Imaging reveals erosion of the greater wing of the sphenoid bone and protrusion of either CSF or brain signal material below the temporal floor (Fig. 24.4). Single or multiple adjacent encephaloceles are seen at operation. Pathology reveals a mix of gliosis, disorganization, or dysplasia in the prolapsed part of the cortex and sometimes with similar pathology in the amygdala. This is a surgically remediable pathology of TLE.

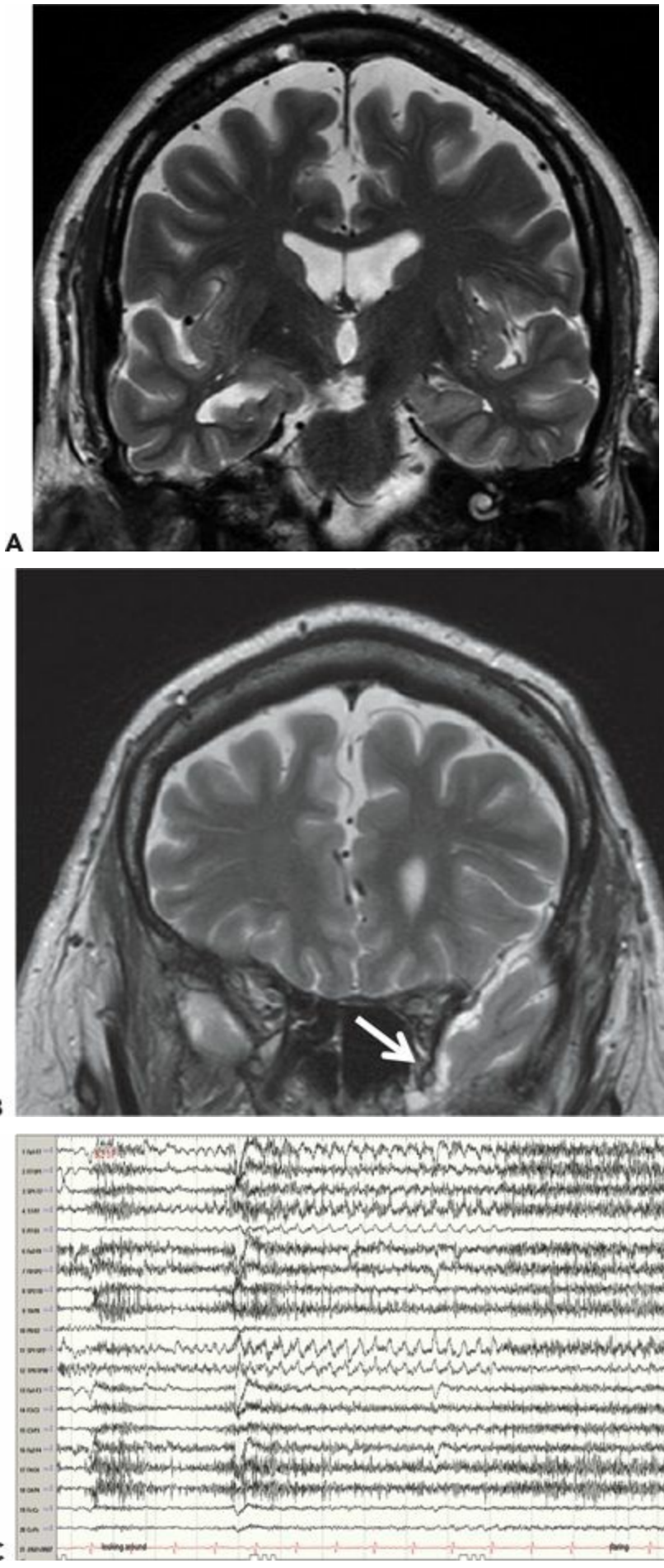


Figure 24.4. Case history: This is a 71-year-old man with seizures since the age of 48 years. Seizures occur without aura or warning. He either stares off or enters a generalized tonic–clonic seizure. Cursory examination of the MRI raised question of right hippocampal atrophy. Interictal sharp waves are left (70%) and left (30%) anterior and mesial temporal while three seizures recorded showed a left temporal-onset pattern. PET study confirmed left temporal hypometabolism. **A:** Right hippocampal atrophy. **B:** Left anterior temporal

encephalocele (white arrow). **C:** Ictal EEG onset in form of rhythmic 3-Hz sharp waves from left anterior temporal region.

Compelling pathologic reports of chronic inflammation, namely the presence of perivascular lymphocytic infiltrates and microglial nodules, intermittently surfaced in the literature of patients surgically treated for TLE (52,53). These pathologic features of chronic inflammation are similar to those found in Rasmussen encephalitis. The TLE cases, however, presented more often with adult age onset and did not exhibit a progressive course of hemispherical damage and malignant epilepsy as seen in typical Rasmussen encephalitis. The jury is still out if this is a real entity or related to neuropathologic criteria that may differ from center to center.

Knowledge on autoimmune mechanisms that can cause epilepsy is rapidly expanding. Autoimmune conditions can be broadly divided into paraneoplastic and nonparaneoplastic conditions, and those with antibodies directed against either intracellular or cell surface antigens (54). When causing epilepsy, the mesial temporal structures are frequently involved; hence, the term limbic encephalitis is used. Clinical, EEG, and imaging features converge in the temporal lobe (55–57). Auras are frequent and prominent, occur independently, and may evolve into complex partial and secondarily generalized seizures. Two-thirds have additional neurocognitive decline. Interictal and ictal EEG findings are usually consistent with mesial TLE. MRI findings often go through a series of changes. Acutely, there is swelling and signal change in the amygdala and hippocampus in more than half of the cases, and less commonly in other temporal structures, which may contrast enhance (a third) and less commonly show restricted diffusion. Later, swelling in the mesial structures subsides and converts to atrophy and sclerosis. One or both temporal lobes can be involved. Although autoimmune limbic encephalitis can occur at all ages (youngest 2.5 years in one series), distinguishing features alerting to the diagnosis include later-onset peaking in the 50s or 60s, abrupt explosive onset, daily seizures (80%), and rapid neurocognitive decline. In addition to identification of an autoantibody, one other test that can be considered diagnostic is the presence of bilateral limbic hypermetabolism on FDG-PET scan. Some of the most common antibodies linked to limbic encephalitis against intracellular antigens include ANNA1 and 2, CRMP-5, amphiphysin, Ma, and GAD antibodies, and all are strongly associated with an underlying malignancy. Additionally, antibodies to cell surface components, such as those to voltage-gated potassium channel complex (VGKC, and associated LGI1, CASPR2), NMDA, GABA, may or may not have an underlying neoplasm; in fact, the majority of VGKC cases are now thought to be autoimmune and not necessarily paraneoplastic and may be the most commonly found antibody in adult patients presenting primarily with seizures (56). Recognition of this diagnosis is important to screen for malignancy and to guide treatment. Effective treatment is contingent on removal of the malignancy when present, or immunotherapy that typically starts with intravenous steroids and immune globulin but may require immunosuppressive drugs for long-term control.

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CHAPTER 25 THE EXTRATEMPORAL EPILEPSIES

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INTRODUCTION AND OVERVIEW

Seizures arising from frontal, parietal, and occipital lobes constitute extratemporal localization-related epilepsies (LRE). They encompass a wide variety of seizure types and syndromes caused by a broad array of conditions, ranging from relatively benign genetic epilepsies to those due to progressive lesions. Their prevalence is not well defined. A study conducted in Rochester, Minnesota, found that patients with partial seizures accounted for 59% of the total population with active epilepsy in 1980, which is probably an underestimation (1); the investigators did not distinguish between temporal and extratemporal lobe epilepsies. The National General Practice Study in the United Kingdom found temporal lobe epilepsy (TLE) in 27% and frontotemporal in 5.6%, so the extratemporal epilepsies constitute perhaps two-thirds to three-quarters of all LRE (2).

Of the extratemporal lobe epilepsies, frontal lobe epilepsy (FLE) is the most common by far, followed by occipital and then parietal lobe epilepsies. This is not surprising based on the relative percentage of cerebral volume each lobe occupies. Clinical seizure patterns are quite varied among the extratemporal lobe epilepsies, with unique clinical presentations and specific seizure types. Diagnosing extratemporal lobe epilepsy (ETLE) is often challenging, as seizure propagation may cause misleading behavior and scalp electroencephalogram (EEG) findings. Many patients may have epilepsy that spans more than one lobe (depending upon lesion size), and the temporal lobe may be involved in the epileptic process along with extratemporal cortex in some patients. Hence, the diagnosis is often muddled, for the epileptogenic process is frequently not as crisply localized as might be wished.

Extratemporal epilepsies may be caused by a wide variety of conditions, including inherited syndromes (e.g., benign epilepsy of childhood with centrotemporal spikes, autosomal dominant FLE, occipital lobe epilepsy, and others) and acquired conditions (e.g., infections, tumors, trauma, stroke, vascular malformations, cortical dysplasias, and others). The extratemporal epilepsies are distinguished primarily by the phenomenology of their seizures, and prognosis largely depends upon the nature of the underlying syndrome (whether a benign genetic cause or not). Treatment for all focal epilepsies usually begins with antiepileptic medication, using drugs that are suitable for all focal epilepsy, as there is no specific therapeutic regimen optimal for ETLE. The prognosis is nonuniform, and surgical management for refractory cases may require extensive evaluation due to challenges with localization and the potential for functional deficits. This chapter discusses the frontal, occipital, and parietal lobe epilepsies, reviewing clinical seizure patterns, specific syndromes and etiologies, and the issues related to evaluation and management for each lobe in turn.

FRONTAL LOBE EPILEPSY

FLE surgery is the second most common type of epilepsy surgery performed; however, FLE may constitute as much as 60% of the LRE population (2). The frontal lobe occupies the largest volume of the brain and may be anatomically subdivided into the anterior frontopolar, orbitofrontal, mesial (or medial), dorsolateral, and opercular regions.

Diagnosing FLE clinically may be difficult, but some features help to distinguish FLE from TLE. The seizure frequency in FLE may be higher than 30 per month, even upward of 100 per month. In addition, patients often have seizures with an older age of onset, that is, after age 5 (3). Semiologic features that help distinguish FLE from TLE include bilateral limb movement at the onset of seizures, absence of oroalimentary automatisms, and a very brief or absent postictal confusional state (4). Vocalization is common, and the seizure duration is generally shorter than the typical temporal lobe seizure, usually <1 minute. Auras may occur with frontal lobe seizures, for instance, localized somatosensory auras may herald a supplementary motor area (SMA) seizure, and fear may denote the state of a seizure originating in the cingulate gyrus.

A variety of conditions may cause FLE. Malformations of cortical development (MCD) represent the largest fraction of patients in whom epilepsy surgery is performed; however, trauma, stroke, and neoplasm (both benign and malignant) are common acquired causes. Other developmental anomalies, meningitis or encephalitis, hamartomas, vascular malformations including arteriovenous malformations, and cavernous hemangiomas, are encountered as well. Genetic causes have also been discovered. Autosomal dominant nocturnal FLE and benign epilepsy with centrotemporal spikes are perhaps the most common observed syndromes. These are further discussed elsewhere.

Seizure Types

Frontopolar Seizures

Seizures originating in the frontopolar regions are perhaps most often due to head trauma. The frontopolar region is susceptible to head trauma, which can cause encephalomalacia and gliosis, though other etiologies can occur (e.g., tumor, vascular malformations). If auras are experienced, they may present with forced thinking, but often, auras do not occur in seizures arising from the frontal pole. Rather, secondary generalization is often the first manifestation. Lengthy seizures with partial responsiveness similar to atypical absence can rarely be seen as well, progressing to tonic or tonic–clonic seizures (5,6).

Orbitofrontal Seizures

Seizures of orbitofrontal origin produce a variety of symptoms, which often are more representative of their pattern of spread rather than where they originate. In children, complex partial seizures without secondary generalization can be associated with autonomic arousal including fear, flushing, piloerection and abdominal pain, and vocalizations with manual automatisms. EEG may demonstrate a pattern of periodic bifrontal sharp and slow waves. Behavior may in part be due to spread to the hypothalamus and temporal lobe (7). Other investigators have found hypermotor activity along with automatisms (and loss of awareness in some patients) and also noted asymmetric tonic posturing, frequent head and body turning, and ictal laughter. Scalp EEG findings may not be localized, and

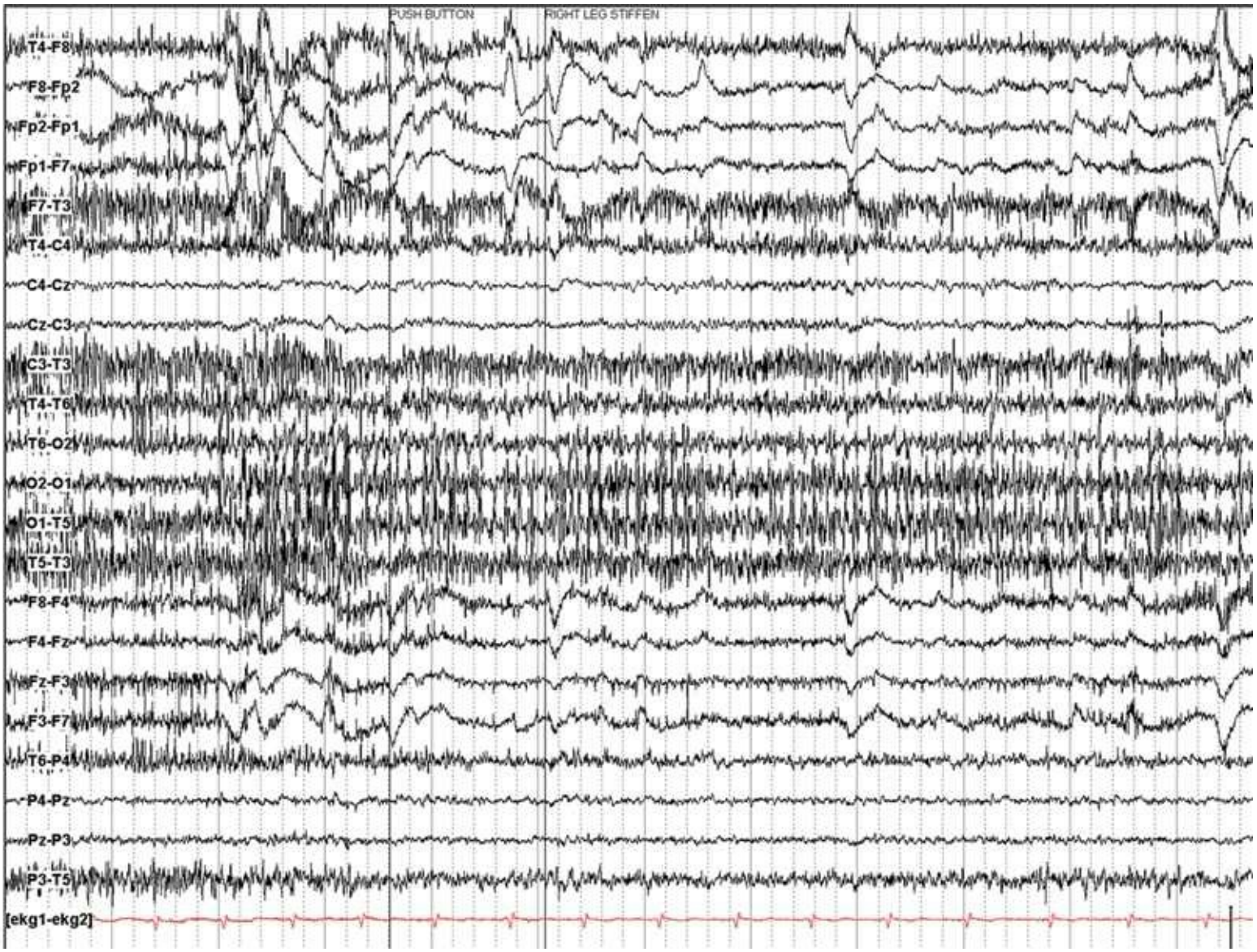
intracranial EEG may be needed for diagnosis (8). Olfactory hallucinations may also occur, presumably related to spread (5). Sphenoidal electrodes might improve the sensitivity of scalp EEG, but often, orbitofrontal seizures have misleading EEG localization. Because of the close connections to the temporal lobes, patients with orbitofrontal seizures may be misdiagnosed as having TLE.

Medial Frontal Seizures

The mesial frontal lobe consists of the medial aspect of the motor strip, SMA, and the anterior cingulate gyrus.

Supplementary Motor Area.

The supplementary motor area, also called the supplementary sensorimotor area, is located immediately anterior to the motor strip on the medial surface of the frontal lobes. Supplementary motor seizures have well-defined clinical characteristics. Patients frequently report somatosensory aura such as numbness in a contralateral limb, which is followed by unilateral or bilateral tonic limb posturing. This has been described as showing a "fencer" posture, the "figure of four" sign, or "M2e" posturing. Patients may then also have whole body movements, vocalizations, and perhaps emotional semiology, with late head and eye version (9). Negative motor seizures rarely may occur as well, with inability to voluntarily move the extremities while the patient is awake. SMA seizures often are nocturnal and occur in clusters, and awareness and consciousness are usually retained unless secondary generalization occurs (10). Surgical removal of the SMA may result in transient akinetic mutism and either unilateral or bilateral weakness or apraxia (the "SMA syndrome"), which usually resolves in 1 to 4 weeks after surgery, but may last as long as 6 months (11,12). Figure 25.1 demonstrates the findings in a patient with SMA epilepsy.


PUSH BUTTON
RIGHT LEG STIFFEN
T4-F8
F8-Fp2
Fp2-Fp1
Fp1-F7
F7-T3
T4-C4
C4-Cz
Cz-C3
C3-T3
T4-T6
T6-O2
O2-O1
O1-T5
T5-T3
F8-F4
F4-Fz
Fz-F3
F3-F7
T6-P4
P4-Pz
Pz-P3
P3-T5
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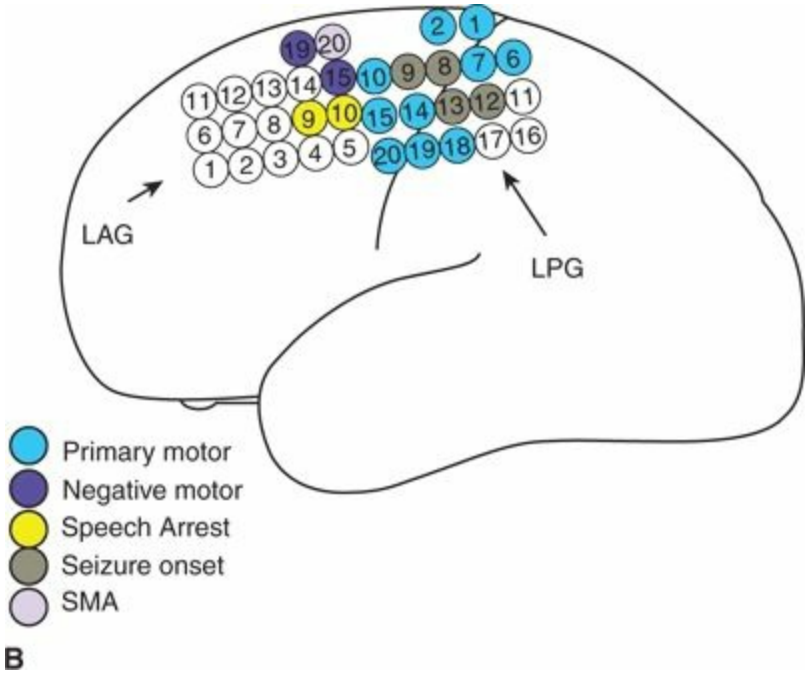
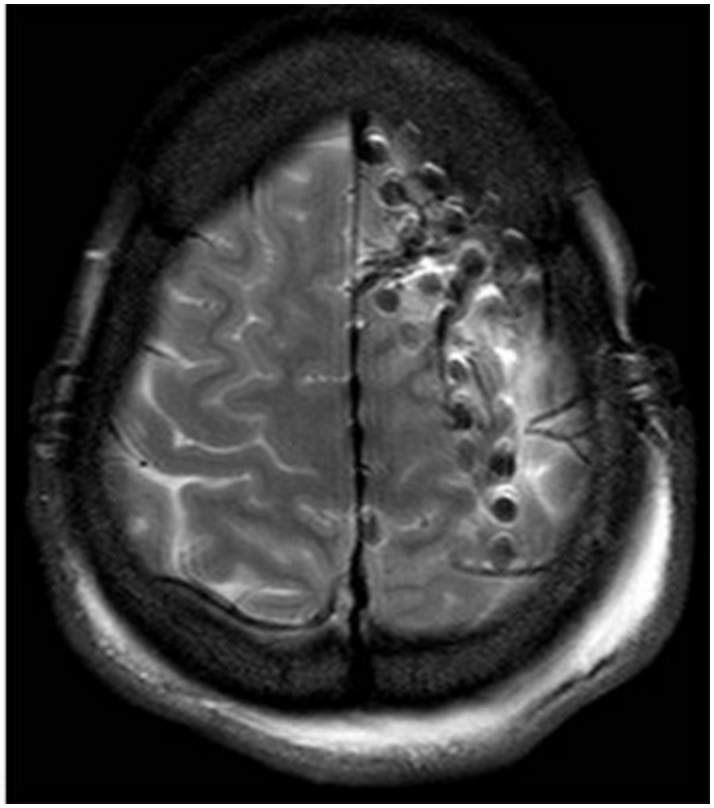
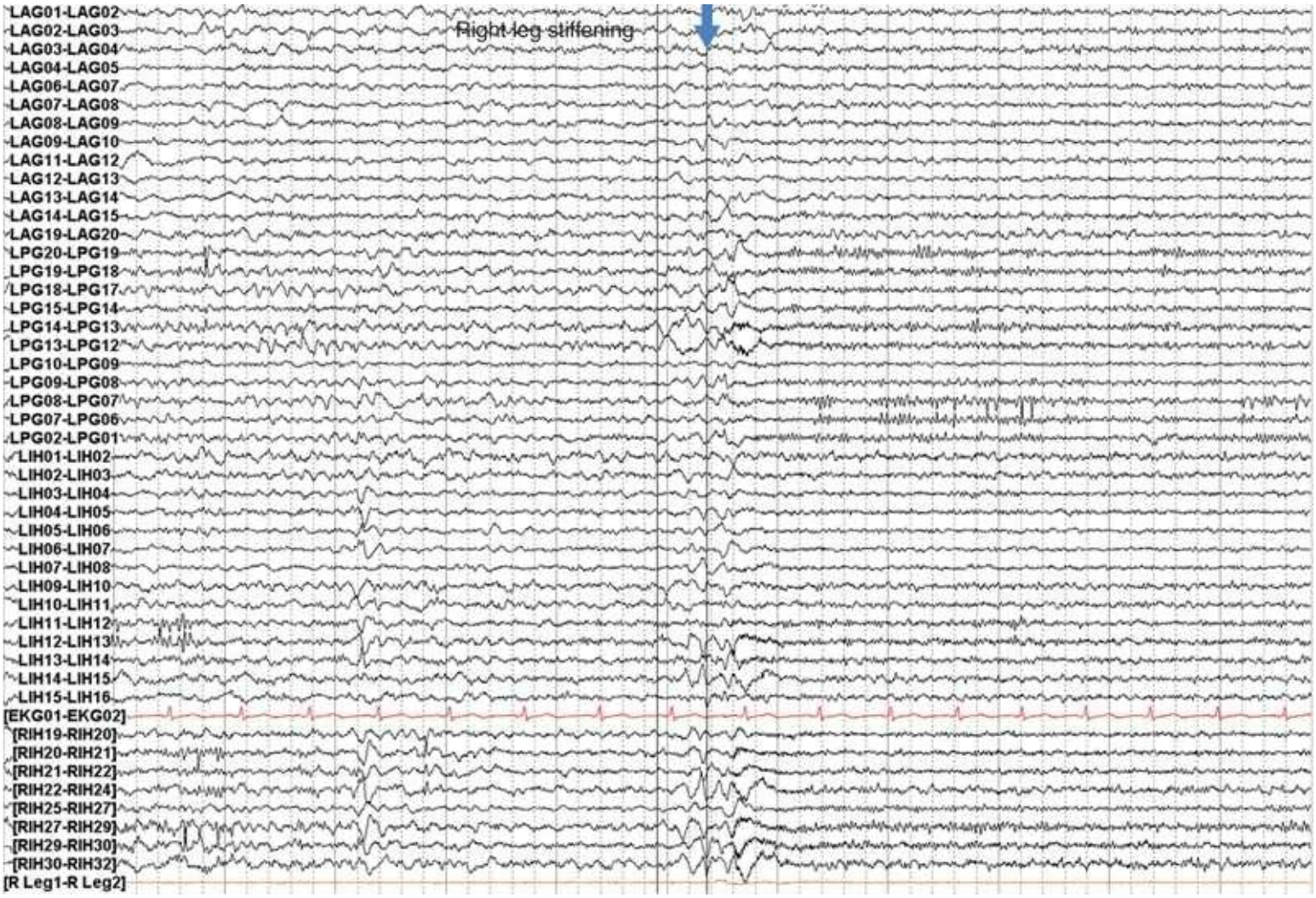
A


LAG
LPG
Primary motor
Negative motor
Speech Arrest
Seizure onset
SMA
B



C



D

Figure 25.1. Dorsolateral FLE with seizures arising from the motor strip: a 21-year-old woman with simple partial seizures since a viral illness at age 9. Seizures began to cluster at age 19 after 10 years of response to medical therapy. The clinical pattern was an aura of nonspecific aura of dizziness, followed by right leg greater than arm tonic stiffening with preserved awareness. Stage I evaluation (**A**) shows CZ beta, which was not clearly determined to be ictal, and abundant muscle artifact. Stage II evaluation with left dorsolateral and interhemispheric subdural electrodes (map, **B**, MRI in **C**) showed ictal onset in primary motor cortex and gamma at

contacts 8, 9, 12, and 13 in the left posterior grid (**D**). Subpial transections over the ictal onset zone were performed.

Anterior Cingulate.

The anterior cingulate gyrus has extensive connections throughout the frontal lobe as well as the limbic system, brainstem, and thalamus. It is involved in emotions, autonomic functions, perception of pain, and motor planning (13). Whereas the amygdala is implicated in the generation of fear in auras of TLE, the cingulate gyrus in the medial frontal lobe is thought to be the generator of fear auras in patients with FLE. This may relate to propagation of ictal discharges to the amygdala. Patients with proven lesional cingulate epilepsy have complex, hypermotor behaviors such as running, kicking, grasping, or thrashing. Behavioral changes including postictal or interictal agitation are seen, which can resolve after lesionectomy (14).

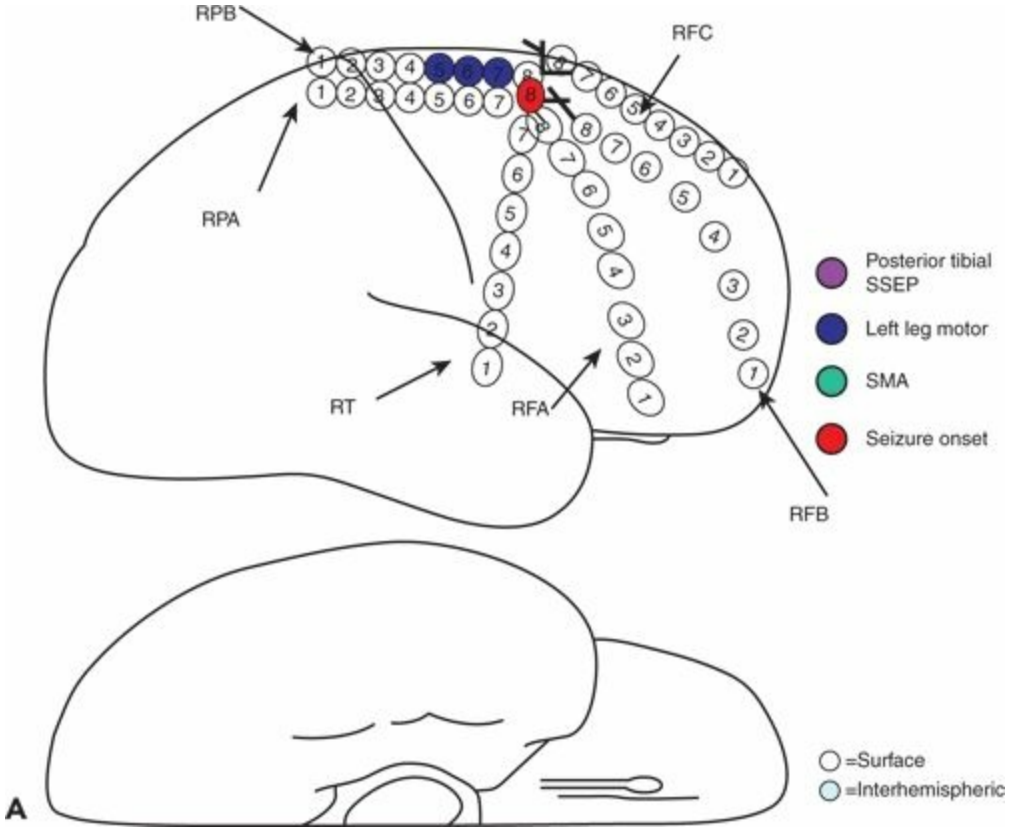
Primary Motor Area

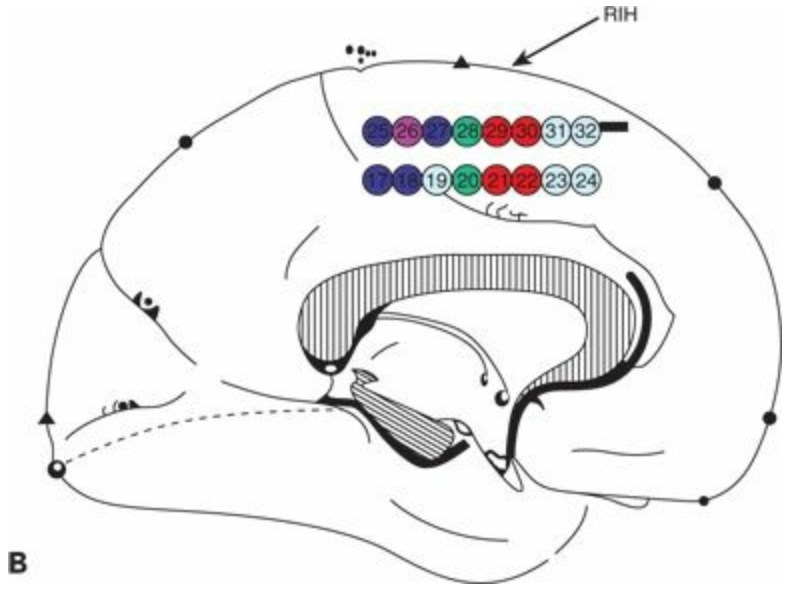
Primary motor cortex in the medial frontal lobe (interhemispheric region) is responsible for movement of the lower extremity and sphincter control. Seizures arising from the leg motor cortex produce clonic movement of the thigh, leg, or foot and may produce bladder or bowel incontinence.

Dorsolateral Frontal Seizures

The dorsolateral frontal lobe includes the lateral primary motor strip, perirolandic region, and premotor areas. Seizures arising from premotor dorsolateral frontal cortex can cause tonic posturing of the arm or face, sensory phenomenon, or psychosensory auras including forced thinking (as seen with frontopolar seizures). Early spread to motor cortex will cause clonic activity while still conscious, whereas temporal lobe seizures are more likely to produce experiential or epigastric auras with motor activity once consciousness is impaired (15). Seizure propagation to Broca's area may cause speech arrest, and contralateral head and eye version commonly occur with spread to the frontal eye fields. The EEG more often shows localized findings than with mesial or orbitofrontal seizure origin because of the close proximity of the cortex to the scalp. The scalp ictal EEG often shows fast activity in the beta frequency range, in contrast to temporal lobe seizures, which more often begin with rhythmic theta discharges. Ictal beta at seizure onset is often well localized in dorsolateral frontal lobe seizures and predicts a good postsurgical outcome, but the same is not necessarily true for all FLE patients (16,17).

Seizures that arise from the primary motor strip differ clinically from those of the SMA or premotor area in that they usually begin with contralateral facial or hand clonic activity followed by spread to the rest of that side of the body (i.e., a jacksonian pattern of spread), with speech arrest and then head and eye version. Patients might remain awake, or these seizures might generalize. Progression to asymmetric tonic limb posturing occurs as the seizure spreads to the SMA (9). These seizures usually have ictal EEG localized to the perirolandic area. Surgical resection of the motor strip will produce permanent weakness and clumsiness unlike the transient deficit associated with SMA resection. Figure 25.2 provides an example of a patient with epilepsy localized to the motor cortex.


RPB
RFC
RPA
RT
RFA
RFB
Posterior tibial SSEP
Left leg motor
SMA
Seizure onset
=Surface
=Interhemispheric
A


RIH
B

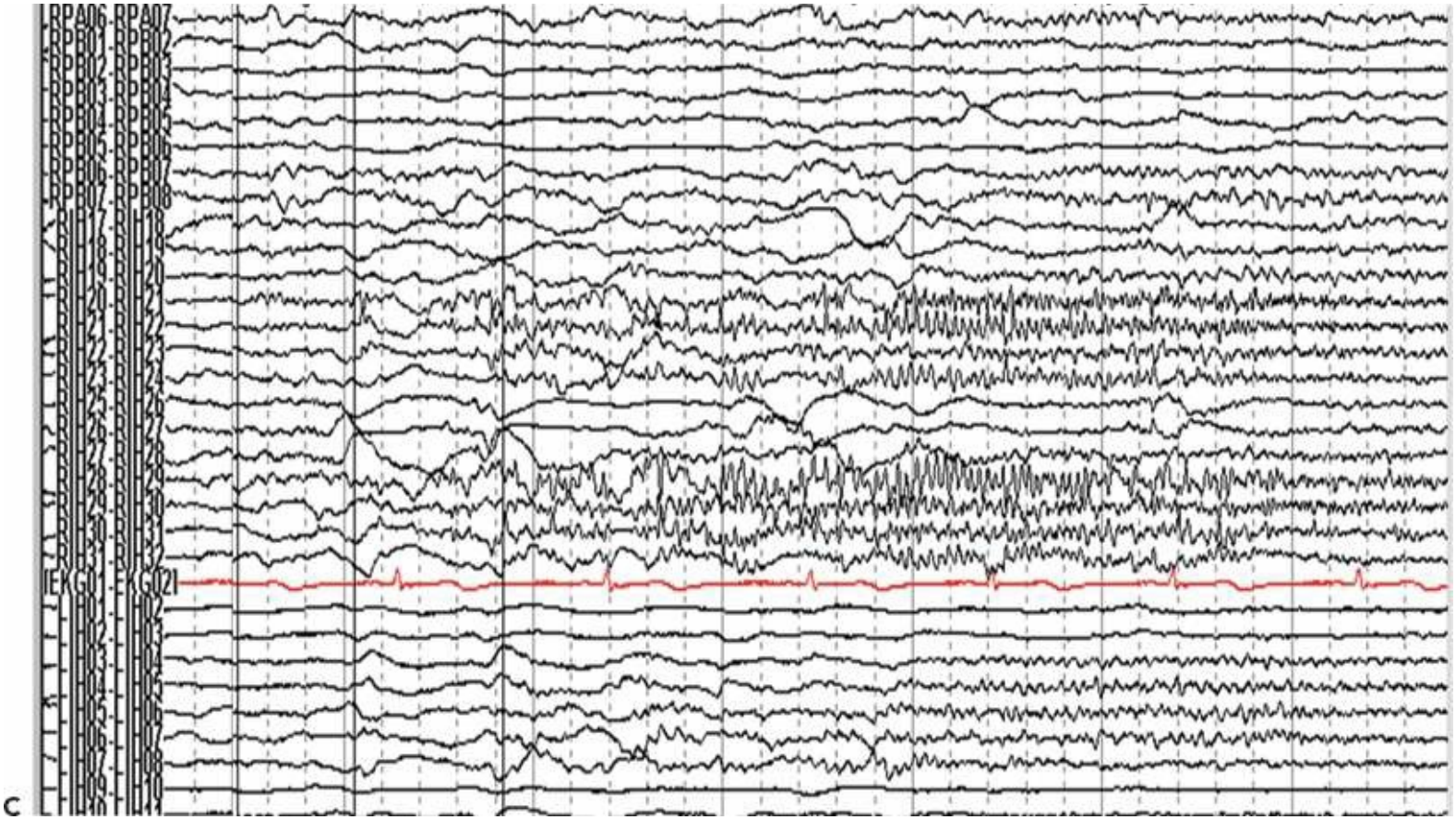


Figure 25.2. Supplementary motor area seizures. A 20-year-old man has refractory GTC seizures and also SPS with left arm tonic extension occurring at night. The ictal surface EEG was nonlocalizing and demonstrated only diffuse attenuation during SPS. **A and B:** Cortical map showing seizure onset seen in the interhemispheric strip electrodes, primary and supplementary areas. **C:** Ictal IEEG with fast activity seen in the right interhemispheric electrodes.

Frontal Opercular and Insular Seizures

The operculum is the region of cortex overlying the insula and is subdivided into frontal, temporal, and parietal opercular cortices. The insula is considered by some as an anatomic part of the temporal lobe and a distinct lobar entity by others. This section will discuss seizures that arise from the frontal operculum and insula where they are confluent, as a subdivision of frontal lobe seizures.

Seizures arising from the frontal operculum often present with gustatory auras, apraxias of swallowing or mastication, and dysarthria. Patients may chew, may salivate, and may complain of abnormal laryngeal sensations, paresthesias in the arm and face, choking sensation, and trouble breathing. Early spread in a posterior and superior direction often causes facial clonic activity. An acquired epileptiform opercular syndrome has been described with ictal manifestations of above symptoms in addition to other seizure types. This has clinical similarities to the structural disease in Foix–Chavany–Marie syndrome and is analogous to Landau–Kleffner syndrome, but with symptoms localizing to the anterior rather than posterior operculum (18). Stereotactic EEG studies show that seizures with frontal opercular and insular onset produce the aforementioned symptoms at onset with hypermotor or asymmetric tonic posturing during sleep (19). This probably reflects variable spread patterns to mesial frontal structures (i.e., anterior cingulate or SMA cortex).

Localization of Frontal Lobe Seizures by EEG

The interictal EEG is often not helpful in the localization of frontal lobe seizures. Only a small proportion of patients have spikes restricted to the frontal lobe focus. Some patients have bifrontal or

generalized spike-and-wave discharges, while others may have only temporal lobe interictal spikes. Other individuals have multifocal spikes, and some patients have a normal interictal EEG (3).

The ictal EEG is often unrevealing in frontal lobe seizures, sometimes obscured by movement and muscle artifact, and at other times either negative or poorly localized. Focal seizure onset occasionally is noted in the scalp EEG, usually with high-frequency beta frequency onset, but more often, the ictal EEG does not provide adequate localizing information. This may be due to the fact that much frontal cortex is buried, either within sulci or in medial or basal regions that are poorly sampled by the scalp EEG and by rapid contralateral spread of ictal discharges via the corpus callosum. Seizures beginning in mesial frontal lobe are particularly difficult to record with scalp EEG. Half of patients with mesial FLE will have generalized epileptiform patterns, nonlateralized midline discharges, or no EEG findings when seizures begin. FLE arising in dorsolateral cortex more often appear lateralized than mesial FLE in the ictal EEG, though remain less well localized than temporal lobe seizures. Incorrect seizure lateralization is more often observed in lateral FLE patients than in mesial FLE patients (20).

When the scalp ictal EEG is nonlocalized—as is common in the extratemporal lobe epilepsies—noninvasive neuroimaging techniques other than magnetic resonance imaging (MRI) including PET-FDG, magnetoencephalography, ictal single photon emission tomography, and functional MRI (including with simultaneous EEG) may help to localize the source of seizures and guide intracranial electrode placement that is required.

A recent series of FLE patients localized by FNIRS (functional near-infrared spectroscopy) showed the promise of this novel technique as an adjunct to video–EEG monitoring (21).

Differential Diagnosis

The clinical patterns of frontal lobe seizures include bizarre behaviors, which may be confused for nonepileptic events. Patients may be misdiagnosed as having parasomnias or receive a diagnosis of psychogenic nonepileptic seizures (PNES) and mistakenly thought to have a primary psychiatric disease. The challenge in diagnosing FLE is partly due to odd ictal behaviors, which may be confounded by ambiguous EEG findings as noted above. It is important to recognize stereotypy of behavior and nocturnal clustering, which suggest frontal lobe seizures rather than PNES or parasomnias. Patients with FLE may have preserved awareness during bilateral body movement, which may include bicycling and large thrashing movements. Ictal eye closure, pelvic thrusting, and prolonged seizure duration (i.e., >5 minutes) suggest PNES rather than FLE.

Surgical Considerations

After failure of medical therapy, surgical planning for FLE should take into account the possibility of eloquent cortex (e.g., areas important for language, movement, personality) in the epileptogenic zone. Intracranial EEG may be performed with subdural grids to over Broca regions and the motor strip, which can be mapped either intraoperatively or extraoperatively at the bedside with electrical stimulation of the cortex. If the seizure focus overlies eloquent cortex, performing multiple subpial transections to preserve columnar organization can minimize postoperative functional deficits or responsive neurostimulation (RNS) can be performed (22). The addition of an anterior corpus callosotomy (ACC) may be considered for FLE patients with frequent secondary generalization, since that procedure alone often offers benefit. For patients who have multifocal or bilateral onset zones,

RNS implantation may also be considered. Deep brain stimulation of the centromedian nucleus was performed experimentally in patients with FLE, but might be more suitable for patients with generalized epilepsy syndromes (23). Vagus nerve stimulation also may be considered for refractory cases that are not candidates for focal resection or fail resective therapy.

Outcome of Surgery for Frontal Lobe Epilepsy

Frontal lobe resections have the worst seizure-free outcomes for epilepsy surgery, with 27% of patients found to be seizure free after surgery in a large metaanalysis (24), though some individual series demonstrate a seizure-free rate as high as 60% (17). In children, frontal lobe resections more often resulted in unsatisfactory outcomes than posterior resections in a meta-analysis of nonlesional cases. The authors found that complex partial seizures rather than generalized tonic–clonic seizures and focal cortical dysplasia identified on pathology were associated with better outcomes (25).

The class I outcome in the series of 16 patients reported by Laskowitz et al. (3) in 1995 was 67%. Fourteen of them had frontal lobe resections, of which half were accompanied by ACC. The remaining two patients received ACC alone. Follow-up was at least 5 years with a mean follow-up period of 46 months. Electrocorticography was performed intraoperatively for most patients, and five patients underwent chronic intracranial monitoring. A lower preoperative seizure frequency was associated with seizure-free outcome as was a later age at onset (3). Another series reported 55% seizure freedom at 1 year, which dropped to 27% at 5 years (26). The presence of generalized interictal spikes, extrafrontal MRI findings including hippocampal sclerosis, a normal MRI with either normal pathology or malformation of cortical development, acute postoperative seizures, and postoperative interictal spikes on EEG correlated with a recurrence of seizures postoperatively (26).

A more recent series at the same center of a larger cohort found 66% seizure freedom at 1-year, 52% at 2-year, and 44% at 5-year follow-up. Longer seizure duration (>5 years) was predictive of poor outcome especially in children and those with MCD and tumors (27). Another recent study of 58 FLE patients who underwent focal resection with long-term follow-up demonstrated a favorable outcome in 60% of patients. They did not find any difference in outcome based on the location of resection (28). An intracranial EEG study noted that an ictal onset zone of <2 cm and delayed spread of the ictal discharges to other lobes were associated with postoperative seizure freedom. Dominant resections were more often followed by poor outcome, probably because the presence of adjacent language cortex limited resection size (17).

OCCIPITAL LOBE EPILEPSY

Occipital lobe seizures may arise from either primary visual or association cortex. Elementary visual auras such as seeing lights and shapes arise from primary cortex, while more complex hallucinations arise from adjacent association cortex in occipital, posterior temporal, or parietal lobes. Eye blinking, eye flutter, and amaurosis are other common clinical phenomena. Gaze deviation, typically ipsilateral, without impairment of consciousness also has been reported (29).

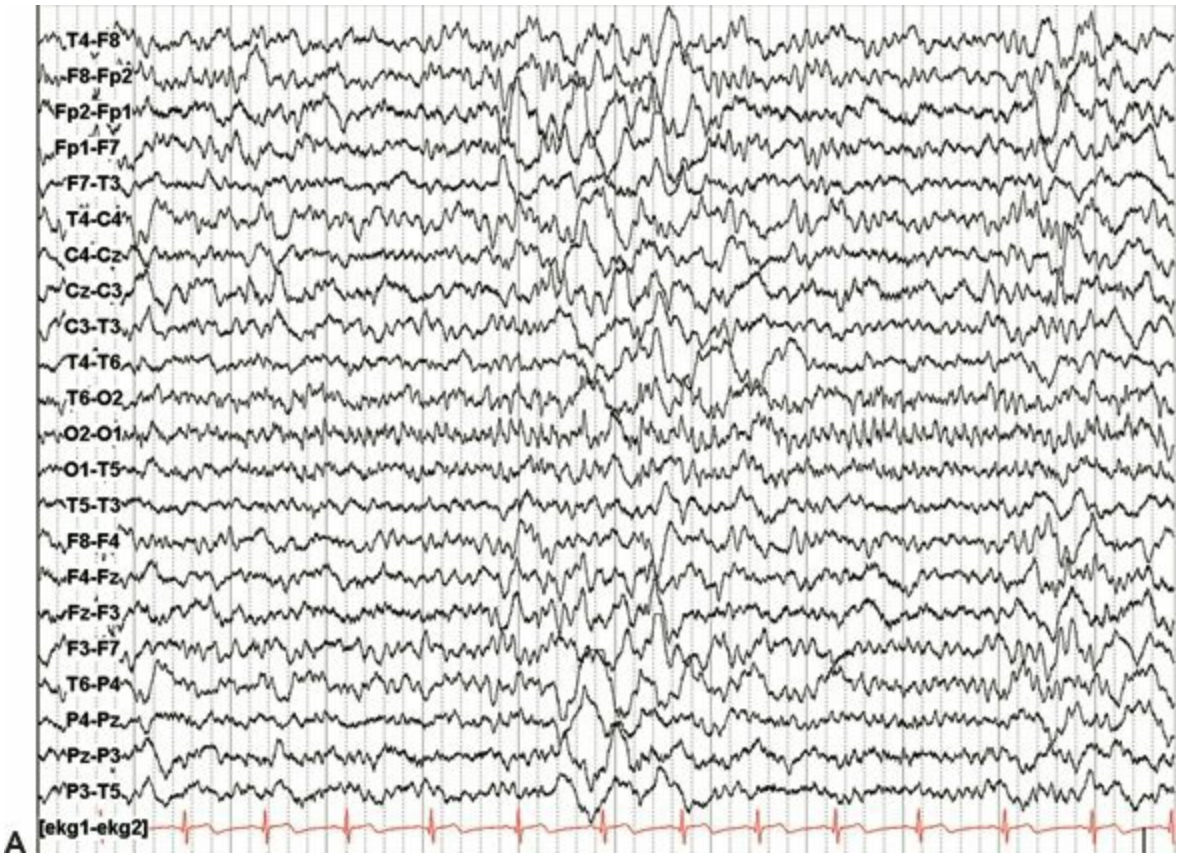
In children occipital lobe epilepsy may be caused by a variety of conditions, such as trauma, tumors, and stroke, but specific causes include celiac disease, childhood occipital epilepsy syndromes including Panayiotopoulos and Gastaut types, mitochondrial disease, and posterior reversible encephalopathy syndrome. Lafora body disease is a form of progressive myoclonic epilepsy in which patients may experience occipital seizures early in the course of illness. Celiac

disease is associated with occipitoparietal lobe calcifications and epilepsy (30). The typical calcifications occur unilaterally and are sinuous and double contoured with associated microgyria. These findings may be confused with Sturge–Weber syndrome but have a different pathophysiology. Children often do not have intestinal symptoms when diagnosed with epilepsy, although some may have had an intestinal syndrome in infancy. Folate levels are characteristically low. Antigliadin antibodies and intestinal biopsy help diagnose the condition, and seizures can be successfully treated with a gluten-free diet when initiated early (31).

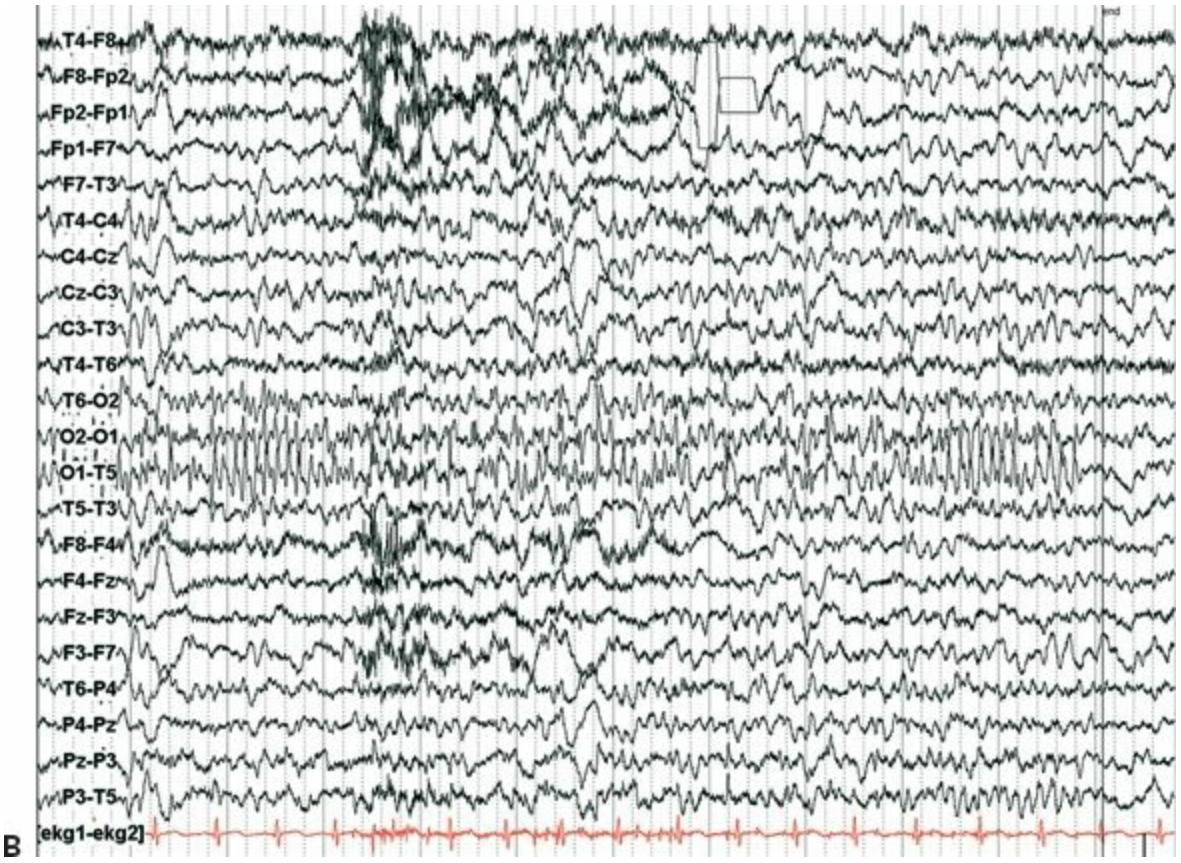
Occipital lobe epilepsy can also be difficult to diagnose. The occipital lobe has three surfaces, the mesial, lateral, and inferior surfaces. Mesial and inferior generators are often difficult to identify and lateralize with scalp EEG. Incorrect localization and lateralization are seen commonly, and generalized seizure patterns can be seen in over one-quarter of patients (20). Patients with occipital epilepsy often have coexisting temporal lobe abnormalities in the EEG and may have dual pathology affecting both occipital and temporal lobes (32).

Surgical Considerations

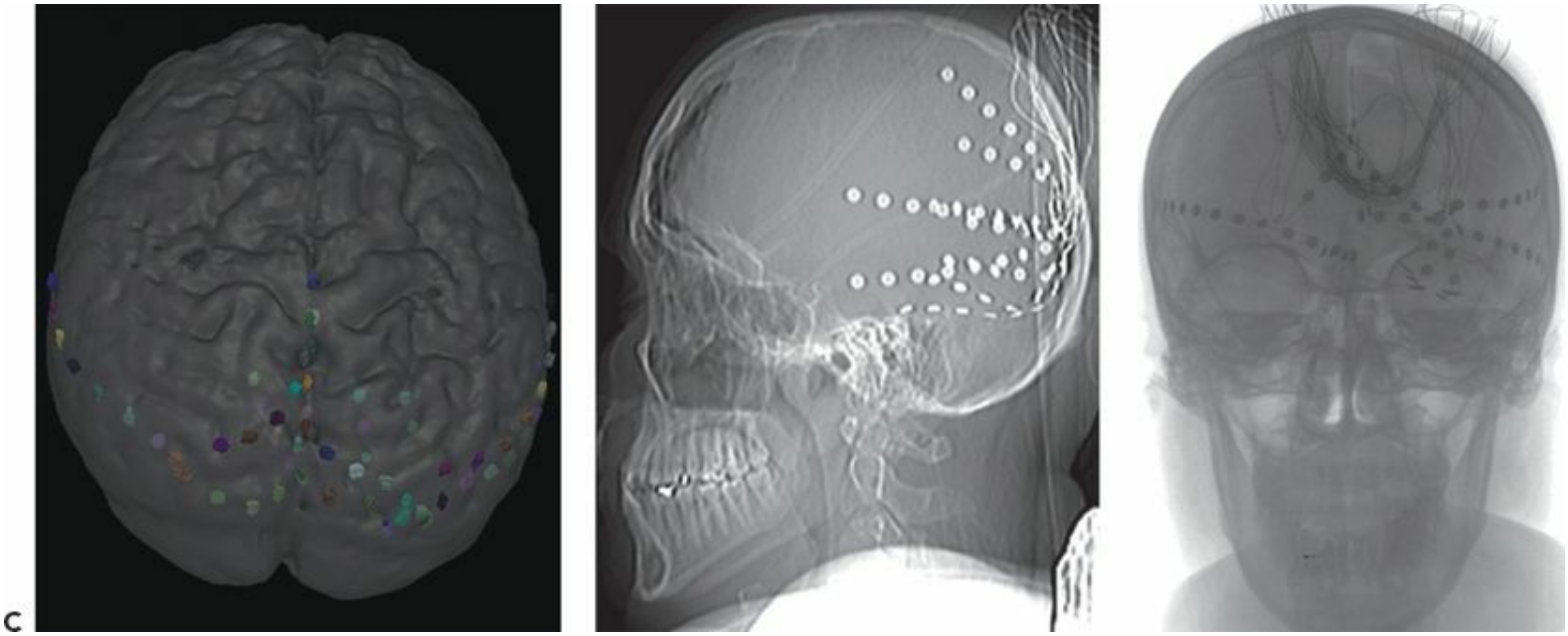
After surgery, 46% of patients are seizure-free based on a meta-analysis with long-term follow-up (24). Satisfactory (meaning Engel I and II) outcomes have been reported between 45% and 70% in studies done since the year 2000, and more recently published series have shown better outcomes than older series with as many as 68% achieving class I or II outcome (33). Although only small series have been reported, it has been noted that resections that include the temporal lobe and hippocampus result in favorable outcomes, which may be due to close connections to mesial temporal structures (32). Also, ample coverage of all three surfaces of the occipital lobe with intracranial electrodes (the lateral, mesial, and tentorial surfaces) is associated with better outcome (32). Cortical mapping to determine the extent of primary visual cortex and utilizing intracranial visual evoked potentials may help minimize postoperative hemianopsias. The desire to spare the visual fields is the main factor limiting the extent of surgical resection, and perhaps seizure-free rates. Figure 25.3 demonstrates an example of occipital lobe epilepsy.

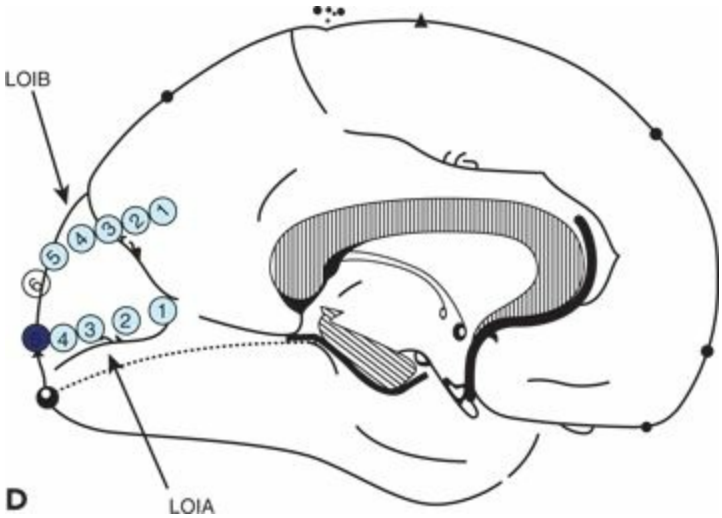

T4-F8
F8-Fp2
Fp2-Fp1
Fp1-F7
F7-T3
T4-C4
C4-Cz
Cz-C3
C3-T3
T4-T6
T6-O2
O2-O1
O1-T5
T5-T3
F8-F4
F4-Fz
Fz-F3
F3-F7
T6-P4
P4-Pz
Pz-P3
P3-T5
[ekg1-ekg2]

A


T4-F8
F8-Fp2
Fp2-Fp1
Fp1-F7
F7-T3
T4-C4
C4-Cz
Cz-C3
C3-T3
T4-T6
T6-O2
O2-O1
O1-T5
T5-T3
F8-F4
F4-Fz
Fz-F3
F3-F7
T6-P4
P4-Pz
Pz-P3
P3-T5
[ekg1-ekg2]

B


C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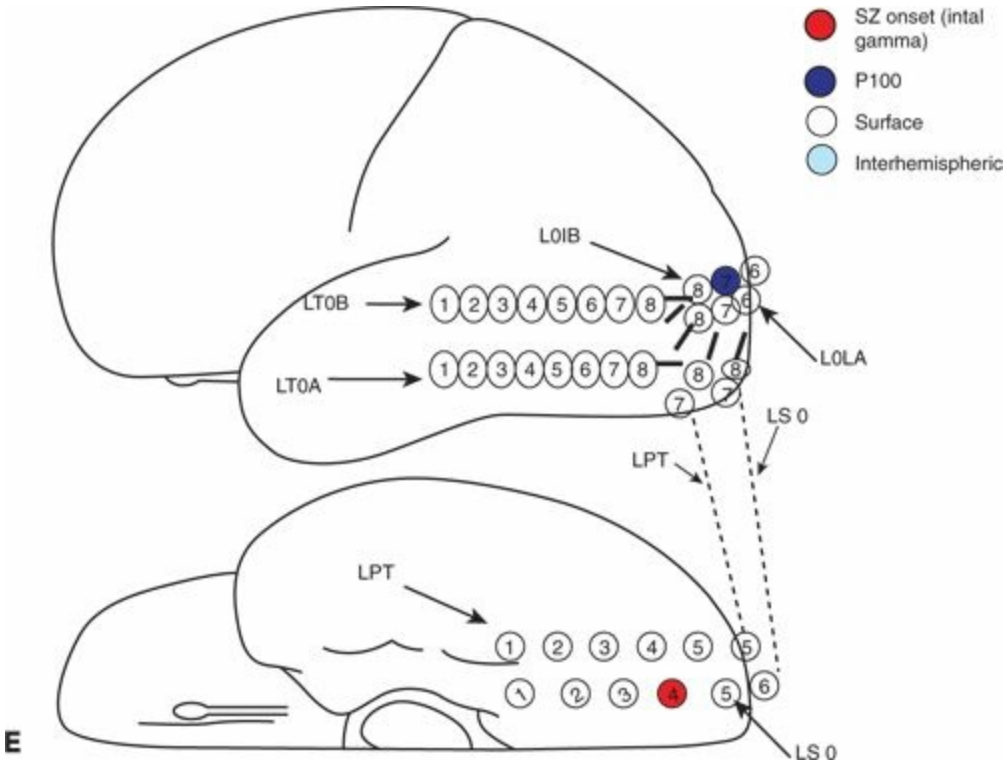
SZ onset (intal gamma)
P100
Surface
Interhemispheric
L0IB
LT0B
LT0A
L0LA
LS 0
LPT
LPT
LS 0
E

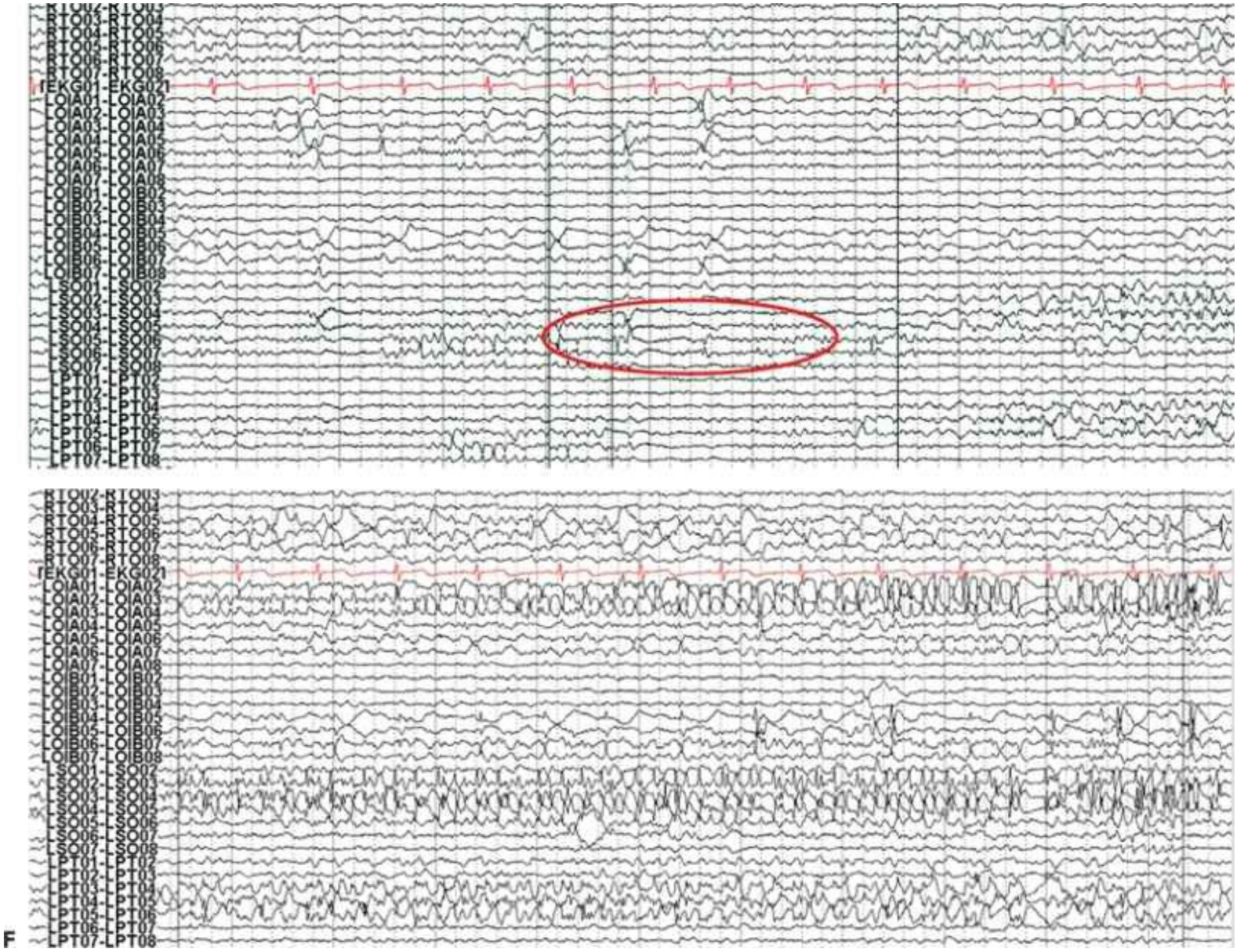

Figure 25.3. Occipital lobe epilepsy in a 15-year-old boy who had medically refractory complex partial seizures with an aura of flashing lights in the right visual field, progressing to oral automatisms and loss of awareness. **A and B:** Development of the left occipital discharge on surface EEG. **C:** 3D MRI rendering and skull x-rays showing the coverage of all three occipital surfaces with subdural strip electrodes. **D and E:** Cortical map with seizure onset at visual evoked responses shown. **F:** Intracranial recording demonstrating left inferior occipital onset of gamma.

PARIETAL LOBE EPILEPSY

The parietal lobe is the least common form of LRE, estimated to be the primary origin of seizures in perhaps 6% to 10% of patients. The diagnosis of parietal lobe epilepsy is perhaps the most challenging of all the extratemporal epilepsies when considering clinical symptoms and signs alone, because the parietal association cortex is often silent, and ictal symptoms only occur after propagation to adjacent lobes. Somatosensory auras, including a sensation of limb movement, and affective and vertiginous auras have been reported, as well as visual auras and rarely, painful sensations (34,35). Progression to tonic posturing is seen when superior or mesial parietal lobe foci spread to the SMA in the frontal lobe; oral and manual automatisms are seen when inferior and lateral parietal lobe seizures spread to the temporal lobes (36).

The interictal EEG of PLE is often unrevealing, and localization with scalp EEG is quite challenging. In one study (20), fewer than half of PLE patients were correctly localized on scalp

EEG, in part because more than one-third of PLE patients had generalized seizure patterns. Independent contralateral EEG discharges were also common (20).

Surgical outcome is similar to FLE cases, and 46% of patients were seizure free after surgery in the largest series of 82 patients (36). A more recent series of 26 patients noted a 54% seizure-free rate (34). Contralateral sensory loss and Gerstmann syndrome are potential postsurgical complications. Cortical mapping with somatosensory evoked potentials may help define primary sensory cortex when planning the extent of surgical resection.

LOCALIZATION OF EXTRATEMPORAL LOBE EPILEPSY

Problems in diagnosing and localizing the extratemporal lobe epilepsies have been discussed in detail above. One must be wary when multifocal or bilateral structural disease is present, and skepticism is always required when interpreting the scalp EEG. Close connections between different lobes of the brain, for example, parietal and frontal lobes or occipital and temporal lobes, may cause rapid and misleading propagation patterns in the EEG. Propagation pathways between the frontal and occipital lobes may also lead to misleading findings (31). Symptoms can be misleading as well; for instance, eye deviation usually is produced by activation of the frontal eye fields but can be seen with occipital foci, which produce ipsilateral version. Sensory disturbances commonly appear with frontal lobe lesions, but parietal lobe seizures produce these as well, and complex visual disturbances may be from the occipital, posterior temporal, or parietal association cortices.

CONCLUSION

The extratemporal lobe epilepsies constitute a fascinating set of conditions to diagnose and manage. They are underrepresented in the medical literature due to the aforementioned difficulties in establishing a correct diagnosis and because ETLE is often not surgically remediable, which can bias literature reports. Specific syndromes such as benign epilepsy of childhood with centrotemporal spikes or celiac disease have a good prognosis, however, and patients and their families can be reassured. The physician faced with a patient with medically refractory LRE should be knowledgeable of the clinical patterns described above to help guide further investigations when surgery is considered. Despite these hurdles, surgical success rates are good, and it is hoped that improved technology and cumulative experience will lead to better outcomes.

ACKNOWLEDGMENT

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CHAPTER 26 MALFORMATIONS OF CORTICAL DEVELOPMENT AND EPILEPSY

GHAYDA M. MIRZAA, RUBEN KUZNIECKY, AND RENZO GUERRINI

The formation and development of the human cerebral cortex is a complex dynamic process that can be broken down into partially overlapping stages occurring over the span of several gestational weeks (1). In a simplified fashion, during the first stage, stem cells deep in the forebrain within the ventricular and subventricular zones lining the cerebral cavity proliferate and differentiate into young neurons or glial cells. During the second stage, neurons migrate away from their place of origin toward the pial surface and settle within the cortical plate. When neurons reach their destination, they arrange themselves into specific "architectonic" patterns, and this third phase involves final organization within the typical six layers of cortex, associated with synaptogenesis and apoptosis.

Any disruption of this process, whether by genetic or environmental factors, may result in malformations of cortical development (MCD). High-resolution magnetic resonance imaging (MRI) facilitates identification of MCD earlier in life, leading to improved diagnosis and clinical management at a younger age, and progress in understanding their pathogenesis. This chapter reviews common cortical malformations associated with epilepsy.

CLASSIFICATION

The 1996 classification scheme categorizes MCD based on the timing of disruption during the developmental stages of the human cortex (cell proliferation, neuronal migration, and cortical organization). Since then, scientific progress in imaging and molecular biology of brain development led to dramatically increased awareness, recognition, and understanding of MCD and related clinical presentations and comorbidities. The most recent update to the classification scheme in 2012 adapts to this gain in knowledge and is therefore genotype based, allowing a better conceptual understanding of these disorders (2). Table 26.1 lists these broad categories, and Table 26.2 outlines the most common genes identified in relation to MCD (3). The nomenclature and classification will undoubtedly continue to evolve during the upcoming years.

Table 26.1 Classification Scheme for Malformations of Cortical Development [a]

I. Malformations due to abnormal neuronal and glial proliferation or apoptosis
   A. Decreased proliferation/increased apoptosis or increased proliferation/decreased apoptosis—abnormalities of brain size
      1. Microcephaly (MIC)
         a. MIC with normal to thin cortex
         b. Microlissencephaly (extreme MIC with thick cortex)
         c. MIC with PMG
      2. Megalencephaly
   B. Abnormal proliferation (abnormal cell types)
      1. Nonneoplastic
         a. Cortical hamartomas of TSC
         b. Cortical dysplasia with balloon cells
         c. Hemimegalencephaly
      2. Neoplastic (associated with disordered cortex)
         a. Dysembryoplastic neuroepithelial tumor
         b. Ganglioglioma
         c. Gangliocytoma

II. Malformations due to abnormal neuronal migration
   A. Lissencephaly and subcortical band heterotopia
   B. Cobblestone complex/congenital muscular dystrophy syndromes
   C. Heterotopias
      1. Subependymal (periventricular) nodular heterotopia
      2. Subcortical (other than band heterotopias) heterotopia
      3. Marginal glioneuronal heterotopia

III. Malformations due to abnormal cortical organization (including late neuronal migration)
   A. PMG and schizencephaly
      1. Bilateral PMG syndromes
      2. Schizencephaly (PMG with clefts)
      3. PMG or schizencephaly as part of multiple congenital anomaly/ID syndromes
   B. Cortical dysplasia with balloon cells
   C. Microdysgenesis

IV. Malformations of cortical development, not otherwise classified
   A. Malformations secondary to inborn errors of metabolism
      1. Mitochondrial and pyruvate metabolic disorders
      2. Peroxisomal disorders

[a]These categories are further listed in an expanded format in reference (3).

Table 26.2 Genetic Etiologies of Malformations of Cortical Development

Malformations and syndromes	Gene[a]
A. Malformations due to abnormal neuronal and glial proliferation or apoptosis	
Decreased proliferation/increased apoptosis or increased proliferation/decreased apoptosis—abnormalities of brain size	
1. Microcephaly (MIC)	
MIC—mild–moderate phenotype (with simplified gyral pattern, normal stature, and relatively high function)	*ASPM*, *MCPH1*, *CDK5RAP2*, *CENPJ*, *STIL*, *CEP152*, *CEP135*, *CDK6*
MIC—severe phenotypes	*CENPJ*
Amish lethal MIC	*SLC25A19*
MIC with other brain abnormalities (PMG, heterotopia)	*ARFGEF2*, *WDR62*, *PNKP*, *NDE1*
MIC postnatal with disproportionate pontocerebellar hypoplasia	*CASK*
MIC with poor growth (microcephalic osteodysplastic primordial dwarfism, Seckel syndrome)	*ATR*, *PCNT*, *CEP152*, *CENPJ*, *ORC1*, *ORC4*, *ORC6*, *CDC6*, *CDT1*, *CEP63*, *RBBP8*, *RNU4ATAC*, *CEP135*
Microlissencephaly (MLIS)	
MLIS group a, $a = p$	
Barth MLIS syndrome (group b), $a = p$	
2. Megalencephaly (MEG)	
MEG—isolated or familial	
PTEN-related MEG–autism (also associated with Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome, and FCD)	*PTEN*
Megalencephaly-capillary malformation (MCAP) syndrome	*PIK3CA*
MEG–polymicrogyria–polydactyly–hydrocephalus (MPPH) syndrome	*AKT3*, *PIK3R2*, *CCND2*
Thanatophoric dysplasia	*FGFR3*
Abnormal proliferation (abnormal cell types)	
1. Hemimegalencephaly (HMEG)	*PIK3CA*, *MTOR*, *AKT3*
2. Focal cortical dysplasia	*PTEN*
3. Tuberous sclerosis complex	*TSC1*, *TSC2*
B. Malformations due to abnormal neuronal migration	
1. Lissencephaly (LIS)	
Classic LIS	
Miller–Dieker syndrome (MDS), $a = p$	*LIS1* + *YWHAE (contiguous gene deletion syndrome of 17p13.3)*
Isolated LIS sequence,	
$a = p$, $p > a$	*LIS1 (PAFAH1B1)*
$a = p$, $a > p$	*DCX (males)*
Other causes of LIS $a = p$, $a > p$	*TUBA1A*, *DYNC1H1*, *KIF2A*, *TUBB2B*, *TUBG1*
Baraitser–Winter syndrome (BWS), $a > p$	*ACTG1*, *ACTB*
Subcortical band heterotopias, $a = p$, $a > p$	*DCX (females)*
LIS with cerebellar hypoplasia (LCH)	
LCH group a, $a = p$, $a > p$, $p > a$	*LIS1*, *DCX*
LCH group b, $a > p$	*RELN*, *VLDLR*
LCH group c-d-f	*TUBA1A*
XLAG, $p > a$	*ARX*
LIS with agenesis of the corpus callosum (ACC), other types	
2. Cobblestone cortical malformations (AR)	
Fukuyama congenital muscular dystrophy	*FKTN*
Walker–Warburg syndrome (WWS)	*POMT2*, *POMGnT1*, *FKRP*, *FKTN*, *LARGE*, *POMT1*
Muscle–eye–brain (MEB) disease	*POMT2*, *POMGnT1*, *FKRP*, *LARGE*, *POMT1*
Mental retardation, MIC, and CMD	*POMT1*, *POMT2*
Bilateral frontoparietal cobblestone malformation (previously PMG)	*GPR56*
Dandy–Walker malformation with CDG	*B4GALT1*
CHIME-like syndrome	*SRD5A3*
CEDNIK syndrome	*SNAP29*
3. Heterotopia (XL, AD)	
Classical bilateral periventricular nodular heterotopia (PNH)	*FLNA*
Ehlers–Danlos syndrome and PNH	*FLNA*
Facial dysmorphism, severe constipation, and PNH	*FLNA*
Fragile-X syndrome and PNH	*FMR1*
Williams syndrome and PNH	
PNH with limb abnormalities (limb reduction abnormality or syndactyly)	
ACC and PNH	
ACC, PMG, and PNH	

Heterotopia (AR)	
MIC and PNH	*ARFGEF2*
Donnai–Barrow syndrome and PNH	*LRP2*
C. Malformations due to abnormal cortical organization	
PMG (XL, AD)	
Rolandic seizures, oromotor dyspraxia	*SRPX2*
ACC, MIC, and PMG	*TBR2 (EOMES)*
PMG, PNH, MIC	*ARFGEF2*
PMG, fetal brain disruption	*NDE1*
PMG, MIC	*WDR62*
Aniridia plus	*PAX6*
Facial dysmorphism and PMG	
MIC, hydrocephalus, and PMG	
DiGeorge syndrome	
Goldberg–Shprintzen syndrome	*KIAA1279*
Micro syndrome	*RAB3GAP1, RAB3GAP2, RAB18*
PMG, CBLH, MIC, ACC	*TUBA1A, TUBB2B, TUB3, TUBA8, TUBB5*

[a]The references for genes associated with MCD can be accessed through the Developmental Brain Disorders Database (DBDB) at https://www.dbdb.urmc.rochester.edu/home. This database is a publicly available, curated database that is dynamically linked to PubMed, GeneReviews, and the UCSC Genome Browser.
a, anterior; CDG, congenital disorders of glycosylation; CMD, congenital muscular dystrophy; PMG, polymicrogyria; SBH, subcortical band heterotopia; p, posterior; PNH, periventricular nodular heterotopia; LIS, lissencephaly; XLAG, X-linked lissencephaly with abnormal genitalia.

MALFORMATIONS OF CORTICAL DEVELOPMENT

Accurate diagnosis of MCD relies primarily on recognition of the malformation on brain MRI, which, in turn, determines correct prognosis and genetic counseling. In the following sections, the genetic, imaging, and functional aspects of the most common MCD are discussed, with special emphasis on epilepsy associated with these disorders.

MCD DUE TO ABNORMAL PROLIFERATION/APOPTOSIS (ABNORMALITIES OF BRAIN SIZE)

Malformations in this group are characterized by an increase or decrease in the number of neurons and glia with corresponding changes in brain size, designated as either microcephaly (MIC) or megalencephaly (MEG). The most common types of MIC and MEG are not typically included under brain malformations because brain structure appears grossly normal in isolated forms. However, detailed studies of neuronal cell types are not available. Furthermore, MIC and MEG often coexist with other developmental brain disorders such as polymicrogyria (PMG) and periventricular nodular heterotopia (PNH) in distinct phenotypes.

Microcephaly Syndromes

MIC is defined as head circumference 3 standard deviations (SDs) or more below the mean for the individual's age and gender. Historically, a confusing combination of terms has been used to describe and classify different types of MIC. When severe congenital MIC is the only abnormality on evaluation, that is, without other brain or somatic abnormalities, the terms primary MIC and

microcephaly vera have been historically used though these terms are often poorly understood (4). Most patients with congenital MIC fall broadly into two clinical groups (5). The first group comprises children with extreme MIC but only moderate neurologic problems, usually moderate intellectual disability (ID) without spasticity or epilepsy. Several genes associated with this phenotype have been identified (see Table 26.2). The second and more important group from an epilepsy standpoint consists of congenital MIC with severe spasticity and epilepsy (6). Children in this group present with severe ID, spastic quadriparesis, gastroesophageal reflux, and poor feeding, leading to failure to thrive. Early-onset intractable epilepsy is common. Brain MRI universally shows a simplified gyral pattern. Other neuroimaging features in this group include increased extra-axial space, delayed myelination, agenesis of the corpus callosum, and disproportionate hypoplasia of the brainstem and/or cerebellum. This clinical spectrum constitutes pathogenetically heterogeneous conditions, as several genes have now been identified in this group (see Table 26.2).

Children with severe congenital MIC are often erroneously diagnosed with lissencephaly (LIS) because of reduced number of broad gyri. However, the cortex is not as thick as in true LIS (Fig. 26.1). The term microlissencephaly applies to the few patients with severe congenital MIC and a truly thickened cortex, and these patients also usually present with intractable epilepsy. By far, the majority of congenital MIC syndromes are inherited in an autosomal recessive manner.

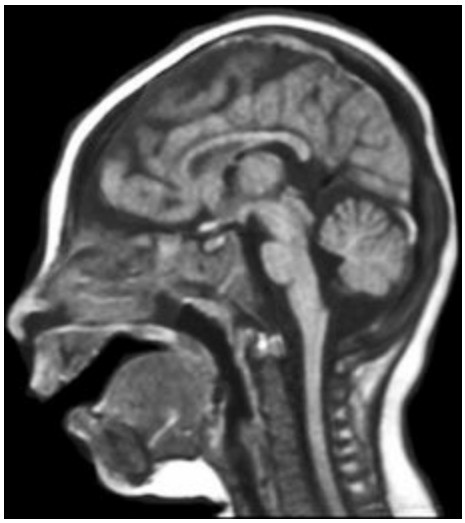

Figure 26.1. Microcephaly. Sagittal MRI demonstrates MIC (<3 SD) with relative preservation of normal sulcal cerebral anatomy.

Postnatal MIC, on the other hand, is characterized by borderline small head size (2 to 3 SD below the mean) at birth that later progresses. Postnatal MIC is a feature of more than 300 developmental syndromes that are beyond the scope of this chapter.

Megalencephaly Syndromes

MEG is defined as an oversized and overweight brain that exceeds the mean by 2 or 3 SD for age and gender. MEG may occur as a mild familial variant with normal brain structure or as part of a growing number of genetic syndromes, including metabolic and nonmetabolic disorders (6). The clinical findings of individuals with MEG vary, but neurologic problems are usually mild to moderate, particularly in the familial form. A subset of patients have severe ID, intractable epilepsy, and other neurologic abnormalities. These severe outcomes are related to the presence of other cortical brain abnormalities, such as PMG. The most common MEG syndromes are associated with characteristic

somatic and neuroimaging features (see Table 26.2).

MCD DUE TO ABNORMAL PROLIFERATION (ABNORMAL CELL TYPES)

Malformations in this group are characterized by abnormal neurons and, often, glia as well. These are usually localized malformations. In some patients, abnormal cell types have been classified as neoplastic, although the malignant potential is low. The most common of these is tuberous sclerosis complex (TSC) (reviewed in Chapter 30).

Hemimegalencephaly

Hemimegalencephaly (HMEG) is a brain malformation characterized by an enlarged and dysplastic cerebral hemisphere (Fig. 26.2). The overgrowth and dysplasia may involve an entire hemisphere, part of a hemisphere, and/or part of the contralateral hemisphere as well. Macroscopically, the involved hemisphere is enlarged with cortical dysgenesis, white matter hypertrophy, and a dilated and dysmorphic lateral ventricle. There is no clear predilection for right or left sides. The microscopic features of HMEG vary significantly and may include PMG, heterotopic gray matter, cortical dysplasia (cortical dyslamination, bizarre enlarged neurons, balloon cells), blurring of the gray–white junction, and increase in the number of neurons and astrocytes (7).

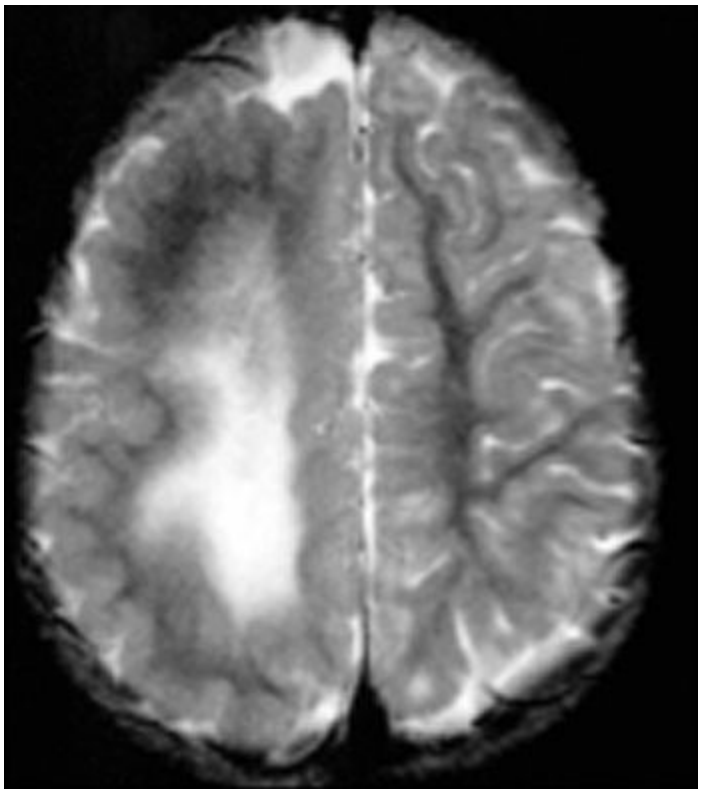

Figure 26.2. Hemimegalencephaly. Axial MRI shows large hemisphere with white matter changes. Note the smooth cortex in the posterior region.

HMEG is most often isolated but can be sporadically associated with neurocutaneous syndromes such as linear nevus sebaceous syndrome, hypomelanosis of Ito, TSC, and neurofibromatosis. HMEG with somatic overgrowth has been reported in Klippel–Trenaunay syndrome and Proteus syndrome

(6). Postzygotic activating mutations in components of the phosphatidylinositol-3-kinase (PI3K)-v-akt murine thymoma viral oncogene homolog (AKT) pathway have been identified in individuals with HMEG (8). Mutations of the same genes have been identified in children with MEG syndromes, such as the megalencephaly capillary malformation (MCAP) and the megalencephaly–polymicrogyria–postaxial polydactyly–hydrocephalus (MPPH) syndromes (9). These mutations lead to gain of function and activation of the PI3K-AKT pathway, a critical cellular pathway that regulates diverse cellular functions such as cell growth, proliferation, survival, apoptosis, tumorigenesis, and brain development.

The classic clinical triad of HMEG is (i) intractable partial seizures with onset in the neonatal period or early infancy, (ii) unilateral or focal neurologic signs (hemiparesis, hemianopia), and (iii) intellectual disability. Seizures are typically partial and almost always intractable to medical therapy. Infantile spasms, tonic seizures, or electroclinical features of Ohtahara syndrome or West syndrome may occur (10).

The MRI appearance of HMEG is characteristic. Most affected individuals have moderate to severe enlargement of one cerebral hemisphere. In some, enlargement may be localized to the frontal or temporoparietal regions, but in others, it may extend to distinct regions of the contralateral hemisphere. Gray matter is almost uniformly abnormal showing areas of thickening and simplification or overfolding, resembling pachygyria or PMG, respectively. The underlying hemispheric white matter may be increased or decreased, with abnormal signal characteristics in some patients. Heterotopia is commonly seen, and the ventricular system is enlarged and/or dysplastic in most patients. Electroencephalographic abnormalities are often broadly distributed throughout the abnormal hemisphere, and most severe cases exhibit a suppression burst pattern early on.

Predictors of poor outcome in HMEG are severity of hemiparesis, smoothness of the cortical surface on MRI, and abnormal activity on electroencephalography (EEG). Anatomical or functional hemispherectomy may improve both epilepsy and ID in selected patients (11). However, some patients do poorly with hemispheric surgery, possibly due to more widespread but asymmetric malformations.

Focal Cortical Dysplasia

The term focal cortical dysplasia (FCD) designates a spectrum of abnormalities of the laminar structure of the cortex, variably associated with cytopathologic features including giant (or cytomegalic) neurons, dysmorphic neurons, and balloon cells (Fig. 26.3). There have been various attempts to classify FCD based on subtle histologic characteristics, and the most recent classification considers clinical presentation and imaging findings, in addition to histopathologic features (12). According to this system, FCD type I refers to isolated lesions, which present either as radial (type Ia) or as tangential (type Ib) dyslamination of the neocortex, microscopically identified in one or multiple lobes. FCD type II is an isolated lesion characterized by cortical dyslamination and dysmorphic neurons without (type IIa) or with balloon cells (type IIb). FCD type III occurs in combination with hippocampal sclerosis (type IIIa) or with epilepsy-associated tumors (type IIIb). FCD type IIIc is found adjacent to vascular malformations, whereas FCD type IIId can be diagnosed in association with epileptogenic lesions acquired in early life (i.e., traumatic injury, ischemic injury, or encephalitis). The pathologic features of the tubers of TSC and FCD type IIb have significant overlap.

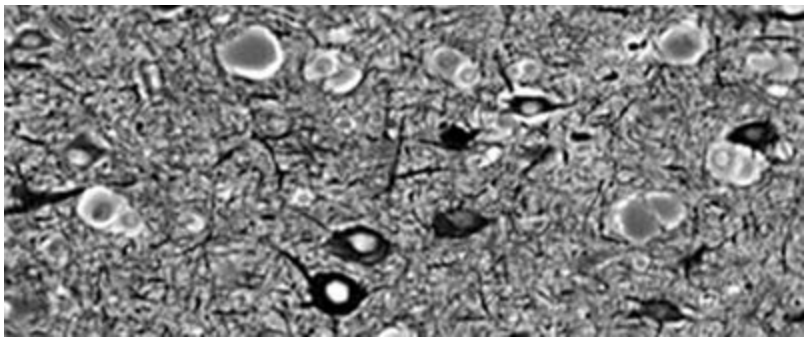

Figure 26.3. Focal cortical dysplasia. Silver staining showing irregular arrangement of big neurons and pale brown balloon cells.

According to the prevailing hypothesis, FCD originates from abnormal migration, maturation, and cell death during ontogenesis (13). The close cytoarchitectural similarities between FCD and cortical tubers of TSC prompted the hypothesis of a common pathogenetic basis, and a study has supported the role of the TSC1 gene in the pathogenesis of FCD, although these data remain to be further substantiated (14). In one paper, human papillomavirus (HPV) infection was implicated in FCD type IIB. The specific HPV 16 oncoprotein E6 (HPV16 E6) is a potent activator of mTORC1 signaling, further suggesting a relationship between FCD and the PI3K-AKT-mTOR pathway (15). Importantly, histopathologic similarities between FCD, HMEG, and the dysembryoplastic neuroepithelial tumors, two highly epileptogenic developmental lesions, further support the hypothesis of a developmental origin. Finally, FCD has been postulated to be linked to perinatal or early postnatal brain injury, with subsequent cell differentiation in the scarred area.

The most common clinical sequelae of FCD are seizures, ID, and focal neurologic deficits. Epilepsy is usually focal, intractable, and often complicated by focal status epilepticus. FCD has been shown to be intrinsically epileptogenic in vivo using electrocorticography during epilepsy surgery and in vitro using cortex resected from patients with intractable epilepsy (16,17).

FCD is rarely visible by computerized tomography (CT), and the mildest malformations may not be visible on current MRIs. Other lesions can be detected by blurring of the cortex–white matter junction on T1-weighted images as well as cortical thickening or abnormal T2 or fluid-attenuated inversion recovery hyperintensity in the white matter of a gyrus or in the depth of a sulcus. The term transmantle dysplasia applies to a band of abnormal signal intensity that extends from the cortex to the superolateral margin of the lateral ventricle (Fig. 26.4). Another subtype of FCD is bottom of the sulcus focal cortical dysplasia (18). This type of FCD can be very small in size and may be easily overlooked on imaging. However, once diagnosed, patients may benefit greatly from surgery as the lesions can often be resected in total.

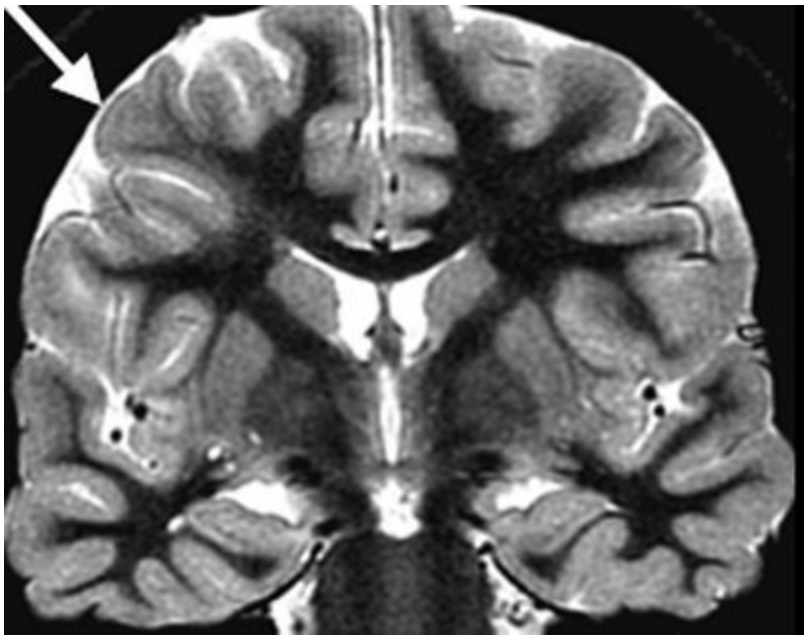

Figure 26.4. Coronal T2W MRI showing an area of irregular cortical folding (arrow) with blurring of the gray–white matter junction and underlying increased signal intensity in the white matter, extending from the subcortex to the ventricular wall. This combination of findings is consistent with FCD.

Cortical Dysplasia with Neoplastic Changes

Several low-grade, primarily neuronal, neoplasms are associated with cortical dysplasia, including dysembryoplastic neuroepithelial tumors, ganglioglioma, and gangliocytoma. Controversy continues over their proper classification. These neoplasms occur most often in children and young adults, and the frequency of these neoplasms in epilepsy surgical series is approximately 5% to 8% (19). Tumors are often located in the temporal lobes, where residual heterotopic neurons in the white matter are also common but can also present in other brain regions. While patients usually exhibit partial seizures that are difficult to control with medication, complete resection of the lesion may lead to seizure freedom.

MALFORMATIONS DUE TO ABNORMAL NEURONAL MIGRATION (NEURONAL MIGRATION DISORDERS)

Lissencephaly and Subcortical Band Heterotopia

LIS is characterized by absent (agyria) or decreased (pachygyria) convolutions, producing cortical thickness and a smooth cerebral surface. Several types of LIS have been recognized. The most common, classical (or type 1) LIS, features a very thick cortex (10 to 20 mm as compared to a normal thickness of 4 mm) without other brain malformations. The cytoarchitecture consists of four primitive cortical layers, rather than the normal six. From the cortical surface inward, these consist of a (i) poorly defined marginal zone with increased cellularity; (ii) superficial cortical gray zone with diffusely scattered neurons; (iii) relatively neuron-sparse zone; and (iv) deep cortical gray zone with neurons often oriented in columns (20, 21).

Subcortical band heterotopia (SBH) consists of bands of gray matter interposed in the white matter between the cortex and the lateral ventricles (Fig. 26.5) (6). LIS and SBH are MCD that manifest along the same spectrum. This conclusion is based on observations of rare patients with areas of LIS that merge into SBH and of multiple families with X-linked LIS in males and SBH in females.

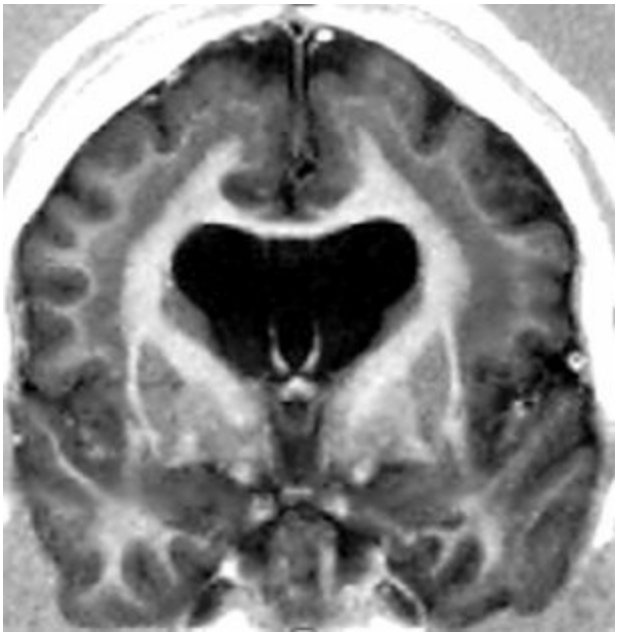

Figure 26.5. SBH. DCX mutation in a female. Coronal T1W image shows typical SBH with relative preservation of cortical anatomy.

The two most common genes associated with classic LIS and SBH are LIS1 and DCX. LIS1 (PAFAH1B1) is responsible for the autosomal form of LIS1, while the doublecortin (DCX) gene is X-linked. Although either gene can result in LIS or SBH, most cases of classic LIS are due to deletions or mutations of LIS1, whereas most cases of SBH are due to mutations of DCX. LIS1-related LIS is more severe in the posterior (p) brain regions (p > a gradient), whereas DCX-related LIS is more severe in the anterior (a) brain (a > p gradient) (Fig. 26.6).

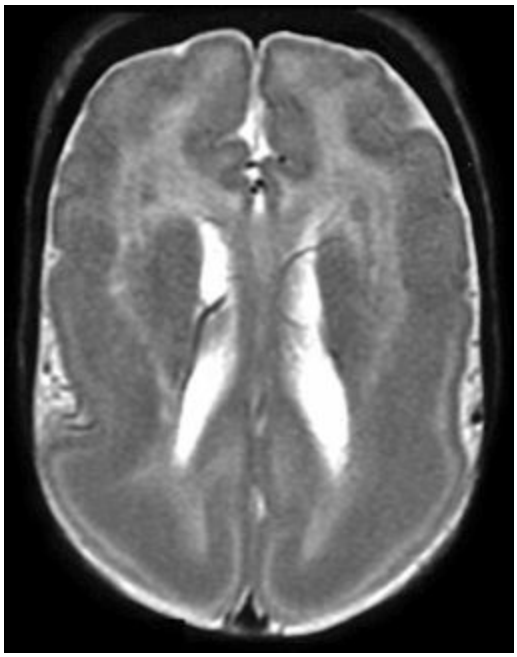

Figure 26.6. Lissencephaly. LIS1 mutation. MRI shows the typical smooth cortex predominantly affecting the posterior regions.

Children with classic LIS often appear normal as newborns but may present with apnea, poor feeding, or hypotonia. Seizures are uncommon during the first few days of life but typically begin before 6 months of age, and the clinical presentation is often similar. Infantile spasms (ISS) occur in 80% of affected children within the first year of life, often appearing initially as hypsarrhythmia on EEG. ISS respond to ACTH or other anticonvulsants in the majority of patients, but in the long term, almost all affected children have frequent seizures and many meet criteria for Lennox–Gastaut syndrome. Profound ID, hypotonia, mild spastic quadriplegia, and opisthotonus are also seen. Many patients require a gastrostomy because of poor nutrition and repeated episodes of aspiration and pneumonia.

In contrast, patients with SBH and the rare patients with partial LIS have mild to moderate ID (although normal intelligence or severe ID has been reported), minimal pyramidal signs, and dysarthria (22). Seizures usually begin during childhood but may appear later in life. Multiple seizures types may occur that can be difficult to control; however, the frequency and severity vary among affected individuals. As with other developmental syndromes, epilepsy may be an independent factor to cognitive delay and overall neurodevelopmental status. EEGs usually show generalized spike–wave discharges or multifocal abnormalities. The neurologic outcome depends on the thickness of the heterotopic band on MRI and associated malformations.

Lissencephaly Syndromes and Genes

The most common LIS syndromes include (i) isolated LIS sequence (caused by DCX in males; LIS1; and, rarely, TUBA1A, TUBB2B, TUBG1, and DYNC1H1), (ii) SBH (DCX in females and rare in males, and LIS1), (iii) Miller–Dieker syndrome (MDS) (contiguous deletion of LIS1 and YWHAE), (iv) several types of LIS with cerebellar hypoplasia (LCH) (RELN and VLDLR), (v) X-linked LIS with abnormal genitalia (XLAG) (ARX), and (vi) Baraitser–Winter syndrome (BWS) (ACTB1 and ACTG1), among others. Table 26.3 lists the frequency of mutations in these syndromes. Careful review of brain imaging and clinical features can distinguish these syndromes and helps with the identification of the causative gene.

Table 26.3 Frequency of Mutations in LIS and SBH Syndromes

	Gene or locus				
Syndrome	*ARX*	*DCX*	*LIS1*	Del 17p	*RELN*
ILS	0	12	24	40	0
LCH	Rare	25	15	0[a]	Rare
MDS	0	0	0	All[b]	0
SBH	0	80	Rare	Rare	0
XLAG	95	0	0	0	0

[a]Deletion of 17p13.3 could be seen in LIS group a (mild vermis hypoplasia).
[b]Miller–Dieker syndrome is partly defined by the deletion.
LIS, lissencephaly; SBH, subcortical band heterotopias; ILS, isolated lissencephaly sequence; LCH, lissencephaly with cerebellar hypoplasia; MDS, Miller–Dieker syndrome; XLAG, X-linked lissencephaly with abnormal genitalia. Figures represent percentages from published series.

Isolated lissencephaly sequence (ILS) consists of classic LIS with mild facial dysmorphism including mild bitemporal hallowing and small jaw (23). ILS associated with mutations of the X-linked DCX gene is characterized by either a severe LIS with no apparent gradient or an a > p gradient and normal facial appearance, whereas mutations or deletions of the LIS1 gene produce LIS with p > a gradient (see Fig. 26.6). The facial appearance may be normal or involve subtle dysmorphism similar to but milder than MDS. Mutations of the tubulin genes (TUBA1A, TUBB2B, TUBG1) are characterized by LIS in addition to other complex developmental brain abnormalities such as PMG, callosal hypoplasia or agenesis, abnormal basal ganglia, and cerebellar hypoplasia (see Table 26.2) (24-27).

MDS is the prototypic LIS syndrome associated with characteristic facial features and other birth defects such as heart malformations and omphalocele. Facial features include prominent forehead, bitemporal narrowing, short nose with upturned nares, protuberant upper lip with a thin vermilion border, and small jaw. LIS in MDS is severe with no apparent gradient or rarely a p > a gradient similar to ILS with LIS mutations. All patients have deletions of chromosome 17p13 that include LIS1 and YWHAE. About 60% to 70% of deletions are detected by karyotype, and the remainder are detectable by fluorescence in situ hybridization or chromosomal microarray (28-31).

LCH affects a small percentage of patients with LIS syndromes. Group a, the most common type, resembles isolated LIS syndrome but with mild cerebellar vermis hypoplasia. Some patients have mutations of DCX or LIS1 but much less frequently than patients with typical ILS. Group b consists of moderate LIS with an a > p gradient, moderate 8- to 10-mm cortical thickness, a globular hippocampus, and a small afoliar cerebellum. Mutations in RELN and VLDLR have been identified in individuals with LCH overall.

XLAG is a variant LIS characterized by a p > a gradient, intermediate 8 to 10 mm cortical thickness, total agenesis of the corpus callosum, often cavitated or indistinct basal ganglia, severe postnatal MIC, and ambiguous or severely hypoplastic genitalia. Affected children have profound ID, hypothalamic dysfunction with poor temperature regulation, intractable epilepsy typically beginning on the first day of life, infancy-onset dyskinesia that may be difficult to distinguish from seizures, and chronic diarrhea. Female relatives, including mothers, have isolated agenesis of the corpus callosum. Mutations of the ARX gene have been found in almost all patients with XLAG.

BWS is a rare but recognizable disorder characterized by congenital ptosis, high-arched eyebrows, hypertelorism, ocular colobomata, and anterior predominant LIS. Other typical features include postnatal short stature, MIC, ID, seizures, and hearing loss. Recently, de novo mutations in ACTB and ACTG1 have been identified in individuals with BWS (see Table 26.2) (32).

Cobblestone Brain Malformations (Cobblestone Complex)

The cobblestone complex (previously known as type 2 or cobblestone LIS) is a severe brain malformation consisting of cobblestone cortex, abnormal white matter, enlarged ventricles often with hydrocephalus, small brainstem, and small dysplastic cerebellum (Fig. 26.7). In the most severely affected patients, the brain surface is smooth, which previously led to the designation LIS, although less severe cobblestone malformations have an irregular, pebbled surface rather than a smooth surface. Severely affected individuals may have progressive hydrocephalus, large posterior fossa cysts (atypical for Dandy–Walker malformation), and occipital cephaloceles. Eye malformations are frequent, and congenital muscular dystrophy is probably always present.

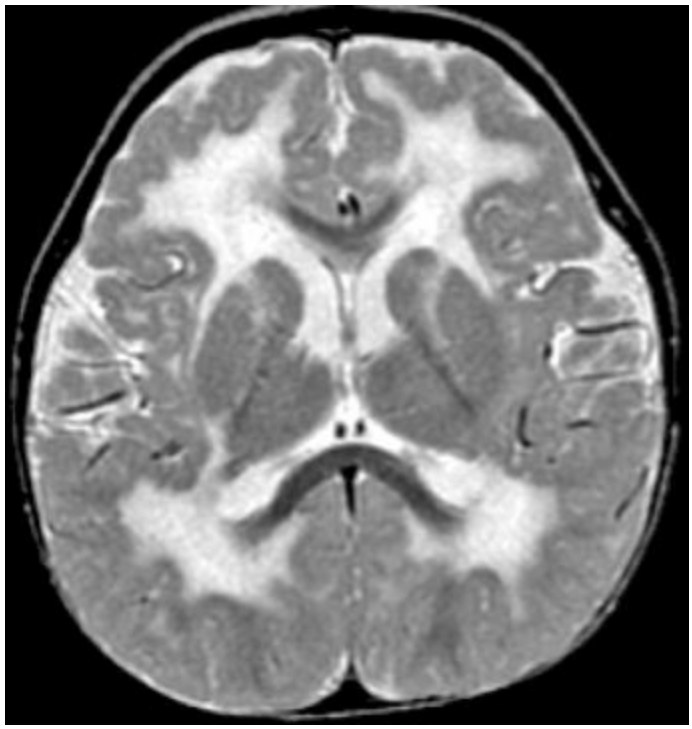

Figure 26.7. Axial T2W MRI shows extensive white matter changes and PMG typical of cobblestone malformation due to a Fukutin mutation.

The cobblestone malformation has been observed in three genetic syndromes that clearly overlap: Fukuyama congenital muscular dystrophy (FCMD), muscle–eye–brain (MEB) disease, and Walker–Warburg syndrome (WWS). All share a clinical course characterized by severe to profound ID, severe hypotonia, mild distal spasticity, and poor vision. Most classic cobblestone syndromes are autosomal recessive in inheritance (33-35).

FCMD consists of relatively mild cobblestone complex, moderate to severe ID, epilepsy, and severe congenital muscular dystrophy with progressive weakness, joint contractures, and elevated serum levels of creatine kinase (CK). Mutations in fukutin (FKTN) are the only known cause of FCMD. A common founder mutation of this gene is present in the Japanese population (36).

MEB disease consists of moderate cobblestone dysplasia with moderate to severe ID, epilepsy, congenital muscular dystrophy or myopathy with weakness, contractures, elevated serum CK levels, and complex eye abnormalities. The latter include retinal and choroidal hypoplasia, optic nerve pallor, high-grade myopia, anterior chamber angle abnormalities, glaucoma, iris hypoplasia, cataracts, and rare colobomas. Mutations of three genes, FKRP, LARGE, and POMGnT1, are primarily found in individuals with MEB. Other genes associated with MEB are listed in Table 26.2 (37, 38).

WWS is characterized by LIS and the most severe brain stem and cerebellar malformations of any of the cobblestone group. Most patients have hydrocephalus, and approximately 25% have occipital cephaloceles. All patients have profound ID, epilepsy, and eye abnormalities similar to those of MEB disease and the same congenital muscular dystrophy or myopathy with elevated serum CK levels and contractures. Mutations of POMT1, POMT2, and FKRP have been found in individuals with WWS.

Heterotopia

Heterotopias are defined as groups of cells found in inappropriate locations in the correct tissue of origin. Heterotopias are subdivided into three main groups based on location: periventricular (usually

nodular), subcortical (either nodular or laminar), and leptomeningeal. Only the first two of these are easily detectable on brain imaging. PNH is by far the most common type. Subcortical nodular heterotopia (SNH) is relatively frequent and often accompanied by irregular folding of the overlying cortex. Its etiology and genetic basis remain unknown. SBH is a mild form of LIS and is classified as such, as previously discussed. We will consider here PNH, which is by far the most frequent and best-known form of nodular heterotopia.

Periventricular Nodular Heterotopia

PNH consists of nodules of gray matter located along the lateral ventricles because of failure of migration of some neurons (3). The distribution ranges from isolated, single lesions to confluent bilateral nodules. The overlying cortex maybe abnormally disorganized, and the heterotopias may show some rudimentary lamination and a variety of neuronal types (39).

The most frequent clinical manifestation of PNH is epilepsy, occurring in 80% to 90% of patients, most of whom have various types of partial seizures that are often intractable (40). One study using depth electrodes in patients with PNH and epilepsy showed the nodules to be intrinsically epileptogenic (41) while, in other patients, the ictal-onset zone is less defined with often simultaneous onset in the cortex and nodules.

In typical PNH, MRI shows nodular masses of gray matter adjacent to the lateral ventricles that often protrude into the lumen (Fig. 26.8). Most are located along the lateral ventricular walls, although more posterior or medial locations may also occur. The nodules may be single or multiple, unilateral or bilateral, large or small, and symmetric or asymmetric. They may be contiguous or separated to resemble "pearls on a string." PNH differ from the subependymal nodules of TSC; as the latter are usually smaller, fewer, inhomogeneous, calcified and have signal intensity resembling white matter. Unilateral or focal PNH may occur in combination with SNH or in association with other MCD such as PMG. Typical bilateral PNH may be associated with mild to moderate hypoplasia of the corpus callosum or cerebellum (42-44).

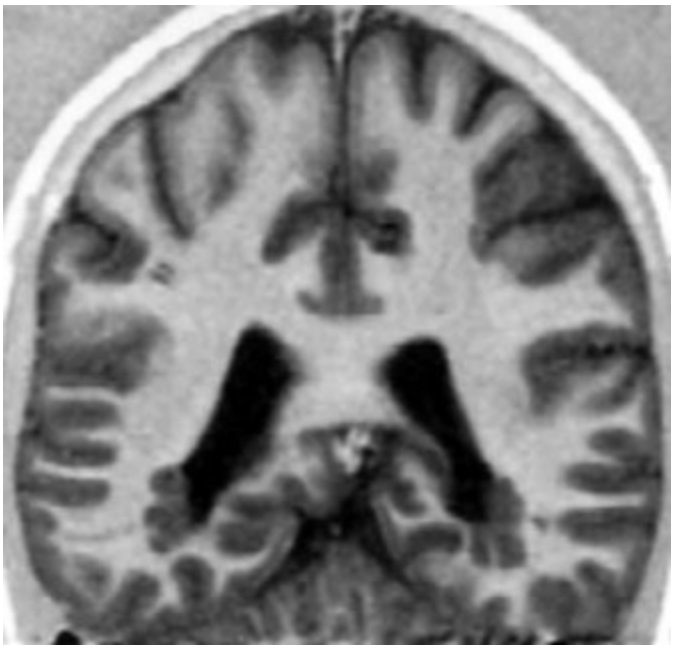

Figure 26.8. Coronal T1W MRI shows gray matter heterotopia lining the posterior ventricular system.

Mutations in the FLNA gene were identified in families of multiple affected individuals with bilateral

PNH (45). FLNA is located on the X chromosome. Mutations in males are thought to be lethal, accounting for the female predominance of PNH. Although approximately 80% of familial PNH cases have FLNA mutations, the mutation detection rate is much smaller (approximately 20%) in individuals with sporadic PNH (46). Individuals with mutations usually have typical bilateral PNH, while most patients with atypical PNH test negative for FLNA mutations. An autosomal recessive form of PNH with MIC due to mutations in ARFGEF2 is present in a small number of children from consanguineous unions. Finally, copy number changes (e.g., duplications of 5p14 and 5p15, and deletions of 6q27 and 7q11.2) have been identified in subsets of patient with focal or diffuse PNH. Therefore, PNH appears to be genetically heterogeneous secondary to abnormalities of genes involved in neuroblast proliferation or initiation of neuroblast migration.

MALFORMATIONS DUE TO ABNORMAL CORTICAL ORGANIZATION

Polymicrogyria

PMG refers to excessive microscopic gyration and is a common cortical malformation. The imaging appearance of PMG varies with the patient's age (47). In newborns and young infants, the malformed cortex is very thin with multiple, very small undulations. After myelination, PMG appears as thickened cortex with irregular cortex–white matter junction (3).

PMG is associated with a wide range of patterns and syndromes and is caused by mutations in several genes. Its pathogenesis, however, remains poorly understood. Brain pathology demonstrates abnormal development or loss of neurons in the middle and deep cortical layers, variably associated with an unlayered cortical structure.

The clinical sequelae of PMG are highly variable depending on etiology, extent, and location of the PMG; the presence of other brain malformations; and complications such as epilepsy. Furthermore, PMG is identified in different disorders such as metabolic syndromes, chromosome deletion syndromes, and multiple congenital anomaly syndromes. Therefore, affected individuals may have a wide spectrum of clinical problems other than those attributable to PMG. The most common form of PMG involves the perisylvian regions in a bilateral and rather symmetric pattern called bilateral perisylvian PMG (BPP) (Fig. 26.9). Patients with BPP typically have oromotor dysfunction including difficulties with tongue, facial, and pharyngeal motor functions resulting in problems with speech production, sucking and swallowing, excessive drooling, and facial diplegia. They may also have an expressive dysphasia in addition to dysarthria, often necessitating the use of alternative communication devices and/or sign language. Examination may show facial diplegia, limited tongue movements, brisk jaw reflex, absence of the gag reflex, and limb spasticity. Mild to moderate ID is seen in as many as 75% of patients (48). Other recurrent topographic patterns of PMG include unilateral perisylvian, bilateral frontal, bilateral frontoparietal, bilateral parasagittal, parietooccipital, bilateral parietooccipital, multilobar, and bilateral generalized PMG (Fig. 26.10). The clinical features of these rarer subtypes of PMG may vary from those seen in BPP, although epilepsy and variable ID are common accompaniments.

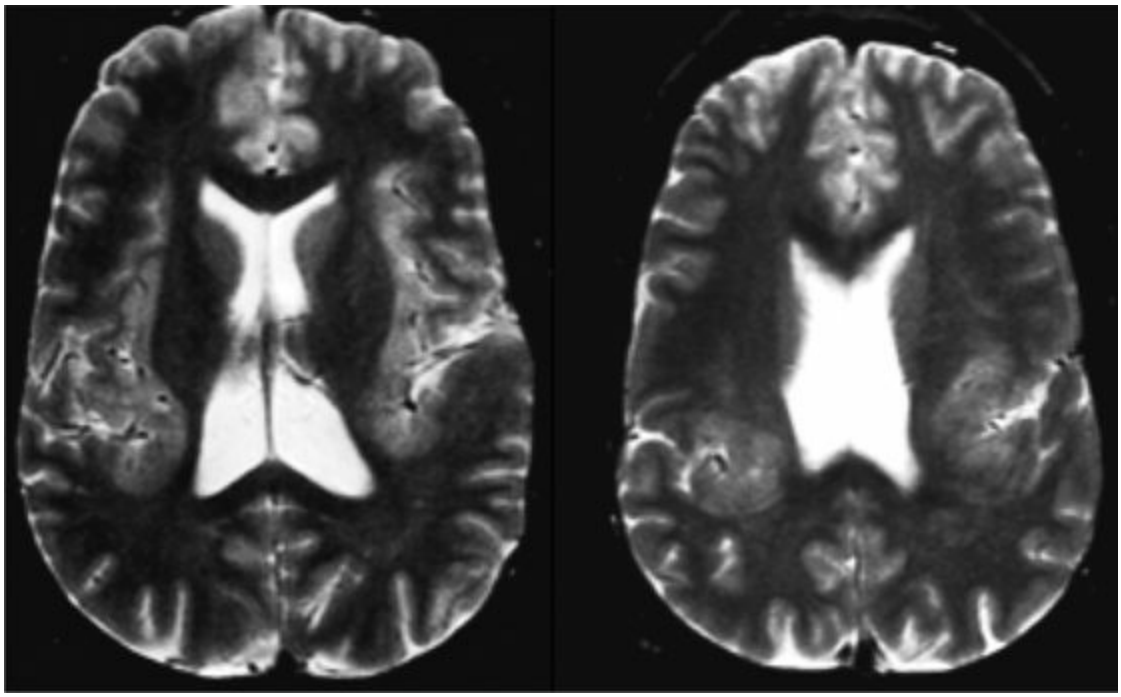

Figure 26.9. Congenital bilateral perisylvian syndrome (CBPS). The axial T2W MRI shows perisylvian PMG. The lesions are often asymmetric.

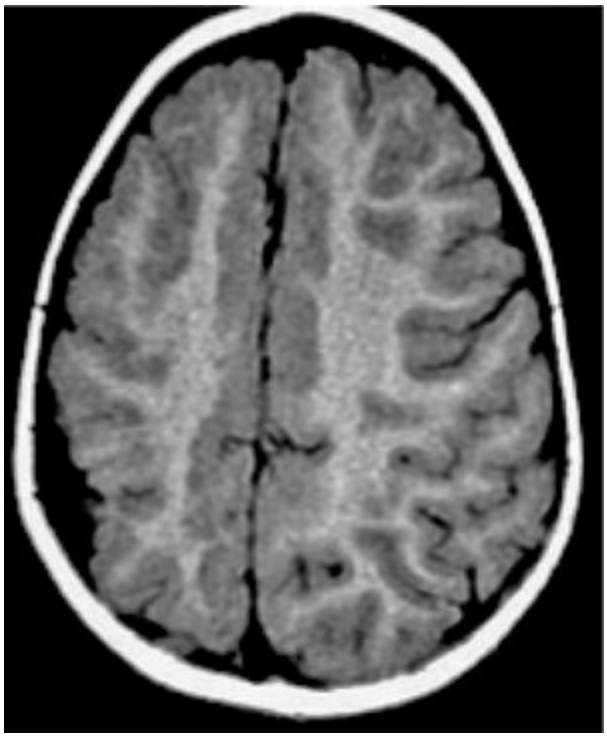

Figure 26.10. Unilateral PMG. Axial T1W image shows evidence of hemispheric atrophy and underlying PMG. Changes are most prominent in the central region.

The frequency of epilepsy in PMG is 60% to 85%. Seizure onset is variable but does not necessarily correlate with the severity of PMG. While most affected individuals present with seizures between 4 and 12 years of age, seizures may not occur until the second decade in some cases. Seizure types include atypical absence (62%), atonic and tonic drop attacks (73%), generalized tonic–clonic seizures (35%), and partial seizures (26%). A small number of patients may present with infantile spasms, in contrast to patients with LIS, TSC, or FCD in which the frequency of spasms is higher. EEG typically shows generalized spike–wave or multifocal discharges with a centroparietal

emphasis (48). Seizures may be intractable in at least 50% of patients.

Using CT and low-field strength MRI, PMG is difficult to discern and may only appear as thickened cortex. The only role for CT in the evaluation of PMG is to assess for evidence of calcification, which is seen in PMG resulting from congenital cytomegalovirus (CMV) infection. Using high-quality MRI with appropriate age-specific protocols, it is possible to reliably differentiate PMG from other MCD (3). The polymicrogyric cortex often appears mildly thickened (6 to 10 mm) on imaging due to cortical overfolding rather than true thickening (49). Using inversion recovery and thin contiguous slices, microgyri and microsulci may be appreciated. Diffusely abnormal white matter signal intensities should raise the question of an in utero infection (such as CMV) or a peroxisomal disorder. Other developmental anomalies seen with PMG include ventricular enlargement or dysmorphism, abnormalities of the corpus callosum and cerebellum, as occurs with the tubulinopathies, for example.

Numerous genetic and nongenetic etiologies have been reported in association with PMG. Nongenetic causes other than hypoxia or hypoperfusion mainly implicate congenital infections. Multiple reports suggest that congenital CMV infection is the single most common cause of BPP (50).

Among the genetic causes, deletion 22q11.2 (or DiGeorge) syndrome is most commonly associated with bilateral PMG. Further, PMG is associated with metabolic syndromes such as Zellweger syndrome due to mutations of the PEX family of genes, although the pathologic changes differ from typical PMG. BPP in association with MEG is seen in the MCAP syndrome (due to postzygotic PIK3CA mutations) and the MPPH syndrome (due to de novo germline mutations in PIK3R2 and AKT3). Furthermore, mutations in SRPX2 have been found in a single family with BPP. Besides these distinct genetic associations, all modes of inheritance have been suggested with PMG, although X-linked inheritance appears to be most frequent.

In summary, MCD are highly recognizable developmental brain disorders whose clinical delineation has improved dramatically due to advanced brain imaging techniques. In conjunction, the number of genes associated with these disorders has risen dramatically over the past decade due to significant advancements in genetic testing technologies. Most MCD are associated with epilepsy and ID and accurate diagnosis facilitates adequate clinical management, prognosis, and genetic counseling.

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CHAPTER 27 BRAIN TUMORS AND EPILEPSY

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Many epidemiologic studies established the frequent coexistence of brain tumors and epilepsy. Recently, significant insights into the mechanisms of epileptogenesis were derived from studying the intricate relationship between the two conditions. This chapter discusses the following:

1. Current data on the prevalence and incidence of epilepsy in brain tumor patients, and vice versa
2. Clinical characteristics of patients with brain tumor and epilepsy
3. Various proposed mechanisms of epileptogenesis in brain tumor patients
4. Medical as well as surgical treatment of brain tumor patients with epilepsy
5. Challenges in the pathologic classification of brain tumors in epilepsy and future directions

EPIDEMIOLOGY

Up to 38% of patients with a primary and 20% of those with a metastatic brain tumor initially seek medical attention following a seizure (1). Conversely, brain tumors cause about 10% to 15% of all adult-onset and 0.2% to 6% of all childhood-onset epilepsies (2–4) and on histopathology represent 26% of all epileptic lesions based on a large European patient series (5).

Major tumor characteristics that determine the likelihood of developing epilepsy include tumor type, grade, and location. As a general rule, the lower the grade of the tumor, the closer it is to the cortex, and the more connected it is to potentially epileptogenic structures (e.g., hippocampus, primary motor cortex, etc.), and the higher are the chances of it producing seizures. The following statistics illustrate these concepts: first, while only 30% to 60% of high-grade gliomas (6,7) and 20% of primary central nervous system (CNS) lymphomas (8) lead to epilepsy, seizures occur in up to 40% of patients with meningiomas (9) and in more than 80% of those with low-grade gliomas (10,11). Second, among patients with a low-grade glioma, cortical location and oligodendroglioma and oligoastrocytoma subtypes are significantly more often associated with epilepsy when compared to deeper midline locations and astrocytoma, respectively (11). Third, while tumors represent up to 56.3% of epilepsy etiologies in temporal lobe epilepsy (TLE) (12), they proportionally account for only half as many (27%) extratemporal lobe epilepsies (13). In one series of 147 patients with newly diagnosed brain tumors, primary location of the tumor also correlated with seizure risk: parietal (80%), temporal (74%), frontal (62%), and occipital (0%) (1). Infratentorial and sellar tumors rarely cause seizures unless they extend into the cerebral hemispheres (3). Careful consideration of these epidemiologic observations, as well as detailed analyses of clinical variables and basic science

investigations, improved our understanding of various mechanisms of epileptogenicity and facilitated the development of targeted treatments.

Table 27.1 summarizes the prevalence of tumors as an epilepsy substrate, while Table 27.2 characterizes the tumor types encountered in medically intractable, chronic epilepsy using data retrieved from the European Epilepsy Brain Bank. Table 27.3 summarizes the prevalence of seizures in various types of brain tumors.

Table 27.1 Neuropathologic Categories in Symptomatic Chronic Human Epilepsies

Category	Numbers (%)	Age OP	Onset	Duration
HS	1908 (32.7%)	33.9 + 10.4	11.3 + 7.7	22.7 + 10.0
DUAL	294 (5.0%)	25.5 + 12.8	9.5 + 7.8	15.9 + 9.9
Tumors	1551 (26.5%)	27.9 + 12.3	16.5 + 10.1	11.8 + 8.8
MCD	930 (15.9%)	18.2 + 12.0	5.9 + 5.7	12.3 + 9.1
Vascular	328 (5.6%)	36.1 + 12.3	23.4 + 11.4	12.7 + 9.0
Glial scars	284 (4.9%)	25.6 + 12.4	10.3 + 8.0	14.7 + 8.6
Encephalitis	96 (1.6%)	20.4 + 12.6	13.3 + 9.4	8.2 + 7.1
No lesion	451 (7.7%)	29.2 + 10.8	12.6 + 7.7	16.1 + 8.0
Total	**5842**	**28.6 + 12.5**	**12.4 + 8.9**	**16.5 + 10.1**

Data retrieved from the European Epilepsy Brain Bank.
HS, hippocampal sclerosis; DUAL, dual pathologies; Tumors, long-term epilepsy-associated tumors; MCD, malformations of cortical development; Age OP, age of patients at surgery (in years); Onset, age at onset of spontaneous seizure activity (in years); Duration, Duration of seizure disorder before surgical treatment (in years).

Table 27.2 Tumor Types Encountered in Medically Intractable, Chronic Epilepsy using Data Retrieved from the European Epilepsy Brain Bank

Entity	Numbers (%)	Age OP	Onset	Duration
GG I°	671 (43.3%)	24.9	12.8	12.7
GG II°/III°	77 (5.0%)	26.9	14.2	11.0
DNET I°	256 (16.5%)	25.2	14.7	10.7
PXA	38 (2.5%)	29.3	18.8	12.2
INET	29 (1.9%)	27.9	14.4	17.7
SEGA	16 (1.0%)	20.1	12.3	9.0
ANET	5 (0.3%)	19.7	2.0	13.0
ASTRO II°/III°	110 (7.1%)	36.2	29.5	6.7
OLIGO II°/III°	97 (6.33%)	38.6	24.5	12.5
PA I°	81 (5.2%)	25.1	14.8	12.1
CYSTS	31 (2.0%)	32.4	21.7	11.6
MENINGIOMA	26 (1.7%)	46.5	38.9	8.4
NOS	62 (3.2%)	29.2	16.1	13.3
OTHER	50 (4.0%)	31.5	25.0	11.3
Total	1549	27.9	16.5	11.7

The table outlines a summary of 1549 long-term epilepsy-associated tumor diagnoses collected at the European Epilepsy Brain Bank (total n = 5842). Seven hundred and nine female and 821 male patients were included. Grading according to WHO I°, II° or III° [84].
GG, ganglioglioma; DNET, dysembryoplastic neuroepithelial tumor; PXA, pleomorphic xantoastrocytoma; INET, isomorphic astrocytoma variant (analogous to WHO I°); SEGA, subependymal giant cell astrocytoma; ANET, angiocentric glioma; ASTRO, astrocytoma; OLIGO, oligodendroglioma incl. mixed gliomas; PA, pilocytic astrocytoma, CYSTS, arachnoid, dermoid, or epidermoid cysts; NOS, highly differentiated neuroepithelial tumor (not otherwise specified); Other, all other tumors with rare frequency (<1%); Age OP, age at operation (mean in years); Onset, age at epilepsy onset (mean in years); Duration, epilepsy duration (mean in years).

Table 27.3 Seizure Frequency in Various Brain Tumor Types

Tumor	Seizure frequency (%)
Dysembryoplastic neuroepithelial tumor (4)	100
Ganglioglioma (3,14)	80–90
Low-grade astrocytoma (3)	75
Meningioma (9)	27–60
Glioblastoma multiforme (3)	29–50
Primary CNS lymphoma (3,8)	10–20

CLINICAL CHARACTERISTICS

Most tumor-related seizures first appear early in the course of the disease, usually as a presenting manifestation (9,10). In 10% to 30% of brain tumor patients, epilepsy develops later in the course of the disease (4,10). In brain tumor patients presenting with seizures, age and presence of associated neurologic deficits may correlate with tumor grade: Children and adolescents usually have no associated neurologic deficits and generally have a low-grade tumor, whereas middle-aged or elderly people often have other associated neurologic deficits on presentation and frequently present with a high-grade brain neoplasm (3,15,16).

Both focal and generalized seizures occur in the setting of brain tumors (10,11,17–19). Even isolated auras have been reported as the only epileptic manifestation of temporal lobe tumors (20). Therefore, in any given patient, seizure semiology is mainly determined by the location of the tumor and its connectivity. However, certain general remarks may be noted. First, seizures that start earlier in the course of a brain tumor are more likely to be generalized: Hildebrand et al. (10) found that while 50% of "early seizures" occurring at or soon after brain tumor diagnosis were generalized and 40% were focal, the converse was true when seizures occurred during the later follow-up phases, with about 75% being focal and only 20% being generalized. Second, in certain special situations, seizure semiology carries a specific tumor-related diagnostic correlation, for example, gelastic seizures and hypothalamic hamartomas.

The observations made above are likely due to distinctly different mechanisms of epileptogenicity that are detailed later. In brief though, younger patients are statistically more likely to have small, slow-growing tumors (developmental tumors, low-grade gliomas, etc.) that take their time to develop focal and remote cellular and pathway changes sufficient to develop epileptogenicity without causing major local tissue damage. As such, patients with low-grade temporal lobe tumors, for example, might not have deficits on a traditional neurologic examination, develop seizures later in the course of the tumor progression, and have more complex partial seizures related to dysfunction of the limbic network. On the other hand, older patients with glioblastoma multiforme (GBM) usually have a larger rapidly growing tumor, causing significant local tissue damage with associated neurologic deficits and seizures starting earlier in the tumor disease course as a result of abrupt tissue necrosis.

Regardless of the tumor type, patients who present with seizures as the initial symptom of a brain tumor are at higher risk of developing epilepsy later (recurrent seizures), even with prophylactic trials of antiepileptic drug (AED) treatment (21,22). Furthermore, up to 50% of those tumor-related epilepsies may become medically intractable, and this is a higher intractability risk than in other epilepsies (10,19,23).

PROPOSED MECHANISMS OF EPILEPTOGENESIS

The development of epilepsy in a brain tumor patient is probably a multifactorial phenomenon. Therefore, even though we will discuss multiple proposed mechanisms of epileptogenicity in brain tumors, it is important to remember that those mechanisms are not mutually exclusive and that in any given patient, epilepsy is likely due to an interplay of all of those variables.

Role of Tumor Type

High-grade tumors may lead to epilepsy by abruptly damaging local tissue, causing tissue necrosis and hemosiderin deposition, and increasing excitability of local and immediately surrounding cortex (4,16,24). Chronic intractable epilepsy is, however, most often caused by lower-grade tumors, specifically low-grade gliomas and developmental tumors—mainly gangliogliomas and dysembryoplastic neuroepithelial tumors (DNET) (12,13,17,25–28). These developmental tumors are surrounded by dysplastic cortex in 25% to 70% of cases (13,28–30) which should be classified as associated Focal Cortical Dysplasia ILAE Type IIIb, or may be associated with coexistent hippocampal sclerosis (14,30,31). In such a setting of "dual pathology," seizures may be predominantly or even independently arising from the dysplasia or hippocampal sclerosis, and not necessarily the tumor. A practical and important implication of this "dual pathology" is the inability

to control seizures surgically in these patients with chronic intractable epilepsy unless both "lesions" are resected (32).

Role of Peritumoral Morphologic Changes

A brain tumor disrupts the tissue around it and causes a variety of morphologic changes that facilitate excitability and thus increase epileptogenicity. Those changes include aberrant neuronal migration, enhanced intercellular communication through increased expression of gap junctions, changes in synaptic vesicles, and increased local concentrations of glutamate and lactate (3,4,24,33). Synaptic transmission, including GABA receptor signaling, may be underexpressed in brain tumor tissues compared with control tissue, further increasing excitability (34,35).

In addition to the above microscopic and molecular changes, gross tumor-related effects include mass effect, local edema, and increased pressure. Also, local infiltrative tumor growth may cause local irritation and epileptogenicity, presumably through inducing tissue hypoxia (36).

Role of Changes to the Microenvironment

Tumors have increased metabolic requirements, and even with increased angiogenesis, eventually lead to intra- and peritumoral hypoxia. This alkalinizes the interstitial pH and causes glial cell swelling and damage, increasing neuronal excitability and facilitating epileptogenic activity (4,37). The risk of epilepsy further increases because of increased inward sodium currents at the level of the astrocytic cell membrane. This results from defective intracellular mechanisms for deoxyribonucleic acid repair and genetic instability also occurring due to tumor-related hypoxia (3). Cortical hemosiderin deposition is also a frequently considered cause for tumor-related epileptogenesis (38).

Role of Genetic Factors

Long-term epilepsy-associated tumors (LEATs) do not share those molecular oncogenes or tumor suppressor genes typically observed in diffusely infiltrating gliomas, such as IDH1 or 1p/19q deletions. In contrast, the oncofetal marker protein CD34 can be frequently identified, and developmental genes are likely to be involved (39). Mutations in B-RAF (40) or mTOR signaling (41) may also play an important role. Other studies have suggested a role for LGI-1 in tumor-related epilepsy (3,4). This is a tumor suppressor gene absent in GBM and other high-grade invasive tumors. It also happens to be responsible for the rare autosomal dominant lateral TLE. Therefore, some authors suggested that LGI-1 plays a role in both tumor progression and epileptogenesis (3,4).

Posttranscriptional and posttranslational alterations have also been implicated in the genesis of epilepsy in brain tumors. For example, LIM domain-binding 2 (LDB2) transcript, critical for brain development during embryogenesis, was one of the strongest reduced mRNAs in gangliogliomas in recent array analyses. Silencing of LDB2 resulted in substantially aberrant dendritic arborization in cultured developing primary hippocampal neurons. This characterizes yet another molecular mechanism operating in gangliogliomas, contributing to the development of dysplastic neurons and an aberrant neuronal network (42). Recent transcriptomic profiling of human peritumoral neocortex tissues revealed that several genes enriched in focal adhesion and cell adhesion molecular pathways may be involved in tumor-induced epilepsy (43). Lastly, the expression of aquaporin-4, a membrane protein implicated in peritumoral edema generation and in drug-resistant hippocampal sclerosis, was reduced in brain tissue from GBM patients without seizures as opposed to GBM patients with

seizures. The aquaporin-4m-RNA levels were identical in these two groups of GBM patients suggesting a posttranslational mechanism (44).

Role of Disruption of Functional Network Topology and Secondary Epileptogenesis

Rather than traditional views conceptualizing the brain as a conglomerate of segregated functional areas, each specifically dedicated to one function, the modern theory of brain networks proposes the presence of cortical networks composed of multiple cortical regions connected via white matter pathways controlling various mainly higher cortical functions and requiring a delicate balance between excitability and inhibition of those multiple pathways to operate correctly (3,34). A disruption of those "normal networks"—as occurs anatomically with a tumor—will disturb this balance, leading to multiple consequences, including deafferentation and release of regulatory inhibition on potentially epileptogenic structures (such as the hippocampus), and the appearance of pathologic, less stable compensatory networks that may themselves be more excitable and thus potentially epileptogenic. This hypothesis is still being investigated, and further research is needed to clarify the full extent of its impact. It might, however, partly explain, among other things, how an epileptogenic focus arises distant from a tumor (14), and why a procedure such as a simple removal of the tumor via a lesionectomy, may not achieve optimal seizure freedom (45).

It has been suggested that in almost one-third of patients with brain tumors and epilepsy, the epileptogenic focus does not correspond to the tumor location. This phenomenon is called secondary epileptogenesis, implying that an actively discharging epileptogenic region induces similar paroxysmal activity in regions distant from the original site. This process is mostly seen with low-grade brain tumors located in the temporal lobe, which frequently present with hippocampal sclerosis (20). In those cases, the "secondary focus" becomes a completely independent epileptic generator that also needs to be removed to achieve seizure freedom in intractable patients. Since young age and long disease duration have been proposed as being the main risk factors for this secondary epileptogenesis (46), early resection of the primary focus—the tumor—has been promoted to avoid the development of an irreversible secondary focus and was actually shown to correlate with better rates of seizure freedom following resective epilepsy surgery (11,17,46).

TREATMENT OF SEIZURES IN THE SETTING OF BRAIN TUMORS

With seizures occurring so frequently in patients with brain tumors, it is important to be aware of the various treatment options available. Very often, adequate treatment of seizures in such a setting requires a multidisciplinary approach, including the patient's neuro-oncologist, neurosurgeon, and epileptologist. Goals of treatment need to be clarified early on in the treatment course, as well as a clear determination of the risk–benefit ratio of various medical and surgical therapeutic options. For example, aiming at complete seizure freedom in a patient with an inoperable, rapidly growing, GBM while concomitantly using five different AEDs with their associated side effects may actually be counterproductive and worsen the patient's quality of life. On the other hand, merely aiming for reduction in seizure frequency in a patient with a developmental tumor would likely be an unacceptable treatment goal as resective epilepsy surgery has a high chance of rendering this patient

seizure free, with a relatively low risk of complications.

The following section reviews current information on medical and surgical aspects of the treatment of seizures in the setting of brain tumors.

Medical Treatment

Anticonvulsant medications are the mainstay of epilepsy treatment in any patient with seizures, including patients with brain tumors. However, little is known about the specific efficacy of different AEDs in the setting of a brain neoplasm. Many patients have recurrent seizures (60% to 70%) despite the use of AEDs, and results of specific AEDs trials are outlined in Table 27.4. First-line AEDs fail in about 60% of patients and, of the remainder, a similar proportion of second-line treatments with monotherapy or polytherapy fails (10,34). A few retrospective studies have favored the use of valproic acid when compared to phenytoin or carbamazepine. Valproic acid was preferred due to the promptness of achieving a therapeutic level, its enzyme-inhibiting properties that may increase the effectiveness of concomitant chemotherapy, and some potential inherent antitumor effects (3,36,54,55). However, it may cause significant bone marrow suppression, especially in combination with chemotherapy. On the other hand, several prospective studies have recently suggested that gabapentin (51), levetiracetam (47,48,52), topiramate (50), or lacosamide (56) may be effective options for add-on therapy. In one prospective series of 26 patients with primary brain tumors who received add-on levetiracetam, usually in combination with valproic acid, a seizure reduction of more than 50% was observed in 65% of patients (47). Similar success rates were seen with levetiracetam used both as add-on or monotherapy (52,57,58). In a small prospective series of 14 patients with intractable seizures and brain neoplasms, gabapentin was added to phenytoin, carbamazepine, or clobazam. Reduction in seizure frequency was seen in all patients, and more than 50% became seizure free (51). In another prospective observational study of 47 glioma patients, initial or add-on therapy with topiramate achieved complete seizure freedom in 56% of patients with a seizure reduction in an additional 20% after a mean follow-up of 16.5 months (59). Most recently, a prospective pilot study following 14 patients with brain tumors and epilepsy showed a 78.6% responder rate with lacosamide (56). All these prospective studies report a low incidence of side effects, although those were slightly higher with topiramate when compared to others.

Table 27.4 Summary of Studies Evaluating Effectiveness of Various AEDs in the Setting of Seizures in Brain Tumors

	Study characteristics			Tumor characteristics		AED characteristics		Outcome	
Study	*N*	Type[a]	Follow-up	Grade	Treatment	Primary drug	Add-on drug	% Seizure free (%)	% Seizure reduction (%)
Hildebrand et al. (10)	234	R	3–276	High, grade II glioma	Surgery Radiation Chemotherapy	VPA CBZ GBP LTG Others		13	NA
Wick et al. (36)	107	R		High, Low	Surgery Chemotherapy Radiotherapy	PHT VPA CBZ		30[b]	
Wagner et al. (47)	26	P	9.3	High	Radiotherapy Chemotherapy Steroids Surgery	VPA	LEV	20	65
Maschio et al. (48)	19	P	7–50	High	Radiotherapy Chemotherapy Steroids Surgery	LTG VPA TOP OXC	LEV	47	72
Newton et al. (49)	41	R	1–2	High	Radiotherapy Chemotherapy Steroids	PHT CBZ	LEV	59	90
Maschio et al. (50)	47	P	3–48 (16.5)	High Metastatic Low	Surgery Steroids Radiotherapy	PHT CBZ PB	TOP	56	76
Perry et al. (51)	14	P	1–6	High	Radiotherapy Steroids	PHT CBZ Clobazam	GBP	57	100
Maschio et al. (52)	29	P	12	High, Low	Radiotherapy Surgery Chemotherapy	PB TPM VPA OXC	LEV (monotherapy)	93	100
Saria et al. (53)	70	R		High, Low	Radiation Surgery Chemotherapy Corticosteroids	Multiple	LCS		66%

[a]P, prospective; R, retrospective.
[b]70% of patients on CBZ had recurrent seizures, as opposed to 51% of those on PHT and 44% of those on VPA.
CBZ, carbamazepine; PHT, phenytoin; PB, phenobarbital; VPA, valproic acid; TOP, topiramate; LTG, lamotrigine.

Few head-to-head studies compare the effectiveness of various AEDs in treating brain tumor–related epilepsy. Levetiracetam was compared to phenytoin in two retrospective series (60,61) and one prospective study (62). All showed similar efficacy in both groups, although the prospective study suggested better tolerability and response rates with levetiracetam (62). Similarly, a retrospective observational study suggested that oxcarbazepine had similar effectiveness and better tolerability when compared to traditional AEDs (63). Interestingly, one observational study comparing the use of valproic acid and levetiracetam used either alone or in combination to other AEDs found the highest percentage of responders (81.5%) in those treated with the levetiracetam plus valproic acid combination (64).

Special Issues Pertaining to Medical Treatment of Epilepsy in Brain Tumors

Medical Intractability of Epilepsy in Brain Tumors

While 20% to 25% of epilepsy patients in general continue to have frequent seizures despite the use of AEDs at adequate serum concentrations, this medical intractability occurs in up to 50% to 60% of patients with seizures and brain tumors (3,11,15,19,24,34,37). This has been attributed to a variety of possible mechanisms. Overexpression of proteins belonging to the multidrug resistance pathway is a frequently discussed mechanism of refractoriness. These proteins are members of the adenosine triphosphate–binding cassette transporter family, normally present in the apical membranes of

endothelial cells. The multidrug-resistance gene (MDR)-1 (ABCB1, P-glycoprotein) and multidrug-resistance–related protein (MRP, ABCC1) contribute to the blood–brain and blood–cerebrospinal fluid barriers by controlling the transport of various lipophilic substances in and out of the brain. Many AEDs, including phenytoin, carbamazepine, lamotrigine, felbamate, and phenobarbital, are substrates for MDR-1 products, and are therefore actively eliminated from the intracellular milieu and brain parenchyma when the MDR proteins are overexpressed. Such overexpression has been found for MDR-1 in cells of patients with gliomas and gangliogliomas (19,24,65) and for another MDR protein, the breast cancer resistance protein, in endothelial cells of brain tumor specimens from astrocytomas, anaplastic astrocytomas, and GBM (37). Gabapentin may be transported via a nonspecific transporter out of the brain. However, levetiracetam does not seem to be a substrate for either MDR-1 or other MDR proteins, while the histone deacetylase–inhibiting effects of valproic acid might reduce the expression of P-glycoprotein and MRP-1, raising interest in the potential usefulness of those AEDs in intractable patients (37). This needs to be confirmed by further studies.

Other proposed mechanisms of AED resistance in brain tumors are reduced drug receptor sensitivity, including ion channels, neurotransmitter receptors, and metabolic enzymes involved in the activity of neurotransmitters, as well as reduction in the concentration of several enzyme-inducing AEDs caused by concomitant use of chemotherapeutic agents. Figure 27.1 illustrates the interaction among various proposed mechanisms of resistance to medical therapy.

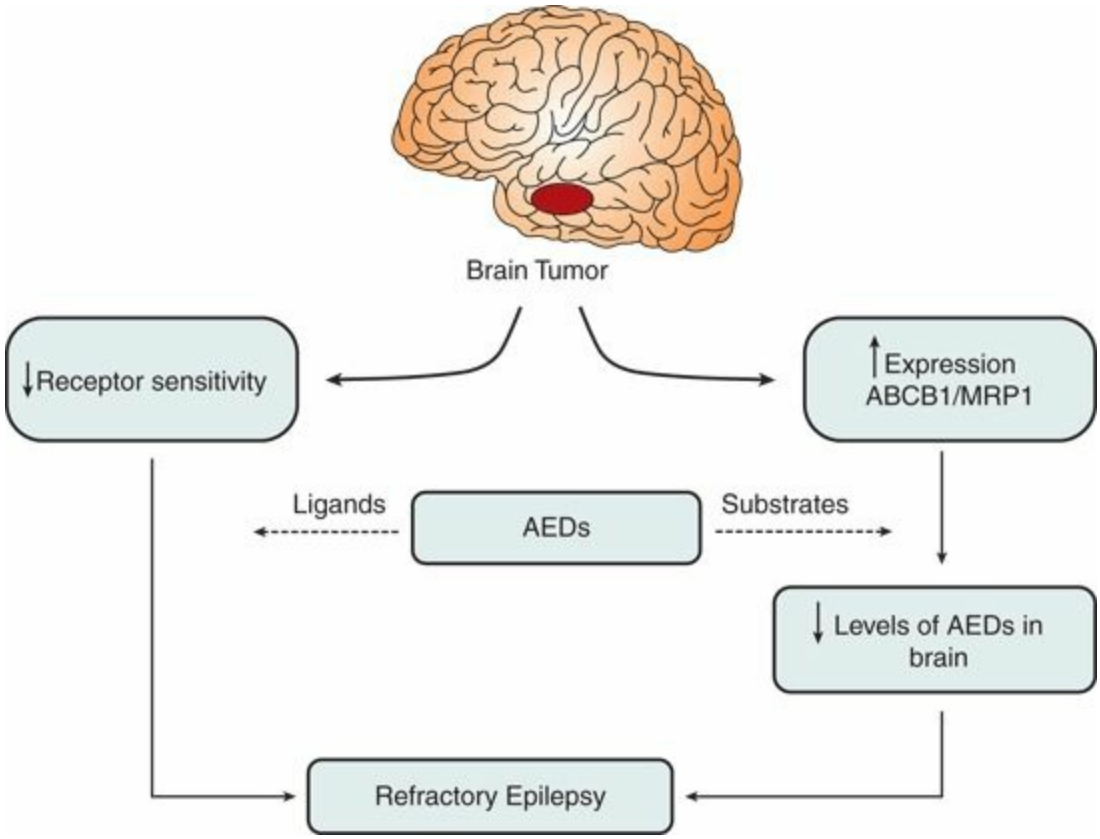

Figure 27.1. Decreased receptor sensitivity and increased expression of multidrug resistance proteins play the most important roles in medical refractoriness seen with brain tumors and epilepsy.

Issues Related to Interactions Between AEDs and Antineoplastic Agents

There is a significant risk for drug–drug interactions during concomitant use of AEDs and chemotherapeutic agents, as both are substrates for the same hepatic metabolic pathways, mainly the cytochrome P450 system. Carbamazepine, phenytoin, phenobarbital, and primidone, and to a lesser

extent lamotrigine and topiramate, have prominent cytochrome P450 enzyme–inducing effects, while valproic acid has an inhibitory effect. Induction or inhibition of these enzymes by AEDs can cause a decrease or increase in anticancer drug concentrations and thus possibly their effectiveness. Similarly, enzyme inhibition or induction by anticancer drugs can lead to toxicity or loss of seizure control (37,66). Newer AEDs such as gabapentin, levetiracetam, and pregabalin do not influence the cytochrome P450 or other metabolic pathways and theoretically only have minimal risk for drug–drug interactions with chemotherapeutic agents (4,24). Focal treatment with AEDs has been investigated in animal models to circumvent efficacy and toxicity challenges, including intraparenchymal injections, self-contained implanted devices, or convection-enhanced delivery (34). Further data are needed before definite statements can be made about the clinical applicability of these investigations.

Dexamethasone is frequently used in the treatment of tumor-associated edema and also interacts significantly with certain AEDs. It competes with phenytoin for protein binding, raising its blood concentration. Conversely, it may cause the opposite effect of lowering phenytoin's serum concentration by affecting its hepatic metabolism (24).

In summary, significant risks for reduced effectiveness and toxicity exist for both chemotherapeutic agents and enzyme-inducing and enzyme-inhibiting AEDs when used concomitantly. The patient should be cautiously observed for side effects, and serum AED blood levels need to be monitored closely.

AED Prophylaxis in Brain Tumors

The American Academy of Neurology published a consensus statement in 2000 recommending that AED prophylaxis should not be used, and current AEDs should be discontinued, in brain tumor patients who do not have a history of seizures (21). A more recent meta-analysis of controlled clinical trials evaluating the effectiveness of seizure prophylaxis in people with brain tumors, performed between 1966 and 2007, found no difference between the treatment interventions and the control groups in preventing a first seizure in participants with brain tumors concluding that the evidence is neutral, neither for nor against seizure prophylaxis, in people with brain tumors (22). The authors recognized that these conclusions apply only for the older AEDs: phenytoin, phenobarbital, and divalproex sodium (22). Therefore, based on current evidence, the decision to start prophylactic AED use in brain tumor patients should ultimately be guided by assessment of individual risk factors and careful discussion with patients, keeping in mind that there is no strong evidence that any of the currently available AEDs reliably prevent a first seizure in a brain tumor patient.

Surgical Treatment

In general, the following questions are considered when evaluating the surgical management of a patient with tumor- associated epilepsy: does this patient really need surgery now to treat his or her seizures, or is medical therapy sufficient? Should any kind of neurophysiologic testing be performed prior to surgery? What type of surgery should be offered? Will a lesionectomy be appropriate, or is a more aggressive resection required? How can this patient be counseled about his or her seizure outcome following surgery? Despite extensive literature on these topics, such decisions remain very much patient dependent, and a careful consideration of all treatment options as well as a clear and educated patient informed consent process represent the cornerstones of a successful "outcome." Although the WHO has published a classification system for brain tumors, only few prognostic and predictive tumor-specific features are available for those tumors typically associated with early-

onset epilepsy (67). Indeed, neuropathologic agreement for microscopic diagnosis is only moderate and is discussed further below. The following segments briefly address some of the questions raised above.

Timing of Surgery: Now or Later?

A critical piece of information that determines the answer to this question is the type and grade of the tumor in question. Alternatively asked, this question is equivalent to deciding whether the patient needs "tumor surgery" or "epilepsy surgery." In patients with a high-grade brain tumor, or one with a high risk of malignant transformation such as gangliogliomas, surgical removal is an essential part of the tumor treatment and should be performed regardless of whether it is believed to help with seizures or not in order to improve the patient's quality of life and chances of survival (16,17,20,24,25,68). On the other hand, most developmental tumors and many low-grade tumors may be observed for years from a tumor treatment perspective or be treated with chemotherapy or radiotherapy. "Tumor surgery" is therefore not required immediately, and the decision to operate would mainly depend on whether a patient's seizures are controlled with AEDs or not. Many epileptologists usually wait until seizures are medically intractable before pursuing surgical tumor removal. However, many studies suggest that a shorter epilepsy duration at the time of tumor resection is an important predictor of postoperative seizure freedom (69,70). In a retrospective review of 332 patients following resection of low-grade gliomas, postoperative seizure control was significantly poorer in patients with longer seizure history ($P < 0.001$) (11). In another study evaluating the seizure outcome of 26 children following resection of their DNETs, all patients with epilepsy duration of <2 years were seizure free at 12 months after surgery as opposed to 7/11 of those with longer seizure history (23). Such observations, together with the high risk of intractability in low-grade tumors (1,3,4), support early removal of low-grade brain tumors associated with epilepsy, especially when the tumor is easily surgically accessible (3). At any rate, a careful preoperative attempt at determining the nature of the tumor should be one of the initial steps in evaluating whether a patient needs immediate surgery or not.

Presurgical Neurophysiologic Evaluation

In most tumor-related epilepsy surgery patients, preoperative video-EEG evaluations confirm that seizures arise from the lobe involved with the tumor. In one study of children with DNET, all but one case had ictal onset discharges unilaterally concordant with the tumor location (23). In another series of adult tumor-related epilepsy patients, the epileptogenic focus as determined by interictal and ictal recordings agreed with the involved lobe in 72% of the cases (28). So, why do we need to perform video-EEG evaluations prior to treating the epilepsy of a brain tumor patient by simply removing the tumor? Several hypothetical and evidence-based outcome data support this practice. First, it is important to acknowledge that even though the above-mentioned studies showed seizures arising from the "same lobe" as the tumor, electrocorticographic recordings usually show that the tumors themselves are electrically inert and that epilepsy often arises from the tissue surrounding the tumor (33). Some have even suggested that seizures arise distant from the tumor in up to a third of patients with brain tumors and epilepsy (10,14). So, a preoperative video-EEG evaluation may provide evidence for the extent of epileptogenicity in the surrounding brain tissues. Figure 27.2 illustrates a case where a subdural EEG evaluation confirmed ictal onset distal from the tumor and where seizure freedom was achieved by resecting both the lesion and surrounding cortex. Second, not all brain

tumors are epileptogenic and not all "spells" are epileptic, so a video-EEG evaluation may be helpful in confirming the epileptic nature of a patient's spells and characterizing the relationship of the epileptogenic focus to the tumor itself (29). Third, some studies have reported better seizure outcomes with the use of intraoperative electrocorticography in tumor surgery and the resection of intraoperatively identified zones of interictal spiking and ictal onsets (3,25,71). In a study of 35 patients with intractable TLE related to benign mass lesions, the number of 3-year postoperative seizure-free incidences for the group that underwent lesionectomy plus additional spike-positive site resection equated to 90.9%. In contrast, in the group that underwent a lesionectomy only, 76.9% were seizure free for 3 years postoperatively (71). However, such results need to be reproduced in larger-scale randomized studies. Lastly, when tumors occur in proximity to eloquent cortex, intra- or extraoperative functional mapping is often essential in determining the extent of the surgical resection (72). For all the above reasons, it is recommended to perform a neurophysiologic evaluation, preferably at least a video-EEG evaluation with ictal recordings, prior to proceeding to surgery in a brain tumor patient with seizures.

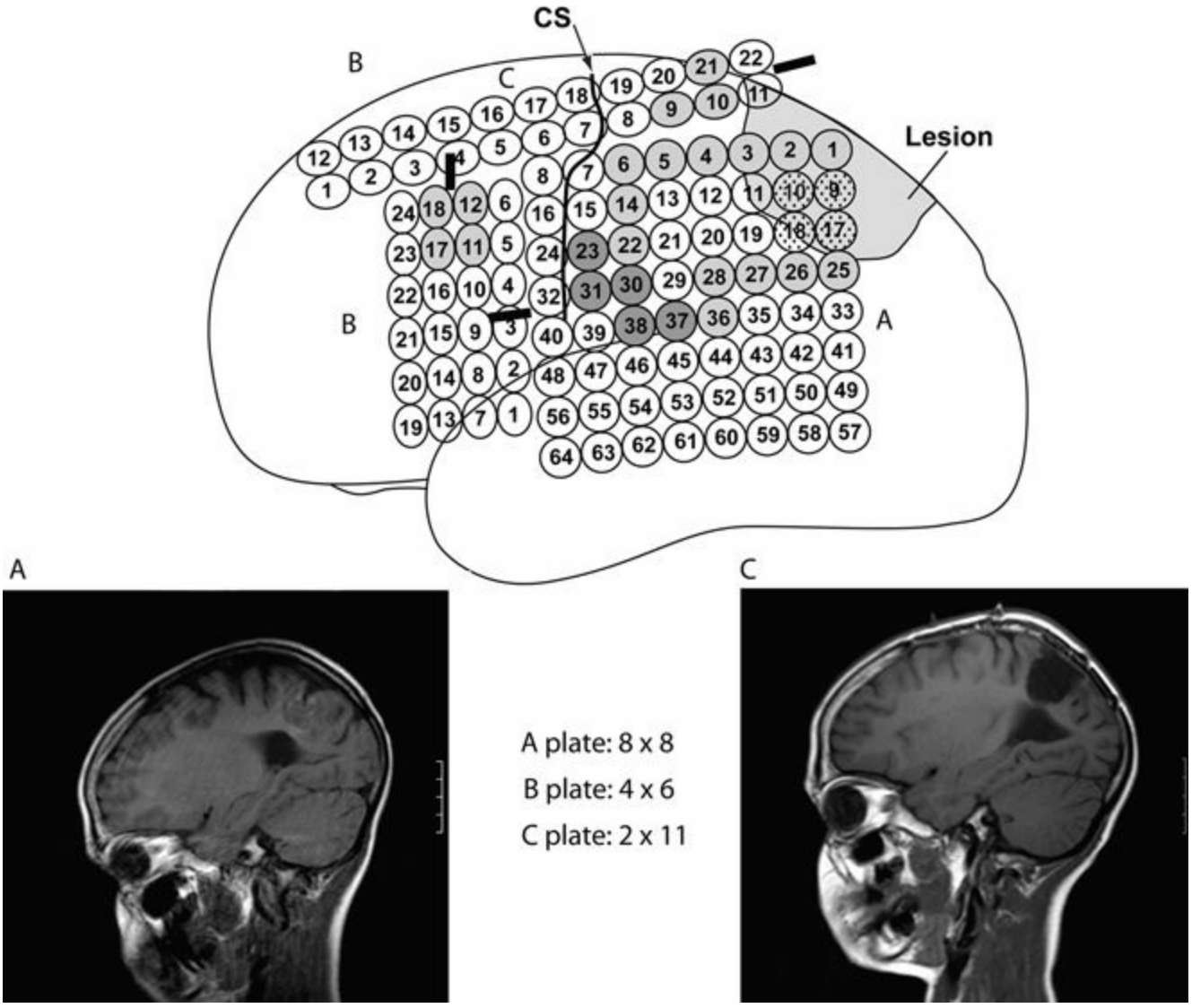

Figure 27.2. This figure illustrates the case of a 10-year-old boy with a left parietal low-grade glioma where subdural EEG recordings showed interictal activity diffusely, both proximal and distal to the lesion (light gray), and two different seizure patterns: one arising from the lesion itself (speckled gray) and one arising somewhat distally from the lesion (dark gray). Central sulcus (CS) location is also illustrated. An "extensive lesionectomy" was performed to include areas of identified epileptogenicity rendering the patient seizure free (follow-up of 2 years). **A** and **C** show the preoperative and postoperative MRI, respectively.

Type of Surgery: Lesionectomy Alone or More Aggressive Resection?

Multiple studies have reported favorable seizure outcomes with complete lesionectomies alone, with seizure freedom rates ranging from 65% to 80% (20,26,27,73). There is evidence, however, to support more aggressive resections in certain situations, most recently from a large meta-analysis evaluating predictors of seizure freedom after resection of supratentorial low-grade gliomas (70). This issue has been investigated most extensively in relation to temporal lobe tumors and epilepsy. In one study of 18 patients who underwent surgical removal of a DNET—12 via temporal lobectomy and 6 via lesionectomy—temporal lobectomy led to a better seizure outcome (Engel Class I, 83.3%; Engel Class IA, 66.7%) than lesionectomy (Engel Classes I and IA, 33.3%) after a mean follow-up of 10.8 years (74). In another study reporting 41 surgical interventions in 38 adults with dual pathology, including 10 with tumors, lesionectomy plus mesial temporal resection resulted in complete freedom from seizures in 11/15 (73%) patients, while only 2/10 (20%) patients who had mesial temporal resection alone and 2/16 (12.5%) who had a lesionectomy alone were seizure free ($P < 0.001$) (75). Such findings have been attributed to the high prevalence of dual pathology in temporal lobe tumors (29,30,76) and to the risk of associated secondary epileptogenesis. This is supported by the persistence of interictal spiking recorded with intraoperative electrocorticography in the hippocampus of 86% of cases and in the amygdala in 64% of the cases after resection of temporal lobe tumors (3). The practice of resecting the mesial temporal structures while removing the tumor is easy to accept and understand when there is preoperative evidence of dual pathology preoperatively, that is when the hippocampus looks dysmorphic or sclerosed on baseline magnetic resonance imaging (MRI). In such cases, the above-mentioned outcome data prompt most surgical centers to resect the hippocampus, especially if neuropsychological testing suggests a low risk for postoperative functional decline. The decision becomes more problematic when the hippocampus looks normal on imaging, especially if baseline neuropsychological testing is normal. Currently, it is difficult to justify resecting a dominant normally appearing hippocampus unless there is compelling evidence, such as extraoperative depth electrode recordings, for example, documenting seizures arising from the mesial structures.

Seizure Outcome

In both temporal and extratemporal epilepsy surgery, a tumoral etiology carries usually a favorable prognosis and is associated with a favorable seizure outcome in as many as 65% to 87% of the cases (11,17,20,26,27,77).

Consistently identified favorable prognostic indicators are complete tumor resection and short epilepsy duration at the time of surgery.

In one study evaluating outcomes of 44 patients with ganglioglioma following surgery, 23/23 patients with a gross total tumor removal were seizure free at last follow-up compared to 1/3 of those with subtotal resections (78). In another review of 332 adults with low-grade glioma, patients with a gross-total resection were 16 times more likely to achieve seizure freedom than after subtotal resection/biopsy alone (11). Residual tumor on postoperative MRI in a cohort of 26 children with DNETs predicted long-term seizure recurrence (23). There is currently little doubt then that a complete resection is the crucial determinant of seizure freedom. Seizure recurrence should prompt an evaluation for tumor recurrence (23,29).

Similarly, a shorter duration of epilepsy at the time of surgery seems to predict more favorable seizure outcomes (11,23,78,79). In a large European series of patients subjected to epilepsy surgery

(EEBB), epilepsy due to a brain tumor showed a mean duration of 12 years (Table 27.2). Considering young age at epilepsy onset (mean 16 years) and increased long-term risk to develop cognitive comorbidities by sustained temporal lobe seizures (77% of all tumors registered at EEBB were localized in the temporal lobe), presurgical evaluation should be envisaged at an early stage of drug refractoriness.

PATHOLOGIC TUMOR CLASSIFICATION: CHALLENGES AND FUTURE DIRECTIONS

It is difficult to describe and classify the paramount histo- and cytologic features within the LEAT spectrum (Table 27.2) using standard microscopic hematoxylin and eosin (H&E) stains, which has promoted diverse classification schemes of histomorphologic LEAT subtypes, that is, the four different variants of a DNT with diffuse and simple forms, as well as complex and nonspecific variants (Figs. 27.3 and 27.4) (80,81). Other strategies tried to incorporate rare or unusual subtypes into well-introduced WHO tumor entities, such as the ganglioglioma (82,83). Any meta-analysis of published LEAT series will be, therefore, almost impossible and generate inconsistent data, despite an existing and systematically revised WHO classification system for brain tumors (84). In a previous review of eight international LEAT series (covering a total of 2055 patients), DNT and GG were identified as most prevalent entities (67). However, reported percentages for both categories reached a huge, although similar variance between 7% and 70%. These figures suggest that the same tumors were classified either as GG or DNT, reflecting rather differences in neuropathology school and training than reliable histopathologic hallmarks. As a consequence, prognostic or predictive features reported so far are inconsistent and cannot be generalized. The enigmatic and controversially discussed risk for malignant progression in a DNT may be an important example.

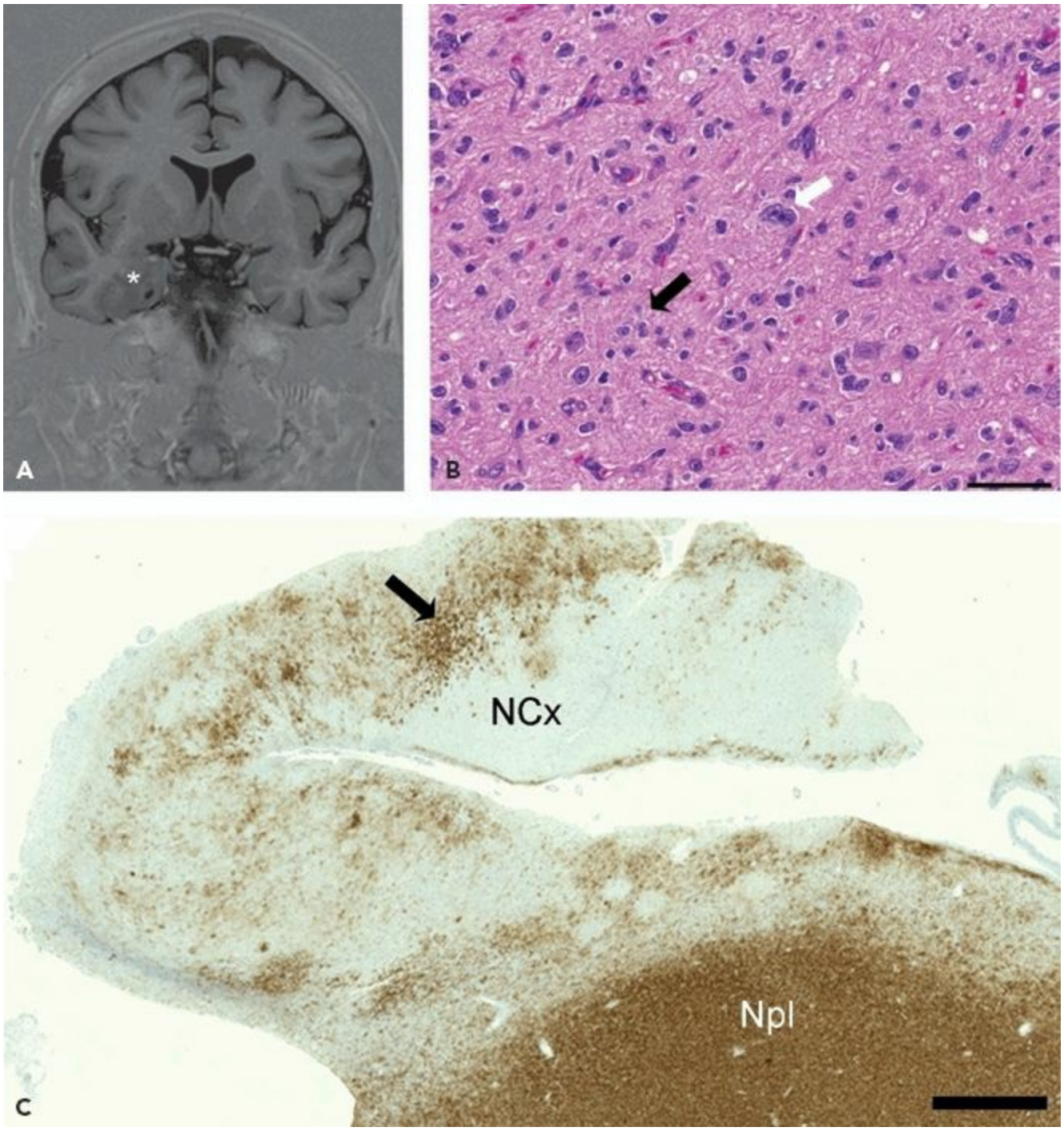

Figure 27.3. Neuropathology findings in a ganglioglioma. This is a 27-year-old male patient suffering from symptomatic epilepsy since age 13. MRI revealed a right temporal cystic lesion (asterisk in **A**), suspicious for a low-grade tumor. The microscopic inspection revealed a mixed glioneuronal tumor with dysplastic neurons (white arrow in **B**) and neoplastically transformed glial cells (black arrow in **B**). The expression of CD34 (brownish color in **C**) is a characteristic immunohistochemical hallmark of this tumor entity (33) and can be observed within the tumor mass (Npl in **C**) as well as tumor infiltration into adjacent neocortex (NCx and black arrow in **C**). The biologic behavior of this tumor corresponds to WHO Grade I without frank signs for atypia or anaplasia.

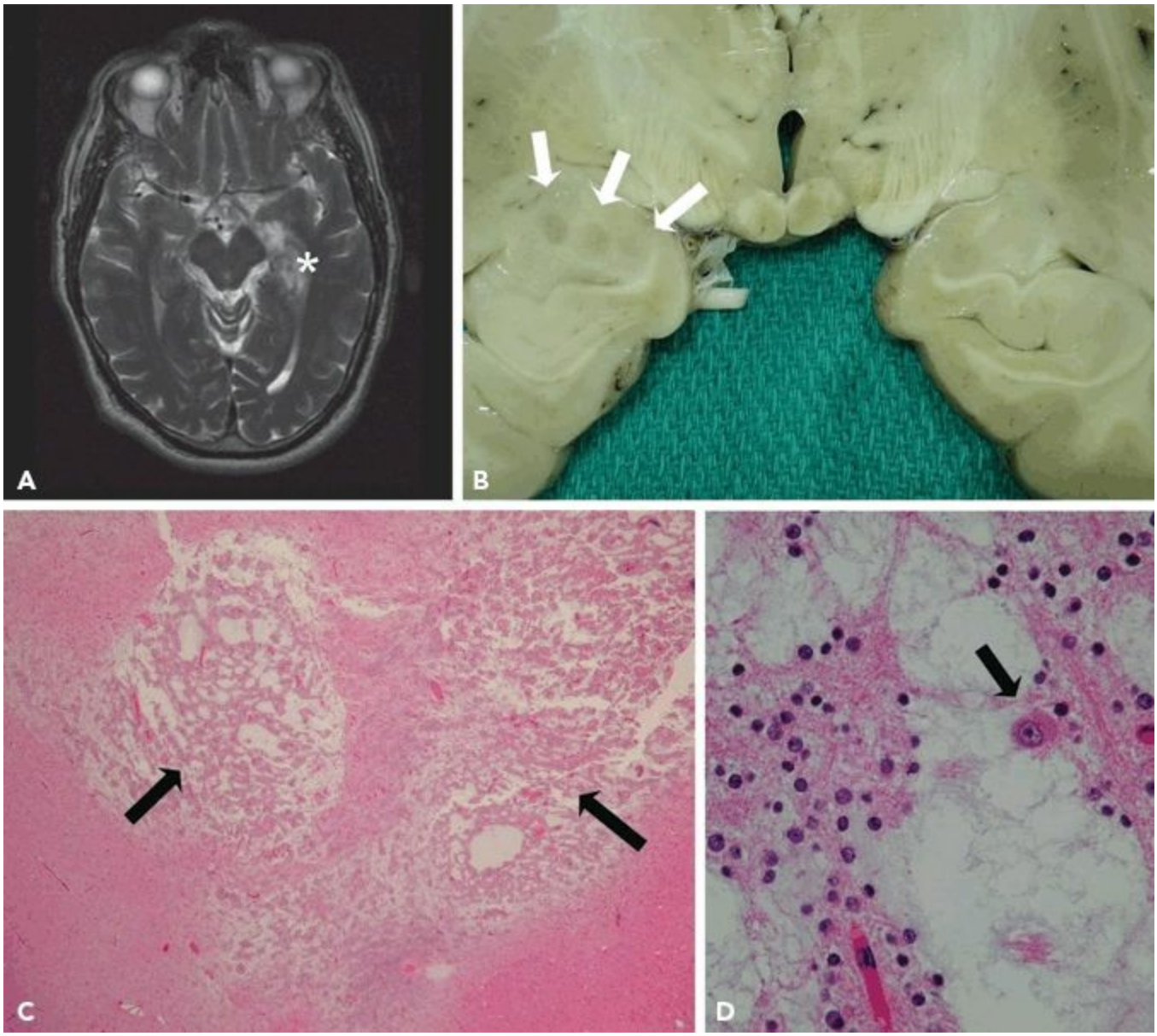

Figure 27.4. Neuropathology findings in a DNT. This 34-year-old male was found dead in his residence, and no anatomic cause of death was evident. He was known to have a seizure disorder, with a stable lesion of the left amygdala first documented 5 years before death; it was hyperintense on T2 (**A**). He was not taking an antiseizure medication. The left amygdala showed subtle enlargement with a multinodular mucinous lesion (arrows in **B**). Microscopically patchy infiltration with focal nodularity (arrows in **C**) and a specific glioneuronal element with "floating neurons" (arrow in **D**), which is characteristic for the histopathologic diagnosis of a dysembryoplastic neuroepithelial tumor (DNET). (Courtesy of Dr. R. Macaulay, Halifax, Canada.)

Increasing availability of surgical tumor specimens may provide the opportunity to clearly characterize the molecular signature of each LEAT variant as well as their molecular pathogenesis and epileptogenic potential. Notwithstanding, such studies will require a reliable terminology use and histopathologic classification that can be reproduced by any other laboratory. Uniform terminology will pave the way for a prospectively designed randomized controlled trials for LEAT treatment providing urgently needed class I evidence for potential biomarkers.

CONCLUSIONS

Tumors constitute a very important cause of chronic intractable epilepsy, and seizures represent a very frequent presenting symptom of brain tumors. Our knowledge of the mechanisms defining the relationship between the two conditions has grown exponentially over the past few years, but a lot

remains to be learned. Several medical and surgical treatment options are available, and multiple potential mechanisms of epileptogenicity in brain tumors have been proposed. So, a diagnostic or a treatment approach focused solely on one mechanistic premise will provide an incomplete view of the true disease pathophysiology and likely be unsuccessful.

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CHAPTER 28 POST TRAUMATIC EPILEPSY

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EPIDEMIOLOGY

Posttraumatic epilepsy (PTE) accounts for around 200 new cases of epilepsy per 100,000 persons per year (1,2). PTE is the most common cause of acquired epilepsy, comprising almost 20% of all cases, and is the leading cause of epilepsy with onset in young adulthood (3,4). Head trauma underlies 6% of all epilepsies in the general population and accounts for 5% of patients seen at specialized epilepsy centers (5,6).

The cumulative risk of late unprovoked posttraumatic seizures (seizures occurring >1 week after injury) consistent with a diagnosis of PTE varies between 2% and 20% in civilian populations suffering from closed head injuries and can be as high as 50% in military series after penetrating head injuries (5). Nearly 40% of these late seizures appear within the first 6 months after injury; 50% to 66% appear by 1 year; and more than 75% appear by 2 years after the injury (7–9). Although the risk of PTE continues to decline as the postinjury seizure-free interval lengthens, late seizures may develop over 15 years after the initial insult (10–12). The probability of PTE 5 years after traumatic brain injury (TBI) is estimated as 0.7% after mild (loss of consciousness [LOC], posttraumatic amnesia for <30 minutes, and no skull fracture), 1.2% after moderate (LOC, posttraumatic amnesia lasting for 30 minutes to 24 hours, or skull fracture), and 10% after severe TBI (brain contusion or intracranial hematoma, LOC, or posttraumatic amnesia for >24 hours) (11). After follow-up for more than 30 years, the probability increases to 2.1% for mild, 4.2% for moderate, and 16.7% for severe TBI. The relative risk (RR) of developing PTE after mild TBI increases twofold, fourfold after moderate TBI, and up to sevenfold or more after severe TBI (Table 28.1) (13,14).

Table 28.1 Risk of Posttraumatic Epilepsy

Risk factors		Cumulative incidence (10)		Relative risk/standardized incidence ratio
		5 y	30 y	
Closed head injury	Mild	0.7%	2.1%	2.22 (95% CI 2.07–2.38) (13) 1.5 (95% CI 1.0–2.2) (10)
Multivariate analysis (10)	Moderate	1.2%	4.2%	2.9 (95% CI 1.9–4.1) (10)
▪ Contusion	Severe	10.0%	16.7%	7.40 (95% CI 6.16–8.89) (13)
▪ Subdural				
▪ Skull fracture				17.0 (95% CI 12.3–23.6) (10)
▪ LOC > 1 d				
▪ Early seizure				
▪ Age ≥ 65 y				
Penetrating head injury (89)		22%–43%	50%	

Although the annual incidence of head injury in the general population has not changed in the past 30 years, the number of survivors of severe head injuries has risen, leading to a higher prevalence of patients with PTE (15). Additionally, there has been a high percentage of head injuries of soldiers from the Iraq and Afghanistan wars, with recent studies reporting 7% to 15% of veterans being diagnosed with or having symptoms of TBI (16). Considering this, one can expect a markedly increased number of veterans with posttraumatic seizures.

PATHOPHYSIOLOGY OF POSTTRAUMATIC SEIZURES

Early Seizures

Early posttraumatic seizures, defined as seizures occurring within 1 week of the initial insult, are triggered by the acute trauma or subsequent complications and have to be differentiated from late, unprovoked posttraumatic seizures defining a diagnosis of epilepsy (11). A variety of mechanisms directly related to the initial trauma can trigger symptomatic seizures: The immediate insult after a head injury leads to diffuse axonal injury due to shearing forces and focal brain damage caused by the direct impact to the skull, movement of the brain within the skull (coup and contrecoup), or penetrating wounds (17–20). Secondary axonal injury ensues caused by retraction and swelling of the injured axons with distal wallerian degeneration (21). Subsequent brain necrosis may result from cytotoxic processes such as the release of free oxygen radicals and cytokines and the influx of calcium into open ion channels (18,22). Complications during the acute recovery phase, for example, hypoxia, increased intracranial pressure, hypotension, ischemia, cerebral edema, intracranial bleeding, electrolyte imbalances, or infections, can cause symptomatic seizures several weeks after the injury (Table 28.2) (7,11,23,24). Overall, 90% of seizures within the first 4 weeks after head injury will happen during the first week and more than half of them within the first 24 hours (25,26).

Table 28.2 Definitions

Seizures	Duration after insult	Increased risk of epilepsy	Prophylaxis
Impact convulsion	At impact. Nonepileptic	–	7 d in *severe* TBI
Early seizure	<1 wk[a]	+	
Immediate seizure	<24 h		
Late seizure	>1 wk[a]	+++	After first late seizure
Posttraumatic seizures	Single or recurrent seizures after TBI, separated by early or late occurrence, not attributable to another obvious cause		
Posttraumatic epilepsy	Late-onset, recurrent, unprovoked seizures after TBI, not attributable to another obvious cause		
Degree of TBI	**LOC**	**Skull fracture**	**Structural brain damage**
Mild	<30 min	–	–
Moderate	>30 min and <24 h	+/–	–
Severe	>24 h	+	+

[a]Four weeks in patients with additional complications that may cause acute symptomatic seizures.
LOC, loss of consciousness; TBI, traumatic brain injury.

The incidence of early posttraumatic seizures depends on the severity of the injury and is seen in approximately 2.5% of head injury patients in population-based studies and in up to 16% of patients admitted after severe head trauma (7,11,27–33). Moderate to severe head injury, in particular the presence of a subdural or intracerebral hematoma, a depressed skull fracture, a penetrating brain injury, or a cortical contusion, increases the incidence of early seizures up to 30% (11,34,35). With mild head injuries, an early seizure often indicates other neurologic or systemic abnormalities and should warrant further evaluation and observation (23,36–38). A structural lesion from the acute injury—for example, an epidural or subdural hematoma—has to be excluded with imaging. On rare occasions, seizures after mild trauma are seen in the context of a preexisting brain pathology (39,40), known as pseudotraumatic epilepsy (41).

Approximately 10% of patients with early symptomatic seizures develop PTE. While early seizures are associated with an increased risk for late seizures, the increased risk for PTE is not a direct consequence of the early seizures (7,11,27–33). Multivariate analysis in a large population-based study demonstrated that the increased risk of late epilepsy can be explained by other factors, for example, the presence of a cerebral contusion or hematoma, in particular subdural hematoma, skull fracture, or age (11).

The presentation of early posttraumatic seizures is variable. Electrographic seizures without clinical correlate that are only detectable by continuous electroencephalogram (EEG) monitoring occur frequently. Based on a study of continuous EEG monitoring in the intensive care unit (ICU), which included mostly patients with severe head injury, 21 out of 94 patients (22%) had posttraumatic seizures within the first week of injury (42). Only six patients had clinically witnessed generalized tonic–clonic seizures, another four patients showed subtle myoclonic movements with an epileptiform EEG correlate, while more than half of the patients had electrographic seizure without associated clinical signs. Frequent posttraumatic electrographic seizures are associated with episodic increases in intracranial pressure and lactate/pyruvate ratio and may be a target for aggressive antiepileptic management (43).

Approximately 10% to 20% of early seizures evolve into status epilepticus, more commonly seen in children (25,44). Generalized convulsive status epilepticus often accompanies underlying secondary complications, such as ischemia or metabolic imbalance. Focal motor status is most common with subdural hematomas or depressed skull fractures and can be refractory to treatment. Patients with early status epilepticus may have a higher risk for late seizures than patients with self-limited early seizures according to one study (45). Patients with early status epilepticus had a 41% 10-year cumulative risk to develop late seizures compared to a 13% risk after brief symptomatic seizures. It remains unclear if this is related to the underlying lesion, the effect of status epilepticus, or a shared susceptibility for prolonged early seizures and epilepsy in some patients.

Late Seizures and Epileptogenesis

“Through trauma, the brain may be injured by contusion, laceration, compression, and it is well known that these insults may result in epilepsy after a ‘silent period of strange ripening.’ That period lasts for months or years, but these insults produce epilepsy in the case of one individual and not in the case of another… Our attention should therefore be directed toward the discovery of this mysterious difference” (46,47).

The development of PTE after a latent period has been an intriguing observation and challenge for more than half a century. The “strange ripening” in PTE is a rare example of human epileptogenesis,

the transformation process of a nonepileptic brain into a brain able to generate recurrent, unprovoked seizures (48). The window between insult and occurrence of these unprovoked seizures offers a unique opportunity to investigate the potential mechanisms leading to epileptogenesis, to identify biomarkers, and to implement therapeutic interventions, which are able to prevent the development of the disease rather than merely suppress the seizures. Most of our understanding of the cellular and molecular mechanisms of epileptogenesis derives from experimental animal models, which are not specifically related to traumatic injury. These studies have shown immediate neuronal and glial responses following an injury, usually leading to significant cell loss in areas of the injured brain and over time. Additional changes involve long-term reorganization of neural circuits including disinhibition and selective loss of inhibitory γ-aminobutyric acid (GABA)ergic neurons and increased glutamatergic excitation. Ultimately, these changes lead to an imbalance between excitatory and inhibitory neurotransmission and increased risk for spontaneous seizures (49–51).

A better understanding of the processes between initial insult and development of epilepsy may provide potential treatment targets to prevent epilepsy. Example of a potentially treatable process are early symptomatic seizures or status after head trauma that could cause progressive changes in neural networks and lead to spontaneous and recurrent late seizures (52). Another example is the highly epileptogenic process of hemosiderin deposition and formation of free iron radicals typical for head trauma (53,54).

Several animal models of PTE—including the fluid percussion model, controlled cortical impact injury model, weight drop injury model, neocortical undercut model, and more recently the blast injury model—have been widely used to investigate epileptogenicity after TBI (33,51,55–57). Based on the fluid percussion model, either a selective loss of hilar interneurons in the dentate gyrus or a relative survival of irritable mossy fibers may lead to persistent granule cell hyperexcitability (58–60). More recent studies have shown that focal brain damage after a single episode of severe fluid percussion injury is able to trigger spontaneous seizures (51,61), which originate from the site of the lesion and become clinically and electrographically more severe over time (62,63).

The controlled cortical impact model utilizes an electronically controlled impactor to apply a focal contusion injury to the cortical surface, allowing for consistent and reproducible results without risk of secondary rebound injuries. Studies have shown that injury to the dentate gyrus leads to mossy fiber sprouting with structural reorganization leading to increased spontaneous excitability (64,65). Recently, a new model of penetrating TBI in rats was developed to more closely mimic wartime TBI. However, it is unclear if this model results in long-term spontaneous seizures (51).

Isolation of a small cortical region by transecting the white matter with a needle leads to epileptiform activity of the pyramidal cell layer in slice recordings in the “cortical undercut” model. Axonal sprouting of the isolated pyramidal cells is associated with an increased number of excitatory connections (66). Furthermore, recent studies have shown a decrease in the GABA output of neocortical fast spiking interneurons that synapse on excitatory postsynaptic targets (67). Early application of tetrodotoxin after the injury blocks action potentials and prevents the development of evoked and spontaneous epileptiform activity in the neocortical slices (68), suggesting that posttraumatic epileptogenesis may be an activity-dependent process. Tetrodotoxin given within 3 days of injury prevented the occurrence of late seizures in an animal model of PTE (69). Several seizure medications have also shown antiepileptic properties in both kindling and posttraumatic animal models of epilepsy including valproate and topiramate with levetiracetam showing antiepileptic properties in a kindling model only (70,71).

The process of epileptogenesis and postinjury recovery overlaps in time and seems to share some

basic mechanisms, including neurogenesis, axonal sprouting, and activity dependence (49). Disease-modifying agents and antiepileptic drugs may, therefore, have a positive (or negative) effect on recovery or epileptogenicity. TBI drug trials aimed to improve injury recovery have not looked at late seizures as an outcome measure or as an adverse effect. There are at least data that seizure medications—including remacemide, topiramate, talampanel, lacosamide, and carisbamate—seem to cause no major benefit nor harm on posttraumatic recovery in animal models (49). Additionally, a recent phase II study of levetiracetam in children suffering severe TBI showed it to be safe and well tolerated (72). Effective prevention of epileptogenicity after trauma will require a clear target, appropriate timing, and should not interfere with adaptive processes necessary for functional recovery (50).

TREATMENT OF EARLY AND LATE SEIZURES

A meta-analysis (70) demonstrated effectiveness of phenytoin (RR 0.33; confidence interval [CI], 0.19 to 0.59) and carbamazepine (RR 0.39; CI 0.17 to 0.92) in the prevention of early seizures after head trauma. A Cochrane Database Review of six trials also concluded a beneficial effect of antiepileptic drugs (RR 0.34; 95% CI 0.21 to 0.54) for prevention of early seizures. Based on the Cochrane estimate, for every 100 patients treated, 10 would be kept seizure free in the first week after TBI (73,74). However, seizure control was not associated with a reduction in mortality, neurologic disability, or diminished occurrence of late seizures (pooled RR 1.28; 95% CI 0.90 to 1.81).

On the basis of an analysis of prospective studies (16,75), the American Academy of Neurology has published recommendations on the use of antiepileptic drug prophylaxis in adults with TBI. Their current recommendation is to use short-term phenytoin prophylaxis in adults only with severe brain injury with the goal to prevent early posttraumatic seizures. Phenytoin may be initiated as an intravenous loading dose as soon as possible after the injury. Data on newer antiepileptic medications for the prophylaxis of early seizures after severe head trauma are limited. Levetiracetam has been used for this indication, and several studies have shown similar effectiveness as phenytoin, with fewer side effects (74,76,77). There are limited data to make definite recommendations on the use of antiepileptic drugs to prevent seizures in children. However, there is level III evidence suggesting that prophylactic phenytoin may be considered in children with severe TBI to reduce the risk of early posttraumatic seizures (78–82). There are no data to support the routine use of antiepileptic drugs beyond the first 7 days after the injury (16). Administration of glucocorticoids after brain injury does not prevent late posttraumatic seizures, and early treatment with steroids has been shown to actually increase seizure activity (83).

Medical prophylaxis of late posttraumatic seizures is currently not recommended. For a long time, phenytoin and phenobarbital were thought to be useful in the prevention of late seizures based on observational studies (84,85). Therefore, these medications were routinely prescribed as prophylactic treatment for the most severely injured patients or those experiencing early posttraumatic seizures for 6 months or more (86). However, more recent randomized, double-blind, prospective evaluations of antiseizure prophylaxis with phenytoin, phenobarbital, carbamazepine, and valproic acid consistently found no benefit (75,87–89), irrespective of the choice of antiepileptic drug (89,90). On the contrary, phenytoin can impair cognition in posttraumatic patients (91), and benzodiazepines and barbiturates may interfere with injury recovery (92).

Late posttraumatic seizures beyond the period of the acute insult reflect permanent changes in the

brain and signal the onset of PTE (27,93–95). After a first late unprovoked posttraumatic seizure, the vast majority of patients (86%) experienced a second seizure within the following 2 years, with the highest risk after a focal injury or coma for over 7 days (95). Treatment initiation in patients after a first late posttraumatic seizure seems appropriate, even if the traditional diagnostic criteria for epilepsy requiring at least two unprovoked epileptic seizures have not been met (16), and the recent move toward a broader epilepsy definition by the International League Against Epilepsy can be interpreted in support of this approach.

POSTTRAUMATIC EPILEPSY RISK FACTORS

Severity of Head Trauma

The risk of developing PTE depends on the severity of the head trauma and the presence of a penetrating injury. The most commonly used criterion for the severity of closed head trauma employed by epidemiologic studies examining civilian populations is based on the duration of LOC or amnesia and the presence of structural brain damage. The extent of the structural brain damage can be assessed by focal features on the neurologic examination, x-rays showing a depressed skull fracture, or findings on computed tomography (CT) scan (11,13). Correlating with the severity of the TBI and an increased risk of PTE are prolonged coma or amnesia (longer than 24 hours), brain contusion, and intracranial hematoma, in particular subdural hematoma, depressed skull fracture, and dural penetration, and, to a lesser extent, linear skull fractures (93,96,97).

The incidence of late posttraumatic seizures after closed head injury depends on the study population and varies between 1.9% and 25.3% (7,11,27–32). In the series reported by Annegers and Coan (see Table 28.1) (11,98), the RR of seizures was 1.5 (95% CI 1.0 to 2.2) after mild injuries with no increase after 5 years, 2.9 (95% CI 1.9 to 4.1) after moderate injuries, and 17.2 (95% CI 12.3 to 23.6) after severe injuries. In this study, mild trauma was defined by the presence of coma or amnesia for <30 minutes and the absence of a skull fracture; moderate head trauma was classified as coma or amnesia lasting between 30 minutes and 24 hours and the presence of a skull fracture in patients without contusion or intracranial hemorrhage; and severe trauma was classified as coma or amnesia for more than 24 hours and/or brain contusion or intracranial hemorrhage (see Table 28.2). According to a recent multicenter study, the highest cumulative probability for PTE after a 2-year follow-up is seen with biparietal contusions (66%), dural penetration with bone and metal fragments (63%), multiple intracranial operations (37%), multiple subcortical contusions (33%), subdural hematoma (28%), midline shift >5 mm (26%), and multiple or bilateral contusions (25%) (32).

In military personnel who survive high-velocity penetrating head injuries during warfare, the long-term risk of PTE is consistently estimated at 50% in series examining the major wars of the 20th century (99,100). The most recent wars in Iraq and Afghanistan have seen an increase in the numbers of head and neck injuries compared to prior conflicts. However, there has been a lower percentage of penetrating head injuries with an increased number of closed head injuries (101). In combination with the better injury survival to death ratio (7.0 compared to 1.6 for World War II and 2.8 for the Vietnam War), the high percentage of patients with head injury will likely amount to a significant incidence of posttraumatic seizures.

Early Seizures

An early seizure increases the risk to develop late epilepsy by more than 25% after moderate and severe head injury (30,35,93,94,97). Mild TBI with early seizures may not carry an increased risk for late epilepsy (98). Late seizures are more likely to begin early (within the first year) if there has been an early seizure.

Age

The influence of age on the development of early seizures is well documented (2,31,93,94). Children younger than age 5 years are more likely than adults to have seizures within the first hour after mild head injury (28,29,44,102). However, in children, unlike adults, early seizures are less predictive of late seizures (7,94).

Patients older than age 65 years are highly vulnerable to more severe brain damage and late PTE from any type of head injury (11,103). Earlier reports suggested an increased vulnerability for the development of late seizures associated with posttraumatic hippocampal sclerosis in children younger than 5 years of age (104,105). These findings have not been confirmed in more recent case series (106–108).

Genetic Factors

The evidence for genetic influences on posttraumatic seizures is conflicting. Some studies (109) reported a higher incidence of seizures in family members of patients with posttraumatic seizures. Other research has failed to demonstrate a similar relationship (12,110). According to a recent report, a family history of epilepsy and mild brain injury independently contributed to the risk of epilepsy (14), which supports the concept that genetic factors play a role even in symptomatic focal epilepsies (111,112). Additionally, specific polymorphisms in the glutamic acid decarboxylase genes were associated with an increased risk of posttraumatic seizures, both during the early and late phases, further implicating genetics in the development of posttraumatic seizures (113).

DIAGNOSIS

Clinical Seizures

The full spectrum of seizure semiology can be seen after head trauma. The site of injury and the underlying structural damage determine the type of focal manifestations (9,12,114,115). Early posttraumatic seizures are likely to present as generalized tonic–clonic convulsions even in the presence of focal brain damage (28,36,116). Late seizures mostly have a focal onset (9,114,115) and may develop subsequent to early generalized seizures (12). An interaction between the site of injury and the time when seizures are first noticed has been described. Seizures appear earliest after lesions of the motor area, followed by temporal lobe and those in the frontal or occipital areas (117).

Diagnostic Pitfalls

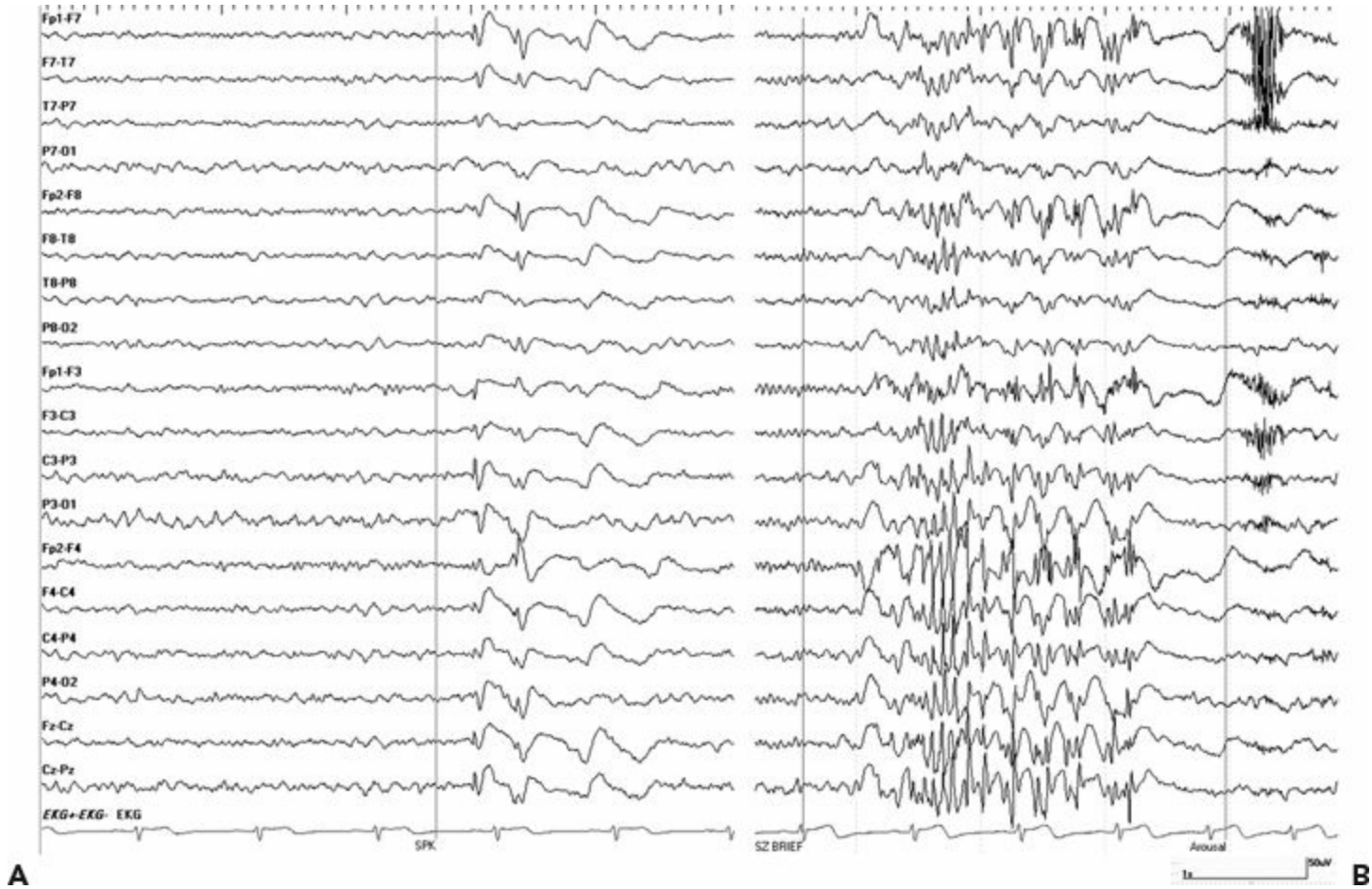
Nonepileptic Posttraumatic Seizures

Head trauma is a risk factor for epilepsy but is also strongly associated with nonepileptic seizure

disorders—presenting in the setting of a somatoform disorder, factitious disorder, or malingering (118,119). The diagnosis can be challenging, particularly in patients with mild head injury and normal routine EEG and magnetic resonance imaging (MRI).

A series of 127 adults diagnosed with intractable posttraumatic seizures who underwent video-EEG (VEEG) monitoring (107,108) had typical events captured in 104 patients (82%) during an average length of stay of 4.6 days (standard deviation [SD] 2.4, median 4). Thirty-six out of the 104 patients (35%) were found to have nonepileptic seizures. There was no difference in the mean duration (19.2 years; SD 11.06, median 18) between onset of seizure-like events and diagnostic referral of patients with epileptic and nonepileptic events. Trauma is a shared risk factor for epileptic and nonepileptic events, but only two patients (1.9%) had both epileptic and nonepileptic seizures. A similar study of 72 children who suffered TBI had paroxysmal events captured with VEEG monitoring, with 17% of children having nonepileptic seizures. Nonepileptic seizures were much more common in the mild TBI group with epileptic seizures more likely in the moderate to severe TBI group (120).

The majority of patients had focal-onset epilepsy: 54% presenting with temporal, 33% with frontal, 5% with parietal, and 3% with occipital lobe epilepsy. Secondary generalized convulsions were more common for extratemporal compared to temporal lobe–onset epilepsy (19% vs. 33%, RR 1.25, P = 0.01). Half of the patients with temporal lobe epilepsy had mesial temporal lobe sclerosis, most of them with a head injury after the age of 5 years. Interestingly, six patients who were initially thought to have symptomatic focal epilepsy for many years were subsequently diagnosed with generalized epilepsy, and four out of five had features of idiopathic generalized epilepsy. This illustrates that the onset of idiopathic generalized epilepsy during teenage years and the high frequency of minor head injuries during the same age can easily delay the diagnosis of the underlying epilepsy syndrome with significant impact on the medical management and outcome (Fig. 28.1).



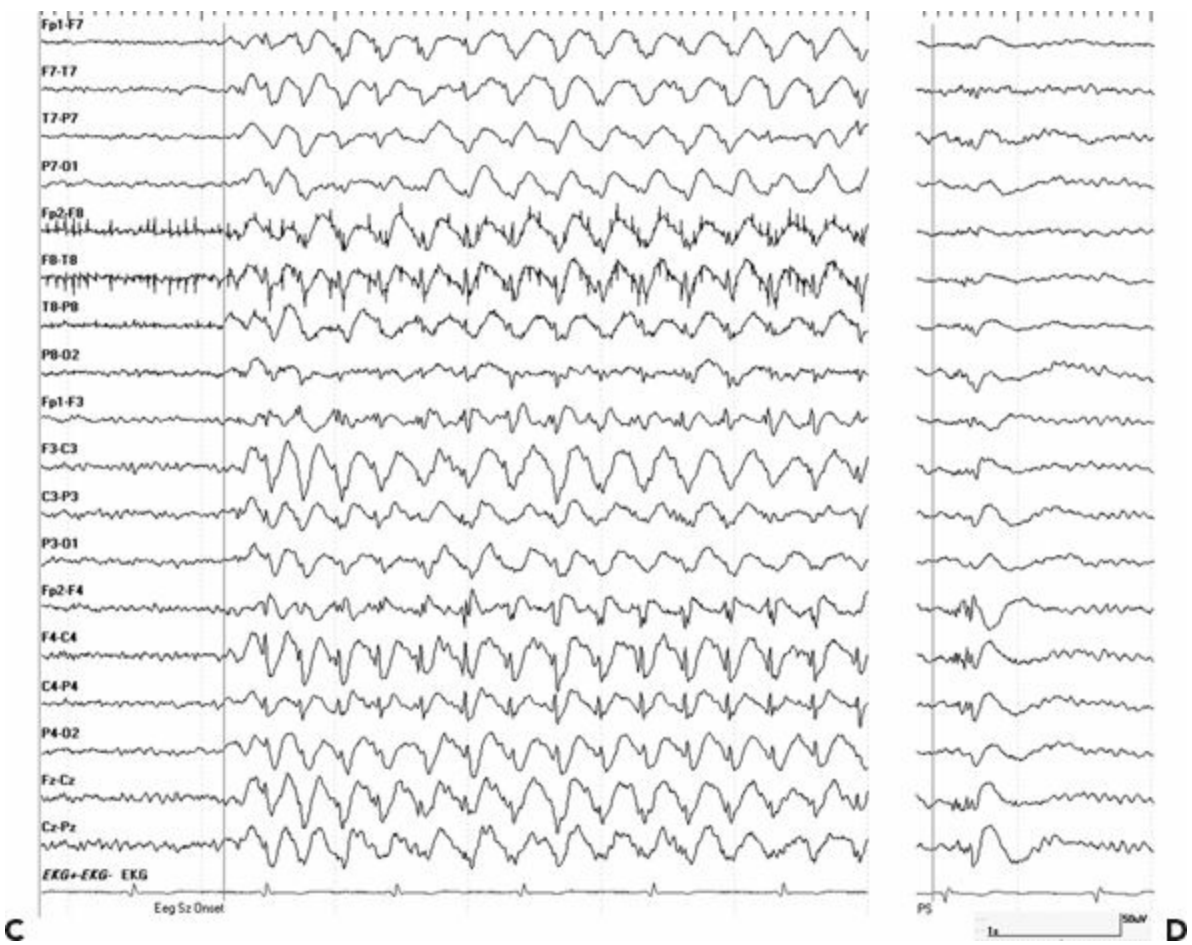
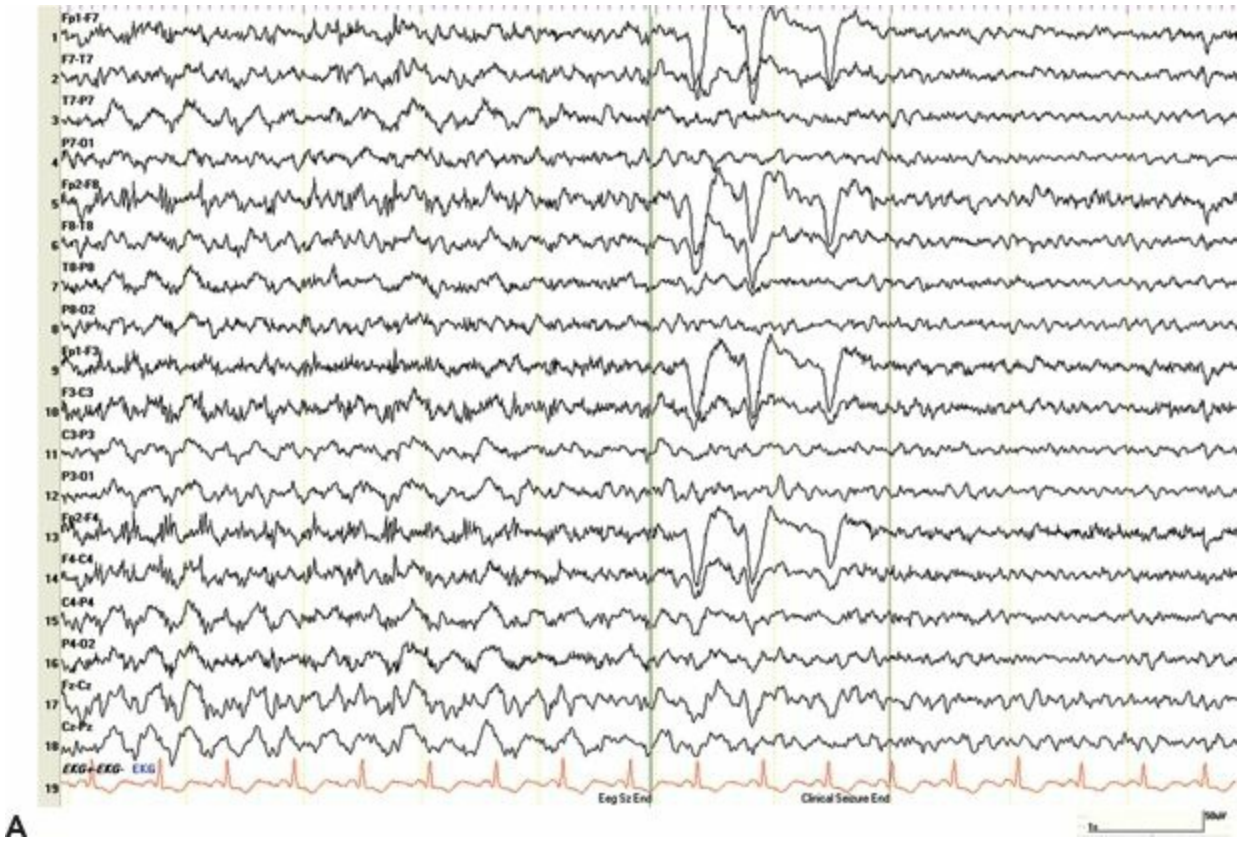


Figure 28.1. A–D: Idiopathic generalized epilepsy versus secondary bilateral hypersynchrony. **A and B (upper panel):** A 39-year-old male diagnosed with PTE after he was hit with baseball bat at age of 13 years. This patient started to have seizures 1 year later and was diagnosed with PTE. He continued to have sporadic generalized convulsions throughout his life and was treated with phenobarbital and phenytoin and later switched to carbamazepine. After starting pregabalin, he developed concentration difficulties, stuttering speech,

and poor concentration and was referred for presurgical workup. VEEG showed interictal generalized spike and waves (A) and polyspikes (B). Myoclonic jerks associated with generalized EEG pattern were recorded. After initiation of valproic acid, he became seizure free. Impression: juvenile myoclonic epilepsy. **C and D (lower panels):**A 29-year-old female with minor head trauma at age 13 years when she fell on ice and briefly lost consciousness. Onset of epilepsy was at age 14. Outside EEG were reported as generalized spike-and-wave discharges consistent with idiopathic generalized epilepsy. She remained seizure free on carbamazepine for many years. As part of pregnancy planning, she was switched to levetiracetam, and this lead to subacute onset of frequent staring and confusion. EEG showed a generalized spike-and-wave pattern more prominent over the right hemisphere (C) consistent nonconvulsive epileptic stupor, and this nonconvulsive status persisted despite loading her with Valproic acid and levetiracetam, with only transient improvement with Ativan. EEG status eventually resolved after carbamazepine was resumed. Interictal EEG showed generalized and right frontal spikes and polyspikes (D). Impression: posttraumatic focal epilepsy with secondary bilateral hypersynchrony on EEG.

Nonepileptic seizures after head trauma pose a particular challenge to the medical community. The risk of developing epilepsy after a mild head injury is low, and even patients with a normal interictal EEG and MRI may develop epilepsy (Fig. 28.2A). Additionally, nonepileptic seizures are not uncommon after minor head injuries, and a delay in diagnosis and antiepileptic therapy not only interferes with rational treatment but also negatively affects long-term prognosis (121). Similar rates of nonepileptic events were found in both civilian and military veterans undergoing VEEG monitoring over a 10-year period. Interestingly, there was a 5-year delay to diagnosis in veterans compared to 1 year for civilians, resulting in veterans receiving more frequent and prolonged unwarranted antiepileptic drug therapy than do civilians (122).



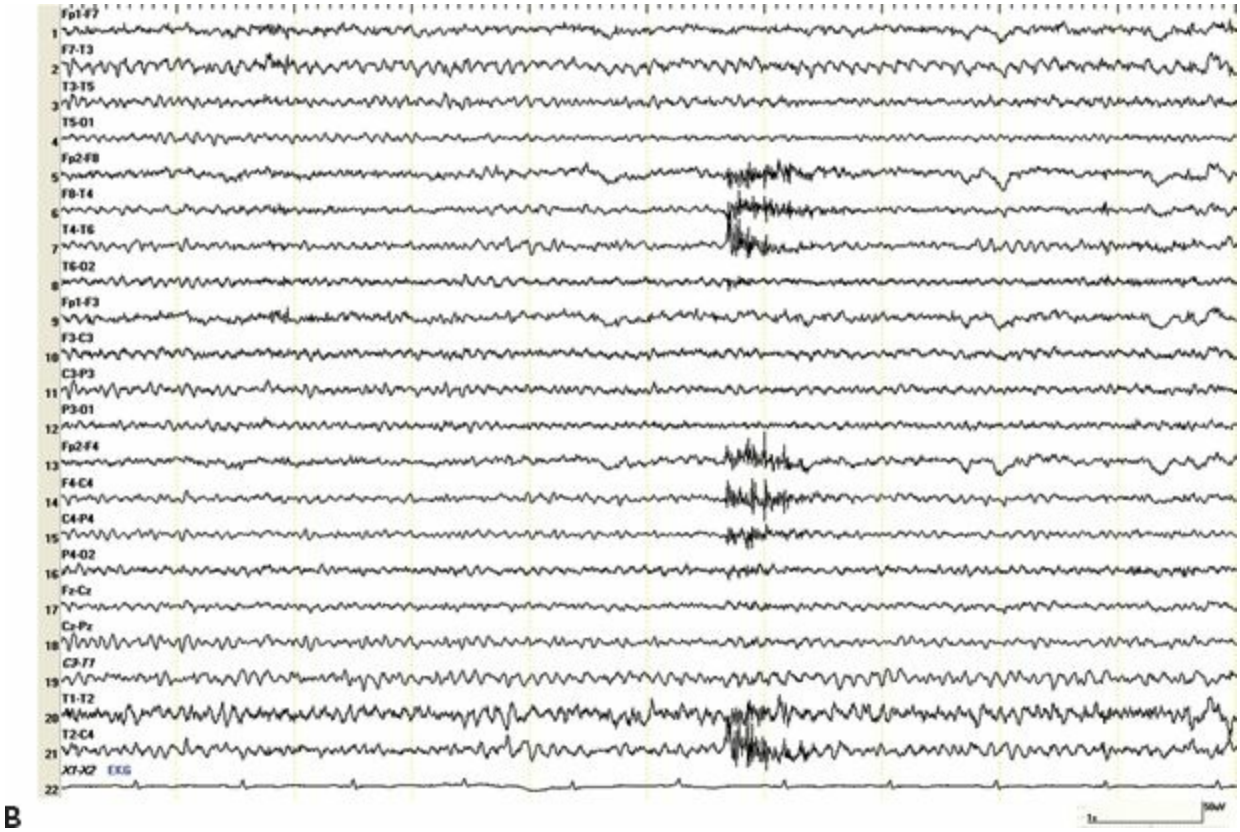


Figure 28.2. A and B: Epilepsy after minor head trauma. **A:** A 50-year-old right-handed male presented with a mild head injury in 2002 when he hit his head on an iron beam at work. There was no LOC. He suffered from a first seizure 6 days later and a second event 10 months later. Both were described as generalized convulsions without warning. Three MRI studies including gradient echo sequences for trauma were normal. Several routine EEGs and prior VEEG monitoring (on medication, no events recorded) were normal, and the concern of nonepileptic seizures was raised. The patient was admitted for a second VEEG monitoring assessment. Within 1 day of discontinuing his medications, carbamazepine and phenobarbital, he developed nonconvulsive status epilepticus. The EEG shows prolonged episodes of generalized slowing with superimposed paroxysmal fast activity in the bifrontal region, clinically associated with staring, occasional lip smacking, and diffuse myoclonic jerks. EEG and clinical seizure activity resolved after administration of Ativan. Impression: PTE after concussion without LOC. **B:** A 50-year-old male with a first seizure 25 years after a mild head trauma. Subsequent CT scan of the brain showed remote left inferior frontal and bilateral temporal contusions. He was treated with antiepileptic medications for 3 years. Two years after stopping the medication, the patient presented with difficulty speaking, brief episodes of unresponsiveness, and ongoing headaches for several days. Routine EEG showed left temporal electrographic seizures lasting around 30 seconds, seen twice during a 30-minute recording, without noticeable clinical changes. Subsequent VEEG showed 6 to 12 seizures per hour, which subsided after temporary burst suppression with midazolam. Impression: late PTE after minor head trauma presenting with nonconvulsive status epilepticus.

There is no clear relationship between the presence of preinjury mental disorders and posttraumatic nonepileptic seizures. However, a high incidence of new psychiatric conditions including posttraumatic stress disorder (PTSD), depression, and anxiety in up to 75% of patients can be noted, often associated with dissociative symptoms and complaints. In some cases, symptoms are not be related to a dissociative problem but may occur in the context of a factitious disorder or due to malingering.

Up to one-third of patients with nonepileptic seizures have a history of head injury, including 78% to 91% having mild injuries (118,119). In the setting of workman's compensation, a diagnostic distinction between epileptic and nonepileptic events is paramount to establish a likely causal relationship between seizures and injury. Secondary gain from disability or workman's compensation has a tendency to perpetuate nonepileptic seizure disorders. In regard to disability estimation, dissociative nonepileptic seizures can be as disabling as epileptic events. However, the disability claim is based on a completely different diagnostic entity, which may influence the chance of approval.

Differentiating epileptic and nonepileptic seizures poses a diagnostic challenge in veterans of the wars in Iraq and Afghanistan. The high number of mild head injuries is associated with a small but definitive risk for PTE and also bears a high risk of PTSD, which is often combined with somatic complaints including seizure-like episodes (123,124).

Nonconvulsive Seizures and Status Epilepticus

There is limited information on the incidence of late posttraumatic nonconvulsive seizures and status (Fig. 28.2B). Particularly, patients with persistent cognitive impairment after head injuries are at risk of subclinical seizures, for a variety of reasons. These patients have a 20% risk to develop epilepsy and may not be able to communicate clinical manifestations of seizures. The caregivers may confuse seizure activity with other causes of impaired or fluctuating cognition and consciousness (23). Even patients who are not cognitively impaired do not recognize more than half of their seizures. The accuracy of a seizure account is even lower in patients with focal seizures with impaired consciousness and with nocturnal seizures. These aspects raise further concerns about the accuracy of seizure reporting in the high-risk patient population with cognitive impairment (125).

Testing

Imaging

Imaging of the brain has been extremely helpful to predict the risk of seizures after head injury. CT and MRI of the brain aid in the determination of the underlying etiology, support the diagnosis in patients presenting with seizure-like events, and may delineate a focal lesion amenable to surgery.

The presence of a focal brain lesion is a risk factor for the development of early seizures as well as late seizures (94,126). The odds ratio of PTE with a focal lesion on CT or MRI scan lies between 2 and 6 (30,31). However, the severity and localization of traumatic brain lesions on MRI do not correlate with the risk for late seizures (127). The presence of cortical or subcortical hemosiderin alone was also not associated with an increased risk of late seizures (30). Only more detailed characteristics of the lesion itself, for example, the relation of hemosiderin deposition to surrounding gliosis or a history of a surgical intervention, may provide additional information regarding epileptogenesis and risk of PTE (128). Functional studies, either with diffusion-weighted MRI or with tomography using radioactive tracers may be more specific in predicting the epileptogenic potential of a structural abnormality (129,130). Recent studies have shown the utility of using quantitative diffusion MRI in detecting hippocampal abnormalities ipsilateral to the site of TBI in animal models that correlate with increased seizure risk (131). Additionally, high-field MRI and diffusion tensor imaging may offer a higher sensitivity to detect diffuse axonal injury in patients with mild head trauma (132,133). Furthermore, longitudinal disease evolution in patients with mild TBI is important. A recent study followed 28 patients with mild TBI with interval MRI scans 1 year later and found statistically significant degrees in atrophy in patients with TBI. The changes were most prominent in the anterior cingulate white matter bilaterally, left cingulate gyrus, and right precuneal gray matter (134).

In spite of a diffuse injury to the closed skull, the epileptogenic process manifested itself more often in a vulnerable brain region such as the hippocampus (135). Surgical series of anterior temporal resections report that 10% of their patients presented with trauma as the major risk factor for epilepsy

(104–106,136). Approximately half of the patients with PTE undergoing epilepsy surgery present with hippocampal sclerosis, and in one-third of these, additional focal neocortical abnormalities are presents (106,107). However, diffuse abnormalities, often global cerebral atrophy, are common in the cases with hippocampal sclerosis. In surgical patients with PTE, there is always the concern that the obvious MRI lesion only represents the "tip of the iceberg" and that neighboring or remote sites, not visible on MRI, are the actual or future culprit for focal epileptogenicity (137). Patients with a neocortical temporal and extratemporal posttraumatic encephalomalacia who are thought to have surgically amenable focal epilepsy based on surface VEEG recording usually require an invasive evaluation to define the precise focus and extent of the epileptogenic lesion. Orbital frontal and anterior temporal–polar cortices are predisposed to neocortical injury after closed head injuries and seem to represent areas particularly susceptible to epileptogenic brain injury.

Diagnostic EEG and Video-EEG Monitoring

EEG patterns during the acute phase of head injury are usually nonspecific and reflect systemic factors in addition to the effects of the acute brain damage (138). In that stage, routine EEG might be helpful to predict recovery from coma (139). Interictal epileptiform abnormalities may appear as early as a week after injury (140). Focal EEG activity seen 1 month after head trauma may predict an increased risk of seizures at 1 year after head injury (30). However, in most studies, the EEG during the early phase after injury proved unhelpful in predicting the development of PTE and does not seem to be an adequate tool to select patients for prophylactic treatment to prevent epileptogenesis and late seizures (115,141,142). The available evidence does not support the use of early EEG changes to predict long-term seizure risk (73). However, the high risk of subclinical seizures acutely after TBI may warrant continuous VEEG monitoring to detect early electrographic seizure activity and initiate treatment (42,143).

After the acute recovery phase, routine EEG can be useful to support the diagnosis of epilepsy in patients with late posttraumatic seizures and to distinguish between focal and generalized epilepsy syndromes (115,144). However, overinterpretation of EEG findings can lead to an erroneous diagnosis of epilepsy in patients with nonepileptic seizures and delay the diagnosis and adequate treatment. Additionally, routine EEGs may capture evidence of nonepileptic events as well. In a retrospective study of outpatient EEGs performed at a veterans hospital for all indications, only 3% of all EEGs had clear epileptiform abnormalities, much lower than previous literature. Of note, almost 6% captured psychogenic nonepileptic events and proved helpful this way to facilitate the diagnosis (145).

Diagnostic VEEG is the gold standard to confirm the clinical diagnosis in patients with pharmacoresistant seizures for more than a year. Monitoring should be done in a setting where antiepileptic medications can safely be withheld. A study in patients with intractable seizures and a history of moderate to severe TBI was able to deliver a definitive diagnosis in 82% of patients during an average length of stay of 4.6 days (SD 2.4, median 4) while off antiepileptic medications (106,107). Unfortunately, referral for monitoring was delayed by an average of 19 years after onset of seizures, irrespective if the seizures proved to be epileptic or nonepileptic. Diagnostic VEEG evaluations not only are helpful to differentiate between epileptic and nonepileptic events but can also influence the choice of medication. Over 5% of patients diagnosed with focal epilepsy may turn out to have an unrecognized generalized epilepsy syndrome (106,107).

TREATMENT

Medical

Seizure remission with medical treatment in patients with posttraumatic seizures ranges from 25% to 40%, but there remains a high risk for seizure recurrence when medications are discontinued. Seizures that develop within the first year after injury are more likely to remit with medication than those that appear later (96). However, the prevailing evidence suggests no significant relation between the occurrence of the first seizure and responsiveness to medication (12,146). Similar to symptomatic epilepsies, a high seizure frequency in the first year of onset predicts future seizure severity and medical intractability (12,147). Seizures that occur after severe head injury and seizures that do not controlled by early treatment tend to persist (95). The chance for spontaneous remission is low, but a medication taper can be justified in selected patients with normal EEG and imaging findings and good response to initial treatment, who have been seizure free for at least 2 years.

Surgical

The selective vulnerability of the hippocampus after blunt head trauma has been well demonstrated in animal models and described in patients with PTE (60). Histopathologic examination in a series of temporal lobectomies and trauma as the major risk factor for epilepsy showed neocortical gliosis in all specimens and hippocampal neuronal loss in 94% of the cases. These findings confirm that a blunt head trauma is able to induce hippocampal epilepsy in the absence of other known risk factors (135). The length of the latent period until the onset of recurrent seizures was inversely related to the age at the time of trauma, which is consistent with prior reports suggesting a particular predilection for posttraumatic hippocampal sclerosis below the age of 5 years (103). However, other studies have demonstrated that trauma may lead to hippocampal sclerosis even at a later age (104,106).

Patients with a history of head trauma who undergo temporal resection are less likely to become seizure free than patients without a history of trauma (55% vs. 40% Engel class Ia) (105). However, these patients may still achieve significant seizure reduction beyond what they can expect from medical management. In a series of 102 patients, 59% of patients with PTE reported a class I outcome with resection after a mean follow-up close to 4 years compared to a 70% class I outcome in all patients undergoing resection. The presence of an isolated focal MRI abnormality—mesial temporal or neocortical—seems critical for a chance of a successful surgical intervention in patients with PTE (104). In a more recent study looking at all epilepsy surgery cases secondary to PTE, 82% had an improvement in seizure frequency with 28% having Engel class I outcomes. Similar to previous studies, patients with focal areas of encephalomalacia on imaging were more likely to have a better outcome (148).

FUTURE DIRECTIONS

The study of PTE yields valuable insights into the complex process of epileptogenesis. The role of neuroprotective agents in TBI and prospective trials with new antiepileptic medications may eventually lead to a reduction in the incidence of PTE. The delayed onset of PTE months or years after the injury offers a unique window for antiepileptic prevention. However, a better understanding of the mechanisms specific to the epileptogenic process after head injuries is required.

The diagnosis of PTE remains a challenge and contributes significantly to treatment failure. More than one-third of patients diagnosed with posttraumatic seizures may have nonepileptic events. Early and late posttraumatic epileptic seizures may go unrecognized, particularly in patients with cognitive impairment and altered level of consciousness. Correct determination of the epilepsy syndrome and appropriate choice of medical and surgical management is crucial to improve treatment outcome.

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CHAPTER 29 EPILEPSY IN THE SETTING OF CEREBROVASCULAR DISEASE

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Cerebrovascular disease (CVD) is a significant cause of seizures and a risk factor for the development of epilepsy in all age groups. Stroke is a common cause of morbidity and mortality in the elderly population and is the leading cause of epilepsy in patients older than 60 years. Seizures occur in 7% to 11% of adult patients who survive strokes, while poststroke epilepsy develops in 2% to 4% (1,2). CVD is less common in the pediatric population, but early vascular insults are associated with an increased incidence of epilepsy as compared to adult patients. Understanding the prevalence, etiology, and risk factors associated with poststroke seizures and epilepsy is of vital clinical importance, and multiple studies have attempted to address these issues (2–5). The management, prognosis, and treatment of seizures and epilepsy associated with CVD are less well known and will remain an important area for investigation (6). Seizures and stroke can co-occur in rare conditions, such as mitochondrial encephalomyopathy (7). Patients with Takayasu arteritis and hyperhomocysteinemia are at high risk for ischemic events in young adults, with an increased susceptibility for seizures (8).

EPILEPSY IN PEDIATRIC CEREBROVASCULAR DISEASE

The past two decades have seen a renewed interest and focus in pediatric stroke. Although relatively uncommon, the reported incidence has increased with better data collection, improved imaging modalities, and better recognition and awareness among physicians. An incidence rate of 2.52/100,000 children per year (0.63/100,000 children per year for ischemic stroke) was found in the first North American population–based study of pediatric stroke from 1965 to 1974 (9). Since then, data from the largest cohort of pediatric stroke patients from the prospective Canadian Ischemic Stroke Registry have shown an incidence of 6/100,000 children per year (3.3/100,000 for arterial ischemic stroke [AIS]) (10). The highest incidence occurs in the neonatal period with estimates as high as 20 to 30/100,000 newborns per year, although a recent population- based epidemiologic study from Switzerland using magnetic resonance imaging (MRI) confirmation of neonatal AIS showed a higher incidence of just over 40/100,000 per year or 1 in 2300 live births per year (11).

Perinatal AIS occurs primarily in term infants and constitutes approximately 25% to 30% of all AISs in children (12,13). Two-thirds have large vessel cortical infarcts (14) compared with childhood stroke in which more than 50% of strokes involve small vessel territories. The anterior circulation is five times more commonly involved than the posterior circulation, and 60% to 65% involve the left middle cerebral artery territory (14–17). Multiple infarcts are seen in 15% to 20% of cases.

Childhood AIS is more common in males (13) and blacks (18), with the mean age of presentation being 4 to 6 years (12,19–21). Ischemic stroke is only slightly more common than is hemorrhagic stroke in the pediatric population (22). Stroke remains one of the top 10 causes of death in children (23) with a mortality rate of approximately 10% (24). Outcome, in general, is better than that seen in adults, mostly due to brain plasticity and the absence of ubiquitous underlying degenerative vascular disease such as atherosclerosis. Morbidity, however, remains a serious complication of pediatric stroke, and a majority of survivors will have residual and persistent neurologic and/or cognitive impairment. Neurologic impairment includes residual hemiparesis in about two-thirds of children, visual field deficits, cognitive and behavioral difficulties, and/or epilepsy (25). The recurrence risk for stroke is variable, depends on the underlying etiology, and has been estimated to be 15% to 20% (25). The etiologies of stroke in childhood vary considerably from those seen in adults, with approximately 20% to 30% of cases remaining unresolved.

Seizures are more commonly seen as a heralding symptom in childhood stroke than in adult stroke. However, even in childhood stroke, as compared to neonatal stroke, motor deficits are more commonly the presenting neurologic symptom than are seizures. Among motor deficits, hemiparesis is a frequent clinical presentation. The reported incidence of stroke-associated seizures and subsequent epilepsy in children with stroke has been highly variable, partly based on few prospective studies, selection bias, small sample size, lack of long-term follow-up, and differing definitions and terminology in the classification of epilepsy. Acute symptomatic seizures at stroke onset occur in approximately 20% to 30% of childhood AIS (reported incidence of 19% to 54%) with epilepsy as a sequela in approximately 25% (reported incidence of 7% to 58%) (21,26–36). In a large retrospective study of remote seizures and epilepsy within a population-based cohort of children with nonperinatal stroke enrolled in the Kaiser Permanente Northern California database, the average annual incidence rate of first remote seizure was 4.4% with a cumulative risk of 16% at 5 years and 33% at 10 years poststroke. The cumulative risk of active epilepsy was 13% at 5 years and 30% at 10 years, and the presence of acute seizures at the time of stroke onset predicted development of active epilepsy (36). Data regarding seizure presentation and subsequent epilepsy risk for hemorrhagic stroke in childhood are much less clear, with only a few descriptive series. Seizures at onset are minimally more common in childhood AIS occurring in approximately 40% (28,29), with the subsequent risk of epilepsy varying between 10% and 39% (28–30).

The situation is different in perinatal AIS where seizures are the most frequent presenting neurologic symptom, occurring in over 80%. Focal neurologic deficits, such as hemiplegia, or generalized symptoms, such as hypotonia or encephalopathy, are uncommon. In a large prospective series (37), 62 of 90 (69%) term infants who presented only with seizures (and without evidence of a more diffuse neonatal encephalopathy) showed MRI evidence of acute focal ischemia (35/62) or hemorrhagic brain injury (27/62). Similarly, in an autopsy series of 592 infants (38), 5.4% were found to have AIS and none showed focal neurologic features during the newborn period; however, 17% had neonatal seizures. Twelve to eighteen percent of all neonatal seizures are associated with perinatal arterial ischemic infarcts (39–42), tend to be focal (75%), and typically present within the first 72 hours of stroke onset. Generalized and subtle seizures, including apnea, and electrographic seizures (43,44) in the absence of clinical findings may occur. The seizures usually last 3 to 5 days (45,46) in duration and tend to be easy to control medically (45,47,48). Acute symptomatic neonatal seizures have been reported in 57% to 70% of cases of cerebral sinus vein thrombosis (CSVT) (49,50). The presence of seizures in perinatal AIS and neonatal CSVT is associated with adverse neurologic and neurocognitive outcome (49–52). Seizure semiology is variable and frequently

includes infantile spasms (50,53,54). In two large series of infantile spasms, perinatal stroke accounted for 5% and 6%, respectively, of symptomatic spasms, and 4.5% and 8%, respectively, of all cases of infantile spasm (53,55). Spasms secondary to perinatal AIS were associated with high rates of subsequent epilepsy and chronic neurologic morbidity, similar to other etiologies of symptomatic spasms (53). In the Canadian pediatric ischemic stroke registry, the risk of epilepsy was 20% following an infarct due to CSVT versus 15% when the stroke was due to an AIS. The data, however, of subsequent epilepsy risk following perinatal AIS have been very inconsistent and have varied considerable from 0% to 50% depending on the nature of the study. The overall "mean" from these studies would suggest a risk of about 22% for the subsequent development of epilepsy (25). In one of the few prospective studies, Wusthoff et al. (56) showed late seizure (LH) occurrence (median age of 8 months) following perinatal AIS in 24% (with 3 of 11 children not having neonatal seizures), with just over half of these patients (13%) subsequently developing epilepsy. Follow-up was, however, just over 2½ years. An Australian study in 2010, on the other hand, showed that the estimated cumulative incidence of epilepsy following perinatal AIS was 55% by 10 years of age (54). Interestingly, in their study, a history of neonatal seizures was not predictive of subsequent epilepsy. Fetal stroke appears to predict the earlier onset of epilepsy in one recent large cohort (57).

The electroencephalogram (EEG) in perinatal stroke is highly variable and frequently normal. Abnormalities include focal or generalized slowing; focal, multifocal, or bilateral spike or spike-and-wave discharges; low-voltage rhythms; and burst suppression. Focal repetitive seizures, including focal status epilepticus, with a normal background EEG should raise the suspicion for a perinatal AIS. Periodic lateralized epileptiform discharges (PLEDs) have also been reported in perinatal AIS in the term infant (58). Thalamic hemorrhage due to suspected or proven neonatal CSVT appears to carry a high risk for subsequent development of an electrical status epilepticus in slow-wave sleep spectrum (59). The presence of an abnormal background on EEG (25) independent of EEG seizures or epileptiform discharges has been associated with hemiplegia on follow-up (14).

For childhood AIS, cortical involvement and stroke size has, not surprisingly, been associated with a subsequent risk for epilepsy (28,56,60). Subcortical infarcts (basal ganglia, thalamus) have also been associated with seizures either as an isolated presenting feature or in combination with hemiplegia (61). The semiology of seizures is variable, and often patients have more than one seizure type including focal motor, complex partial seizures, with or without secondary generalization, and, occasionally, primary generalized seizures. Clinical and subclinical status epilepticus has variably been reported (35,62,63). The occurrence of seizures and/or altered level of consciousness at the initial presentation of childhood AIS has been associated with increased mortality at 6 months or with unfavorable neurologic outcome (32).

> Infantile hemiplegia offers some of the most typical instances of cortical epilepsy, and it may be well to consider how far it is likely that surgical interference can here be successful—Sir William Osler (64).

Surgical intervention for intractable epilepsy as a consequence of perinatal stroke dates back to the latter part of the 19th century (64,65). The first detailed series of hemispherectomy in children as a treatment option for intractable epilepsy, however, can be traced back to Krynauw in 1950. Histopathology of the resected specimens documented infarcts due to vascular ischemia/stroke as the etiology in a number of his cases (66). Seizure freedom with surgical intervention for refractory epilepsy secondary to AIS is good (67).

EPILEPSY IN ADULT CEREBROVASCULAR DISEASE

Epidemiology

The reported incidence of poststroke seizure and epilepsy has varied in the literature from 3.3% to 13%, although heterogeneous study designs, inconsistent use of terminology, and variable follow-up periods have made them difficult to interpret (68). The Oxfordshire Community Stroke Project prospectively followed 675 patients with a first stroke for a minimum of 2 years and found a 7.7% prevalence of poststroke seizures (1). The Seizures After Stroke Study prospectively followed 1897 patients for a mean follow-up time of 9 months and found 168 patients with poststroke seizures (8.9%) (2). Multiple studies have also differentiated early, late, and recurrent seizures as having different clinical characteristics and prognoses (69–71). A study by Berges et al. retrospectively evaluated 3205 patients and identified 57 patients with early-onset seizures (within 2 weeks of the stroke in the study) and 102 patients with late-onset seizures (>2 weeks from the stroke). They found that the later-onset seizures were significantly more likely to recur (and develop into poststroke epilepsy) than were the early seizures (70). In a retrospective study of Rochester Minnesota residents, 192 patients were identified with poststroke seizures, including 91 patients with acute symptomatic seizures and 101 patients with unprovoked seizures (3). Two key points were made by this study: The acute symptomatic seizures had a much higher 30-day mortality (41.9%) versus the unprovoked seizures (5%), and the recurrence rate was 33% for the acute symptomatic seizure group and 71.5% for the unprovoked seizure group.

The International League Against Epilepsy has developed definitions for early and late poststroke seizures that have been variably defined in the past:

- Acute symptomatic seizure: Epileptic seizure within the first 24 hours after onset of stroke
- Early poststroke seizure: One or more seizures within the first week after the stroke
- Late poststroke seizure: One unprovoked epileptic seizure at least 1 week after the stroke
- Poststroke epilepsy: Two or more unprovoked epileptic seizures at least 1 week after the stroke

The prevalence of poststroke epilepsy has been reported variably from 2% to 4.1% with follow-up periods ranging from 9 months to 7 years (1,2,69–74). A large prospective study followed 1195 patients for 7 years and found 38 patients (3.2%) with poststroke epilepsy (74).

Status epilepticus also occurs in poststroke patients with an overall prevalence reported at 1.5% of all new-onset strokes, which represents 10% of the patients presenting with poststroke seizures (75–77). The number of the patients is small, but these patients tend to have early-onset status, nonconvulsive seizures with no apparent clinical signs, and increased mortality.

In conclusion, poststroke seizures occur in 7% to 11% of new-onset strokes. Approximately one-third of these occur as acute symptomatic or early-onset seizures. Based on the extensive Dijon Stroke Registry of 4411 stroke patients, and in contradiction to previous studies, early epileptic seizures were not associated with higher risks of mortality at 1 month and 1 year or with unfavorable functional outcome after acute stroke (78). Contrarily, the unprovoked or LHs are predicted to have 50% to 70% recurrence rates and thus frequently develop into poststroke epilepsy. The prevalence of poststroke epilepsy is 2% to 4% in patients with new-onset strokes. Status epilepticus occurs after

stroke in a smaller portion of patients (1.5%) but is associated with an early onset and high mortality. A high incidence of 4% to 26% of seizures after subarachnoid hemorrhage was recently reported (79), and it is likely that this is overestimated as a result of inclusion of misdiagnosed decerebrate posturing as seizure activity (8).

An increasing practical problem is that poststroke seizure activity may result in Todd paresis mimicking acute stroke occurrence. Twenty out of 648 patients (3.3%) enrolled in a monocentric stroke registry actually had Todd paresis (80). Eleven out of 539 patients in another study who all underwent thrombolysis turned out to have postictal paresis (81). However, thrombolysis with rt-PA itself was rarely an independent risk factor for seizure occurrence in the acute phase of ischemic stroke (82).

New-onset seizures in the elderly of no obvious cause are often indicators for underlying subtle CVD. These patients have been found to be at significantly increased risk for subsequent stroke (83,84). Accordingly, a sophisticated and comprehensive workup including high-resolution MRI is necessary in these patients to detect otherwise unknown CVD.

The magnitude of seizure risk and the major risk factors were similar to older ischemic stroke patients. However, young patients using anxiolytic medication at the time of stroke onset and psychiatric comorbidity were at high risk for acute symptomatic seizures, and antidepressant use was a significant risk factor for LHs (85).

Pathophysiology

Much of the pathophysiology of poststroke seizures requires further investigation. Based on animal models, acute symptomatic seizures are thought to arise from the penumbra surrounding the infarction (86). Occlusion of middle cerebral artery blood flow in rats is associated with epileptic spiking over the region of proposed penumbra. The ischemia is hypothesized to release glutamate, causing excitotoxicity and early seizures. Other factors proposed to effect early seizures are deposits of hemosiderin-causing focal cerebral irritability, fluctuations in cerebral ions concentrations, and loss of inhibitory GABAergic circuits (87,88). The pathogenesis of LHs and poststroke epilepsy is even less clear. Etiologic factors include the formation of a gliotic scar with reorganization of axonal connections, loss of GABAergic pathways, the presence of hemosiderin in cortical neurons, and free radical formation and membrane peroxidation. Another possible trigger of LHs is recurrent ischemia at the site of the previous stroke. This mechanism was proposed after a series of positron emission tomography studies (77,89).

Advanced epigenetic studies suggest that disruption of chromatin modifications play a role in both stroke and seizures. The gene repressor element-1 silencing transcription factor (REST) is activated in adult neurons in response to ischemia and seizures orchestrating epigenetic remodeling and silencing of subsets of transcriptionally responsive target genes implicated in neuronal death (90,91).

Predictors of Poststroke Epilepsy

A number of clinical factors have been proposed to predict which patients would develop poststroke seizures and epilepsy. Cortical location, stroke severity, and hemorrhagic stroke all were shown to be independent risk factors on multivariate analysis (1,2,69,73,74,92). In addition to the cortical localization, an island of spared cortex, infarct with irregular borders, temporal–parietal location, and posterior cerebral artery infarcts have all been hypothesized to increase the risk of poststroke

epilepsy (93). A recent review of intracerebral hemorrhage (ICH) found that 8% of all patients had clinically detectable seizures, with 90% occurring in the first 3 days (94). In a prospective study in ICH, the median delay between ICH and LS was 9 months, and cortical involvement was the only factor associated with the occurrence of LS (95).

One out of 100 unprovoked first seizures is caused by brain arteriovenous malformations (BAVMs). BAVM patients experience seizures in 20% to 30% of cases (96). BAVMs are considered to be models for epileptogenic lesions as a result of perilesional gliosis, hemorrhage, steal phenomena, and iron deposits.

The analysis of the angioarchitecture of unruptured BAVMs in a huge data set of 1299 BAVMs identified location, fistulous component in the nidus, venous outflow stenosis, and the presence of a long pial course of the draining vein as the strongest predictors of seizures (97). A small study (98) revealed further evidence for the importance of venous infarcts in ictogenesis, and in these patients, the risk for seizure recurrence was 10-fold (26.6%) as compared to patients with ischemic strokes (2.7%).

Cerebral cavernous malformations (CCMs) are associated with seizures as the initial presentation in 25% of cases. After a single seizure associated with a CCM, there is a 94% chance of recurrence. Thus, once CCMs are found in association with a seizure, they require treatment with antiepileptic medications and possibly surgery if they become medically intractable. Factors that have been shown to increase the likelihood of seizures include supratentorial location, cortical involvement and archicortical/mesiotemporal locations (99). Lobar localization, the number of cavernomas, and the size of the lesion/hemosiderin rim have been more controversial (100).

Diagnostic Studies in Poststroke Epilepsy

The value of EEG in predicting poststroke seizures and epilepsy has been controversial (101). In a retrospective study of 110 patients who developed poststroke seizures (12 early seizures, 98 LHs), EEGs were compared in patients who had a first seizure after stroke as compared to a control group of stroke patients without seizures. PLEDs have been associated with increased risk of seizures in prior studies and were also predictive in this study. However, PLEDs were only recorded in 5.8% of patients who would later develop seizures and none in the control group without seizures. Thus, PLEDs were predictive (more often with early seizures) but were rarely observed. Frontal intermittent rhythmic delta (FIRDA) was observed in 24.6% of the seizure group compared to 1.1% of the control group. Diffuse slowing also occurred more frequently in the seizure group (21.7%) than in the control group (5.1%). Focal slowing was equally represented in both groups. Normal EEGs were seen in only 8.5% of the seizure group, while 53.8% of the control group was normal. The authors concluded that PLEDs, FIRDA, and diffuse slowing are the typical EEG findings of early seizures, while FIRDA and diffuse slowing may suggest an increased risk to develop late-onset seizures. The findings of a normal EEG poststroke would suggest decreased risk of developing late-onset seizures (101). In a prospective study of 100 patients who received continuous EEG (CEEG) after acute stroke, 17% were found to have epileptiform discharges or seizures (102). Stroke severity (measured by National Institute of Health Stroke Scale [NIHSS]) was the only independent predictor of epileptiform discharges and/or seizures on CEEG. In a study of 102 patients with nontraumatic ICH who underwent CEEG monitoring, 32% were found to be having seizures (103). In addition, patients who expanded their hemorrhage by 30% or more were twice as likely to have electrographic seizures. Many of the seizures recorded were without clinical signs. Cortical location and severity of

the ICH were related to increased seizure risk. PLEDs were associated with increased mortality. Twenty-eight percent of the seizures were recorded after 24 hours, but only 5% were recorded after 48 hours. In conclusion, poststroke EEG may be useful in prediction of future seizures if PLEDs, FIRDA, or diffuse slowing are noted, and CEEG may be of value in high-risk patients with severe ischemic stroke and ICHs.

Emergency imaging after acute stroke, including perfusion studies, suggests that a large area of postictal hypoperfusion without a corresponding arterial lesion is more likely the correlate of a postictal paresis rather than a stroke and therefore would contraindicate thrombolysis (104). Seizures can lead to additional harm to the infarcted area as demonstrated by magnetic resonance diffusion-weighted imaging findings (105).

Treatment

The treatment of poststroke seizures and epilepsy has been controversial (6). In animal models of ischemia, antiepileptic medications had a neuroprotective effect; however, the same has not been demonstrated in humans (106). First-generation antiepileptics (phenytoin, phenobarbital, and benzodiazepines) were shown to worsen functional recovery in animal models of stroke (107). Unfortunately, there are no randomized controlled trials of treatment for patients with poststroke seizures or epilepsy. The risk of seizure recurrence after an early seizure ranges from 13% to 43%. This is similar to the recurrence risk of 24% that is quoted to patients with a single seizure and normal imaging and EEG studies. However, the risk of recurrent seizures after a single late-onset seizure is in the range of 54% to 66%; thus, some have advocated treatment with antiepileptic drugs (AEDs) after even a single late-onset seizure, while others prefer to treat after a second unprovoked seizure (68,77,108). When medications are used, these seizures tend to respond to monotherapy, with relatively rare recurrence (most notably due to noncompliance). As most of the patients with stroke-associated seizures are elderly, the specific aspects of reduced liver and renal metabolism, higher sensitivity to drug side effects, and potential interactions through liver enzyme–inducing antiepileptic agents due to intrinsic factors as well as comedication have to be considered. The new generation of AEDs seems to have significantly fewer interactions. Though no studies have been conducted in poststroke epilepsy patients per se, a study compared lamotrigine, gabapentin, and carbamazepine in the elderly (with stroke the most likely etiology of the majority of seizures) (109). Seizure control was similar among all three drugs, but tolerability favored lamotrigine and gabapentin. The ultimate goal to prevent poststroke epilepsy has never been successfully demonstrated in humans due to lack of statistical power and methodological pitfalls (110).

With regard to surgical treatment strategies, the role of intervention and modality for seizure outcome in BAVM patients is currently not certain. It has been reported that complete obliteration of BAVMs correlates with good seizure outcome in multimodality therapy (111). Outcome data on the surgical therapy of CCM-associated epilepsy are also scarce: in a small series seizure of a highly specialized epilepsy center, seizure freedom in drug-resistant CCM patients was accomplished in 80%, and outcome in patients with sporadic seizures was 91% after a mean follow-up of 107 to 137 months (112). Extensive resections and complete removal of hemosiderin fringe brain tissue surrounding CCMs (112,113) and early intervention (114) were found to improve short-term and long-term seizure outcome.

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CHAPTER 30 EPILEPSY IN THE SETTING OF NEUROCUTANEOUS SYNDROMES

AJAY GUPTA

Neurocutaneous syndromes are genetically and clinically heterogeneous congenital diseases with common characteristics of distinct cutaneous stigmata in association with neurologic disease, and involvement of various organs and systems. Cutaneous findings, noted by the patient, the family, or a family physician, are usually the tip-off for suspecting a neurocutaneous disease. In a few neurocutaneous syndromes, epilepsy is the most common presenting symptom. Identification and chronic management of these patients with complex epilepsy issues often fall into the hands of neurologists and epileptologists, who sometimes lead a team of various specialists in a multidisciplinary clinic model to provide disease-based clinical care. Recognition of neurocutaneous syndromes associated with epilepsy is therefore of critical importance for neurologists and epileptologists. Accurate early diagnosis is vital to counsel the patient and the family regarding chronicity of the condition, choose appropriate antiepileptic drugs for epilepsy, ensure timely selection of candidates for epilepsy surgery, guide testing and consulting for coexisting morbidities, and, when appropriate, refer for genetic testing and counseling. In this chapter, we discuss diagnosis and treatment of such conditions. While our focus is on the diagnosis and treatment of epilepsy in these conditions, we touch upon important aspects of comorbid neuropsychiatric conditions, and other organ system involvement that impact decision making for medical and surgical treatment of epilepsy. Clinical, radiographic, and pathologic findings are presented in the pictorial atlas (Chapter 5).

TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis complex (TSC) is a multisystem genetic disease with an autosomal dominant pattern of inheritance. The prevalence is reported to be 1 in 6000 to 10,000 (1). Seizures are one of the most common presenting symptoms in TSC, and most patients with TSC develop lifelong refractory epilepsy. The classic Vogt triad of mental retardation, seizures, and adenoma sebaceum that was used to diagnose TSC in the pre–magnetic resonance imaging (MRI) and gene testing era is found in only 29% of TSC patients (2,3). Diagnostic criteria for clinical diagnosis of TSC have been developed and are clinically useful (4). However, TSC remains a disease with extremely variable expression, and approximately 7% of the patients with TSC1 or TSC2 mutation may not meet diagnostic criteria for TSC, and 15% of patients who meet the criteria for TSC may not have a detectable mutation or deletion in TSC1 or TSC2 (5). Approximately 60% of the patients are the only family member affected, suggesting a new spontaneous mutation (6). Mutations in two genes have been identified in patients with TSC. TSC1 is located at chromosome 9q34 and encodes a protein called hamartin. TSC2 is located at chromosome 16p13.3 and encodes a protein called tuberin. Although located on different chromosomes, the two genes code two proteins that work in the same biochemical pathway, the mTOR (mammalian target of rapamycin) pathway that is critical to cell

cycle regulation. Although most patients have mutations localizable to either TSC1 or TSC2 by currently available testing, 15% of patients may not have a detectable known mutation (7). Such patients should be screened for TSC 1 and 2 gene deletions. Sporadic mutations are more common in the TSC2 gene. TSC1 seems to have less severe phenotypic expression. Specifically TSC1 patients appear to have fewer seizures, fewer intracranial lesions, and less severe mental retardation (7). Both parents of a child who has TSC should be examined for evidence of the disease. When the index case has an identified pathogenic mutation, family members at risk could be screened by looking for that specific mutation. In a case with no identifiable mutations, the family screening could begin by testing of the biologic parents including a complete physical examination including a Wood lamp inspection of the skin, dilated eye examination, MRI of the head, and renal ultrasonography. If the biologic parents have no evidence of TSC, the recurrence risk for their next child is low due to a remote possibility of gonadal mosaicism; if either parent has the disease, the risk for another affected child is 50%.

Pathogenic mutations in TSC 1 or TSC 2 genes activate the mTOR cascade, resulting in abnormal growth and proliferation in various organs and systems. An understanding of this mechanism provided a unique opportunity to test already available mTOR inhibitor drugs such as rapamycin as a potential therapeutic agent targeting TSC-related tumoral diseases in the brain, kidneys, and lungs (8–10). Later, clinical trials led to the FDA approval of mTOR inhibitor everolimus as a treatment option in selected TSC patients with subependymal giant cell astrocytomas (SEGA) and renal angiomyolipomas (9,11–13).

Epilepsy and Neurologic Manifestations in TSC

Seizures are one of the most common presentations in TSC and occur in up to 80% patients with TSC. Most TSC patients with seizures tend to present early in life, and 70% of TSC patients develop epilepsy by the age of 1 year (3,14). A typical patient is an infant who presents with infantile spasms with no prenatal and perinatal adverse events (15–17). Lifelong neurologic morbidity of TSC is usually defined early in life by intractable epilepsy and global cognitive delay that typically go hand in hand. Early onset of epilepsy is one of the most important risk factors for continuing seizures and cognitive disability later in life (18). Most infants with epileptic spasms, despite going into remission with antiepileptic treatment (vigabatrin, ACTH, or other medications), develop complex partial, focal motor, tonic, or generalized tonic–clonic seizures later in life. It is generally accepted that most seizures in TSC are partial-onset seizures from one or more cortical tubers. Infrequently, a TSC patient may present with seizures later during teenage years or adulthood with exclusively partial seizures (3,18,19).

Electroencephalography (EEG) has no specificity to the diagnosis of TSC. A variety of abnormal findings could be seen during the interictal period including a picture of hypsarrhythmia during infancy and Lennox–Gastaut syndrome in older children and adults. Westmoreland found that 88% of TSC patients had abnormal recordings; 75% had epileptiform discharges, and focal slowing occurred in 13%. The epileptiform discharges were multifocal in 25% and focal in 23%; hypsarrhythmia occurred in 19% and generalized spike–wave discharges in 8% (19). Approximately 70% of focal spikes were in the temporal lobe. A variety of seizure onsets (ictal EEG) could be observed ranging from exclusively well-localized focal seizures with partial semiology to generalized or nonlocalized ictal EEG onset with generalized motor or bland seizures. It remains unclear if the threshold of epileptogenicity from the tuber(s) changes throughout the patient's lifetime. It is also not known if and

how multiple epileptogenic tubers interact with each other (or kindle each other), leading to an unpredictable course of epilepsy. Cusmai et al. (20) reported that during follow-up EEG, although some epileptic foci disappeared (usually occipital foci), others became evident, especially in the frontal regions (consistent with posterior–anterior migration of epileptic foci in childhood). The study also found that, although there was no correlation between the number of EEG foci and the number of cortical tubers, in 25 of 26 patients in this series, there was an EEG and MRI topographic correlation between at least one large tuber (larger than 10 mm in the axial plane and larger than 30 mm in the coronal plane) and an EEG focus. Secondary bilateral synchrony appeared in 35% of children with tuberous sclerosis after the age of 2 years, especially during drowsiness and sleep (20,21).

Fifty to sixty-five percent of TSC patients have mild to moderate mental retardation. IQ appears to be bimodally distributed in patients with tuberous sclerosis. On the good side of the spectrum are the few patients who have no or infrequent seizures beginning after early childhood with no or mild learning disabilities and an IQ that is lower than that of siblings without TSC. On the guarded side of the spectrum are TSC patients who present with infantile spasms or catastrophic epilepsy with onset before 12 months of age and who end up with moderate to severe mental retardation, limited or no speech, and inability to ambulate (22). Autism is commonly described in TSC patients and is reported in 25% to 50% of patients. Between 26% and 58% of children with tuberous sclerosis and infantile spasms have autism, compared with 13% of patients with infantile spasms who do not have tuberous sclerosis (22–24). The association between autism and tuberous sclerosis therefore appears to be more than coincidental. Both the number of tubers and their topography seem to play an important role in the cognitive outcome. The persistence of epileptic foci in anterior and posterior areas is thought to be important in the development of autistic traits, such as severe disability in verbal and nonverbal communication, stereotypies, and complete indifference to social interaction. Patients with multiple cortical lesions are likely to have developmental delay and intractable seizures. However, it is not possible to predict neurocognitive function or burden of epilepsy in an individual TSC patient by brain MRI alone. Patients with TSC also have other neuropsychiatric morbidity in the form of high frequency of hyperactive and aggressive behavior, and rarely self-mutilation (23). SEGA may grow and obstruct the CSF flow presenting with symptoms and signs of hydrocephalus requiring tumor excision with or without placement of a ventriculoperitoneal shunt.

Nonneurologic Lesions in TSC

TSC patients have a multitude of cutaneous lesions such as hypomelanic macules (ash leaf spots), adenoma sebaceum (facial angiofibromas), forehead plaques, shagreen patches, and ungual or subungual fibromas. In Gomez's series of 300 tuberous sclerosis patients, skin lesions were seen in 96%, followed by seizures in 84%, retinal hamartomas in 47%, and mental impairment in 45% (3). Patients with TSC may have many visceral lesions including cardiac rhabdomyomas, retinal astrocytomas (hamartoma) in the eyes, renal cysts and angiomyolipomas, hepatic cysts, and pulmonary leioangiomyomatosis.

Brain Involvement and Neuroimaging in TSC

TSC is associated with a variety of brain lesions, and these are cortical tubers, white matter lesions, subependymal nodules (SEN), and SEGA (25,26). Histologically, each of the four types of intracranial lesions is composed of clusters of giant cells with varying degrees of neuronal and

astrocytic differentiation, and the presence of cells that are transitional forms between these two types. On an unenhanced brain CT, cortical and subcortical white matter lesions in TSC appear hypodense and may be mistaken for a remote insult; however, the presence of multiple lesions and associated calcified SEN usually clarify the diagnosis. Many unsuspecting patients are identified to have TSC for the first time by a brain CT done as a part of workup for unrelated questions (e.g., in the emergency room after a head trauma).

While brain CT is helpful in noticing calcified lesions in TSC, brain MRI is the neuroimaging procedure of choice to elicit the extent of all lesions. Age is an important factor in the interpretation of brain MRI in TSC. Cortical tubers are hyperintense on T2 and FLAIR sequences, and hypointense on T1 sequences in patients with mature myelination. In newborns and infants with immature myelination, the tubers are hyperintense to unmyelinated white matter on T1 sequences and appear hypointense on T2-weighted images. This effect of immature myelination on the brain MRI findings in infants with TSC is felt to be secondary to the increased water content in unmyelinated regions of the brain. There is evidence to suggest that cortical tuber count and location are associated with increased risk of infantile spasms (27). There also appears to be a correlation between increased number of tubers, development of early seizures, and developmental delay.

There are three types of white matter lesions in TSC (25,26). These are, in the order of common occurrence, thin linear bands extending radially from the ventricular surface to cortical tubers, wedge-shaped bands with apices near ventricles, and amorphous lesions in the deep white matter. The white matters lesions tend to be predominant in frontal lobes.SEN are often near the caudate head or caudothalamic groove. They are variable in appearance and signal intensity. SEN do not usually obstruct CSF flow, but may uncommonly do so by mechanical pressure against the foramen of Monro. SEN may rarely enhance on gadolinium administration in a nodular or ring-like fashion, and enhancement is better appreciated at higher signal strengths. When small, SEN are better seen on CT than MR because of the presence of calcification. SEGA are slow-growing tumors. They are typically located near the foramen of Monro and are believed to originate from SEN. However, rarely SEGA may also appear in other locations in the brain. Typically, there is no edema in brain parenchyma adjacent to the SEGA. Most SEGA are benign, although there are rare cases of malignant degeneration. The symptoms of SEGA are mainly due to their location. TSC patients with SEGA often present with acute or chronic increased intracranial pressure suggesting chronic or intermittent obstruction at the level of the foramen of Monro. Incidence of SEGA in various studies on TSC is reported to be 1.7% to 26%. A series in a moderate-sized group of patients reported 8.2% (28). SEGA are generally iso- to hypointense to brain parenchyma on T1 and hyperintense on T2-weighted images. SEGA are heterogeneous in appearance. Flow voids may be identified within these lesions. They often have internal susceptibility artifact reflecting hemorrhage or calcification. SEGA usually show contrast enhancement. SEGA should be suspected and periodic screening scans are indicated if SEN show increased size and contrast enhancement.

Medical Treatment of Epilepsy

The first-line treatment for seizures is antiepileptic medications. Many case series and randomized clinical trials show that vigabatrin is particularly effective in the treatment for infantile spasms and partial seizures during infancy in TSC (29–31). Vigabatrin may cause irreversible peripheral field visual defects after long-term use, and most experts agree not to use vigabatrin beyond 6 to 12 months of treatment. Corticotropin (ACTH) provides an alternative treatment; the response of children with

tuberous sclerosis and infantile spasms to corticotropin is similar to the response of children with cryptogenic infantile spasms; however, those with tuberous sclerosis have a higher relapse rate. Vigabatrin may be superior compared to ACTH considering the similar or marginally better rate and rapidity of seizure remission, ease of oral administration, lack of serious side effects in the short term, and significantly lower cost of treatment (29–31). Many experts use Vigabatrin as the first-line drug in infantile seizures in the setting of TSC. Other antiepileptic treatments could be used in TSC following the general guidelines of partial versus generalized seizures. However, one should keep in mind that most seizures in patients with TSC are partial in origin despite an overwhelming electroclinical picture of generalized epileptic encephalopathy and, therefore, not contraindicating antiepileptic drugs that are effective only for partial epilepsy. Coexisting renal morbidity in TSC warrants cautious use of topiramate and zonisamide, and ketogenic diet. Extra caution is required for monitoring preexisting neuropsychiatric and behavior issues that may paradoxically show worsening with antiepileptic drug(s). Recently, mTOR inhibitors have been proposed as an option for treatment of epilepsy in TSC. However, it remains controversial, and at the time of writing this chapter mTOR inhibitors are not approved by the FDA (USA) for treatment of epilepsy in patients with TSC, but treatment trials are ongoing, suggesting encouraging preliminary results (32).

Surgical Treatment and Outcome of Epilepsy in TSC

Like in any other refractory partial epilepsy, when medical treatment fails, evaluation for the possibility of epilepsy surgery should be considered early in every patient with TSC (33). Frequency of medical intractability of seizures is higher in TSC and reported to be approximately 50% in patients with tuberous sclerosis and partial epilepsy (18). Seizure freedom or effective control of debilitating seizures after epilepsy surgery would likely improve quality of life in patients and families with TSC. However, two key rules for planning surgical strategy, localization of the epileptogenic zone (EZ) and minimizing risk of a permanent new postoperative deficit(s), pose additional challenges unique to TSC. These challenges emanate from multiple factors, often age related, and in complex interaction with each other. First, the presence of multiple bilateral tubers, sometimes partially or nearly confluent, on the brain MRI portrays a possibility of multiple epileptogenic lesions. The tubers often intermingle with white matter abnormalities and defy accurate identification of margins even on a high-resolution brain MRI making anatomical delineation for surgery inaccurate. Second, the patient is frequently a child or a cognitively disabled young adult with stereotypic nonfocal seizure semiology (epileptic spasms, bland seizures with behavior arrest, tonic or atonic seizures with falls) and a scalp video-EEG that often shows overwhelming generalized or multiregional interictal abnormalities and nonlocalizable ictal onset. Considering recent reports of a single epileptogenic lesion on the brain MRI leading to generalized and multiregional interictal and ictal abnormalities on scalp EEG, a scenario of multiple epileptogenic lesions with such an EEG appears to be an insurmountable condition for epilepsy surgery (Chapter 88). Third, young age along with cognitive delay and behavior issues renders cooperation for noninvasive mapping of eloquent functions, whenever necessary, challenging or even impractical. And lastly, lack of long-term longitudinal postoperative outcome studies makes family counseling before surgery imprecise as there is always a potential concern for emergence of epileptogenicity from the nonresected tubers. It is therefore no wonder that in the quest for a successful surgical strategy in TSC, multiple presurgical investigative tools in various combinations and recipes have been reported in the published case series from various centers (33).

Multimodal presurgical tools such as 18F fluorodeoxyglucose–positron emission tomography (PET), alpha-[(11)C] methyl-L-tryptophan (AMT)-PET, ictal single photon emission computed tomography, and magnetoencephalogram (MEG) coregistered to the brain MRI have been used in varying combinations with claims of success; however, there is no perfect formula for identification of the epileptogenic tuber, and neither have any tools, alone or in combination, been shown to improve the rate of seizure freedom after surgery (33–40). A logical step-by-step by investigation tailored to each patient remains the cornerstone of presurgical evaluation in TSC. Recently, in patients with unidentifiable EZ (epileptogenic tuber(s)) on multimodal noninvasive investigations, bilateral subdural and depth electrode implantation encompassing wide regions of brain bilaterally followed by a focused search for the epileptogenic tuber(s) with staged resection(s) has been reported from one center (41). Palliative procedures, such as corpus callosotomy or partial or complete resection of the "most" epileptogenic tuber (cause of most frequent or most severe seizures), could also help in some patients with TSC where surgery is done to minimize injuries, abolish the most disabling seizures with falls and loss of consciousness, and prevent episodes of life-threatening status epilepticus.

Published series on epilepsy surgery in TSC have reported high rates of success in alleviating or significantly improving seizures in most patients who undergo surgery. In a systematic review of literature published between 1960 and 2006, Jansen et al. (42) reviewed a sample of 177 TSC patients who underwent epilepsy surgery and were subjects in 25 published articles in peer-reviewed journals. Not surprisingly, authors found these observational case series incomparable due to extreme variability in the collection and reporting of data (42). However, in a composite analysis, 75% TSC patients were either seizure free (57%; 0.1 to 47 [mean 3.7] years follow-up) or >90% improved in seizure frequency (18%; 0.5 to 20 [mean 4.2] years follow-up). Also of interest was the finding that a large number of TSC patients who underwent surgery had generalized and multiregional interictal scalp EEG abnormalities (48%) and nonlocalizable ictal onset (46%) findings; however, the presence of focal versus nonfocal scalp EEG abnormalities had no statistically significant relationship to seizure remission after surgery (42). Obviously, these patients were selected for epilepsy surgery based on other (not studied in the paper) criteria(s) such as semiology, functional deficits, dominant tuber(s) on the brain MRI, nuclear imaging studies, or MEG, again highlighting the point that generalized and multiregional EEG abnormalities on the scalp video-EEG does not preclude surgical candidacy in a child with a solitary or multiple lesions (such as in TSC). In a recent series of 33 TSC patients who underwent epilepsy surgery, complete removal of epileptogenic tissue detected by MRI and intracranial EEG, regional scalp interictal EEG patterns, and agreement of interictal and ictal EEG localization were the most powerful predictors of seizure-free outcome (43). Other significant predictors included occurrence of regional scalp ictal EEG patterns, fewer brain regions affected by tubers, presence of preoperative hemiparesis, and one-stage surgery. Remaining factors such as age at seizure onset, incidence of infantile spasms or other seizure types, duration of epilepsy, seizure frequency, mental retardation, as well as types and extent of resections did not influence outcome (43).

Overall, despite additional challenges of epilepsy surgery in TSC, the findings from the published TSC series are quite similar to the proven principles and practice of epilepsy surgery in children with extratemporal epilepsy substrates (Chapter 89). The investigation to find the culprit tuber and perituberal regions (and define the EZ) is, therefore, best individualized to each patient considering all aspects of his or her clinical condition and goals of epilepsy surgery. No formula fits all TSC patients. Every TSC patient with refractory epilepsy should undergo presurgical evaluation using a

customized approach. In a few refractory patients who were not candidates for resective surgery or did not benefit from resection, vagus nerve stimulator implantation may offer some palliative benefit (44–46).

STURGE–WEBER SYNDROME

Sturge–Weber syndrome (SWS) or Sturge–Weber–Dimitri syndrome is also known as encephalotrigeminal angiomatosis or encephalofacial angiomatosis. SWS was first described in 1879 by Sturge, who thought that the neurologic features of the syndrome resulted from a nevoid condition of the brain similar to that affecting the face. Volland in 1912 and Weber in 1922 described the intracranial calcifications, and Dimitri was the first to report a case with calcifications seen on skull roentgenogram. SWS is a sporadic disease presumed to be caused by somatic mutation. Prevalence of SWS is estimated in one study to be 1 in 50,000. In a recent tissue-based study, SWS (brain tissue) and port-wine stains (PWSs) (cutaneous tissue) were shown to be caused by somatic mosaic mutations in the GNAQ gene leading to disruption of normal vascular development (47). The study group identified a nonsynonymous single-nucleotide variant (c.548G-->A, p.Arg183Gln) in GNAQ in samples of affected tissue from 88% of the participants (23 of 26) with the SWS and from 92% of the participants (12 of 13) with apparently nonsyndromic PWSs, but not in any of the samples of affected tissue from 4 participants with an unrelated cerebrovascular malformation or in any of the samples from the 6 controls (47).

Characteristic clinical features of SWS are unilateral facial PWS, ipsilateral pial angiomatosis, epilepsy, stroke-like episodes and glaucoma. Neurologic manifestations include seizures, varying degrees of mental retardation, migraine-like headaches, intermittent or progressive stroke-like episodes with focal deficits such as hemiparesis, hemiatrophy, aphasia, and hemianopsia (26,48,49).

Chronic cortical ischemia from angiomatous malformation leading to calcification and laminar cortical necrosis have been proposed as likely mechanisms of brain injury. During the sixth week of intrauterine life, the primitive embryonal vascular plexus develops around the cephalic portion of the neural tube and under the ectoderm in the region destined to be the facial skin. In SWS, it is hypothesized that the vascular plexus fails to regress, as it should in the embryo in the ninth week, resulting in angiomatosis of related tissues (50). The intracranial lesion is thought to be related to proliferation of leptomeningeal vessels in the subarachnoid space, which causes shunting of blood away from the brain tissue resulting in decreased blood flow, decreased venous return (venous stasis), and consequent focal hypoxia leading to cellular death. This is seen radiographically as gliosis, volume loss, and calcification.

Epilepsy and Neurologic Manifestations in SWS

Seizures are the most common neurologic presentation, and occur in 75% to 80% of children with SWS. Only 10% to 20% of children with unilateral port-wine nevus of the forehead have a leptomeningeal angioma. Typically, SWS involves occipital and posterior parietal lobes ipsilateral to the port wine nevus, but it can affect other cranial regions and both cerebral hemispheres. Bilateral brain lesions occur in 15% of children. Bilateral hemispheric involvement increases the risk of seizure. The age range of seizure onset varies between birth and 23 years with a median age of 6 months (51). The risk of developing seizures is highest in the first 2 years of life and occurs earlier in patients with bilateral disease. The most common type of seizure is a partial seizure, usually a focal

motor with hemitonic, hemiclonic semiology. Secondary generalized seizures are also uncommonly seen, usually later in childhood and adolescence. There is also an increased incidence of prolonged seizures or status epilepticus in SWS patients. In many SWS patients, seizures tend to cycle with relapsing clusters over a few days, and then remit for many days to weeks. Fever and infection may trigger the onset of seizure clusters in many children. Seizures frequently accompany stroke-like episodes. Onset of a motor deficit may precede a cluster or prolonged seizures rather than seizures followed by Todd paralysis; however, this distinction could be difficult in children. Hemiparesis is often discovered for the first time around the seizure clusters before it becomes an obvious permanent deficit. It remains unclear if fixed hemiparesis is a stuttering progressive hemiparesis that occurs due to acute (seizures, stroke-like episodes) over chronic (hypoxia from leptomeningeal angiomatosis) injury, raising the question of SWS being a progressive disease. Fixed hemiparesis contralateral to the facial angioma eventually occurs in 50% of children. Transient episodes of hemiplegia, not related to clinical or EEG evidence of seizure activity, may also occur. As a general rule, children with SWS do not exhibit significant mental retardation in the absence of seizures. Hemiparesis and hemisensory loss increase in frequency with age. Hemianopsia is often present by the time hemiparesis is manifested. SWS patients may also have associated migraine-like headache, attention deficit disorder, and mild to severe cognitive impairment (51,52). Sixty to eighty percent of SWS patients have some degree of mental retardation, and 47% to 60% are reported to have moderate to severe mental retardation in two studies. Bilateral hemispheric involvement usually shows increased severity of mental retardation (53). Intensity of seizures rather than age of onset or hemiparesis were correlated with the presence and severity of mental retardation (54).

EEG could serve as a noninvasive tool for diagnosis of brain involvement in newborns and young infants who have not yet developed neurologic symptoms and signs. Commonly seen EEG abnormalities are slowing and attenuation of background activity on one (ipsilateral to the disease) or both (likely bilateral disease) sides, epileptiform spikes coexisting with background abnormalities, and only epileptiform spikes without background abnormalities. A few patients may have bilateral independent or generalized spike discharges. Quantitative EEG (qEEG) has been claimed to provide an objective measure of EEG asymmetry that correlates with clinical status and brain asymmetry seen on MRI (55).

Nonneurologic Lesion in SWS

The hallmark cutaneous lesion of SWS is the unilateral facial capillary angioma (i.e., port-wine stain or nevus flammeus) in the distribution of cranial nerve V. The dermatologic lesion of a facial PWS is usually present during birth. It is a flat lesion of variable size, involving the upper eyelid and forehead. The size of the cutaneous angioma does not predict the size of the intracranial angioma. It is unilateral in 70% cases, almost always ipsilateral to the brain involvement. Usually it is in the V1 distribution with variable V2 and V3 involvement. Patients with V1 involvement are at risk for neurooocular lesions. Some experts feel that facial angioma is not a sine qua non, and up to 5% of patients with SWS do not have facial angiomas. Nevi may be found on the nape of the neck above or below the hairline, the upper trunk, or even the extremities and hence may escape recognition on a cursory examination. Even when facial angiomas are bilateral, intracranial involvement tends to be unilateral or dominant (asymmetric) on one side (26,49,53). Glaucoma is diagnosed in 15% of SWS patients at birth, 61% in the first year of life, and 72% by the age of 5 years (56). Presence of vascular malformation in the distribution of the V1 segment increases the probability of glaucoma.

The presence of buphthalmos and amblyopia in newborns with SWS may suggest glaucoma. There may be associated vascular abnormalities in the conjunctiva, sclera, retina, and choroid. In SWS, glaucoma is usually found with ipsilateral choroidal angiomas. This elevated intraocular pressure may be due to elevated episcleral venous pressure (57). Dilated episcleral and retinal vessels are present with V1 involvement. There is increased incidence of retinal detachment secondary to hemorrhages from the choroidal hemangiomas. Eye involvement may result in acute or chronic visual loss that may not be readily apparent in a young infant without an ophthalmologic examination by an expert.

Brain Involvement and Neuroimaging in SWS

Characteristic brain MRI findings in SWS are enhancement of the leptomeningeal angioma, enlarged transmedullary veins, choroid plexus hypertrophy, white matter abnormalities, calcification, and patchy parenchymal gliosis (neuronal loss) (Chapter 5). However, the brain MRI may only show subtle or no abnormalities in young infants who are, at a later date, shown to have SWS. Unenhanced CT scan of the brain, although routinely not done, may show cortical calcification typically described as "tram track" or "gyriform" appearance. Calcification may be absent or minimal in neonates and infants. On brain MRI, calcified lesions are best visualized on gradient or susceptibility sequences where they exhibit gyriform susceptibility artifact (low signal areas). Contrary to what might be anticipated intuitively, neither MR venography nor MR angiography are generally helpful in the diagnosis and severity of SWS (26).

Medical Treatment of Epilepsy in SWS

Broad-spectrum antiepileptic medications that are effective in partial seizures may control seizures. Onset of epilepsy before 2 years of age increases the risk of mental retardation and refractory epilepsy. Clinical progression may have a stuttering course with unpredictable periods of rapid worsening, episodes of intense seizure clusters and status epilepticus, and stroke-like episodes as discussed in the previous section (49,51,55). There is a higher risk for neurologic complications in widespread or bihemispheric disease. Aspirin 3 to 5 mg/kg/day is often recommended with SWS as primary prevention or secondary prevention (after first stroke-like episode), but its efficacy is controversial, and there have been no randomized controlled clinical trials. In one case series, patients who received prophylactic aspirin were found to have 65% fewer strokes than those who did not (58). In another series, 58 SWS patients who took aspirin were analyzed in a retrospective chart review (59). The majority of SWS patients on aspirin had neurologic outcomes reflecting reasonable seizure control (91%), no or mild hemiparesis (57%), no vision impairment (71%), and no or mild cognitive impairment (80%). Forty-nine patients reported no significant side effects, and nine reported either allergic reaction or minimal to significant bleeding on aspirin. This study's clinical observations provide support for a low-dose aspirin use under clinical supervision in SWS (59). Regular evaluation by an ophthalmologist is recommended, particularly in those patients with choroidal lesions. Medical and surgical treatment of glaucoma includes beta-blockers, carbonic anhydrase ophthalmic drops, and surgery. Salvaging (or preventing) visual loss by aggressive glaucoma management has important implications for future epilepsy surgery that likely involves ipsilateral posterior quadrant resection with permanent postoperative contralateral hemianopsia (48).

Surgical Treatment and Outcome of Epilepsy in SWS

About 50% of patients with SWS may have medically refractory epilepsy. Epilepsy in SWS is amenable to surgical treatment in most refractory patients with SWS (48). Peterman et al. (52) followed 25 patients with SWS for more than 5 years and reported spontaneous remission or controlled epilepsy in nearly half. In medically refractory patients, presurgical evaluation should be promptly considered. General principles of pediatric epilepsy surgery apply to SWS children (Chapter 89). The timing of surgery is important. Considering that the disease may be progressive in some SWS patients, some experts argue that early resective surgery may be useful in halting the progressive brain involvement, neurologic deficits, and cognitive impairment. Visually guided complete excision of the angiomatous cortex with or without the guidance of intraoperative electrocorticography is generally considered the primary surgical strategy. Extensive hemispheric resection and hemispherectomy could be considered in children with extensive unilateral brain involvement and a fixed hemiparesis. The completeness of resection or disconnection of diseased tissue is an important factor in achieving epilepsy control. 70% to 80% patients may be seizure free or significantly improved (>75% to 90% seizure reduction) after surgery, and early surgery may improve developmental outcome in refractory patients. The prognosis for intellectual outcome is better in patients who underwent surgery earlier (preferably before the age of 3 years) compared with those who were operated on later (48,60–64). In patients with bihemispheric disease and intractable generalized seizures, corpus callosotomy could be considered. However, very few patients with SWS have undergone this procedure (65).

LESS COMMON NEUROCUTANEOUS SYNDROMES

Epidermal Nevus Syndrome

Epidermal Nevus syndrome (ENS) is a sporadic neurocutaneous disorder without any known familial cases. Somatic mutation is postulated as the underlying genetic mechanism. The defining cutaneous feature of ENS is congenital epidermal nevi that are usually raised (palpable), and may be band-like, round, oval, or linear in configuration. Cutaneous lesions may be subtle to detect due to their skin-like color and velvety appearance in infancy; however, they may become verrucous orange or brown later in life. A wide variety of epidermal congenital lesions have been linked to ENS, such as linear sebaceous nevus (of Jadassohn), nevus verrucosus, ichthyosis hystrix, nevus unius lateris, and inflammatory linear verrucous epidermal nevus. The cutaneous lesions may differ somewhat in histology. Characteristically, the dermis is not involved, and there is thickening and hyperkeratosis of the epidermis with hyperplasia of the sebaceous glands. Some investigators prefer to group the cutaneous lesions together, whereas others maintain that these are separate entities on the basis of histologic differences (66). The potential for malignant transformation exists after puberty. Heterogeneity of cutaneous findings in ENS is not just limited to the skin. Brain involvement also tends to be variable ranging from focal cortical dysplasia to hemispheric dysplasia and hemimegalencephaly (67). In this chapter, we use the term epidermal nevus syndrome to encompass all these entities. Besides cutaneous manifestations, there is a wide spectrum of clinical presentation involving multiple organs and systems. Ocular, dental, and skeletal abnormalities, as well as

malignancies, have been reported. Ocular involvement reported in approximately 25% of cases includes microphthalmia, proptosis, choristomas (including dermoids and epidermoids), cataracts, and colobomas (68).

Brain Involvement, Epilepsy, and Its Treatment in ENS

Pathogenesis of brain involvement is postulated to be vascular dysplasia and migrational anomalies. Brain involvement is usually ipsilateral or asymmetric bilateral (worse ipsilateral) to the cutaneous findings. However, there is no consistent relationship between the side of the nevus and CNS abnormality. Various types of brain malformations and migration abnormalities are reported; however, classical involvement of the brain presents as hemimegalencephaly (including 17 out of 60 patients in Pavone's study) (67,69–71). In a series of 60 patients, Solomon and Esterly (66) reported moderate to severe CNS involvement in 30 (50%). Reported clinical, EEG, and imaging findings include mental retardation, seizures, hyperkinesis, hydrocephalus, porencephaly, cortical atrophy, nonfunctioning cerebral venous sinuses, hemimacrocephaly or macrocephaly, hemimegalencephaly, infantile spasms with hypsarrhythmia or hemihypsarrhythmia, and other seizure types such as myoclonic, complex partial, partial motor, and generalized seizures (67,69–72). In other words, ENS has a wide spectrum of findings; however, in general, the neurologic involvement is severe. Seizure onset is usually within the first year of life. Seizures are usually daily, are catastrophic, and fail to respond to medical treatment. Pediatric epilepsy surgery (Chapter 89) principles should again guide the testing, timing, and surgical strategy. Anatomic or functional hemispherectomy is the treatment of choice in patients with hemimegalencephaly (73). Important considerations before epilepsy surgery in ENS patients include careful examination and investigations to elicit the clinical severity of other organ/system involvement in the patient. Counseling of parents is critical as the long-term outlook for neurocognitive development is guarded in ENS. Histopathologic examination of the brain resected in epilepsy surgery cases has shown a spectrum of dysplastic abnormalities, including diffuse cortical dysplasia, gyral fusion, pial glioneuronal hamartomas, cortical astrocytosis, and foci of microcalcification.

Neurofibromatosis 1

In neurofibromatosis type 1 (NF1), seizures occur in 3% to 5% of individuals, a rate that is slightly higher than in the general population. Korf et al. (74) found that 21 (5.4%) of 359 children with neurofibromatosis had seizures. In a recent retrospective cross-sectional review of 536 individuals with NF1, 9.5% had a history of at least one unprovoked seizure, and 6.5% had documented epilepsy (75). Age of presentation varied from 4 days to over 20 years. Cognitive impairment is often present in those NF1 patients who have seizures. A variety of seizure types, including infantile spasms, absence, generalized convulsions, and complex partial seizures, have been reported (74,76,77). Seizures were due to tumors (hamartomas), cortical malformations, and mesial temporal sclerosis. Complex partial seizures or other types of focal seizures appear to be the most common type, and have been reported in the absence of obvious structural lesions. Reports of epilepsy surgery in NF1 are scant. In a recent published survey of epilepsy surgery in NF1, data from 25 European epilepsy surgery centers identified only 12 patients from 8 centers who underwent resections (78). MRI abnormalities were present in all patients but one, with unilateral temporal in eight, bilateral temporal in one, and multilobar or hemispheric in two. One year after surgery, eight patients were seizure free, one had worthwhile improvement, and the remaining three had experienced no benefit.

Histology revealed dysembryoplastic neuroepithelial tumors in five, hippocampal sclerosis in four, mixed pathology in one, polymicrogyria in one, and no histologic abnormality in the remaining patient (78).

These observations suggest that all individuals with NF1 and a new seizure should undergo MRI despite previous normal neuroimaging. In addition, epilepsy in NF1 patients typically requires more aggressive therapy than that in those without NF1, and selected NF1 patients are candidates for epilepsy surgery and surgery should be investigated as an option in a timely manner.

RARE NEUROCUTANEOUS CONDITIONS WITH EPILEPSY

Incontinentia Pigmenti

Incontinentia pigmenti, which occurs almost exclusively in females (X-linked dominant condition), presents in the neonatal period with erythematous bullous lesions that become crusted and pigmented. Children with this disorder may develop seizures (13.3%), mental retardation (12.3%), or spasticity (11.4%) (79). A variety of dysplastic brain MRI findings may be seen (79).

Hypomelanosis of Ito

Seizures and mental retardation are also seen in approximately two-thirds of children with hypomelanosis of Ito, in which irregular, hypopigmented skin lesions along the embryonal lines of dermatologic fusion are seen. Seizures are more severe in early-onset cases and consist of infantile spasms or myoclonic seizures. Choroidal atrophy, corneal opacities, deafness, dental anomalies, hemihypertrophy, hypotonia, and macrocephaly may also be seen (80,81). Reported CT and brain MRI findings include cerebral atrophy, porencephaly, and low-density areas in the white matter. Autopsy showed gray matter heterotopias and abnormal cortical lamination in a patient in one series indicative of abnormalities in neuronal migration (81).

Neurocutaneous Melanosis

This is a rare disorder in which patients have congenital cutaneous nevi and leptomeningeal melanosis leading to CNS manifestations (82–85). Patients have multiple congenital cutaneous nevi, the largest of which typically measure more than 5 cm. A 2.5% risk of developing neurocutaneous melanosis (NM) with CNS involvement is quoted in patients with large congenital melanocytic nevi (82). This disease may be lethal early in life, but some patients survive into their 20s. NM patients usually present with seizures or increased intracranial pressure. Cranial nerve palsy, hemiparesis, myelopathy, or psychiatric disorders may coexist. NM is believed to be a sporadic neurocutaneous disorder and is not transmitted as a single gene disorder. Most common brain MR findings in NM patients is T1 shortening (increased signal) in temporal lobe and infratentorial brain areas on noncontrast exams. There is variable ventriculomegaly. There may be thickening of leptomeninges of brain and spine as demonstrated on contrast enhancement. Leptomeninges may appear to be normal on T1- and T2-weighted sequences. Usually there is leptomeningeal enhancement. However, cases have been described without the leptomeningeal involvement. There may also be pachymeningeal (dural)

involvement (83–85).

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CHAPTER 31 EPILEPSY IN THE SETTING OF INHERITED METABOLIC AND MITOCHONDRIAL DISORDERS

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INTRODUCTION

There are more than 11,000 well-recognized and well-characterized inherited disorders in humans, with many of them associated with seizures and epilepsy. The daunting task for the clinician is to recognize these important diagnoses in the patient with epilepsy so that optimal medical treatment, family counseling, and prognosis can be provided. The presentation is often not distinct enough to allow precise identification of the disorder on the basis of clinical criteria alone. Instead, the physician must observe a patient over a period of time and begin screening tests to detect abnormalities suggestive of the underlying disorder. These abnormalities point the way toward further diagnostic evaluations, which may culminate in the definitive diagnosis of the inherited disorder and actual detection of the defective gene. In other circumstances, important clues are present when a child is first seen, but these features can be easily overlooked if the clinical data are not synthesized and analyzed in an orderly way. Advances in genomics and genetic testing methodologies have transformed diagnosis as well. With the availability of next-generation sequencing gene panels and whole exome sequencing, patients are now at times diagnosed rapidly without the need for extensive metabolic testing.

In general, the scalp electroencephalogram (EEG) has low specificity but high sensitivity for diagnosing, determining severity, and monitoring brain dysfunction over a period of time in children of all ages. Although various EEG patterns are reported in the literature as being typical of an inborn error of metabolism, rarity of metabolic disorders, ascertainment bias, and limited repertoire of possible EEG findings in the face of enormous variability in spectrum and severity of metabolic disorders reduce the usefulness of EEG in suggesting a specific diagnosis. EEG may, however, supplement clinical assessment and other test results in shortening the list of possible diagnoses.

How can clinicians mentally organize this wealth of material? One method is to group diseases according to categories on the basis of the subcellular organelle involved: mitochondrial, lysosomal, peroxisomal, and so on. Another method is to group diseases according to metabolic or catabolic pathways, such as organic aciduria, aminoaciduria, and fatty acid oxidation. However, the clinical presentation within these groups may be diverse and dissimilar. Another method of grouping is to organize diseases according to their clinical presentation. This can be performed by age, but many different disorders are responsible for seizures and epilepsy within any defined age group. Diseases may also be organized on the basis of specific characteristics of the seizures and the epilepsy syndromes. As each metabolic and mitochondrial disorder may present along a biologic spectrum, with more severe involvement presenting earlier and in a more devastating fashion, various epilepsy

syndrome presentations can occur due to the same disorder. Early myoclonic epilepsy (EME), West syndrome, and progressive myoclonus epilepsy are three well-recognized epilepsy syndromes in which there is a high likelihood of an inborn error of metabolism. In other instances, metabolic and mitochondrial diseases can masquerade as forms of cryptogenic epilepsy.

In the organization of this chapter, we group the various disorders first by their age at onset (early infancy or later infancy and childhood onset) followed by the metabolic process or organelle affected. We also list, in tabular form (Table 31.1), the various cryptogenic or symptomatic epilepsy syndromes that might be mistaken for these disorders. In addition, we discuss clinical and EEG features of certain disorders that may provide clues to the underlying etiology. Additionally, we also review the appropriate screening tests that may be performed, where applicable, followed by more definitive diagnostic procedures. Genetic information is listed for each condition when known.

Table 31.1 Metabolic Diseases Masquerading as Epilepsy Syndromes

Neonatal seizures

- Organic acidurias
- Urea cycle defects
- Peroxisomal disorders: Zellweger syndrome
- Molybdenum cofactor deficiency/sulfite oxidase deficiency
- Pyridoxine-, pyridoxal phosphate–, or folinic acid–responsive epilepsy
- Mitochondrial disorders
- Disorders of biotin metabolism
- Glucose transporter defect (Glut-1 deficiency)
- Disorders of fructose metabolism

Early myoclonic encephalopathy/early infantile epileptic encephalopathy

- Glycine encephalopathy (nonketotic hyperglycinemia)
- Serine deficiency (3-phosphoglycerate dehydrogenase deficiency)
- Creatine synthesis or transport disorders
- Organic acidurias, especially propionic academia
- Mitochondrial disorders, especially those leading to Leigh syndrome
- D-glycine acidemia

Cryptogenic epilepsies with progressive neurologic decline

- GM1 and GM2 gangliosidoses
- Neuronal ceroid lipofuscinosis
- Infantile neuroaxonal dystrophy
- Glut-1 deficiency
- Late-onset multiple carboxylase deficiency
- Disorders of cerebral and peripheral folate metabolism
- Disorders of neurotransmitter synthesis
- Arginase deficiency (urea cycle defect)
- Amino and organic acidurias (variant phenotypes)
- Sialidoses

West syndrome, generalized

- Pyruvate dehydrogenase deficiency
- Pyruvate carboxylase deficiency
- Congenital disorder of glycosylation type III
- Organic and amino acidurias

Progressive myoclonus epilepsies

- Lafora disease (EPM2A/B gene mutations)
- Unverricht–Lundborg disease (EPM1 gene mutations)
- Mitochondrial diseases including MERRF/MELAS, and POLG1 gene mutations
- Dentatorubral–pallidoluysian atrophy
- Neuronal ceroid lipofuscinosis
- GM1 and GM2 gangliosidoses
- Sialidoses

MERRF, myoclonic epilepsy with ragged-red fibers; MELAS, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes.

For an up-to-date review of an individual metabolic disease or to find a lab where an analyte or gene test can be sent, we recommend visiting the NIH GeneReviews site at http://www.genetests.org.

METABOLIC DISORDERS IN THE NEWBORN AND YOUNG INFANT

Disorders of Neurotransmitter Synthesis and Removal

Tetrahydrobiopterin and Guanine Triphosphate Cyclohydrolase Deficiency

Tetrahydrobiopterin (BH4) is a cofactor for the enzymes involved in converting tyrosine and tryptophan to levodopa and serotonin. Deficiencies in BH4 lead to disruptions in the neurotransmitter amines, levodopa, and serotonin. It is one of several disorders of neurotransmitter production. Defects most commonly occur due to abnormalities of guanine triphosphate cyclohydrolase (GTPCH), the first enzyme involved in the multistep process of converting guanine triphosphate to BH4. However, defects in other enzymes in the pathway have also been identified.

GCH1 is the gene involved in GTPCH enzyme formation. Autosomal dominant mutations lead to early onset dopa-responsive dystonia (Segawa disease), and autosomal recessive mutations lead to a neonatal onset encephalopathy. Genetic testing for GCH1 mutations and several other enzyme deficiencies in the BH4 synthesis pathway is available as are gene panels to screen for mutations in many of the genes involved in neurotransmitter synthesis.

Symptoms typically involve variable and fluctuating levels of psychomotor retardation, convulsions, microcephaly, swallowing difficulties, truncal hypotonia, limb hypertonia, involuntary movements, and oculogyric crises. Some of these symptoms begin shortly after infancy. A diurnal pattern of worsening of symptoms may be described. Of clinical note, other enzyme abnormalities both before and after BH4 production (including α-amino decarboxylase [AADC] deficiency involved in converting levodopa to active dopamine) can lead to identical symptoms (1).

Diagnosis of many of the neurotransmitter disorders is typically made by measuring levels of spinal fluid neurotransmitter metabolites (5-hydroxyindoleacetic acid and homovanillic acid) and precursors (biopterin, neopterin, and 3-methyl-dopa). Elevations in plasma and cerebrospinal fluid (CSF) phenylalanine may be seen in the amino acid profile of some patients, but this finding is frequently not present (1). Urine pterin concentrations can aid in differentiation between the various defects of biopterin synthesis, though this testing is not readily available in North America at this time.

Treatment includes tetrahydrobiopterin supplementation, pharmacotherapy with levodopa–carbidopa, and 5-hydroxytryptophan. Pyridoxine is an important cofactor, and supplementation may benefit patients. In AADC deficiency a dopamine agonist and monoamine oxidase inhibitor are used. Treatment is beneficial to varying degrees (2).

Glycine Encephalopathy (Formerly Nonketotic Hyperglycinemia)

In this autosomal recessive inborn error of amino acid metabolism, large amounts of glycine accumulate in the body, especially the brain, because of a defect in the multienzyme complex for glycine cleavage. The enzyme system is confined to the mitochondria and is composed of four protein

components (designated P, H, T, and L), three of which have a gene identified. GLDC, localized to 9p22, is the most common gene affected, with mutations leading to abnormal functioning of the P protein (3).

The pathophysiology of nonketotic hyperglycinemia (NKH) has not been fully elucidated, but the elevated glycine is believed to impact the central nervous system (CNS) via its role as an inhibitory transmitter in the brainstem and spinal cord, and an excitatory transmitter in the cortex. The majority of cases present within the first 48 hours of life with lethargy, respiratory difficulties, apnea, and seizures that are often myoclonic or characterized as infantile spasms. Cortical malformations or corpus callosum defects may be present. A burst-suppression EEG pattern with variable intervals between the bursts alternating with epochs of greater continuity is characteristic. The combination of early-onset seizures with prominent myoclonus and variable burst-suppression EEG is also called EME, as described by Aicardi. Glycine encephalopathy is an important cause of EME evolving to hypsarrhythmia, although this is more commonly observed in Ohtahara syndrome. Ohtahara syndrome is thought by some authorities to be more commonly associated with structural abnormalities and not as highly associated with errors of metabolism (1).

Later-onset forms of this disease have also been described, with patients having varying degrees of epilepsy, retardation, and movement abnormalities. An adolescent/adult-onset form presents with associated spastic paraparesis and optic atrophy (4).

Laboratory testing reveals elevations of glycine in the plasma, urine, and CSF amino acid profile. The absence of excess ketones in the blood and urine, and of abnormal organic acids in the urine, helps to differentiate NKH from other conditions associated with hyperglycinemia, such as propionic and methylmalonic acidemias. The ratio of CSF to serum glycine is also helpful, as it is significantly elevated in patients with NKH. Genetic sequencing for the three known loci is clinically available (5).

There is no effective long-term treatment for this disorder. High doses of benzoate may reduce CSF glycine and improve seizure control, but it does not appear to stop the development of mental retardation (6,7). Because benzoate treatment may deplete carnitine levels, carnitine supplementation is recommended when benzoate is used (8). Dextromethorphan, an NMDA antagonist, has been tried for this condition as well. Valproic acid should be avoided because it induces hyperglycinemia. Strychnine, a glycine antagonist, and diazepam have been reported to blunt seizures, but have not influenced the long-term outcome (9). Prognosis is poor, with progressive microcephaly and intractable epilepsy. Even when treated, death often occurs within the first few months to years of life (10).

A transient form of NKH exists with similar early clinical and biochemical findings. In this condition, glycine concentrations normalize between 2 and 8 weeks of life, and prognosis is favorable (11).

Serine and 3-Phosphoglycerate Dehydrogenase Deficiency

3-Phosphoglycerate dehydrogenase (PHGDH) deficiency is an autosomal recessive condition that results in impaired L-serine biosynthesis due to a mutation in the PHGDH gene (1p12). Serine is the precursor of D-serine and glycine, both potent neurotransmitters. Serine also has a role in myelin production (12).

Typically there is a pre- or perinatal onset of symptoms including congenital microcephaly, intractable seizures, spastic quadriparesis, and profound cognitive delays. The magnetic resonance

imaging (MRI) may show white matter lesions. The condition is often misdiagnosed as cerebral palsy. Reduced serine levels are found in CSF amino acid specimens though glycine levels are not always low. Plasma serine and glycine levels may only be low in fasting specimens but are not reliable indicators as they may also be normal (13).

Enzyme activity can be measured in skin fibroblasts. Genetic testing is clinically available. Treatment involves supportive care and L-serine supplementation (14).

Succinic Semialdehyde Dehydrogenase Deficiency

Succinic semialdehyde dehydrogenase (SSADH) deficiency is an autosomal recessive disorder impairing γ-aminobutyric acid (GABA) catabolism. The enzyme is involved in the second and final step of GABA degradation. GABA, an inhibitory neurotransmitter, accumulates (15). The ALDH5A1 (6p22) gene encodes this enzyme, and mutations here account for over 97% of cases (16).

The disorder is slowly progressive with infancy to childhood onset. Seizures occur in more than 50% of patients. Other symptoms include varying degrees of ataxia, hypotonia, speech delay, and mental retardation. A movement disorder with hyperkinetic movements, choreoathetosis, dystonia, and myoclonus can be seen with earlier onset, and presenting as a more severe form of this disease. Aggressive behaviors and self-injury may also occur (17).

Diagnosis is initially made by finding elevations of 4-hydroxybutyric (4HB) acid in urine organic acids, plasma, or CSF. Of clinical note, the 4HB peak can be easily missed on routine organic acid analysis due to its coeluting with a large urea peak. Thus, one must ensure that the lab processing the specimen is monitoring for this ion. Variable elevations of glycine can be seen in the amino acid profile. Confirmatory gene sequencing is clinically available. The EEG may show generalized background slowing and spike discharges (18).

Treatment of this disorder is symptom based. Vigabatrin, an irreversible inhibitor of GABA transaminase, has been used in some individuals with positive responses (including increased socialization, behavioral improvement, increased alertness, and reduced ataxia), but treatment with this agent has worsened symptoms in others. Valproate use is contraindicated as it may inhibit residual SSADH enzyme activity (19–21).

Vitamin and Mineral Metabolism–Related Diseases

Pyridoxine- (and Folinic Acid–) Responsive Epilepsy

In pyridoxine-responsive epilepsy, refractory seizures typically develop within the first several days of life. These may be characterized by infantile spasms or have a variety of partial, myoclonic, and atonic features. Atypical presentations include a later onset of seizures, seizures that initially respond to treatment and then become intractable, and seizures with only a partial initial response to pyridoxine.

The disorder occurs due to a mutation in the ALDH7A1 gene (5q31). The ALDH7A1 gene encodes for the protein antiquitin, which is involved in lysine catabolism. While it is not directly involved in pyridoxine metabolism, disruptions of antiquitin function secondarily deplete pyridoxine (22). Pyridoxine plays several critical roles in the brain, including the conversion of levodopa to dopamine and glutamate inactivation via glutamic acid decarboxylase.

Diagnosis has typically been made clinically, with seizures abating after a high dose of

intravenous (IV) pyridoxine (100 to 500 mg). The initial EEG is characterized by generalized bursts of high-voltage delta activity interspersed with spike and sharp waves and periods of asynchronous attenuation. After treatment there is conversion of the EEG to a burst-suppression pattern, and later normalization with subsequent doses. This change occurs within minutes and may persist for hours, or even a day (23). Confirmatory testing is via spinal fluid analysis, as described below. Testing for ALDH7A1 mutations is clinically available.

A clinical and genetic link has been made between folinic acid–responsive epilepsy, pyridoxine-responsive epilepsy, and ALDH7A1 mutations, thus leading one to conclude that folinic acid– and pyridoxine-responsive seizures are one and the same. Previously it was believed that folinic acid–responsive epilepsy was a rare yet separate metabolic epileptic encephalopathy with a diagnosis made by identifying a characteristic peak of a yet unknown compound in spinal fluid neurotransmitter analysis (24).

More recently, a patient with folinic acid–responsive epilepsy was found to respond to pyridoxine supplementation (25). Eventually, individuals with folinic acid–responsive epilepsy were identified as having ALDH7A1 mutations and patients identified as having pyridoxine-dependent epilepsy (mutation confirmed cases) were found to have the characteristic folinic acid–responsive epilepsy peak identified in their CSF (26).

In evaluating these patients, plasma, urine, and spinal fluid levels of pipecolic acid may also be elevated though this chemical is not a sensitive biomarker (27). A link also exists to elevated urinary and CSF concentration of α-aminoadipic semialdehyde (α-AASA), and clinical testing for this compound is available. The characteristic peak of this yet unidentified compound is found when spinal fluid neurotransmitter testing is run. Spinal fluid folate levels are normal in this condition. As the link between folinic acid– and pyridoxine-responsive epilepsy is secure, routine CSF analysis for diagnosis is crucial. Early treatment is also critical, as it improves developmental outcome. Maintenance therapy with pyridoxine and folinic acid is necessary. Onset of disease may extend beyond the newborn period, making this disorder a consideration in older infants with refractory seizures as well (28,29). Due to pyridoxine and folic acid's relatively decreased ability to cross the blood–brain barrier, treatment with pyridoxal 5-phosphate and folinic acid is recommended.

Pyridoxal-L-Phosphate-Responsive Epilepsy

Some neonates and children with an epileptic encephalopathy seemed to respond to pyridoxal-L-phosphate (PLP) supplementation as opposed to pyridoxine. Further research showed that some of these individuals had a defect in an enzyme pyridoxal/PLP—pyridox(am)ine 5′-phosphate oxidase (PNPO) required for the synthesis of intracellular PLP from dietary pyridoxine. Eventually, the PNPO gene (17q21.2) was identified and these mutations were confirmed as the cause of this relatively rare condition. The clinical presentation in these children is similar to those with pyridoxine-dependent epilepsy and disorders of neurotransmitter metabolism as described above. Treatment, however, requires PLP as opposed to pyridoxine (30). Diagnosis is aided by measuring pyridoxal 5-phosphate levels in spinal fluid.

Molybdenum Cofactor Deficiency and Sulfite Oxidase Deficiency

The rare conditions of molybdenum cofactor deficiency (MOCOD) and sulfite oxidase deficiency present shortly after birth, also with a progressive encephalopathy, feeding difficulties, hypotonia, and refractory partial, myoclonic, or apparently generalized seizures. Dysmorphic features, lens

dislocation, and hepatomegaly are all characteristic findings (31). The two conditions have an essentially identical clinical phenotype, likely due to both conditions leading to the loss of sulfite oxidase function. As typical of all of these diseases, later-onset and relatively milder and varying phenotypes have been described in the literature.

Molybdenum cofactor is critically needed for the proper function of three enzymes: sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. Sulfite oxidase converts sulfite to sulfate. Xanthine dehydrogenase converts xanthine to hypoxanthine to eventually form uric acid. Aldehyde dehydrogenase is involved in the reverse reaction of hypoxanthine to xanthine (32).

MOCOD is due to mutations in one of two genes, MOCS1, at 6p21.3 or MOCS2, at 5q11 (33). Sulfite oxidase deficiency is typically due to mutations in the SUOX gene on chromosome 12 (34).

Patients typically present with a metabolic crisis, developing irritability, opisthotonic posturing, and seizures. The EEG in these patients may show multifocal paroxysms and a burst-suppression pattern. Neuroimaging may show poor differentiation between the gray and white matter, severe cerebral and cerebellar atrophy, and multiple cystic cavities in the white matter. Diagnosis is made by a variety of methods. Since MOCOD and isolated sulfite oxidase deficiency both result in high levels of urinary sulfites, a sulfite dipstick on a fresh urine sample may detect abnormalities, though this test has a high false-negative rate (35,36). Plasma uric acid levels may be low in MOCOD, but not in sulfite oxidase deficiency. Both disorders will lead to an accumulation of urine S-sulfocysteine. The two disorders can be distinguished on laboratory testing as elevations of urine purines and pyrimidines (xanthine and hypoxanthine) occur in MOCOD but not in sulfite oxidase deficiency. The enzyme deficiencies can be demonstrated in cultured fibroblasts and liver tissue. Genetic testing is clinically available. No effective treatment has yet been identified and prognosis is poor, with death occurring within the first days to weeks of life (37). Clinical trials with cyclic pyranopterin monophosphate, an intermediary precursor of molybdenum cofactor, are planned after they showed potential benefit in slowing disease progression in several patients with MOCOD (38).

Cerebral Folate Deficiency

Folate is concentrated in the nervous system, and the CSF concentrations of folate are higher than the serum concentrations. Deficiencies in cerebral folate lead to a slowly progressive encephalopathy, with intractable seizures. If it occurs in conjunction with systemic folate deficiency, megaloblastic anemia, mouth ulceration, diarrhea, and failure to thrive may also be seen. Neuroimaging may reveal calcifications in the occipital lobes and basal ganglia (39).

Reductions in cerebral folate can occur primarily due to a mutation in the gene encoding the folate transporter (FOLR1) or secondarily due to systemic disease, gut malabsorption syndromes such as colitis, primary mitochondrial disorders (40), many other metabolic diseases (see section Methylenetetrahydrofolate Reductase Deficiency), and certain genetic syndromes (Rett syndrome) (41). Most patients with cerebral folate deficiency do not have a defect in the FOLR1 gene (42). This condition is different from folinic acid–responsive epilepsy described above.

There is also an association of lactose autoantibodies cross reacting with and blocking the folate receptor, potentially leading to a secondary cerebral folate deficiency (43). A lactose-free diet has been considered as a treatment in these situations (44). However, testing for folate autoantibodies is not clinically available and this association needs further study.

The disorder is typically diagnosed by finding low levels of methyltetrahydrofolate (MTHF) in CSF. Normal amino and organic acids analysis and normal plasma folate levels help exclude other

potentially treatable causes. If another syndromic, metabolic, or systemic cause of low cerebral folate is not identified, specialized testing for folate autoantibodies is available on a research basis (43).

Treatment involves supplementation with IV and oral folate. Folinic acid may be used since it has better blood–brain barrier penetration than does folic acid. If lactose-mediated autoantibodies are identified, a lactose-free diet might be considered (44). Outcome is still poor.

Methylenetetrahydrofolate Reductase Deficiency

Methylenetetrahydrofolate reductase deficiency (1p36.3) is the most common inborn error of folate metabolism (45). The metabolic defect results from insufficient production of 5-MTHF, which is needed for the remethylation of homocysteine to methionine, because of a deficiency in methylenetetrahydrofolate reductase. In affected individuals, a progressive neurologic syndrome develops in infancy. Children with this disorder have acquired microcephaly and seizures characterized by intractable infantile spasms, generalized atonic and myoclonic seizures, and focal motor seizures. EEG findings vary from diffuse slowing of background activity to continuous spike–wave complexes or multifocal spikes. The early-onset form differs from the late-onset form. The latter presents with progressive motor deterioration, schizophrenia-like psychiatric symptoms, and recurrent strokes; seizures are uncommon. Homocystinuria and elevated serum concentrations of homocysteine with reduced or normal serum methionine are the main biochemical features. These findings can be caused by several other amino acid disorders as well. Dietary supplementation with folic acid, betaine, and methionine has proven beneficial. In the acute setting, high-dose methionine has been effective in stopping seizures (46).

Defects in methionine biosynthesis are also associated with seizures. Convulsions are frequent and are predominantly generalized, although myoclonic seizures with hypsarrhythmia have been reported. Diagnostic laboratory findings are megaloblastic anemia, homocystinuria, decreased methionine, and normal folate and cobalamin concentrations in the absence of methylmalonic aciduria (46). These conditions are typically diagnosed via extended newborn screening (NBS) in North America and treated presymptomatically. Thus patients presenting with new-onset epilepsy who have obtained extended NBS are less likely to have this condition.

Inborn Errors of Creatine Metabolism

Creatine represents a storage depot of adenosine triphosphate (ATP) for various tissues including the brain. Depletion of cerebral creatine due to inborn errors in synthesis or transport leads to a progressive encephalopathy and epilepsy. Creatine forms via a two-step enzymatic path, with arginine converted to guanidinoacetate via arginine:glycine amidinotransferase (AGAT) and then to creatine via guanidinoacetate N-methyltransferase (GAMT). Deficiencies in both enzymes have been identified, and the genetic loci for AGAT and GAMT are known. Creatine, once formed, is transported into the cell via a specific transporter, and abnormalities in creatine transport can also occur due to defects in the SLC6A8 gene at Xq28 (47).

Development can be delayed from the beginning or after a regression beginning between 3 months and 2 years of age. Seizures may present in the first months of life with generalized tonic–clonic, astatic, absence, myoclonic, or partial events. Multifocal epileptiform discharges have been reported on the EEGs of affected individuals (48). Other clinical features may include dystonia, dyskinesias, microcephaly, and autistic behaviors (49). A mild form presenting with severe speech delay, mild autism, and infrequent seizures has also been identified (50).

Diagnosis is typically via quantifying urine, plasma, and/or spinal fluid guanidinoacetate and creatine. Low creatinine is not a reliable marker of the condition. Brain magnetic resonance spectroscopy (MRS) shows a reduced creatine peak (51).

Supplementation with creatine monohydrate (350 mg/kg/day to 2 g/kg/day) has led to improvement in affected individuals though not in patients with creatine transporter disorders (47).

Early-Onset Multiple Carboxylase Deficiency (Holocarboxylase Synthetase Deficiency)

Early-onset multiple carboxylase deficiency presents in the first week of life with lethargy, respiratory abnormalities, irritability, poor feeding, and emesis. A skin rash is present in more than 50% of patients. Generalized tonic convulsions, partial motor seizures, and multifocal myoclonic jerks develop in 25% to 50% of cases. This disease is tested for in the neonate in certain states via expanded NBS and can often be treated prior to symptom onset.

A deficiency in the enzyme holocarboxylase synthetase (HLCS) leads to a decrease in holocarboxylase. As this enzyme links biotin to four carboxylases in the mitochondria and one in the cytosol, an inactivity of all carboxylases results. The HLCS gene locus is 21q22.1. Although rare, this condition is very important to recognize because prompt treatment with biotin may result in dramatic improvement. Laboratory findings demonstrate ketoacidosis and a characteristic pattern on organic acid analysis. Hyperammonemia may be seen with acute episodes. Electrographically, a burst-suppression pattern or multifocal spikes are observed. Definitive diagnosis can be made by enzyme assays, and gene sequencing. Treatment with biotin (10 mg/day) produces clinical improvement (52).

Late-Onset Multiple Carboxylase Deficiency (Biotinidase Deficiency)

This disease is also screened for in certain states via expanded NBS. The disorder involves the body's ability to recycle biotin via biotinidase. The BTD gene has been identified at the 3p25 locus (53).

When not diagnosed early, seizures are a prominent feature occurring in 50% to 75% of affected children. In fact, seizures are the presenting feature in 38% of patients and may be generalized tonic–clonic, partial, myoclonic, or infantile spasms. Symptoms often begin at 3 to 6 months of age, with hypotonia and developmental delay. Seborrheic or atopic dermatitis and alopecia are common. As the disease progresses, ataxia, optic atrophy, and sensorineural hearing loss develop. Later-onset and/or milder phenotypes exist due to partial enzyme deficiency. EEG findings may include a suppression-burst pattern, absence of physiologic sleep patterns, poorly organized and slow waking background activity, and frequent spike and spike-slow-wave discharges (54).

Diagnosis is typically made via abnormalities in urine organic acid and plasma acylcarnitine analysis. Biotinidase enzyme activity can be measured in leukocytes and cultured fibroblasts. Genetic sequencing is clinically available. When this condition is considered as a differential diagnosis, a therapeutic trial with high-dose oral biotin should be started while awaiting test results.

Menkes Disease (Kinky-Hair Disease)

An X-linked disorder of copper absorption, Menkes disease was first described by Menkes et al. in 1962. Defects in the copper transporting ATPase gene (ATP7A, Xq12–q13) impairs intestinal copper absorption, reduces copper export from tissues, and decreases the activity of copper-dependent

enzymes, including dopamine β-hydroxylase (55).

A characteristic twisting of the hair shaft, resulting in "kinky hair" of the head and eyebrows, is noted on microscopic examination of the poorly pigmented hairs. Affected boys may be premature and may have neonatal hyperbilirubinemia or hypothermia. Progressive neurologic deterioration with spasticity is present by 3 months of age, and children may have associated bone and urinary tract abnormalities as well. The disease has a rapidly fatal course (1).

Seizures are a prominent feature in Menkes disease, with intractable generalized or focal convulsions. Infantile spasms have also been reported (56). Stimulation-induced myoclonic jerks may be present. Multifocal spike and slow-wave activity can be seen on the EEG, sometimes resembling hypsarrhythmia (57).

Laboratory testing reveals extremely low serum copper and ceruloplasmin levels. Elevations in CSF lactate may be seen, and there is low total copper content in the brain. Neuroimaging may show brain atrophy, focal areas of necrosis, and subdural collections. Brain magnetic resonance angiography (MRA) shows dilated and tortuous intracranial blood vessels. Genetic testing of the ATP7A gene via sequencing and deletion analysis identifies almost all patients with Menkes (55).

There is no fully effective treatment. Daily copper injections may be beneficial if administered early in the course of the disease.

Overlap exists between Menkes disease and occipital horn syndrome (58). It is now known that both Menkes and occipital horn syndrome conditions are allelic due to mutations in the same gene (58).

Disorders of Carbohydrate Metabolism

Glut-1 Transporter Deficiency Syndrome

The Glut-1 transporter deficiency syndrome was first described in 1991 (59). This autosomal dominant condition results from a loss of functional glucose transporters, encoded by the SLC2A1 gene, that mediate glucose transport across the blood–brain barrier (60). Clinical features include developmental delay, ataxia, hypotonia, infantile seizures, and acquired microcephaly. There is a reduction in the CSF-to-blood glucose ratio to half of normal (typically, CSF glucose is <40 mg/dL). In addition, a low lactate concentration might be seen. Additional confirmation of impaired glucose transport can be performed through assays in erythrocytes (61), and clinical genetic testing is available.

Seizures, specifically neonatal ones, are often the first identified feature of this syndrome though patients with later onset and mild epilepsy have been described. Typical seizure types include absence, myoclonic, astatic, generalized tonic–clonic, and partial–complex. About 10% of patients have no clinical seizures. A normal EEG is commonly seen between seizures, although generalized 2.5- to 4-Hz spike–wave discharges are observed in more than one-third of children older than 2 years of age (62).

Affected individuals without early-onset refractory epilepsy have been identified, and a screening for lumbar puncture should be considered in those individuals as well (63). Early initiation of the ketogenic diet is effective in the treatment of seizures as well as overall disease progression, as it provides an alternative cerebral energy source (64).

More recently, patients with Glut-1 diseases presenting with early-onset atypical absence epilepsy and, less frequently, idiopathic generalized epilepsy have been identified (65,66). Some

patients may present with isolated movement disorders. Paroxysmal exertional dyskinesia (PED) is now recognized as an allelic variant of Glut-1 deficiency (67,68). Some patients with PED also have epilepsy. In patients without the classic presentation, hypoglycorrhachia may be milder. Genetic testing is often needed for diagnosis (69).

Other Disorders

Fructose 1,6-bisphosphatase deficiency, a rare, potentially life-threatening disorder of gluconeogenesis, presents within the first few days of life with respiratory abnormalities, hypotonia, lethargy, hepatomegaly, irritability, and convulsions. Laboratory findings reveal lactic acidosis, ketosis, hypoglycemia, elevated plasma concentrations of alanine, and the presence of abnormal urinary organic acids with glycerol and glycerol-3-phosphate (70). The FBP1 gene is located at 9q22.2–q22.3 (71). Neurologic sequelae can be prevented by avoidance of hypoglycemia.

Hereditary fructose intolerance (fructose 1,6-biphosphate aldolase deficiency) may be seen in the neonatal period in infants who are formula fed and given fructose or sucrose early in life. Symptoms include profound hypoglycemia, emesis, and convulsions. If the disease is readily diagnosed, fructose and sucrose can be eliminated from the diet before significant cerebral injury occurs (70).

Mitochondrial Disorders

Disorders of energy metabolism typically present with later-onset epilepsy outside of the immediate newborn period. However there are exceptions to the rule, especially when discussing the ever-growing array of mitochondrial phenotypes.

Mitochondria are the cell's energy factories, though they also have a key role in initiating apoptosis, and reactive oxygen species formation and removal. When not functioning properly, organs most dependent on cellular energy show symptoms—especially the brain. While multi-organ involvement and lactic acidosis were initially described as sine qua nons of the disease, these findings are not reliably present and the vast majority of patients do not present with the classically described syndromes. These phenotypes, such as MELAS, myoclonic epilepsy with ragged-red fibers (MERRF) and at least 10 others, created order to a set of novel and often unrelated symptoms prior to our current knowledge of the disease. We now know that almost any unexplained neurologic symptom can be due to mitochondrial dysfunction, especially refractory epilepsy. The epilepsy may occur in isolation, or with other neurologic problems including optic nerve disease, retinal pigmentary changes, hearing loss, developmental delays, neuropathy, and myopathy. Myoclonic epilepsy has been associated with mitochondrial disease, but patients with almost any seizure type, including generalized epilepsy, are seen (72).

These conditions typically occur due to genetic abnormalities leading to aberrant mitochondrial function. Over 1500 nuclear DNA (nDNA) genes are involved in mitochondrial formation and function, along with maternally inherited mitochondrial DNA (mtDNA) providing an additional 37 genes. Thus, most cases of mitochondrial disease are autosomal recessive in inheritance, and <20% have a maternal mtDNA-based inheritance pattern. Diagnostic testing initially involves looking for a combination of biochemical abnormalities in plasma amino acids, acylcarnitines, lactate, pyruvate, and urine organic acids (73).

While biochemical and pathologic studies of mitochondria in muscle and other tissue are at times needed to provide a diagnosis, advances in genomic medicine has led to the availability of a wide array of next-generation sequencing testing for mitochondrial disease. For some patients, diagnosis is

routinely made using DNA testing, circumventing the need for invasive studies.

Treatment varies and includes preventing worsening during metabolic or physiologic stresses, avoiding mitochondrial toxins and poisons, use of select cofactors and supplements, and providing symptomatic care (74).

Pyruvate Dehydrogenase Deficiency

The mitochondrial pyruvate dehydrogenase (PDH) complex is composed of three enzymes: pyruvate decarboxylase (E1), dihydrolipoyl transacetylase (E2), and dihydrolipoyl dehydrogenase (E3). The E1 enzyme is itself a complex structure, a heterotetramer of two α and two β-subunits. The E1 α-subunit is particularly important, as it contains the E1 active site. Mutations in the PDHA1 gene (Xp22.2–p22.1) encoding for this region are the most common cause of PDH deficiency (75).

PDH deficiency has a wide variety of clinical presentations, ranging from acute lactic acidosis in infancy with severe neurologic impairment in affected males to a slowly progressive neurodegenerative disorder in some males and more commonly females. Structural abnormalities, such as agenesis of the corpus callosum, are often present on neuroimaging (76). Epilepsy frequently occurs and includes infantile spasms and myoclonic seizures. EEG findings include multifocal slow spike–wave discharges (77). The ketogenic diet may benefit these patients.

Pyruvate Carboxylase Deficiency

Pyruvate carboxylase is a biotin-responsive enzyme that converts pyruvate to oxaloacetate in the citric acid cycle. Two predominant clinical presentations occur with pyruvate carboxylase deficiency. The neonatal type (type B) manifests with severe lactic acidemia and death in the first few months of life. The infantile and juvenile type (type A) begins in the first 6 months of life with episodes of lactic acidemia precipitated by an infection. Developmental delay, failure to thrive, hypotonia, and seizures, including infantile spasms with hypsarrhythmia, may be seen (78). A benign form (type C) also has been described with recurrent metabolic acidosis and normal neurologic development (79).

Seizures are related to the energy dysfunction that occurs secondary to Krebs cycle dysfunction. Treatment with the ketogenic diet or corticotropins may markedly exacerbate the disorder and should be avoided (80,81).

Leigh Syndrome

Leigh syndrome (subacute necrotizing encephalomyopathy) is both a clinical and radiologic phenotype and may be related to various metabolic defects, including syndromic and nonsyndromic mitochondrial disease, and PDH deficiency. Biochemical defects in both nuclear and mitochondrially encoded genes have been identified with this condition. It is genetically heterogeneous, and depending on the etiology, may be autosomal recessive or dominant, X-linked, or maternally inherited (82).

The clinical presentation is often acute to subacute, involving regression, cranial nerve and bulbar dysfunction, progressive hypotonia, lactic acidosis, and failure to thrive. The disease progresses with spasticity and central respiratory failure. Neuroimaging shows bilateral, fairly symmetric, basal ganglia, thalamic, and midbrain lesions that can fluctuate in severity. Varying degrees of white matter lesions may also be present along with cortical and cerebellar atrophy (83).

A variety of different seizures, including focal and generalized seizures, have been described (84). Infantile spasms and hypsarrhythmia may occur (85,86). In addition, there have been cases of epilepsia partialis continua (EPC) (87). EEG features do not appear to be distinctive enough to contribute to the clinical diagnosis of Leigh syndrome (88).

Disorders of Amino and Organic Acids Metabolism

Amino and organic acids predominantly form from the catabolism of proteins and carbohydrates. Any enzymatic defect in these metabolic pathways leads to an accumulation of potentially acidic compounds, and partial inhibition of the citric acid and urea cycles. Acidosis and hyperammonemia ensue leading to encephalopathy and, at times, seizures. These disorders, when most severe (a severe enzyme deficiency), typically present in the newborn period, especially after an infant is exposed to a protein or carbohydrate challenge in the diet. For some, this means after feeding in the first week of life, while for others it is after the introduction of solid foods. Regardless of the type of amino or organic acid disorder, the acute presentation is often the same. Milder enzyme deficiencies may present with a later sudden-onset epileptic encephalopathy (later infancy, childhood, or in the adult years) in the midst of a physiologic stressor (illness, surgery, fasting) that leads to accelerated catabolism. Thus, many of these metabolic disorders should be considered in a patient with an acute to subacute epileptic encephalopathy of later onset as well when an etiology for the problem remains unknown. With the advent and increased utilization of expanded NBS in states across this country, and internationally, many “classic” inborn errors of metabolism are now diagnosed and treated before they lead to neurologic symptoms. Conditions such as phenylketonuria (PKU), propionic or methylmalonic acidemia, and other relatively well-known amino or organic acid and fat metabolism disorders have become chronic conditions with improved neurologic outcomes due to early diagnosis and preventative care. However, there is no “standardized” NBS protocol, and the diseases screened for may vary from state to state and country to country. Thus, while many inborn errors of metabolism may now be excluded by the extended newborn screen, familiarity with the diseases screened for in one’s area is useful. As genetic knowledge of these conditions has evolved, we have moved from making an analyte-based diagnosis from blood and urine testing to confirmatory molecular genetic diagnostic studies. The treatment for all of these diseases is often very similar in the acute encephalopathy period—correct any metabolic derangements (acidosis/hyperammonemia), stop the introduction of the toxic substance by making the patient NPO, stop catabolism with dextrose-containing fluids, and prescribe any metabolic scavengers if needed. Below we discuss a few of the disorders where seizures are a prominent feature.

Phenylketonuria

One of the most frequent autosomal inborn errors of metabolism, occurring in 1 in 10,000 to 15,000 live births, PKU is caused by a deficiency in hepatic phenylalanine hydroxylase (89). As a consequence of the metabolic defect, toxic levels of the essential amino acid phenylalanine accumulate.

Currently, diagnosis is typically made with NBS, and in fact, this was the condition that led to the advent of NBS by Dr. Robert Guthrie in the 1960s. NBS is able to diagnose 100% of these patients. If the patient has not received NBS, routine amino acid analysis in plasma will identify elevated phenylalanine (90).

PKU occurs due to mutations in the PAH gene (12q23.2). Mutations in this gene account for more

than 99% of cases (91).

If untreated, severe mental retardation, behavioral disturbances, psychosis, and acquired microcephaly can result. Seizures are present in 25% of affected children. The majority of children with PKU (80% to 95%) are also found to have abnormalities on the EEG. An age-related distribution of EEG findings and seizure types has been observed since a 1957 report by Low et al. (92). Infantile spasms and hypsarrhythmia predominate in the young infant. As children mature, tonic–clonic and myoclonic seizures become more frequent, and the EEG evolves to mild diffuse background slowing, focal sharp waves, and irregular generalized spike and slow waves (93,94). Donker et al. (95) showed proportionate increases in delta activity as levels rose during phenylalanine loading.

Primary treatment is a phenylalanine-free diet. With early detection and institution of this diet, the neurologic sequelae of hyperphenylalaninemia can be prevented or significantly minimized (96).

Maple Syrup Urine Disease

Maple syrup urine disease (MSUD) is an autosomal recessive condition due to a defect in the branched-chain α-keto acid dehydrogenase complex (BCKAD), and was first reported by Menkes et al. in 1954 (97).

The enzyme defect leads to accumulation of the branched-chain amino acids—valine, leucine, isoleucine—and their keto acids in body tissues and fluids. This disease is now tested for in most extended NBS panels and diagnosed prior to the onset of symptoms.

The BCKAD enzyme complex has four components, and three genes (BCKDHA/19q13.1–q13.2, BCKDHB/6p22–p21, and DBT/1p31) have been identified and mutations in these genes make up over 95% of cases (98).

Feeding difficulties, irritability, and lethargy are observed during the first few weeks of life. If left untreated, these signs may progress to stupor, apnea, opisthotonos, myoclonic jerks, and partial and generalized seizures. A characteristic odor can be detected in the urine and cerumen, but this may not be detectable until several weeks after birth. Milder variants of MSUD present with poor growth, irritability, or developmental delays later in infancy or childhood (1).

Laboratory testing reveals a metabolic acidosis and elevated blood and urine ketones. Hypoglycemia and hyperammonemia are rarely present in this disease. Ferric chloride testing of the urine causes a gray-green reaction, and the 2,4-dinitrophenylhydrazine test is positive. A marked elevation in branched-chain amino acids/branched-chain keto acids in the plasma, urine, and CSF amino acid profile is observed, and the presence of L-alloisoleucine is pathognomonic for this condition. Definitive testing can be performed by enzyme assay and molecular genetic studies (99).

The EEG shows diffuse slowing and a loss of reactivity to auditory stimuli. The "comb-like rhythm" characteristic of MSUD was initially reported by Trottier et al. in 1975, when bursts of a central mu-like rhythm were observed in four affected patients (100). Tharp described resolution of this pattern in an affected infant when dietary therapy was initiated (101). Korein et al. (100) observed a paroxysmal spike and spike–wave response to photic stimulation in 7 of 15 affected patients.

Pathologic studies reveal diffuse myelin loss and increased total brain lipid content. Cystic degeneration of the white matter associated with gliosis is observed. Disordered neuronal migration may occur with heterotopias and disrupted cortical lamination.

Acute treatment is aimed at counteracting the effects of hypoglycemia, acidosis, and ending

catabolism. Dialysis or exchange transfusion rarely is necessary. Dietary therapy with protein restriction, thiamine supplementation, and elimination of branched-chain amino acids from the diet is the mainstay of treatment (99).

Histidinemia

Histidinemia or histidase deficiency is also associated with infantile spasms and myoclonic seizures. Other features include developmental delay and an exaggerated startle response. A diet low in histidine may be partially beneficial.

Isovaleric Acidemia

This condition is screened for by extended NBS. Symptoms develop during the neonatal period in half of the children with isovaleric aciduria (gene locus 15q14–q15). The presentation typically involves poor feeding, vomiting, dehydration, and a progressive encephalopathy manifested by lethargy, tremors, seizures, and coma. Depressed platelets and leukocytes may be seen, and the urine odor has been described as similar to that of "sweaty feet." Cerebral edema is present, and seizures are most often partial motor or generalized tonic. The EEG shows dysmature features during sleep. Distinctive biochemical findings include metabolic acidosis, ketosis, lactic acidosis, and hyperammonemia. High urine concentrations of isovalerylglycine in urine organic acids and isovalerylcarnitine in acylcarnitine analysis are diagnostic. Genetic testing is clinically available (102).

Propionic Acidemia

This condition is screened for by extended NBS. The symptoms of propionic acidemia also appear during the neonatal period, with 20% of affected newborns having seizures as the first symptom. Characteristic features include vomiting, lethargy, ketosis, neutropenia, periodic thrombocytopenia, hypogammaglobulinemia, developmental retardation, and intolerance to protein. Patients may have very puffy cheeks and an exaggerated cupid bow upper lip. Mutations have been identified in both the α-subunit (13q32) and β-subunit (3q21–q22) of propionyl coenzyme A (CoA) carboxylase (103). Generalized seizures are typical, although partial seizures have also been reported. The EEG shows background disorganization, with marked frontotemporal and occipital slow-wave activity. In 40% of children, myoclonic seizures develop later in infancy, and older children may have atypical absence seizures. Biochemical findings include metabolic acidosis, ketosis, and elevation of branched-chain amino acids and propionic acid (104).

Methylmalonic Acidemia

This condition is screened for by extended NBS. Methylmalonic acidemia may be caused by deficiencies of the enzyme methylmalonyl-CoA mutase or adenosylcobalamin synthetic enzymes. Methylmalonic acidemia occurs in association with homocystinuria in the combined deficiency of methylmalonic-CoA mutase and MTHF: homocysteine methyltransferase (105,106). Forms responsive to vitamin B_{12} have been reported (107). Stomatitis, glossitis, developmental delay, failure to thrive, and seizures are the major features. Lesions of the globus pallidus on computed tomography or MRI are characteristic.

Diffuse tonic seizures and partial seizures with secondary generalization are the most frequent seizure types. Seizures may be characterized by eyelid clonus with simultaneous upward deviation of the eyes. In a review of 22 patients, Stigsby et al. (104) described abnormalities on the EEG in seven patients, consisting of multifocal spike discharges and depressed background activity in two, excessive generalized slowing in two, and mild background slowing with lack of sleep spindles in three. Two children were reported to have myoclonus and a hypsarrhythmic EEG pattern (108).

3-Methylglutaconic Aciduria

This condition is screened for by extended NBS. Severe developmental delay, progressive encephalopathy, and seizures are features of 3-methylglutaconic aciduria with normal 3-methylglutaconyl-CoA hydratase. This disorder results from a mutation on chromosome 9 in the gene encoding the enzyme 3-methylglutaconyl-CoA hydratase. Seizures occur in one-third of cases, and infantile spasms have been reported early in the course of the disorder. The typical organic acid abnormality includes marked elevations in 3-methylglutaconic acid and 3-methylglutaric acid in the urine (109).

3-Hydroxy-3-Methylglutaric Aciduria

This condition is screened for by extended NBS. Seizures are the presenting symptom in 10% of patients with 3-hydroxy-3-methylglutaric aciduria, a disorder caused by a deficiency in the enzyme that mediates the final step of leucine degradation and plays a pivotal role in hepatic ketone body production. The odor of the urine may resemble that of a cat. The chromosome location for this disorder is 1pter-p33 (110).

Glutaric Acidemia Type I

This condition is screened for by extended NBS. Glutaric acidemia type I is a more common autosomal recessive disorder of lysine metabolism that is caused by a deficiency in glutaryl-CoA dehydrogenase (19p13.2). Seizures are often the first clinical sign of metabolic decompensation after a febrile illness. Vigabatrin, L-carnitine, baclofen, and riboflavin supplementation have been suggested (111).

Urea Cycle Disorders

Urea cycle disorders (UCDs) occur due to partial or complete deficiencies of enzymes involved in the body's attempt to remove waste nitrogen that forms from protein and carbohydrate catabolism. The incidence of these disorders is as high as 1:25,000, though later-onset diseases from partial defects are often underdiagnosed. All of these disorders are autosomal recessive except for ornithine transcarbamylase (OTC) deficiency which is X-linked dominant, but can present in both males and females. OTC is the most common of these disorders, accounting for over 50% of patients with UCDs (112).

The clinical manifestations of most of these disorders are similar and result, at least in part, from hyperammonemia. Typically, affected newborns present with poor feeding, emesis, hyperventilation, lethargy, or convulsions 1 to 5 days after birth. These signs lead to deepening coma, with decorticate and decerebrate posturing and progressive loss of brainstem function. Brain imaging and pathology

reveal cerebral edema with pronounced astrocytic swelling (113). Later onset disease due to partial enzyme deficiencies can present with progressive spasticity of the lower extremity, episodic vomiting, or episodic fluctuating encephalopathy with or without seizures. Some individuals may be symptom free until in the midst of a physiologic stressor that leads to an acute metabolic decompensation (114).

The clinical diagnosis is confirmed by elevations in serum ammonia, absence of urine ketones, and respiratory alkalosis. In contrast, metabolic acidosis and ketosis frequently occur with disorders of organic acid or pyruvate metabolism. Characteristic findings in plasma amino and urine organic acids, along with measurements of urine orotic acid can help differentiate among the various enzymatic defects. Measurements of plasma citrulline and argininosuccinic acid may also be helpful. Definitive diagnosis is established via gene sequencing if the enzymatic defect is identified by screening biochemical tests in blood and urine. If the enzyme defect needs further defining or confirmation, biochemical analysis in skin fibroblasts or liver can be performed (115).

The EEG may show a low-voltage pattern, with diffuse slowing and multifocal epileptiform discharges (116). Two patients studied by Verma et al. (117) in 1984 demonstrated episodes of sustained monorhythmic theta activity. In patients with acute neonatal citrullinemia, a burst-suppression pattern has been described (118).

In the acute setting, hemodialysis, ammonia scavengers and protein restriction have been used to reduce serum ammonia and can be lifesaving. Protein restriction and medical therapy aimed at lowering serum ammonia are recommended in the long-term management of these children. Liver transplantation has been successful in correcting the enzyme deficiency, reducing ammonia levels, and reversing neurologic deficits in select patients (119,120).

Fatty Acid Oxidation Defects

The multienzyme, multistep process of fatty acid oxidation also occurs inside the mitochondria. Deficiencies of any of the enzymes involved, including carnitine palmitoyltransferase types I and II, may present in the newborn period (121). The infantile type of carnitine palmitoyltransferase II deficiency presents as severe attacks of hypoketotic hypoglycemia, sometimes associated with cardiac damage, culminating in sudden death. A deficiency in carnitine acylcarnitine translocase also may produce seizures, apnea, and bradycardia in the neonatal period. Seizures may infrequently occur in other defects of fatty acid oxidation, though they are not their most prevalent feature. When they occur, they are often due to associated hypoglycemia or hepatic dysfunction.

Peroxisomal Disorders

Peroxisomes play an important role in the body's ability to break down very-long-chain-fatty acids (VLCFA) including pristanic acid via beta-oxidation and phytanic acid via alpha-oxidation. They are also involved in the biosynthesis of bile acids, plasmalogens, and pipecolic acid (122).

Disorders of the peroxisome have been divided into three categories: (i) disorders of peroxisomal biogenesis (Zellweger syndrome spectrum [ZSS]), (ii) disorders of a single peroxisomal enzyme (X-linked adrenoleukodystrophy [XALD], acyl-coenzyme A [acyl-CoA] oxidase deficiency); and (iii) disorders with deficiencies of multiple peroxisomal enzymes (rhizomelic chondrodysplasia punctata). The discussion that follows is limited to ZSS and acyl-CoA oxidase deficiency. XALD is discussed with the later-onset conditions (1).

Zellweger Syndrome Spectrum

The ZSS is the most common peroxisomal disorder in early infancy, with an estimated incidence of 1:50,000. This disorder was previously categorized as three distinct diseases (ZS, neonatal adrenoleukodystrophy, and infantile Refsum disease), but is now known to be a single condition with a varying spectrum of phenotypic severity. The ZSS phenotype is caused by mutations in any of several different PEX genes involved in peroxisome biogenesis, of which at least 12 have been identified. PEX1 mutations are the most common cause of ZSS (123).

Diagnosis is made via sending a peroxisomal enzyme or VLCFA panel that measures plasma levels of VLCFA, phytanic and pristanic acid, and plasmalogens. VLCFA alone can be the initial screening test, though one must keep in mind that the degree of elevation may vary and that false negatives can occur (124). Confirmatory molecular genetic testing is available as well.

Dysmorphic features may be noted shortly after birth. Within the first week to several months of life, the affected child develops encephalopathy, hypotonia, and hyporeflexia. Seizures occur in 80% of patients, including partial, generalized tonic–clonic (rare), and myoclonic seizures, and atypical flexor spasms. Multisystem abnormalities of the brain, kidneys, liver, skeletal system, and eyes may occur. Eye abnormalities include cataracts, glaucoma, corneal clouding, optic nerve hypoplasia, pigmentary retinal degeneration, and Brushfield spots. The presence of the latter, along with hypotonia and a dysmorphic appearance, may cause confusion in the diagnosis of Down syndrome versus ZSS. Findings on neuroimaging can include pachygyria or polymicrogyria localized to the opercular region and cerebellar heterotopias (125).

Patients with ZSS have partial motor seizures originating in the arms, legs, or face. The seizures do not culminate in generalized seizures and are easily controlled with medication. The interictal EEG of patients with ZS shows infrequent bilateral independent multifocal spikes, predominantly in the frontal motor cortex and surrounding regions. Less frequently, hypsarrhythmia is observed (126).

Presently, only symptomatic treatment is available for this condition.

Acyl-Coenzyme A Oxidase Deficiency

Acyl-CoA oxidase deficiency was initially described in two siblings by Poll-The et al. (127). Clinical features included hypotonia, pigmentary retinopathy, hearing loss, developmental delay, adrenocortical insufficiency, absence of dysmorphic features, and onset of seizures shortly after birth. A deficiency in acyl-CoA oxidase was identified, resulting from a deletion in its coding gene (17q25). In children with acyl-CoA oxidase deficiency, serum VLCFA levels are elevated, whereas pipecolic acid levels are normal. Cortical malformations are generally absent, and the interictal EEG may show continuous diffuse high-voltage theta activity (128).

Tay–Sachs and Sandhoff Disease

GM2 gangliosidosis is an autosomal recessive lysosomal disorder that invariably includes seizures as a prominent feature. The infantile forms of GM2 gangliosidosis include Tay–Sachs disease, caused by a deficiency in hexosaminidase A (Hex A), and Sandhoff disease, caused by a deficiency in Hex A and B. The enzymatic defect leads to intraneuronal accumulation of GM2 ganglioside. Tay–Sachs disease does not have any extraneural involvement, and the clinical presentation is that of a progressive encephalopathy (1).

The HEXA gene is localized to chromosome 15 (15q23–q24), and mutations are found more

commonly in the Ashkenazi Jewish population of Eastern or Central European descent. The overall incidence of 1 in 112,000 live births in the general population increases to 1 in 3900 in this defined group (129).

Development appears to be normal until 4 to 6 months of age, when hypotonia and loss of motor skills are evident. Within the next several months to years, spasticity, blindness, and macrocephaly develop. The classic cherry-red spot is present in the ocular fundi of more than 90% of patients. Seizures become prominent, with frequent partial motor, complex partial, and atypical absence seizures that respond poorly to medication. Myoclonic jerks are frequent and are often triggered by an exaggerated startle response to noise (1).

The EEG is normal early in the course of disease. Gradually, background activity slows, with bursts of high-voltage delta activity and very fast central spikes. Diffuse spike and sharp-wave activity may be noted with acoustically induced myoclonic seizures. EEG amplitude declines as the disease progresses (130).

Enzymatic studies in leukocytes and skin fibroblasts reveal an isolated absence or deficiency in hexosaminidase A activity. Clinical genetic testing is available. Prenatal diagnosis and carrier detection for high-risk populations are also available (1).

Sandhoff disease is associated with a mutation of the β-subunit of hexosaminidase, (HEXB) located on chromosome 5 (5q13) (131). Unlike Tay–Sachs disease, there is no association with a particular ethnic group. Clinical presentation is similar to that of Tay–Sachs; however, distinguishing features in some patients include hepatosplenomegaly and skeletal involvement. Enzymatic testing demonstrates the diminished activity of hexosaminidase A and B. Detection of N-acetylglucosamine-containing oligosaccharides in the urine and foam cells in the bone marrow is also diagnostic. As with Tay–Sachs disease, no treatment is immediately available (1).

Krabbe Disease (Globoid Cell Leukodystrophy)

Globoid cell leukodystrophy (Krabbe disease) is another lysosomal disorder occurring in this age group and is due to a deficiency of galactocerebrosidase (GALC) enzyme activity. The GALC gene is located at chromosome 14q31 (132).

Depending on the severity of the enzyme deficiency, there are four phenotypic presentations of the disorder: (i) infantile onset, before the age of 6 months; (ii) late infantile onset, between ages 6 months and 3 years; (iii) juvenile onset, between ages 3 and 7 years; and (iv) adult onset, beginning after 7 years of age. The majority of cases begin within the first 3 to 6 months of life with irritability, poor feeding, emesis, and rigidity. Muscular spasms induced by stimulation are prominent. Blindness and optic atrophy ensue. Initially, increased tendon reflexes are present and then gradually diminish as breakdown of peripheral myelin occurs (133).

Partial or generalized clonic or tonic seizures, as well as infantile spasms, are seen, which may be difficult to distinguish from muscular spasms (134). In contrast to what is observed in many classic white matter diseases, seizures occur early in the course of Krabbe disease in 50% to 75% of infants with the disorder. EEG characteristics include a hypsarrhythmia-like pattern with irregular slow activity and multifocal discharges of lower amplitude than that typically seen with West syndrome. In a 1969 study of seven infants by Kliemann et al., six children had prominent β activity occurring independently in the posterior temporal regions and vertex that was superimposed over slower, high-amplitude waves. This activity was observed to be state dependent and to occur in long runs without any apparent clinical manifestations. In the terminal stages of the disease, little electrical

activity is detected (135).

Diagnosis is made by measuring GALC enzyme activity in leukocytes or skin fibroblasts, followed by confirmatory gene sequencing. The disease is relentlessly progressive, with death by 1 to 2 years of age (133).

GM1 Gangliosidosis Types I and II

GM1 gangliosidosis occurs due to lysosomal β-galactosidase (GLB) deficiency, and mutations in the GLB1 gene localized to chromosome 3 (3p21.33). GLB deficiency leads to the accumulation of GM1 ganglioside and degradation products in nerve cells and other tissues. In the infantile form, the affected child is initially developing typically and then has a regression in development by 3 to 6 months of age, with rapid neurologic deterioration following. Seizures develop by 2 years of age. Clinical features may include coarse facial features, hepatomegaly, bone deformities (dysostosis multiplex), visual abnormalities, hypotonia, progressive microcephaly, and hematologic abnormalities. A macular cherry-red spot can be seen. Diagnosis is determined by findings of reduced GLB enzyme activity in leukocytes or skin fibroblasts, urine galactose-containing oligosaccharides in association with elevated keratan sulfate, vacuolization in blood lymphocytes or bone marrow, and distinctive findings on long bone and spine radiographs. Definitive testing is via molecular genetics (136).

The juvenile form of the condition typically has a slower neurologic progression. Cerebral manifestations with regression of developmental milestones and visual symptoms are typically present by 2 to 4 years of age (136).

EEG features of both forms include background slowing, with increasing, irregular slow activity as the disease progresses. In type II, a fluctuating 4- to 5-cycle temporal rhythmic discharge has been observed (137).

Progressive Encephalopathy with Edema, Hypsarrhythmia, and Optic Atrophy

Progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy (PEHO) syndrome, described by Salonen et al. (138) in 1991, is characterized by infantile spasms, arrest of psychomotor development, hypotonia, hypsarrhythmia, edema, and optic atrophy. Characteristic features include epicanthal folds, midfacial hypoplasia, protruding ears, gingival hypertrophy, micrognathia, and tapering fingers. Edema develops over the limbs and face. The progressive decline seen with this disease suggests a metabolic defect, although no biochemical marker has been identified. Based on the pattern of inheritance associated with the disease, it is presumed to be an autosomal recessive disorder. Neuroimaging shows progressive brain atrophy and abnormal myelination. Hypoplasia of the corpus callosum has been reported. Seizures generally begin as infantile spasms with associated hypsarrhythmia on the EEG. Later, other seizure types may be seen, including tonic, tonic–clonic, and absence seizures. The EEG may evolve to a slow spike–wave pattern. Prognosis is poor in children with this disorder, with survival only into adolescence (139).

METABOLIC DISORDERS OF LATE INFANCY, CHILDHOOD, AND ADOLESCENCE

While many of the previously discussed disorders can have a later onset of symptoms, there are

several disorders that typically begin outside of the newborn and early infancy period. A few of these disorders are discussed below.

Neuronal Ceroid Lipofuscinoses

The neuronal ceroid lipofuscinoses (NCLs) are a group of diseases that result in storage of lipopigments in the brain and other tissues. At least five clinical subtypes have been reported, as well as rare, atypical forms, and most are transmitted as autosomal recessive traits. The disorder can present at any age, from infancy through adulthood.

The condition occurs due to a genetic defect leading to impaired lysosomal function and intra- and extralysosomal storage. Thus far at least fourteen genes (CLN 1–14) have been identified, leading to the various phenotypes, though depending on the type of mutation, there is significant overlap between age of onset and symptoms (140).

Evaluation for this condition begins with quantification of palmitoyl-protein thioesterase (PPT1) and tripeptidyl-peptidase (TPP1) enzyme levels in leukocytes. Based on the enzyme deficiency found and age of onset, targeted gene sequencing is performed. If these levels are normal or the patient has an adult onset of symptoms, electron microscopy of skin for characteristic abnormalities and/or lymphocytes for vacuoles is recommended. This approach has evolved from the previous one of obtaining a skin biopsy as the diagnostic test in all patients. In rare instances, storage product identification in cells from a rectal suction or conjunctival biopsy is necessary. With advances in genetic knowledge, this type of testing is now infrequent. A next-generation sequencing panel of the various NCL genes is available (141,142).

Visual loss is a feature of almost all except the adult form of NCL either as the presenting symptom or occurring months to years after disease onset. The infantile form typically presents between 6 and 24 months of age with developmental regression, myoclonus, ataxia, and visual failure. Other features include incoordination of limb movements, acquired microcephaly, and optic atrophy. Seizures are prominent, including myoclonic jerks and astatic, atonic, or generalized seizures. EEG features aid in the diagnosis, with an early attenuation and progressive loss of the background. Neuroimaging may show progressive cerebral and cerebellar atrophy (143).

Epilepsy begins between the ages of 2 and 4 years in the late infantile form, followed by cognitive decline, ataxia, and eventually visual failure with optic atrophy. Early development is normal or mildly delayed. Multiple seizure types develop as well, with staring, generalized tonic–clonic, myoclonic, and atonic components. As the disease progresses, irregular myoclonus evoked by proprioceptive stimuli, voluntary movement, or emotional fluctuations become prominent. A characteristic EEG pattern of occipital spikes on low-frequency photic stimulation is observed. Giant visual evoked responses and somatosensory evoked potentials are seen as well. Juvenile-onset disease presents with visual loss between the ages of 4 and 10 years. Epilepsy begins a year to several years later, with multiple seizure types. The treatment of these conditions is symptomatic. Life span varies from several years to adulthood depending on the severity of the enzyme defect (143).

Metachromatic Leukodystrophy

Metachromatic leukodystrophy is the result of a deficiency of arylsulfatase A (ASA), leading to an accumulation of lipid sulfatide. Late infantile, juvenile, and adult-onset subtypes occur with about half of patients presenting between the ages of 1 and 2 years. Hypotonia, weakness, and unsteady gait

suggestive of a neuropathy or myopathy are the most common presenting symptoms with the late-infantile form. These symptoms are followed by a progressive decline in mental and motor skills (144).

Partial seizures develop late in the clinical course in 25% of patients with the late-infantile form of metachromatic leukodystrophy and in 50% to 60% of patients with the juvenile-onset form (145,146). A progression from normal EEG features to diffuse slowing with epileptiform discharges correlates well with clinical decline (147). Bone marrow transplantation, especially if performed prior to the onset of neurologic symptoms, may be beneficial in some patients and may be accompanied by improvements in clinical neurophysiologic studies (148).

Diagnosis is initially made by quantifying ASA enzyme activity in leukocytes or cultured skin fibroblasts. Urine sulfatide activity can be measured. Molecular genetic testing of the ARSA gene (22q13.3–qter) is clinically available. Treatment is symptomatic (149).

Mucopolysaccharidoses

The mucopolysaccharidoses are a family of lysosomal storage disorders caused by a deficiency in several enzymes involved in the degradation of glycosaminoglycans. The various mucopolysaccharidoses share many clinical features, including a progressive course, multisystem involvement, organ enlargement, dysostosis multiplex, and abnormal facial features (150).

A subtype with a primarily neurologic phenotype is Sanfilippo syndrome (mucopolysaccharidosis type III), in which only heparan sulfate is excreted in the urine; four different forms have been described, each associated with a different enzymatic defect. The gene locus is 17q25.3 (151).

Generalized seizures develop in about 40% of patients with Sanfilippo syndrome, but these are often easily controlled with AEDs. Progressive dementia and severe behavioral disorders are other features. In a meticulous study of one patient, the EEG showed lack of normal sleep staging, absence of vertex waves and sleep spindles, and an unusual alteration of low-amplitude fast activity (12 to 15 Hz) with generalized slowing (152). Bone marrow transplantation was successful in several cases but not useful in others. Enzyme replacement therapy is available for some of these conditions (153).

Sialidosis Type I

Sialidosis type I, an autosomal recessive disorder of late childhood to adolescence, is characterized by progressive visual loss, polymyoclonus, and seizures. The myoclonus can be debilitating and is stimulated by voluntary movement, sensory stimulation, or excitement. Increased myoclonus with cigarette smoking and menstruation has been reported. As the disease progresses, cognitive decline, cerebellar ataxia, and blindness with optic atrophy occur. Dysmorphic features, bony abnormalities, and hepatosplenomegaly are absent. The EEG contains rhythmic spiking over the vertex, with a positive polarity overlying a low-voltage background (154). Neuroimaging shows diffuse cerebral and cerebellar atrophy. Diagnosis can be made by detection of an increase in sialic acid—containing oligosaccharides in the urine, vacuolated lymphocytes in the peripheral blood, and foamy histiocytes in bone marrow smears. Enzyme assays for deficiency of α-neuraminidase, the structural components of which are encoded on chromosome 10, offer definitive diagnosis. The gene defect has been localized to 6p21.3 (155).

Sialidosis Type II (Galactosialidosis)

Sialidosis type II, the juvenile form of this group of disorders, has features similar to those of sialidosis type I. Distinguishing characteristics are the less prominent myoclonic activity and the additional clinical features of coarse facies, corneal clouding, dysostosis multiplex, and hearing loss. Inheritance is autosomal recessive, and a higher incidence of this form of the disease is found in Japan. In the majority of cases, a partial deficiency of GLB can be seen in addition to neuraminidase deficiency (galactosialidosis), which may be the result of a defect in protective protein; the gene locus coding for this protein is 20q13.1. The EEG contains moderate-voltage generalized 4 to 6 per second paroxysms (156).

Gaucher Disease Type III

Three types of Gaucher diseases are known: type I, a chronic form with adult onset; type II, a rare form associated with infantile demise; and type III, a chronic form with neurologic involvement. These disorders result from a mutation in the gene encoding acid β-glucosidase (1q21), which leads to accumulation of glucosylceramide in the lysosomes of cells in the reticuloendothelial system (157). In the rare type III form, hepatosplenomegaly may be present from birth or early infancy, which may cause type III to be confused with the more common type I form of Gaucher disease. When neurologic symptoms develop in childhood to early adulthood, type III can be clearly distinguished from type I, in which cerebral features are absent. Frequent myoclonic jerks and tonic–clonic seizures ultimately develop. A supranuclear palsy of horizontal gaze is present in the majority of cases and is an important diagnostic sign. Generalized rigidity, progressive cognitive decline, and facial grimacing may be present. Paroxysmal EEG abnormalities may be seen prior to the onset of convulsions, with worsening as the disease progresses; diffuse polyspikes and spike–wave discharges are also seen. The most characteristic EEG findings are rhythmic trains of spike or sharp waves at 6 to 10 per second (158). The diagnosis can be made by the clinical findings in combination with Gaucher cells detected in the bone marrow. Another laboratory abnormality is an elevated serum acid phosphatase. Unlike type I disease, which is prevalent in the Ashkenazi Jewish population, type III is reported predominantly in Sweden. A multimodal approach is suggested with enzyme replacement therapy and deoxynojirimycin analogs aimed at blocking the synthesis of glucocerebroside to lessen the systemic manifestations. Therapeutic trials with bone marrow transplantation have shown some success in improving CNS manifestations of Gaucher disease type III (159).

Neuroaxonal Dystrophies

Axonal dystrophies include infantile neuroaxonal dystrophy, pantothenate kinase–associated neurodegeneration (formerly Hallervorden–Spatz disease), and Schindler disease. Pantothenate kinase-associated neurodegeneration is not discussed here, as seizures are not a prominent feature.

Infantile neuroaxonal dystrophy (Seitelberger disease) is an autosomal recessive disorder affecting both the central and the peripheral nervous systems. Characteristic pathologic features of axonal spheroids within the peripheral and central nervous systems are seen. Clinical features begin between 1 and 2 years of age with psychomotor regression, hypotonia, and development of a progressive motor sensory neuropathy. Seizures occur in one-third of patients, with onset of convulsions after 3 years of age. The EEG finding of high-amplitude fast activity (16 to 24 Hz), unaltered by eye opening or closure, is characteristic of all children with this disorder, regardless of the occurrence of seizures. During sleep, the fast activity may persist, and K complexes are typically

absent (160). Seizure types described with infantile neuroaxonal dystrophy include myoclonic and tonic (161,162). A video–EEG case report by Wakai et al. (163) described tonic spasms and an electrographic correlate of a diffuse, one-second, high-voltage slow complex, followed by desynchronization suggestive of infantile spasms.

Schindler disease results from a deficiency in α-N-acetylgalactosaminidase (22q11). Affected patients appear normal at birth, but progressive neurologic decline becomes evident in the second year. Manifestations include spasticity, cerebellar signs, and extrapyramidal dysfunction. Generalized tonic–clonic seizures and myoclonic jerks are common. EEG abnormalities include diffuse and multifocal spikes and spike–wave complexes (164).

Mitochondrial Diseases in Older Infants and Children

An overview of mitochondrial disease in infants is outlined in an earlier portion of this chapter.

POLG1 Disease, Including Childhood-Onset Epilepsia Partialis Continua, and Alpers Disease

The mtDNA polymerase gamma (POLG) is a nuclear gene required for mtDNA replication. Over the recent past, mutations of this gene have been linked to a wide array of growing phenotypes. While many of these phenotypes do not have seizures as their primary or only feature, a phenotype with EPC as the initial and often only manifestation is known as is a form with progressive myoclonic epilepsy (165).

POLG mutations are also the principal cause of Alpers disease (166).

Alpers and Alpers–Huttenlocher diseases are characterized by a rapidly progressive encephalopathy with intractable seizures and diffuse neuronal degeneration. Seizures are often partial complex or myoclonic though they can evolve to include multiple types. The EEG may show rhythmic slowing, predominating either in the posterior or anterior derivations, sometimes admixed with periodic brush-like patterns (167). Varying amounts of liver disease is also present. Symptoms may begin at any age, and liver disease may not be present for years. Encephalopathy and liver disease can stabilize with partial resolution of symptoms. Disease onset after exposure to valproate and valproate-related worsening of existing symptoms is characteristic of this condition (168,169). There is recent debate about whether patients with encephalopathy and epilepsy of undetermined etiology need to receive POLG testing prior to initiating valproate therapy (170).

MERRF and MELAS

While we now understand that many patients with primary mitochondrial disease may not present syndromically or with maternally inherited disease, the initially described conditions designated by acronyms remain an important cause of mitochondrial disease and epilepsy. Two of these syndromic presentations of mitochondrial disease are described below.

Onset of MERRF occurs before 20 years of age, with ataxia and predominantly myoclonic seizures. Affected individuals may have short stature, neurosensory hearing loss, optic atrophy, myopathy, or encephalopathy. EEG findings may include background slowing, focal epileptiform discharges, and atypical spike or sharp and slow-wave discharges that have a variable association with the myoclonic jerks. Suppression of these discharges during sleep is characteristic. As with many of the progressive myoclonus epilepsies, giant somatosensory evoked potentials are observed.

Lactic acidosis and the presence of ragged-red fibers on muscle biopsy are common features of the diagnosis. The inheritance pattern is compatible with maternal transmission. In the majority of cases, a point mutation at position 8344 of the mitochondrial gene for transfer ribonucleic acid (tRNA)-lysine has been identified (171). Other mtDNA point mutations are also known to lead to this phenotype.

Classically, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) presents in childhood with the sudden onset of stroke-like episodes. Migraine-like headaches, progressive deafness, seizures, cognitive decline, and myopathic features may accompany these symptoms. EPC can be seen, and seizures often evolve into partial or generalized status epilepticus. Myoclonic seizures are prominent in individuals with MELAS. Strokes are often occipital in location, and seizures may present with visual auras and migraine. Lactic acid is elevated in the blood, and ragged-red fibers can be present on muscle biopsy. Four-point mutations are predominantly seen with MELAS. Three of these (3243, 3250, and 3271) affect the mtDNA gene of tRNA-leucine. The other mutation involves a coding region of complex I of the respiratory chain (172). Intravenous L-arginine has been used to prevent the morbidity of acute metabolic strokes in these patients, and its regular use has become more routine (173).

Dentatorubral–Pallidoluysian Atrophy

Dentatorubral–pallidoluysian atrophy (DRPLA) is a rare autosomal dominant disease due to a trinucleotide (CAG) expansion of the ATN1 gene on chromosome 12p (12p13.31). Clinical manifestations are dependent on the length of the unstable trinucleotide repeats and vary from a presentation of juvenile-onset progressive myoclonic epilepsy to an adult-onset syndrome with ataxia, dementia, and choreoathetosis. The juvenile form can also be variable in its presentation. In general, symptoms begin in infancy to early childhood with myoclonus, ataxia, dementia, opsoclonus, or seizures that can be generalized tonic–clonic, atypical absence, or atonic. Pathologic features are striking, with neuronal loss and gliosis in the dentatorubral and pallidoluysian structures (174).

The EEG characteristically shows bursts of slowing, irregular spike–wave discharges, and multifocal paroxysmal discharges. A photoparoxysmal response is seen, and myoclonic seizures can often be triggered by photic stimulation (175).

Congenital Disorders of Glycosylation

Congenital disorders of glycosylation (CDG) are multisystemic diseases characterized by a defect in the synthesis of N-linked glycoproteins and glycolipids. Over 50 disorders of glycosylation have now been identified leading to altered protein folding and stability (176).

CDG type Ia, phosphomannomutase-2 deficiency, is the best characterized of these syndromes (gene PMM2, 16p13.3–p13.2). The most common symptoms include infant-onset failure to thrive and hepatopathy. Developmental delays, cerebellar hypoplasia, ataxia, progressive neuropathy involving the legs, retinal degeneration, and skeletal deformities are also common. Subcutaneous tissue changes with an odd distribution of fat, retracted nipples, and odd facies, including almond-shaped eyes, have been described. Imaging studies reveal cerebellar hypoplasia. A unique pattern of coagulation changes is associated with the syndrome, including depression of factor XI, antithrombin III, protein C, and, to a lesser extent, protein S and heparin cofactor II. These changes may account for stroke-like episodes observed in affected children. Clinical neurophysiologic studies demonstrate interictal

epileptiform discharges and giant somatosensory evoked potentials. Screening for this condition involves initially assessing transferrin glycosylation status via mass spectroscopy; more sensitive testing of a variety of glycosylated proteins via a mass spectroscopy N-glycan panel is also available (177). Mass spectroscopy testing is preferred in detecting less common disorders of glycosylation.

Disorders of Peroxisome Metabolism: X-linked Adrenoleukodystrophy

XALD is an X-linked genetic defect in one of the peroxisomal membrane transport proteins. The condition occurs due to mutations in the ABCD gene (Xq28) and leads to three varied phenotypes. The childhood onset form begins in early school age with attention deficit and cognitive regression.

Partial motor seizures, often with secondary generalization, and generalized tonic–clonic seizures can occur. Status epilepticus has been the initial presenting symptom, and EPC has also been reported. Diagnosis is made by quantifying VLCFA levels in plasma, followed by gene sequencing and confirmation (178). The EEG is characteristic, with high-voltage polymorphic delta activity and loss of faster frequencies over the posterior regions (179).

Adrenomyeloneuropathy and isolated Addison disease presentations account for the other phenotypes and are typically not associated with epilepsy.

Progressive Myoclonic Epilepsies

The progressive myoclonic epilepsies are a collection of disorders presenting with the triad of myoclonic seizures, tonic–clonic seizures, and neurologic dysfunction that often manifests as dementia and ataxia. Onset generally begins in childhood through adolescence, though they may begin later in life. If myoclonic features are not prominent, children with this syndrome may be erroneously diagnosed with Lennox–Gastaut syndrome. For this reason, a careful history to detect myoclonic features is important in children with intellectual deterioration and frequent seizures (180).

Previously discussed disorders that can lead to this phenotype include mitochondrial cytopathies (especially POLG mutations, MERRF, and MELAS), sialidoses, some of the other lysosomal diseases, DRPLA, and NCL. The two disorders below are listed separately since they are atypical storage diseases and are routinely tested for via direct molecular genetic testing.

Lafora Body Disease

Lafora body disease is an autosomal recessive disease that occurs due to mutations in either the EPM2A (6q24) or EPM2B (6p22.3) genes, encoding for the proteins laforin and malin (181). Laforin prevents the accumulation of phosphate on glycogen while malin is a ubiquitin ligase that regulates laforin. Defects in these genes lead to phosphate accumulation on glycogen and glycogen precipitation. Accumulation of this unbound glycogen leads to the formation of Lafora bodies and neuronal dysfunction (182).

Symptoms typically begin in the teen years, with focal, multiregional, or generalized myoclonus. The myoclonus is brought out by action, touch, light, and stress. Generalized tonic–clonic seizures may also occur. A prior childhood history of an isolated febrile or afebrile seizure may exist. Cognitive symptoms may lag by months or years and initially include visual hallucinations, personality changes, confusion, and ataxia. The visual hallucinations frequently represent occipital

seizures (183).

Generalized bursts of spikes and polyspikes superimposed on a normal background may be seen initially on the EEG. The presence of spikes in the posterior quadrant is a distinguishing feature that suggests the diagnosis with the appropriate clinical scenario (184). As the disease progresses, the EEG becomes increasingly disorganized. A photoconvulsive response can be seen with photic stimulation.

On neuroimaging, cerebellar atrophy is occasionally observed. Intracytoplasmic inclusion bodies (Lafora bodies) are seen on electron microscopy of a skin, liver, or muscle biopsy. A negative biopsy does not exclude the diagnosis. Molecular genetic testing is the preferred route of diagnosis. There is no effective treatment for this disorder, and the average life span after onset is 2 to 10 years (183).

Unverricht–Lundborg Disease (Baltic Myoclonus)

This autosomal recessive progressive encephalopathy is characterized by relentless myoclonus and generalized seizures due to defective function of the cystatin B protein and mutations in the CSTB gene (21q22.3). Testing for a common dodecamer repeat (that leads to over 90% of cases) and gene sequencing is clinically available (185).

Onset is in childhood or adolescence with seizures that are predominantly myoclonic and frequently occur after awakening. Absence and atonic seizures are also observed. Myoclonus can become quite disabling, interfering with speech and swallowing, and is often provoked by voluntary movement and excitement. Cognition is generally retained, although a mild decline may be observed later in the disease course. A labile affect and depression are commonly seen. Cerebellar ataxia, tremors, hyporeflexia, wasting of the distal musculature, and signs of chronic denervation on electromyography may be seen as the disease progresses (186).

The EEG reveals progressive slowing, with generalized 3-to-5-per-second spike–wave-like bursts that are frontally predominant. Paroxysmal flicker responses and generalized spikes and polyspikes are seen with photic stimulation (187,188). Although this disorder occurs worldwide, it has an especially high incidence in Finland, Estonia, and areas of the Mediterranean.

Phenytoin and AEDs predominantly affecting sodium channels can worsen symptoms (189). Death occurs in the third to fourth decade of life.

Disorders of Amino Acid Metabolism: Homocystinuria

Disorders of transsulfuration include cystathionine β-synthase deficiency, the most frequent cause of homocystinuria; the gene locus is 21q22.3 (190). The condition is screened for by extended newborn testing in many states and thus treated presymptomatically. When untreated, mental retardation, behavioral disturbances, and seizures are manifestations of CNS involvement; ectopia lentis, osteoporosis, marfanoid habitus, and scoliosis are other common clinical findings (191). Some patients respond to pyridoxine therapy. Generalized seizures occur in about 20% of patients with pyridoxine-nonresponsive homocystinuria and in 16% of patients with the pyridoxine-responsive form. EEG features are relatively nonspecific, with slowing and focal interictal epileptiform discharges that may ameliorate with treatment (192). Thromboembolism, malar flushing, and livedo reticularis reflect vascular system involvement. Biochemical abnormalities include homocystinemia, methioninemia, decreased cystine concentration, and homocystinuria.

DIAGNOSTIC INVESTIGATION IN METABOLIC AND MITOCHONDRIAL DISORDERS

The diagnosis of genetically determined metabolic diseases can be complicated for many reasons. We suggest that a metabolic basis be considered for all unexplained epileptic conditions of infancy or childhood until proven otherwise. Routine interrogation of blood, urine, and CSF samples as discussed in this chapter will be informative in a significant subset of patients, and alternative treatment options may emerge. Before obtaining appropriate metabolic, biochemical, or tissue specimens, the physician should try to formulate a differential diagnosis. Age at onset, type of epilepsy, associated clinical findings, family history, ethnicity, and neurologic examination continue to be the most important considerations in initial diagnostic possibilities. Neurologists experienced in metabolic disorders can often narrow the list of possible disorders at the first clinical encounter. Therefore, a consultation with a metabolic specialist is useful before or after initial screening tests are performed.

The presence of macular cherry-red spots, abnormal appearance of the hair, or a peculiar distribution of fat over the posterior flanks or thighs immediately suggests a diagnosis of Tay–Sachs disease, Menkes disease, or CDG, respectively. Deceleration of head growth during infancy, with consequent acquired microcephaly, may imply Glut-1 transporter deficiency, another defect of energy metabolism, the infantile form of neuronal ceroid lipofuscinosis, or Rett syndrome, among other possibilities. Dislocated lenses and a seizure followed by a stroke are characteristic of homocystinuria and MOCOD. Seizures with stroke-like episodes also suggest CDG, mitochondrial disorders or OTC deficiency. Genetically determined metabolic diseases often have a saltatory historical pattern in contrast to neurodegenerative diseases, which are inexorably progressive.

Evaluation in the Absence of Overt Clinical Clues

In certain circumstances, the underlying problem will not be intuitively obvious and the patient's disorder may masquerade as a form of cryptogenic epilepsy.

Certain screening tests can be used to help narrow the differential diagnosis. A complete blood cell count with differential and platelet count should be obtained in every case. Bone marrow depression occurs in the organic acidemias, and the peripheral smear may reveal important clues such as a macrocytic anemia or vacuolated lymphocytes. A complete serum chemistry profile will uncover acidosis, and electrolyte disturbances or specific organ dysfunction. A low blood urea nitrogen may suggest a defect involving the urea cycle. Calcium and magnesium concentrations should be determined in every case. A low uric acid concentration raises the possibility of MOCOD. Ammonia elevations point toward amino and organic acidopathies when mild, and urea cycle defects when marked. Quantitative measurement of plasma amino acids and urine organic acids provide diagnostic clues about disorders of amino and organic metabolism, mitochondrial disease, UCDs and disorders of vitamin metabolism.

When faced with refractory epilepsy without an etiology at any age, spinal fluid analysis is mandatory to exclude certain treatable causes of the epilepsy. An elevated CSF protein concentration is characteristic of demyelinating and inflammatory conditions, including certain mitochondrial disorders, metachromatic leukodystrophy and globoid cell leukodystrophy. A low CSF glucose concentration is consistent with hypoglycemia caused by a defect of gluconeogenesis or Glut-1 transporter defects. Lactate and pyruvate values are elevated in CSF disorders of cerebral energy

metabolism, including PDH deficiency, pyruvate carboxylase deficiency, numerous disturbances of the respiratory chain, certain defects of neurotransmitter synthesis and Menkes disease. A low CSF lactate value may be seen in Glut-1 transporter defects. CSF amino acids can provide additional information in disorders of ammonia, amino acid, organic acid, and mitochondrial metabolism. Elevations in threonine can be seen in pyridoxal 5-phosphate-dependent seizures. Elevations in glycine may point toward glycine encephalopathy (NKHG). Abnormally low serine concentrations point to PHGD deficiency.

Spinal fluid neurotransmitter analysis should also be routine in these circumstances. This testing includes measuring the neurotransmitter amines, biopterin, neopterin, and 5-MTHF levels. A low CSF 5-MTHF concentration suggests a defect involving folate metabolism, whether due to systemic disease, another inborn error of metabolism or primary cerebral folate deficiency. Abnormal CSF dopamine, and serotonin metabolites, along with biopterin and neopterin help diagnose disorders of neurotransmitter synthesis. In addition, if a special peak of a yet unknown compound appears on high-performance liquid chromatograms (routinely performed as part of spinal fluid neurotransmitter testing), the finding is diagnostic of pyridoxine- and folinic acid–responsive epilepsy due to ALDH7A1 mutations.

More focused testing for specific disorders may also be needed. These include transferrin and glycan analysis via mass spectroscopy for disorders of N-glycosylation, urine S-sulfocysteine for sulfite oxidase or MOCOD, lysosomal enzyme analysis in leukocytes for various storage disorders or PPT1 or TPP1 levels in leukocytes for the NCLs. A peroxisomal panel in blood or at least VLCFA levels will help diagnose ZSS and XALD. In addition, urine oligosaccharides, sialic acid levels, and glycosaminoglycans help better elucidate the cause of certain storage disorders. Urine guanidinoacetate and creatine levels are sent for diagnosing disorders of creatine synthesis. Urine and spinal fluid pipecolic acid and α-AASA levels are elevated at times in pyridoxine-dependent epilepsy.

Tissue biopsy specimens also provide important information in establishing a diagnosis. Specimens of skin, peripheral nerve, and skeletal muscle may provide useful clues as well. These tissues can be sent for electron microscopy, histopathologic staining, and selective biochemical analysis. Only rarely are a liver or brain biopsy necessary. Rectal and conjunctival biopsies are infrequently performed.

At times, but less frequently, the EEG features may be sufficiently distinctive to suggest the diagnosis of a limited number of conditions (Table 31.2). In other disorders, the EEG features can help narrow the differential diagnosis. For example, a burst-suppression pattern is seen in patients with NKH, PKU, MSUD, and molybdenum cofactor/sulfite oxidase deficiency, in addition to other disorders. Some distinctive EEG features include a comb-like rhythm with 7- to 9-Hz central activity, which is seen in patients with MSUD and propionic acidemia; vertex-positive polyspikes, seen in sialidosis type I; bioccipital polymorphic delta activity, seen in XALD; and 16- to 24-Hz invariant activity, seen in those with infantile neuroaxonal dystrophy.

Table 31.2 Electroencephalographic Patterns and Their Associated Disorders

Electroencephalogram pattern	Disorder
Comb-like rhythm	MSUD, propionic acidemia
Fast central spikes	Tay–Sachs disease
Rhythmic vertex-positive spikes	Sialidosis type I
Vanishing electroencephalogram	Infantile neuronal ceroid lipofuscinosis type I
High-amplitude 16- to 24-Hz activity	Infantile neuroaxonal dystrophy
Diminished spikes during sleep	Progressive myoclonus epilepsy
Giant somatosensory evoked potentials	Progressive myoclonus epilepsy
Marked photosensitivity	Progressive myoclonus epilepsy and neuronal ceroid lipofuscinosis, particularly type II
Burst-suppression pattern	Neonatal citrullinemia, NKH, propionic acidemia, Leigh syndrome, D-glycine acidemia, MOCOD, Menkes disease, HLCS deficiency, neonatal adrenoleukodystrophy
Hypsarrhythmia	Zellweger syndrome, neonatal adrenoleukodystrophy, neuroaxonal dystrophy, NKH, PKU, congenital defect of glycosylation type III

Brain imaging provides important information, although findings are rarely specific. Progressive atrophy is associated with neuronal ceroid lipofuscinosis, mitochondrial diseases, and certain storage disorders. White matter signal abnormalities are characteristic of peroxisomal disease (especially XALD), storage disorders, some mitochondrial diseases, disorders of neurotransmitter synthesis, MOCOD, disorders of creatine transport and synthesis, and some organic acidurias. Calcification of the cerebral cortex and basal ganglia is seen with select inherited metabolic diseases. Brain MRA may show abnormal dilatation and tortuosity of intracranial blood vessels in patients with Menkes disease. Brain MRS may demonstrate elevated lactate levels in those with various mitochondrial diseases, elevated N-acetylaspartic acid in patients with Canavan disease, or depressed creatine levels in those with inborn errors of creatine metabolism.

When the clinician is asked to evaluate a child with a progressive encephalopathy manifesting with seizures and no overt clinical clues, a screening paradigm must be used. There is seemingly no limit to the number of tests that can be performed, and the financial burden of these investigations can quickly become considerable. Accordingly, we propose the following screening tests, which should be tailored to the age and symptoms at presentation.

To some extent, the differential diagnosis can be pared down by calling to mind a discrete list of diseases for each of the different epilepsy syndromes (see Table 31.1). Nevertheless, it is likely that screening evaluations will need to be performed. Table 31.3 presents metabolic diseases associated with seizures and common biochemical abnormalities. Table 31.4 presents treatable or modifiable metabolic disorders that should not be overlooked.

Table 31.3 Metabolic Diseases and Biochemical Abnormalities

Seizures and metabolic acidosis
- Pyruvate dehydrogenase complex deficiency
- Pyruvate carboxylase deficiency
- Mitochondrial encephalomyopathies
- Amino and organic acidurias
- Multiple carboxylase deficiency disorders

Seizures and hypoglycemia
- Glycogen storage diseases
- Fructose 1,6-bisphosphatase deficiency
- Hereditary fructose intolerance
- Galactosemia
- Organic acidemias
- Disorders of N-glycosylation

Seizures and hyperammonemia
- Urea cycle defects, including hyperammonemia–hyperornithinemia–homocitrullinuria disorder
- Biotinidase deficiency
- Organic acidurias
- Fatty acid oxidation disorders
- Carnitine palmitoyltransferase type I deficiency
- Mitochondrial cytopathies

Table 31.4 Treatable or Modifiable Metabolic Disorders

Category	Disorder	Screening Test(s)	Notes
Common disorders	Amino and organic acidopathies	Amino acids, plasma	Fasting or preprandial specimens preferred; urine amino acids and urine acylcarnitines should be obtained selectively
	Mitochondrial cytopathies	Organic acids, urine	
	Fatty acid oxidation disorders	Lactate/pyruvate	
	Urea cycle disorder	Acylcarnitines, plasma	
	Biotinidase deficiency	Ammonia	
		Biotinidase activity	
Require spinal fluid for diagnosis	Glut-1 transporter defects	CSF glucose	Obtain pre-LP plasma glucose for comparison
	Glycine encephalopathy (NKHG)	CSF amino acids	Obtain pre-LP plasma amino acids for comparison
	Serine deficiency (PHGDH deficiency)	CSF amino acids	Obtain pre-LP plasma amino acids for comparison
	Pyridoxine- and folinic acid–responsive epilepsy	Identification of an unknown compound peak when CSF neurotransmitter amines are tested	CSF and urine pipecolic acid, α-AASA, and CSF threonine may also be elevated
	Defects of neurotransmitter synthesis	CSF neurotransmitter amines, biopterin, and neopterin	
	Cerebral folate deficiency	CSF methyltetrahydrofolate	Need plasma folate for comparison
	Pyridoxal phosphate responsive epilepsy	CSF pyridoxal phosphate level	CSF threonine may also be elevated
Less common disorders	Disorders of creatine synthesis	Urine guanidinoacetate	Plasma levels may also be obtained
		Brain MRS	
	Sulfite oxidase/molybdenum cofactor deficiency	Uric acid, plasma	Uric acid is normal in sulfite oxidase deficiency
		Urine *S*-sulfocysteine	
	Disorders of copper metabolism	Plasma copper and ceruloplasmin	24-h urine collections may be needed
	Thyroid transporter defects	T3, free T4 and TSH	TSH alone is not an accurate screening tool

General Studies

- Complete blood cell count with differential
- Electrolytes, CO_2, BUN/creatinine, and liver enzymes (Chem-20)
- Uric acid levels in blood and urine
- Blood ammonia
- Blood lactate/pyruvate
- Plasma amino acids
- Plasma acylcarnitines
- Urine organic acids
- Electroencephalography
- MRI and MRS

Additional Tests to Consider

- VLCFA and/or peroxisomal panel (which also checks phytanic and pristanic acid levels)
- Lysosomal enzyme analysis in leukocytes
- Biotinidase level, followed by biotin administration
- CSF for

    - Routine studies, especially glucose, lactate, and pyruvate; a concomitant pre-LP plasma glucose sample is needed for comparison to accurately evaluate for GLUT1 disease, CSF and plasma glucose should be obtained on fasting specimens with the patient not receiving dextrose-containing IV fluids.
    - Amino acids; a concomitant pre-LP plasma amino acid sample is needed for comparison
    - Neurotransmitter levels including biogenic amines (dopamine and serotonin metabolites), neopterin, and biopterin. This testing automatically screens for the peak of an unknown compound seen in cases of pyridoxine-dependent/folinic acid–responsive epilepsy (this testing can even be obtained after performing a therapeutic trial of pyridoxine, folinic acid, or pyridoxal 5-phosphate)
    - 5-MTHF for cerebral folate deficiency
    - Pyridoxal 5-phosphate for PNPO deficiency
    - α-AASA levels
    - Succinyladenosine for adenylosuccinase deficiency (a disorder of purine/pyrimidine metabolism)
- PPT1/TPP1 levels for neuronal ceroid lipofuscinosis (recommended prior to obtaining skin biopsies)
- An N-glycan panel for disorders of glycosylation
- Serum copper/ceruloplasmin
- Urine guanidinoacetate and creatine for disorders of creatine synthesis or transport
- Urine S-sulfocysteine for sulfite oxidase and/or MOCOD
- Urine oligosaccharides and/or mucopolysaccharides
- Urine purine/pyrimidine analysis
- Urine α-AASA levels

Selective

- Skin biopsy for
    - Electron microscopy
    - Fibroblast culture with fibroblasts sent for enzymatic assays (mitochondrial disorders, NCLs, PDH and PC deficiencies, lysosomal storage disease)
- Muscle biopsy (mitochondrial disorders)
- Nerve biopsy (neuroaxonal dystrophy)
- MRS (mitochondrial disorders and disorders of creatine synthesis and transport)
- Bone marrow for Gaucher cells

Focused Genetic Testing

- Chromosome oligo- or SNP-array analysis (comparative genomic hybridization)
- Methylation studies of chromosome 15q12 for Prader–Willi/Angelman syndrome followed by UBE3A gene sequencing if Angelman syndrome is suspected
- Rett/MECP2 and CDKL5 gene sequencing and deletion analysis
- EPM1 (Unverricht–Lundborg/Baltic myoclonus) and EPM2A/B (Lafora body disease) testing for PME

- Select nDNA and mtDNA gene analysis for mitochondrial disease; a variety of next-generation sequencing gene panels are available
- POLG1 gene sequencing for brain–liver disease (Alpers phenotype) or EPC
- Consideration of next-generation sequencing epilepsy gene panels. The clinician needs to be aware of the genes tested and whether deletions/duplications for those genes are also assessed. This testing now routinely includes genes for many treatable or modifiable epilepsy conditions, and diagnostic results may allow one to avoid invasive testing.
- Consideration of exome sequencing

TREATMENT OF METABOLIC AND MITOCHONDRIAL DISORDERS

The treatment of seizures associated with inherited metabolic and mitochondrial diseases should focus on the metabolic disturbance. Seizures associated with hypoglycemia, hyponatremia, hypocalcemia, and hypomagnesemia respond best to correction of these disturbances and should be treated with appropriate replacement therapy. Dietary treatment is beneficial for many inherited metabolic diseases, including defects of the urea cycle, defects of fatty acid oxidation, gluconeogenic defects, aminoacidopathies, organic acidurias, and the Glut-1 deficiency syndrome and can lead to a better neurologic outcome if started early.

In particular, the ketogenic diet is effective in controlling seizures in patients with the Glut-1 deficiency syndrome, and it improves cognitive outcome in patients with PDH deficiency. Blood ketones should be monitored directly, and every effort should be made to maintain a significant ketonemia with blood B-hydroxybutyrate values around 5 mM. Urine ketone measures can be misleading and falsely reassuring.

PKU can be well treated with a diet low in phenylalanine. Protein restriction is recommended for defects of the urea cycle and most amino acidopathies, and fat restriction is advised for defects involving fatty acid oxidation. Pyridoxine-dependent epilepsy and other vitamin-responsive syndromes often respond to prompt administration of the specific vitamin or cofactor. A lactose-free diet may aid those with primary cerebral folate deficiency. Enzyme protein replacement has proved effective in patients with Gaucher disease. Bone marrow transplantation has been used to treat patients with select lysosomal disorders, mucopolysaccharidoses, and adrenoleukodystrophy. Some patients with urea cycle defects, gangliosidoses, or leukodystrophies have improved with liver transplantation.

A general rule of thumb in regards to acute treatment when any metabolic disorder leading to epilepsy is suspected as follows:

- Make the patient NPO; this prevents the intake of any potentially harmful compound in the diet.
- Begin dextrose-containing IV fluids; dextrose is used here as a dietary substrate and not just to prevent hypoglycemia. It is also a metabolic signal to the cells to end catabolism. A high glucose delivery (D10 or D20) can also be used with insulin if needed. Insulin also serves as a metabolic signal to the body to end catabolism and helps maintain normoglycemia.
- Correct any electrolyte disturbances.
- Prevent fasting and dehydration by administering IV fluids.
- Avoid medications that may worsen acidosis including lactated Ringer's, and valproic acid

(when possible).
- Begin empiric trials of pyridoxine, pyridoxal 5-phosphate, biotinidase, and folinic acid while awaiting test results.
- Consider beginning IV levocarnitine while awaiting test results.

Conventional AEDs may be useful adjuncts to the specific treatment of a metabolic disorder but are often ineffective when used alone. In some circumstances, patients with metabolic derangements or neurodegenerative disorders may worsen with AED treatment that may be contraindicated—for example, phenytoin in patients with Unverricht–Lundborg disease; corticotropin and ketogenic diet in those with pyruvate carboxylase deficiency; ketogenic diet in patients with organic acidurias; and valproate in individuals with urea cycle, fatty acid oxidation, and mitochondrial defects. Metabolites of valproate interfere with β-oxidation, and valproate use depletes carnitine stores. Valproate is also an inhibitor of mitochondrial complex 1 and 4 and can lead to a fatal hepatopathy in patients with mitochondrial POLG gene mutations. Valproate, topiramate, zonisamide, and acetazolamide are relatively contraindicated with the ketogenic diet. Kidney stones are a complication associated with the ketogenic diet, as well as with acetazolamide, zonisamide, and topiramate use. Carnitine should be considered as a supplement in patients with any metabolic disorder that presents with seizures, particularly when valproate is used. An experimental report of inhibited glucose transport with phenobarbital raises concern for its use in patients with Glut-1 deficiency syndrome.

Conclusions

Seizures are often part of the clinical picture of inherited metabolic disorders, particularly when these conditions first appear during the neonatal period or infancy. Unfortunately, the clinical presentation of seizures is seldom distinctive enough to allow immediate diagnosis. Nevertheless, the timing of onset, certain characteristic clinical features, family history, and EEG findings may facilitate recognition of the more common diagnoses (see Table 31.1). Why seizures commonly accompany some metabolic diseases and infrequently occur in others is only partially understood, but certain correlations are intuitively obvious. Defects in energy metabolism are commonly associated with seizures—for example, the Glut-1 deficiency syndrome, other hypoglycemic syndromes, and defects of pyruvate metabolism; the Krebs cycle; and the respiratory chain. Also, seizures frequently accompany inherited metabolic disorders that affect neurotransmission, such as glycine encephalopathy, pyridoxine-dependent epilepsy, and GABA transaminase deficiency. A more fundamental common mechanism may be operative in many of these conditions. For example, an alteration in the ratio of glutamic acid to GABA may exist in disorders associated with cerebral energy failure and in conditions affecting the GABA shunt. Any inherited metabolic condition in which the extracellular glutamate concentration is elevated and the extracellular GABA concentration is lowered would lower the seizure threshold. Recent studies have confirmed this speculation in patients with symptomatic hypoglycemia, NKH, and pyridoxine-dependent epilepsy.

In contrast, defects of fatty acid oxidation are less likely to be associated with epilepsy. Fatty acids do not serve as oxidizable fuels for brain metabolism. Brain function is compromised mainly when the patient is subjected to fasting and hypoketotic hypoglycemia develops. Under these conditions, the brain is deprived of its two primary fuels, glucose and ketone bodies, and disturbed consciousness and seizures may occur. An exception is short-chain acyl-CoA dehydrogenase

deficiency, which is frequently associated with seizures in the absence of hypoglycemia.

Metabolic diseases provide some important insights into the neurochemical determinants of the epileptic state. Alterations of neurotransmission and ion channels are common themes in the pathophysiology of these diverse metabolic conditions. All infants and young children seen with unexplained seizure disorders (cryptogenic epilepsy), and adolescents and adults with unexplained epilepsy that began in childhood should be evaluated for an inherited metabolic disorder. Careful study of patients will continue to identify novel inherited metabolic disorders and lead to more direct and effective treatments of these conditions.

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CHAPTER 32 CENTRAL NERVOUS SYSTEM INFECTIONS AND EPILEPSY

GAGANDEEP SINGH AND J.M.K. MURTHY

The association between central nervous system (CNS) infections and seizures and epilepsy has received little attention in the recent past as many infectious disorders have been controlled to a considerable extent in high-income countries. However, these disorders continue to pose significant health problems in resource-poor countries of the world. Moreover, infectious disorders sporadically engender interest in high-income countries owing to travel to and immigration from endemic resource-poor countries, thereby leading to imported cases.

The list of CNS infectious disorders is long, but few are noteworthy in consideration of their association with epilepsy. Meningitis (pyogenic, tubercular, and aseptic), encephalitis, cerebral malaria, neurocysticercosis (NCC), and toxocariasis are discussed herein. Human immunodeficiency virus infection is beyond the scope of this chapter.

SELECTED CNS INFECTIONS

Bacterial Meningitis

Meningitis is characterized by inflammation of the meninges, often involving the cerebrum via vasculitic infarctions or abscesses. The three most common organisms responsible for bacterial meningitis are Streptococcus pneumoniae, Neisseria meningitidis, and Hemophilus influenzae. Notwithstanding a dramatic drop in its incidence owing to the routine vaccination programs in childhood, H. influenzae type 1b remains the most common organism responsible for bacterial meningitis in the western world. In rest of the world, S. pneumoniae and N. meningitides are the commonly responsible organisms. Seizures occur in nearly a third of patients during the acute phase of infection in bacterial meningitis.

Viral Encephalitis

Encephalitis, which refers to inflammation of cerebral parenchyma, manifests with seizures, altered consciousness, behavior, and cognition, and focal neurologic deficits. Over 100 different viruses cause endemic, epidemic, or sporadic forms of encephalitis (1). The endemic forms exhibit specific geographic predilections, for example, West Nile virus, La Crosse, St. Louis, eastern and western equine encephalitis viruses in the United States, tick-borne encephalitis in Eastern Europe, Japanese B encephalitis and Nipah viruses in Asia and Murray Valley encephalitis virus in Australia. In addition, up to 60% of suspected viral encephalitis episodes remain etiologically undiagnosed (1).

Herpes viruses, including Herpes simplex type 1 (HSV-1), are the commonest cause of sporadic encephalitis worldwide (2–4). These viruses (including Varicella zoster virus, Human herpesvirus 6,

and Human herpesvirus 7) are uniquely neurotropic and can remain latent in the nervous system, particularly the trigeminal sensory ganglion for long periods of time following acute infection. HSV-1 has an affinity for involvement of inferior frontal and mesial temporal cortices. Interesting in this context is the demonstration of HSV-1 genome by polymerase chain reaction techniques in resected temporal lobe specimens from patients with intractable mesial temporal lobe epilepsy who otherwise had no prior encephalitic episodes (5). These findings have not been replicated in other studies, though (6). Similarly, genomes of another herpes virus, HHV-6, have been demonstrated in resected human epileptic tissue (7,8). The virus, HHV-6, is causally associated with rare cases of limbic encephalitis in immunocompromised individuals. In immunocompetent individuals, however, the virus remains dormant in the nervous tissue without any pathogenic repercussions. Thus, while these findings are of interest, the role of herpes virus infection in medically refractory mesial temporal lobe epilepsy apart from cases with antecedent HSV-1 encephalitis remains speculative.

Cerebral Malaria

The microparasite, Plasmodium, of which four species are known (P. vivax, P. falciparum, P. malariae, and P. ovale) is responsible for malaria. Cerebral malaria, one of its most serious forms, is associated with P. falciparum infestation. The parasite is transmitted to humans by the bite of the female Anopheles mosquito. The bite releases P. falciparum sporozoites, which undergo a series of transformations to eventually parasitize human red blood cells. The parasitized red blood cells get sequestered in the cerebral microcirculation. During this process, various inflammatory mediators, such as intracellular adhesion molecule-1 and interleukins are released, which in turn lead to microvascular occlusion, microinfarcts, and damage to the blood–brain barrier (9).

Cerebral malaria presents with fever, coma, and seizures. Seizures might occur in both cerebral malaria and uncomplicated malaria. Since malaria typically presents as an acute febrile illness in children <5 years of age, many of the seizures particularly in uncomplicated malaria may actually be febrile seizures. Moreover, seizures in cerebral malaria differ from febrile seizures of uncomplicated malaria in being prolonged, complex, and at times occurring at rectal temperatures below 38°C. The seizures are believed to be the result of sequestration of parasitized red blood cells in the cerebral microcirculation and possibly related to an up-regulation of several interleukins. Other factors associated with seizures in cerebral malaria include hypoglycemia, raised intracranial pressure, and electrolyte imbalance. The incidence of seizures in cerebral malaria varies geographically as the reported incidence in series of patients from Southeast Asia was 20% but amounted to nearly 80% in African reports (10,11). It is unclear whether these differences are true or the result of an ascertainment bias.

Neurocysticercosis

Infestation of the brain with the larval stage (cysticercus) of the macroparasite, Taenia solium, is known as NCC (12). Human beings are definitive hosts and harbor the adult tapeworm/s in their intestines, while pigs, the intermediate hosts, carry the larval stage. Humans get infested by the larval stage accidentally by ingesting Taenia eggs through fecal–oral contamination. The eggs develop into embryos, which penetrate the intestinal wall to enter the blood stream and get lodged in various organs, including brain, muscles, subcutaneous tissue, and eyes. In the brain, the larvae (cysticerci) might lodge in the cerebral parenchyma, subarachnoid space, or the ventricles. Here, they pass

through a series of pathologically distinct evolutionary stages (Fig. 32.1A– I) (13). Correspondingly in imaging studies, the cysticerci appear to pass from a live or active stage (vesicular stage on pathologic studies), that is, without any breakdown of the blood–brain barrier and little host inflammatory response in the surrounding brain parenchyma (see Fig. 32.1B and C) eventually to a dead or inactive (fibrocalcified) parasite (see Fig. 32.1H) (14,15). The intervening stage is known as the "degenerating," "transitional," or "encephalitic" stage (colloidal and granulonodular stages on pathologic studies) characterized by breakdown of the blood–brain barrier and consequent development of surrounding host inflammatory response (see Fig. 32.1D–F).

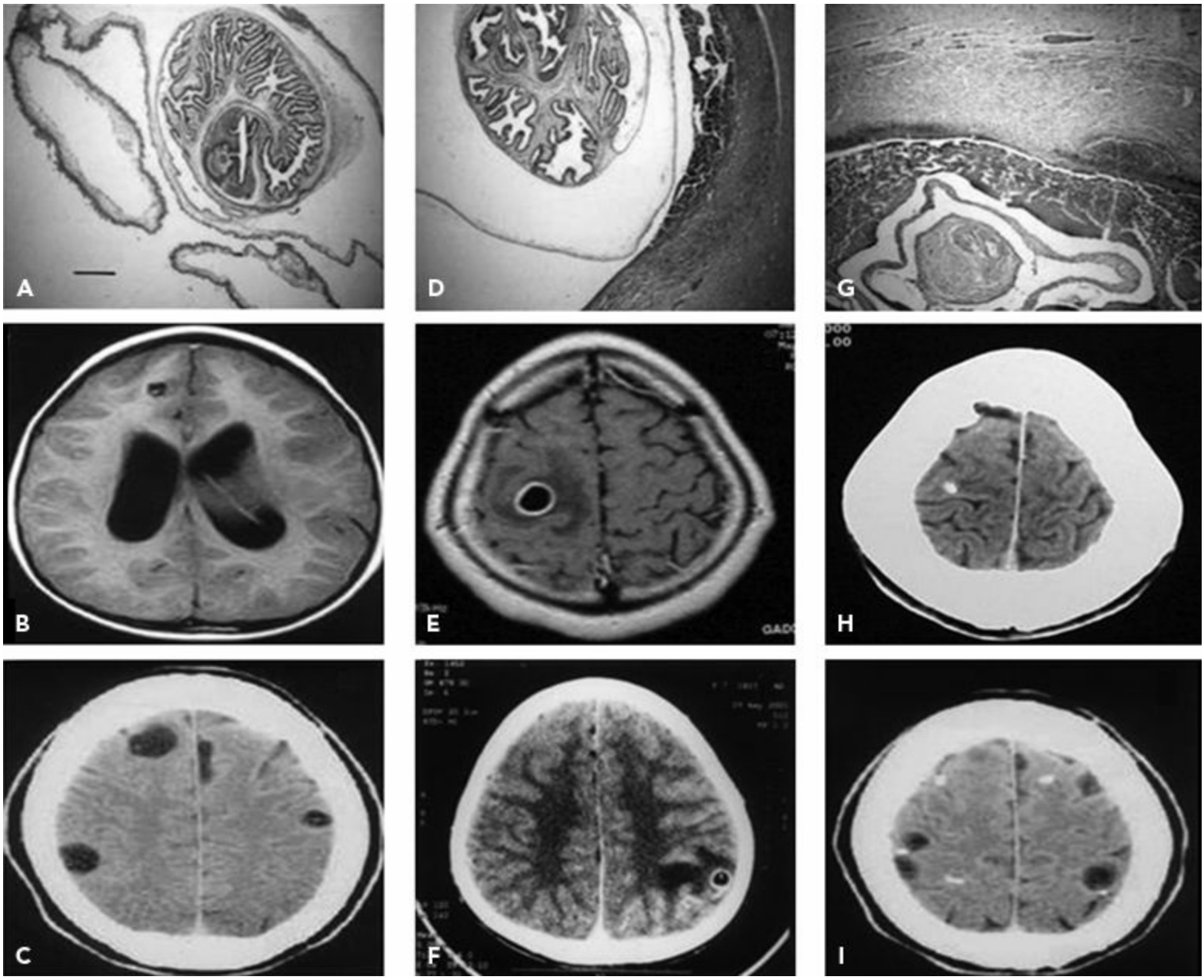


Figure 32.1. Histopathologic and imaging stages of the T. solium cysticercus in the brain parenchyma. **A:** Histologic features of the vesicular stage with a well-defined cysticercus including its extensive canalicular network and no surrounding inflammation. **B:** T1-weighted MRI showing a cyst in its active (vesicular) stage with a well-defined eccentric scolex and no surrounding edema. **C:** Unenhanced CT showing multiple active vesicular cysts. **D:** Histologic features of the colloidal stage (corresponding to the degenerating or encephalitic/transitional on imaging) with surrounding inflammation. **E:** Gadolinium-enhanced MRI demonstrating a ring-enhancing lesion in the brain parenchyma corresponding to the degenerating (transitional or encephalitic) stage. **F:** Contrast-enhanced CT showing a similar ring-enhancing lesion probably corresponding to the granular–nodular pathologic stage. **G:** Histologic depiction of the fibrocalcific parasite corresponding to the dead or inactive parasite with little surrounding inflammation. **H:** CT appearance of inactive, fibrocalcific nodule. **I:** CT demonstrating multiple NCC, some live, active and others calcified, thus multiple

stages at any given point of time. (**A, D**, and **G**, Courtesy of Alfonso Escobar, UNAM, Mexico; **B, C**, and **I**, from Singh G, Prabhakar S. Taenia solium Cysticercosis: From Basic to Clinical Science. Oxon, UK: CAB International, with permission.)

Symptoms of cysticercosis are almost always the result of brain infestation and depend on the location, stage, and number of cysts in the brain. Seizures, which occur in nearly 80% of cases of NCC, are most characteristic of parenchymal location (16). The number of cysts in the brain also has a bearing on the clinical presentation. When cysts are extremely frequent, especially in 100s, the clinical presentation is dominated by features of raised intracranial pressure, dementia, and focal neurologic deficits (17). Conversely, patients with solitary cysticercus granuloma or a small number of cysts present with few seizures, and these are usually easily controlled with antiepileptic drugs (AEDs) (18).

Other CNS Infections

Several CNS infections are notable for their association with seizures and epilepsy. CNS tuberculosis, especially when presenting with cerebral tuberculoma, bacterial brain abscess, fungal infections including cryptococcal meningitis, and subacute sclerosing panencephalitis deserve mention due to a notable frequency of both early and late unprovoked seizures (19).

BURDEN OF CNS INFECTIONS

The epidemiology of many CNS infectious disorders has changed in the recent past, and these changes have perhaps impacted their association with epilepsy. For instance, the introduction of H. influenzae type b (Hib) and S. pneumoniae conjugate vaccines has led to a decline in the incidence of bacterial meningitis in the United States from 2/100,000 in the 1990s to 1.38/100,000 in 2007 (20). Likewise, attempts to control transmission of N. meningitides meningitis and malaria in sub-Saharan Africa and of cysticercosis in South and Central Americas have led to a prefatory decline in the incidence of these disorders. At the same time, land development and increasing human traffic between endemic resource-poor countries and high-income countries have also contributed to the changing epidemiology of CNS infections. For example in the United States where T. solium was once considered eradicated, large numbers of NCC cases have been reported from states with the largest volume of Latino immigrants, that is, California, Texas, and Oregon (21). In California alone, where NCC is a reportable disease, there occurred 805 hospitalizations with a discharge diagnosis of NCC in 2009, amounting to 304 hospitalized people (estimated incidence: 0.8/100,000) with six deaths (22). Nearly 85% of those hospitalized were Latinos.

An estimated 19,000 hospitalizations and 1400 deaths with a diagnosis of viral encephalitis take place each year in the Unites States (4). Elsewhere, the burden has not been precisely investigated but is probably enormous. About 30,000 to 50,000 cases of Japanese B encephalitis are recorded annually from South and Southeast Asia (23). In sub-Saharan Africa, where over 80% of malaria episodes are recorded, an estimated 600,000 cases of cerebral malaria occur each year among children, of whom 100,000 (20%) die and 20,000 are left with serious neurologic sequelae beyond 6 months (24,25). Likewise, in this region, the estimated annual incidence of meningococcus meningitis is 20/100,000 population, amounting to 500,000 cases each year (26). The estimated burden of NCC in Latin America alone is 400,000 among a population of 75 million (27). A high prevalence of NCC, albeit of lesser magnitude, has also lately been documented in South Asia and sub-Saharan Africa (28,29).

ASSOCIATION BETWEEN CNS INFECTIONS AND EPILEPSY

Longitudinal data representing the magnitude of risk of epilepsy following a CNS infection episode are available for the Olmsted County community in Minnesota (30). In this community, the 20-year risk of unprovoked seizures was 22% following an episode of encephalitis with early (<7 days) seizures, 10% in the absence of early seizures, 13% after an episode of bacterial meningitis with early seizures, and only 2% after meningitis in the absence of early seizures. Aseptic meningitis does not appear to increase the risk of late unprovoked seizures. In incidence studies from western high-income countries, CNS infections constitute the putative etiology in 5% of new-onset epilepsies (31). Community-based figures on incidence in resource-poor countries are not available but numbers are probably even higher.

Lately, the association between several infectious disorders and epilepsy has been studied in endemically specified geographic regions. Both in Latin America and India, a number of case–control studies using serology or brain imaging as evidence of infection have demonstrated a significant association between cysticercus infection and epilepsy (32–34). These studies have consistently shown that NCC is a risk factor for roughly one-third of active epilepsies in endemic communities (32). Likewise, studies using standard case definitions for cerebral malaria from Kenya, Mali, and Gabon have established a moderate association between the cerebral malaria and epilepsy (35–37). In contrast with these association studies, in which causality between the infection and epilepsy appears plausible, studies in disparate locations (including Burundi, Bolivia, and Italy) have also suggested an association between exposure to Toxocara canis (dog roundworm) and epilepsy (38–40). It might be clarified here that the demonstration of an association does not imply causality between T. canis infection and epilepsy. For one reason, brain infection with T. canis has rarely been documented either by imaging or pathology. For another, it is possible that a confounding variable, for example, socioeconomic deprivation, which is a risk factor for both T. canis infection and epilepsy, might account for the association. Moreover, the findings of an association have not been confirmed in other regions (33).

SEIZURES IN RELATION TO CNS INFECTIONS (PROVOKED VERSUS UNPROVOKED)

Seizures are common during the active (often acute) phase of CNS infections and are referred to as "early," "acute asymptomatic," or "provoked" seizures. In the Olmsted County community, 15% of all acute symptomatic seizures were associated with CNS infections, yielding an age-adjusted incidence of 5.2/100,00 person-years (41). Early seizures occur in 33% of the cases with bacterial meningitis, 40% to 60% of HSV encephalitis, and in up to 67% of Japanese B encephalitis (1,42).

In many acute CNS infections, seizures may occur as subtle nonconvulsive seizures or as convulsive status epilepticus. Both convulsive and nonconvulsive status epilepticus have been documented in bacterial meningitis, HSV and Japanese B encephalitides, and cerebral malaria (43–45). The documentation of status epilepticus during the acute infection episode correlates with increased intracranial pressure and poor outcome (43,45).

The structural and pathophysiologic correlates of seizures during acute infections vary and include focal hemorrhagic necrosis in the cerebral cortex (HSV-1 and other encephalitides),

vasculitis and infarcts (bacterial meningitis), cerebral abscesses (pyogenic, tubercular and fungal), the release of interleukins, anti-infective medications (e.g., imipenem, flouroquinones, and isoniazid), raised intracranial pressure and disruption of the blood–brain barrier (46).

The definition of acute symptomatic seizures was recently revised (47). In the context of CNS infections, seizures might be considered as acute symptomatic (or provoked) if these occur during the phase of active infection. The categorization of acute symptomatic or provoked seizures as early seizures is easily understood in acute CNS infections (e.g., bacterial meningitis, viral encephalitis, and cerebral malaria) but becomes problematic in the case of chronic CNS infections such as NCC. It has been suggested that seizures occurring in relation to the degenerating stages (colloidal vesicular or granulonodular stages) of NCC are provoked, while those occurring in relation to the inactive (or fibrocalcified) stage are unprovoked (48). The degenerating stages are characterized by a breakdown of the blood–brain barrier and host inflammatory response surrounding the cerebral cysticercus. The cellular and molecular phenomena associated with inflammatory degeneration probably provoke seizures (49). Even so, recent follow-up studies of patients with calcified cerebral cysticerci have shown that roughly 50% continue to have seizures. Of these, in 50% without ongoing seizures, the occurrence of seizures is related to an unpredictable and sporadic release of antigenic material from the calcified cysticercus remnants, thereby engendering breakdown of the blood–brain barrier and inflammatory response in the surrounding cerebral parenchyma (50). These episodes are characterized by contrast enhancement and surrounding edema around the calcified cysticercus (Fig. 32.2). Hence, these unpredictable events underscore the problems in categorizing seizures in relation to NCC as “acute symptomatic” or “unprovoked.”

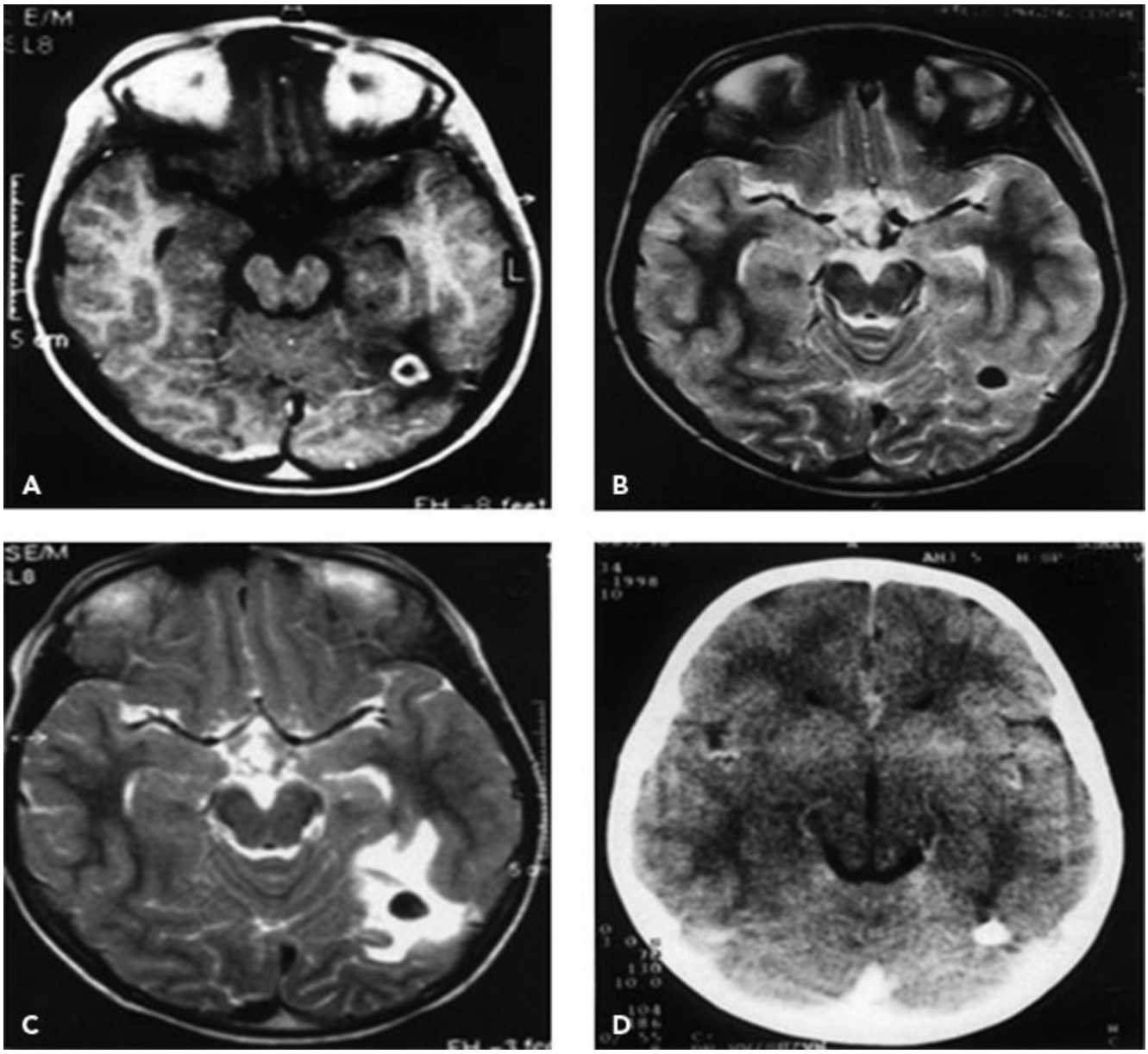


Figure 32.2. Resolution of a cysticercus granuloma and the subsequent reappearance and resolution of perilesional edema. **A:** Initial gadolinium-enhanced MRI in a patient with recent seizures showing a single annular-enhancing lesion. **B:** Follow-up T2-MRI 6 months later showing resolution with calcification. **C:** T2-MRI performed another 14 months later, when the patient developed seizure recurrence, showing perilesional edema around the calcific nodule. **D:** CT scan performed another 6 months later showing resolution of the edema around the calcific nodule. (From Singh G, Prabhakar S. Taenia solium Cysticercosis: From Basic to Clinical Science. Oxon, UK: CAB International, with permission.)

The occurrence of early seizures during the CNS infection episode increases the risk of late unprovoked seizures (amounting to epilepsy if recurrent) (30). This risk might be as high as 24% when the infection episode associated with early seizures leaves behind a structural residue in the cerebral parenchyma (51). In addition, the risk of a late seizure is particularly high when the infection episode is accompanied by status epilepticus instead of an uncomplicated seizure.

TREATMENT CONSIDERATIONS

There are few data in the form of clinical trials and observational follow-up studies to support the choice and duration of AED treatment in people with epilepsy associated with CNS infections. Treatment policies might therefore follow guidelines for treatment of symptomatic epilepsies associated with structural cerebral lesion(s). Two additional issues merit consideration. One is the

putative effect of treatment interventions in relation to the infectious disorder on the subsequent risk of development and outcome of epilepsy. The other is the range of drug interactions between AEDs and medications used to treat the infectious disorder.

The treatment of CNS infections comprises antibiotics for bacterial meningitis, antivirals for viral encephalitis, antimalarial medications for cerebral malaria, and antihelminthic agents (albendazole and praziquantel) for NCC. Other agents, for example, corticosteroids in bacterial meningitis and NCC and AEDs during the active phase of the infectious disorder, might also be administered. When administered early during the course of bacterial meningitis, corticosteroids reduce the risk of certain neurologic sequelae (e.g., sensorineural deafness), but the effect of the risk of development of unprovoked seizures has not been studied. The administration of AEDs during the acute infection episode (in bacterial meningitis, viral encephalitis, and cerebral malaria) does not appear to influence the risk of development of subsequent epilepsy.

Treatment of NCC comprises of antihelminthic agents (albendazole and praziquantel) with or without corticosteroids. A randomized, placebo-controlled trial of albendazole in people with live NCC demonstrated significantly improved clearance of the parasite with treatment (52). However, the benefits of administration of albendazole with respect to seizure outcome were less certain. Overall, there was no significant difference in the number of subjects in the treated and placebo groups who remained seizure free over a 30-month follow-up period (52). Many more controlled trials have studied the effects of albendazole and corticosteroids in people with NCC. Meta-analyses of trials of antihelminthic treatments and corticosteroids alone in solitary cysticercus granuloma have suggested that while antihelminthic treatment is associated with greater chances of seizure freedom, treatment with a short course of corticosteroid alone does not influence seizure recurrence rates (53).

The other issue of concern is the range of drug interactions between AEDs and anti-infective medications used in the treatment of CNS infections. These interactions (Tables 32.1 and Table 32.2) might adversely impact not only the treatment of the infectious disorder leading to reduced chances of a cure but also epilepsy resulting either inadequate seizure control due to reduced AED levels or conversely, AED toxicity.

Table 32.1 Effect of Anti-Infective Agents on AEDs

Anti-infective agent	Indication for use	Interaction/effect	Putative mechanism of effect	References
Meropenem	Bacterial meningitis; severe sepsis	Reduced plasma levels of valproic acid	Unknown	(54)
Chloramphenicol[a]	Brain abscess	Phenytoin and phenobarbital toxicity	Hepatic enzyme inhibition	(55)
Isoniazid[b]	CNS tuberculosis	Increased plasma levels of carbamazepine, valproic acid, phenobarbital, and ethosuccimide	Hepatic enzyme inhibition	(56–58)
Rifampicin[b]	CNS tuberculosis	Reduced plasma levels of carbamazepine, phenobarbital, phenytoin, ethosuccimide, and lamotrigine	Hepatic enzyme induction	(59)

[a]Chloramphenicol is rarely if ever used in western countries but continues to be used in some resource-poor countries.
[b]Since isoniazid and rifampicin is invariably used in combination in the treatment of tuberculosis, they balance out each other's effect on AED levels.

Table 32.2 Effect of Aeds on Plasma Levels of Anti-Infective Agents

AEDs	Interaction/effect on anti-infective agent	Mechanism of action	Indication for use of anti-infective agent	References
Phenytoin, carbamazepine	Reduced plasma levels of praziquantel	Hepatic enzyme induction	NCC	(60)
Phenytoin, carbamazepine	Reduced plasma levels of albendazole[a]	Hepatic enzyme induction	NCC	(61)

[a]The clinical significance of this interaction is uncertain.

SURGICALLY REMEDIABLE EPILEPSY IN RELATION TO CNS INFECTIONS

Heretofore, the prognosis for seizure control with standard single AEDs in disorders such as NCC was believed to be good. Furthermore, antecedent CNS infection (e.g., meningitis and encephalitis) conferred a poor prognosis following surgery for medically intractable epilepsy owing to the widespread cerebral damage sustained thereof. Thus both, the development of refractoriness to AED treatment in NCC and the potential for benefit following surgical treatment for epilepsy following meningitis and encephalitis, were not well appreciated, largely due to absence of systematic follow-up studies of CNS infections.

MEDICALLY REFRACTORY EPILEPSY IN ASSOCIATION WITH CALCIFIED CEREBRAL CYSTICERCI

Rare cases with AED-refractory seizures shown to arise from the vicinity of a calcified cerebral cysticercus and having benefited from surgical lesionectomy alone have been documented (62,63). Perhaps more common is the occurrence of mesial temporal lobe epilepsy with hippocampal sclerosis and a calcified cysticercus located within or in its close proximity (62,64). The hippocampus is not a preferred location for the cysticercus. In general, the cysts commonly lodge in the frontal and parietal lobes, in keeping with the differential proportion of blood supply delivered to various lobes of the brain (65). However, when a cyst does lodge within or close to the hippocampus, the likelihood of developing recurrent and poorly controlled seizures appears to be high, partly due to vulnerability of the hippocampus to insults and partly due to presence of neuronal circuitry conducive to epileptogenesis. In this situation, the prognosis for seizure control following standard temporal resections that include the calcified cysticercus is excellent (62).

A distinct clinical scenario is the finding of one or more calcified cerebral cysticercus lesions in association with unilateral hippocampal sclerosis upon imaging studies in people with medically refractory mesial temporal lobe epilepsy. Calcified cysticerci might be identified on imaging studies in a sizeable proportion of completely asymptomatic individuals in communities that are endemic for T. solium infestation (66). Hence, it is not surprising that a proportion of patients undergoing presurgical evaluation in epilepsy centers located in endemic regions (e.g., Brazil or India) demonstrate one or more calcified cysticerci on imaging studies. This might imply that the calcified

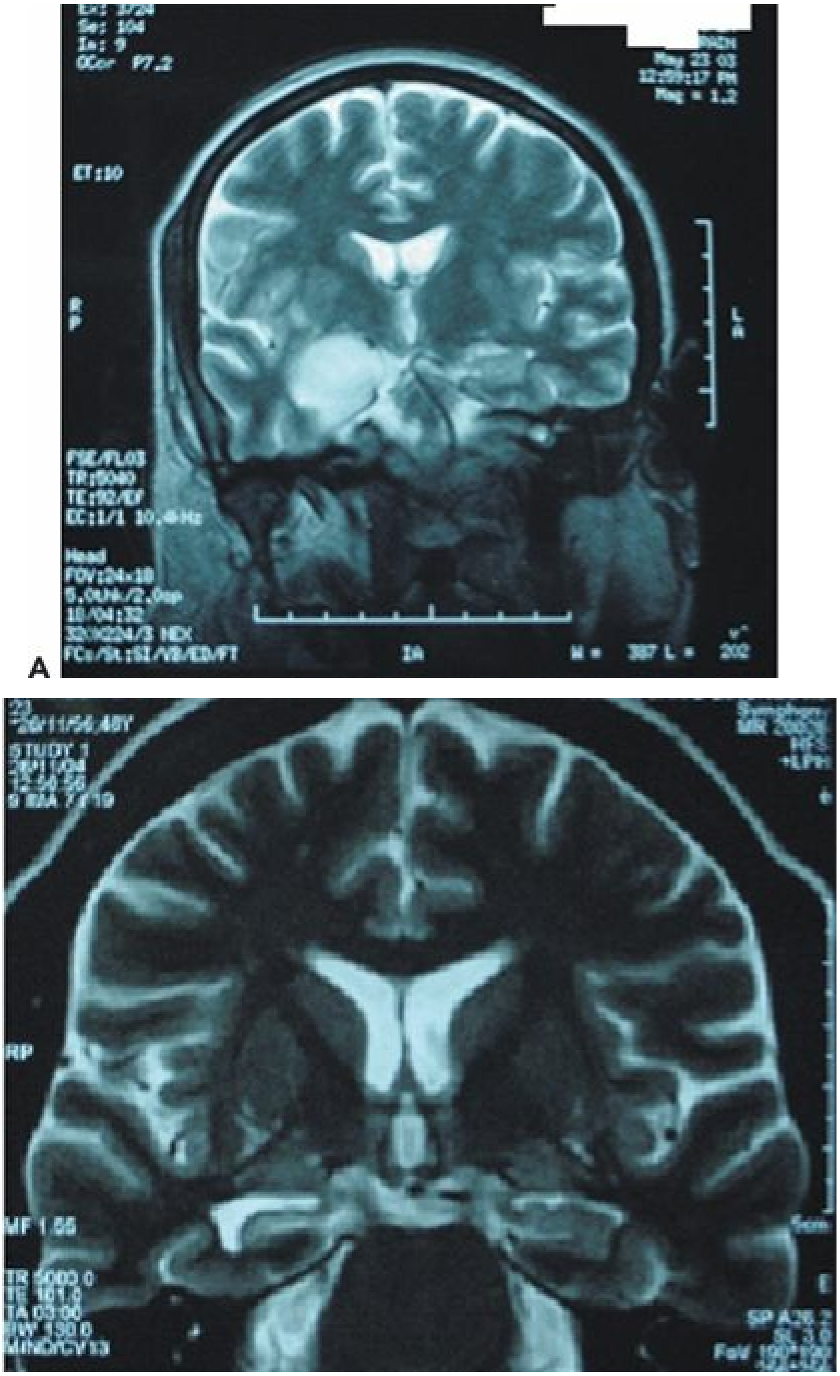
cysticerci are detected as mere coincidental findings on imaging studies in people with hippocampal sclerosis.

A cross-sectional study at a Brazilian epilepsy center found a significant association between calcified cysticerci and hippocampal sclerosis but not other substrates for surgically remediable epilepsy (e.g., tumors, developmental malformations, etc.) (67). A moot point relating to the implied association between the calcified cysticercus and hippocampal sclerosis is whether NCC interacts with the development of the hippocampal pathology (e.g., as an antecedent or as a result of kindling initiated by NCC-associated seizures) or if the occurrence of NCC and hippocampal sclerosis is purely coincidental. Another controversial area is whether the interaction influences the choice of surgical approaches to medically intractable epilepsy with hippocampal sclerosis and calcified NCC. A Brazilian report of 32 patients with hippocampal sclerosis in association with calcified NCC described Engel Class I seizure outcome in 82% following standard anteromesial temporal resection alone (68). Conversely, in a report from India, seizure freedom was observed in only one out of four patients following temporal resection alone (62). In another two patients in whom independent seizures were demonstrated to arise from both the hippocampus and the calcified NCC, complete seizure freedom was obtained following temporal resection along with lesionectomy (resection of the calcified NCC) due to suspected dual pathology. Although these data are preliminary, it is recommended that the surgical approach to hippocampal sclerosis associated with calcified NCC be decided on a case-by-case basis, keeping in mind that seizures might arise from either the hippocampus or from both, the hippocampus and the calcified NCC.

MEDICALLY INTRACTABLE EPILEPSY WITH ANTECEDENT MENINGITIS AND ENCEPHALITIS

The development of medically intractable epilepsy with antecedent meningitis or encephalitis can take place in one of the following three forms:

1. Unilateral hippocampal sclerosis with antecedent meningitis or encephalitis: The antecedent infection (more commonly meningitis and less commonly encephalitis) usually occurs before the age of five years (69). Mesial temporal lobe epilepsy (Fig. 32.3) follows the infection episode after a latent period of several years (70,71). The prognosis for seizure control following standard temporal lobe resections is excellent (72).
2. Bilateral hippocampal sclerosis with antecedent meningitis or encephalitis: Although there is a potential for independent seizure origin from either or both mesial temporal lobes, epilepsy surgery might still be a feasible option provided that a sufficient number of seizures have been recorded and are demonstrated to arise from only one side (69,73).
3. Neocortical epilepsies with antecedent meningitis or encephalitis: The infection episode (most often encephalitis) takes place after the age of five years (69). The epilepsy has an onset soon after the infection episode and has a catastrophic evolution (70). The seizure outcome following neocortical resection is not good. It is unclear whether the poor outcome is related to inadequate localization of the epileptogenic zone or to the presence of multiple epileptogenic foci.



A
B

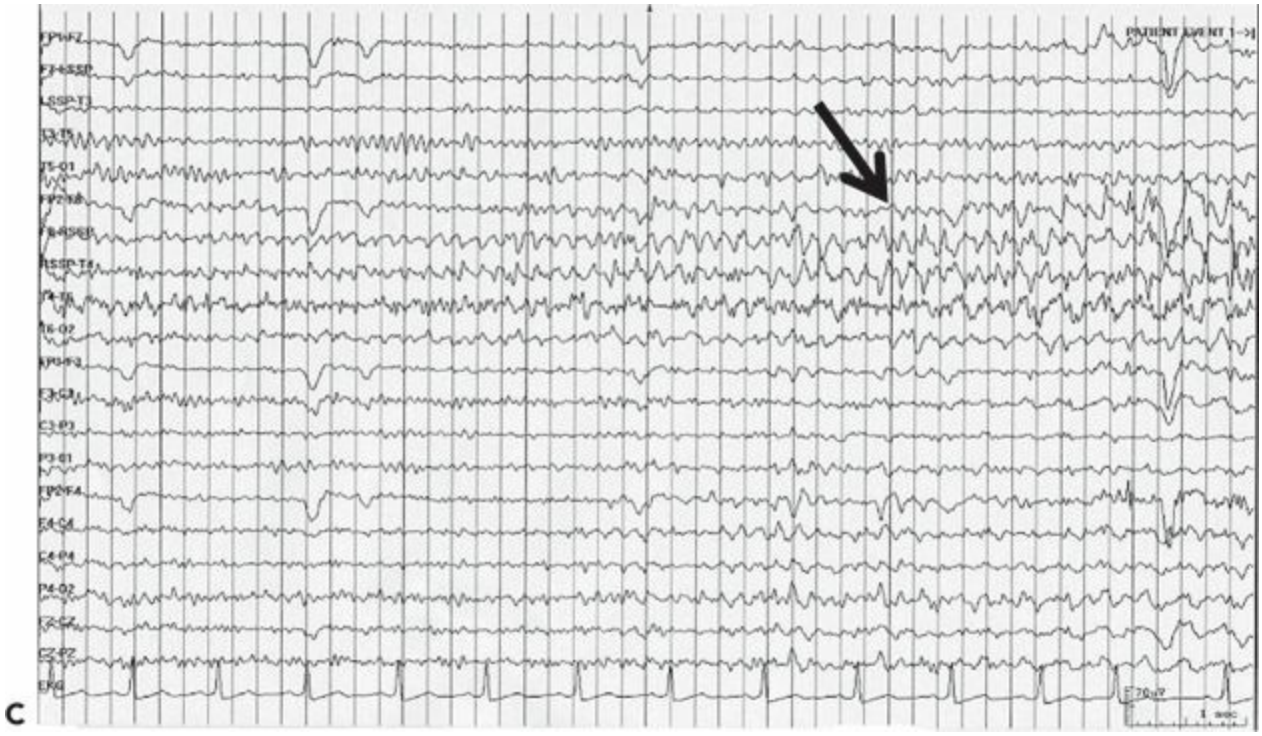


Figure 32.3. Postencephalitic epilepsy. **A:** T2-weighted coronal MRI demonstrating predominantly right mesial temporal hyperintensity and swelling during presumed HSV-1 encephalitis. **B:** Follow-up coronal T2 MRI of the same patient 2 years later revealed sclerosis within an atrophic right hippocampus. **C:** Ictal EEG in the same patient demonstrating an electrographic seizure origin from the right temporal lobe.

SEIZURE OUTCOME AND PROGNOSIS

There are virtually no systematic data on seizure recurrence rates, remission following standard AED treatment, the proportion of patients who go on to develop intractable epilepsy and mortality in people with postmeningitic/encephalitic epilepsy. In the absence of such data, it might be assumed that course and outcome of postmeningitic/encephalitic epilepsy is similar to other symptomatic epilepsies.

A follow-up study of people with mixed collection of NCC (including single and multiple, active and inactive stages) documented seizure recurrence in 40% over 2 years (74). Factors associated with seizure outcome in people with NCC have been studied in some detail. These include the stage, number (solitary versus multiple), and perhaps location of the cyst/s in the cerebral parenchyma. In follow-up studies of a solitary degenerating cysticercus granuloma, seizure recurrence rates of up to 48% over a period of 6 to 15 months have been documented (18). On the other hand, a follow-up study (mean duration of 66 months) of solitary granuloma following resolution documented a recurrence rate of 15% (75). Thus, it appears that seizure outcome might be classified according to the stage in the evolution of the cysticercus: (1) outcome during the period in which the cyst is actively degenerating and (2) outcome following resolution (i.e., the inactive stage of cysticercus). The risk of seizure recurrence is high as long as the cyst is degenerating but is reduced once the cyst resolves. In the postresolution period, the risk remains comparatively high when the cyst resolves leaving behind a calcified residue. Roughly 50% of people with a calcified NCC continue to have seizures in the postresolution period (50).

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CHAPTER 33 AUTOIMMUNE ISSUES IN EPILEPSY

AHSAN N.V. MOOSA

Recognition of the role of autoimmune mechanisms in the pathogenesis of several acquired neurologic disorders has improved our ability to treat disorders previously considered untreatable. This had the greatest impact on disorders of myelin in the peripheral and central nervous system leading to improved outcome for patients with inflammatory neuropathies and multiple sclerosis. In the field of epilepsy, the role of autoimmune mechanisms has been long overlooked. Recent research in the field of autoimmune/limbic encephalitis (LE) has yielded a variety of autoantibodies against target antigens that are considered to be closely linked to epileptogenesis and cognition (1). This raised the possibility that autoimmune mechanisms may play a role in the pathogenesis of some acquired focal epilepsy syndromes and neuropsychiatric disorders. This may have profound practical implications as treatment of epilepsy has traditionally been toward preventing seizures with antiseizure medications, with little or no role for treatment for the primary etiology of epilepsy. Furthermore, nearly one-third of patients with epilepsy do not have a specific etiology for their epilepsy (2,3). Identification of a specific etiology that has therapeutic implications may potentially affect the outcome of these patients (4).

In this chapter, we review the current role of autoimmune antibodies in epilepsy and related conditions under two sections. The first section deals with various types of autoimmune LE and the roles of newly recognized autoantibodies. The second section attempts to review the current status of autoimmune mechanisms in patients in whom the major manifestation is epilepsy. An excellent review of Rasmussen encephalitis (RE) can be found in Chapter 23. This will not be discussed in this chapter. Well-known systemic autoimmune disorders such as systemic lupus erythematosus, sarcoidosis, celiac disease, and their manifestations as seizures or epilepsy are not discussed here.

AUTOIMMUNE ANTIBODIES AND LIMBIC ENCEPHALITIS

In the past, LE was essentially synonymous with paraneoplastic LE, related to cancers (frequently small cell lung cancer) in adults with poor prognosis (5). Anti-Hu, anti-Ta, and anti-Ma were the major antineuronal antibodies associated with paraneoplastic LE; in some patients, no specific antibodies were detected. In the past decade, recognition of the other autoantibodies against neuronal surface and their frequent occurrence outside the paraneoplastic setting has revolutionized the management of patients with LE (1,6). Antibodies linked with paraneoplastic/autoimmune encephalitis can be categorized into four broad categories: (i) onconeuronal antibodies to intracellular nuclear or cytoplasmic antigens; (ii) antibodies to synaptic antigens; (iii) antibodies to neuronal cell surface antigens; and (iv) antibodies of unclear significance (1). The antibodies in the

later three categories have been shown to be associated with isolated refractory epilepsy (Fig. 33.1).

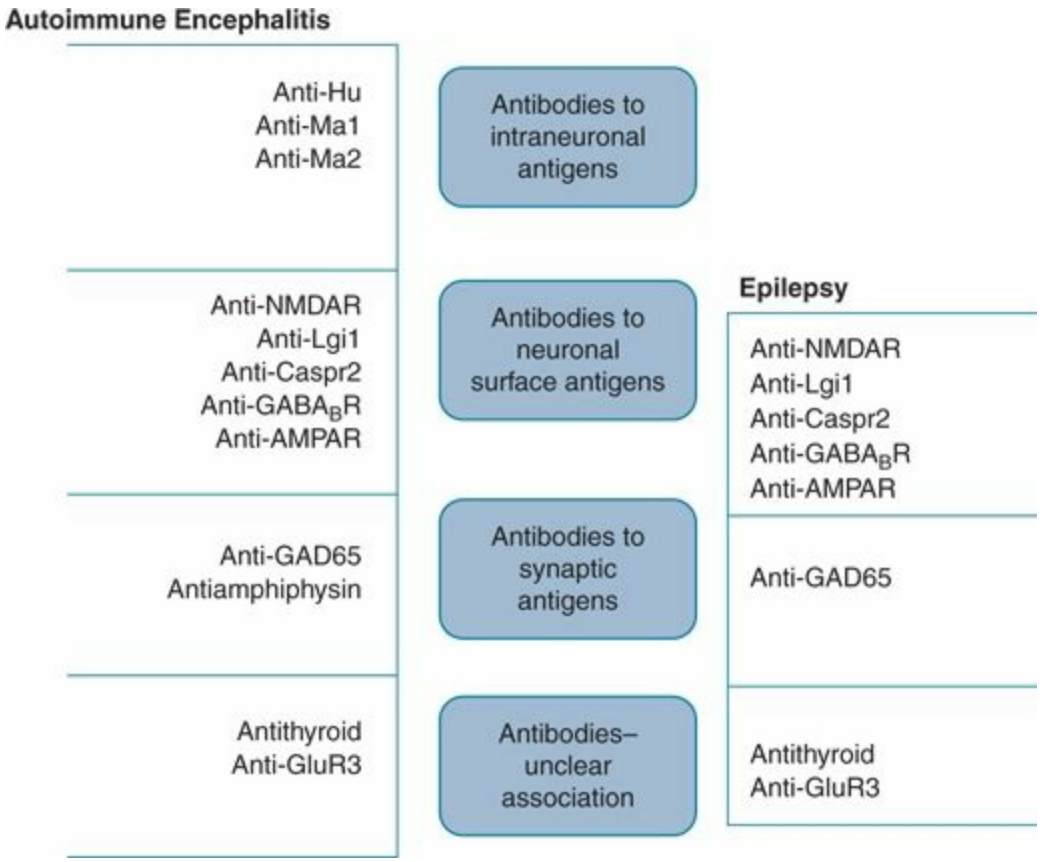

Figure 33.1. Four broad categories of autoantibodies noted in LE and refractory epilepsy.

(i) Onconeural Antibodies to Intracellular Antigens

Antibodies in this group were the first ones to be recognized in classical paraneoplastic encephalitis (5). The target antigens for the antibodies in this group include Hu, Ma1, and Ma2; these antigens reside in the cytoplasm or nucleus of the neurons (5,7,8). Because of the intracellular location of the antigens, the antibodies have poor access to these antigens and are generally not considered to be pathogenic. Most of the neurologic disorders that occur in this setting are T-cell mediated. The antibodies merely serve as a disease marker and are likely not directly involved in the neuronal injury. These antibodies are strongly linked to cancers with shared target antigens in the neoplasm and in the neurons. Presence of these antibodies in a patient with a presentation compatible with paraneoplastic syndrome warrants a diligent search and surveillance for occult tumors. Most well studied in this group are the anti-Hu antibodies, which are present in nearly 20% of patients with small cell lung carcinoma (SCLC). However, only 0.01% of patients with SCLC develop paraneoplastic features, presumably due to high tolerance to anti-Hu in normal individuals (1,9). Paraneoplastic syndromes with these antibodies include peripheral neuropathy, cerebellar ataxia, LE, autonomic disorders, and brainstem encephalitis. Recovery from these paraneoplastic syndromes is incomplete, and immunotherapies targeted to antibodies are often ineffective. Primary manifestation as chronic epilepsy is uncommon in this group of disorders.

(ii) Antibodies to Synaptic Antigens

The two classical antibodies in this group are anti-glutamic acid decarboxylase (GAD) antibodies

and antiamphiphysin antibodies. Antigens GAD65 and amphiphysin are located in the presynaptic terminals and thus are intracellular in location but are exposed to the extracellular environment during the recycling of the synaptic vesicles. Antibodies to both these antigens are associated with stiff person syndrome (10,11). The amphiphysin antibody is strongly associated with breast cancer, but anti-GAD is commonly nonparaneoplastic. Existing evidence supports both cell-mediated and antibody-mediated injury in anti-GAD antibody–associated disorders and predominantly antibody-mediated injury in amphiphysin-related conditions.

Anti-GAD Antibodies in Limbic Encephalitis and Epilepsy

Anti-GAD antibodies have been reported with multiple clinical syndromes such as stiff person syndrome, progressive encephalomyelitis with rigidity and myoclonus, ataxia, LE, and epilepsy (11–13). However, the exact pathogenic significance of the antibodies in causation of LE is debatable. In a series of 53 patients with LE, 9 (17%) were found to have anti-GAD antibodies and 10 patients had antibodies to VGKC complex (14). Patients with anti-GAD antibodies were younger, more likely to have refractory epilepsy, had less satisfactory response to immunotherapy, and also were more likely to harbor other antibodies. None of the patients with anti-GAD antibodies had neoplasms. The pathogenic role of anti-GAD antibodies (limited access to target antigen) has been questioned as GAD65 is a predominantly intracellular protein. Other yet to be characterized antibodies may play a role in the pathogenesis, and anti-GAD may be a marker for this disorder. From this perspective, the status of this anti-GAD encephalitis may be similar to antithyroid antibody–related neurologic disorders such as Hashimoto encephalopathy (HE). Anti-GAD antibodies have been studied in patients with epilepsy outside the setting of LE. In a case-controlled study of 253 patients with epilepsy, anti-GAD antibodies were noted in 15 (5.9%) epilepsy patients compared to 3 (1.5%) of 200 controls; temporal lobe epilepsy (TLE) predominated in this study (15). As noted in other studies, patients with anti-GAD antibodies were more likely to have other autoantibodies.

(iii) Antibodies to Neuronal Surface Antigens

Characterization of antibodies to neuronal cell surface antigens has advanced the field of autoimmune encephalitis significantly in the past decade (6). Research in patients with previously unknown nonparaneoplastic syndromes lead to discovery of several antibodies that have relevance to epilepsy. Some of the target antigens of these antibodies include N-methyl-D-aspartate (NMDA) receptors (16), voltage-gated potassium channel (VGKC) complex proteins (17–19), α-amino- 3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (20), and γ-aminobutyric acid B ($GABA_B$) receptors (21). The antibodies to these cell surface antigens have ready access to their targets and are likely to be pathogenic (1,6). Similarities between the symptoms of pharmacologic dysfunction of the receptors and these autoimmune disorders further strengthen the role of the antibodies in the pathogenesis. Clinical observation of recovery from the disease after immunotherapy targeted to reduce antibodies further confirms the pathogenic role of these antibodies (1).

VGKC Complex Antibodies

Antibodies to VGKC were initially recognized in neuromyotonia and later in Morvan syndrome. Later in 2001, initial reports of LE related to VGKC were reported (22). Early reports suggested that these

antibodies targeted potassium channel receptor subunits Kv1.1 and Kv1.2 (17,22). Subsequently, it was recognized in vitro studies, that antibody testing using cells expressing VGKC subunits were negative, thereby suggesting a possible role of other target antigens closely linked to VGKC (18,23). Further research in this area revealed three candidate antigens—Lgi1, Caspr2, and contactin-2. Lgi1 is a synaptic protein that binds to ADAM23 (a presynaptic protein) and ADAM22 (a postsynaptic protein), and it regulates the Kv1.1 and Kv1.2 subunits of VGKC. Caspr2 is located in the juxtanodal regions of the myelinated axons, and this along with contactin-2 and other proteins enables accumulation of VGKC subunits in the juxtanodal region. Lgi1 is primarily a CNS protein (hippocampus), and the Caspr2 is present in both the central and peripheral nervous system. The roles of the Lgi1 and Caspr2 are well established in LE, but contactin-2 was frequently noted along with other antibodies, and hence, its pathogenic significance is poorly understood (1,18,19,23).

In a series of 96 patients with "VGKC antibodies" (antibodies to VGKC extracted from mammalian brain tissue), only 3 had antibodies to potassium channel subunits (23). Majority of antibodies were directed to other proteins closely associated with VGKC: 55 patients had antibodies against Lgi1 antigen, 19 against Caspr2, and 5 against contactin-2. Remaining 18 patients had no antibodies to any of these antigens. Lgi1 antibodies are typically associated with nonparaneoplastic LE; neuromyotonia and Morvan syndrome presentations were much less frequent with Lgi1 antibodies (23). Recent reports suggest that some patients with Lgi1 antibodies may have a unique faciobrachial (sometimes crural) dystonic seizures, and this may herald the onset of LE (24,25). Sleep disorders (hypersomnia, insomnia, REM behavioral disorders) are frequent in one-third of patients. Hyponatremia was common (34 of 55 patients) in patients with Lgi1 antibodies. Two-thirds of patients with LE had medial temporal signal changes on MRI. Patients with Caspr2 antibodies had more variable manifestations including LE (7 of 19 cases), neuromyotonia (7 of 19 cases), and Morvan syndrome (3 of 19 cases). Caspr2 is also more closely linked to a paraneoplastic syndrome (thymomas). Response to immunotherapy is often good in these patients especially if they are nonparaneoplastic (18,19,23). It is interesting to note reports of mutations of genes of Lgi1 and Caspr2 being linked to seizures and encephalopathy (26,27).

Anti-NMDAR Encephalitis

Anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis was first reported in 2007 as a paraneoplastic encephalitis in young women with ovarian teratoma (16). Classical clinical features include a prodromal phase of viral illness–like symptoms, followed by behavioral and neuropsychiatric symptoms of LE (delusions, hallucination, change in mood, behavior, personality, and temporal lobe seizures). Later, decreased level of consciousness, autonomic instability, extrapyramidal disorders, and not infrequently hypoventilation requiring mechanical ventilation may ensue (16,28). Abnormal sleep patterns—most frequently insomnia and occasionally hypersomnia—may occur. Despite a severe clinical course, most patients respond to immunotherapy and tumor removal. These patients were detected to have antibodies that target the NR1 subunit of the NMDAR, in their serum and CSF. In vitro studies in rodent brain have shown that these antibodies decrease the number of synaptic NMDA receptors. Later, it was discovered that anti-NMDAR encephalitis may occur as a nonparaneoplastic disorder (29,30). Several hundred cases have been since reported in both sexes and in all age groups, including young children. In children, nonparaneoplastic NMDAR encephalitis is more common (30–32). Seizures occur in more than two-thirds of patients and are common in both children and adults. Autonomic dysfunction is less frequent in children. Most

recently, the California encephalitis project that study the epidemiology of encephalitis found anti-NMDAR encephalitis as the leading cause for encephalitis in patients aged <30 years (33).

In a series of 100 patients that included children and adults, brain MRI has been reported to be abnormal in 55% of cases. Distributions of abnormalities include cortical/subcortical T2/FLAIR signal abnormalities (most frequently in temporal lobes), 39%; cerebellar, 6%; brainstem, 6%; and basal ganglia, 5%. Contrast enhancement was noted in the cortex, basal ganglia, or meninges in 14%. CSF analysis showed pleocytosis in 95% of patients. Oligoclonal bands were reported in 26% of patients. CSF abnormalities may vary depending on the stage of the disease, with CSF pleocytosis in the early stages and oligoclonal bands in the later stages of the disease. EEG abnormalities can be nonspecific with slow wave and/or focal epileptiform abnormalities (28). Recently, a unique EEG pattern termed as "extreme delta brush" has been noted in 30% of adult patients with anti-NMDAR encephalitis (34). This pattern consists of a diffuse, delta (approximately 1 Hz) slowing with superimposed bursts of beta frequency activity in the frontal regions, thus morphologically resembling the delta brushes seen in neonates.

Treatment consists of corticosteroids, intravenous immunoglobulin, and/or plasma exchange as first-line therapy. Tumor removal is critical for rapid recovery in paraneoplastic cases. In patients with poor response to first-line therapy, treatment with cyclophosphamide or rituximab may be necessary. Response to treatment is good with over 75% (in a series of 100 patients) making substantial or full recovery. Patients with tumor that was removed early recovered better than those without tumor. Relapses may occur in 15% of patients (28).

Anti-AMPA Receptor Encephalitis

Anti-AMPA receptor encephalitis is another newly recognized cause for paraneoplastic and nonparaneoplastic autoimmune encephalitis, first reported in 2009 (20). AMPA are a form of glutamate receptors formed by tetramers of GluR1, R2, R3, and R4 subunits. AMPA receptors in hippocampus are composed predominantly of GluR1 and R2 heteromers. Using sera and CSF from patients with LE positive for immunoreactivity to neuropil antigens (negative for previously known antibodies) on tissue studies, the target antigen was determined to be GluR1/R2 receptors (1,20,35). Further studies confirmed that these antibodies decrease the number of AMPA receptors and thus are directly pathogenic. Immunohistochemistry of the tumor tissues in paraneoplastic cases confirmed expression of GluR1/R2 antigen in the tumor cells. In a series of 10 patients, the median age at presentation was 60 years. LE was the primary manifestation in these patients, presenting with a subacute memory loss, confusion, and disorientation. Seizures were reported in four patients, with refractory status epilepticus in one. CSF pleocytosis is common, and bilateral medial temporal lobe abnormalities on MRI typical of LE were noted in 80% of patients. Seven of 10 patients had underlying neoplasms—tumors of the thymus in 3, lung in 2 and breast in 2 patients (20).

Immunotherapy used in these patients was similar to treatment described earlier in anti-NMDAR encephalitis. All nine patients who received immunotherapy improved. Relapses of LE were reported in five patients. Prevention and treatment of relapses are important for long-term prognosis. Neurologic prognosis is unaffected by the tumor per se, but presence of other antibodies may influence the outcome (20). One patient with anti-GAD antibodies and another with anti-CRMP2 had poor outcome. This may indicate additional T-cell–mediated injury mechanisms, which often respond poorly to immunotherapy.

Anti-$GABA_B$ Receptor Encephalitis

Anti-$GABA_B$ receptor encephalitis was first reported in 2010 from a pool of patients with paraneoplastic/immune-mediated encephalitis negative for previously well-recognized antibodies (21). A subsequent series of 20 patients with anti-$GABA_B$ antibodies emphasized the LE presentation in 17 patients; others presentations include ataxia, opsoclonus–myoclonus syndrome, and status epilepticus (36). Similar to anti-AMPA receptor encephalitis, patients with anti-$GABA_B$ receptor encephalitis are older (median 60 years). Seizures are frequent in up to 80% of patients. Striking MRI T2/FLAIR signal abnormalities in one or both medial temporal lobe abnormalities occur in two-thirds of patients. Mild pleocytosis was noted in 68% of patients, and minimal elevation of CSF protein is common. About half of the patients with anti-$GABA_B$ receptor encephalitis had SCLC, and a quarter had other onconeuronal antibodies to antigens such as Ri, amphiphysin, or SOX1; two patients without tumor had NMDAR and GAD65 antibodies. Of 17 patients (in a series of 20) with anti-$GABA_B$ receptor encephalitis who had immunotherapy, complete neurologic recovery was noted in 7 and partial recovery in 8 patients. Presence or absence of tumor determines the long-term prognosis, worse in the former (36,37).

(iv) Antibodies of unclear significance: Antithyroid antibodies and Hashimoto Encephalopathy

Hashimoto encephalopathy (HE) was one of the early recognized entities with presumed autoimmune basis with excellent response to steroids in many cases. Unlike other cases with LE, the presentation in HE is variable. Two common presentations include acute encephalopathy with myoclonus and generalized tonic-clonic seizures, and stroke-like presentation with encephalopathy (38,39). Presence of antithyroid antibodies (anti–thyroid peroxidase and/or antimicrosomal) associated with Hashimoto thyroiditis was a clue to the autoimmune nature of the disorder. Later, it was confirmed that the thyroid antibodies per se do not have any direct pathogenic role, and they may serve merely as a marker for the autoimmune disorder. It is well known that patients with preexisting autoimmune disorders are more prone to develop other autoimmune disorders. Thus, HE may be viewed as an autoimmune neurologic disorder in a patient with Hashimoto thyroiditis. As thyroid antibodies are relatively common in general population, any altered mental status in a patient with thyroid antibodies carries the risk of being labeled as HE. Hence, many authors preferred to include treatment response to steroids as a key criterion in the diagnosis of this disorder. As the thyroid antibodies has no relevance to the disease (other than a surrogate marker), alternate terms such as “steroid-responsive encephalopathy associated with autoimmune thyroiditis” (SREAT) has been proposed (40).

In a review of 85 patients with HE, the mean age at presentation was 44 years (range, 9 to 78 years) with women 3.5 times more commonly affected than men (38). Clinical manifestations included seizures (66%), myoclonus (38%), status epilepticus (12%), stroke-like episodes (27%), and psychosis (38%). A Creutzfeldt–Jakob disease–like presentation has also been described. Mild elevations of protein in CSF are common. Brain MRI frequently show varying degrees of white matter abnormalities without any diagnostic pattern. EEG may show slowing or epileptiform abnormalities and not infrequently triphasic waves. Thyroid status ranged from hypo- to hyperthyroidism, but subclinical hypothyroidism was the most common abnormality. Of those treated with steroids, 96% improved with therapy. A remitting–relapsing course was noted in as high as 60%

of patients. As clinical features of SREAT and other autoimmune LE related to known antibodies (e.g., VGKC complex, NMDAR, etc.) overlap, all patients should undergo testing for these better established entities (40,41). Thus, the diagnosis of SREAT remains a diagnosis of exclusion.

EPILEPSY WITH AN OCCULT AUTOIMMUNE ETIOLOGY

The field of autoimmune/LE has advanced tremendously in the past decade with the discovery of newer antibodies and recognition of nonparaneoplastic entities. As seizures are a common manifestation in patients with autoimmune encephalitis, researchers attempted to study the autoimmune mechanisms in patients with refractory epilepsy. Furthermore, many of the target antigens to recently recognized antibodies were closely linked to epileptogenesis. Autoantibodies in patients with refractory epilepsy have been reported in the recent years, but the true pathogenic role of these antibodies in patients with isolated refractory epilepsy is still a matter of debate (4,42–45). As some of these autoantibodies may be present in normal population, the significance of the "positive antibodies" in the serum should be carefully interpreted. This is similar to a positive antinuclear antibody in a patient with chronic aches and pains, and trying to make sense if the patient has an underlying autoimmune disorder. Large case–control studies are required to address the significance of such results.

Autoimmune Mechanisms in Adult-Onset Temporal Lobe Epilepsy

Similarities in the involvements of substrates (temporal and other limbic structures) in TLE and LE prompted researchers to postulate LE as an initiating event in some adult-onset TLEs (46,47). As a significant proportion of adult-onset TLE do not have a precise etiology, the autoimmune hypothesis appeared exciting and was explored. Bien et al. (47) studied a series of 38 patients with adult-onset TLE (median age at onset, 37.5 years) and found a possible autoimmune etiology in 20 (53%) patients. Nine of these patients had definite preceding LE, and the other 11 had features of hippocampal swelling preceding atrophy, suggesting an inflammatory process at the onset. Referral bias and lack of control data may have affected the results in this study, but the possibility of autoimmune process as etiology in some patients with adult-onset TLE remains. However, the lack of inflammation on most surgical temporal lobectomy specimens is a major argument against an active ongoing inflammatory process. One of the plausible ways to explain the lack of inflammation on histopathology is to postulate two different phases for LE-related TLE: an acute or subacute inflammatory phase of LE and a chronic phase of TLE (46,47). The initial inflammatory phase could be for few weeks or months with a monophasic course followed by a chronic course of medically intractable epilepsy. Surgery is typically performed in the later phase thus potentially explaining the lack of active inflammation. This may also mean that anti-inflammatory immunotherapy may not be effective once chronic epilepsy is established. Whether the course of the epilepsy may be affected by early immunotherapy remains to be proven.

Febrile Infection–Related Epilepsy Syndrome

New-onset refractory status epilepticus (NORSE) without an obvious etiology is the hallmark of febrile infection–related epilepsy syndrome (FIRES) (48–50). This syndrome has been reported by

various authors under different names, including devastating epilepsy in school-age children (DESC), acute encephalitis with refractory repetitive partial seizures (AERRPS), and fever-induced refractory epileptic encephalopathy in school-age children (FIRES). Another related entity NORSE was primarily reported in adults and may be different from FIRES. In a retrospective multicenter study of 77 patients with FIRES, the median age of onset of FIRES was 8 years (49). Patients often have a prodromal febrile illness followed by explosive-onset epilepsy. Seizures are usually partial with or without secondary generalization. EEG shows multifocal epileptogenicity (commonly temporal and frontal regions) in majority of cases. Seizures are refractory despite aggressive medical therapy. Most patients require continuous intravenous sedative medications to achieve medication- induced burst suppression (49).

In the series of 77 patients with FIRES, prognosis was poor in majority. Nine patients (12%) died during the acute phase, and 93% of survivors had refractory epilepsy on follow-up. Only 12 of the survivors recovered to a relatively normal cognitive level (49). Extensive workup for infections and metabolic and genetic causes has been negative in these patients. Common abnormal findings on MRI include bilateral hyperintense signal changes in hippocampi and occasionally in the peri-insular region. Autoimmune mechanisms have been proposed as the etiology, but no definite evidence has been found to support this hypothesis; published reports with brain biopsy reported no inflammation (51). A recent study on known neuronal antibodies has not shown any markers. No treatment has been shown to have a consistent positive response. Anecdotal success with steroids or IVIG has been reported, but several patients in large series showed no response to multiple modes of immunomodulation. The pathogenesis of FIRES remains unresolved at this time.

Autoantibodies in Chronic/New-Onset Epilepsy

Autoimmune mechanisms have been explored in other types of chronic/new-onset epilepsy as well. Initial reports suggested increased occurrence of GAD antibodies in patients with epilepsy, more frequently in TLE (15). Recent studies reported the occurrence of other antibodies in patients with epilepsy.

In a recent prospective case-controlled study of 114 children with new-onset epilepsy and 65 children without epilepsy, 9.7% in the epilepsy cohort were positive for one of the autoantibodies compared to 4.6% of controls (difference not statistically significant) (52). VGKC, NMDAR, and Caspr2 were the antibodies detected; two patients had both VGKC and NMDAR antibodies detected in their serum. Seven of the 10 positive patients had been categorized as “unknown cause” based on the recently proposed etiologic categories of epilepsy by ILAE. Other three patients had “known etiologies” that include MELAS (Mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes), partial callosal agenesis and heterotopia, and febrile seizure plus syndrome. Positive antibodies in well- established genetic conditions raise concerns about “false- positive” tests. Authors of this study are appropriately cautious about the significance of the positive antibodies alerting to the possibility of an epiphenomenon secondary to neuronal injury and activated immune system (52,53). In a similar study in adults, the antibodies were noted to be equally prevalent in new-onset epilepsy as well as established cases of chronic epilepsy, arguing against this being an epiphenomenon (54). Of note, none of the patients in these studies received any immunotherapy driven by antibody testing.

Another recent retrospective study provides more compelling evidence to support autoimmune etiology with some insight into the response to treatment (55). In this case series, 32 patients with

suspected autoimmune epilepsy were studied. Recurrent medically refractory seizures were the primary manifestation in this cohort. Autoimmune etiology was supported by one or many of the following features: positive autoantibodies (91%), inflammatory findings on CSF (31%), and "inflammatory pattern" on MRI (63%). Autoantibodies detected include VGKC complexes (56%), GAD65 (22%), and CRMP-2 in two patients; and anti-NMDAR, Ma-2, and ganglionic acetylcholine receptor antibody in one patient each. Findings from this study suggest that patients with unusually high seizure burden, multifocal epilepsy, coexisting other autoimmune disorders, and prior history of tumors are more likely to have an autoimmune etiology. Majority of patients in this study (27 of 32) received immunotherapy. At a median follow-up of 17 months, 67% were seizure free and 81% reported significant improvement. Majority of the patients in this series had daily seizures despite two or three antiepileptic drugs prior to immunotherapy, and thus the improvement in seizure control is beyond expected for usual change of antiepileptic drugs, which was not restricted during the immunotherapy. Patients with shorter time before initiation of immunotherapy responded better than patients who were treated late (55). This report suggests that, it may be reasonable to consider immunotherapy such as a course of steroids or intravenous immunoglobulin in patients with evidence for autoimmunity and refractory epilepsy. Potential benefits of immunotherapy should be carefully weighed against the risks of the treatment, and the treatment for each patient should be individualized.

Positive Autoantibodies: True Positive or False Positive?

Understanding the true significance of a positive antibody test in serum has always been a problem in autoimmune disorders as these antibodies may be present in normal population or it may be a nonspecific marker of immune activation following tissue injury. In general, any positive diagnostic test should be validated by comparison with a diagnostic gold standard test. However, no such gold standard test exists in this new field of autoimmune epilepsy. In the absence of such a specific gold standard test to compare with, a definitive clinical diagnosis is critical to assign the significance of a positive autoantibody test. This is best illustrated in the experience of positive GluR3 antibodies in RE. Early reports of GluR3 antibodies in RE raised the possibility of this being antibody-mediated encephalitis. However, later reports showed that GluR3 is neither a specific nor a sensitive marker for RE (56–58). It was noted to be positive in other focal epilepsies and was concluded that these antibodies were an epiphenomenon (58). In the case of RE, the significance of the antibody test could be studied, as the diagnosis of RE could be made with reasonable confidence on clinical and radiologic grounds. In the recent reports of "autoimmune epilepsy," there is no such gold standard to determine if these antibodies are truly significant. Establishing a clinical diagnostic gold standard may be required to verify the utility of these antibody tests.

Lancaster and Dalmau (1) caution about the false-positive antibodies in serum and warn against overreliance on serum testing in LE. Antibody tests using cell-based assay are generally considered significant when both serum and CSF shows typical well-defined antibodies in a compatible clinical setting. If only serum is tested positive and CSF is negative, these researchers recommend further testing of the serum using rat brain immunohistochemistry and cultures of neurons. If the tissue studies show immunoreactivity, an autoimmune diagnosis can be made. Such approaches have been used in identifying the antibodies (NMDAR) in schizophrenia, and the differences in results of antibody positivity among different studies were considered to be due to various degrees of specificity (some based on cell-based assay alone) (1,59). Similar approaches may be required to determine the significance of these antibodies in patients with isolated refractory epilepsy.

CONCLUSION

In the field of LE, many of the unknowns of the past have been proven to be autoimmune syndromes mediated by specific autoantibodies. Similarly, it remains to be proven if some patients with epilepsy of "unknown etiology" finally get categorized to be "autoimmune epilepsy." Currently, for general neurologists and epileptologists, investigating and treating a patient with an unequivocal presentation of LE poses minimal challenges. The workup (CSF analysis, testing for autoantibodies, imaging to look for occult tumors) and aggressive immunotherapy (steroids, intravenous immunoglobulins, and/or plasma exchange, and for refractory cases, cyclophosphamide and/or rituximab) are fairly straight forward from the existing current literature. On the contrary, investigating for autoimmune etiology in patients with isolated epilepsy presentation is faced with several questions. Who should be tested? How to interpret the results? How to distinguish true- from false-positive tests? What is optimal or sufficient autoimmune therapy? Further large-scale studies are needed to answer these questions. Acute/subacute presentation with difficult to control epilepsy, unknown etiology, preexisting autoimmune disorders, prior history of neoplasms, signs of CNS inflammation on MRI, focal hypermetabolic regions on brain fluorodeoxyglucose–positron emission tomography, CSF pleocytosis, elevated neopterins or presence of oligoclonal bands in CSF may be some of the indicators that may alert to the possibility of autoimmune epilepsy (55). Autoimmune workup and a trial of immunotherapy may be considered in selected patients with strong indicators of autoimmune epilepsy.

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SECTION C DIAGNOSIS AND TREATMENT OF SEIZURES IN SPECIAL CLINICAL SETTINGS

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CHAPTER 34 FEBRILE SEIZURES

SYNDI A. SEINFELD AND MICHAEL DUCHOWNY

Children with febrile seizures usually have better outcomes than children with epileptic convulsions. Although research supports most febrile seizures as being relatively benign, it is now accepted that a subgroup of children will experience consequences.

The National Institutes of Health (NIH) Consensus Development Conference on the Management of Febrile Seizures defined a febrile seizure as an event, usually occurring between 3 months and 5 years of age, which is associated with fever (1). There cannot be an intracranial infection or defined cause of the seizure. The International League Against Epilepsy Commission gives another operational definition of febrile seizures. It defines a febrile seizure as a seizure occurring in childhood after 1 month of age that is associated with a febrile illness not caused by a central nervous system (CNS) infection (2). These definitions emphasize age specificity and the absence of underlying brain abnormalities. In clinical practice both definitions must be interpreted with caution as intracranial infection may not be readily apparent, especially in very young infants.

The documented incidence of febrile seizures, from multiple studies, is 2% to 5% in the United States and Western Europe (3,4), but higher in other countries. For example, Japan has an incidence over 8% (5), India up to 10% (6) and Guam up to 14% (7). Familiarity with the clinical manifestations and long-term prognosis of these common events is essential in caring for affected individuals. Epidemiologic studies have been especially useful in identifying features of the seizures or the patients that are at risk for adverse consequences. Understanding these factors forms the basis of proper seizure management and family counseling.

PREDISPOSING FACTORS

Genetics

There is no consensus regarding the mode of inheritance of febrile seizures or their clinical expression. Currently most febrile seizures are assumed to have a polygenic basis (8). Febrile seizures are approximately two to three times more common among family members of affected children than in the general population (9,10). Significantly higher concordance rates are seen for febrile seizures in monozygotic twins as compared to dizygotic twins in multiple twin registries (11). A higher incidence of afebrile epilepsy has been found in first-degree relatives of patients with febrile seizures (12,13). The occurrence of febrile seizures in first-degree relatives is a risk factor for febrile seizure recurrence (14).

Sodium channel and GABA receptor gene mutations have been identified in families with febrile seizure related syndromes (15–17). Despite the identification of multiple febrile seizure loci and mutated genes, little evidence points to their direct contribution in the majority of febrile seizures reported in the most affected individuals.

The autosomal dominantly inherited syndrome of generalized epilepsy with febrile seizures plus

(GEFS+) was first described in a large kindred from rural Victoria, Australia (15). The clinical phenotype includes febrile seizures in early childhood, followed by persistent febrile seizures beyond age 6 years and a variety of heterogeneous afebrile generalized seizure phenotypes. Affected children typically cease having seizures by mid-adolescence. A missense mutation in the gene that encodes the neuronal voltage-gated SCN1A in families of GEFS+ patients has been identified in approximately one-third of patients with Dravet syndrome, a disorder typically presenting in infancy with febrile status epilepticus followed by multiple pharmaco-resistant seizure types (18). As the initial development and EEG studies are normal in children with Dravet syndrome, early diagnosis may be extremely challenging. The emergence of other seizure types and developmental regression between the ages of 1 and 4 years provide clues to diagnosis. Intellectual functioning is almost always severely impaired in children with Dravet syndrome.

Age

The onset of febrile seizures generally follows a bell-shaped pattern. Ninety percent of seizures occur within the first 3 years of life (4), 4% before 6 months, and 6% after age 3 years. Approximately 50% appear during the second year of life, with a peak incidence between ages 18 and 24 months (4). Children with longer febrile seizures have a younger median age at first febrile seizure (19). The limited age range in febrile seizures has never been satisfactorily explained, but presumptively is genetically determined.

Fever

Febrile seizures typically occur relatively early in an infectious illness. The contribution of the rate of rise versus the final temperature reached in inducing the seizure has been debated, but is not thought to cause febrile seizures. The incidence of febrile seizures does not increase in proportion to temperature elevation, and febrile seizures are generally uncommon in the later stages of a persistent illness. Febrile seizures typically are associated with common childhood illnesses, but none of the common childhood infectious illnesses is uniquely capable of activating febrile seizures.

Febrile seizures that occur after vaccination have not been found to be different from febrile seizures from any other cause, although vaccinations trigger the onset of seizures in one-third of patients with Dravet syndrome (20). The previously used whole-cell diphtheria/tetanus/pertussis and measles-containing vaccines have an established association with febrile seizures, but a newer acellular diphtheria, tetanus, and pertussis (DTaP) vaccine is less reactogenic and does not increase the risk of febrile seizures (20).

Associated Factors

The Danish birth cohorts (Aarhus Birth Cohort, Aalborg-Odense Cohort and the Danish National Birth Cohort) have demonstrated that low birth weight and short gestational age are significant risk factors for febrile seizures (21). Another study that evaluated occurrence of febrile seizures concluded that fetal growth retardation is associated with increased risk of febrile seizures and that adverse environmental and genetic factors during pregnancy may be important in the development of febrile seizures (22).

Proinflammatory cytokines have also been implicated in the pathogenesis of febrile seizures. Interleukin (IL)-1β, tumor necrosis factor-α, and nitrite levels are all increased in the CSF of children

with a febrile seizure (23). Increased secretion of IL-6 and IL-10 by liposaccharide-stimulated mononuclear cells is higher in patients with a history of previous febrile seizures (24). Other studies have proposed that there is a link between febrile seizures and a systemic respiratory alkalosis, irrespective of the severity of the underlying infection (25).

TYPES OF FEBRILE SEIZURES

Simple Febrile Convulsions

Simple febrile convulsions are solitary events, lasting <15 minutes and lacking focality. They occur in neurologically normal children and are not associated with persistent deficits. The source of the fever is always outside the CNS.

Simple febrile seizures are the most common type of febrile seizures. The current American Academy of Pediatrics (AAP) guideline for evaluation of a first simple febrile seizure is that the clinician should identify the source of the fever when a child presents within 12 hours of a simple febrile seizure (26). Because seizures in the setting of a febrile illness may result from CNS infection, trauma, or electrolyte disturbance, laboratory investigation is usually warranted even when findings on the physical examination are normal.

The evaluation of simple febrile seizures should rely primarily on careful history taking, and judicious laboratory and radiologic testing. The American Academy of Pediatrics, through its Committee on Quality Improvement, published practice parameters dealing with the evaluation of the child with a first febrile seizure and the long-term treatment of the child with simple febrile seizures that were updated in 2011 (26). The new recommendations suggest that for the first episode of simple febrile seizure a lumbar puncture is indicated only with signs suggestive of meningitis. Lumbar puncture should also be considered if there has been prior antibiotic treatment or in infants between ages 6 and 12 months if the child is not properly vaccinated against Haemophilus and Streptococcus pneumoniae.

Multiple studies evaluating the role of lumbar puncture in patients with simple febrile seizures provide no support for routine CSF sampling. Recent US studies suggest that the risk of bacterial meningitis presenting as a first simple febrile seizure is very low (27,28). The need for a lumbar puncture when a patient presents with febrile status epilepticus has not been revised. As part of the FEBSTAT study, 136 children had CSF samples from a non-traumatic lumbar puncture done on initial presentation, and it was confirmed that febrile status epilepticus rarely causes CSF pleocytosis (29). The CSF glucose and protein levels were unremarkable, and the temperature, age, seizure focality, and seizure duration did not affect results. Thus, CSF pleocytosis should not be attributed to febrile status epilepticus.

Electroencephalography has not been particularly useful in the evaluation of simple febrile seizures. Hospitalization is rarely necessary following a simple febrile seizure.

Complex Febrile Seizures

Febrile seizures that do not meet the criteria for simple febrile seizures are considered “complex.” The concept of a “complex” febrile seizure originated with epidemiologic studies indicating that several patient- and seizure-related variables predicted higher rates of subsequent epilepsy: seizure duration longer than 15 minutes, focal seizure manifestations, seizure recurrence within 24 hours,

abnormal neurologic status, and afebrile seizures in a parent or sibling (30). Six percent of patients with two or more risk factors developed afebrile epilepsy by the age of 7 years, compared with only 0.9% if risk factors were absent (30).

Febrile seizure duration can be represented by a model that accounts for two populations of children. One has a short duration and the other has a long duration, with a cutoff between the two being 10 minutes (19). Prolonged febrile seizures, lasting more than 10 minutes, are unlikely to stop spontaneously (31). If a patient presents with focal complex febrile seizure one should consider performing brain MRI to evaluate for a structural abnormality as an explanation for the seizure (31).

Studies conducted at the Mayo Clinic reveal a less favorable prognosis for patients with complex febrile seizures (32). Seventeen percent of neurologically impaired children with complex febrile seizure manifestations developed epilepsy by the third decade, compared with 2.5% of children who lacked risk factors. The occurrence of focal, recurrent, and prolonged seizures raised the risk for afebrile episodes to nearly 50%. Developmental delay and a younger age are associated with prolonged febrile seizures (19).

Complex febrile seizures must be managed more aggressively than simple febrile seizures. Meningitis must be excluded by history, but when there is a concern of fever etiology a CSF examination and neuroimaging studies are indicated.

Although children with complex febrile seizures are expected to have a higher rate of abnormal EEG recordings, confirmatory data are sparse. An EEG to evaluate for underlying focal abnormalities can assist with education and evaluation planning.

Febrile Status Epilepticus

Although most febrile seizures are self-limited, prolonged episodes and febrile status epilepticus are not rare, and constitute an important subgroup of complex febrile seizures. The phenomenology of febrile status epilepticus is currently being investigated in a prospective multi-center study. The study, Consequences of prolonged febrile seizures (FEBSTAT), recruited 199 children aged 1 month through 5 years who had a febrile seizure that lasted more than 30 minutes (31). Children recruited most often had focal seizures that were usually their first febrile seizure. Seizure duration in this group was typically very prolonged suggesting that the longer the seizure continued, the less likely it was to spontaneously cease.

The FEBSTAT study performed baseline EEGs within 72 hours of the episode of febrile status epilepticus. Review of their baseline EEGs showed that there was focal slowing or attenuation in a substantial proportion of children, and the slowing and attenuation were highly associated with MRI evidence of acute hippocampal injury (33). The study concluded that these EEG findings may be used as a sensitive and readily obtainable marker of acute injury associated with febrile status epilepticus.

An association between female sex and febrile status epilepticus has been observed in some studies (34), whereas others (4,31,35) have found a slight male predominance.

RISK ASSESSMENT IN FEBRILE SEIZURES

Febrile Seizure Recurrence

Approximately one-third of patients with febrile seizures experience additional attacks; of this group, one-half will have a third seizure (36,37) and 9% experience more than three attacks (30).

Age of onset is the most important predictor of febrile seizure recurrence. One-half of all infants younger than 1 year of age at the time of their first febrile seizure will have a recurrence, compared with 20% of children older than 3 years of age. Young age at onset, a history of febrile seizures in first-degree relatives, low-grade fever in the emergency department, and brief interval between fever onset and seizure presentation are strong independent predictors of febrile seizure recurrence (38). Recurrences generally occur within 1 year but are no more likely in children who had a complex febrile seizure than in those who experienced a simple febrile seizure. There is no evidence supporting a statistically significant relationship between the duration of a first febrile seizure and a recurrence (19).

Children with multiple risk factors experience the highest rates of febrile seizure recurrence. The presence of two or more risk factors is associated with a 30% or greater recurrence risk, whereas three risk factors are associated with a 60% or greater recurrence risk (38).

Epilepsy and the Association of Febrile Seizures with the Development of Hippocampal Sclerosis

Between 1.5% and 4.6% of children with febrile seizures develop afebrile seizures (39–42). This rate is significantly higher than in the general population and reflects primarily infants and children with one or more complex febrile seizures (30,43). The presence of a neurodevelopmental abnormality, a family history of epilepsy, and prolonged duration of fever are also proven risk factors for the development of epilepsy after experiencing a febrile seizure (44).

Although this association between febrile seizures and epilepsy is well documented, the mechanism that underlies this association is much less clear. A long-term goal of the prospective FEBSTAT study is to better define the relationship between prolonged febrile seizures, hippocampal sclerosis (HS) and mesial temporal lobe epilepsy (MTLE). Prior retrospective studies conducted in adults with MTLE found a significant association with febrile seizures but there has been no prospective confirmation of this relationship. To-date, the FEBSTAT study has performed a baseline MRI, with special attention to the hippocampus on 191 of the recruited children. A statistically significant abnormal or equivocally increased hippocampal T2 signal following febrile status epilepticus was observed in 22 children compared with none in the control group (31,45). Figure 34.1 demonstrates an example of MRI changes that have been seen in children that have had an episode of febrile status epilepticus. In addition, developmental abnormalities of the hippocampus were more common in the febrile status epilepticus group, with hippocampal malrotation being the most common finding. These imaging findings demonstrate that children with febrile status epilepticus are at risk for acute hippocampal injury and abnormalities in hippocampal development (45). Longer follow-up will be required to document whether these children develop MTLE and at what rate.

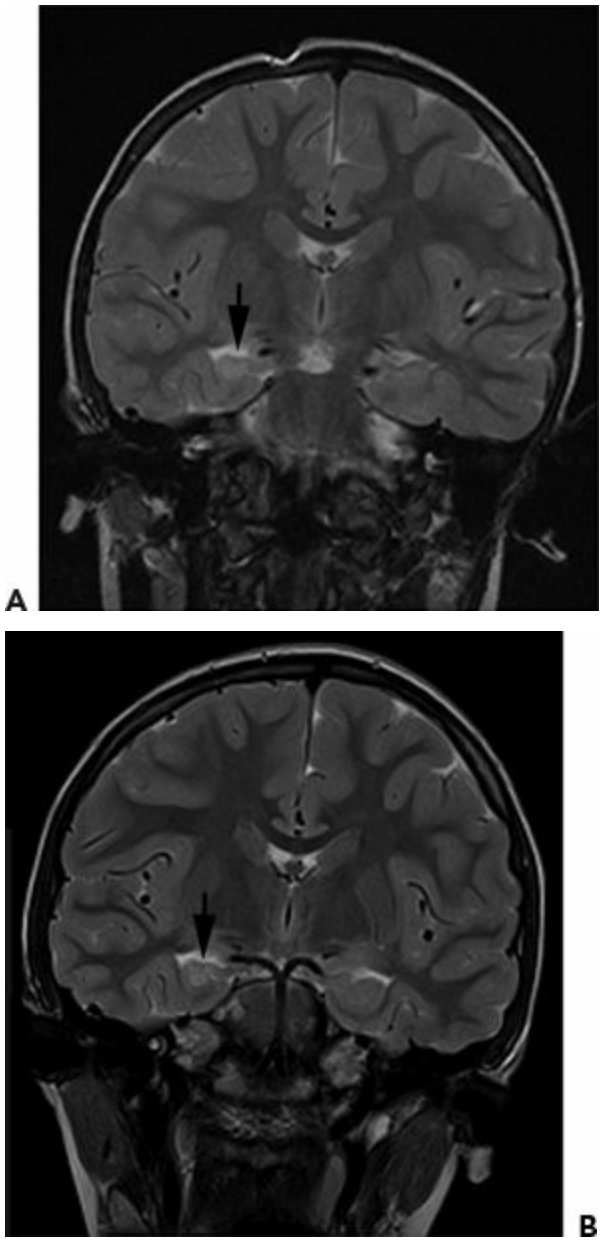

Figure 34.1. Brain MRI of a child that had a 2-hour febrile convulsion. **A:** Coronal image obtained from brain MRI performed <6 months after febrile status epilepticus. Image shows abnormal high T2 signal in the right hippocampus with slight volume loss. **B:** Coronal image obtained from brain MRI performed approximately 5 years after febrile status epilepticus. Image shows increased T2 signal intensity within the right hippocampus with associated slight volume loss.

Human Herpes Virus

Human herpes virus 6 (HHV6) is a common childhood infectious agent responsible for roseola infantum and several severe infectious syndromes. In immunocompromized patients, reactivation of viral activity may lead to severe limbic encephalitis. Examination of temporal lobectomy specimens reveals a high incidence of active HHV6B replication in hippocampal astrocytes (46). This association suggests a possible link between early viral infection, complex or prolonged febrile seizures and later HS.

As part of the FEBSTAT study, serum was evaluated for the presence of HHV-6A, HHV-6B, or HHV-7 DNA and RNA (31,47). The study concluded that HHV-6B infection is commonly associated with febrile status epilepticus, and HHV-7 infection is less frequently associated. Together HHV infections were identified in one-third of the febrile status epilepticus subjects (47). The study did not detect HHV-6B or HHV-7 DNA in the CSF of 23 subjects who presented in febrile status epilepticus

and had a documented HHV-6B or HHV-7 viremia.

FEBRILE SEIZURES AND NEUROPSYCHOLOGICAL STATUS

The consequences of febrile seizures on later intellectual functioning and behavior of children has been studied extensively. A cohort of 381 children with simple and complex febrile seizures was compared with a control group on measures of academic progress, intelligence, and behavior; there were no differences between groups in any measures (48).

Two large, longitudinal, population-based studies provide strong evidence that febrile seizures do not adversely affect neuropsychological status. Ellenberg and Nelson (49) studied intellectual and academic function following febrile seizures in 431 sibling pairs 7 years of age who were part of the National Collaborative Perinatal Project. Children with febrile seizures and normal intelligence achieved reading and spelling milestones at rates similar to those of their seizure-free siblings. The National Child Development Study, completed in the United Kingdom, also found that children with febrile seizures did not differ from controls in behavior, height, head circumference, or academic achievement (40). It is important to remember that the consequences of febrile seizures can be influenced by seizure duration.

THERAPY

It is accepted that antipyretic agents do not reduce the risk of febrile seizure or seizure recurrence. Prophylactic antiepileptic drug (AED) therapy for febrile seizures should be withheld, as the benefits of treatment do not outweigh the risks. Recurrent febrile seizures and later afebrile epilepsy, which are the major sequelae of a febrile seizure, are both rare. Despite their anxiety, family members should be counseled about the merits of withholding prophylactic treatment.

There are exceptions to the use of AEDs following the occurrence of complex febrile seizures, for example when there is significant risk for later epilepsy. However, even seemingly life-threatening seizures must be evaluated cautiously because neurologic impairment and death are extremely unlikely, even after febrile status epilepticus. The NIH consensus panel found that high-risk patients with two risk factors (e.g., abnormalities on neurologic examination, prolonged focal seizure, and family history of epilepsy) still had only a 13% chance of developing epilepsy. Moreover, although phenobarbital reduced febrile seizure recurrence, there is no firm evidence that the prevention of recurrent febrile seizures diminishes the risk for later epilepsy.

Febrile seizures often cease by the time a child is examined, but prolonged episodes should be treated similar to seizures of any other etiology. A child that is actively having a seizure should receive acute abortive treatment by 5 minutes after seizure onset. All prolonged convulsions carry an increased risk of complications, and treatment should be initiated before 5 minutes after seizure onset to help prevent prolonged seizure activity and consequences. A prolonged FS should be treated promptly by emergency medical services (EMS) or the emergency department. Initially a benzodiazepine should be used, for example rectally administered diazepam gel, but if continued seizure activity a full status epilepticus protocol should be initiated (44).

CONCLUSIONS

Febrile seizures are the most common seizure presentation in infancy and early childhood and are usually benign. Most events are self-limited and carry only a modest risk for febrile seizure recurrence. Febrile seizures are thus a genetically predetermined, age-dependent response to fever and are not classified as epilepsy. Treatment with prophylactic AEDs is not indicated. Febrile status epilepticus is frequently unrecognized and prolonged seizures frequently need medication to terminate the seizure (31). Unfortunately a small percentage of children with prolonged febrile seizures do have long term consequences.

Fewer than 10% of patients with febrile seizures experience severe or recurrent attacks. Risk factors for complex episodes are known, and the likelihood of developing epilepsy remains <5%. Diagnostic procedures or treatment should be performed on an individual basis; febrile status epilepticus must be treated as a medical emergency. Underlying neurologic disorders require investigation, and "epileptic seizures exacerbated by fever" should be distinguished from febrile seizures per se. There is no evidence that prophylactic administration of AEDs prevents the occurrence of later epilepsy.

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CHAPTER 35 NEONATAL SEIZURES

KEVIN CHAPMAN, ELI M. MIZRAHI, AND ROBERT RYAN CLANCY

Neonatal seizures are a classic and ominous neurologic sign that can arise in any newborn infant. Their significance lies in their high incidence, association with acute neonatal encephalopathies, substantial mortality, neurologic morbidity, and the concern that seizures per se could extend the acute brain injury. Seizures in the neonate differ clinically and electrographically from those in mature infants and children. Diagnostic and treatment decisions remain limited by a paucity of rigorous scientific data for this population. This chapter reviews the significance of neonatal seizures; the pathophysiologic basis of clinical, electroclinical, and electrographic seizures; prognostic expectations; and etiologies and surveys current treatment options that might themselves pose a risk to the developing brain.

HISTORICAL BACKGROUND

The appearance of "seizures," "fits," or "convulsions" in newborn infants has been known since antiquity. It was naturally assumed that clinical seizures in neonates were always associated with abnormal, excessive, paroxysmal electrical discharges arising from repetitive neuronal firing in the cerebral cortex. Despite the identification of electroclinical correlations of seizures in mature individuals, progress in understanding the nosology of neonatal seizures was only recently notable. Although some neonatal seizures are accompanied by simultaneous epileptic discharges seen on EEG, not every clinical event in a neonate presenting as an abrupt "attack" is truly epileptic, and the relationship between neonatal seizures and the conventional connotations of the term epilepsy demands careful scrutiny. Thus, seizures in the neonate are now distributed into three classes (Fig. 35.1). "Electroclinical" seizures are abnormal, clinically observable events that are consistently founded on a specific epileptic mechanism and coincide with an obvious electrographic seizure during simultaneous EEG monitoring. "Clinical-only" seizures refer to other abnormal-appearing abrupt clinical events that are not associated with simultaneous electrographic seizure activity during EEG monitoring; they may be considered a type of nonepileptic seizure; "EEG-only" seizures lack definite clinical seizure activity; they are also called "subclinical" or "occult."

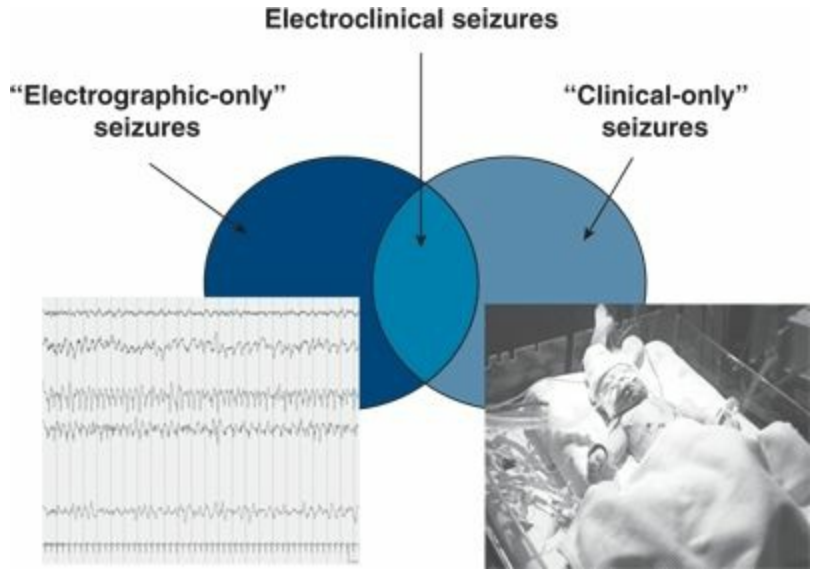


Figure 35.1. Three types of "seizures" in the newborn: "electrographic only," "electroclinical," and "clinical only."

SIGNIFICANCE OF NEONATAL SEIZURES

Incidence

The incidence of seizures in the first 28 days of life, one of the highest risk periods for seizures in humans, ranges between 1% and 5%. Depending on the methodology used, seizures occur at a rate of 0.95 to 5.5 per 1000 neonates (1–6), most within the 1st week of life (3). Unfortunately, most of these studies relied on clinical findings to identify seizures, which may underestimate the actual incidence. Incidence varies with specific risk factors. Lanska et al. (3) reported the incidence of seizures in all neonates to be 3.5 per 1000, but 57.5 per 1000 in very-low-birth-weight (<1500 g) infants, 4.4 per 1000 in low-birth-weight (1500 to 2499 g) infants, and 2.8 per 1000 in normal-birth-weight (2500 to 3999 g) infants. Scher et al. (7,8) described seizures in 3.9% of neonates younger than 30 weeks of conceptional age and in 1.5% of those older than 30 conceptional weeks.

The human newborn is especially vulnerable to a wide range of toxic or metabolic conditions. It is now well established that the neonatal brain itself may be especially prone to seizures when injured. One suspected mechanism of enhanced seizure susceptibility in the newborn is the relative imbalance between inhibition and excitation. Compared with more mature brains, the neonatal brain exhibits delayed maturation of inhibitory circuits and precocious maturation of excitatory circuits (9). According to studies in the neonatal rat, γ-aminobutyric acid (GABA)—the major inhibitory neurotransmitter in the mature brain—may exert paradoxically excitatory effects in early CNS development (10,11).

A developmentally dependent cation chloride cotransporter channel (KCC2)—which extrudes chloride into the extracellular space—does not reach mature levels in the rat hippocampus until after the third postnatal week (Fig. 35.2). Instead, early in development, the NKCC1 transporter predominates and actively transports chloride into the neuron. Thus, when the ligand-dependent $GABA_A$ receptor is activated in the immature rat, extracellular chloride follows its electrochemical gradient out of the neuron resulting in depolarization. After the appearance of KCC2, the intracellular concentration of chloride is kept low, and activation of the $GABA_A$ receptor allows chloride to run along its electrochemical gradient into the neuron. This leads to hyperpolarization and allows for the

inhibitory action of the receptor (12,13). Current electrophysiologic evidence suggests that this excitatory-to-inhibitory switch in the rat hippocampus is complete by postnatal day 14 (14,15), an age that may reflect the developmental state of a human toddler.

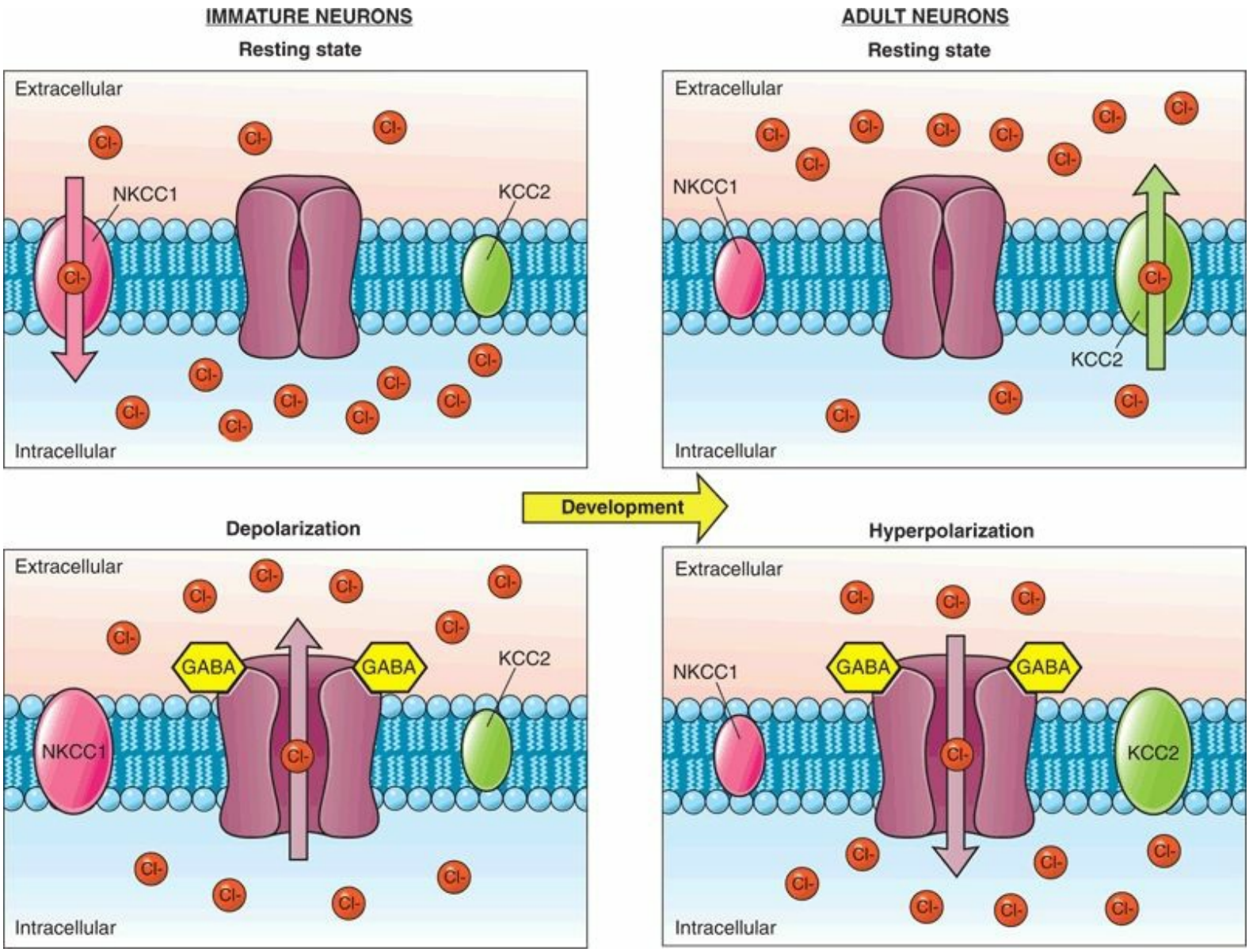


Figure 35.2. Changes in chloride homeostasis during development. In the immature neuron (left portion of panel), the NKCC1 cotransporter is primarily expressed and allows chloride to accumulate in the neuron. When GABA binds to its receptor, the negatively charged chloride ions leave the cell leading to depolarization of the neuron. In the mature neuron (right portion of panel), the chloride cotransporter KCC2 that functions to transport chloride out of the cell predominates. When GABA binds to its receptor, chloride enters the cell causing hyperpolarization of the neuron.

The paradoxical depolarizing effect of GABA during the neonatal period potentially contributes to the refractoriness of neonatal seizures to phenobarbital and benzodiazepines. Interestingly, recurrent neonatal seizures in rodent models lead to an increase in intracellular chloride via a NKCC1-dependent mechanism (16,17). In some experimental models of induced neonatal seizures, inhibition of the NKCC1 transporter with bumetanide alters chloride transport and significantly enhances the anticonvulsant effects of phenobarbital in the neonatal rat hippocampus (17,18). Clinical studies evaluating bumetanide add-on therapy are currently ongoing.

Glutamatergic receptors also regulate excitability in the immature neuron and undergo developmental changes that contribute to the propensity of the neonate to seizures. These receptors

can have various functional properties based on their subunit composition that changes during development. N-methyl-D-aspartate (NMDA) receptors in immature neurons express primarily the NR2B subunit that prolongs the duration of the excitatory postsynaptic potential. Increased expression of the NR2C, NR2D, and NR3A subunits confers a reduced sensitivity to blockade by magnesium, resulting in increased excitability (19).

Prognostic Significance

Neonatal seizures are a powerful prognostic indicator of mortality and neurologic morbidity. The summary report from Bergman et al. (2) of 1667 patients noted an overall mortality of 24.7% before 1969 and 18% after 1970. According to Lombroso (20), mortality decreased modestly from about 20% previously to 16% in the early 1980s. These improvements probably reflect better obstetrical management and modern neonatal intensive care. All of these studies relied on seizure diagnosis by clinical criteria and did not require EEG confirmation.

Survivors of neonatal seizures face an exceptionally high risk for cerebral palsy, often with mental retardation and chronic postnatal epilepsy. The National Collaborative Perinatal Population (NCPP) study (21,22) examined numerous clinical perinatal factors for their association with severe mental retardation, cerebral palsy, and microcephaly (Fig. 35.3). The clinical diagnosis of "neonatal seizures" was independently and significantly associated with these adverse outcomes and eclipsed only by "intracranial hemorrhage" in forecasting them.

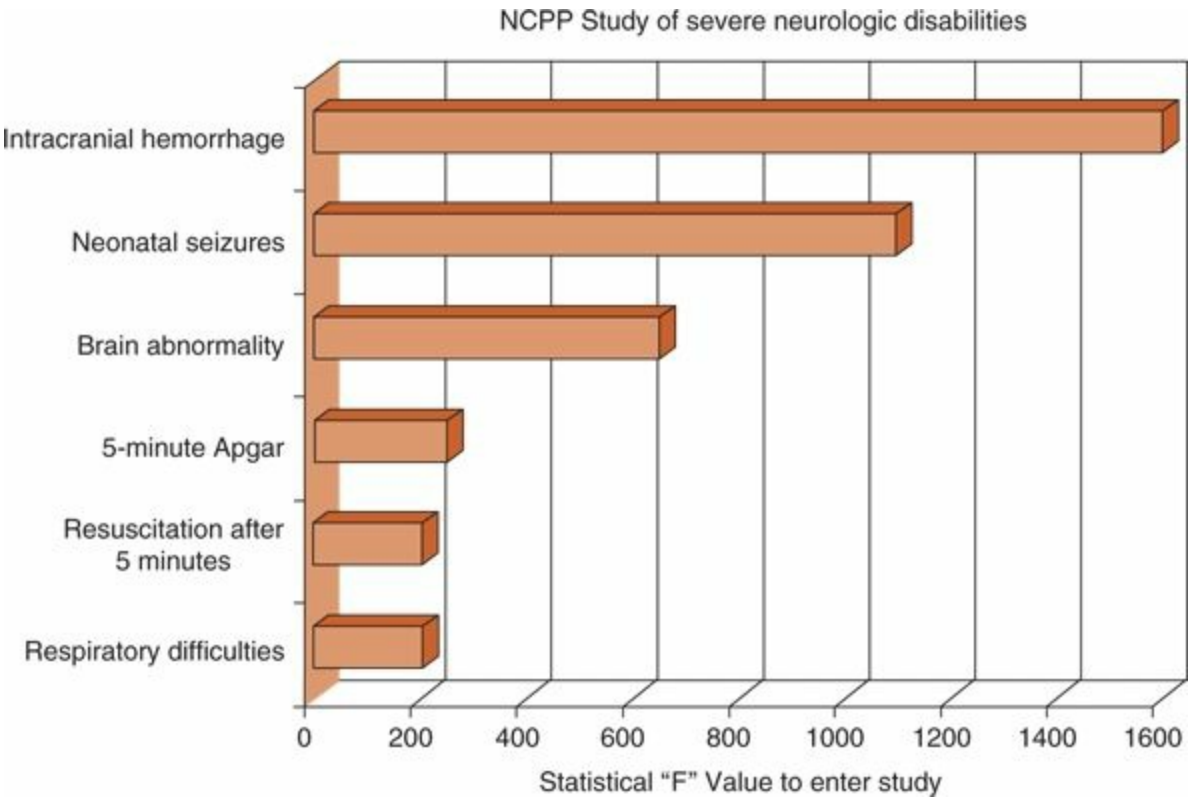


Figure 35.3. The National Collaborative Perinatal Population (NCPP) study prospectively followed more than 34,000 mothers to identify perinatal events associated with adverse outcomes. Fifty neonates were found with subsequent severe neurologic handicaps. Six independent variables, including neonatal seizures, were associated with such neurologically devastating outcomes. (Adapted from Nelson KB, Broman SH. Perinatal risk factors in children with serious motor and mental handicaps. Ann Neurol. 1977;2(5):371–377.)

Contemporary studies of the prognosis after neonatal seizures have emphasized the inclusion of infants whose seizure type was confirmed by EEG monitoring. Pisani et al. (23) identified 106

consecutively admitted neonates with video EEG–confirmed seizures over a 5-year period. The mortality rate was 19% with a favorable outcome found in only 34% of patients. Cerebral palsy was identified in 37% and developmental delay in 34%, and 21% had postnatal epilepsy at 24 months of follow-up.

Of the 207 full-term infants with video EEG–confirmed seizures prospectively enrolled by the Clinical Research Centers for Neonatal Seizures between 1992 and 1997, 28% died (24). Two-year follow-up data were available for 122 patients, or 86% of the survivors. Abnormal neurologic findings were noted in 42%. A Mental Developmental Index (MDI) score below 80 was present in 55%, a Psychomotor Developmental Index (PDI) score <80 in 50%, and chronic postnatal epilepsy in 26%.

Whether seizures themselves adversely affect the developing brain is difficult to determine from clinical studies. Seizure burden may appear to influence outcome because some infants who experience brief, infrequent seizures may have relatively good long-term outcomes, whereas those with prolonged seizures often do not fare as well. However, easily controlled or self-limited seizures may be the result of transient, successfully treated, or benign CNS disorders of neonates, while medically refractory neonatal seizures may stem from more sustained, less treatable, or more severe brain disorders. Legido et al. (25) studied 40 neonates with electrographic seizures detected on randomly timed routine EEG examinations and monitored them for cerebral palsy, mental retardation, and epilepsy. Overall neurologic outcome was more favorable in those with two or fewer seizures per hour than in those with more. In the subgroup with seizures caused by hypoxia–ischemia, cerebral palsy was more frequent when more than five seizures occurred per hour. However, these results might equally reflect more severe underlying injuries that triggered both the additional short-term seizures and greater morbidity on long-term follow-up. In another study, a higher seizure burden was independently associated with a worse neurodevelopmental outcome in hypoxic–ischemic encephalopathy (HIE; see section titled “Diffuse Hypoxic–Ischemic Etiologies” later in this chapter) even after controlling for the severity of hypoxic–ischemic brain injury (26).

A randomized trial was conducted evaluating the utility of treating electrographic seizures detected on amplitude-integrated EEG (aEEG; see section titled “Amplitude-Integrated EEG” later in this chapter). Patients with moderate to severe HIE and clinical seizures were started on aEEG, but they were randomized to treatment of seizures using only clinical evaluation or a combination of aEEG and clinical seizures. There was a trend to shorter seizure duration with treatment of both clinical and electrographic seizures compared to only those observed clinically. In addition, the group also found that a longer duration of seizure was associated with a greater severity of brain injury on MRI (27).

Attempting a balanced approach, McBride et al. (28) followed up 68 high-risk neonates with birth asphyxia, meningitis, and other stressors linked to neonatal seizures. All infants underwent long-term EEG monitoring. Forty developed electrographic seizures, while 28 did not. Based on logistic regression analysis, electrographic neonatal seizures were significantly correlated with death and cerebral palsy. Other investigators (29), using proton magnetic resonance spectroscopy (^{1}H-MRS), found an association of measures of seizure severity with impaired cerebral metabolism measured by lactate/choline and compromised neuronal integrity measured by N-acetylaspartate/choline and suggested this as evidence of brain injury not limited to structural damage detected by magnetic resonance imaging (MRI).

Clinical or EEG-detected seizures are relatively common after newborn heart surgery (NBHS) (30) and generally connote “gray matter” injury or dysfunction. In the Boston Circulatory Arrest Study

(BCAS), postoperative EEG seizures were detected in 27/136 (19.8%) and were associated with an 11-point reduction in the Bayley Scales of Infant Development (BSID) at 1-year follow-up (31). By 16 years of age, 139 (87%) of the original cohort of survivors participated in neurocognitive follow-up measuring academic achievement, memory, executive functions, visuospatial skills, attention, and social cognition. After adjustment for all other covariables, the occurrence of seizures in the postoperative period was the medical variable most consistently related to worse outcomes. The scores of both treatment groups tended to be lower than those of the test normative populations, with substantial proportions scoring ≤1 SDs below the expected mean (32).

EEG seizures were also detected commonly after NBHS at Children's Hospital of Philadelphia. EEG seizures were detected in 11% of 164 infants participating in the APOE polymorphisms study (33). At the 1-year follow-up evaluation, abnormal or suspect examination results occurred in 41/99 (41%) patients without seizures, compared with 11/15 (73%) patients with postoperative seizures ($P < 0.027$). Moreover, frontal-onset seizures predicted lower MDI scores ($P < 0.03$), but not lower scores ($P < 0.2$), compared with non–frontal-onset seizures (34). Neurocognitive testing was repeated in 132 (87%) of 151 survivors at 4 years. The outcomes assessed included cognition, language, attention, impulsivity, executive function, behavior problems, academic achievement, and visual and fine motor skills. Developmental evaluations were performed. After covariate adjustment, occurrence of an EEG seizure was associated with worse executive function ($P < 0.037$) and impaired social interactions/restricted behavior ($P < 0.05$). Seizures were not significantly associated with worse performance for cognition, language, attention, impulsivity, academic achievement, or motor skills (all $P > 0.1$) (35).

Neonatal Seizures Are Harmful to the Neonatal Rodent Brain

Neonatal seizures may be intrinsically harmful to the brain (36). Most seizures were long assumed to be the innocuous, albeit conspicuous, result of an acute injury, and the subsequent long-term neurodevelopmental abnormalities the result of their underlying causes, not the seizures themselves. Basic laboratory studies focused on the effects of seizures on the developing brain have not resolved the controversy (37–41). Immature animals are more resistant than older animals to some seizure-induced injury (42). The immature brain may be resistant to acute seizure-induced cell loss (39); however, functional abnormalities such as impairment of visuospatial memory and reduced seizure threshold (43) occur after seizures, and seizures have been noted to induce changes in brain development, including altered neurogenesis (44), synaptogenesis, synaptic pruning, neuronal migration, and the sequential expression of genes including neurotransmitter receptors and transporters (45,46).

While neonatal seizures seem to induce little histologic damage to the brain (42), studies have revealed that recurrent seizures can produce long-lasting changes in the developing brain, making them more prone to epilepsy and impairing future learning and behavior. Holmes et al. (47) documented impaired spatial learning and memory, decreased activity levels, significantly lower threshold to pentylenetetrazol-induced seizures, and sprouting of CA3 mossy fibers in adult rats that had recurrent neonatal seizures compared to those without neonatal seizures.

Alterations in receptor subunit expression have been implicated as a cause for some of the changes following neonatal seizures. Status epilepticus induced in neonatal rats produced decreased expression of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor GluR2 subunit and increased susceptibility to kainate-induced seizures later in life (48). Another study

demonstrated that a single episode of seizures in neonatal rat pups (at P7) produced long-lasting alterations in excitatory glutamatergic synapses that impaired working memory in adulthood (49). Recurrent neonatal seizures likewise produced decreased NR2A expression (50). Hypoxia-induced neonatal seizures appear to decrease long-term potentiation in the hippocampus through an AMPA-mediated mechanism that is suspected to impair synaptic plasticity leading to cognitive impairment (51).

The most frequent clinical setting for the occurrence of neonatal seizures in both term and preterm neonates is following hypoxic–ischemic injury (52). A rodent study of hypoxia-induced seizures demonstrated a decrease in GluR2 receptor expression allowing an increase in calcium influx that may contribute to the chronic epileptogenic effects of hypoxia-induced neonatal seizures (53). Treatment with AMPA receptor antagonists, but not NMDA receptor or $GABA_A$ receptor antagonists, after hypoxia-induced seizures in neonatal rats reduced the susceptibility to seizures and seizure-induced injury later in life (54). Likewise, topiramate—which acts mechanistically in part by blocking AMPA/kainate receptors—exerts anticonvulsant activity against perinatal hypoxia-induced seizures (55). These studies highlight the potential utility of topiramate in neonates with seizures associated with hypoxic–ischemic encephalopathy, but the lack of an intravenous formulation makes treatment in critically ill children challenging (56). Nevertheless, in July 2013, the FDA approved the development of an orphan drug formulation of intravenous topiramate, specifically with the neonatal population in mind. Topiramate was found to be safe in one study of infants with HIE who were treated with hypothermia and oral topiramate; however, there was no difference in short-term outcomes (57).

A concern with recurrent neonatal seizures is the concept that "seizures beget seizures"—with recurrent seizures inducing secondary ictal-onset zones. An elegant study by Khalilov et al. (58) attempted to determine if GABA or NMDA signaling was required for creation of a secondary epileptogenic focus. Recurrent seizures were induced in one hippocampus with repeated doses of kainate that eventually propagated to the other hippocampus and established a secondary epileptogenic focus. Addition of an NMDA receptor antagonist to the seizure-naïve hippocampus (not stimulated with kainate) inhibited the creation of a "mirror focus." Interestingly, GABA-ergic synapses in this system became excitatory in the secondary focus, which is known to be an important contributor to epileptogenesis in the neonatal hippocampus. This study again supports the possible role of NMDA receptor antagonists in the clinical treatment of neonatal seizures.

Finally, neonatal seizures in rats alter the subsequent composition of the $GABA_A$ receptor. Each $GABA_A$ receptor is a pentamer in which five subunits assemble into a functional ligand-gated receptor (Fig. 35.4). The specific composition of an individual $GABA_A$ receptor depends on developmental age. In the studies of Zhang et al. (10), rats with neonatal seizures had a substantially higher proportion of the α_1 $GABA_A$ subunit than did control animals (Fig. 35.5) (59). Higher levels of the α_1 $GABA_A$ subunit may provide a protective role in decreasing the severity or frequency of seizures later in life following earlier neonatal seizures (60).

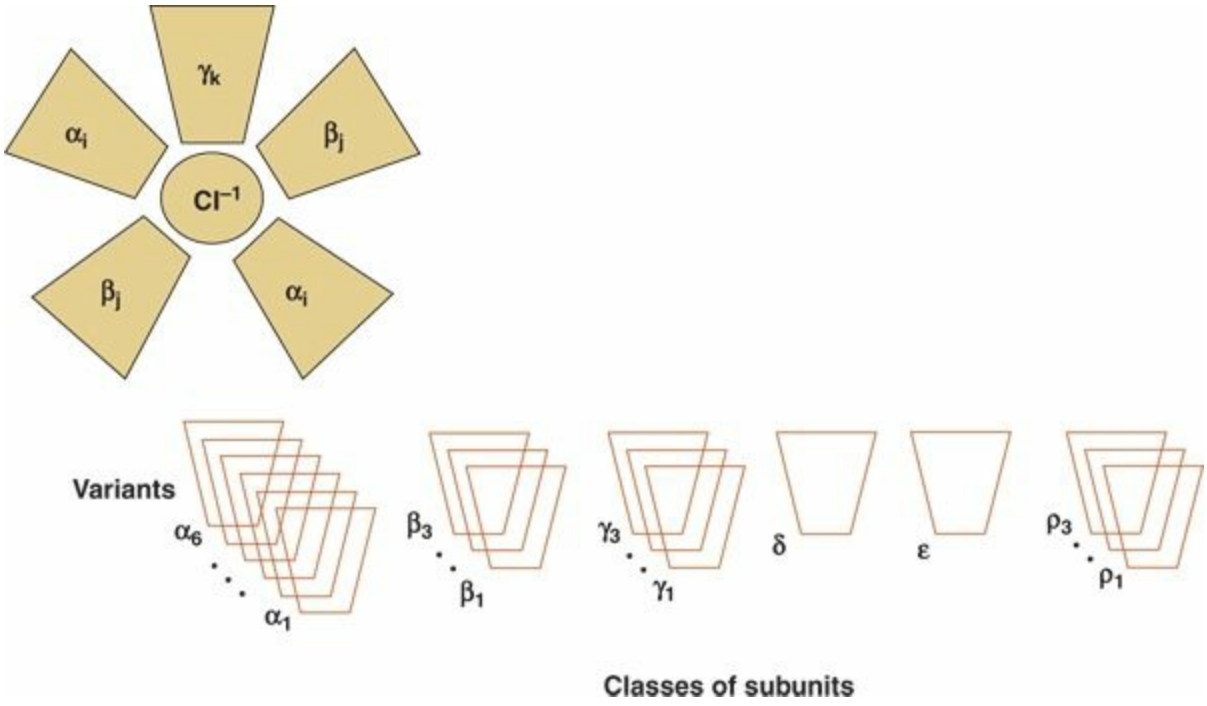


Figure 35.4. The γ-aminobutyric acid receptor is a pentamer structure composed of six possible classes of subunits. The subunits themselves may have multiple variants that are expressed at different developmental ages.

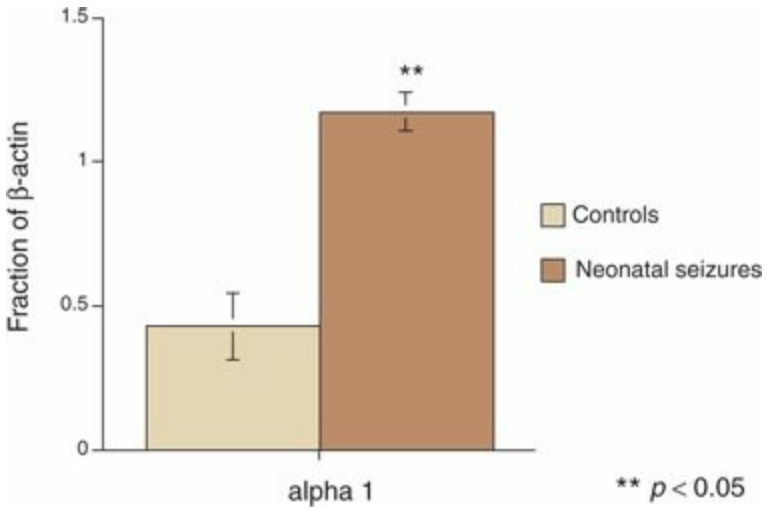


Figure 35.5. Rat pups subjected to seizures had significant differences in α-aminobutyric acid subunit receptor composition in later life compared with control animals. (Adapted from Brooks-Kayal AR, Shumate MD, Jin H, et al. Gamma-Aminobutyric acid (A) receptor subunit expression predicts functional changes in hippocampal dentate granule cells during postnatal development. J Neurochem. 2001;77(5):1266–1278.)

CLASSIFICATION AND CLINICAL FEATURES OF NEONATAL SEIZURES

Application of a syndromic classification to neonatal seizures is limited when considered in light of the classification of the International League Against Epilepsy (ILAE) (61). Almost all neonatal seizures are thought to be symptomatic, an acute reaction, or consequence of a specific etiology. The most recent ILAE classification addresses only five neonatal syndromes: benign neonatal seizures, benign familial neonatal epilepsy (BFNE), early myoclonic encephalopathy (EME), Ohtahara syndrome, and migrating partial seizures of infancy (61). These are discussed later.

Seizures in the neonate are uniquely different from those in older infants and children. These differences are based on mechanisms of epileptogenesis, the developmental state of the immature brain, and the relatively greater importance of nonepileptic mechanisms of seizure generation in this age group. Neonatal seizures may be classified by (i) clinical manifestations, (ii) the relationship between clinical seizures and electrical activity on the electroencephalogram, and (iii) seizure pathophysiology.

Clinical Classifications

A number of clinical classifications of neonatal seizures have been published (62–66). Early classifications focused on the clinical differences between seizures in neonates and those in older children: neonatal seizures were reported to be clonic or tonic, not tonic–clonic; when focal, they were either unifocal or multifocal. Later classifications included the term myoclonus. Another distinguishing feature of neonatal seizures is the occurrence of events described initially as "anarchic" (62) and thereafter "minimal" (67) or "subtle" (65). These events included oral–buccal–lingual movements such as sucking and chewing; movements of progression, such as bicycling of the legs and swimming movements of the arms; and random eye movements. First considered epileptic in origin, they were later deemed to be exaggerated reflex behaviors and thus were called "brainstem release phenomena" or "motor automatisms" (64). Table 35.1 lists the clinical characteristics of neonatal seizures according to a current classification scheme (68) that can be applied through observation.

Table 35.1 Clinical Characteristics, Classification, and Presumed Pathophysiology of Neonatal Seizures

Classification	Characteristics	Pathophysiologic basis
Focal clonic	Repetitive, rhythmic contraction of muscle groups of the limbs, face, or trunk May be unifocal or multifocal May occur synchronously or asynchronously in muscle groups on one side of the body May occur simultaneously but asynchronously on both sides Cannot be suppressed by restraint	Epileptic
Focal tonic	Sustained posturing of single limbs Sustained asymmetric posturing of the trunk Sustained eye deviation Cannot be provoked by stimulation or suppressed by restraint	Epileptic
Generalized tonic	Sustained symmetric posturing of limbs, trunk, and neck May be flexor, extensor, or mixed extensor/flexor May be provoked or intensified by stimulation May be suppressed by restraint or repositioning	Presumed nonepileptic
Myoclonic	Random, single, rapid contractions of muscle groups of the limbs, face, or trunk Typically not repetitive or may recur at a slow rate May be generalized, focal, or fragmentary May be provoked by stimulation	Epileptic or nonepileptic
Spasms	May be flexor, extensor, or mixed extensor/flexor May occur in clusters Cannot be provoked by stimulation or suppressed by restraint	Epileptic
Motor automatisms ocular signs	Random, roving eye movements or nystagmus (distinct from tonic eye deviation) May be provoked or intensified by tactile stimulation	Nonepileptic
Oral–buccal–lingual movements	Sucking, chewing, tongue protrusions May be provoked or intensified by stimulation	Nonepileptic
Progression movements	Rowing or swimming movements Pedaling or bicycling movements of the legs May be provoked or intensified by stimulation May be suppressed by restraint or repositioning	Nonepileptic
Complex purposeless movements	Sudden arousal with transient increased random activity of limbs May be provoked or intensified by stimulation	Nonepileptic

Seizure Pathophysiology

Clinical seizures may be classified as epileptic or nonepileptic (Table 35.2). Some clinical neonatal seizures are clearly epileptic, occurring in close association with EEG seizure activity, involving clinical events that can be neither provoked by stimulation nor suppressed by restraint and directly triggered by hypersynchronous cortical neuronal discharges. The following properties of the developing brain intensify seizure initiation, maintenance, and propagation: increases in cellular and synaptic excitation and a tendency to enhance propagation of an epileptic discharge (40,69–71). The clinical events that are most clearly epileptic in origin are focal clonic, focal tonic, some types of myoclonic, and rarely spasms (see Tables 35.1 and Table 35.2). Electrical-only seizures (also called subclinical or occult) are, by definition, epileptic.

Table 35.2 Classification of Neonatal Seizures by Electroclinical Findings

- Clinical seizures with a consistent electrocortical signature (epileptic)
  - Focal clonic
    - Unifocal
    - Multifocal
    - Hemiconvulsive
    - Axial
  - Focal tonic
    - Asymmetric truncal posturing
    - Limb posturing
    - Sustained eye deviation
  - Myoclonic
    - Generalized
    - Focal
  - Spasms
    - Flexor
    - Extensor
    - Mixed extensor/flexor
- Clinical seizures without a consistent electrocortical signature (presumed nonepileptic)
  - Myoclonic
    - Generalized
    - Focal
    - Fragmentary
  - Generalized tonic
    - Flexor
    - Extensor
    - Mixed extensor/flexor
  - Motor automatisms
    - Oral–buccal–lingual movements
    - Ocular signs
    - Progression movements
    - Complex purposeless movements
- Electrical seizures without clinical seizure activity

Best considered nonepileptic in origin (64) are events that occur in the absence of electrical seizure activity but that have clinical characteristics resembling reflex behaviors. Such clinical events, whether provoked by stimulation or arising spontaneously, can be suppressed or altered by restraining or repositioning the infant. The clinical events may grow in intensity with increases in the repetition rate of stimulation (temporal summation) or the sites of simultaneous stimulation (spatial summation). Some types of myoclonic events, generalized tonic posturing, and motor automatisms can be classified as "nonepileptic" (see Tables 35.1 and 35.2).

Paroxysmal clinical changes related to the autonomic nervous system have been proposed as manifestations of some seizures. These include stereotyped, episodic alterations in heart rate, respiration, and blood pressure (72–74). Skin flushing, salivation, apnea (75,76), and pupillary dilation may also be autonomic signs of seizures, but they are usually associated with other clinical manifestations, except in the therapeutically paralyzed infant (64).

Electrographic Seizures

Although visual observation is critical to the detection of clinical neonatal seizures, the electroencephalogram offers the most important means of confirmation and characterization. Infants with normal background activity are much less likely to develop seizures than are those with significant background abnormalities (77).

Interictal Background and Prediction Value

The ongoing cerebral electrical activity is the stage on which the drama of the episodic electrographic seizure unfolds. In many ways, the integrity of the EEG background is as critical than the mere presence or absence of the seizures themselves. For example, with or without electrographic seizures, an extremely abnormal EEG background (burst suppression or isoelectric recording) inherently conveys a sense of profound electrophysiologic disruption and forecasts a high risk for death or adverse neurologic outcome. Conversely, a nearly normal interictal EEG background suggests relatively preserved neurologic health despite the unwanted intrusion of the seizures.

The interictal background also occasionally can offer clues to seizure etiology. Persistently unifocal sharp waves (arising from a very limited region of the cortex) may suggest a restricted injury such as localized subarachnoid hemorrhage, contusion, or stroke, whereas multifocal sharp waves suggest diffuse dysfunction. Hypocalcemia is a consideration if a well-maintained background features excessive bilateral central spikes. Inborn errors of metabolism, such as maple syrup urine disease, are sometimes associated with distinctive vertex wicket spikes. Pseudoperiodic discharges raise the suspicion of herpes simplex virus encephalitis or an acute destructive localized lesion such as stroke or hemorrhage. A grossly abnormal electroencephalogram in the absence of any obviously acquired disease suggests cerebral dysgenesis.

Interictal EEG spikes per se have uncertain diagnostic significance (78). Interictal focal sharp waves and spikes are not typically considered indicators of epileptogenesis in the same way as they are in older children and adults. Compared with those of age-matched neonates without seizures (79,80), the interictal records of infants with electroencephalogram-confirmed seizures have background abnormalities, excessive numbers of "spikes" (lasting <200 msec) compared with sharp waves (lasting >200 msec), excessive occurrence of spikes or sharp waves per minute, and a tendency for "runs," "bursts," or "trains" of repetitive sharp waves. However, only a few infants with confirmed seizures exhibit all of these interictal characteristics, and many show no excessive spikes or sharp waves. Routine duration interictal EEGs are inadequate to characterize neonatal seizure burden (81).

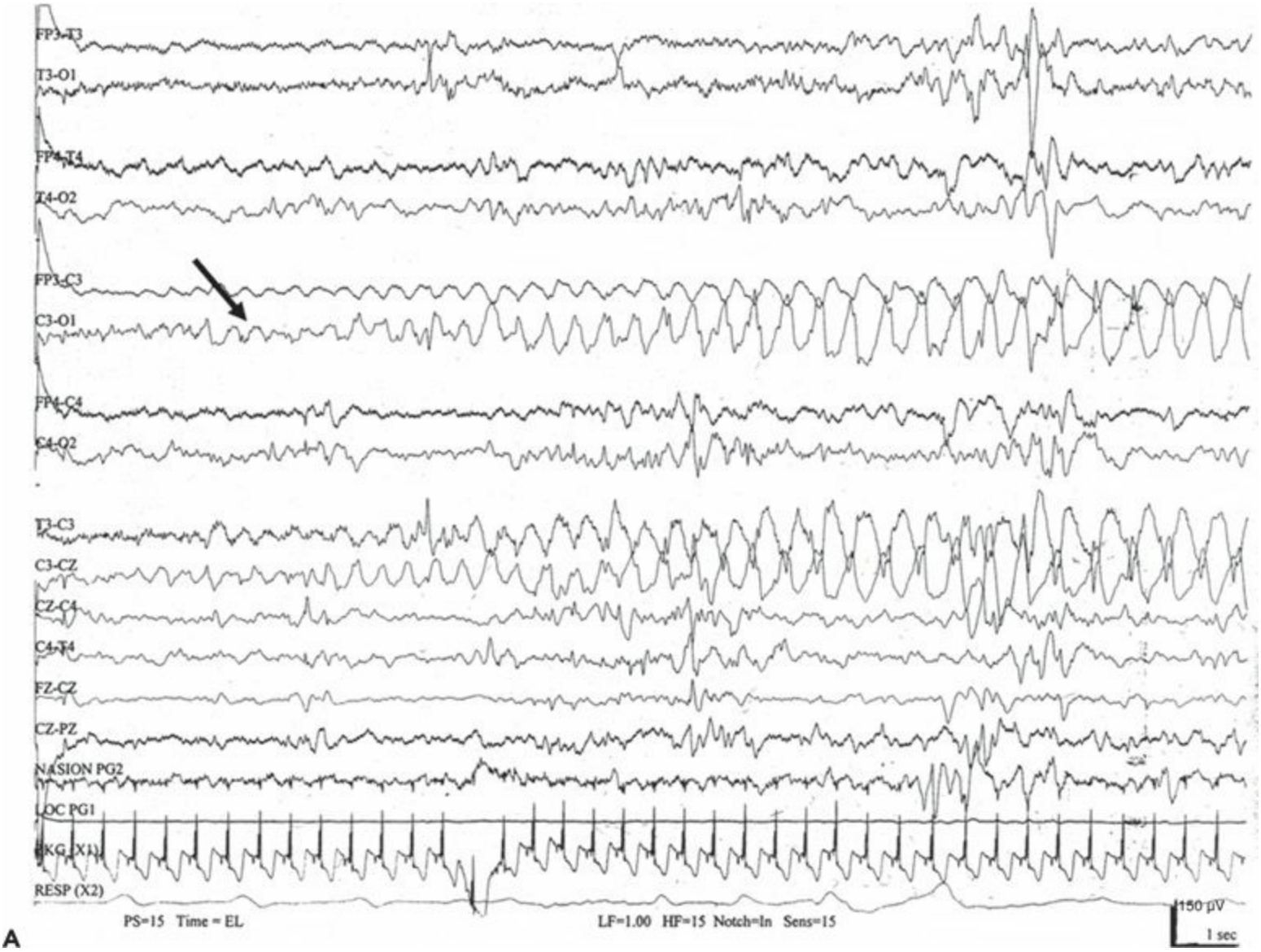
Characteristics

At the heart of the epileptic process is the abnormal, excessive, repetitive electrical firing of neurons. Affected neurons lose their autonomy and are engulfed by the synchronized bursts of repeated electrical discharges. As excitatory neurotransmission fails, the electrophysiologic cascade is interrupted and the seizure ends. Electrographic seizures in the neonate have varied appearances and are relatively rare before 34 to 35 weeks conceptional age. The morphology, spatial distribution, and temporal behavior of the seizure discharges may differ within and between individuals. Despite the differences between the term and preterm neonatal brain, the variety of types of electrographic seizures does not differ between them (82).

Morphology

An electrographic seizure is a discrete abnormal event lasting at least 10 seconds, with a definite beginning, middle, and end (83). No single morphologic pattern characterizes a seizure (Fig. 35.6). Even in the same patient, the ictal EEG activity may appear pleomorphic. The "typical" neonatal seizure begins as low-amplitude, rhythmic, or sinusoidal waveforms or spike or sharp waves. As the

seizure evolves, the amplitude of the ictal activity increases, while its frequency slows (84). Spikes or sharp waves are not necessarily present. Instead, rhythmic activity of any frequency (delta, theta, alpha, or beta) can make up the ictal patterns at the scalp surface.



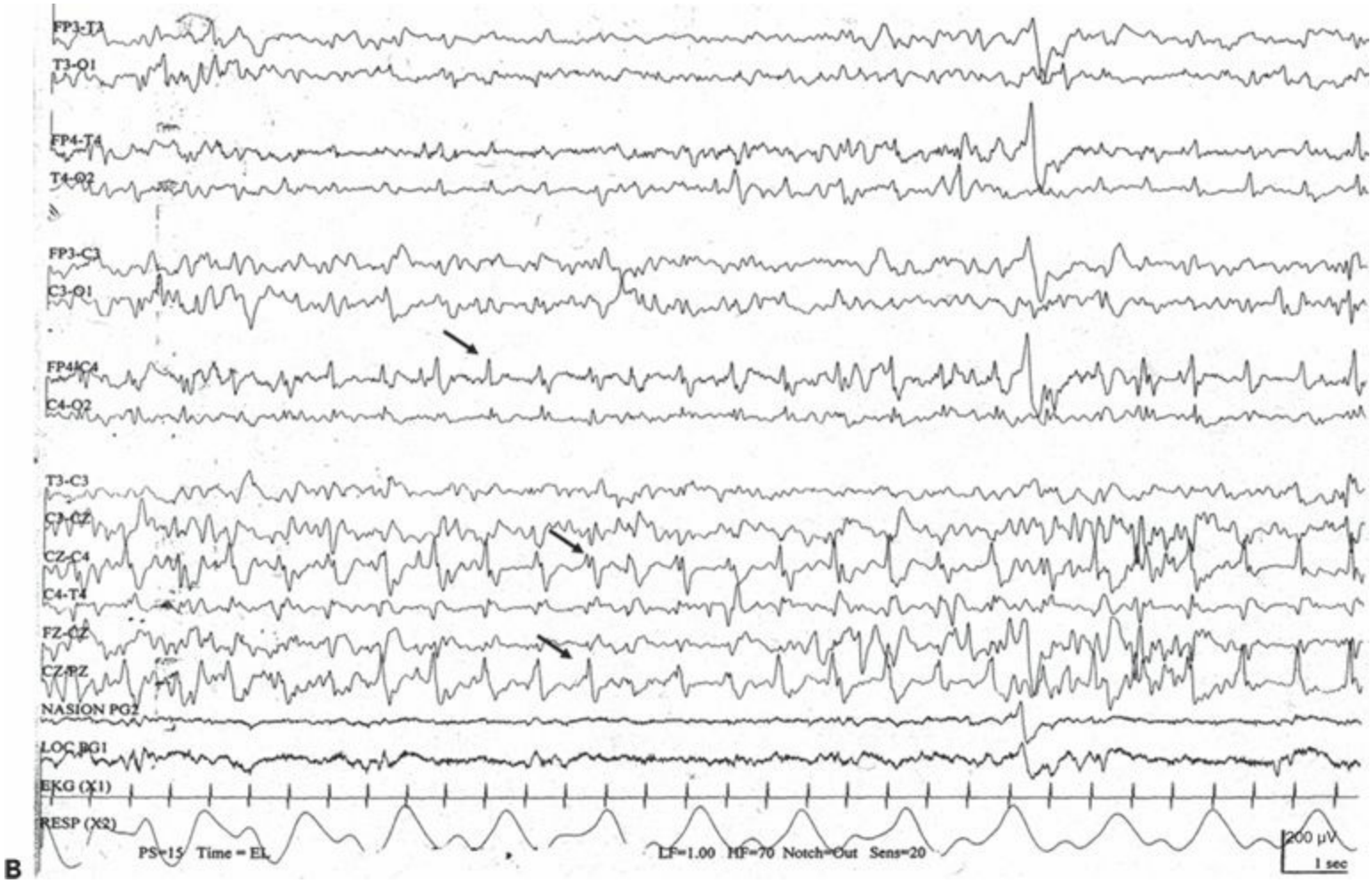


Figure 35.6. No single morphologic pattern characterizes electrographic neonatal seizures; rather, their distinctive behavior as a discrete, evolving electrographic event identifies them as ictal. **A:** A focal seizure arises from C_3 (arrow) as low-amplitude, rhythmic theta activity that gradually changes to higher- amplitude delta activity. **B:** An electrographic seizure is in progress as repetitive spikes in the right frontopolar, central, and midline vertex regions (arrows).

Spatial Distribution

In older children, generalized seizures may appear simultaneously, synchronously, and symmetrically in both hemispheres. In the neonatal brain, which lacks the physiologic organization necessary for such exquisite orchestration, individual seizures always arise focally and then migrate and spread. Seizures may also migrate from one hemisphere to another (68). Occasionally, simultaneous focal seizures may appear to behave independently, spreading to all brain regions and superficially masquerading as a "generalized seizure." However, the ictal patterns are not those of the truly generalized seizures.

Diffuse causes of encephalopathy such as meningitis, hypoglycemia, or hypoxia–ischemia may cause focal seizures or induce multiple seizures that each originate from different scalp regions—so-called multifocal-onset seizures; those that arise from the same scalp location are unifocal onset and raise the possibility of a localized structural abnormality such as a stroke (83), reflecting the restricted functional disturbance.

Temporal Profile

The typical duration of an individual electrographic neonatal seizure is about 1 to 2 minutes and is followed by an interictal period of variable length (Fig. 35.7). These temporal characteristics were

obtained from relatively brief tracings randomly selected during a variety of acute encephalopathies (8). A study of the temporal characteristics of 15 patients with HIE found the median seizure duration to be 206 seconds (interquartile range IQR 98 to 331 seconds) (85). Eleven of 15 patients had a total seizure duration in excess of 30 minutes per hour, a commonly used definition for neonatal status epilepticus, since solitary, prolonged electrographic seizures are uncommon in newborns. Repetitive brief serial seizures are much more characteristic than prolonged seizures lasting many hours. Other investigators have also reported status epilepticus during therapeutic hypothermia for neonatal HIE (86).

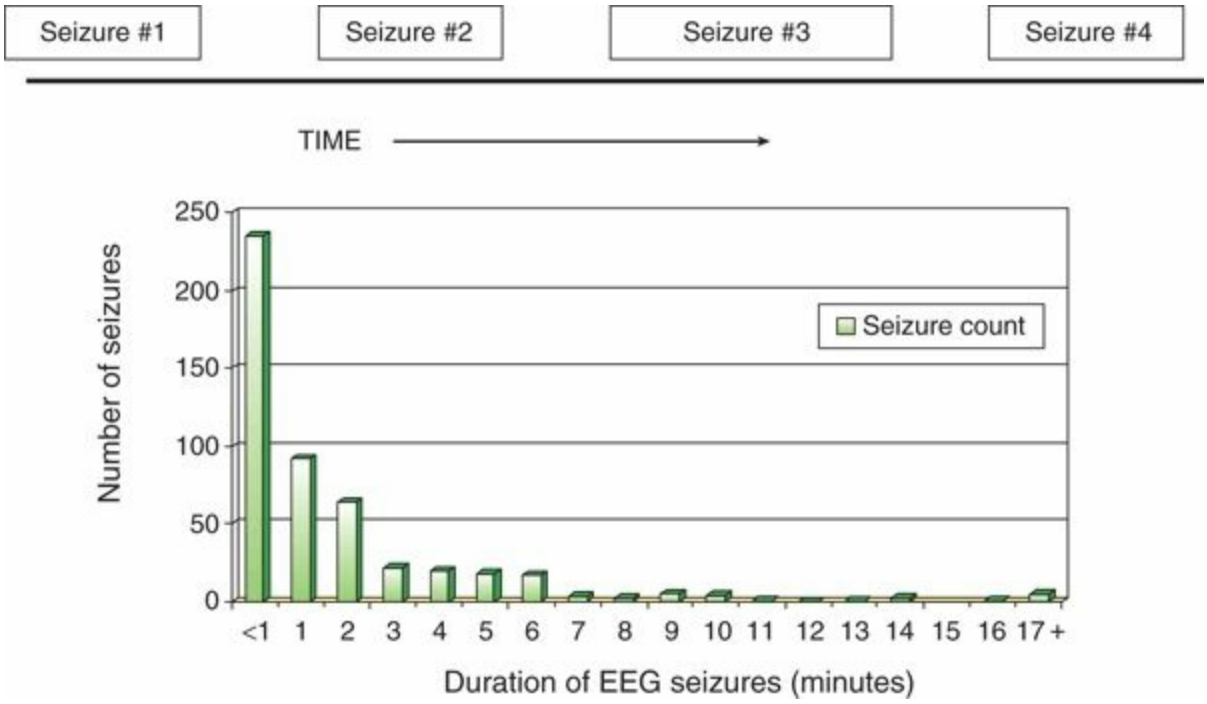


Figure 35.7. In most neonates with electrographic seizures, the electroencephalogram shows a series of brief ictal events, typically lasting <2 minutes, followed by varying- length interictal periods. The histogram shows the distribution of durations (minutes) of 487 electroencephalographic seizures recorded from 42 neonates. (Adapted from Clancy RR, Legido A. The exact ictal and interictal duration of electroencephalographic neonatal seizures. Epilepsia. 1987;28(5):537–541.)

Neonates may demonstrate events that have morphologic characteristics of electrographic seizures with a duration of <10 seconds. These discharges have been termed brief rhythmic discharges (BRDs) or brief intermittent rhythmic discharges (BIRDs) (87). The significance of these discharges is unclear. A study of 340 subjects noted that BIRDs had a higher association with leukomalacia or hypoglycemia and were associated a higher risk of neurodevelopmental abnormalities (88). Another limited study found no significant difference in mortality and neurodevelopmental outcome for subjects with BIRDs or electrographic seizures; however, subjects with BIRDs only were less likely to have postnatal seizures (89). Given their frequent association with clear electrographic seizures, care should be taken to scrutinize the EEG closely for seizures.

Special Ictal Electroencephalographic Morphologies

Some ictal patterns unique to the neonatal period are associated with severe encephalopathies. Electrical seizures of the depressed brain are long, low in voltage, and highly localized. They may be unifocal or multifocal and show little tendency to spread or modulate. Not associated with clinical seizures, they occur when the EEG background is depressed and undifferentiated and suggest a poor

prognosis. Alpha (α) seizure activity (90–92) is characterized by sudden, transient, rhythmic activity in the α frequency range (8 to 12 Hz) in the temporal or central region, unaccompanied by clinical events. An α discharge usually indicates a severe encephalopathy and poor prognosis.

Video-EEG monitoring has been the basis of clinical investigations into the classification, therapy, and prognosis of neonatal seizures (93–95). It has become more widely available, but remains limited at many locations.

Amplitude-Integrated EEG

Amplitude-integrated EEG (aEEG) is becoming increasingly used in the neonatal intensive care unit setting for bedside evaluation of cerebral activity. While various techniques are available, limited arrays of 2 or 4 two electrodes are commonly used to acquire data that are then processed and compressed to provide a simple trend of the background EEG activity in those regions (Fig. 35.8). Advantages over conventional EEG include widespread availability, ease of application, and the lack of dependence on specially trained neurophysiologists. The compressed data provides information about the background of the EEG that can be used for prognostic purposes, including inclusion in therapeutic neuroprotection (e.g., cerebral head cooling) (96). There is acceptable agreement between conventional EEG and aEEG background classifications when the tracings are normal or when markedly abnormal. For example, both techniques would correctly identify a flat or burst suppression tracing. However, the agreement between these two techniques is much poorer among the middle-ground, "moderately abnormal" aEEGs (97).

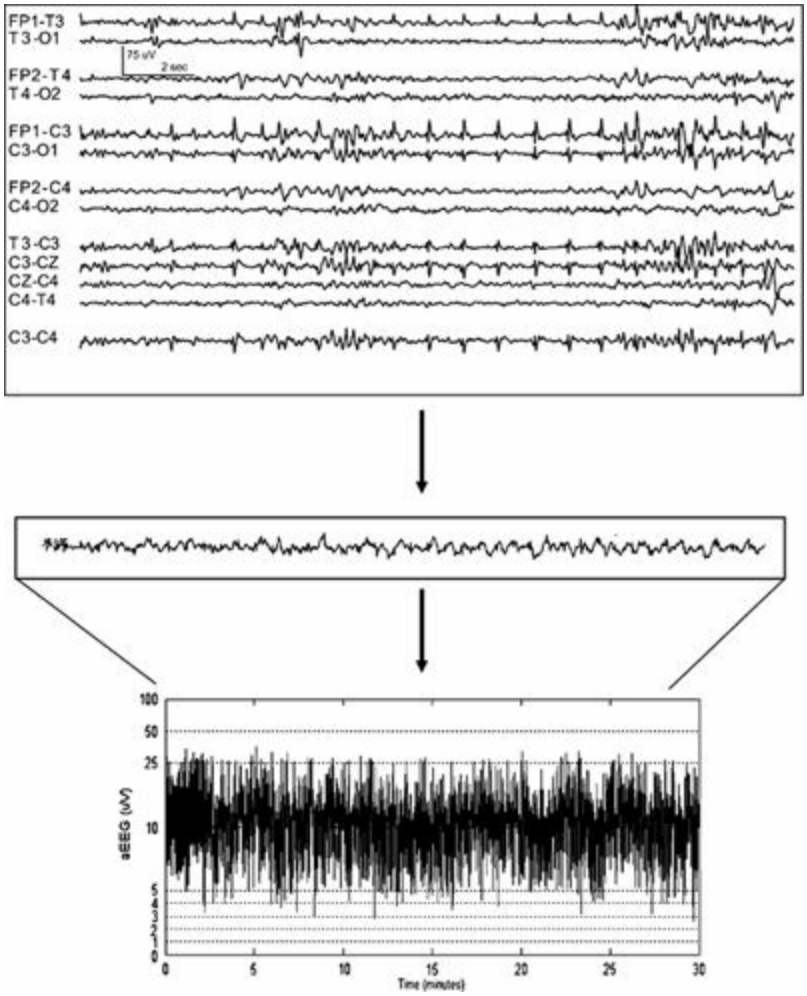


Figure 35.8. The routine neonatal EEG examination typically displays 12 or more channels from the full array of the 10 to 20 system.

Cerebral function monitors, such as aEEG, use a single channel from a pair of scalp electrodes (commonly the left and right parietal regions) and then process the raw EEG to a compressed display, which is very useful for reviewing long-term trends.

Neonatal seizures can be detected with aEEG as sudden elevations of the lower and upper margins of the background tracing (Fig. 35.9). Studies comparing neonatal seizure detection between aEEG and conventional EEG demonstrate that only 22% to 57% of infants with seizures are accurately identified by neonatologist readers. These readers correctly detected 12% to 38% of the seizures confirmed by conventional EEG (Table 35.3) (98,99). Certain seizure characteristics influence their identification: amplitude, duration, number of seizures per hour, and the spatial restrictions imparted by sampling just 1 or 2 electrode pairs (99). Clearly, aEEG cannot supplant conventional EEG but can provide very useful complementary information that may guide decision making at the bedside in real time.

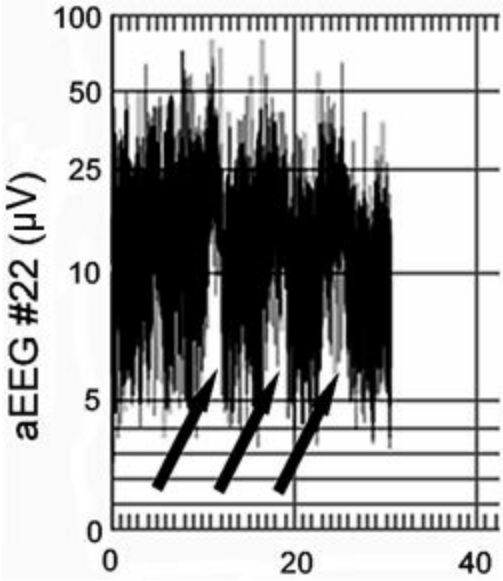


Figure 35.9. Thirty-minute aEEG in a term infant with three captured seizures (arrows).

Table 35.3 Comparisons of Conventional and Amplitude-Integrated EEG for Seizure Detection

Diagnostic tool	Neonates with seizures (%)	EEG seizures per neonate (%)
Conventional EEG ("gold standard")	100	100
Single channel of "raw" EEG (C3 → C4)	94	78
aEEG of single-channel EEG (C3 → C4)	22–57	12–38
Single channel of "raw" EEG at the forehead (Fp3 → Fp4)	66	46

Continuous EEG Monitoring (cEEG) of Neonates

The ACNS has published guidelines that provide a recommendation for monitoring neonates in the ICU (100). Listed indications for cEEG include evaluation for electrographic seizures and to judge

the severity of encephalopathy. The committee recommended monitoring of high-risk neonates for seizures for 24 hours and, if seizures are detected, until the patient is seizure free for at least 24 hours. The ACNS has also published a guideline for standardized terminology and categorization of cEEG in neonates (101).

Measures of Electrographic Seizure "Burden"

Most electrographic neonatal seizures do not provoke distinctive clinical signs (102) (Fig. 35.10). It would be useful to develop measures of the "burden" of electrographic seizures in individual infants.

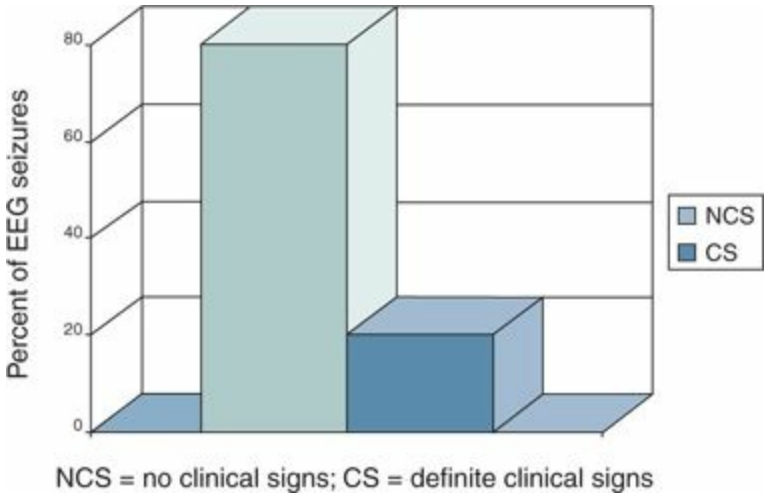


Figure 35.10. In one study, only 20% of electrographic neonatal seizures produce definite clinical signs. (Adapted from Clancy RR, Legido A, Lewis D. Occult neonatal seizures. Epilepsia. 1988;29(3):256–261.)

The simplest measure is to simply consider them dichotomously "present" or "absent." However, the number of recorded electrographic seizures varies widely, so a simple seizure frequency count could be used (Fig. 35.11). For example "there were four seizures in the 1st hour and two in the 2nd hour of monitoring." Because individual electrographic seizures also vary in length, another measure of EEG seizure burden is to describe the percentage of time in which seizure activity is present in any brain region. This can range from a 0% if no seizures are captured to 100% if the entire record demonstrates seizure activity anywhere in the brain. Unfortunately, there is only a modest (albeit statistically significant) correlation between seizure frequency counts and the percentages of the recordings showing seizure activity (99). The most detailed measure of seizure burden further incorporates knowledge of their numbers, durations, and spatial distributions. Individual electrographic seizures may remain confined to their area of origin or may spread substantially to other regions (103). This varies considerably among individual neonates (Fig. 35.12) (95). A comprehensive approach to measure EEG seizure burden, temporal–spatial analysis, reduces the entire neonatal montage into five nonoverlapping areas of interest (104): (Fig. 35.13). The percentage of ictal time at each of these five regions gives the most comprehensive picture of the geographic distribution of seizure burden. Future investigations may determine whether a "dose–response" curve exists between this fuller, temporal–spatial measure of seizure burden and eventual long-term neurodevelopmental follow-up.

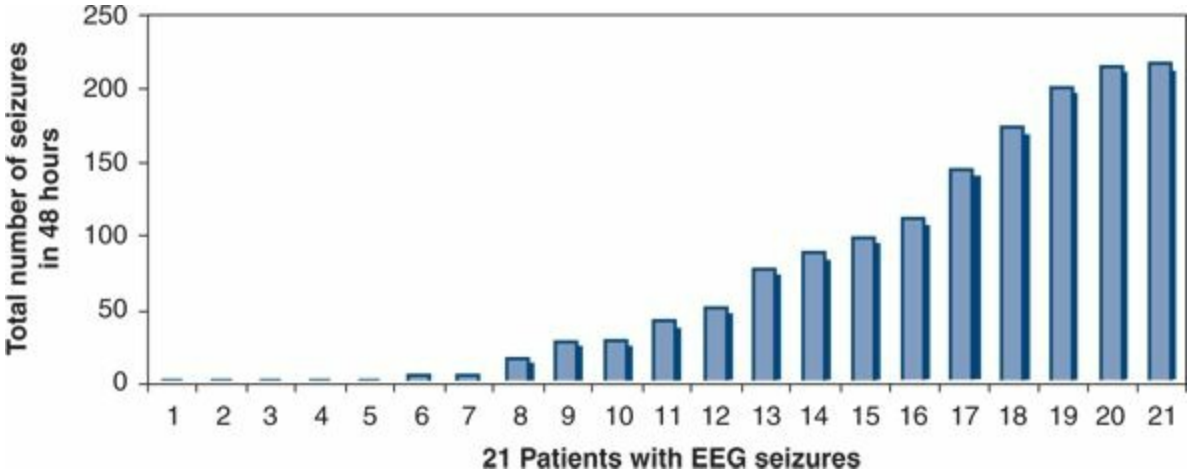
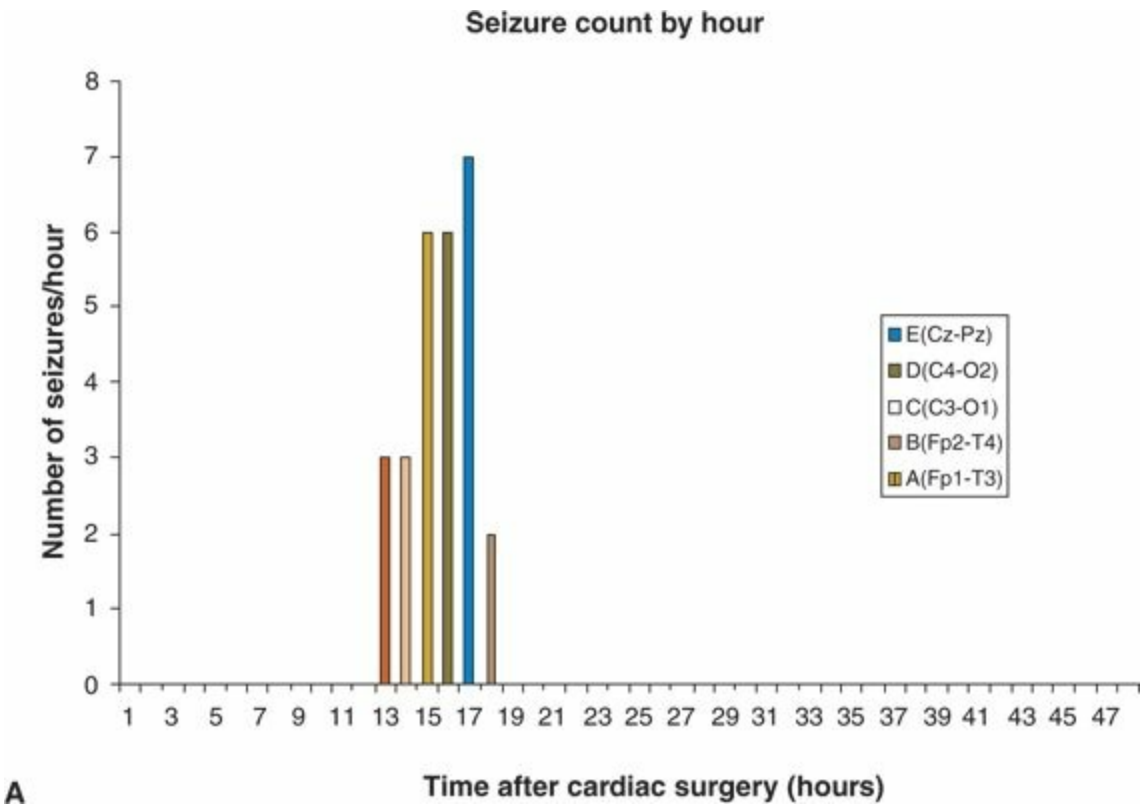


Figure 35.11. Distribution of the total number of electrographic neonatal seizures during 48 hours of electroencephalograph monitoring after newborn heart surgery. From 1 to 217 seizures occurred during the study period. (Adapted from Sharif U, Ichord R, Saymor JW, et al. Electrographic neonatal seizures after newborn heart surgery. Epilepsia. 2003;44:164.)



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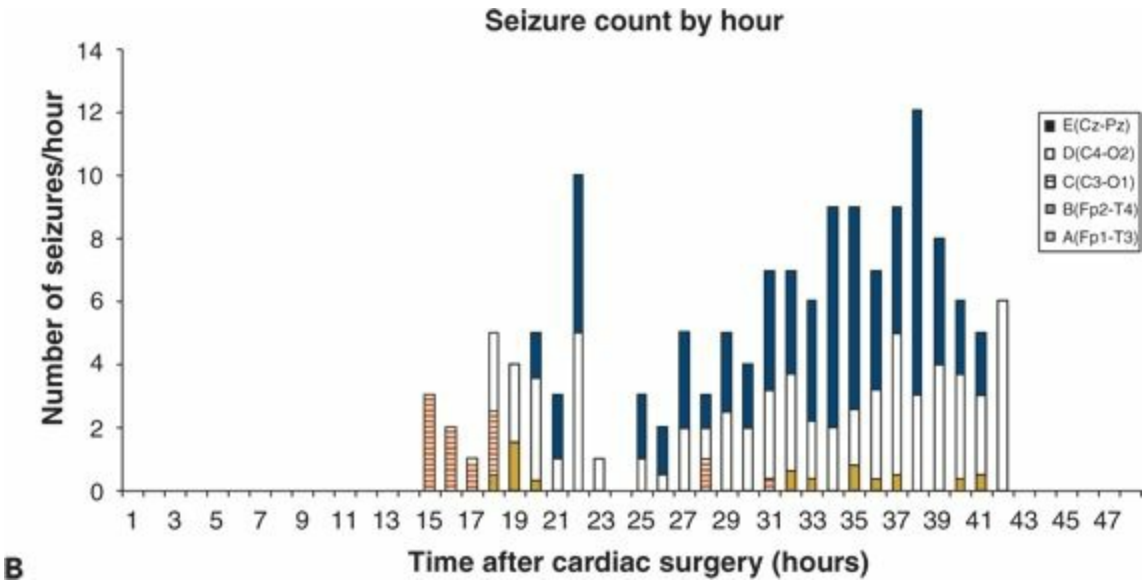


B

Figure 35.12. The spatial distribution of electroencephalographic (EEG) seizures varies among neonates. **A:** All EEG seizures begin in a single brain region (C_4–O_2). **B:** EEG seizures begin in four locations (C_Z–P_Z, C_4–O_2, C_3–O_1, and Fp_2–T_4). (Adapted from Sharif U, Ichord R, Saymor JW, et al. Electrographic neonatal seizures after newborn heart surgery. Epilepsia. 2003;44:164.)

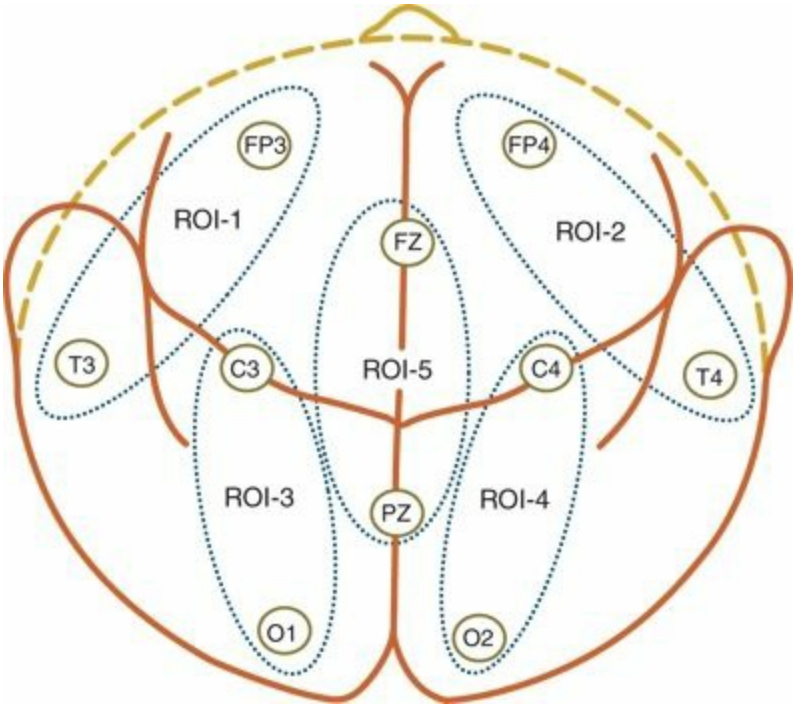


Figure 35.13. The entire array of the standard neonatal electroencephalogram can be reduced to five nonoverlapping regions of interest that identify the spatial characteristics of electroencephalographic seizures.

ETIOLOGIC FACTORS

Acute or chronic conditions can give rise to seizures. In most cases, specific causes can be determined after analysis of clinical and laboratory information (Table 35.4). Table 35.5 lists potential causes of neonatal seizures, but only a few are discussed in detail.

Table 35.4 Data to Determine the Etiology of Neonatal Seizures

Clinical	Complete history, general physical and neurologic examinations, eye examination
Neuroimaging	Computerized tomographic or magnetic resonance imaging
Blood tests	Arterial blood gases and pH
	Sodium, glucose, calcium, magnesium, ammonia, lactate and pyruvate, serum amino acids
	Comprehensive "neogen" panel[a]
	TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus, and herpes simplex) titers
	Biotin
Urine tests	Reducing substances, sulfites, organic acids
	Toxicologic screen
Cerebrospinal fluid tests	Red and white blood cell counts
	Glucose and protein
	Culture
	Neurotransmitter profile[b]

[a]Varies by US states.

[b]In the proper clinical context.

Table 35.5 Etiologies of Neonatal Seizures

Acute	Chronic
Acute neonatal encephalopathy (includes classic hypoxic–ischemic encephalopathy, both ante- and intrapartum)	Isolated cerebral dysgenesis, e.g., lissencephaly, hemimegalencephaly
Arterial ischemic stroke	Cerebral dysgenesis associated with inborn errors of metabolism
Sinovenous thrombosis	Chronic infection (TORCH [toxoplasmosis, other infections, rubella, cytomegalovirus, and herpes simplex] syndromes)
Extracorporeal membrane oxygenation	Neurocutaneous syndromes
Congenital heart disease	▪ Incontinentia pigmenti (Bloch–Sulzberger syndrome)
Vein of Galen malformation	▪ Hypomelanosis of Ito
Giant arteriovenous malformation	▪ Sturge–Weber syndrome
Hypertensive encephalopathy	▪ Tuberous sclerosis
Intracranial hemorrhage (subdural subarachnoid, intraventricular, intraparenchymal)	▪ Linear sebaceous nevus (epidermal nevus syndrome)
Trauma (intrapartum and nonaccidental)	Genetic conditions
Infections (sepsis, meningitis, encephalitis)	▪ 22Q11 microdeletion
Transient, simple metabolic disorders	▪ ARX (aristaless-related homeobox) mutations
Inborn errors of metabolism (including pyridoxine-dependent seizures)	
Intoxication	Specific very early onset epilepsy syndromes
	▪ Fifth-day fits (benign neonatal convulsions)
	▪ Benign familial neonatal seizures
	▪ Early myoclonic encephalopathy
	▪ Early infantile epileptic encephalopathy
	▪ Migrating partial seizures of infancy

Acute Causes

Diffuse Hypoxic–Ischemic Etiologies

Probably the most common cause of neonatal seizures, "acute neonatal encephalopathy" (105) is characterized by depressed mental status (lethargy or coma), seizures, axial and appendicular hypotonia with an overall reduction in spontaneous motor activity, and clear evidence of bulbar dysfunction with poor sucking, and swallowing, and an inexpressive face (106). Care should be taken to separate this generic designation from neonatal HIE. Not every infant who is acutely encephalopathic has suffered hypoxia–ischemia (107). The American College of Obstetricians and Gynecologists Task Force on Neonatal Encephalopathy and Cerebral Palsy suggests four diagnostic criteria for HIE: (i) evidence of metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH value <7 and base deficit >12 mmol/L), (ii) early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation, (iii) subsequent cerebral palsy of the spastic quadriplegic or dyskinetic type, and (iv) exclusion of other identifiable etiologies such as trauma, coagulation disorders, infectious conditions, or genetic disorders (108). These four conditions should occur in the context of a "sentinel" hypoxic event immediately before or during labor, such as uterine rupture, abruption of the placenta, or prolapse of the umbilical cord. There should also be a sudden and sustained fetal bradycardia or the absence of fetal heart rate variability; persistent, late, or variable decelerations; Apgar scores of 0 to 3 after 5 minutes; and, in most, multisystem involvement within 72 hours of birth. Examples of multisystem malfunction (109) include acute renal tubular necrosis, elevated values of liver function tests, necrotizing enterocolitis from bowel ischemia, and depressed blood cell lines (e.g., thrombocytopenia) because of ischemic injury of the bone marrow (110). Early imaging studies should show acute diffuse cerebral abnormalities consistent with hypoxia–ischemia. A recent intriguing investigation in this specific hypoxic–ischemic scenario is the development of intraneuronal alkalosis as a specific trigger for seizures, which can be treated by unique paradigms of ventilatory management in which normocapnia was gradually, rather than abruptly, restored (111,112).

Other conditions that can clinically mimic acute neonatal HIE are some of the inborn errors of metabolism, pyridoxine dependency, stroke, coagulopathies, sinovenous thrombosis, and "fetal sepsis syndrome" (113–116), which can occur with sepsis or chorioamnionitis (117,118). The latter is suspected in a mother with abdominal pain and tenderness, fever, leukocytosis, and foul-smelling amniotic fluid and can be confirmed by pathologic examination of the placenta and umbilical cord (119).

Perinatal stroke is defined as a cerebrovascular event occurring between 28 weeks of gestation and 7 days of age. The incidence is 1 in 4000 live births (120). There are two main clinical presentations: (i) acute appearance of neonatal seizures, hypotonia, feeding difficulties, and, rarely, hemiparesis (83,119,121,122) (Fig. 35.14) and (ii) later discovery of stroke through the gradual appreciation of a congenital hemiparesis or the onset of a partial seizure disorder in an infant apparently healthy at birth. Risk factors include congenital heart defects (CHDs), blood and lipid disorders, infection, placental disorders, vasculopathy, trauma, dehydration, and extracorporeal membrane oxygenation (ECMO).

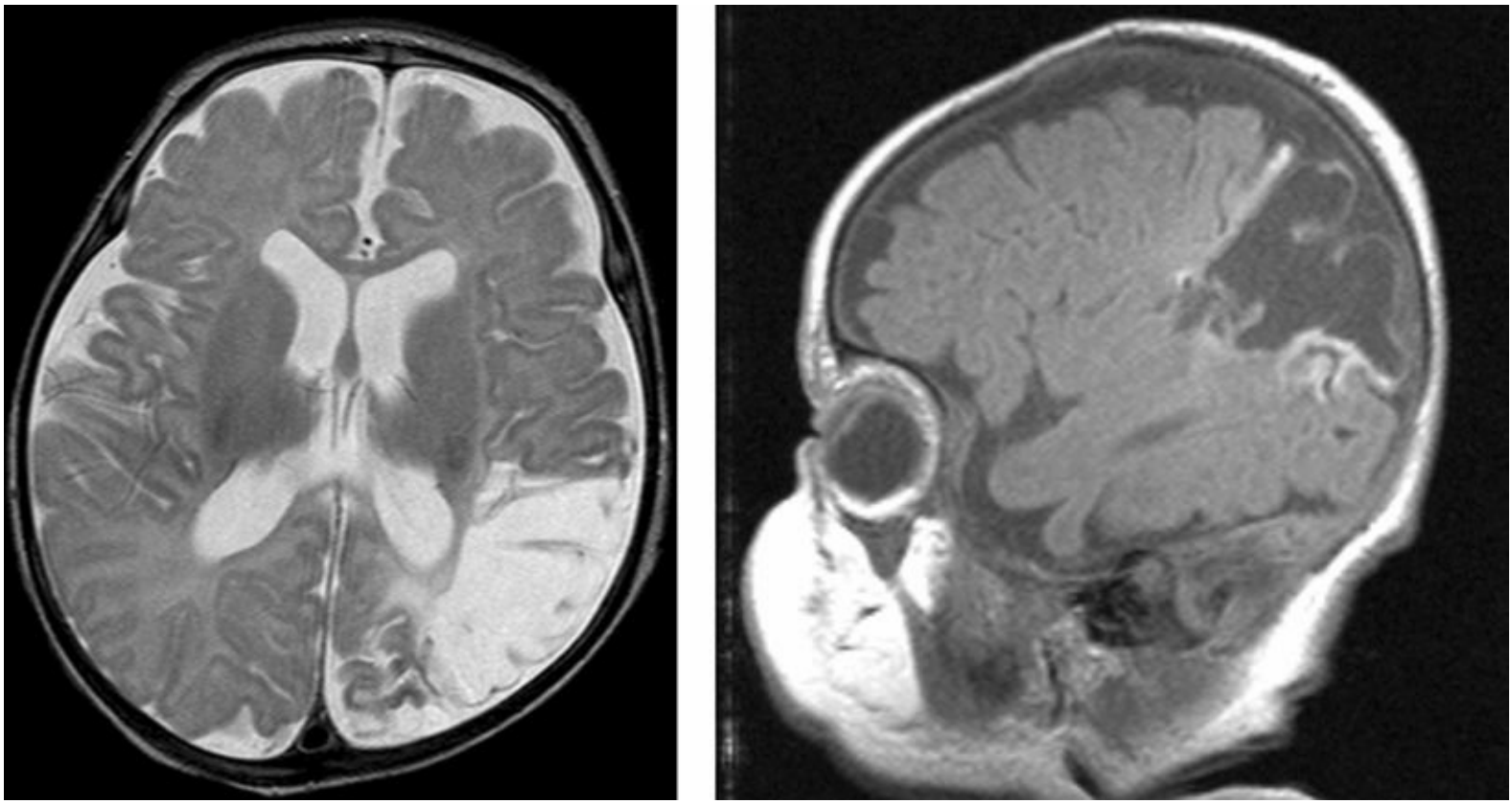
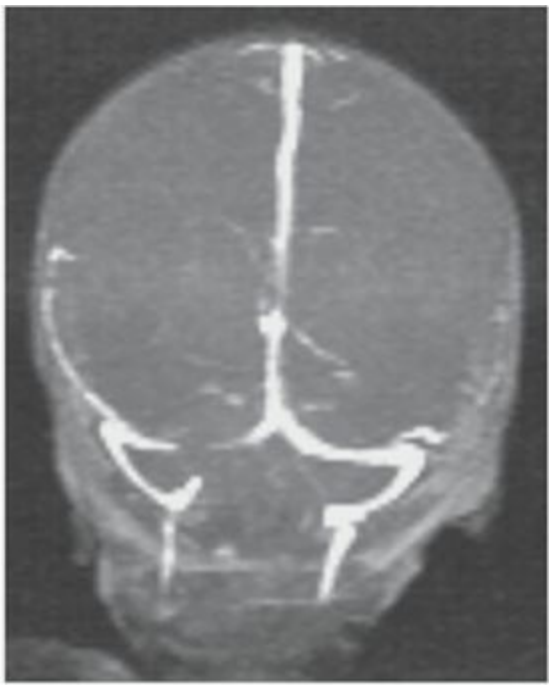


Figure 35.14. Arterial ischemic stroke in the distribution of the left middle cerebral artery in a 41-week–estimated gestational age infant with a prothrombotic disorder.

Cerebral sinovenous thrombosis is estimated to occur at a rate of 0.67 cases per 100,000 children per year (123,124) in neonates and older children. The neonatal presentation most frequently includes seizures (57% to 71%) and other nonspecific CNS signs such as lethargy (35% to 58%), but only infrequently frank hemiparesis (123,125) (Fig. 35.15). Maternal risk factors associated with thrombosis included preeclampsia/hypertension, gestational diabetes, and meconium aspiration or meconium-stained placenta (125). The sagittal and transverse sinuses are most commonly involved, but multiple sinus thromboses also occur. The reported outcomes include a variable mortality rates from 2% to 13%; 21% developed normally while 60% had cognitive impairment, 64% had motor impairment, and 40% had epilepsy (125,126).



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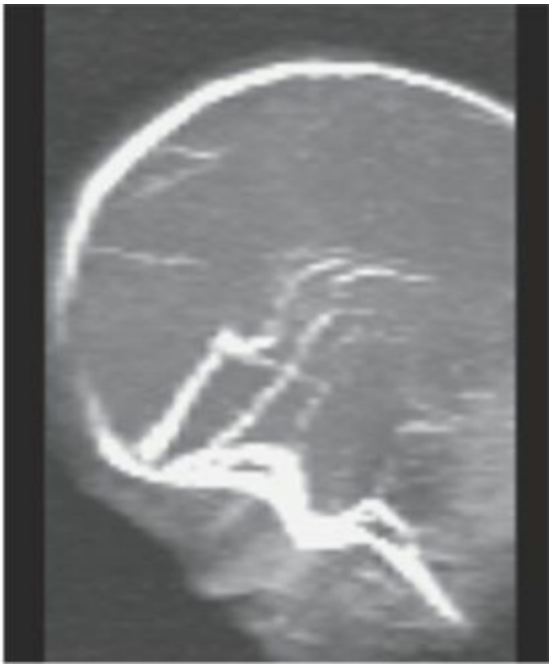

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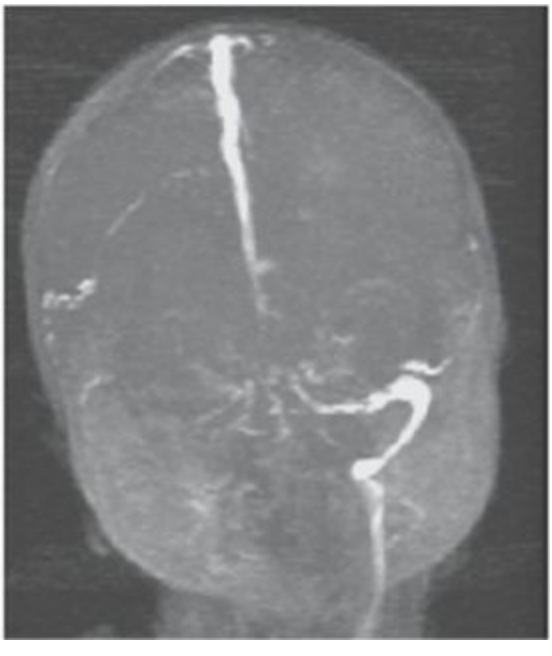

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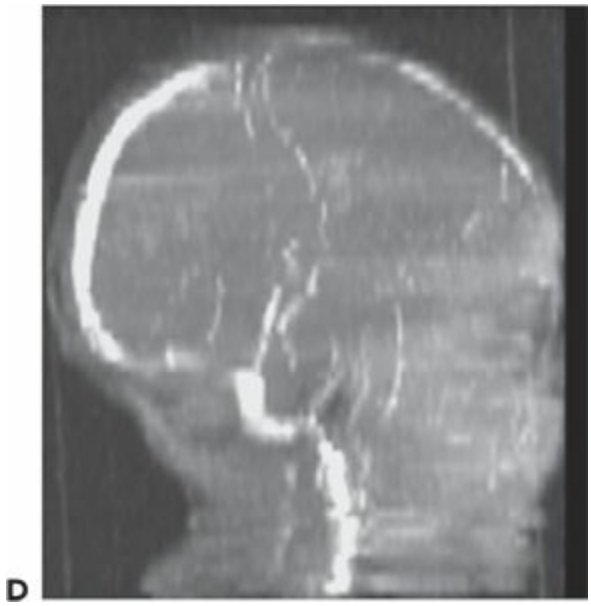

Figure 35.15. Magnetic resonance venogram of a 2-week-old term infant admitted for seizures, lethargy, and dehydration. **A,B:** Thrombosis of the right transverse sinus was noted on the 1st day of hospitalization. **C,D:**By day 10, the thromboses had extended to the sigmoid, jugular, and straight sinuses.

ECMO is an effective therapy for newborn infants with life-threatening respiratory failure unresponsive to maximum conventional medical support. However, the procedure requires ligations of the right common carotid artery and right jugular vein at a time when the infants' underlying lung disease may render them particularly vulnerable to the effects of diffuse CNS hypoxia–ischemia. The high rate of subsequent neurologic morbidity among survivors raises the possibility that ECMO itself may contribute to ischemic–reperfusion brain injuries (127). A high proportion of survivors have MRI-identified focal parenchymal brain lesions, often announced by seizures during ECMO. Cerebral hemorrhage and infarction have been reported in 28% to 52% of ECMO-treated infants (128).

CHDs enhance the risk for neonatal seizures (129), which can arise preoperatively or postoperatively. Strokes may occur from multiple mechanisms including right-to-left intracardiac shunting or embolization during cardiac catheterization (130). CHDs also may be associated with the presence of other midline somatic defects including CNS anomalies. Seizures can arise from concurrent cerebral dysgenesis as well (131). Hypocalcemia may trigger seizures in the setting of DiGeorge syndrome. However, seizures usually arise after NBHS; they do not occur at random, but, rather, are influenced by suspected or confirmed genetic disorders, aortic arch obstruction, or the need for prolonged deep hypothermic circulatory arrest (132). This population is especially valuable for neuroprotection trials, because the child's status can be determined before surgery (133).

Metabolic Etiologies

Hypoglycemia, hyponatremia, hypernatremia, hypocalcemia, hypomagnesemia, and acute hyperbilirubinemia (acute kernicterus) can be associated with neonatal seizures. These conditions are detectable by simple screening tests (see Table 35.4).

Hypoglycemia may itself cause brain damage independent of the seizures. Causes of hypoglycemia that should be evaluated in children include simple prematurity, maternal diabetes, nesidioblastosis, galactosemia, defects of gluconeogenesis, glycogen storage diseases, and respiratory chain defects. Glucose transporter type I syndrome (GLUT I deficiency) is characterized by infantile seizures that usually begin between 6 and 12 weeks of life, developmental delay, ataxia,

and progressive microcephaly (134–136). Affected newborns appear normal at birth. Neonatal seizures, initially rare, increase in frequency as the developmental delay becomes evident. The resultant diminution in transported glucose at the blood–brain barrier markedly reduces brain and cerebrospinal fluid values. Genetic studies often implicate mutations in SLC2A1. The ketogenic diet is a highly effective treatment modality since it provides an alternate form of fuel for the CNS.

Inborn Errors of Metabolism

For a detailed discussion, see Chapter 31. The discussion below is limited to the diagnosis of common neonatal conditions amenable to treatment with a specific intervention.

Maple syrup urine disease, ketotic and nonketotic hyperglycinemia, and urea cycle disorders may all induce a severe acute encephalopathy with seizures. Nonketotic hyperglycinemia has a catastrophic clinical presentation (aptly named glycine encephalopathy) with intractable seizures, coma, hiccups, apnea, pupil-sparing ophthalmoparesis, spontaneous and stimulus-provoked myoclonus, and a burst suppression pattern on electroencephalography (137). Glycine levels are elevated in the blood and cerebrospinal fluid. The disorder represents an inability to cleave glycine, which is both an excitatory and inhibitory neurotransmitter. Treatment involves an NMDA receptor antagonist, as well as magnesium, sodium benzoate, and dextromethorphan.

The ketotic hyperglycinemias and propionic and methylmalonic acidemias present with overwhelming multisystem failure and dehydration, ketoacidosis, and fulminant CNS signs such as seizures, vomiting, and coma. Diagnosis is made by serum amino acid surveys and measurement of specific enzyme activity.

Carbamoyl phosphate synthetase deficiency, ornithine carbamoyltransferase deficiency, citrullinemia, and argininosuccinic acidemia are among the large number of urea cycle abnormalities, and each causes neonatal seizures in the 1st days or weeks of life. Coma and prominent bulbar dysfunction are noted with ophthalmoparesis, fixed pupils, absent gag reflex, poor sucking, and apnea. The degree of serum ammonia elevation may correlate with the discontinuity in the abnormal EEG backgrounds (138).

Biotinidase deficiency may produce alopecia, seborrheic dermatitis, developmental delay, hypotonia, and ataxia. Seizures may begin as early as the 1st week of life. The diagnosis is made by measurement of blood levels of biotinidase activity. Oral administration of free biotin daily is the treatment.

Pyridoxine-dependent seizures (139,140) usually arise between birth and 3 months of age, although atypical cases have been reported up to 3 years. Some seizures can be appreciated in utero (141). The neonate presents with agitation, irritability, jitteriness, diminished sleep, and intractable clonic seizures. The EEG patterns are entirely nonspecific and include abnormal backgrounds, excessive multifocal sharp waves, and focal electrographic seizures evolving to hypsarhythmia later in the 1st year. Intravenous administration of 50 to 100 mg of pyridoxine causes cessation of seizures and disappearance of epileptiform EEG activity within a few hours of administration. Lifelong therapy with pyridoxine 50 to 100 mg/day is necessary. Despite early treatment, some neonates are eventually retarded and show MRI evidence of a leukodystrophy. Mutations in α-aminoadipic semialdehyde (α-AASA) dehydrogenase (antiquitin) leading to inactivation of pyridoxal phosphate (PLP) have been found in multiple individuals with pyridoxine-dependent seizures (142). PLP is an essential cofactor in multiple enzymatic reactions, including the formation of GABA. Elevations of urinary α-AASA can be used as a screening tool for identifying individuals with antiquitin mutations.

However, this should not substitute for a pyridoxine trial, especially in the acute setting. Mutations in pyridox(am)ine 5′-phosphate oxidase may cause early neonatal seizures due to decreased synthesis of PLP. Treatment with PLP is necessary to overcome this defect (143).

Folinic acid–responsive neonatal seizures were first described by Hyland as the unexpected appearance of seizures in term infants during the first few hours or days of life (144). Subsequently intractable, the seizures were associated with severe developmental delay, progressive atrophy on MRI examination, and frequent bouts of status epilepticus. Analysis of cerebrospinal fluid by means of high-performance liquid chromatography with electrochemical detection consistently revealed a characteristic peak that aided in diagnosis. Seizures ceased and the EEG pattern improved after the administration of 2.5 mg of folinic acid twice daily. Gallagher et al. (145) identified the biochemical marker for folinic acid–responsive seizures in two individuals who were controlled with pyridoxine. They identified gene mutations in antiquitin in those two individuals along with seven other individuals with folinic acid–responsive seizures. The authors suggest that the two conditions are allelic and recommend considering treating patients with α-AASA dehydrogenase deficiency with both pyridoxine and folinic acid.

Deficiency of the molybdenum cofactor and isolated sulfite oxidase deficiency are autosomal recessive errors that produce severe neurologic symptoms resulting from a lack of sulfite oxidase activity (146). The presentation includes poor feeding, an abnormally pitched cry, jitteriness, and intractable seizures with the presence of sulfites in the urine. Synthesis of molybdenum cofactor requires the activities of at least six gene products including gephyrin (147), a scaffolding protein present at inhibitory synapses. Unfortunately, there is no effective treatment, and prognosis for neurologic recovery and survival is poor.

Neonatal Intoxications

Lidocaine or mepivacaine inadvertently injected into the fetal scalp during local pudendal analgesia for the mother, cocaine, heroin (148), amphetamines, propoxyphene, and theophylline also may cause seizures.

Chronic Causes

Cerebral Dysgenesis

Some neonatal seizures result from long-standing disorders, such as cerebral dysgenesis, neurocutaneous syndromes, genetic disorders, or very early onset epilepsy. An MRI scan should be performed early to uncover cerebral dysgenesis (149). In lissencephaly or hemimegalencephaly (Fig. 35.16), no acute cause for seizures such as neonatal depression or birth trauma is present, and the infant appears outwardly well yet experiences seizures. The identification of cerebral dysgenesis on neuroimaging should not dissuade the clinician from seeking evidence of inborn errors of metabolism, as both may coexist (e.g., cytochrome oxidase deficiency, glutaric aciduria types I and II, 3-hydroxyisobutyric aciduria, 3-methylglutaconic aciduria, 3-ketothiolase deficiency, sulfite oxidase deficiency, pyruvate dehydrogenase deficiency, neonatal adrenoleukodystrophy, fumaric aciduria, long ketotic hyperglycinemia, and Zellweger syndrome) (150).

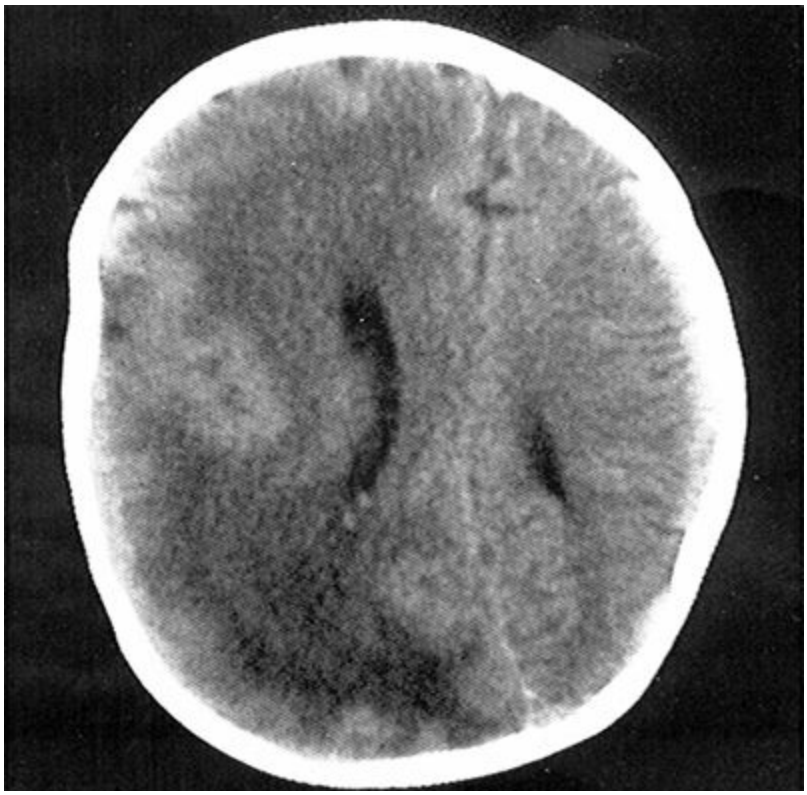

Figure 35.16. Computed tomography scan of the head showing right hemimegalencephaly with dysplastic and enlarged right cerebral hemisphere. Brain magnetic resonance imaging provides better resolution and definition of the abnormality and reveals subtle involvement of the contralateral hemisphere.

TORCH Infections

Chronic TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus, and herpes virus) infections can be identified by ophthalmologic changes, microcephaly, periventricular calcifications on neuroimaging, and appropriate serologic blood tests. Congenital infections acquired before the 4th month of gestation may cause an acquired form of migration defect and give rise to "dysgenetic" patterns on computed tomography (CT) or MRI scanning (151).

Neurocutaneous Syndromes

Among the neurocutaneous syndromes that may give rise to neonatal seizures is familial incontinentia pigmenti, a mixed syndrome of different mosaicisms (152). This X-linked dominant state is presumably lethal in males. Perinatal inflammatory vesicles are followed by verrucous patches that produce a distinctive pattern of hyperpigmentation and finally dermal scarring. The cause is a mutation in the IKBKG (NFκB essential modulator) gene (previously NEMO) located on Xq28 that renders cells susceptible to apoptosis when exposed to tumor necrosis factor alpha (TNF-α) (153). In contrast to the familial form, sporadic incontinentia pigmenti maps to Xp11 and is considered its "negative" pattern. Better known as hypomelanosis of Ito, its cutaneous lesions appear as areas of hypopigmentation.

Tuberous sclerosis may create neonatal seizures in two basic ways (154): first, through cortical tubers, which in the neonate may be easier to appreciate on CT scan than on MRI, and second, embolic stroke from intracardiac tumors. In the neonate, the classic neurocutaneous signs are often not apparent, except for hypomelanotic macules noted at or soon after birth; however, these may be evident only on skin examination under a Wood's lamp.

Linear sebaceous nevi are a family of disorders with distinctive raised, waxy, sometimes verrucous nevi on the scalp or face, associated with hemihypertrophy, hemimegalencephaly, and neonatal seizures (155).

Sturge–Weber syndrome is a sporadic syndrome featuring the distinctive port wine stain and associated vascular anomaly over the cortical surface. It may manifest with neonatal seizures.

Epilepsy Syndromes of Early Infantile Onset

In the 1970s, French neurologists coined the "fifth-day fits" (benign neonatal convulsions) to describe an electroclinical syndrome in which seizures unexpectedly arose between the 4th and 6th days of life (156). More than half had a distinctive "theta pointu alternant" pattern in which the bursts of cerebral electrical activity in the discontinuous parts of the record showed sharply contoured theta waves, especially in the central regions. This EEG pattern has also been recognized in patients with unmistakable HIE.

Benign familial neonatal epilepsy is the first idiopathic epilepsy syndrome discovered to be caused by a single gene mutation (157,158). Partial seizures unexpectedly begin by the 3rd day of life in neurologically normal-appearing patients, 10% to 15% of whom progress to epilepsy. Defects in KCNQ2 have been found to have a broad phenotypic spectrum ranging from classical BFNE to severe neonatal encephalopathy (157,159). BFNC with myokymia (160) has been reported as a separate mutation of KCNQ2, also on 20q13.3.

Migrating partial seizures in infancy constitute a constellation of unprovoked, alternating electroclinical seizures and subsequent neurodevelopmental devastation that was described in 1995 by Coppola et al. (161). Although multifocal neonatal seizures are not uncommon after infections, metabolic disorders, and hypoxia–ischemia, they can also accompany cerebral dysgenesis and some other neonatal seizure syndromes. In migrating partial seizures in infancy, healthy infants without cerebral dysplasia display multifocal partial seizures that arise independently and sequentially from both hemispheres (Fig. 35.17) within the first 6 months of life and progress through a period of intractability, ultimately leading to severe psychomotor retardation. As described in the original paper and later case reports, prognosis was very poor, with 28% mortality and the majority of survivors profoundly retarded and nonambulatory; however, later patients have fared somewhat better (162). A genetic etiology is presumed with a KCNT1 mutation found in two patients in a larger study of 14 patients (163).

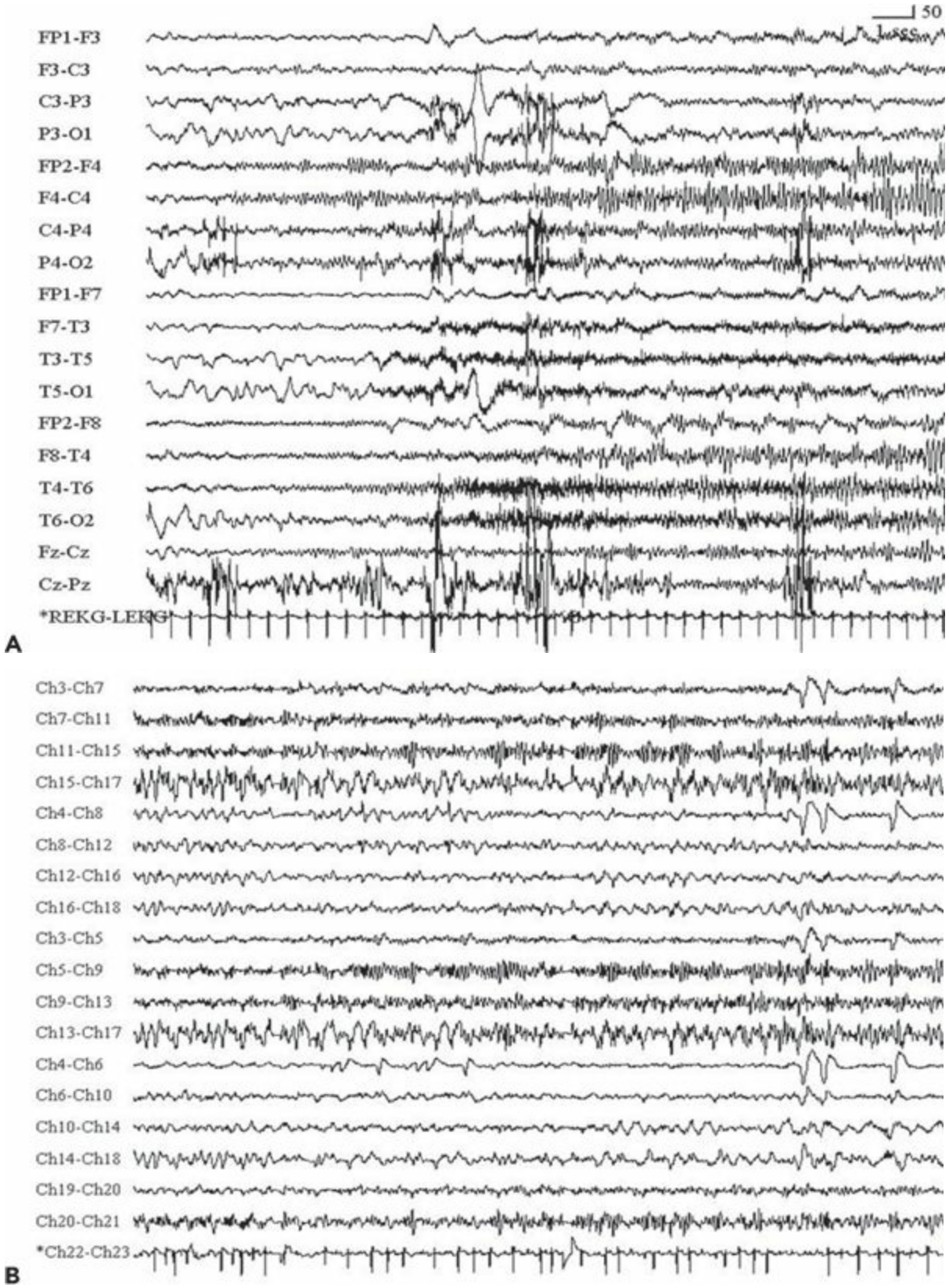

Figure 35.17. Migrating partial seizures in infancy. Seizure originating from the right hemisphere **(A)**, followed by one arising from the left hemisphere **(B)** (odd channel numbers represent the left hemisphere, and even channel numbers represent the right hemisphere). Note that the time axis of the electroencephalogram rhythm strip is slightly compressed. The time and amplitude calibration bar appears at the top of the figure: 1 second and 50 μV. (Adapted from Marsh E, Melamed S, Clancy R. Migrating partial seizures in early infancy: expanding the phenotype of a rare neonatal seizure type. Epilepsia. 2003;44:305, with permission.)

First described by Aicardi and Goutieres (164), EME is characterized by maternal reports of sustained, rhythmic fetal kicking, oligohydramnios or polyhydramnios, normal Apgar scores, and seizure onset from the 1st day of life to several months (typical age, 16 days). Clinical seizures

include erratic fragments of myoclonic activity, massive myoclonia, stimulus-sensitive myoclonia, and partial seizures. Electroencephalograms are eventually markedly abnormal, frequently with a burst suppression background. The myoclonic limb movements tend to occur during the burst periods of the burst suppression background (Fig. 35.18). All patients are completely resistant to antiepileptic drugs (AEDs). Other clinical features are progressive decline in head circumference percentiles, bulbar signs (especially apnea), feeding difficulties, cleft or high-arched palate, and severe psychomotor delay. A recent case report identified a disruption of the tyrosine protein kinase receptor ErbB4 in a patient with EME (165).

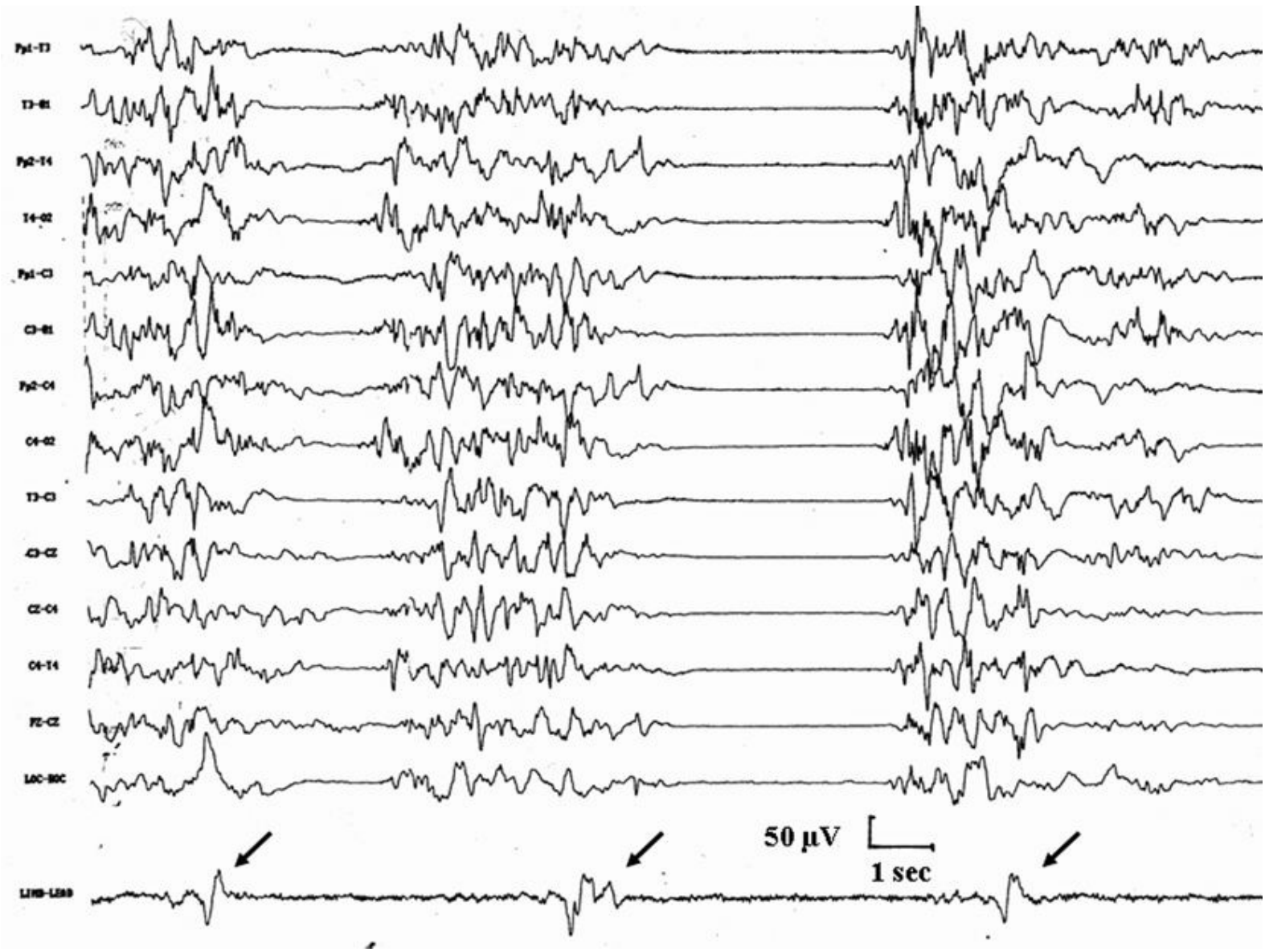

Figure 35.18. Burst suppression electroencephalographic pattern of early myoclonic epilepsy. The abnormal myoclonic movements, detected by the bottom electromyographic channel (arrows), occur during the "burst" periods of the tracing.

Early infantile epileptic encephalopathy (EIEE), also known as Ohtahara syndrome, is characterized by intractable tonic seizures in the setting of a severe encephalopathy and a burst suppression background pattern (166). In fact, the EEG findings alone appear similar to those of EME, and there is discussion that they may represent a spectrum of disease (167). Many infants with EIEE harbor overt cerebral dysgenesis or cortical dysplasias. Survivors often develop typical infantile spasms with hypsarhythmia and Lennox–Gastaut syndrome accompanied by multifocal spikes on the electroencephalogram. Cases of EIEE have been found in patients with ARX mutations (168).

Recently, 5 of 13 patients with EIEE were found to have mutations in the gene encoding syntaxin binding protein 1 (STXBP1) (169). The STXBP1 gene plays an important role in synaptic vesicle release.

TREATMENT

Despite the decadelong recognition of neonatal seizures, treatment recommendations rest almost entirely on conventional wisdom and traditional practices. Because AEDs are used to treat neonatal seizures of epileptic origin, initial consideration is given to the clinical and EEG features of the events. Discussion has also centered on the advisability of treating all epileptic neonatal seizures, as some are brief, infrequent, and self-limited. On the one hand, if the burden of seizures will be minimal, the infant need not be exposed to acute and long-term drug therapy. On the other hand, epileptic neonatal seizures that are long, frequent, and not self-limited are treated acutely and vigorously with AEDs.

No studies unequivocally demonstrate the efficacy of barbiturates in the treatment of neonatal seizures. In a randomized, controlled study (170), thiopental was administered soon after perinatal asphyxia. Seizures were diagnosed by clinical signs and occurred in 76% of treated infants and in 73% of a control (placebo) group. High doses of phenobarbital given after perinatal asphyxia resulted in a lower rate of recurrent seizures compared to placebo, although the difference was not statistically significant (171). Another randomized study using phenobarbital prophylactically in neonates with perinatal asphyxia found a statistically significant decrease in the incidence of neonatal seizures compared with placebo control (172). This study has some limitations, including a small number of patients with seizures and lack of EEG data for clinical confirmation or identification of electrographic seizures. In another study of 31 acutely ill neonates with electrographic seizures detected during continuous electroencephalograph monitoring, only two had a complete cessation of both clinical and EEG seizures with AEDs (173). Six had an equivocal electroclinical response. Clinical seizures stopped in 13, although the electrographic seizures persisted. The remaining 10 had persistent electroclinical seizures. Two studies (94,103) reported a mixed response of electroclinical seizures to phenobarbital. In a non–placebo-controlled comparison study (174), electrographic seizures ceased in 43% of the group treated with phenobarbital and in 45% of the group given phenytoin; however, the lack of a placebo control precluded determination of absolute efficacy. Video-EEG monitoring demonstrated cessation of seizures in 11 of 22 infants after administration of 40 mg/kg phenobarbital (94). In the remaining 11 nonresponders, 3 of 5 went on to respond to lignocaine while 0 of 6 responded to a benzodiazepine. According to a Cochrane review (175), "… at the present time, anticonvulsant therapy determined in the immediate period following perinatal asphyxia cannot be recommended for routine clinical practice, other than in the treatment of prolonged or frequent clinical seizures." In addition, another Cochrane review noted (176), ". . . there is little evidence from randomized controlled trials to support the use of any of the anticonvulsants currently used in the neonatal period."

In summary, despite the frequent empiric selection of phenobarbital in clinical practice for the treatment of neonatal seizures, evidence of its efficacy is limited, and animal studies raise concern that phenobarbital itself may have deleterious effects on the young nervous system (see section titled "Potential Deleterious Effects of Antiepileptic Drug Administration on the Immature CNS" later in the chapter). Few drugs for use in the newborn have been subjected to adequately powered, randomized, placebo-controlled investigations to demonstrate real safety and efficacy. Drugs with

potential for the treatment of neonatal seizures are no exception.

Nevertheless, in ordinary clinical practice, it is common to administer AEDs in an effort to reduce or eliminate seizures in the newborn. Early studies of neonatal seizures recommended loading doses of phenobarbital 15 to 20 mg/kg, with the intention of generating serum levels between 15 and 20 μg/mL, and followed by maintenance doses of 3 to 4 mg/kg/d.

The "mg/kg" dose of phenytoin should be calculated to achieve, but not exceed, free concentrations of 3 μg/mL (174,177). The dosing formula (3 μg/kg) × Vd (L/kg)/(% free binding) assumes a volume of distribution of 1 L/kg. Phenytoin has nonlinear pharmacokinetics: steady-state plasma concentrations at one dosing schedule do not predict those at another schedule (178,179). There are also variable rates of hepatic metabolism, serum binding, decreases in elimination rates during the 1st weeks of life, and variable bioavailability with different generic preparations. A redistribution of the AED after the initial dose decreases brain concentrations thereafter; thus, dosage must be tailored to the individual patient after therapy begins. Furthermore, phenytoin is strongly alkalotic and may lead to local venous thrombosis or tissue irritation. The use of fosphenytoin may reduce these risks.

While phenobarbital remains first-line therapy for neonatal seizures, there is some debate about second-line therapy. In two surveys of pediatric epileptologists in the United States and Europe, phenobarbital was identified as the treatment of choice, while intravenous benzodiazepines and fosphenytoin or phenytoin were also considered first-line therapy (180,181).

Benzodiazepines, typically lorazepam (0.15 mg/kg) and diazepam (0.3 mg/kg), can be effective therapies for refractory patients. Side effects of acute administration include hypotension and respiratory depression.

Alternative or adjuvant AEDs have also been empirically prescribed for refractory neonatal seizures. Clonazepam, lidocaine (182–184), and midazolam (185,186) are administered intravenously; carbamazepine (187), primidone (188), vigabatrin (189), and lamotrigine (190) are given orally. Levetiracetam has shown some efficacy in the treatment of neonatal seizures (191–193). A recently released anticonvulsant, ezogabine, works primarily as a potassium channel opener. In BFNE due to KCNQ2 mutations, seizures can arise from as little as a 20% disturbance in potassium conductance, making this an attractive candidate for future consideration in treating neonatal seizures, which typically respond incompletely to GABA-ergic medications.

The neuroprotective and antiseizure effects of topiramate in animal models suggest a promising role in the treatment of neonatal seizures. Limited case series reviewing the utility of topiramate in refractory neonatal seizures have shown some encouraging results. In one study, four of six patients had a favorable response with doses up to 10 mg/kg/d (194), while in another, three patients became seizure free following administration (195). An IV formulation of topiramate is under early investigation in the adult population (196), and the FDA has given approval to develop intravenous topiramate as an orphan drug in July 2013.

The administration of antiepileptic medications may terminate the clinical manifestation of the seizure while the electrographic discharge continues (174). This disconnect is often termed uncoupling and poses serious concerns for the clinician and researchers in determining response rates to AEDs. Scher et al. (197) found 58% of patients continued experiencing electrographic seizures after an administered AED had stopped their clinical seizures. This phenomenon may be explained by the caudal–rostral maturational switch from NKCC1 to KCC2, allowing medications to be more effective against brainstem and spinal cord neurons before more rostral structures (13). The relatively high rates of uncoupling stress the importance of EEG documentation of resolution of neonatal

seizures.

Chronic Postnatal Epilepsy and the Need for Long-Term Treatment

Chronic postnatal epilepsy is relatively common in the wake of neonatal seizures (Fig. 35.19). For many patients, permanent, fixed brain injuries, such as resolving stroke, ischemia, or traumatic lesions, serve as the nidus for future epilepsy. As mentioned, repeated neonatal seizures may have "instructed" the brain how to have future seizures, resulting in a persistent lowering of the seizure threshold (43) and the development of chronic epilepsy. In infants with EME or EIEE, neonatal seizures represent the beginning of very early onset epilepsy, which persists by its nature. The most common occurrence, however, is epilepsy after neonatal seizures triggered by acute neonatal conditions.

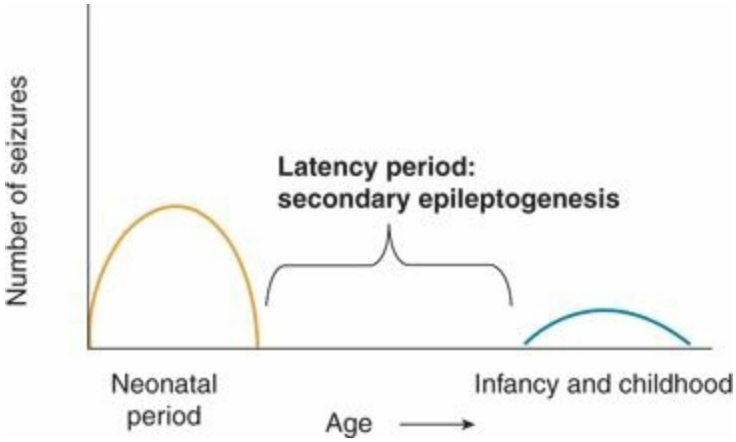

Figure 35.19. Acute neonatal seizures are often followed by chronic postnatal epilepsy. A latent period, during which secondary epileptogenesis develops, gives rise to spontaneous, unprovoked seizures.

Ellenberg et al. (198) found that approximately 20% of survivors of neonatal seizures experienced one or more seizures up to 7 years of age; nearly two-thirds of the seizures occur within the first 6 months of life. Other researchers (24,103,199–201) reported rates ranging from 17% to 30%. The 56% noted by Clancy et al. (202,203) may be explained by their inclusion of only infants whose EEG seizures were captured on a routine duration EEG. It is likely that some were discovered just by chance, but a large fraction of the group was probably in status epilepticus. Glass et al. also reported that after status epilepticus from HIE, 83% went on to develop postneonatal epilepsy (204).

Partial and generalized seizures characterize postneonatal epilepsy and do not seem to be preventable by the long-term administration of AEDs after neonatal seizures. It is not rare for catastrophic forms of epilepsy to arise after neonatal seizures including infantile spasms and the Lennox–Gastaut syndrome.

Not all neonates require extended therapy after acute seizures have been controlled, although no criteria for long-term maintenance AED use have been sufficiently studied. Reported schedules for discontinuation of maintenance therapy range from 1 week to 12 months after the last seizure (205); one currently used schedule withdraws AEDs 2 weeks after the last seizure (206).

Potential Deleterious Effects of Antiepileptic Drug Administration

on the Immature CNS

AEDs prevent or interrupt electrographic seizures by the blockade of voltage-dependent sodium channels and glutamatergic excitatory neurotransmission and enhancing of GABA-mediated inhibition. However, in this critical time of early brain development, suppression of synaptic transmission may have incidental undesirable consequences, because neuronal and synaptic pruning are activity dependent. Since the 1970s, it has been known that rat pups fed phenobarbital have later reductions in brain weight and in total brain cell count (207). How AEDs may harm the developing rat brain remains under investigation, but evidence suggests that these drugs may trigger apoptotic neurodegeneration in the rodent forebrain and suppress an endogenous neuroprotective system already in place (208). The clinical impact of these findings is less certain. Most neonates are given phenobarbital because of seizures, and it is difficult to determine how much of any long-term aftermath is the result of the seizures' underlying etiology, the attacks themselves, or the medications administered to suppress them. Some neonates receive phenobarbital for other reasons, such as to provide sedation or to accelerate hepatic maturity in neonatal hyperbilirubinemia, and appear to experience no ill effects. Likewise, benzodiazepines are commonly administered for sedation or to reduce agitation, and no obvious adverse effects are associated with their use, although careful studies are lacking.

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CHAPTER 36 SEIZURES ASSOCIATED WITH NONNEUROLOGIC MEDICAL CONDITIONS

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Seizures frequently arise during the course of medical illnesses that do not primarily affect the central nervous system (CNS). The truism that appropriate treatment depends on correct diagnosis emphasizes the importance of the differential diagnosis. A patient's history, including a review of medications and physical examination, should be informed by a consideration of the seizures as a symptom of CNS dysfunction. The urgency to pursue a diagnosis is related to the time of presentation following the seizure. In a neurologically intact patient without progressive symptoms, quick (within days), but not emergent (within hours), evaluation may be appropriate. Within the first 24 hours, vital signs, level of consciousness, and focality on examination determine urgency. The need for emergent neuroimaging studies and lumbar puncture depends on the likelihood of intracranial lesion, CNS or systemic infection, a patient's metabolic state, and the possibility of drug or alcohol intoxication. In a patient who presents more than 1 week after an initial seizure, recurrent attacks establish the diagnosis of epilepsy.

Several factors predispose a patient to seizures, including (i) changes in blood–brain barrier permeability as a result of infection, hypoxia, dysautoregulation of cerebral blood flow, or microdeposition of hemorrhage or edema secondary to vascular endothelial damage; (ii) alteration of neuronal excitability by exogenous or endogenous substances, such as excitatory and inhibitory neurotransmitters; (iii) inability of glial cells to regulate the neuronal extracellular environment; (iv) electrolyte imbalances; (v) hypoxia–ischemia; and (vi) direct and remote effects of neoplasm (1). Some patients without epilepsy may be genetically prone to seizures secondary to systemic factors.

Understanding the interaction of other organ systems is necessary for the appropriate management of seizures. In patients with hepatic or renal dysfunction, changes in pharmacokinetics induced by metabolic dysfunction alter treatment with antiepileptic drugs (AEDs). In cases of hepatic dysfunction, plasma concentrations must be correlated with serum albumin and protein levels and, if possible, free (unbound) levels. Patients with hepatic and renal failure may have normal serum and albumin levels, but altered protein binding, resulting in elevated concentrations of free drug (2).

METABOLIC DISORDERS

Metabolic disorders, although often suspected during outpatient evaluation of new-onset seizures, are found in <10% of patients and usually involve glucose metabolism (3). In the hospital setting, disorders of electrolytes and fluid balance predominate. Encephalopathies may be associated with electrolyte disturbances, hypocalcemia, hypercalcemia, hypoglycemia, hypothyroidism, thyrotoxic storm, adverse effects of drugs, organ failure, and many other conditions.

Hyponatremia

Because electrolyte disturbances are usually secondary processes, effective management of associated seizures begins with identification and treatment of the primary disorder in conjunction with cautious correction of the electrolyte disturbance. Hyponatremia, defined as a serum sodium level lower than 115 mEq/L, is one of the most frequently reported metabolic abnormalities, affecting 2.5% of hospitalized patients (4). Neurologic symptoms occur often in patients with acute hyponatremia (5,6), and convulsions in this setting have a mortality rate estimated to exceed 50% (7). Correction to levels higher than 120 mEq/L is essential; however, the rate of correction is controversial. Rapid correction of hyponatremia is associated with central pontine myelinolysis, manifested as pseudobulbar palsy and spastic quadriparesis (8). Originally described in patients with alcoholism and malnutrition, the condition was later observed in dehydrated patients undergoing rehydration (9), and in one small study (10), it was accompanied in each patient by a recent rapid increase in serum sodium levels. Pathologic features include symmetrical, noninflammatory demyelination in the basis pontis, with relative neuronal and axonal sparing. In animal models of central pontine myelinolysis, rapid correction of sustained vasopressin-induced hyponatremia with hypertonic saline was followed by demyelination (11). Some authorities consider a correction of more than 12 mEq/L/day to be unnecessarily aggressive (10).

Levels of serum sodium are most commonly reduced as a result of either sodium depletion or water "intoxication," or both (7); these are examples of hypoosmolar hyponatremia. Hyponatremia with normal osmolality is rare but may accompany hyperlipidemia or hyperproteinemia. Hyperosmolar hyponatremia occurs in such hyperosmolar states as hyperglycemia and is discussed later in this chapter. Hypoosmolar hyponatremia may occur with normal extracellular fluid volume, hypovolemia, or hypervolemia (12). Hypoosmolar hyponatremia with hypovolemia may follow renal (diuretic use, Addison disease) or extrarenal (vomiting, diarrhea, or "third spacing") loss. The syndrome of inappropriate antidiuretic hormone secretion, hypothyroidism, and some psychotropic agents may lead to hypoosmolar hyponatremia with normal volume. Hypoosmolar hyponatremia with hypervolemia, frequently seen with clinical edema, occurs in patients with cardiac failure and acute or chronic renal failure. The therapeutic implications of these conditions are significant, because appropriate treatment for normovolemic or hypervolemic hyperosmolar hyponatremia is water restriction. Hypovolemic hyponatremia is managed by replacement of water and sodium (12).

Finally, hyponatremia is sometimes considered to be an iatrogenic effect of prescribed medications, including diuretics, carbamazepine, oxcarbazepine, theophylline, amiodarone, and serotonin reuptake inhibitors (13). Hyponatremia can also be a complication of abuse of illicit substances, such as 3,4-methylenedioxy-N-methamphetamine (MDMA, or "ecstasy") (14,15).

Hypocalcemia

Although seizures resulting from severe hypocalcemia (<6 mg/dL) are relatively uncommon, they occur in approximately 25% of patients who present as medical emergencies (16). Severe, acute hypocalcemia most often follows thyroid or parathyroid surgery. Late-onset hypocalcemia with seizures may appear years after extensive thyroid surgery (17); the condition is believed to be rare and is not well understood. Hypocalcemia frequently complicates renal failure and acute pancreatitis (7) and may also occur along with vitamin D deficiency and renal tubular acidosis. Nutritional rickets is still reported, although rarely in the United States, occasionally with hypocalcemic seizures (18). Tetany is the most common neuromuscular accompaniment of hypocalcemia (19). Manifesting as

spontaneous, irregular, repetitive action potentials that originate in peripheral nerves, tetany is sometimes confused with a seizure. Latent tetany may be unmasked by hyperventilation or regional ischemia (Trousseau test). In the average adult, an intravenous (IV) bolus of 15 mL of 10% calcium gluconate solution (a calcium concentration of 9 mg/mL) administered slowly, along with cardiac monitoring, followed by infusion of the equivalent of 10 mL/hour of the same solution, should relieve seizures (20).

Hypomagnesemia

Hypomagnesemia is associated with seizures, but usually only at levels lower than 0.8 mEq/L (21). Because a related hypocalcemia may be produced by a decrease in, or end- organ resistance to, circulating levels of parathyroid hormone, magnesium levels should be measured in the patient with hypocalcemia who does not respond to calcium supplementation. Convulsions are treated with intramuscular injections of 50% magnesium sulfate every 6 hours. Because transient hypermagnesemia may induce respiratory muscle paralysis (21), IV injections of calcium gluconate should be administered concurrently.

Hypophosphatemia

Profound hypophosphatemia may accompany alcohol withdrawal, diabetic ketoacidosis, long-term intake of phosphate-binding antacids, recovery from extensive burns, hyperalimentation, and severe respiratory alkalosis. A sequence of symptoms consistent with metabolic encephalopathy involves irritability, apprehension, muscle weakness, numbness, paresthesias, dysarthria, confusion, obtundation, convulsive seizures, and coma (22). Generalized tonic–clonic seizures have been noted at phosphate levels lower than 1 mg/dL, and affected patients may not respond to AED therapy (23).

Disturbances in Glucose Metabolism

Hypoglycemia and nonketotic hyperglycemia may be associated with focal seizures; such seizures do not occur with ketotic hyperglycemia, however, probably because of the anticonvulsant action of the ketosis (24). Ketosis also involves intracellular acidosis with enhanced activity of glutamic acid decarboxylase, which leads to an increase in γ-aminobutyric acid (GABA) and a corresponding increase in seizure threshold.

Nonketotic hyperglycemia, with or without hyperosmolarity, may produce seizures and, in animal models, increases seizure frequency through brain dehydration, provided a cortical lesion is present (25). Focal motor seizures and epilepsia partialis continua, well-known complications of nonketotic hyperglycemia, occur in approximately 20% of patients (26).

Rarely, patients with focal seizures associated with nonketotic hyperglycemia may have reflex- or posture-induced epilepsy provoked by active or passive movement of an extremity (27,28) and usually have nonreflex seizures as well, related perhaps to an underlying focal cerebral ischemia. Such seizures are refractory to conventional anticonvulsant treatment. In fact, phenytoin may further increase the serum glucose level by inhibiting insulin release (29). Thus, correction of the underlying metabolic disturbance is of utmost importance.

Hypoglycemia is particularly seizure provoking and is most frequently related to insulin or oral hypoglycemic agents, although occasionally the etiology may not be obvious. Another common cause is the use of drugs that interact with oral hypoglycemic agents (30). Islet cell dysmaturation syndrome,

characterized by islet cell hyperplasia, pancreatic adenomatosis, and nesidioblastosis, is associated with infantile hyperinsulinemic hypoglycemia. Bjerke et al. (31) reported on 11 infants with this condition, 8 of whom presented with hypoglycemic seizures. Five infants had preoperative neurologic impairment. All showed improvement postoperatively, but only one infant had normal findings on neurologic examination. Early diagnosis is a decisive factor in averting long-term complications; treatment entails resection of the pancreas.

Hypoparathyroidism

Seizures occur in 30% to 70% of patients with hypoparathyroidism, usually along with tetany and hypocalcemia. They may be generalized tonic–clonic, focal motor, or, less frequently, atypical absence and akinetic seizures. Restoration of normal calcium levels is important for seizure prevention.

Thyroid Disorders

Hyperthyroidism is associated only rarely with seizures, although generalized and focal seizures have occurred in 10% of patients with thyrotoxicosis (32). Typically, thyrotoxicosis may be associated with nervousness, diaphoresis, heat intolerance, palpitations, tremor, and fatigue. Hashimoto thyroiditis often coexists with other autoimmune disorders (33), such as Hashimoto encephalopathy, a steroid-responsive relapsing condition (34) that produces seizures even in euthyroid patients (35).

Seizures have been reported in patients with myxedema. As many as 20% to 25% of patients with myxedemic coma have generalized convulsions. Also, patients with hypothyroidism may have obstructive sleep apnea (36) with hypoxic seizures (37).

Adrenal Disorders

Seizures are uncommon with adrenal insufficiency but may occur in patients with pheochromocytoma (38). More commonly, a pheochromocytoma-induced hypertensive crisis may trigger a hypertensive encephalopathy, characterized by altered mental status, focal neurologic signs and symptoms, and/or seizures. Other neurologic complications include stroke caused by cerebral infarction or an embolic event secondary to a mural thrombus from a dilated cardiomyopathy. Intracerebral hemorrhage may also occur because of uncontrolled hypertension. Additional symptoms are tremor, nausea, anxiety, sense of impending doom, epigastric pain, flank pain, constipation or diarrhea, and weight loss. These spells may last minutes to an hour. Blood pressure is almost always markedly elevated during the episode.

Uremia

A change in mental status is the hallmark of uremic encephalopathy, which also involves simultaneous neural depression (obtundation) and neural excitation (twitching, myoclonus, generalized seizures). Epileptic seizures occur in up to one-fourth of patients with uremia, and the reasons are quite varied.

Phenytoin is the AED usually administered to nontransplanted patients with uremia (see section Transplantation and Seizures later in this chapter). Critical changes in the pharmacokinetics of AEDs include (i) increased volume of distribution, producing lowered plasma drug levels; (ii) decreased protein binding, creating higher free drug levels; and (iii) increased hepatic enzyme oxygenation,

yielding increased plasma elimination (2). Because patients with uremia have plasma protein–binding abnormalities and because phenytoin is highly plasma bound, drug administration is different from that in nonuremic patients. In one study, a 2 mg/kg IV dose produced a level of 1.4 μg/mL in patients with uremia, compared with 2.9 μg/mL in control patients (39). In nonuremic patients, up to 10% of phenytoin is not protein bound, whereas in uremic patients, as much as 75% may not be protein bound. Thus, free phenytoin levels (between 1 and 2 μg/mL) should be used instead of total phenytoin levels to assess therapeutic efficacy (40). With gabapentin, pregabalin, lacosamide, and levetiracetam, which are eliminated via renal excretion, the usual total dose should be reduced equivalently to the reduction in creatinine clearance (41–43).

The treatment of renal failure may also lead to dialysis disequilibrium, characterized by headache, nausea, and irritability, which may progress to seizures, coma, and death attributable to the entry of free water into the brain, with resultant edema. Dialysis dementia, caused by the toxic effects of aluminum, is now rare. Renal transplant recipients may experience cerebrovascular disease, opportunistic infections, or malignant neoplasms, particularly primary lymphoma of the brain.

In uremic patients with renal insufficiency, adverse reactions to antibiotics are a common cause of seizures (44). Patients may have focal motor or generalized seizures, or myoclonus. In uremia, reduced protein binding increases the free fraction of highly protein-bound drugs in serum (and therefore in the CNS). Raised concentrations of neurotoxic agents, such as cephalosporins especially cefepime and ceftazidime, may increase seizure susceptibility, which may be enhanced further by the altered blood–brain barrier.

The hemodialysis patient represents a special challenge because of decreased concentrations of dialyzable AEDs. Plasma protein binding determines how effectively a drug can be dialyzed. Higher protein biding makes the medication less dialyzable. (45). Hence, levels of a drug such as phenobarbital (40% to 60% protein bound) will decrease during dialysis more than will levels of valproic acid (80% to 95% bound). One way, albeit cumbersome, to avoid “losing” an agent is to dialyze against a dialysate containing the drug. Another option, if seizures occur near the time of dialysis, is to use a highly protein-bound drug, such as valproic acid. For special considerations in the kidney transplant patient, see section Transplantation and Seizures.

Inborn Errors of Metabolism

Metabolic errors, either inborn or acquired, occur most often in early childhood. Phenylketonuria is the most common of several aminoacidopathies that may be associated with infantile spasms, and myoclonic or tonic–clonic seizures occur in one-fourth of these patients (46). Evidence of hypsarrhythmia may be seen on the electroencephalogram (EEG), but a high proportion of patients have abnormal EEGs without seizures.

Although hereditary fructose intolerance does not usually involve neurologic impairment, a small number of children experience seizures that are sometimes related to prolonged hypoglycemia (47).

Because excess ammonia is excreted as urea, disorders of the urea cycle, such as hyperammonemia, may be associated with symptoms ranging from coma and seizures to mild, nonspecific aberrations in neurologic function (46).

Various storage diseases result from abnormal accumulation of normal substrates and their catabolic products within lysosomes. The absence or inefficiency of lysosomal enzymes in such conditions as sphingolipidoses, mucopolysaccharidoses, mucolipidoses, glycogen storage diseases, and glycoproteinoses may give rise to seizures (46).

Purine syndromes and hyperuricemia are not usually associated with seizure disorders unless mental retardation or dementia coexists. Allopurinol is an important adjunctive treatment in some patients.

Porphyria

The disorders of heme biosynthesis are classified into two groups: erythropoietic and hepatic. Seizures and other neurologic manifestations occur only in the hepatic group, which comprises acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria (48). Seizures affect approximately 15% of patients, usually during an acute attack (49) often precipitated by an iatrogenically introduced offending agent. The generalized (occasionally focal) seizures may begin up to 28 days after exposure to the agent. The epileptogenic mechanism is not well understood. Some authors have suggested that δ-aminolevulinic acid and porphobilinogen, both structurally similar to the neurotransmitters glutamate and GABA, are toxic to the nervous system, although clinical evidence refutes this contention (48).

A cornerstone of the treatment is the provision of a major portion of daily caloric requirements by carbohydrates to lower porphyrin excretion. Glucose prevents induction of hepatic δ-aminolevulinic acid synthetase in symptomatic patients, as does IV hematin. Porphyrogenic drugs, such as phenytoin, barbiturates, carbamazepine, succinimides, and oxazolidinediones, should be avoided. Drugs are considered unsafe if they induce experimental porphyria in animals. Using chick embryo hepatocyte culture, Reynolds and Miska (49) found that carbamazepine, clonazepam, and valproate increased porphyrin to levels comparable with those achieved with phenobarbital and phenytoin. In the past, bromides were recommended for the long-term management (50) and diazepam, paraldehyde, and IV magnesium sulfate therapy for the acute treatment of seizures (51). Serum bromide levels should be maintained between 60 and 90 μg/dL. Many side effects and a long half-life make bromides difficult to use. Bromides are excreted by the kidney, and paraldehyde is excreted unchanged by the lungs (the remainder by the liver). Levetiracetam has been used increasingly in patients with porphyria based on its efficacy, broad-spectrum control, and lower risk for exacerbating porphyria (52). Larson et al. (53) reported on one patient with intractable epilepsy who was safely managed with low-dose clonazepam and a high-carbohydrate diet after phenytoin and carbamazepine use had independently precipitated attacks. In two separate studies, gabapentin controlled complex partial and secondarily generalized seizures in patients with porphyria (54,55). Because gabapentin is excreted unmetabolized by the kidneys, it does not induce hepatic microsomal enzymes (56) and should not worsen hepatic cellular dysfunction. Alternatively, vigabatrin, which also does not induce hepatic metabolism, may be a useful antiseizure medication in patients with porphyria. Table 36.1 lists agents that are safe and unsafe to use in patients with porphyria (57).

Table 36.1 Safe and Unsafe Agents in Patients with Porphyria

Safe agents	Unsafe agents
Acetaminophen	Barbiturates
Acetazolamide	Carbamazepine
Allopurinol	Chloramphenicol
Aminoglycosides	Chlordiazepoxide
Amitriptyline	Diphenhydramine
Aspirin	Enalapril
Atropine	Ergot compounds
Bromides	Erythromycin
Bupivacaine	Ethanol
Chloral hydrate	Flucloxacillin
Chlorpromazine	Flufenamic acid
Codeine	Griseofulvin
Corticosteroids	Hydrochlorothiazide
Diazepam	Imipramine
Gabapentin	Lisinopril
Heparin	Methyldopa
Insulin	Metoclopramide
Levetiracetam	Nifedipine
Meclizine	Oral contraceptives
Meperidine	Pentazocine
Morphine	Phenytoin
Penicillins (see unsafe agents for exceptions)	Piroxicam
	Pivampicillin
Procaine	Progesterone
Prochlorperazine	Pyrazinamide
Promethazine	Rifampin
Propoxyphene	Sulfonamides
Propranolol	Theophylline
Propylthiouracil	Valproic acid
Quinidine	Verapamil
Streptomycin	Oral contraceptives
Temazepam	
Tetracycline	
Thyroxine	
Trifluoperazine	
Warfarin	

Adapted from Gorchein A. Drug treatment in acute porphyria. Br J Clin Pharmacol. 1997;44:427–434.

OXYGEN DEPRIVATION

Perinatal Anoxia and Hypoxia

Whether it occurs in utero, during delivery, or in the neonatal period, significant anoxia can extensively damage the CNS and lead to neonatal seizures, which carry a risk for increased mortality. The pathophysiology, classification, diagnosis, evaluation, and treatment of neonatal seizures are covered in Chapter 35.

Adult Anoxia and Hypoxia

In adults, anoxic or hypoxic seizures are residuals of cardiac arrest, respiratory failure, anesthetic misfortune, carbon monoxide poisoning, or near-drowning. Precipitating cardiac sources typically are related to embolic stroke, 13% of which involve seizures (58) or hypoperfusion or hyperperfusion of

the cerebral cortex (2). Approximately 0.5% of patients who have undergone coronary bypass surgery experience seizures without evidence of focal CNS injury (59). In patients with respiratory disorder, acute hypercapnia may lower seizure threshold, whereas chronic stable hypoxia and hypercapnia rarely cause seizures. Subacute bacterial endocarditis can lead to septic emboli and intracranial mycotic aneurysms, which can produce seizures either from focal ischemia or from subarachnoid hemorrhage. Syncopal myoclonus and convulsive syncope may result from transient hypoxia.

Subtle seizures may involve only minimal facial or axial movement (60), increasing the suspicion for nonconvulsive status epilepticus that typically signifies a poor prognosis (61,62). Myoclonic status epilepticus or generalized myoclonic seizures that occur repetitively for 30 minutes are usually refractory to medical treatment (63). Concern has been raised that myoclonic status epilepticus may produce progressive neurologic injury in comatose patients resuscitated from cardiac arrest (63). When postanoxic myoclonic status epilepticus is associated with cranial areflexia, eye opening at the onset of myoclonic jerks, and EEG patterns that include generalized bilateral independent epileptiform discharges or burst suppression pattern, the outlook for neurologic recovery is grim (64).

Treatment is directed mainly toward preventing the cascade of hypoxic injury. Barbiturate medication and reduction of cerebral metabolic requirements by continuous hypothermia may prevent the delayed worsening (65). Frequently, the seizures cease after 3 to 5 days. Phenobarbital 300 mg/day, clonazepam 8 to 12 mg/day in three divided doses, and 4-hydroxytryptophan 100 to 400 mg/day have been recommended (66), as has valproic acid (67). Levetiracetam 1000 to 3000 mg/day may also be useful for posthypoxic seizures and myoclonus with less sedating effects (68).

ALCOHOL

Generalized tonic–clonic seizures occur during the first 48 hours of withdrawal from alcohol in intoxicated patients and are most common 12 to 24 hours after binge drinking (69). Seizures that occur more than 6 days following abstinence should not be ascribed to withdrawal. Interictal EEG findings are usually normal. Partial seizures often result from CNS infection or cerebral cicatrix caused by remote head trauma. Recent occult head trauma, including subdural hematoma, should be considered in any alcoholic patient. Although the incidence of alcoholism in patients with seizures is not higher than in the general population, alcoholic individuals do have a higher incidence of seizures (70).

The treatment depends on associated conditions, but replacement of alcohol is generally not recommended. To prevent the development of Wernicke–Korsakoff syndrome, thiamine should be administered prior to IV glucose. Magnesium deficiency should be corrected, as reduced levels may interfere with the action of thiamine. Preferred treatment is with benzodiazepines or paraldehyde. In countries outside the United States where paraldehyde is available, it may be administered in doses of 0.1 to 0.2 mL/kg orally or rectally every 2 to 4 hours. Diazepam, lorazepam, clorazepate, and chlordiazepoxide in conventional dosages are equally useful (71).

INFECTIONS

Infection is associated with seizures, both directly via parenchymal invasion by the pathogen and indirectly via neurotoxins. Direct parenchymal infections may be bacterial, fungal, mycobacterial, viral, spirochetal, or parasitic. Neurodegenerative disorders, such as Creutzfeldt–Jakob disease and

subacute sclerosing panencephalitis, can also result from CNS infection.

Meningitis

Patients with seizures, headache, or fever (even low grade) should undergo lumbar puncture once a mass lesion has been excluded. In the infant with diffuse, very high intracranial pressure, lumbar puncture should be delayed until antibiotics and pressure-reducing measures are initiated. The pathogenic cause of bacterial meningitis varies with age: In newborns, Escherichia coli and group B streptococcus are most common; in children 2 months to 12 years of age, Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitidis are usual; in children older than 12 years of age and in adults, S. pneumoniae and N. meningitidis are found most often; in adults older than 50 years of age, H. influenzae is increasingly being reported. In infants, geriatric patients, and the immunocompromised, Listeria monocytogenes must also be considered.

Encephalitis

The herpes simplex variety is the most common form of encephalitis associated with seizures (72). Fever, headache, and confusion are punctuated by both complex partial and generalized seizures secondary to the propensity of the virus to produce a hemorrhagic encephalitis involving the temporal lobe. Equine encephalitis, St. Louis encephalitis, and rabies also produce seizures.

Diazepam or lorazepam may be used for the acute control of seizures caused by meningitis or encephalitis. Recurrent seizures or the development of status epilepticus indicates the need for maintenance AED therapy.

Nonbacterial Chronic Meningitis

Lyme disease, a tick-borne spirochetosis, is associated with meningitis, encephalitis, and cranial or radicular neuropathies in up to 20% of patients. Seizures are not a prominent feature. Treatment consists of high-dose IV penicillin G in addition to AEDs (73).

Neurosyphilis is another spirochetal cause of seizures, which occasionally are the initial manifestation of syphilitic meningitis. In the early 20th century, 15% of patients with adult-onset seizures had underlying neurosyphilis. The incidence decreased dramatically over the years; however, the recent upsurge in primary syphilis among younger individuals is reflected in the report that seizures occur in approximately 25% of the patients with symptomatic neurosyphilis. The diagnosis rests on the demonstration of positive serologic findings and clinical symptoms, but the signs are not pathognomonic and often overlap with those of other diseases. IV penicillin remains the treatment of choice.

Sarcoidosis involves the CNS in approximately 5% to 15% of cases. Neurosarcoidosis should also be considered in patients with nonbacterial meningitis and seizures (74).

Opportunistic CNS Infections

Acquired immunodeficiency syndrome (AIDS) is associated with several unique neurologic disorders, and seizures may play a major role when opportunistic infections or metabolic abnormalities, especially cerebral toxoplasmosis or cryptococcal meningitis, occur. Listeria monocytogenes should also be considered in immunocompromised patients. Metabolic abnormalities,

particularly uremia and hypomagnesemia, predispose patients infected with the human immunodeficiency virus (HIV) to seizures. New-onset epilepsia partialis continua as an early manifestation of progressive multifocal leukoencephalopathy in patients with HIV-1 infection has been reported (75). CNS lymphoma in HIV-infected patients may also give rise to seizures.

Parasitic CNS Infections

In some areas, neurocysticercosis is the most commonly diagnosed cause of partial seizures. The adult pork tapeworm resides in the human small bowel after ingestion of infected meat. The oncospheres (hatched ova) penetrate the gut wall and develop into encysted larval forms, usually in the brain or skeletal muscle. Computed tomography (CT) scans reveal calcified lesions, cysts with little or no enhancement, and usually no sign of increased intracranial pressure. In the past, treatment involved the use of only praziquantel 50 mg/kg/day for 15 days or albendazole 15 mg/kg/day. However, while undergoing therapy, most patients had clinical exacerbations, including worsening seizures, attributed to inflammation with cyst expansion caused by the death of cysticerci. For this reason, treatment with the antihelminthic drug and steroids has been advocated. Antihelminthic agents by themselves do not change the course of neurocysticercosis or its associated epilepsy. A trial of antihelminthic agents combined with steroids or steroids alone showed comparable efficacy in terms of patients who were cyst free at 1 year or seizure free during follow-up (76).

Hydatid disease of the CNS (echinococcal infection) may result from exposure to dogs and sheep. Echinococcal cysts destroy bone, and a large proportion of such cysts are found in vertebrae. On CT scans, echinococcal brain cysts are fewer and larger than the cysts associated with cysticercosis. Treatment is usually surgical, largely because mebendazole and flubendazole have been associated with disease progression in up to 25% of patients. Nonetheless, adjuvant chemotherapy may be warranted in some cases (77).

Trichinosis may be encountered wherever undercooked trichina-infected pork is consumed. Complications of CNS migration include seizures, meningoencephalitis, and focal neurologic signs; eosinophilia is common during acute infection. Muscle biopsy may be necessary for diagnosis (72).

Cerebral malaria is similar to neurosyphilis, in that almost every neurologic sign and symptom has been attributed to the disorder. Diagnosis requires characteristic forms in the peripheral blood smear. Treatment depends on whether chloroquine resistance is present in the geographic region of infection.

Toxoplasmosis is a parasitic infection that affects adults, children, and infants. Use of immunosuppressive agents in patients with malignancies or transplants (see related sections later in this chapter), as well as recognition of AIDS, has emphasized the need to reconsider the neurologic sequelae of toxoplasmosis. Diagnosis may be elusive. Cerebrospinal fluid may reveal normal findings or mild pleocytosis (78). Serologic data may be difficult to interpret because encephalitis caused by Toxoplasma gondii may occur in patients who reactivate latent organisms and do not develop the serologic response of acute infection. CT scanning may reveal typical lesions. Therapy includes pyrimethamine and sulfadiazine or trisulfapyrimidines.

Cytomegalovirus retinitis, the most common ocular opportunistic infection in patients with AIDS (79), is increasingly being treated with a combination of foscarnet and ganciclovir. Foscarnet is also used to treat cytomegalovirus esophagitis associated with AIDS, but seizures have occurred with this agent, possibly as a result of changes in ionized calcium concentrations (80).

Systemic Infections

Systemic infection involving hypoxia (e.g., pneumonia) or metabolic changes may give rise to seizures. Through an indirect, poorly understood mechanism, seizures are prominent in two serious gastrointestinal (GI) infections: shigellosis and cholera. Ashkenazi et al. (81) demonstrated that the Shiga toxin is not essential for the development of the neurologic manifestations of shigellosis and that other toxic products may play a role.

Zvulunov et al. (82) examined 111 children who had convulsions with shigellosis and were followed for 3 to 18 years. No deaths or persistent motor deficits occurred. Only one child developed epilepsy by the age of 8 years; 15.7% of the children had recurrent febrile seizures. The convulsions associated with shigellosis have a favorable prognosis and do not necessitate long-term follow-up or treatment.

Most clinical manifestations of cholera are caused by fluid loss. Seizures, which are the most common CNS complication, occasionally occur both before and after treatment and may result from hypoglycemia or overcorrection of electrolyte abnormalities. The cornerstone of treatment, however, is fluid replacement. Up to 3% of body weight, or 30 mL/kg, should be administered during the first hour, followed by 7% for the next 5 to 6 hours. Lactated Ringer solution given IV with potassium chloride or isotonic saline and sodium lactate (in a 2:1 ratio) is used. Adjunctive treatment with a broad- spectrum antibiotic shortens the duration of diarrhea and hastens the excretion of Vibrio cholerae.

The seizures associated with shigellosis and cholera infection may share a common pathogenesis. Depletion of hepatic glycogen and resultant hypoglycemia are typically reported in children with these illnesses (83).

GASTROINTESTINAL DISEASE AND SEIZURES

In nontropical sprue, or celiac disease, damage to the small bowel by gluten-containing foods leads to chronic malabsorption. Approximately 10% of patients have significant neurologic manifestations, with the most frequent neurologic complication being seizures (reported in 1% to 10% of patients), which are often associated with bilateral occipital calcifications (84,85). Possible mechanisms include deficiencies of calcium, magnesium, and vitamins; genetic factors (86); and isolated CNS vasculitis (87). Malabsorption may be occult, and seizures may be the dominant feature. Strict gluten exclusion usually produces a rapid response.

Inflammatory bowel disease (ulcerative colitis and Crohn disease) is associated with a low incidence of focal or generalized seizures. Unsurprisingly, generalized seizures frequently accompany infection or dehydration. In approximately 50% of all patients with focal seizures, a vascular basis is suspected (88).

Whipple disease is a multisystem granulomatous disorder caused by Tropheryma whippelii (89). Approximately 10% of patients have dementia, ataxia, or oculomotor abnormalities; as many as 25% have seizures (90). Early treatment is important, as untreated patients with CNS involvement usually die within 12 months (91). Some patients develop cerebral manifestations after successful antibiotic treatment of GI symptoms (92). Although several agents that cross the blood–brain barrier, such as chloramphenicol and penicillin, have been suggested for treatment (93), a high incidence of CNS relapse led Keinath et al. (94) to recommend penicillin 1.2 million units and streptomycin 1.0 g/day for 10 to 14 days, followed by trimethoprim–sulfamethoxazole 1 double-strength tablet twice a day

for 1 year. Treatment of the underlying disease may not prevent seizures; however, in which case, AEDs in a suspension or elixir are usually required because malabsorption is a significant problem (95).

Hepatic Encephalopathy

Wilson disease, acquired hepatocerebral degeneration, Reye syndrome, and fulminant hepatic failure, among other disorders, may lead to hepatic encephalopathy. Manifestations progress through four stages. Stage 1 is incipient encephalopathy. In stage 2, mental status deteriorates and asterixis develops. In stage 3, focal or generalized seizures may occur. Stage 4 is marked by coma and decerebrate posturing.

The incidence of seizures varies from 2% to 33% (96). Hypoglycemia complicating liver failure may be responsible for some seizures. Hyperammonemia is associated with seizures and may contribute to the encephalopathy of primary hyperammonemic disorders; treatments that reduce ammonia levels also ameliorate the encephalopathy (96). Therapy should be directed toward the etiology of the hepatic failure; levels of GI protein and lactulose must be reduced. Long-term use of AEDs is not usually required unless there is a known predisposition to seizures (e.g., previous cerebral injury). Little experience with the use of AEDs has actually been reported. Those AEDs with sedative effects may precipitate coma and are generally contraindicated. Valproic acid and its salt should be avoided. Nonhepatic metabolized AEDs including levetiracetam and gabapentin are more likely to be efficacious and avoid further exacerbation of the liver failure.

INTOXICATION AND DRUG-RELATED SEIZURES

This section is not to be used as a guide to the management of drug intoxication. Rather, it reviews specific instances of intoxication during which intractable seizures sometimes develop.

Prescription Medication–Induced Seizures

Many medications provoke seizures in both epileptic and nonepileptic patients (Table 36.2). Predisposing factors include family history of seizures, concurrent illness, and high-dose intrathecal and IV administration. The convulsions are usually generalized with or without focal features; status epilepticus may occur in up to 15% of patients (97). Because many medical conditions result from polypharmacy, drug- induced seizures may be more common in geriatric patients.

Table 36.2 Agents Reported to Induce Seizures

Analgesics	Alfentanil, fentanyl, mefenamic acid, meperidine, pentazocine, propoxyphene, tramadol
Antibiotics	Ampicillin, carbenicillin, cephalosporins, imipenem, isoniazid, lindane, metronidazole, nalidixic acid, oxacillin, penicillin, pyrimethamine, ticarcillin
Antidepressants	Amitriptyline, bupropion, doxepin, fluoxetine, imipramine, maprotiline, mianserin, nomifensine, nortriptyline, paroxetine, sertraline, trazodone, venlafaxine
Antineoplastic agents	Busulfan, carmustine (BCNU), chlorambucil, cytosine arabinoside, methotrexate, vincristine
Antipsychotics	Clozapine, clomipramine, chlorpromazine, fluphenazine, haloperidol, olanzapine, perphenazine, pimozide, prochlorperazine, quetiapine, risperidone, thioridazine, trifluoperazine
Bronchial agents	Aminophylline, theophylline
General anesthetics	Enflurane, ketamine, methohexital
Local anesthetics	Bupivacaine, lidocaine, procaine
Sympathomimetics	Ephedrine, phenylpropanolamine, terbutaline
Others	Alcohol, amphetamines, anticholinergics, antihistamines, aqueous iodinated contrast agents, atenolol, baclofen, chloroquine, copper toxicity, cyclosporine, domperidone, ergonovine, flumazenil, folic acid, foscarnet, ganciclovir, hyperbaric oxygen, insulin, lithium, mefloquine, methylphenidate, methylxanthines, oxytocin, phencyclidine, ritonavir, tacrolimus (FK506)

Intoxication from treatment with tricyclic antidepressants (TCAs) has led to generalized tonic–clonic seizures at therapeutic levels in approximately 1% of the patients (98). Because desipramine is believed to have a lower risk for precipitating seizures than other drugs in this class, the agent is preferred in patients with known epilepsy (99). Physostigmine may reverse the neurologic manifestations of TCA reactions; however, because it may also cause asystole, hypotension, hypersalivation, and convulsions, this agent should not be used to treat TCA-induced seizures. Benzodiazepines are preferred as the initial treatment. The combination of clomipramine with valproic acid may result in elevation of clomipramine levels with associated seizures (100).

Fluoxetine, sertraline, and other selective serotonin reuptake inhibitors (SSRIs) have an associated seizure risk of approximately 0.2%. The SSRIs may have an antiepileptic effect at therapeutic doses (101). Fluvoxamine overdose has also been reported to provoke status epilepticus (102). When combined with other serotonergic agents or monoamine oxidase inhibitors, however, they may induce the "serotonin syndrome" of delirium, tremors, and, occasionally, seizures (103). Venlafaxine, a serotonin and norepinephrine reuptake inhibitor, has emerged as a common cause of

drug-induced seizures (104). There are reports of serotonin syndrome developing after concomitant use of antibiotics such as linezolid and the SSRI paroxetine, citalopram (105), and mirtazapine (106). Over-the-counter substances used in combination with SSRIs that have precipitated the serotonin syndrome include St. John's wort (107).

Antipsychotic agents have long been known to precipitate seizures (97). Both the phenothiazines and the haloperidol have been implicated, but the potential is greater with phenothiazines, and seizures occur more frequently with increasing dosage (108). Clozapine, an atypical antipsychotic agent (dibenzodiazepine class) used for the treatment of intractable schizophrenia, also produces an increased incidence of seizures with increasing dosage (109). Lithium may also precipitate seizures (110). If reduction of dosage is not practical, phenytoin or valproate may be added; however, carbamazepine should be avoided because antipsychotic agents may induce agranulocytosis.

The use of theophylline and other methylxanthines may lead to generalized tonic–clonic seizures; rarely, patients may experience seizures with nontoxic levels of theophylline. Seizures resulting from overdosage are best treated with IV diazepam. Massive overdosage may induce hypocalcemia and other electrolyte abnormalities (111).

Lidocaine precipitates seizures, usually in the setting of congestive heart failure, shock, or hepatic insufficiency. General anesthetics, such as ketamine and enflurane, are also implicated (see section Central Anticholinergic Syndrome). Alfentanil is a potent short-acting opioid agent that may induce clinical and electroencephalographic seizures (112). Meperidine, pentazocine, and propoxyphene, among other analgesic drugs, infrequently cause seizures (113).

Verapamil intoxication may be associated with seizures through the mechanism of hypocalcemia, although hypoxia also may have a contributing role (114). Interestingly, other calcium channel blockers have not been reported to produce this adverse effect.

Many antiparasitic agents and antimicrobials, particularly penicillins and cephalosporins in high concentrations, are known seizure precipitants. It should be noted that some antibiotics, such as the fluoroquinolones, may lower the seizure threshold. Carbapenem antimicrobials also have significant neurotoxic potential, with meropenem perhaps having the lowest incidence (115,116). Lindane, an antiparasitic shampoo active against head lice (Pediculosis capitis), has a rare association with generalized, self-limited seizures; it is best to use another agent should reinfestation occur. Seizures have not been reported with permethrin, another antipediculosis agent.

Severe isoniazid intoxication involves coma, intractable seizures, and metabolic acidosis. Ingestion of >80 mg/kg of body weight produces severe CNS symptoms that are rapidly reversed with IV administration of pyridoxine at 1 mg per every 1 mg of isoniazid (117). Conventional doses of short-acting barbiturates, phenytoin, or diazepam are also recommended to potentiate the effect of pyridoxine (118).

Recreational Drug-Induced Seizures

Alldredge et al. (119) retrospectively identified 49 cases of recreational drug-induced seizures in 47 patients seen between 1975 and 1987. Most patients experienced a single generalized tonic–clonic attack associated with acute drug intoxication, but seven patients had multiple seizures and two had status epilepticus. The recreational drugs implicated were cocaine (32 cases), amphetamines, heroin, and phencyclidine; a combination of drugs was responsible for 11 cases. Seizures occurred independently of the route of administration and were reported in both first-time and chronic abusers. A total of 10 patients (21%) reported prior seizures, all temporally associated with drug abuse.

Except for one patient who experienced prolonged status epilepticus causing a fixed neurologic deficit, most patients had no obvious short-term neurologic sequelae (119). Marijuana is unlikely to alter the seizure threshold (120) and is a common drug utilized by epileptics for self-medication. Patients with seizures who test positive for marijuana on toxicologic screening should be investigated for other illicit drugs and alcohol use.

Cocaine commonly gives rise to tremors and generalized seizures. Seizures can develop immediately following drug administration, without other toxic signs. Convulsions and death can occur within minutes of overdose. Pascual-Leone et al. (121) retrospectively studied 474 patients with medical complications related to acute cocaine intoxication. Of 403 patients who had no seizure history, approximately 10% had seizures within 90 minutes of cocaine use. The majority of seizures were single and generalized, induced by IV or "crack" cocaine, and were not associated with any lasting neurologic deficits. Most of the focal or repetitive attacks involved an acute intracerebral complication or concurrent use of other drugs. Of 71 patients with previous non–cocaine-related seizures, 17% presented with cocaine-induced seizures, most of which were multiple and of the same type as they had previously experienced (121).

The treatment of choice for recreational drug-induced seizures is lorazepam or clonazepam. Bicarbonate for acidosis, artificial ventilation, and cardiac monitoring are also useful, depending on the duration of the seizures. Urinary acidification accelerates excretion of the illicit drug. Chlorpromazine has also been recommended because it raised, rather than lowered, the seizure threshold in cocaine-intoxicated primates (122).

Acute overdose of amphetamine causes excitement, chest pain, hypertension, tachycardia, and sweating, followed by delirium, hallucinations, hyperpnea, cardiac arrhythmias, hyperpyrexia, seizures, coma, and death. Seizures are treated with benzodiazepines or, if long-term antiepileptic therapy is indicated, with phenytoin. Acidification of urine may enhance drug excretion.

Methamphetamine is a synthetic agent with toxic effects, including seizures, that is similar to those with amphetamine and cocaine (123). The amphetamine derivative (MDMA) stimulates the release and inhibits the reuptake of serotonin (5-HT) and other neurotransmitters, such as dopamine, to a lesser extent. Mild versions of the serotonin syndrome often develop, when hyperthermia, mental confusion, and hyperkinesia predominate (123). MDMA may also cause seizures in conjunction with rhabdomyolysis and hepatic dysfunction (124).

γ-Hydroxybutyric acid (GHB), or sodium oxybate, is an agent that is approved for use in patients with narcolepsy who experience episodes of cataplexy and excessive daytime sleepiness, It is also a popular agent among recreational drug users. GHB is a naturally occurring inhibitory substance in the human brain. GHB is believed to bind to $GABA_B$ and GHB-specific receptors. It blocks dopamine release at the synapse and produces an increase in intracellular dopamine. This is followed by a time-dependent leakage of dopamine from the neuron. Its abuse potential is secondary to its ability to induce a euphoric state, hallucinations, and relaxation without a hangover effect. Additional effects of increased sensuality and disinhibition further explain the popularity of the agent. Abusers will often ingest sufficient quantities to lead to a severely depressed level of consciousness. It is not uncommon to observe seizures in these cases. With acute overdose, patients have experienced delirium and transient respiratory depression, which can be fatal (125). The toxicity of GHB is dose dependent and can result in nausea, vomiting, hypotonia, bradycardia, hypothermia, random clonic movements, coma, respiratory depression, and apnea. Deaths involving solely the use of GHB appear to be rare and have involved the "recreational abuse" of the drug for its "euphoric" effects. Combining GHB with other depressants or psychoactive compounds may exacerbate its effects. GHB abuse frequently

involves the use of other substances, such as alcohol or MDMA (126).

CENTRAL ANTICHOLINERGIC SYNDROME

Many drugs used as anesthetic agents and in the intensive care unit may cause seizures. Although a discussion of each agent is beyond the scope of this chapter, we review the central anticholinergic syndrome (127), a common disorder associated with blockade of central cholinergic neurotransmission, whose symptoms are identical to those of atropine intoxication: seizures, agitation, hallucinations, disorientation, stupor, coma, and respiratory depression. Such disturbances may be induced by opiates, ketamine, etomidate, propofol, nitrous oxide, and halogenated inhalation anesthetics, as well as by such H_2-blocking agents as cimetidine. An individual predisposition exists for central anticholinergic syndrome that is unpredictable from laboratory findings or other signs. The postanesthetic syndrome can be prevented by administration of physostigmine during anesthesia.

OTHER SEIZURE PRECIPITANTS

Heavy metal intoxication, especially with lead and mercury, is a well-known seizure precipitant. Ingestion of lead from paint and inhalation of lead oxide are specific hazards among young children. Hyperbaric oxygenation provokes seizures, possibly as a toxic effect of oxygen itself. Some antineoplastic agents, such as chlorambucil and methotrexate, precipitate seizures. Table 36.2 lists other agents reported to induce seizures (128).

Increasingly utilized prophylactically and as alternative medicine, many herbs and other alternative treatments may increase the risk for seizures (129). This may be through intrinsic proconvulsive effects of contamination by heavy metals. These include cyanobacteria (aka spirulina, blue–green algae), ephedra (ma huang), Ginkgo biloba, pennyroyal, primrose oil, sage, star anise, star fruit, and wormwood. In addition, many herbs may have an effect on AED concentrations via the cytochrome P450 and P-glycoprotein systems.

More recently, there has also been concern that seizures may also be induced following consumption of energy drinks and supplements. It has been proposed that large consumption of compounds rich in caffeine, taurine, and guarana seed extract may provoke seizures (130). With the large consumption of energy drinks around the world, there is concern that there may be underestimation of the potential effects to induce seizures. Discussions also infer that the high intake of caffeine may induce sleep deprivation, or the concomitant higher consumption of alcohol with energy drinks may also be precipitating factors inducing seizures (131).

ECLAMPSIA

A condition unique to pregnancy and puerperium, eclampsia is characterized by convulsions following a preeclamptic state involving hypertension, proteinuria, edema, and coagulopathy, as well as headache, drowsiness, and hyperreflexia. Eclampsia is associated with a maternal mortality of 1% to 2% and a rate of complications of 35% (132). In the United States, magnesium sulfate is the chosen therapy, whereas in the United Kingdom, such conventional AEDs as phenytoin and diazepam are used (133,134). The antiepileptic action of magnesium sulfate is accompanied by hypotension, weakness, ataxia, respiratory depression, and coma. The recommended therapeutic range is 1.8 to 3.0 μmol/L; however, weakness and ataxia appear at 3.5 to 5.0 μmol/L and respiratory depression at 5.0

μmol/L (135). Kaplan et al. (136) argue that magnesium sulfate is not a proven AED; even at therapeutic levels, 12% of patients continued to have seizures in one study (137). The use of magnesium sulfate or conventional AEDs for preeclamptic or eclamptic seizures remains controversial. Because eclamptic seizures are clinically and electrographically indistinguishable from other generalized tonic–clonic attacks, the use of established AEDs, such as diazepam, lorazepam, and phenytoin, is recommended (136). In a randomized study of 2138 women with hypertension during labor (138), no eclamptic convulsions occurred in women receiving magnesium sulfate, whereas seizures were frequent with phenytoin use. Methodologic problems, however, involved the route of administration of the second phenytoin dose after loading and the low therapeutic phenytoin level at the time of the seizure.

Magnesium sulfate has a beneficial effect on factors leading to eclampsia and can reverse cerebral arterial vasoconstriction (139). By the time a neurologist is consulted, however, the patient will have received magnesium sulfate and will typically require additional AED treatment to control the seizures.

MALIGNANCY

Mechanisms for induction of seizures in patients with cancer include direct invasion of cortex or leptomeninges, metabolic derangements, opportunistic infection, and chemotherapeutic agents (140). Limbic encephalitis is a paraneoplastic syndrome seen in patients with small cell carcinoma, ovarian cancer commonly teratomas, germ cell tumors of the testes, or, less commonly, Hodgkin disease. Patients usually present with amnestic dementia, affective disturbance, and sometimes a personality change. During the illness, both complex partial and generalized seizures may occur. Paraneoplastic limbic encephalitis associated with anti-Hu (antineuronal nuclear antibody type 1) antibodies may present with seizures and precede the diagnosis of cancer (141). If the etiology of new-onset seizures is not defined in a patient with known cancer, frequent neuroimaging studies should assess the individual for metastatic disease. Chapter 33 details other paraneoplastic disorders that can present with seizures, including anti-NMDA receptor encephalitis.

Opsoclonus–myoclonus syndrome (myoclonic infantile encephalopathy) occurs most frequently in young children (mean age, 18 months). Approximately half of the cases have been reported in patients with neuroblastoma, but only approximately 3% of all neuroblastoma cases are complicated by the syndrome. Opsoclonus–myoclonus syndrome has been reported with carcinoma, including breast, ovarian, and small cell lung cancer, but occurs idiopathically as well. Because the idiopathic and paraneoplastic syndromes are indistinguishable clinically, opsoclonus–myoclonus syndrome should always prompt a search for neuroblastoma in children and these other cancers in adults. Symptoms respond to steroid or immunosuppressive therapy. In the majority of cases, successful treatment of the neuroblastoma or surgical resection of the primary cancer may lead to remission; however, the syndrome may reappear with or without tumor recurrence (142).

Finally, chronic treatment with nonhepatic metabolized AEDs including levetiracetam and gabapentin avoid drug interactions that may reduce the efficacy of chemotherapeutic agents.

VASCULITIS

Seizures as a manifestation of vasculitis may occur as a feature of encephalopathy, as a focal neurologic deficit, or in association with renal failure (143). The incidence of seizures increases with

the duration and severity of the underlying vasculitis (144) and ranges from 24% to 45% (145). The relationship of the seizure disorder to the underlying disease may not always be clear, however. A confounding feature of AED therapy is the occurrence of drug-induced systemic lupus erythematosus (146). Although this association has been challenged—the seizures were believed to be an initial manifestation of lupus—phenytoin-associated lupus and spontaneous lupus do have different loci of immunoregulation (147). Systemic necrotizing vasculitis and granulomatous vasculitis rarely present with seizures. Among patients with giant cell arteritis with nonocular signs, seizures occur in 1.5% (147). Behçet disease is associated with neurologic involvement in 10% to 25% of patients. Onset is usually acute, and seizures occasionally occur.

TRANSPLANTATION AND SEIZURES

Organ transplantation has led to newly recognized CNS disorders and new manifestations of old disorders. Seizures may occur in up to a third transplant patients. Seizures in patients anticipating or having undergone transplantation may be difficult to manage for several reasons: (i) these individuals are frequently metabolically stressed; (ii) preexisting diseases and preceding therapies may have affected the CNS (e.g., candidates for bone marrow transplantation may have received L-asparaginase, which is associated with acute intracerebral hemorrhage and infarction and ischemic seizures); and (iii) immunosuppressive agents, particularly cyclosporine and tacrolimus (FK506), may themselves provoke seizures.

Some transplant patients appear to have an increased risk for seizures. Wijdicks et al. (148) concluded that most new-onset seizures in 630 patients undergoing orthotopic liver transplantation resulted from immunosuppressant neurotoxicity (cyclosporine and FK506) and did not indicate a poor outcome. Vaughn et al. (149) reported that of 85 patients who had received a lung transplant, 22 had seizures (including 15 of 18 patients with cystic fibrosis); in patients younger than age 25 years, particularly those given IV methylprednisolone to prevent rejection, the seizure risk was increased. Bone marrow transplant recipients with human leukocyte antigen mismatch and unrelated donor material have an enhanced risk for seizures from cyclosporine neurotoxicity (150). Foscarnet, used to treat cytomegalovirus hepatitis following bone marrow transplantation (151), may also precipitate seizures (80). For the acute management of prolonged seizures, benzodiazepines are least likely to induce the enzyme system responsible for metabolizing immunosuppressant drugs (152).

Long-term management of transplant recipients with seizures is determined after the etiology has been ascertained. Because allograft survival is decreased with phenytoin or phenobarbital and steroids (153), the use of AEDs has been discouraged (154). The half-lives of prednisolone and, probably, cyclosporine (150) are decreased when phenobarbital, phenytoin, or carbamazepine is administered. Valproic acid is a reasonable choice, except in hepatic transplantation patients and in bone marrow transplantation patients during engraftment.

Levetiracetam and gabapentin may be useful in patients undergoing hepatic or bone marrow transplantation. These agents have renal elimination as unchanged drug from the systemic circulation, with very little protein binding and fewer drug interactions than other AEDs. Use of these AEDs in patients with renal failure must be modified, however.

When AEDs other than valproic acid, levetiracetam, lacosamide, or gabapentin are used, the doses of immunosuppressive agents should be increased to ensure therapeutic immunosuppression. Cyclosporine levels should be determined.

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

The clinical syndrome of posterior reversible encephalopathy syndrome (PRES) involves headache, encephalopathy, visual symptoms, and seizures. Conditions that may predispose to develop PRES include preeclampsia/eclampsia, posttransplantation, immune suppression, infection, autoimmune disease, chemotherapy, dialysis, and multiple metabolic disorders. Seizures have been noted relatively frequently in PRES. Clinical seizures occurred in more than 85% of cases of which there were multiple seizures in more than one-third of patients. Although infrequent, patients may also present with status epilepticus. Of those patients who recover, it is rare that they will have recurrent seizures (155,156).

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CHAPTER 37 SLEEP AND EPILEPSY

NANCY FOLDVARY-SCHAEFER AND SILVIA NEME-MERCANTE

The relationship between sleep and epilepsy has been recognized since antiquity. In recent years, interest in the intersections of sleep medicine and epileptology has resulted in substantial progress in several important areas. Herein, we review the more firmly established relationships between sleep and epilepsy and sleep disorders in people with epilepsy.

SEIZURES AND THE SLEEP–WAKE CYCLE

Nineteenth century investigators recognized that most seizures occurred during evening or nighttime hours and that insufficient sleep activated seizures. Gowers classified seizures as nocturnal, diurnal, and diffuse. He noted that 21% of institutionalized patients had seizures exclusively at night, 42% only during the day, and 37% either night or day (1). Peaks in seizure occurrence during the night occurred most often near the end of the sleep period (05:00 to 06:00) and less often 1 to 2 hours after sleep onset, whereas diurnal seizures clustered in the early morning and late afternoon (2). Decades later, Janz found that generalized tonic–clonic seizures (GTCs) occurred in sleep in 44%, at awakening in 33%, and randomly in 23% of people with epilepsy (3). Important in the care and counseling of patients presenting with sleep-related seizures is that seizures occur during wakefulness within 2 years of epilepsy onset in 11% to 30% of cases (4,5). Several epilepsy syndromes are now recognized for seizures that occur predominately or exclusively from sleep (Table 37.1).

Table 37.1 Sleep-Related Epilepsy Syndromes

- Benign focal epilepsy of childhood with centrotemporal spikes
- Early-onset childhood occipital epilepsy (Panayiotopoulos syndrome)
- Nocturnal frontal lobe epilepsy
- Autosomal dominant nocturnal frontal lobe epilepsy
- Lennox–Gastaut syndrome (tonic seizures)
- Landau–Kleffner syndrome
- Epileptic encephalopathy with continuous spike-and-wave during sleep

In a study examining the distribution of 600 focal seizures across the sleep–wake cycle recorded during video–electroencephalogram (EEG) evaluations, 43% were found to arise from sleep, the majority from non–rapid eye movement (NREM) stage 1 (23%) or 2 (68%), and none arose from REM sleep (6). Secondary generalization tends to occur more often during sleep (28%) than wakefulness (18%), and frontal lobe seizures tend not to secondarily generalize during sleep (6–8). Differences in peak seizure occurrence in relation to the rise in salivary melatonin between patients with temporal and frontal lobe epilepsy were observed. Temporal lobe seizures occurred most frequently in the 6 hours before and frontal seizures 6 to 12 hours after the dim light melatonin onset,

suggesting that circadian influences may underlie some of these clinical observations (9).

Recent work has focused on clock time of seizures in different epilepsy syndromes. Using scalp EEG recordings, two studies found that temporal lobe seizures occurred more often during daytime hours with a peak incidence from 15:00 to 19:00, whereas extratemporal seizures peaked between 19:00 and 23:00 (10) or in the early morning hours associated with awakening (11). In an investigation involving 131 adult patients, peak timing of seizures varied by location of the seizure-onset zone identified by invasive EEG recordings (12). Specifically, mesial temporal lobe seizures had two peaks between 16:00 to 19:00 and 07:00 to 10:00, while neocortical temporal and occipital seizures peaked between 16:00 and 19:00, and frontal and parietal seizures between 04:00 and 07:00. In the second invasive EEG study, among 33 focal epilepsy cases, temporal lobe seizures occurred preferentially during the day (11:00 to 17:00), frontal seizures at night (23:00 to 05:00), and parietal seizures in the evening (17:00 to 23:00) (13).

The peak occurrence of generalized seizures was found to vary by seizure type with tonic–clonic seizures peaking between 06:00 and 09:00, tonic seizures between 21:00 and 24:00, absence seizures between 09:00 and 12:00, atonic seizures between 12:00 and 18:00, and myoclonic seizures between 06:00 and12:00 (14). Timing of epileptic spasms was found to be age dependent with peaks between 09:00 to 12:00 and 15:00 to 18:00 in children ≤3 years and between 06:00 to 09:00 in those older than 3 years (15).

Patients with sudden unexpected death in epilepsy (SUDEP) are more likely to have a history of nocturnal seizures than are people living with epilepsy (36% vs. 17%) (16). Most sleep-related cases of SUDEP occur between in the early morning hours (04:00 and 08:00). While the mechanisms underlying seizure timing are poorly elucidated, further investigation is warranted given the potential for therapeutic interventions.

EFFECTS OF SLEEP ON SEIZURES AND THE EEG IN EPILEPSY

The first systematic study of the diagnostic yield of sleep on the EEG was performed by Fred and Erma Gibbs in 1947 (17). Among 500 epilepsy patients, interictal epileptic discharges (IEDs) were observed in 36% of wake EEGs, increasing to 82% with sleep. Sleep activated additional epileptic foci in some patients who had only one focus during wake. The detection of IEDs by recording sleep was greatest for patients with focal seizures and least with absence seizures. Patients with psychomotor seizures often had normal wake EEGs, but 95% had IEDs during sleep.

Since these early observations, the activating effect of sleep on seizures and the EEG has been extensively investigated (18). The neuronal networks that generate wake, NREM sleep, and REM sleep give rise to different physiologic characteristics influencing the likelihood of seizure and IED occurrence (19,20). NREM sleep is a state of EEG synchronization and relative preservation of antigravity muscle tone. Synchronous oscillations of cortical neurons that generate sleep spindles, K complexes, and tonic background slow waves during NREM sleep promote seizure propagation and IEDs. In contrast, REM sleep is a desynchronized state characterized by the loss of skeletal muscle tone. Desynchronization of the EEG impedes seizure propagation during REM sleep and wake. Preservation of antigravity muscle tone during NREM sleep permits the expression of seizure-related movements, while its absence during REM sleep blocks the clinical expression of seizures.

Many studies demonstrate that NREM sleep activates IEDs in focal epilepsies (21,22). Interictal

spikes increase at sleep onset, peaking in stage 3 (slow-wave sleep [SWS]), and then declining in REM sleep to levels lower than wakefulness. Similarly, the field of an IED typically increases in NREM sleep, becoming more diffuse—even generalized in SWS compared to light NREM sleep and more restricted in REM sleep. The extent and laterality of IEDs during REM sleep may be useful in confirming the primary epileptogenic zone in patients with pharmacoresistant temporal lobe epilepsy (TLE) (21,22).

Variations in IEDs with the sleep–wake cycle are also observed in the generalized epilepsies, although sleep is a less important activator because IEDs are often present in the wake EEG (23). Sleep further activates IEDs in patients with absence and/or GTC seizures (23,24). Typically, spikes increase with sleep onset progressively through SWS, diminish sharply in REM sleep, and increase again in the morning after awakening. Generalized spike–wave discharges become more disorganized, increased in amplitude, and slow in frequency in NREM sleep, whereas their morphology in REM sleep and wakefulness is similar (24). The EEG is most abnormal after the morning awakening or nighttime arousals in patients with awakening epilepsies such as juvenile myoclonic epilepsy. In contrast, the EEG tends to be normal during wakefulness or show an increase in IEDs during sleep in the generalized sleep epilepsies.

EFFECTS OF SLEEP DEPRIVATION ON EPILEPSY

The effect of sleep deprivation on epilepsy has been the subject of much investigation. In the first systematic study, sleep-deprived EEGs were performed after 26 to 28 hours of wakefulness, and IEDs were seen in 34% of 89 subjects with at least one seizure and a normal routine EEG, 56% of 34 patients with convulsive epilepsy and IEDs on routine EEGs, and 0% of 20 patients with neurologic disorders other than epilepsy (25). Subsequent work suggested that for most seizure types, spontaneous sleep and sleep-deprived EEGs produce similar activation rates, and seizures are more likely to be activated by sleep or sleep deprivation in patients with generalized rather than focal epilepsy (24). In a study comparing the yield of different EEG protocols, IEDs were recorded in 28% of subjects only following total sleep deprivation (TSD), defined as 24 hours of more of sustained wakefulness, compared to routine wake and drug-induced sleep EEGs, and TSD activated a new epileptic focus in 7% of cases (26). As the yield of recording IEDs due to repeated recordings was estimated to be in the range of 14% to 19%, the authors claimed their findings were unlikely to be due to sampling effects. In recent study involving patients with new-onset epilepsy, IEDs were observed in 92% of TSD EEGs versus 58% of drug-induced sleep and 44% of routine recordings (27). Similarly, a prospective study of 721 subjects who had a second EEG (routine, drug-induced sleep or TSD) after an inconclusive initial EEG found a significantly greater percentage containing IEDs after TSD as compared to a second routine record (23% vs. 10%) (28). Comparative studies largely confirm that TSD activates IEDs in 23% to 93% of patients with definite or suspected seizures (18). Whether the activation of IEDs on EEG produced by sleep deprivation is due to sleep itself (greater amounts of sleep recorded, sampling effects) or because TSD exerts an independent activating effect is uncertain.

The effects of less extreme degrees of sleep deprivation on the EEG are not fully elucidated. Among 71 patients with focal epilepsy, the odds of a seizure the next day decreased for each hour of sleep the prior night (29). In another study based on 2-year sleep and seizure diaries completed by 14 adults with TLE, the probability of a seizure was significantly greater after a night of sleep deprivation (at least 1.5 hours less than usual) compared with normal sleep (30). Indeed, sleep

deprivation is reported as a seizure precipitant by up to one-third of people with epilepsy (3,29,31). Several studies using transmagnetic stimulation have reported a significant increase in cortical excitability following sleep deprivation in people with epilepsy compared to controls (32). These findings suggest that modest amounts of sleep loss can activate seizures and the EEG.

EFFECTS OF EPILEPSY THERAPIES ON SLEEP

Antiepileptic drugs (AEDs) have variable effects on nocturnal sleep and wakefulness (Table 37.2). The effects of AEDs may be due in part to a consolatory effect on sleep. Some AEDs tend to cause more sleepiness and drowsiness, while others can lead to insomnia.

Table 37.2 Effects of Chronic Antiepileptic Drug Therapy on Sleep Architecture[a]

	Sleep efficiency	Sleep latency	Stage 1	Stage 2	Stage 3	REM
Older AEDs						
Benzodiazepines	↑	↓	—	—	↓	↓
Carbamazepine	0	0	0	0	0	0
Ethosuximide	—	—	↑	—	↓	—
Phenobarbital	↑	↓	—	↑	0	↓
Phenytoin	0	↓	↑	↑	↓	0
Primidone	—	↓	—	—	—	0
Valproate	—	0	↑	↓	0	0
Newer AEDs						
Gabapentin	0	0	0	0	↑	↑
Lamotrigine	0	0	0	↑	↓	↑
Levetiracetam	0	0	↑	↑	↑	↓
Pregabalin	—	—	—	↓	—	↑
Tiagabine	↑	0	↓	0	↑	0
Topiramate	0	↓	0	0	0	0
Zonisamide	—	—	—	—	—	—

0, denotes no change; —, denotes not reported.

[a]Includes data acquired after achieving steady state.

Barbiturates and benzodiazepines suppress REM sleep, reduce sleep latency, and increase sleep efficiency, while phenytoin and valproic acid appear to increase light NREM sleep and increase arousals and awakenings (33). Carbamazepine (CBZ) is the most extensively investigated older AED. Studies suggest that the short- and long-term effects of CBZ on sleep differ. For example, a single 400-mg dose of controlled release CBZ in adults with newly diagnosed TLE and controls produced a significant reduction in REM sleep and increased stage shifts and REM sleep fragmentation, effects that reversed after 1 month of treatment (33).

Newer AEDs also affect sleep architecture but appear to have more favorable effects than do some of the older agents, perhaps contributing to their antiseizure properties. In particular, lamotrigine (LTG), topiramate, and zonisamide produce minimal alterations in sleep architecture in adult patients on relatively low-dose therapy, and LTG produced an increase in REM sleep in two studies (33–36). Gabapentin produced a deepening of sleep, increasing SWS percentage, and reducing sleep fragmentation in healthy subjects (37) and increased REM sleep in patients with epilepsy (33). Similarly, pregabalin was associated with a significant reduction in the number of awakenings and improvement in wake after sleep onset (38) and an increase in REM sleep (39) in patients with focal epilepsy, suggesting improvements in sleep continuity. Studies exploring the

effects of levetiracetam are conflicting, but generally also show consolatory effects on sleep in both healthy subjects and adults with epilepsy (40,41). Finally, in several studies, tiagabine has been shown to increase SWS and reduce sleep fragmentation in older, otherwise healthy adults (42).

Like AEDs, vagal nerve stimulation (VNS) produces alterations in sleep and wakefulness. Although improved daytime alertness has been observed, VNS stimulus intensity >1.5 mA has been associated with a reduction in REM sleep and increased awakenings, wake after sleep onset, and stage 1 sleep, suggesting a shift to lighter sleep stages and more sleep fragmentation (43). VNS therapy can produce cyclical reductions in airflow during sleep that at time meets the polysomnographic (PSG) criteria for sleep apnea in adults and children with epilepsy (44,45). Lowering the stimulus frequency from 30 to 20 Hz was shown to ameliorate VNS-induced respiratory events (46). Therefore, PSG should be performed prior to VNS implantation in all patients due to the potential development of sleep apnea. Patients should be monitored after implantation for sleep apnea symptoms. Repeat PSG should be performed in those with new-onset snoring, witnessed apnea, or daytime sleepiness and in patients with previously diagnosed sleep apnea as treatment adjustments may be required.

Sleep Organization in Epilepsy

A number of sleep architectural abnormalities have been reported in people with epilepsy. These include disruption and lability of REM sleep with reduced percentage of sleep time spent in REM sleep; increased percentage of wake after sleep onset; prolonged sleep or REM sleep onset; and increased number of arousals, awakenings, and stage shifts (47). These findings hold true even in seizure-free patients and are observed in patients with genetic generalized epilepsies and TLE, although more so in the latter. Sleep organization is more disrupted in TLE than in FLE, with more time wake after sleep onset, more awakenings, increased duration of light NREM sleep, reduced sleep efficiency, and reduced SWS (7,22).

Nocturnal generalized motor seizures in adults with genetic generalized epilepsy or focal epilepsy are associated with a decrease in total sleep time and REM sleep, prolonged REM latency, and increased light NREM sleep, increased percentage of time wake after sleep onset, and increased arousals (22,48). In a video–EEG series of TLE, a significant decrease in REM sleep was found on nights following daytime seizures, an even greater decrease in REM sleep on nights of seizures, and the greatest amount of REM suppression on nights in which seizures occurred early in the sleep period before the first appearance of REM sleep (48). Both diurnal and nocturnal seizures prolonged REM latency. Nocturnal, but not diurnal, seizures increased stage 1 sleep and decreased SWS. In a large study involving adults with epilepsy, compared to seizure-free patients, those who had generalized motor seizure during the day had significantly prolonged REM latency, increased stage 2 sleep, and decreased SWS and REM sleep the following night (49). A recent study reported a significant reduction in time in bed, total sleep time, REM sleep, SWS, and sleep efficiency as well as a significant increase in wake time after sleep onset in children with pharmacoresistant epilepsy compared to children with benign focal epilepsy and normal controls (50). In turn, a significant increase in REM sleep was observed in patients with mesial TLE seizure free at 2 years following resective surgery (51). Taken together, these findings suggest that sleep is inherently unstable in people with epilepsy; this instability promotes seizures, and seizures in turn fragment sleep, thus facilitating the epileptic process.

SLEEP–WAKE COMPLAINTS AND SLEEP DISORDERS IN EPILEPSY

Many sleep disorder symptoms and some primary sleep disorders including excessive daytime sleepiness (EDS), insomnia, and obstructive sleep apnea (OSA) are two to three times more common in people with epilepsy than in the general population (52–57) and adversely affect quality of life (52,54–56). This subject has been the focus of a comprehensive review (58).

EDS and insomnia are two of the most common complaints of people with epilepsy, often attributed to the effects of AEDs and seizures. One-third to one-half of the epileptic population report EDS (54,59). In a recent study involving 152 adults with epilepsy, 55% suffered from insomnia and more than 70% were rated as "poor sleepers" (56). Insomnia and poor sleep quality were significantly correlated with number of AEDs and depressive symptoms. As in the general population, sleep problems are more common among adults with epilepsy taking psychotropics for the treatment of mood disorders (55). In children with epilepsy, sleep problems are also common and adversely affect behavior and academic performance (57). Disturbed sleep, snoring, limb movements in sleep, daytime hyperactivity, EDS, and bedtime refusal are more common in children with epilepsy than in age-matched controls (57).

The prevalence of OSA in adults with epilepsy exceeds general population estimates of 25% for men and 10% for women (60). In the first PSG study, 33% of 39 patients (50% of males; 19% of females) with pharmacoresistant focal epilepsy without sleep complaints had OSA defined by an apnea–hypopnea index (AHI) of ≥10 (61). Predictors of OSA included male gender, higher body mass index (BMI), and a history of snoring, witnessed apnea, or nocturnal seizures. In a recent study involving 130 adults with epilepsy unselected for sleep disorders symptoms, the prevalence of OSA (AHI ≥ 10) was 30%, 16% having moderate-to-severe disease (62). Predictors of OSA included older age, dental problems, and higher standardized AED dose, a measure of drug burden. Male gender, older age, higher BMI, hypertension, and dental problems were associated with having a higher AHI. In older patients with epilepsy, the presence of sleep apnea is associated with worsening seizure control or late-onset seizures (63). Potential contributing factors include the effects of AEDs on upper airway tone as well as AEDs and inactivity leading to weight gain and endocrinopathies such as polycystic ovarian syndrome and hypothyroidism.

Understanding the predictors of OSA and other sleep disorders in epilepsy is important since treatment of OSA reduces seizures in 40% to 86% of cases, children included (58,64,65). A recent retrospective study found that continuous positive airway pressure (CPAP) therapy reduced seizure frequency by more than 50% (from 1.8 to 1 seizure per month) in 41 adults in the absence of AED adjustments (64). In another study, use of CPAP in 6 patients with focal epilepsy produced a marked reduction in spike rate on EEG, suggesting that sleep consolidation and correction of desaturation and hypercapnia may reduce epileptogenicity (66). These findings underscore the importance of routine screening and treatment of sleep disorders in people with epilepsy.

COMPLEX NOCTURNAL MOVEMENTS AND BEHAVIORS: DIFFERENTIATING NOCTURNAL SEIZURES AND PARASOMNIAS

While the differential diagnosis of abnormal sleep-related movements and behaviors is extensive, the focus of evaluation is usually on the distinction between nocturnal seizures and parasomnias (67). Parasomnias are undesirable physical events or experiences that occur during entry into sleep, within sleep, or during arousals from sleep that involve complex, seemingly purposely, goal-directed behaviors without consciousness. The primary parasomnias pertinent to this discussion are the NREM arousal disorders (confusional arousals, sleep terrors, and sleepwalking). Seizures in nocturnal frontal lobe epilepsy (NFLE) have a wide range of complexity and severity, overlapping considerably with disorders of arousal. Complex motor features typically of the hypermotor type involving complex movements of the trunk and proximal extremities that are repetitive, high-amplitude, and high-velocity, and asymmetric tonic seizures having dystonic, dyskinetic, and repetitive proximal movements are characteristic of NFLE (68). The lifetime prevalence of arousal disorders is nearly fivefold greater in relatives of probands with NFLE than in controls, suggesting an intrinsic link between the two (69).

A dysfunctional arousal mechanism involving the cholinergic system is hypothesized to underlie the shared pathophysiology of NFLE and NREM parasomnias. Mutations in the neuronal acetylcholine receptor in the autosomal dominant form of NFLE suggest a molecular basis for the disorder. These ion channel receptors are widely distributed on neuronal and glial membranes in cortical and subcortical regions, regulating the release of acetylcholine, gamma-hydroxybutyric acid, and glutamate, and producing a modulatory effect on arousals at the cortical and thalamic levels. Receptor mutations confer a gain of function with increased sensitivity to acetylcholine that is postulated to produce changes in the excitability of cortical and subcortical networks preferentially affecting the mesial frontal area facilitating intrinsic epileptogenesis and altering arousal mechanisms by destabilizing sleep (70). Activation of common pattern generators is thought to underlie the similar semiological manifestations of nocturnal seizures and arousal disorders (71). These are genetically determined neural circuits located in the mesencephalon, pons, and spinal cord that code for self-sustained patterns of behavior subserving innate motor behaviors essential for survival, such as feeding, locomotion, defense, and copulation.

The diagnosis of nocturnal seizures and parasomnias is often achieved through a comprehensive clinical history including timing, frequency, semiology, and evolution of typical events (Table 37.3). The Frontal Lobe Epilepsy and Parasomnias (FLEP) scale has been proposed as an adjunctive tool to identify patients with NFLE (Table 37.4) (72). A score of 0 or less is unlikely to be seen in epilepsy, whereas patients scoring 3 or greater generally have epilepsy. Laboratory testing is recommended for those with an FLEP score of +1 to +3. If diagnostic uncertainty persists despite routine clinical, EEG, and imaging assessments, video PSG with EEG (VPSG-EEG) may be warranted. This procedure combines PSG with 21-channel EEG to evaluate unexplained nocturnal behaviors when epileptic seizures are suspected, particularly when primary sleep disorders are under consideration and episodes are frequent. Due to the limitations of capturing a typical event in one night of recording, long-term VEEG is preferred when episodes do not occur at least every other night, primary sleep disorders such as OSA are not suspected, a history of postictal agitation or wandering exists, and patient cooperation is uncertain. In a recent VPSG-EEG analysis of 120 events of 44 patients with NFLE or NREM arousal disorders, 94% were correctly classified using a diagnostic decision tree based on a cluster analysis (73).

Table 37.3 Differentiating Nocturnal Frontal Lobe Epilepsy and Parasomnias

Feature	NFLE	Arousal disorders	REM behavior disorder
Age of onset	Variable, typically first or second decade	Usually first decade	Over 50
Sleep stage of origin	NREM 1 or 2, sleep–wake transitions	NREM 3	REM sleep
Timing of episodes	Anytime	First one-third of sleep period	Last one-third of sleep period
Duration of episodes	5–60 s	2–30 min	Seconds to 2 min
Frequency of episodes	Nightly clusters	Sporadic, rare clusters	Sporadic, rare clusters
Onset and offset	Sudden	Gradual	Sudden
Semiology of episodes	Highly stereotyped, hypermotor, asymmetric tonic/dystonic	Not stereotyped, variable complexity	Not highly stereotyped, vocalizations with self-protective behaviors and dream recall
Level of consciousness during episodes	Usually preserved	Variable	Poorly responsive
Postictal confusion	Typically absent	Present	Absent
Risk of injury	Low	High	Moderate
VPSG-EEG findings	Epileptic activity in <50%	SWS arousals, rhythmic delta pattern	REM sleep without atonia

From Foldvary-Schaefer N, Aksheikhtaha Z. Complex nocturnal behaviors: nocturnal seizures and parasomnias. Continuum (Minneap Minn). 2013;19(1):104–131.

Table 37.4 The Frontal Lobe Epilepsy and Parasomnia Scale

Clinical feature		Score
Age at onset	<55 y	0
	≥55 y	−1
Duration of typical event	<2 min	+1
	2–10 min	0
	10 min	−2
Typical number of events in single night	1 or 2	0
	3–5	+1
	>5	+2
Time of night events most commonly occur	Within 30 min of sleep onset	+1
	Other times	0
Events associated with definite aura	Yes	+2
	No	0
Wandering outside bedroom during events	Yes	−2
	No (or uncertain)	0
Complex, directed behaviors during events	Yes	−2
	No (or uncertain)	0
Prominent dystonic posturing, tonic limb extension, or cramping during events	Yes	+1
	No (or uncertain)	0
Event stereotypy	Highly stereotyped	+1
	Some variability/uncertain highly variable	0
		−1
Patient recollection of events	Yes, lucid recall	+1
	No or vague recollection only	0
Speech during events; if so, subsequent recollection of speech	No	0
	Yes, sounds only or single words	0
	Yes, coherent with incomplete or no recall	−2
	Yes, coherent speech with recall	+2
	Total score	

Modified from Derry CP, Davey M, Johns M, et al. Distinguishing sleep disorders from seizures: diagnosing bumps in the night. Arch Neurol. 2006;63(5):705–709.

CONCLUSION

Over a century of work has confirmed important links between sleep and epilepsy. Several epilepsy syndromes are now recognized for seizures that occur predominately or exclusively from sleep and investigations exploring the mechanisms underlying variations in seizure timing in epilepsies arising

from different regions is underway. Sleep is a critical modulator of IEDs and seizures, and significant sleep deprivation activates seizures and epileptic EEG abnormalities. People with epilepsy are prone to sleep instability, in part due to seizures, AEDs, and VNS therapy. The prevalence of insomnia and sleep apnea is increased in epilepsy patients, and untreated sleep disorders further increase daytime sleepiness and seizures. These observations underscore the importance of the routine assessment of sleep and wake complaints in people with epilepsy.

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CHAPTER 38 STATUS EPILEPTICUS

HOWARD P. GOODKIN AND JAMES J. RIVIELLO, JR.

Status epilepticus (SE) is a life-threatening medical emergency that requires prompt recognition and immediate treatment. SE is not a disease in itself but rather a manifestation of either a primary central nervous system (CNS) insult or a systemic disorder with secondary CNS effects. It is important to identify and specifically treat the precipitating cause, thus preventing ongoing neurologic injury and seizure recurrence. A team approach, with an organized and systematic treatment regimen, planned in advance, is needed, including one for refractory status epilepticus (RSE). It is imperative that SE treatment rigorously adhere to basic neuroresuscitation principles—the ABCs (airway, breathing, circulation). Although the initial approach is standard, once the patient is stabilized, management must be individualized with the goal of terminating the seizure and treating the underlying condition.

DEFINITION

SE can present in many different forms that range from the easily recognized prolonged overt generalized convulsive SE to the more difficult to recognize nonconvulsive SE (NCSE) that is characterized by a prolonged continuous ictal electrographic discharge pattern, with or without obvious clinical signs. Given the broad range of clinical presentations and that the underlying mechanisms permitting prolonged seizures are not completely known, it has been difficult to develop definition and classification systems that are well accepted, comprehensive, mechanistic, and clinically useful.

At first, Gastaut's classic operational definition of SE as "an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epilepticus condition" (1) may seem vague, cumbersome, and insufficient as it fails to provide adequate guidance to the clinician. However, it has the advantage of allowing for a dynamic interpretation.

Other proposed operational definitions have attempted to be more precise by including a time duration (2,3). However, the basis for the time chosen has varied. As experimental studies demonstrated an increased risk of neuronal injury after 30 minutes when homeostatic mechanisms fail, the Working Group on Status Epilepticus of the Epilepsy Foundation of America (EFA) defined SE as >30 minutes of either a continuous seizure or two or more sequential seizures without full recovery of consciousness (4). In defining SE, others have chosen to emphasize the need for the prompt care of the patient and chosen to define the seizure duration required to fulfill the definition of SE in the 5- to 10-minute range (5). It is expected that future definitions of SE will continue to better define the mechanisms that underlie the self-sustained nature of these prolonged seizures.

CLASSIFICATION

The classification of the epilepsies and seizures is evolving (6). The classification of SE is no

different, and multiple schemas for the classification of SE have been proposed throughout the years. Traditionally, the prolonged, continuous, or repetitive seizures of SE have been separated from the self-limited seizures and classified into two broad categories—either generalized or focal (partial)—based on a combination of the electrographic pattern and seizure semiology (7–12).

In contrast, other proposed classification schemas have placed an emphasis on seizure semiology. One proposal divided SE into the categories of aura status, autonomic status, dyscognitive status, motor status (simple motor, i.e., focal motor without alteration of consciousness, and complex motor, i.e., focal motor with dyscognitive features), and special status (e.g., hypomotor status) (13). A more familiar predominantly semiologically based SE classification system divides SE into three broad categories of simple focal, convulsive, and nonconvulsive (14). However, the division between convulsive SE and NCSE may not be so obvious as subtle convulsive SE or NCSE—characterized by no obvious clinical signs despite marked impairment of consciousness and bilateral EEG discharges—may evolve from convulsive SE or follow its unsuccessful treatment.

In a study of 458 patients from the Netherlands (1980–1987) (15–17), generalized convulsive SE occurred in 346 (77%), NCSE in 65 (13%), and simple partial SE in 47 (10%). Of patients with NCSE, 40 had complex partial SE and 25 had absence SE. In this study, within the nonconvulsive group of SE patients, focal signs occurred more often with complex partial SE and a fluctuating consciousness was more common with absence SE, with the majority of patients in both groups having prior epilepsy (15). With simple partial SE, 46 patients had somatomotor features and 1 had aphasia with hallucinations (16).

As future classification systems are developed, psychogenic nonepileptic SE, which occurs in adults (18) and children (19,20), should likely be included as a special category to assure clinical recognition of these events. Pseudostatus epilepticus may occur as an expression of Munchausen syndrome (factitious disorder by proxy) (21).

THE CLINICAL AND ELECTROGRAPHIC STAGES OF STATUS EPILEPTICUS

The clinical stages of SE include the premonitory (prodromal) stage, the incipient stage, the early stage, the "transition stage" to the late or established stage, the refractory stage (22), and postictal stage (Table 38.1).

Table 38.1 Stages of Status Epilepticus

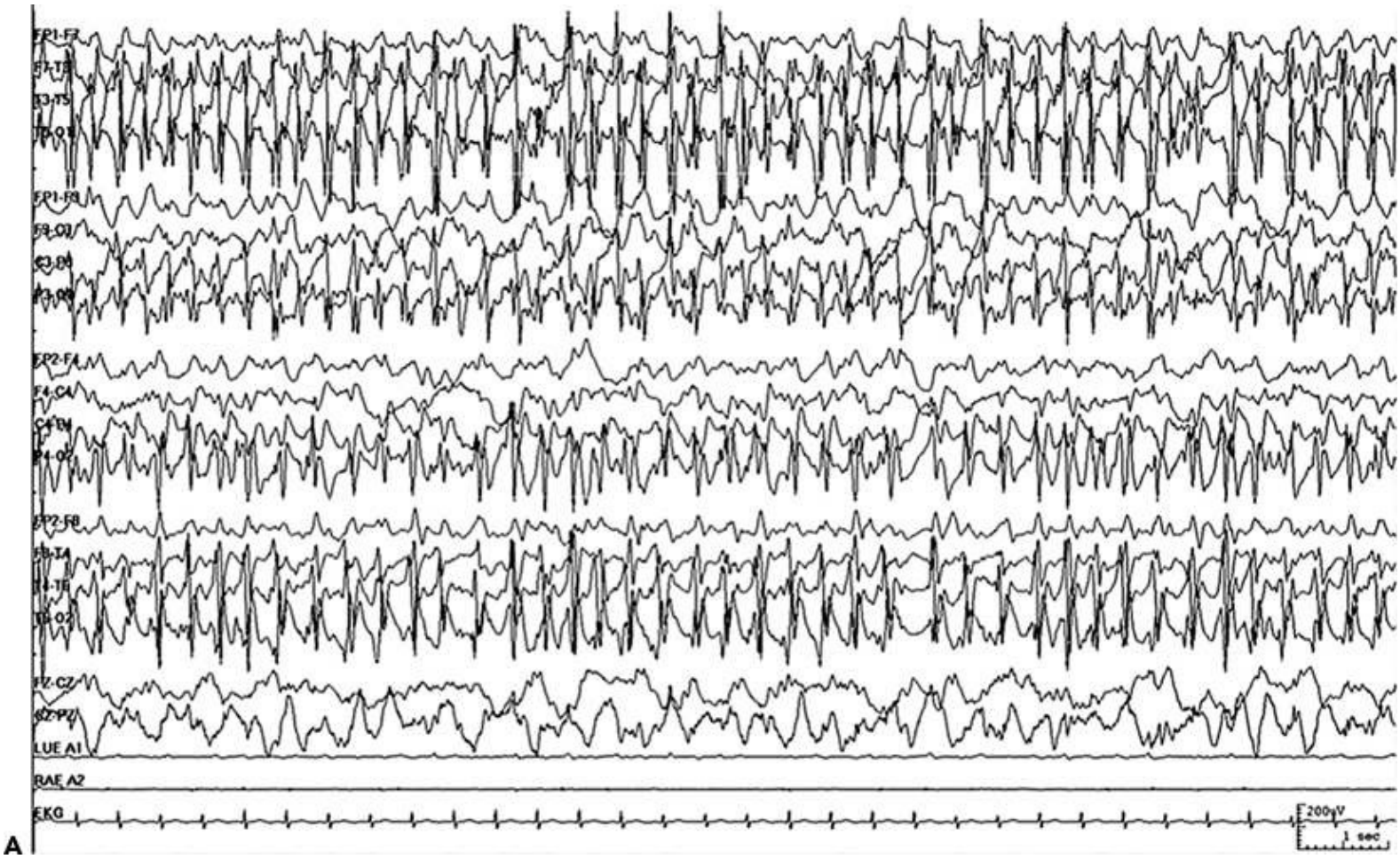
Premonitory	
Incipient[a]	0–5 min
Early[a]	5–30 min
Transition	From early to established
Established (late)	30–60 min
Refractory	After 60 min
Postictal	

[a]Special circumstances of the early and incipient stages for which early anesthetic therapy should be considered are listed in Table 38.2.

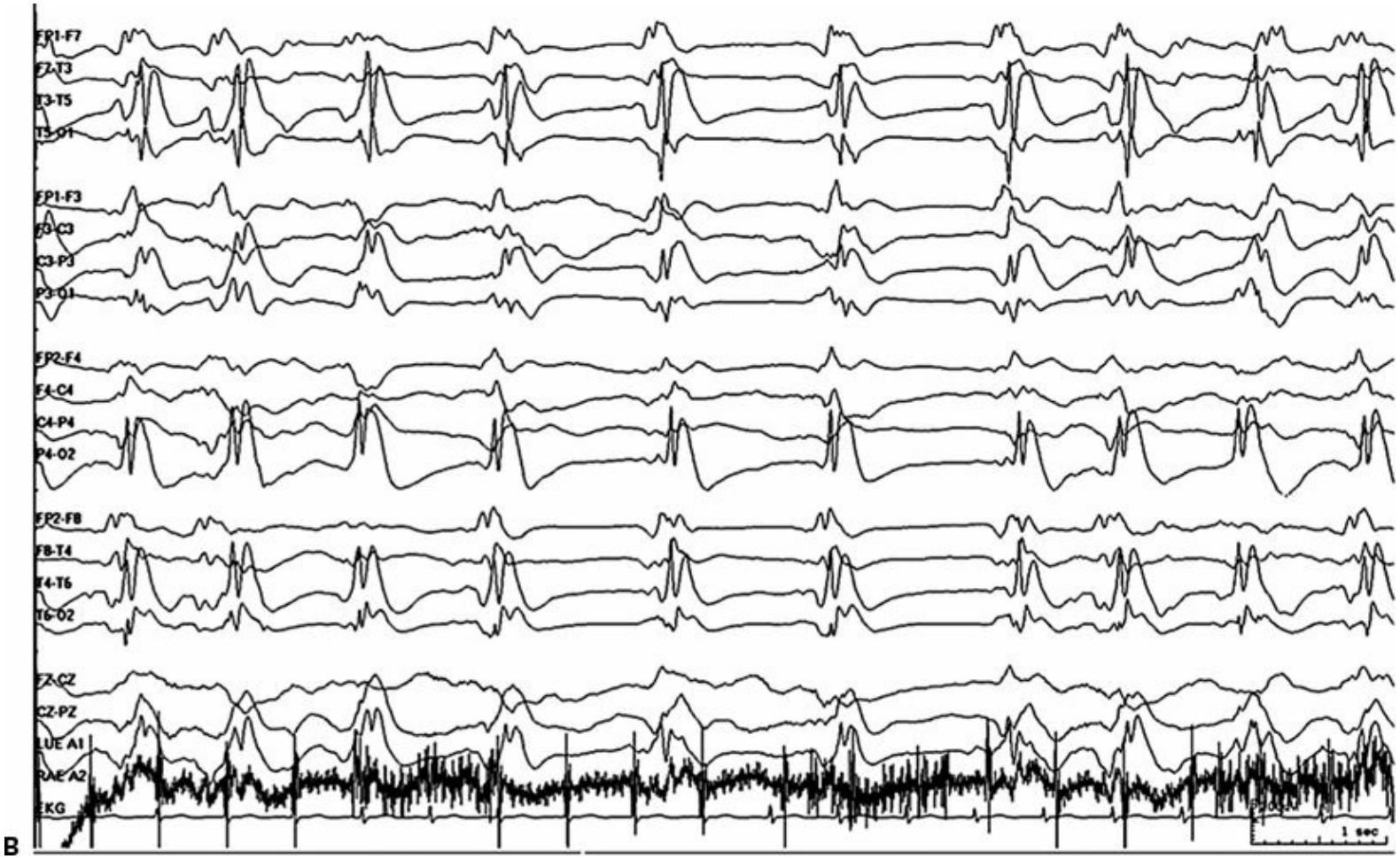
The premonitory stage consists of confusion, myoclonus, or increasing seizure frequency, the early stage consists of a continuous seizure, and the refractory stage may consist of subtle generalized

convulsive SE or NCSE. It has now become clear that the "transition" stage from the early to the late stage of SE is not fixed in time and may vary depending on the underlying etiology. SE should not be considered refractory if therapy has been inadequate.

A predictable sequence of EEG progression occurs during the clinical stages in experimental models and humans: (i) discrete seizures with interictal slowing, (ii) waxing and waning of ictal discharges, (iii) continuous ictal discharges, (iv) continuous ictal discharges punctuated by flat periods, and (v) periodic epileptiform discharges (PEDs) on a flat background (Fig. 38.1) (23,24). However, every episode of SE does not pass through every one of these defined stages (25) (Fig. 38.2). The PED stage may also consist of either lateralized or bilateral patterns (23). The response to treatment appears to depend on the electrographic stage (see below: Trends in Patients with Status Epilepticus). In one study (23), discrete seizures were all controlled with diazepam (six of six patients); whereas in the PED stage, the seizure stopped in only one of six patients and overt clinical seizures were converted to either subtle or electrographic seizures in the five of six patients.

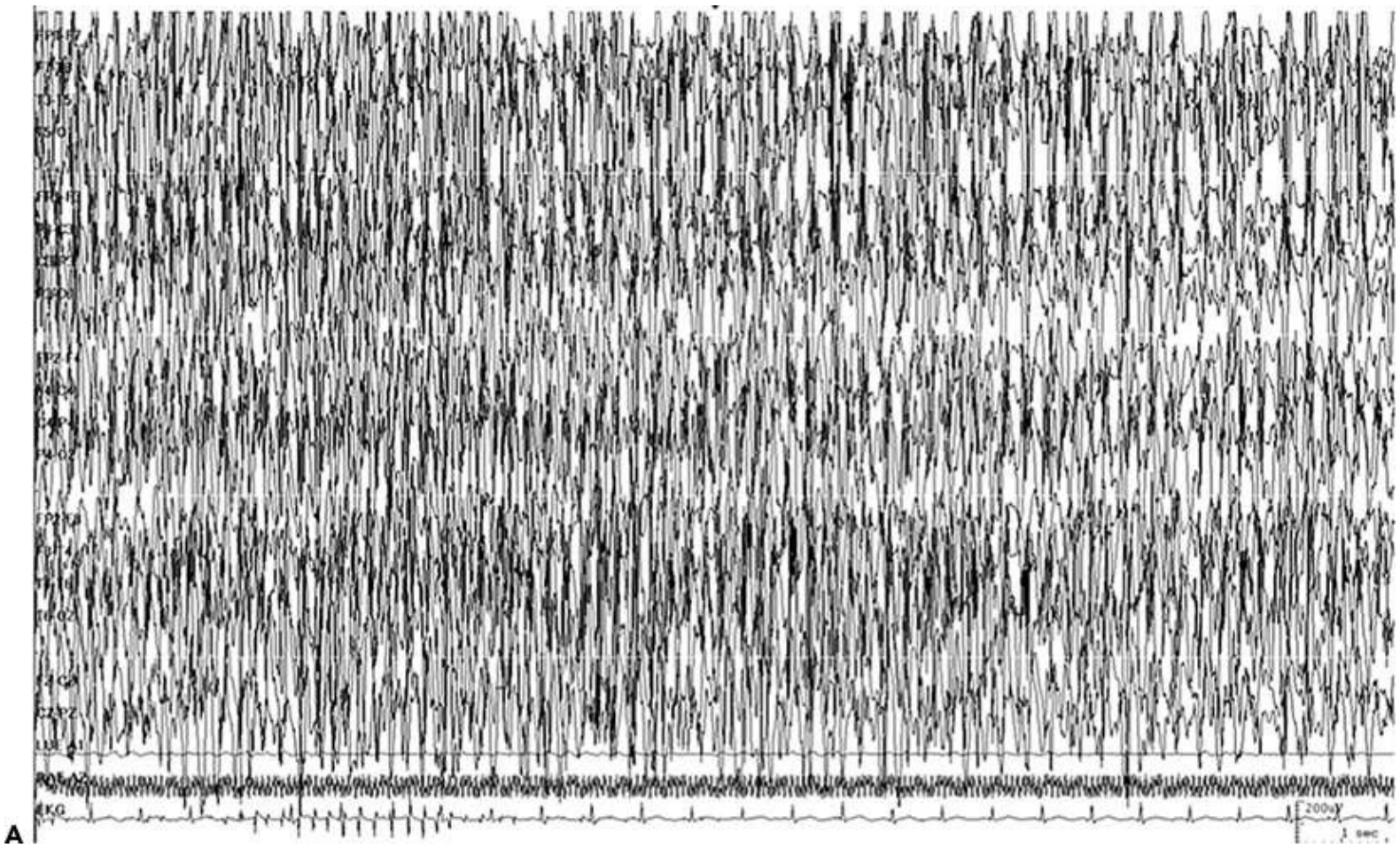


A



B

Figure 38.1. A: Continuous ictal discharges. **B:**PEDs on a flat background.



A

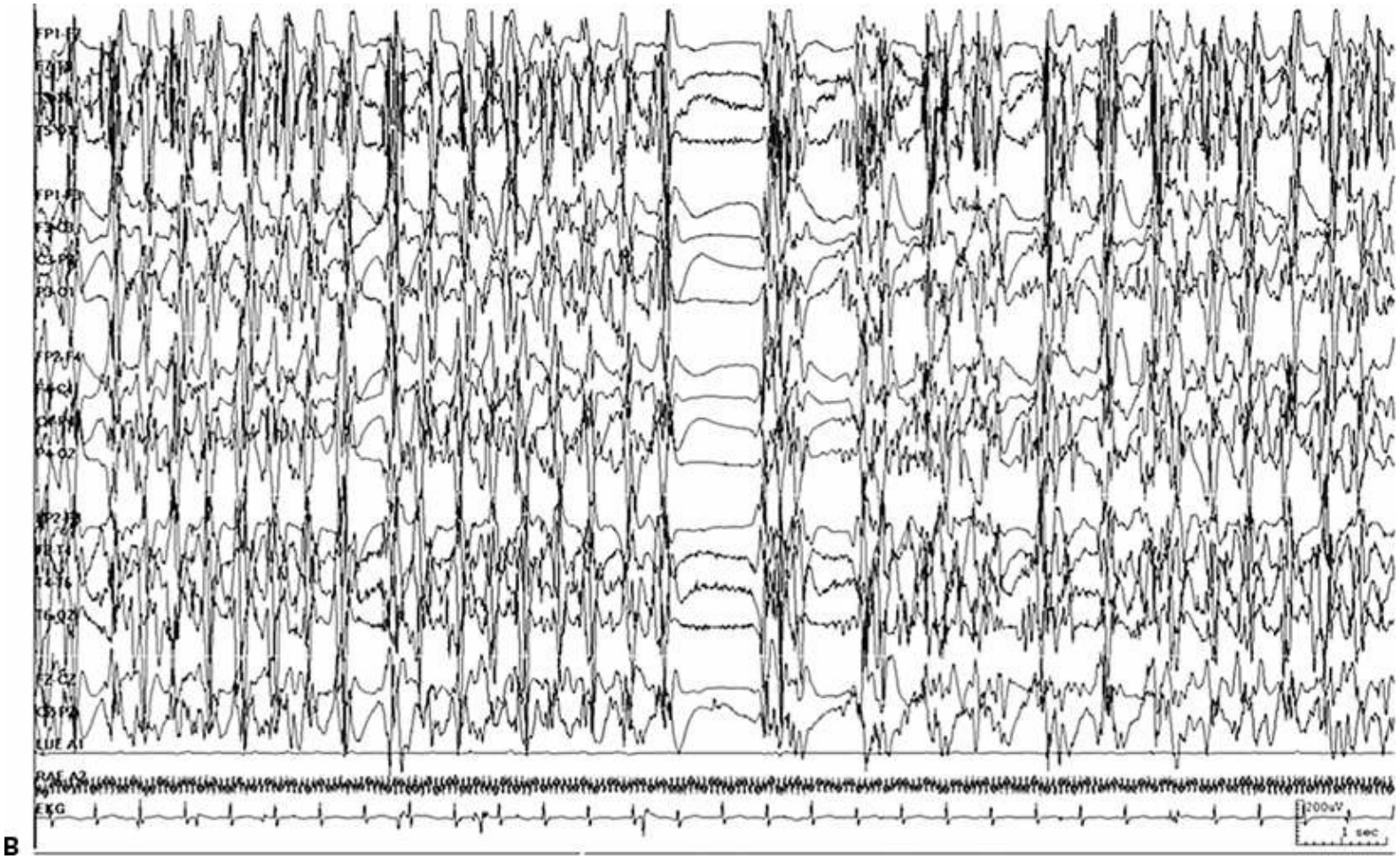


Figure 38.2. Same patient, different seizure. **A:** Continuous ictal discharge. **B:** Continuous ictal discharges punctuated by flat periods.

TRENDS IN PATIENTS WITH STATUS EPILEPTICUS

As prolonged seizures are unlikely to spontaneously cease, the overall trend in SE has been to decrease the time duration required for diagnosis and to treat as soon as possible. Although the EFA Working Group defined SE as a seizure duration >30 minutes, the Working Group recommended treatment as soon as 10 minutes after seizure onset (5). Lowenstein et al. (6) proposed an operational definition for generalized convulsive SE in adults and older children (>5 years of age) of ≥5 minutes of either a continuous seizure or two or more discrete seizures between which there is incomplete recovery of consciousness. In the Veterans Affairs (VA) Cooperative Study (26), which compared various first-line antiepileptic drugs (AEDs), treatment for SE was initiated at 10 minutes, and the San Francisco Prehospital Treatment study used 5 minutes (27). Beran has questioned waiting even as long as 5 minutes to treat an ongoing seizure (28). Similarly, Lowenstein and Alldredge had recommended immediately proceeding to anesthesia in the special case of SE developing while in the ICU (2). Table 38.2 lists other special circumstances for which immediate treatment during the early stage or even the incipient stage of SE (see Table 38.1) is recommended (29).

Table 38.2 Special Circumstances of the Early Stage

Postoperative patients, especially cardiac surgery and neurosurgery
Brain tumor, head trauma, increased intracranial pressure, intracranial hematoma, subarachnoid hemorrhage
Stroke: Ischemic, hemorrhagic
CNS infections (meningitis, encephalitis, brain abscess)
Organ failure, especially hepatic or multisystem failure
Hyperthermia, malignant hyperthermia, hyperthyroidism
Metabolic disorders prone to increased intracranial pressure, diabetic ketoacidosis, or organic acid disorders

Clinical data characterizing the duration of a typical seizure support this trend of earlier treatment. A typical clinical seizure rarely lasts as long as 5 minutes. A typical generalized tonic–clonic seizure lasts 31 to 51 seconds, with a postictal phase of a few seconds to 4 minutes (30). In an inpatient study, mean seizure duration was 62 seconds, with a range of 16 to 108 seconds (31). In complex partial seizures in children, the typical duration was 97 seconds (32). In a prospective study of new-onset seizures in children, the frequency distribution of seizure duration was best described as the sum of two groups: one with a mean of 3.6 minutes (76% of cases) and the other with a mean of 31 minutes (24% of cases); if the seizure duration was 5 to 10 minutes, it was unlikely to cease spontaneously within the next few minutes (33).

The trend for the prompt treatment of SE during the early stage is supported by clinical and experimental studies characterizing the treatment of SE. In the prospective VA Cooperative Study, the first-line treatment of shorter-duration overt generalized SE was more successful than the first-line treatment of the more prolonged subtle SE, independent of treatment arm. In addition, in post hoc analysis, it was demonstrated that when the first-line AEDs failed, there was only a 5.3% response to a third AED (22). Although the response rate to treatment with a third AED was higher (58%) in a retrospective study of 83 episodes of SE in 74 patients (34), it has been posited that this difference reflects earlier treatment.

A time-dependent efficacy of treatment has also been observed in experimental models of SE. Following induction of SE with the combination of lithium and the cholinergic agonist pilocarpine, diazepam was effective in controlling SE shortly after onset but was effective in only 17% of rats in the late electrographic stages of SE (35). This finding was later confirmed in a second model of SE for both diazepam and phenytoin (36). This decrease in the benzodiazepine response occurs rapidly after the onset of SE and in young animals with ages corresponding to a human toddler (37–39). Diazepam and the other benzodiazepines enhance the function of a subset of benzodiazepine-sensitive $GABA_A$ receptors. Several studies (40–43) have demonstrated that the surface expression of these $GABA_A$ receptors declines during SE and have postulated that this reduction in surface expression, which is the result of activity-dependent, subunit-specific trafficking of $GABA_A$ receptors, partially accounts for the time-dependent efficacy of the benzodiazepines.

PATHOPHYSIOLOGY

Mechanistically, SE occurs when factors that "normally" terminate seizures fail allowing the seizure to persist and self-propagate (5,44). What are these pathophysiologic mechanisms? In simplistic terms, SE results from decreased cerebral inhibition, excessive cerebral excitation, or a combination of both. A rapid modification in the properties of $GABA_A$ receptors (37,45) and excitatory amino

acid receptors (46,47) through mechanisms such as altered receptor trafficking (see above) likely contributes to the reduction in inhibition and increase in excitation.

Excessive excitation itself may cause neuronal injury and cell death, referred to as excitotoxic injury. This has been demonstrated in experimental models, such as in kainic acid–induced limbic seizures (48), but its occurrence in humans had been questioned. An outbreak of domoic acid poisoning, an excitotoxic agent, with acute symptoms, including SE, was associated with neuronal loss and astrocytosis that was greatest in the hippocampus and amygdala; this is similar to the seizures induced by kainic acid (49,50). A survivor developed epilepsy and, after death, autopsy revealed hippocampal sclerosis (51).

Prolonged seizures in anesthetized baboons cause irreversible neuronal injury (52,53). Lothman outlined the alterations in systemic and brain metabolism occurring with prolonged SE (54): decreased brain oxygen tension, mismatch between the sustained increase in oxygen and glucose utilization and a fall in cerebral blood flow, and depletion of brain glucose and oxygen. In the incipient or early stages of SE, brain compensatory mechanisms may protect against neuronal injury. However at some point, the ability to compensate for neuronal injury is exhausted, and the risk of neuronal injury increases. This point defines the transition stage from early to late (established) SE. During all stages, the ability to compensate requires adequate airway and good breathing, circulation, and cerebral blood flow.

EPIDEMIOLOGY OF STATUS EPILEPTICUS

There have been two large, population-based studies in the United States—one performed in Richmond, Virginia (55) and the other in Rochester, Minnesota (56). These two studies estimate that 60,000 to 150,000 episodes of SE occur per year in the United States resulting in approximately 55,000 deaths per year. Overall, SE accounts for 1% to 8% of hospital admissions for epilepsy. Between 4% and 16% of patients with epilepsy will have at least one episode of SE, with one-third of the cases occurring as the presenting symptom in patients with a first unprovoked seizure, one-third in patients with established epilepsy, and one-third in those with no history of epilepsy (57).

The incidence has varied by location: the rate in the study performed in Richmond was 41/100,000 (55) and the rate in the Rochester study was 18/100,000 (56). Lower rates were observed in a study performed in California (58), where the overall rate of generalized convulsive SE was 6.2/100,000, and in European studies, where the incidence rate was 9.9/100,000 in Switzerland (59), 15.8/100,000 in Germany (60), and 13.1/100,000 in Bologna (61).

A consistent finding across studies is that higher incidence rates occur at the extremes of life. For example, in the California study, the incidence rate for children <5 years of age was 7.5/100,000 and the incidence rate for the elderly was 22.3/100,000. In children, SE is most common in the very young, especially those <2 years of age (62). In the community- based prospective North London Status Epilepticus in Childhood Surveillance Study (NLSTEPSS), the incidence of SE during childhood was from 17 to 23/100,000/year (63). For children with epilepsy, SE typically occurs within 2 years of the onset of epilepsy (64), and recurrent SE is more likely with an underlying neurologic disorder (65).

ETIOLOGY OF STATUS EPILEPTICUS

As previously noted, SE is not a disease but the end result of multiple causes. These causes may be

acute or remote to the episode. There may be a remote cause for the epilepsy with a new acute precipitant for the episode of SE. SE may be observed as part of a progressive encephalopathy resulting from a genetic disorder. In some cases, the cause of the SE may remain unknown (66).

In several studies of adult SE, trauma, tumor, and vascular disease were the most frequently identified causes, although idiopathic and unknown causes were also common (67–70). Etiology also differs among centers and by ages. In San Francisco, noncompliance with AEDs and alcohol withdrawal were the two most common etiologies (Table 38.3) (67,70), whereas cerebrovascular damage was the most common etiology in Richmond (71).

Table 38.3 Etiology in the San Francisco Studies: Changes Over Time

Etiology	1970s (number of cases)	1980s (number of cases)
Anticonvulsant withdrawal	27	48
Alcohol related	15	43
Drug intoxication	10	14
CNS infection	4	12
Refractory epilepsy	—	10
Trauma	3	8
Tumor	4	7
Metabolic disorders	8	7
Stroke	15	6
Cardiac arrest	4	6
Unknown	15	8

CNS, central nervous system.

From refs Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980s. Neurology. 1993;43:483–488; Aminoff MJ, Simon RP. Status epilepticus. Causes, clinical features and consequences in 98 patients. Am J Med. 1980;69:657–666.

For children in North London, the age-adjusted incidence for acute symptomatic SE was 16.9% in those <1 year of age, 2.5% in those 1 to 4 years, and 0.1% in those 5 to 15 years of age. The incidence of an acute on remote (remote symptomatic with an acute precipitant) was 6%, 5.3%, and 0.7%, respectively. A prolonged febrile seizure occurred in 4.1/100,000, acute symptomatic causes in 2.2/100,000, remote symptomatic in 2.3/100,000, acute on remote in 2.1/100,000, idiopathic in 1.4/100,000, cryptogenic in 0.2/100,000, and unclassified in 1/100,000 (63).

As the Richmond study included adults and children, the etiologies in these two groups can be directly compared (Table 38.4). In adults, cerebrovascular disease was the most common etiology, occurring in 25.2%, versus only 3.3% in children, whereas in children, fever or infection was the most common cause, occurring in 35.7% versus only 4.6% in adults. Medication change was a major cause in both adults and children—20% in children versus 19% in adults (71). The incidence of tumors was higher in older studies (68,69).

Table 38.4 Comparison of Etiology in Children and Adults in the Richmond Study

Etiology	% Of children (<16 years)	% Of adults (>16 years)
Cerebrovascular	3.3	25.2
Medication change	19.8	18.9
Anoxia	5.3	10.7
EtOH/drug-related	2.4	12.2
Metabolic	8.2	8.8
Unknown	9.3	8.1
Fever/infection	35.7	4.6
Trauma	3.5	4.6
Tumor	0.7	4.3
CNS infection	4.8	1.8
Congenital	7.0	0.8

CNS, central nervous system.

From ref DeLorenzo RJ, Towne AR, Pellock JM, et al. Status epilepticus in children, adults, and the elderly. Epilepsia. 1992;33(suppl 4):S15–S25.

PROGNOSIS OF PATIENT WITH STATUS EPILEPTICUS

Although many people may survive an episode of SE, even refractory SE, with no or limited untoward effects (72,73), SE can be life threatening and has been associated with long-term neurologic sequelae. The prognosis of SE depends partially on etiology (74), duration (2,75), and age (62). Recently, concern has been raised that prognosis may be affected by the use of anesthetic agents and the need for intubation and mechanical ventilation (76).

The mortality rate in modern, general SE series ranges from 4% (77) to 37% (78) and is higher with an acute precipitant (78). An acute precipitant is more likely when there is no prior history of epilepsy (78,79), but may also be responsible for death in persons with known epilepsy with SE. In one series, 63% of patients survived, 28.6% died from the underlying cause, 6.6% died from other causes, and 1.8% died from the SE itself (78). In a retrospective study of 74 patients (80), the mortality rate was 21% (14/85) and was higher with acute symptomatic seizures and older ages. Interestingly, in a study limited only to patients with de novo SE (81), SE occurring in patients already hospitalized, the mortality was very high—61% (25/41).

Short-term versus long-term mortality was compared using data from the Rochester study (82–84): Mortality was 19% (38/201) within the first 30 days, but cumulative mortality was 43% over 10 years (82). The long-term mortality risk increased with an SE duration >24 hours, acute symptomatic etiology, and myoclonic SE (82).

In the Richmond study, the mortality rate was 32% when the duration was >60 minutes versus only 2.7% when the duration was 30 to 59 minutes (85). Other factors associated with a high mortality rate in the Richmond study included anoxia and older age, whereas a low mortality rate was associated with alcohol and AED withdrawal (85).

In the Netherlands study (17), prognosis of patients with generalized convulsive SE was related to treatment adequacy. A favorable outcome occurred in 263 of 346 patients (76%), with outcome related to cause, duration >4 hours, more than one medical complication, and quality of care. In order to analyze the treatment effects, therapy was classified as insufficient when the wrong AED dose or route was used, if an unnecessary delay occurred, if mechanical ventilation was not used despite respiratory insufficiency or medical complications, or if neuromuscular paralysis was used without

EEG monitoring (in order to detect seizure activity). The most common reason for classifying therapy as insufficient was an inadequate AED dose. In the patients with a favorable outcome (n = 263), therapy was classified as good or sufficient in 85.6% and considered insufficient in only 10.3%; in those with sequelae (n = 45), therapy was inadequate in 22.2%. When the morbidity was from SE itself, insufficient therapy occurred in 50% of patients. With the occurrence of death (n = 38), therapy was sufficient in 44.7% of patients, and in cases of death due to SE itself, therapy was considered insufficient in 62% of patients (17).

The mortality rate in pediatric SE ranges from 3% to 11% and is also related to etiology and age (77,86–92). In one study, the mortality was 4%, occurring only with acute symptomatic or progressive symptomatic etiologies (86). In NLSTEPSS, the overall mortality was 3%. In the Richmond study, for children ranging in age from 0 months to 16 years (n = 598), the overall mortality rate was 6.2% (37 of 598). The highest rates occurred during the first 6 months of life (24%; 18 of 75) and between 6 and 12 months of age (9.25%; 5 of 54) with a low rate (2.98%; 4 of 469) in children older than 1 year (93). The difference likely reflects a higher incidence of symptomatic SE in the youngest children. With respect to morbidity following SE in children, a minority of children will have new-onset motor dysfunction and loss of previously obtained milestones (77,92). A Canadian study of SE reported 34% of 40 children with an SE duration of 30 to 720 minutes had subsequent neurodevelopmental deterioration (94). Even in children with febrile SE, speech deficits have been reported (95).

An increase in morbidity and mortality has also been reported with NCSE, which is related to SE duration (36 hours to >72 hours) (96). However, this increased morbidity with NCSE is controversial (97–99). Following cardiopulmonary resuscitation, SE, status myoclonus, and myoclonic SE are predictive of a poor outcome (100). On EEG, burst suppression (101) and PEDs are predictive of a poor outcome (102), whereas a normal EEG is associated with a good prognosis (103).

MANAGEMENT OF STATUS EPILEPTICUS

The initial management of patients with SE begins with the ABCs—airway, breathing, and circulation (Table 38.5). Diagnostic studies are then selected, depending on a patient's history and physical examination (not all studies need to be obtained for every patient). Serum glucose should be checked immediately with bedside glucose testing to rapidly diagnose hypoglycemia. A complete blood count may be helpful for diagnosing infection, although leukocytosis may occur with SE. Electrolytes, calcium, phosphorous, and magnesium values may also be helpful. Lumbar puncture (LP) should be considered in the febrile patient, although CSF pleocytosis may occur without infection, presumably due to a breakdown in the blood–brain barrier (104). In one study, the highest CSF white blood cell count from SE alone (no acute insult) was 28×10^6/L (105). If there is concern about increased intracranial pressure or a structural lesion, LP can be deferred until neuroimaging is performed. If there is evidence of infection, antibiotics can be administered prior to LP. In those taking an AED, levels should be obtained as low AED levels may contribute to the development of SE in both adults and children (106,107). A practice parameter on the diagnostic assessment of the child with SE has been produced (108). When done, electrolytes or glucose were abnormal in 6%, blood cultures were abnormal in 2.5%, a CNS infection was found in 12.5%, an ingestion was found in 3.6%, an inborn error of metabolism was found in 4.2%, and AED levels were low in 32%.

Table 38.5 Immediate Management of Status Epilepticus

The A B Cs:
▪ Stabilize and maintain the Airway; position head to avoid airway obstruction
▪ Establish Breathing (i.e., ventilation): administer oxygen by nasal cannula or mask
▪ Maintain the Circulation: start intravenous (IV) line
▪ Monitor the vital signs: pulse (ECG monitoring), respiratory rate, blood pressure, temperature, pulse oximetry; check bedside glucose
Start intravenous (IV) line:
▪ Use normal saline
▪ Consider thiamine 100 mg, followed by 50 mL of D50%
▪ Determine what studies are needed
▪ Consider CBC, electrolytes, calcium, phosphorus, magnesium, AED levels, toxicology
▪ Lumbar puncture (especially if febrile)
▪ Neuroimaging, cranial CAT scan, or MRI
▪ EEG, if diagnosis initially in doubt
Points from history:
▪ Has an AED been given (prehospital treatment or inpatient), is the patient on any AEDs (especially phenobarbital or phenytoin), or are there any allergies or has the patient ever had Stevens–Johnson syndrome?
▪ Characteristics of past seizures: is there a history of status epilepticus?
▪ Are treatable causes present (any acute precipitants)?
▪ Fever or illness, head trauma, possible electrolyte imbalance, intoxications, toxin exposure?
▪ Are chronic medical conditions present, or is the patient on steroid therapy? (if so, needs stress coverage)

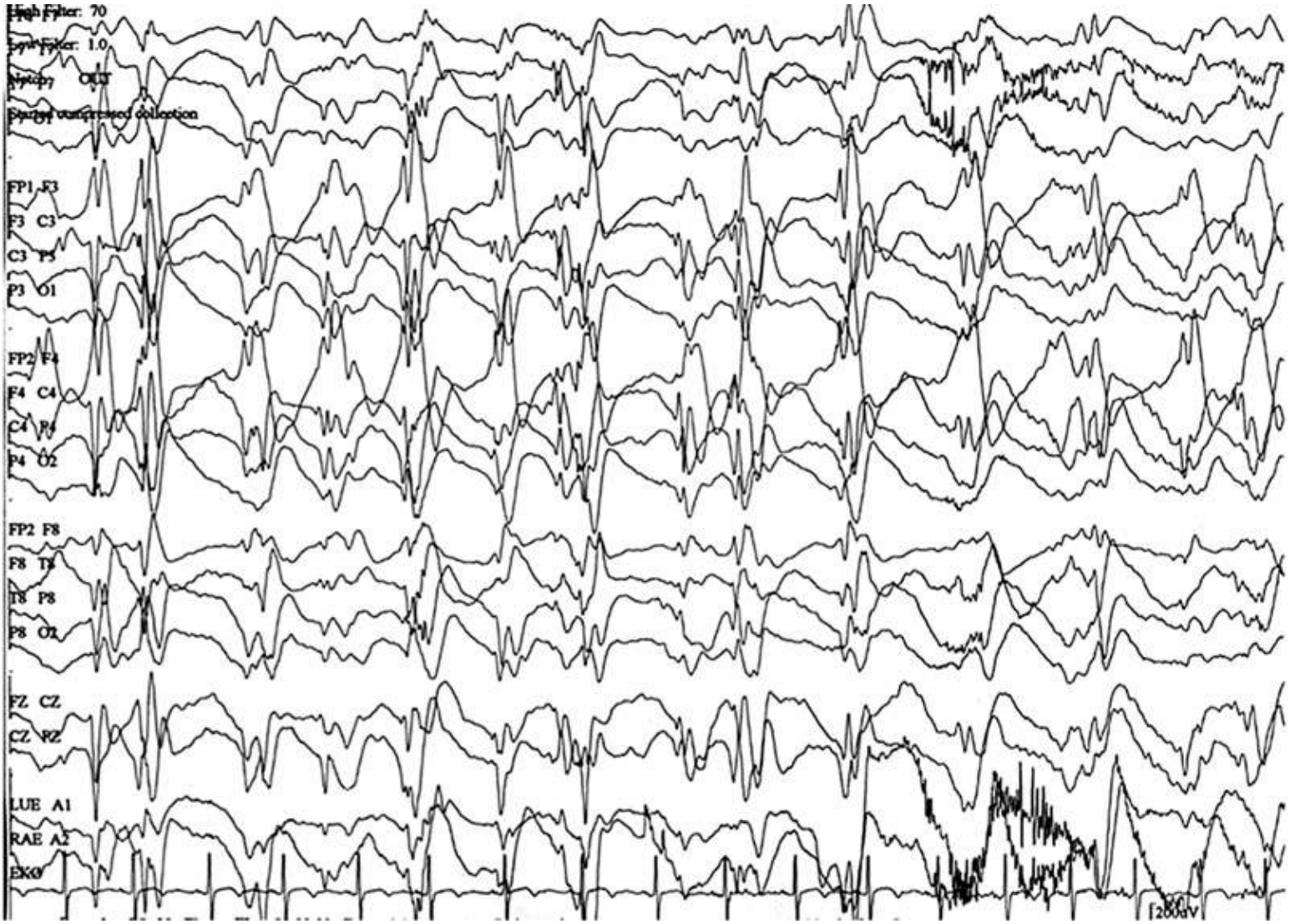
ECG, electrocardiogram; CBC, complete blood count; AED, antiepileptic drug; CAT, computerized axial tomography; MRI, magnetic resonance imaging; EEG, electroencephalography.

Neuroimaging options include cranial computed axial tomography (CAT) scan and magnetic resonance imaging (MRI). CAT scans are readily available on an emergency basis and should identify all disorders demanding immediate intervention, such as tumor or hydrocephalus, but may not show the early phases of infarction. CAT scan and MRI may detect focal changes, which may be transient (109), secondary to a focal seizure (suggesting the origin of the focus), with MRI the more sensitive technique. Although these lesions may mimic those of ischemic stroke, they are reported to cross vascular territories (110). Changes in diffusion-weighted images and the apparent diffusion coefficient suggest both cytotoxic and vasogenic edema (111). Progressive changes also occur, such as hippocampal atrophy and sclerosis, or global atrophy (112,113). In the FEBSTAT study, a prospective study of children between 1 month and 5 years of age who have experienced an episode of febrile SE, 9% (17/191) were found to have increased T2 signal in the hippocampus, maximum in Sommer sector, when imaging was completed within 72 hours of presentation, and another approximately 2.5% (5/191) had an equivocal finding. None of the 96 children with a first simple febrile seizure who made up the control group were found to have a similar increase in signal (114). Repeat imaging in this cohort obtained approximately 1 year later demonstrated retarded hippocampal growth after febrile SE and, in several of the children with acute findings, the development of imaging characteristics of hippocampal sclerosis (115). The North London Group found in a cohort of 80 children that 20% to 30% of the children (0.18 to 15.5 years) had evidence of

hippocampal volume loss on MR imaging of the brain 1 month following an episode of convulsive SE of any etiology (116). In a fatal case of unexplained SE, high-signal lesions in the mesial temporal lobes and hippocampal neuronal loss were reported (117). In general, neuroimaging should be performed in all patients with new-onset SE, especially if there is no prior history of epilepsy.

Intoxication with certain agents, particularly theophylline (79,81,118) and isoniazid (INH) (119), which may involve acidosis (120) and is treated with pyridoxine (vitamin B_6) (121), may predispose individuals to generalized convulsive SE or NCSE. Immunosuppressants such as cyclosporine (122) or tacrolimus and ifosfamide (123) may predispose individuals to NCSE, which may also occur when phenytoin and carbamazepine are used in patients with idiopathic generalized epilepsy (124); lithium (125), tiagabine (126), and amoxapine (127) may also be implicated. Fatal SE has occurred with flumazenil; therefore, caution should be exercised in patients with a history of seizures and chronic benzodiazepine use or when a mixed overdose is suspected (128).

An EEG is not immediately needed for treatment. Indications for emergency EEG include unexplained altered awareness (to exclude NCSE) (Fig. 38.3), the use of neuromuscular paralysis in a patient with SE, high-dose suppressive therapy for refractory SE, and no return to baseline or improvement in mental status following control of overt convulsive movements (to exclude ongoing subtle SE) (129). NCSE occurs in 14% of adults (130) and 26% of children (131) in whom generalized convulsive SE has been controlled after treatment. In a retrospective study of children who experienced an episode of convulsive SE and subsequently underwent continuous EEG monitoring in an intensive care setting, a third were discovered to have electrographic seizures (132). In another study, NCSE was detected in 8% of all comatose patients (101). Therefore, the EEG should be used when the diagnosis is in doubt, especially in patients with pseudoseizures.


High Filter: 70
Low Filter: 1.0
Synchronized compressed collection
FP1 F3
F3 C3
C3 P3
P3 O1
FP2 F4
F4 C4
C4 P4
P4 O2
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P8 O2
FZ CZ
CZ PZ
LUE A1
RAE A2
EKG

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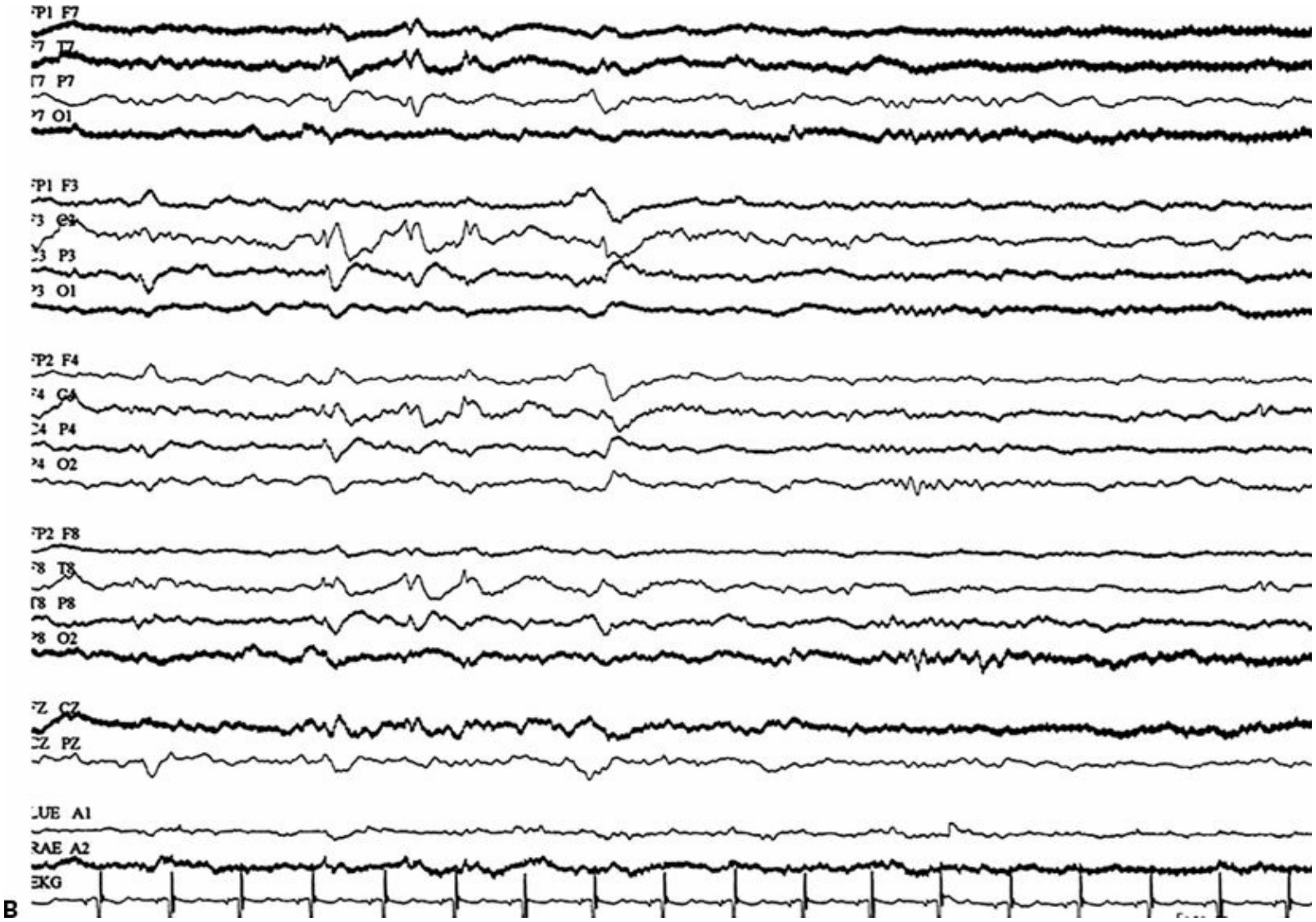

Figure 23.3. A: Nonconvulsive SE: continuous ictal discharges, slow spike and wave, with altered awareness. **B:**Nonconvulsive SE: electroencephalogram after lorazepam, now with improved awareness.

ANTIEPILEPTIC DRUG THERAPY FOR STATUS EPILEPTICUS

Treatment should be aimed at controlling SE as soon as possible, particularly before brain compensatory mechanisms fail. Despite adequate oxygenation and ventilation, such failure has been reported within 30 to 60 minutes in experimental SE (54) and within 30 to 45 minutes in humans (2). Systemic and metabolic changes occur early, with increases in blood pressure, lactate, and glucose levels. Both respiratory and metabolic acidosis may develop, although the former is more common (133). Initially, brain parenchymal oxygenation, lactate, glucose, and oxygen utilization remain stable, cerebral blood flow increases, but cerebral glucose slightly decreases. In later stages, blood pressure may be normal or decrease slightly, glucose may decrease, and hyperthermia and respiratory compromise may occur, leading to hypoxia and hypercarbia. Decreases in brain parenchymal oxygenation, cerebral blood flow, and brain glucose all contribute to an energy mismatch (54). Neuron-specific enolase, a marker of brain injury, is elevated in the serum following both convulsive and NCSE (134,135).

Neuronal injury may occur in the absence of metabolic derangement. In paralyzed and ventilated baboons given bicuculline, a $GABA_A$ receptor competitive antagonist, to induce electrographic SE

(52,53), neuronal loss was observed in the neocortex and hippocampus. Brain lesions following flurothyl-induced SE in the paralyzed and well-oxygenated rat include hypermetabolic infarction of the substantia nigra (136). In humans, neuronal loss was seen following SE in three patients without hypotension, hypoxemia, hypoglycemia, or hyperthermia (137).

Most of the AEDs used to treat SE have the potential for respiratory and cardiac depression, especially when administered by a loading dose (138) or when an excessive dose is used (139). Therefore, protecting the airway, controlling ventilation, and monitoring cardiac and hemodynamic function are mandatory. Intravenous (IV) administration is the preferred route for the treatment of SE, especially in the inpatient setting, but if IV access is difficult, intramuscular (IM), rectal, or intranasal routes have been used.

Primary AEDs for SE

The benzodiazepines (lorazepam, diazepam, midazolam), phenytoin or its prodrug form fosphenytoin, and phenobarbital are the current drugs of first choice for the initial therapy in patients with SE (Table 38.6). However, some advocate the early use of the secondary agents (e.g., valproic acid, levetiracetam, anesthetics).

Table 38.6 First-Line (Emergent Initial Therapy) Intravenous Antiepileptic Drugs

AED	Dose	Rate	Max
Lorazepam	0.1 mg/kg	2 mg/min (2–5)	8 mg
Diazepam	0.2 mg/kg	5 mg/min	16–20 mg
Fosphenytoin	20 mg PE/kg	Up to 3 mg PE/kg/min	150 mg/min (adult)
Phenytoin	20 mg/kg	Up to 1 mg/kg/min	50 mg/min (adult) 25 mg/min (child) 20 mg/min (elderly)
Phenobarbital	20 mg/kg	1 mg/kg/min	100 mg/min (adult) 30 mg/min (child)

Treatment of SE is typically initiated with a benzodiazepine. Diazepam was rapidly applied to the treatment of SE soon after its discovery and has remained a mainstay of treatment. Theoretically, compared to lorazepam, diazepam should have a more rapid onset of action because of greater lipid solubility (138). However, this high lipid solubility results in a rapid redistribution to inactive tissues, such as fat, which can result in high rates of seizure recurrence (140,141).

Lorazepam has been used in both adults and children (142,143). Although expected to have a slower time to onset than diazepam, the times of onset of lorazepam 4 mg and diazepam 10 mg in the treatment of SE in adults were similar (144). In that double-blind study, SE was controlled in 89% of episodes with lorazepam versus 76% with diazepam, with similar rates of adverse events (144). Because of a smaller volume of distribution, lorazepam should have a longer anticonvulsant activity and, thus, a lower rate of seizure recurrence than diazepam (145,146). In a recently completed prospective randomized multicenter trial, lorazepam 0.1 mg/kg IV and diazepam 0.2 mg/kg IV were equally effective in terminating convulsive SE in children (3 months to younger than 18 years) in the emergency department. Interestingly, at these doses, there were no differences in the rate of recurrence up to 4 hours (147).

Midazolam, due to its water solubility, may be administered intranasally or intramuscularly if there is no IV access, and it has been associated with less sedation and respiratory depression (148).

The efficacy of intramuscular midazolam in the out-of-hospital treatment of convulsive SE in children and adults was prospectively compared to intravenous lorazepam in the double-blind, randomized RAMPART trial (149). Upon emergency department arrival, seizures had stopped in 73.4% of the subjects in the midazolam group and 63.4% in the lorazepam group. Seizure recurrence was low in both groups, and there was no difference in adverse events. Although designed as a noninferiority study, the results do support statistical superiority of intramuscular midazolam in the prehospital treatment of convulsive SE.

Phenytoin may be administered by an IV loading dose in normal saline (it precipitates with dextrose) at 20 mg/kg (15 mg/kg in the elderly), which rapidly achieves a therapeutic level without respiratory depression or sedation and can also provide maintenance therapy (150–152). This lack of sedation is important for monitoring mental status, such as in patients with head trauma. The infusion rate should be no faster than 1 mg/kg/min in a child (not to exceed 25 mg/minute), 50 mg/minute in an adult, and 20 mg/minute in the elderly. Pulse and blood pressure should be monitored. If hypotension develops, the infusion rate should be decreased. In adults, a therapeutic level should be maintained for up to 24 hours after a loading dose has been administered (153), but may not last as long in children (153). A level obtained 2 hours after loading may help guide the timing of maintenance therapy with phenytoin (153).

IV phenytoin has an alkaline pH and contains solvents that can cause vascular irritation, cardiac depression, and hypotension. The purple glove syndrome, consisting of distal limb edema, discoloration, and pain, may occur following IV phenytoin infiltration; treatment may require fasciotomies and amputation. In one series, purple glove syndrome occurred in nine of 152 patients (154); in a prospective series, it occurred in only three of 179 patients (155). The syndrome has also been reported following oral dosing in a child (156).

The phosphate ester prodrug of phenytoin, fosphenytoin, is dosed as phenytoin equivalents (PE) at 20 mg PE/kg. It can be administered in a dextrose solution. Fosphenytoin is water soluble and may be given by the IM route, with paresthesias and injection site pruritus as possible adverse effects. Bioavailability is 100% compared to phenytoin, and the conversion half-life is 7 to 15 minutes (157). Fosphenytoin is rapidly converted to phenytoin by serum and tissue alkaline phosphatases (158). It may be difficult to maintain therapeutic levels in infants, and additional doses may be required (159); subtherapeutic free phenytoin levels also occur in older children (160). A 2-hour phenytoin level is suggested to ensure conversion (160). Side effects are more likely in patients with hypoalbuminemia, renal failure, or hepatic failure and in the elderly, because of the presence of higher free phenytoin levels. In these patients, the infusion rate should be decreased by 25% to 50% (157). The only advantage of IV phenytoin over IV fosphenytoin is significantly lower cost.

Phenobarbital has been used to treat SE in all age groups. Respiratory depression and sedation occur. Caution is advised, especially when phenobarbital is administered in combination with other sedative AEDs (such as benzodiazepines). In a randomized trial of diazepam and phenytoin versus phenobarbital (10 mg/kg IV), phenobarbital resulted in a shorter median seizure time (5 minutes vs. 9 minutes) and response latency (5.5 minutes vs. 15 minutes), with a similar incidence of intubation, hypotension, and arrhythmia (161). The loading dose for phenobarbital is 15 to 20 mg/kg, administered at a rate no higher than 100 mg/minute in older children and adults and 20 mg/kg in neonates and infants (160).

The landmark VA Cooperative Study (26) compared the efficacy of various first-line agents—lorazepam (0.1 mg/kg), phenobarbital (15 mg/kg), diazepam (0.15 mg/kg) plus phenytoin (18 mg/kg), and phenytoin alone (18 mg/kg)—in the treatment of SE with successful treatment defined as control

of the seizure within 20 minutes (27). Treatment efficacy of overt generalized convulsive SE was similar with lorazepam (65%), phenobarbital (58%), and diazepam plus phenytoin (56%), whereas phenytoin alone was associated with lower efficacy (44%). This result may be related to a 4.7-minute infusion time with lorazepam versus 33 minutes with phenytoin alone.

Second-Line Agents for Status Epilepticus

Sodium valproate (VPA) has been available in IV form since 1995 (Depacon, Abbott Laboratories, North Chicago, IL) (162). Although it is not yet approved by the U.S. Food and Drug Administration (US FDA) for the treatment of SE, doses of 15 to 33 mg/kg have been administered safely in adults (163–172) at a rate of 20 to 50 mg/minute (164). In a review of 13 elderly patients with SE and hypotension, a mean loading dose of 25 mg/kg at 35 mg/minute was associated with no change in blood pressure (165). In one study, an infusion rate of 3 mg/kg/min was associated with hypotension in 2 of 72 patients (168).

One study has suggested that VPA may be an appropriate first-line medication under narrow conditions (173). Two studies have evaluated IV phenytoin versus IV VPA as first-line therapy for SE. The first used IV VPA 30 mg/kg over 15 minutes or IV PHT 18 mg/kg at a rate of 50 mg/minute; if SE continued, the other AED was used (174). Used as initial therapy, SE was controlled in 66% with VPA versus 42% with PHT; in the refractory patients, VPA was effective in 79% versus 25% with PHT. The side effects were similar. In the second study (175), there was equal efficacy (88% for both) with side effects of 12% with PHT versus none with VPA. In diazepam-resistant SE, 31/41 (76%) episodes of SE were controlled with a VPA 25 mg/kg loading dose over 30 minutes. The probability of successful treatment with VPA was time-dependent: if the VPA was given early (within 3 hours), next-line therapy with anesthesia was required in only 5%, but when VPA was given later, anesthesia was needed in 60% (176).

In children, loading doses of 10 to 30 mg/kg have been used, with most using the higher-dose ranges; an infusion rate of 1 mg/kg/h was not associated with serious side effects (169). A 20-mg/kg loading dose should produce a serum level of 75 mg/L (170). Valproate is safe in adults and children (163,168,172). One study reported on 48 IV VPA doses, mean 22 mg/kg (range 7.5 to 41.5 mg/kg) with a mean infusion rate of 5 mg/minute, with only 1 adverse event, burning at the infusion site (177). Hypotension occurred in one child at an infusion rate of 30 mg/kg/h (0.5 mg/kg/min) (171). A loading dose of 10 to 25 mg/kg over 30 minutes has been used in neonates (178).

Levetiracetam (LEV) is available in an IV preparation and has been used to control SE (179,180), typically as second-line therapy. A recent retrospective multicenter observational study identified that this agent was not uncommonly used following benzodiazepine failure (181). The pharmacokinetic profile is similar for IV and oral LEV with no difference following an oral or IV dose of 500 to 1500 mg in adults (182). LEV levels peak within 2 hours, a steady state is achieved within 2 days, and there are no significant drug interactions (183). IV LEV with a mean loading dose of 944 mg (range 250 to 1500 mg) controlled 16/18 episodes of SE following benzodiazepine failure (184). A 20 mg/kg loading dose followed by 15 mg/kg BID after 6 hours controlled SE in 82% overall and in 11/12 (92%) as first-line therapy (185). 2/50 (4%) developed thrombocytopenia. In a study comparing the effectiveness of PHT, VPA, and LEV following benzodiazepine failure, LEV 20 mg/kg was found to fail more often than VPA 20 mg/kg. In that study, LEV accounted for approximately 17% of second-line treatment failures (186). In nine children with acute seizure exacerbations or refractory SE, a loading dose of 10 to 30 mg/kg was given over 30 minutes, with a mean dose of 228 mg/kg/d.

One child had an increase of seizures, and no agitation or behavioral problems occurred (187).

Lacosamide, which enhances the slow inactivation of voltage-gated sodium channels, was approved by the U.S. FDA in 2008 for adjunctive therapy for focal-onset seizures in patients 17 years of age and older. However, as it is available in an intravenous formulation, it is not surprising that it has been used for the treatment of SE with some success in both adults and children (188–192). A loading dose of 400 mg appears to be more effective than 200 mg in the treatment of refractory seizure clusters and SE (193). In a more recent retrospective study, lacosamide (median bolus dose of 400 mg) as a third-line agent administered at a median of 19 hours after SE onset following the failure of a benzodiazepine and LEV successfully terminated the status in 7 of 21 patients (194).

TREATMENT GUIDELINES FOR STATUS EPILEPTICUS

Standard treatment guidelines are needed in advance of all medical emergencies, to improve the quality of emergency care (195,196). The treatment guideline can then be analyzed and modified if the data demonstrate that the protocols are not resulting in improved care (197,198). To this end, there are a few randomized clinical trials, the EFA Working Group timetable (4), treatment surveys (199), and various societies' treatment guidelines, that can assist in this process (200,201). A survey of the UK Intensive Care Society revealed that only 12% of the respondents used a specific protocol (202) and that first-line therapy was frequently with a benzodiazepine plus phenytoin. In a US survey of neurologists and intensivists (N = 106), 76% used lorazepam first, with 95% using phenobarbital or phenytoin if lorazepam failed (203). A survey of epileptologists was conducted to establish consensus guidelines for first-line, second-line, and third-line treatment options for epilepsy syndromes (204). A treatment of choice was determined if selected by >50% of respondents. Lorazepam was considered the treatment of choice for generalized convulsive, focal, and absence SE, with diazepam or phenytoin considered first-line treatment for generalized convulsive SE and focal SE; diazepam and sodium valproate were considered first-line treatment for absence epilepsy (204).

Prior to the VA Cooperative Study, the EFA Working Group suggested either lorazepam or diazepam as first-line therapy, but now, lorazepam is initially used by many (2,203,204). European guidelines have used either lorazepam or diazepam for first-line therapy. Most guidelines still use either phenytoin or phenobarbital if a benzodiazepine fails, but there is increasing use of either VPA or LEV. We use 0.1 mg/kg lorazepam initially for children, at a maximum dose of 4 mg when IV access is available; if IV access is not available, diazepam or lorazepam can be administered rectally or fosphenytoin or midazolam via the IM route. However, although there are theoretical reasons to support the use of lorazepam over diazepam (as discussed above), a review of randomized clinical trials in children found no evidence that treatment with IV lorazepam was better than treatment with diazepam (205), which is further supported by the results of a prospective, randomized clinical trial comparing lorazepam to diazepam in the treatment of pediatric SE (147).

The Neurocritical Care Society guideline for the evaluation and management of SE states that definitive control of SE should be obtained within 60 minutes of onset. Treatment occurs in stages, first line through fourth or fifth line. This guideline suggested the use of emergent initial therapy (first line), urgent control therapy (second line), and refractory therapy (third through fifth line) in order to emphasize the need for the emergent control of SE (201).

Treatment of Refractory Status Epilepticus

Refractory SE occurs when seizures persist despite adequate treatment with a first- and second-line agent (201). The mortality in adults with refractory SE varies from 39% to 48% (206) and in children, from 16% to 43.5% (66,207,208). Etiology is a very important determinant, with a higher mortality among acute symptomatic patients (17,34,66,78,80). In children, the data also demonstrate that etiology is related to prognosis (66).

If convulsive activity has stopped but mental status does not improve, NCSE must be excluded, which occurs in 14% of adults (130) and 25% of children (131), and in 8% of those with unexplained coma (101). An immediate EEG is performed, if available; if not available, additional empiric AED therapy must be considered.

If SE persists following the use of the second conventional AED, then continuous intravenous infusion AEDs should be administered (Table 38.7). The treatment goal is to stop SE immediately and to prevent seizure recurrence. However, it is important to recognize that continuous infusion AEDs have been linked with several untoward effects including mechanical ventilation, hypotension, and infection as well as potentially increasing the risk of death (76,209–212).

Table 38.7 Agents Used in Refractory Status Epilepticus

Intravenous:
Pentobarbital
Midazolam
Thiopental
Propofol
Phenobarbital
Diazepam
Lorazepam
Ketamine
Lidocaine
Chlormethiazole
Etomidate
Magnesium (especially for eclampsia)
Rectal:
Paraldehyde
Chloral hydrate
Others:
Hypothermia, with pentobarbital
Inhalational agents, especially isoflurane
Vagal nerve stimulation (VNS)
Ketogenic diet

Pentobarbital has been the most widely used agent under these circumstances (213–220), administered at 2 to 10 mg/kg followed by a continuous infusion. Midazolam has a shorter half-life and is associated with less sedation (148,221–226). Adults with RSE with maximum midazolam infusion rates of approximately 3 mg/kg/h were found to have less withdrawal seizures and potentially lower risk of mortality at discharge compared to those in which the maximum infusion rate was lower at 0.4 mg/kg/h (227). High-dose phenobarbital is also used; it is associated with less cardiovascular depression than pentobarbital (228,229) but has a longer half-life.

Other agents used include benzodiazepines (230,231), thiopental (232), lidocaine (233–235), inhalational anesthetics such as isoflurane (Forane, Baxter Pharmaceuticals, Deerfield, IL)

(235–237), and propofol (238,239). Propofol has two main advantages: a rapid onset and a short duration of action. One study with pentobarbital and propofol in adults showed equal efficacy, but propofol controlled SE in 2.6 minutes versus 123 minutes with pentobarbital (238). Another study in children with RSE reported an efficacy of 64% with propofol versus 55% with thiopental, and no side effects with propofol, with infusion rates <5 mg/kg/h (240,241). Propofol may cause metabolic acidosis with prolonged use in children (242,243). In adults, deaths have occurred with high propofol infusion rates (244), which is known as propofol infusion syndrome (245). Even in an adult study that showed equal efficacy for seizure control, a 57% mortality rate was reported with propofol versus only 17% with midazolam (221). Therefore, propofol should be used with caution, especially in children and ideally for a short time only, and the infusion rate should not exceed 67 μg/kg/min (246). Immediate control can be achieved and then another agent used if long-term suppression is needed.

The N-methyl-D-aspartate receptor antagonist ketamine may also have a role in the treatment of RSE (247–252). A recent multicenter retrospective review of 58 subjects from 10 academic medical centers treated with ketamine found that ketamine was potentially successful in up to a third of the episodes of SE. Ketamine was not successful when used after a failure of seven or more drugs or when introduced at least 8 days after SE onset. In those in which ketamine was deemed to contribute to the control of SE, the dosing was >0.9 mg/kg/h. Overall, ketamine was found to be well tolerated with many of the untoward effects that occurred during the ketamine dosing being attributed to the concurrent medications (253).

Chlormethiazole (254), etomidate (255), and clonazepam (256) are used in Europe; paraldehyde (257) and chloral hydrate (258) may be administered rectally, although paraldehyde is no longer available in the United States. Hypothermia (259–261), vagal nerve stimulation (262), and surgery (263) have also been used. The ketogenic diet may also have a role, especially in children diagnosed with febrile infection–related epilepsy syndrome (264–266).

To date, no prospective study has been conducted in patients with refractory SE. In a systematic review of refractory SE treatment with pentobarbital, propofol, or midazolam (267), pentobarbital was associated with better seizure control than the other two agents. In the UK survey (N = 408), if first-line treatment failed, 142 (35%) of the respondents used a benzodiazepine infusion and 130 (32%) used a general anesthetic. If seizures continued, 333 (82%) used thiopentone and 56 (14%) used propofol (202). Based on the consensus guidelines, the drug of choice for "therapeutic coma" in patients with generalized convulsive SE and focal SE was pentobarbital, and first-line agents were midazolam and propofol; for absence seizures, pentobarbital was the drug of choice, with no other first-line options, and midazolam was considered second-line therapy (204). In the US survey, when generalized convulsive SE was refractory to two AEDs, 43% of respondents used phenobarbital, 16% used valproate, and 19% gave one of three agents (pentobarbital, midazolam, or propofol) by continuous infusion (203).

Whether clinical seizures alone or both clinical and electrographic seizures need complete control is controversial (201,268,269). In this situation, many clinicians use continuous infusion AEDs titrated to a burst suppression pattern on EEG, aiming for complete control of both the clinical and electrographic seizures. Some aim only for control of clinical seizures (without EEG monitoring). In the US survey, the titration goal with a continuous infusion was burst suppression in 56% of respondents versus elimination of seizures in 41% (203), whereas in a European survey, up to 70% titrated the EEG to a burst suppression pattern (270). However, the outcome is not related to the extent of EEG burst suppression and is more dependent on etiology (271).

Even if a burst suppression pattern is the goal, the degree of suppression needed is unclear. We

have used a burst suppression pattern as the clinical end point, aiming for an interburst interval of at least 5 seconds in duration (66,272). In an analysis of the depth of EEG suppression with barbiturate anesthetics (pentobarbital or thiopental) in adults, persistent seizure control was better with electrocerebral inactivity on EEG (17 of 20) versus a burst suppression pattern (6 of 12 patients) (273,274). Using a midazolam infusion to eliminate all clinical and electrographic seizures and reaching burst suppression only if needed, acute treatment failure occurred in 18% of episodes, breakthrough seizures in 56%, posttreatment seizures in 68%, and treatment failure in 18% (225). In the systematic review, breakthrough seizures occurred less frequently with titration to EEG background suppression (53%) versus titration to seizure suppression only (4%). However, hypotension occurred more often with titration to background suppression (267).

Prolonged continuous infusion AEDs can be used (66,275), usually with various AED combinations. A continuous infusion AED is used initially for a short time (12 to 24 hours); the infusion is then tapered, and if SE recurs, the sequence restarts (55,66,272). Mirski et al. (276) recommended prolonged therapy with a potentially good prognosis: a healthy patient (no premorbid illness), a self-limited disease, and with neuroimaging not indicating a poor prognosis. Bramstedt et al. (277) recommended ethically withholding suppressive therapy if only expected to sustain organic life. We have treated children for prolonged periods of up to 146 days (66,275), and a 26-year-old with encephalitis was treated for 11 months (278). In our experience with children, no survivor of acute symptomatic refractory SE (n = 7) returned to baseline, and all subsequently developed refractory epilepsy; seizure recurrence was reported upon drug tapering in two children and within 1 to 16 months in the other five (225). In our entire group with refractory SE, 32% returned to baseline (66), and in the adult systematic review, only 29% (48 of 164 patients) returned to baseline (267).

Infectious or inflammatory disorders may predispose to refractory SE. In one series, 7/22 had "presumed encephalitis" (66,275). Kramer also reported severe RSE from "presumed encephalitis" (279). Holtkamp reported encephalitis as a predictor for RSE (280) and referred to this as a "malignant variant" (281). Wilder-Smith defined the syndrome of new-onset refractory status epilepticus (282). Characteristic features include female gender, young age, previous good health, CSF pleocytosis, antecedent febrile illness, and prolonged treatment. We reported complete seizure control during suppression in 5/7 in this group, with then a seizure recurrence and the development of refractory epilepsy ranging from 1 to 16 months later (275). The occurrence of this latent period raises the question if neuroprotective, antiepileptic, or even immunomodulatory agents might be helpful in this situation. Although the RSE that accompanies so-called febrile infection–related epilepsy syndrome (FIRES) has been attributed to acute neuroinflammation (283,284), the absence of a latent period has led others to hypothesis that FIRES is best conceptualized as chronic neocortical epilepsy with explosive onset (285).

Several specific repetitive disorders have been reported in SE: Stimulus-induced rhythmic, periodic, or ictal discharges (286) and cycling seizures (287) have been reported. Acute encephalitis with refractory, repetitive partial seizures has been described in children with encephalitis (288,289). These have an abrupt onset in the setting of a fever following an antecedent infection; are brief, focal seizures; occur with an escalating frequency; and are resistant to standard anticonvulsants and require high-dose suppressive therapy for control.

Prehospital Treatment

The advent of intrarectally administered AEDS permits the premonitory or early stage to be treated

prior to hospital arrival (290–292), although other routes of administration are also used. The prospective San Francisco Prehospital Treatment study (N = 205) found that lorazepam was potentially more effective than was diazepam in terminating SE out of hospital (59% response with lorazepam vs. 43% response with diazepam and 21% response with placebo; P = 0.001) (27). In a retrospective study of 38 children with generalized convulsive SE, use of prehospital diazepam (0.6 mg/kg rectally) was associated with a shorter seizure duration (32 minutes vs. 60 minutes) and a reduced likelihood of seizure recurrence in the emergency department (58% vs. 85%), with no difference with respect to intubation (293). Rectal diazepam can be administered at home for the treatment of SE or serial seizures; the maximum dose is 20 mg. A rectal gel preparation, Diastat (Xcel Pharmaceuticals, San Diego, CA), is available, which is easier to administer (294–296). Although only approved by the US FDA for the treatment of selected, refractory, patients on stable regimens of AEDs for the treatment of seizure exacerbation, Diastat is used as a therapeutic remedy for SE at home; IV benzodiazepines are still preferable for the treatment of inpatients. Lorazepam can be administered sublingually (297), and midazolam can be given by intranasal or buccal mucosa routes (298), with rapid buccal absorption documented by serum levels and EEG beta activity (299). The efficacy of intranasal midazolam (0.2 mg/kg) is equivalent to that of IV diazepam (0.3 mg/kg) for the treatment of prolonged febrile seizures (300), and buccal midazolam (10 mg) and rectal diazepam (10 mg) have shown equal efficacy for seizures >5 minutes (298). As previously noted, the RAMPART study demonstrated the utility of intramuscular midazolam in the prehospital treatment of convulsive SE (149). Paraldehyde is included in a UK pediatric treatment protocol (196), but as previously noted, it is no longer available in the United States.

Emergency Department or Inpatient Treatment

Lorazepam 0.1 mg/kg should be administered initially. A suggested treatment sequence follows, as outlined in Table 38.8 (301–303).

Table 38.8 A Suggested Timetable for the Treatment of Status Epilepticus

Time (min)	Action	
0–5	Diagnose status epilepticus by observing continuing seizure activity (time = 0) Give oxygen by nasal cannula or mask; position head for optimal airway patency Obtain vital signs and pulse oximetry Establish IV line; draw venous blood samples for glucose level, serum chemistries, hematology studies, toxicology screens, and AED levels (if applicable) If hypoglycemia is established, or blood glucose measurement not available, administer glucose; in adults, give thiamine first (100 mg), followed by 50 mL of 50% glucose by direct push into IV line; in children, give 2 mL/kg of 25% glucose	
5	If seizure continues, give lorazepam 0.1 mg/kg, at 2 mg/min	
10–20	If seizure continues, give fosphenytoin 20 mg PE/kg, or if not available, phenytoin 20 mg/kg (in children, give a second dose of lorazepam 0.1 mg/kg, before giving fosphenytoin or phenytoin)	
20	Give phenobarbital 20 mg/kg	
30	Give additional fosphenytoin 10 mg PE/kg	
40	IV valproate 40 mg/kg	
40–60[a]	Continuous intravenous infusion AEDs (intravenous anesthesia):	Pentobarbital 5–15 mg/kg loading dose Midazolam 0.2 mg/kg loading dose Propofol 1–2 mg/kg loading dose Thiopental 5 mg/kg All followed by intravenous infusions

[a]May consider the use of continuous intravenous infusion AEDs after failure of the first two AEDs [RSE, Neurocritical Care Society Guideline (201)].

AED, antiepileptic drug.

Modified from refs Gastaut H. Classification of status epilepticus. Adv Neurol. 1983;34:15–35; Lowenstein DH, Alldredge BK. Status epilepticus. N Engl J Med. 1998;338:970–976; Riviello Jr JJ, Claassen J, LaRoche SM, et al. Treatment of status epilepticus: an international survey of experts. Neurocrit Care. 2012;18:193–200; Brophy GM, Bell R, Claassen J, et al.; and the Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17:3–23.

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CHAPTER 39 APPLICATION OF ELECTROENCEPHALOGRAPHY IN THE INTENSIVE CARE SETTING

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INTRODUCTION

Convulsive seizures have been described since we have been recording human history (1). The discovery of nonconvulsive seizures in critically ill patients has been a more recent development (1). It has been known that convulsive seizures can lose the convulsive component and degenerate into subtle clinical signs (ictal nystagmus, subtle facial twitches), and the electrical activity of seizure may persist after clinical signs have stopped (2). It has also been appreciated that primary neurologic injuries can result in epileptiform discharges and seizures (2). However, the scope of the problem was not appreciated until the late 1990s and onward when the technology of portable digital video EEG and the development of neurologic specialty ICUs provided the environment that led to the investigations that highlighted the prevalence of nonconvulsive seizures in the critical care setting. In the last 10 years, the interest and volume of ICU EEG studies have increased with the awareness of nonconvulsive seizures. The challenge going forward will be to define the benefits of critical care monitoring and the selective use in high-risk cases. In this chapter, data describing the incidence of seizures, the length of monitoring recommended, preliminary outcome studies, and the current state of practice in ICU EEG monitoring are discussed in the setting of adult and pediatric patients.

CONTINUOUS EEG MONITORING IN ADULT PATIENTS

The use of continuous EEG (cEEG) monitoring in adult patients has increased dramatically with the awareness of nonconvulsive seizures and the high-risk conditions that require close monitoring. One aspect of this awareness is having neurointensivists who specialize in the critical needs of patients with primary neurologic injury. Neuro-ICUs provide a concentrated area of expertise, and EEG equipment can be focused on these high-risk patients (1). Patients in the medical ICU, in the surgical ICU, and located throughout the hospital can also be at risk and have been studied in the use of ICU EEG. The coordination of the epileptologist with the neurointensivist provides an effective partnership in treating patients at risk for nonconvulsive seizures. The role of ICU EEG has primarily been to detect subclinical seizures, but the detections of nonepileptic spells (myoclonic jerks, posturing, subtle twitching), monitoring the level of sedation, detecting ischemia in the setting of vasospasm, and developing a prognosis have all been described.

EEG Seizure Epidemiology

A number of studies have attempted to estimate the incidence of nonconvulsive seizures in patients presenting to the hospital. However, these studies are biased to some degree resulting in a range of incidence from 8% to 37% of patients with altered mental status in the hospital have EEG seizures recorded. Initial studies were conducted with patients presenting for emergency EEG, and thus the population was selected to include the patients that clinicians felt were likely having seizures. Privitera et al. (3) studied 198 patients prospectively with altered mental status presenting for emergency EEG and found that 74 (37%) were having seizures. A study by Towne et al. (4) examined 236 patients who presented to the ICU in coma, but without a clinical signs or suspicion of seizure. In this sample, 19 patients (8%) had EEG changes consistent with nonconvulsive status epilepticus. In a large retrospective series, Claassen et al. (5) reviewed 570 patients with unexplained altered mental status and found 110 patients (19%) were having electrographic seizures. Thus, in multiple institutions with different patient populations and different study designs, the consistent result has been that a significant portion of patients (approximately 20%) evaluated in the critical care setting with altered mental status have electrographic seizures recorded, most without clinical signs.

Certain etiologies of altered mental status in the critical care setting have been shown to have particular risk for nonconvulsive seizures. By identifying patients at highest risk for seizures, they can be targeted for early EEG monitoring and resources directed away from lower-risk patients. Patients with intracranial hemorrhage (ICH), ischemic stroke, traumatic brain injury (TBI), anoxic brain injury, central nervous system (CNS) infections, and subarachnoid hemorrhage (SAH) are particularly at risk (Fig. 39.1).

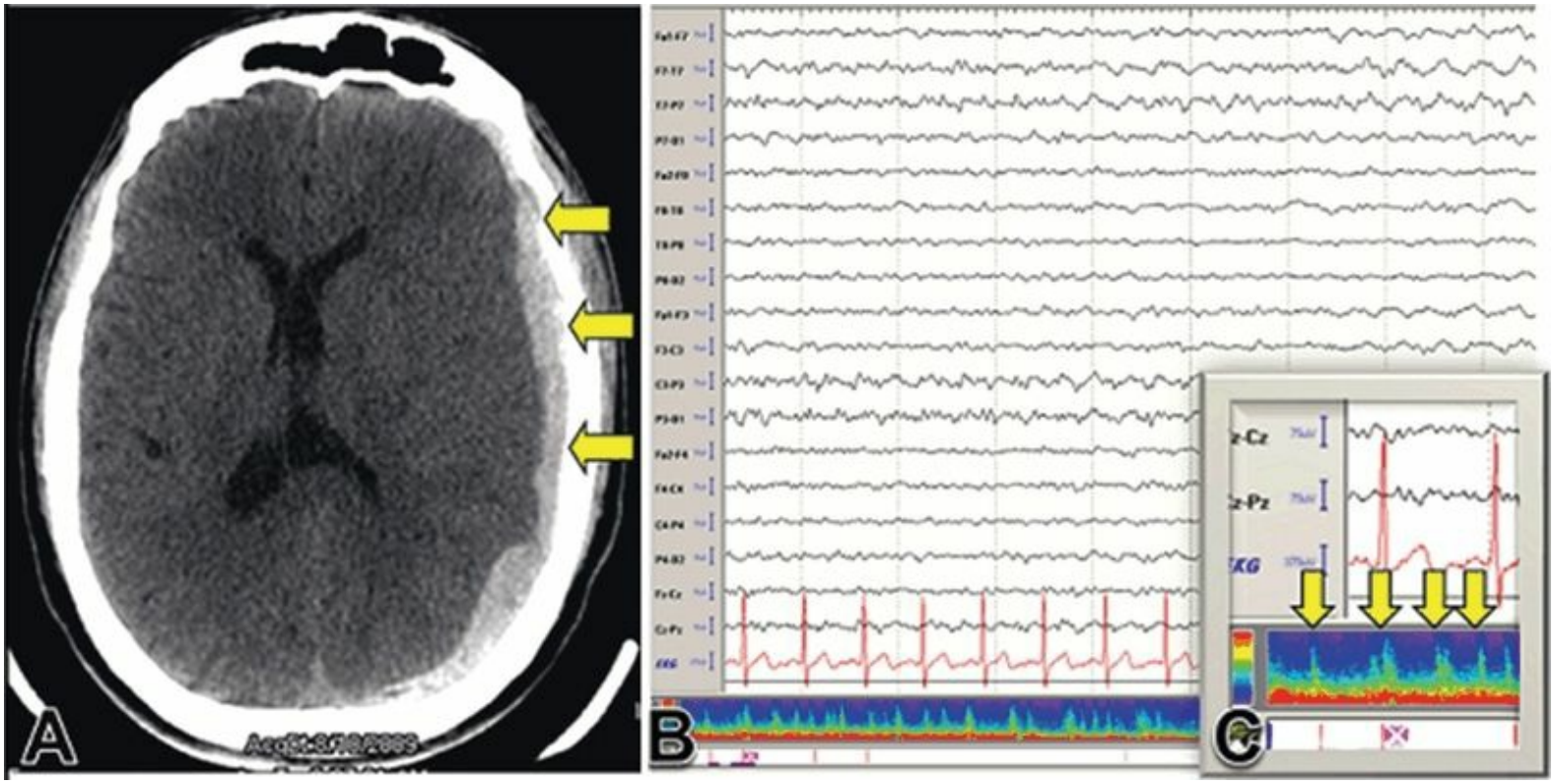

Figure 39.1. A: Patient who presented with altered mental status and headache with a CT brain showing a left hemisphere subdural hematoma with midline shift (arrows). **B:**EEG of this patient showing left hemisphere seizure pattern that is slowly evolving in frequency. **C:**Expansion of the DSA trend analysis showing multiple seizures in the record (arrows).

Intracranial Hemorrhage

In a study by Claassen et al. (6), 102 patients with ICH were recorded on cEEG and 18% were found to be having electrographic seizures and 31% were associated with seizures in some form at presentation (19 had clinical seizures prior to cEEG recording). Seizures in this series were more likely to be recorded with hemorrhages that expanded by 30% or more and with cortical bleeds. A study by Vespa et al. (7) studied 63 patients with ICH and found 18 (28%) with seizures on cEEG monitoring. Seizures were recorded most often in lobar hemorrhages, but were found in 21% of subcortical hemorrhages as well.

Ischemic Stroke

A series of 177 patients with acute ischemic stroke were described by Mecarelli et al. (8) with 15 patients (6.5%) having seizures on EEG monitoring. It was also noted that periodic lateralized epileptiform discharges were recorded in 6% of patients with stroke, and this subset of patients had a 71% incidence of seizures. In the series by Claassen et al. (5), 6 patients of the 56 with ischemic strokes (11%) had seizures recorded on cEEG monitoring. The rate of seizures detected in acute ischemic stroke has been consistently less than ICH and TBI; however, the rates of chronic epilepsy after the acute symptomatic seizures will require future studies.

Traumatic Brain Injury

Acute TBI has been associated with EEG seizure activity that often occurs in the first 14 days after injury. A study by Vespa et al. (9) described 94 patients with TBI who underwent cEEG monitoring, and 21 patients (22%) had electrographic seizures. Another series of 70 patients with TBI found 23 patients (33%) with electrographic seizures recorded on cEEG monitoring. The seizures in these series were often not adequately treated with “prophylactic” doses of phenytoin and required cEEG for diagnosis as well as management of ongoing seizure treatments.

Anoxic Brain Injury

The detection of seizures in the setting of anoxic brain injury has been described in multiple series and often carries a grim prognosis. The use of therapeutic hypothermia has changed the use of cEEG for prognosis (10). A study looking at 101 patients with anoxic injury after cardiac arrest found 12 patients (12%) to have nonconvulsive status epilepticus. The majority of these patients had EEG recorded in the first 8 hours of monitoring (with 12 hours of the cardiac arrest). The outcome in this study was dismal with only one of the patients with EEG seizures survived to a vegetative state. The background reactivity of cEEG recordings to painful stimulation has been reported to have strong predictive value of prognosis after anoxic injury (11). In a study of 34 patients with anoxic brain injury, 7 patients (20%) had EEG seizures recorded. Among the nonsurvivors of the cohort, 75% had nonreactive background to stimulation, 73% had prolonged discontinuous activity (burst suppression), and 47% had seizures. The survivors in the cohort all had reactive backgrounds and did not have EEG seizure activity. The background reactivity changes seen in this study were noted during therapeutic hypothermia. A study of 95 patients with anoxic injury found 26 patients (27%) with EEG seizures. They also described two seizures patterns, one arising from burst suppression and one arising from a cEEG background (12). Seizures were still associated with a dismal prognosis

with mortalities around 100% in most studies, but 2 (out of 10) patients who had seizures arising from a cEEG pattern regained consciousness.

CNS Infections/Inflammation

Encephalitis or meningoencephalitis is a risk factor for seizures and has been reported to be associated with EEG seizures in 6% to 29% of patients (5,13). In a study of patients with bacterial meningitis, seizures occurred in 121 of 696 patients (17%). The patients with seizures had worse outcomes (41% mortality) than patients without seizures (16% mortality). Viral encephalitis has also been shown to have risk of EEG seizures with 5% of all seizures being attributed to suspected viral encephalitis in one study (14). Autoimmune encephalitis is becoming increasingly recognized as an etiologic agent in critical care status epilepticus. Some of these patients have a paraneoplastic disorder with antibodies against an occult tumor, but many have autoantibodies without an obvious source. Patients often present with refractory status epilepticus that does not respond to traditional antiseizure medications and requires aggressive immunotherapy. There is also evidence that some patients with infectious viral encephalitis (herpes encephalitis) can develop autoantibodies that then contribute to the generation of seizures and neurologic deterioration (15,16). There has also been a typical EEG pattern often present on the initial EEG of some patients with anti-NMDA receptor encephalitis. This pattern, the so-called delta brush, which is characterized by high-amplitude delta waves and overlying fast activity, may be helpful for identifying these patients and guiding therapy (17).

Subarachnoid Hemorrhage

EEG seizures have been reported in 3% to 26% of comatose patients with SAH. Claassen et al. (18) studied 247 patients with SAH and found EEG seizures in 17 patients (7%). SAHs with associated subdural hemorrhage or cerebral infarction were predictive of patients with seizures. Patients with seizures reported poorer quality of life and experience prolonged recovery times. Another study examined 389 patients with SAH and found 11 patients with nonconvulsive status epilepticus (3%). Patients with poor neurologic grade and associated structural lesions (intracerebral hemorrhage and stroke) were more likely to have seizures (19). In addition to being at risk for EEG seizures, patients with SAH are at risk for delayed cerebral ischemia (DCI). DCI may result in stroke and cause a clinical deficit, but in poor-grade SAH, there is often no neurologic exam to follow (patients are often comatose). Quantitative EEG trend monitoring of cEEG recording has been shown to detect DCI prior to cerebral infarction and in time for intervention. Claassen et al. (20) examined 34 patients with SAH and identified 9 patients with DCI. For patients who experienced DCI, the alpha–delta ratio was significantly decreased (24%) compared to an increase (3%) in the alpha–delta ratio for those patients without DCI. In a study from Montreal, 13 patients were studied with quantitative EEG and 8 patients were determined to have DCI. DCI was predicted by using a quantitative EEG method termed the composite alpha index (CAI). In 3 of the 8 patients, changes in the CAI predicted the changes of DCI 24 hours prior to clinical change (21). cEEG has also been used to develop prognosis in poor-grade SAH. When 116 patients were followed for functional outcome, predictors of poor outcome were periodic epileptiform discharges, electrographic status epilepticus, and the absence of sleep architecture (22).

EEG Monitoring Duration

Determining the length of cEEG monitoring in adult patients admitted to the neuro-ICU with altered mental status is complex and can vary based on etiology, EEG findings, and the degree of altered mental status. If time to first seizure is examined, then a 40% yield of seizures is found at 20 minutes, 50% yield at 1 hour, and 80% to 90% yield at 24 hours for most patients (5). Thus, a minimum recording time of cEEG monitoring for a patient with altered mental status in the critical care setting is 24 hours; however, some situations may require additional monitoring. Patients who have periodic lateralizing epileptiform discharges (PLEDs) have been shown to have a delayed detection of seizure onset that requires 48 hours of monitoring (5). Patients with PLEDs also have a 50% to 70% chance of having seizures recorded sometimes during the record demonstrating the importance of monitoring this population on cEEG monitoring (23,24). Comatose state has also been associated with a prolonged need for monitoring, and 48 hours has been suggested as a minimum time of recording (5). In patients with intracerebral hemorrhage, EEG seizures were detected in 56% in the first hour and 94% by 48 hours, suggesting prolonged monitoring may also be useful in this population (6). Monitoring patients for DCI after SAH typically requires up to 7 to 10 days of monitoring depending on the patient's clinical course (20,21). Finally, patients with EEG seizures in the record require additional monitoring. In patients who do not present with clinical signs, video EEG is necessary to make the diagnosis, and once the nonconvulsive seizures have been treated, an additional 48 hours of continuous monitoring is common practice, but may vary based on the clinical needs.

EEG Seizures and Outcome

The use of cEEG in the critical care setting has dramatically increased the number of patients diagnosed with seizures in the hospital. Unfortunately, there is not a wealth of outcome data to guide treatment of these seizures and to understand their significance. Outcome studies have shown that patients with an acute neurologic injury (stroke, hemorrhage) with seizures have a worse functional outcome than patients with the same primary neurologic injury without seizures. Such findings may suggest that the seizures may contribute to the extent of injury. Research addressing the effect of treating these acute symptomatic seizures on functional outcome is required. The majority of outcome studies that have been done to date have focused on anoxic brain injury (11,12). From these studies, it is clear that EEG seizures in the setting of anoxia are a negative prognostic sign and are typically associated with a 90% to 100% mortality. Treatment of EEG seizures in anoxic brain injury has not been shown to improve outcome. The use of cEEG to demonstrate reactive background during therapeutic hypothermia has been shown to predict outcome (12). Future studies will need to address the effect of treating nonconvulsive seizures in other etiologies and the factors that predict the development of chronic epilepsy after nonconvulsive seizures are recorded in the setting of an acute neurologic injury.

Current Practice and Guidelines

The use of cEEG has rapidly increased in the past decade. Patients with altered mental status and/or acute neurologic injury are at risk for nonconvulsive seizures and are candidates for monitoring. The number of patients that meet these criteria is often daunting, and a conservation of resources is needed. Focusing on the high-risk etiologies (presented above) and the patients with the most profound altered mental status is a good practice to utilize equipment in the high-yield patients. There

is a consensus statement that was published by the neurointensive care section of the European Society of Intensive Care Medicine (25). Their conclusions were to use EEG monitoring in convulsive status epilepticus and to rule out nonconvulsive status epilepticus in brain-injured patients and in comatose ICU patients without primary brain injury who have unexplained and persistent alerted consciousness.

CONTINUOUS EEG MONITORING IN PEDIATRIC PATIENTS

cEEG monitoring in critically ill children is generally performed in multidisciplinary pediatric and neonatal ICUs. There are few designated pediatric or neonatal neuro-ICUs, so care is generally provided by collaborating intensivists, encephalographers, and intensive care neurology consult teams. Despite the paucity of dedicated pediatric or neonatal neuro-ICUs, judicious use of cEEG has seen a growing footprint in the last 5 years. The pediatric literature is rich with available data highlighting the important role played by cEEG in optimizing neurologic health–related outcome in critically ill neonates and children.

Electrographic Seizure Epidemiology

Observational studies of children undergoing clinically indicated cEEG in pediatric intensive care units have reported electrographic seizures in 10% to 40% of children, and about one-third of children with electrographic seizures have a sufficiently high seizure burden to be categorized as electrographic status epilepticus (26–38). Indications for cEEG differ across studies, but most included a primary indication related to "acute ongoing encephalopathy." The largest study of cEEG in critically ill children retrospectively enrolled 550 children from 11 tertiary care centers in North America. Electrographic seizures occurred in 30% of 550 children, and in 33% of children with electrographic seizures, the seizure burden was classified as electrographic status epilepticus. Many children with electrographic seizures would not be identified without cEEG. In the multicenter study, 35% of children had exclusively EEG-only seizures (37), and these data are consistent with other single-center studies (26,27,29–31,33–36,39). Several studies have demonstrated that EEG-only seizures occur even in children who have not received any or recent paralytics, indicating there is an ongoing dissociation of electrical brain activity and outward mechanical signs (electromechanical uncoupling) (35,36). Identifying children at higher risk of electrographic seizures is complex since electrographic seizures have been reported in both large heterogeneous cohorts (37) and smaller single brain insult etiology cohorts (28,32–34). However, several risk factors have been reported including infants being at higher risk than older children (29,32,34,35,37), convulsive seizures (30,37,39), or status epilepticus (29) prior to cEEG, the presence of acute structural brain injury (28–30,32–34,39), and the presence of interictal epileptiform discharges (29,33,37,39), or periodic epileptiform discharges (26). Although these risk factors are statistically significant, the absolute difference in seizure risk is often only 10% to 20%, so these risk factors may have limited clinical utility in selecting patients to undergo cEEG.

Critically ill neonates are also at high risk for electrographic seizures (40–43), and about one-third of neonates with electrographic seizures have a sufficiently high seizure burden to be categorized as electrographic status epilepticus (41,43,44). Seizures have been identified as common in some specific cohorts of neonates including 33% to 65% of neonates treated with therapeutic

hypothermia for hypoxic–ischemic encephalopathy (41–43), as well as many neonates with stroke, undergoing extracorporeal membrane oxygenation, with meningoencephalitis, and in the perioperative period of congenital heart disease surgery (40). EEG monitoring is often advocated for neonates at risk for seizures for three main reasons. First, clinical factors and interictal EEG features have a limited ability to predict which neonates will experience seizures during acute hospitalization. Second, about 80% to 90% of electrographic seizures in neonates are EEG-only seizures, particularly after administration of anticonvulsants, which may terminate electroclinical seizures while EEG-only seizures persist (electromechanical uncoupling), and therefore would not be identified even with optimal clinical observation. Third, even experienced bedside caregivers have difficulty distinguishing between electroclinical seizures and nonepileptic movements in critically ill neonates based on clinical observation alone, leading to underdiagnosis of seizures and overdiagnosis of nonepileptic events as seizures. Due to these issues with clinical diagnosis alone, the American Clinical Neurophysiology Society's guideline on neonatal EEG monitoring states that "conventional video-EEG monitoring is the gold standard for neonatal seizure identification and quantification and should be used whenever available for seizure identification and differential diagnosis of abnormal appearing, paroxysmal clinical events. It is the ideal tool to measure the exact number and duration of seizures, their site(s) of onset and spatial patterns of migration (45)."

EEG Monitoring Duration

Decisions regarding the duration of cEEG must balance the physician's interest in identifying seizures with practical concerns regarding the significant resources cEEG requires. A number of observational studies of critically ill children undergoing clinically indicated cEEG have reported that about 50% and 90% of patients with electrographic seizures are identified with 1 hour and 24 to 48 hours of cEEG, respectively (26,27,29,30,33,35,36,39). These data are consistent with current clinical practice. The Neurocritical Care Society's status epilepticus guideline strongly recommends performing 48 hours of cEEG following acute brain insult in comatose patients (46).

In neonates with hypoxic–ischemic encephalopathy (41–43) or cardiac surgery (40), most seizures occur in the initial 48 hours. Few data are available regarding other acute brain insult types. The American Clinical Neurophysiology Society's guideline addressing cEEG in critically ill neonates recommends performing 24 hours of cEEG (45).

There are two important limitations regarding the timing data. First, most of the studies were observational studies in which patients underwent 1 to 3 days of clinically indicated cEEG, so some patients may have experienced seizures after cEEG discontinuation. In specific circumstances, seizures are known to occur later in time, such as following cardiac arrest resuscitation (28) or in neonates with hypoxic–ischemic encephalopathy (15,16). Second, most of these studies used timing at the onset of cEEG and not the onset of the acute brain insult. This makes generalizability to a given patient difficult since patients may present or be transferred at varying times relative to insult onset.

Electrographic Seizures and Outcome

Several studies in critically ill children have reported associations between a high seizure burden and worse clinical outcome after adjustment for potential confounders related to acute encephalopathy etiology and critical illness severity (31,37,47,48). A prospective observational study of 1 to 3 channel EEGs in 204 critically ill neonates and children found that electrographic seizures were

associated with a higher risk of unfavorable neurologic outcome (odds ratio 15.4) in a multivariable analysis that included age, etiology, pediatric index of mortality score, Adelaide coma score, and EEG background category (31). Several other studies aimed to evaluate the effect of seizure burden and classified children as having no seizures, electrographic seizures, or electrographic status epilepticus. A single-center study of 200 children in the pediatric ICU with outcome assessed at discharge identified an association between electrographic status epilepticus (but not electrographic seizures) and higher mortality (odds ratio 5.1) and worsening pediatric cerebral performance category (odds ratio 17.3) in multivariable analyses including seizure category, age, acute neurologic disorder, prior neurodevelopmental status, and EEG background category (47). A larger multicenter study of 550 children in the pediatric ICU reported an association between electrographic status epilepticus (but not electrographic seizures) and mortality (odds ratio 2.4) in a multivariable analysis that included seizure category, acute encephalopathy etiology, and EEG background (37). A single-center prospective study evaluated 259 critically ill infants and children who underwent cEEG. Seizures occurred in 36% of subjects, and these constituted status epilepticus in 9% of subjects. The mean maximum seizure burden per hour was 15.7% in subjects with neurologic decline versus 1.8% in subjects without neurologic decline. In a multivariable analysis that adjusted for diagnosis and illness severity, for every 1% increase in the maximum hourly seizure burden, the odds of neurologic decline increased by 1.13. Seizures were not associated with mortality (38). A study addressing long-term outcome obtained follow-up data at a median of 2.7 years following ICU admission from 60 children who were neurodevelopmentally normal prior to pediatric ICU admission and underwent clinically indicated cEEG. Multivariable analysis including acute neurologic diagnosis category, EEG background category, age, and several other clinical variables identified an association between electrographic status epilepticus (but not electrographic seizures) and unfavorable Glasgow Outcome Scale (Extended Pediatric Version) category (odds ratio 6.36), lower Pediatric Quality of Life Inventory scores (23.07 points lower), and an increased risk of subsequently diagnosed epilepsy (odds ratio 13.3) (48).

In neonates, several studies that have adjusted for the severity of brain injury have reported an association between electrographic seizures or electrographic status epilepticus and worse neurodevelopmental outcomes (49–52). A prospective study of 77 term neonates with hypoxic–ischemic encephalopathy adjusted for initial injury on magnetic resonance imaging (MRI) and still identified an association between seizure category and full-scale intelligence quotients at 4 years (49). A study of 129 neonates with encephalopathy adjusted for the initial degree of clinical encephalopathy and for brain injury severity on MRI and still identified an association between neonatal status epilepticus and an increased risk for subsequent epilepsy (hazard ratio 35.8) (50). A study of 106 neonates utilized multivariable analysis including cerebral ultrasound findings and identified an association between status epilepticus and an increased risk for adverse neurologic outcomes (odds ratio 20.3) and postneonatal epilepsy (odds ratio 6.5) (51). A study of 218 term neonates with neonatal encephalopathy included multivariable analysis including hypothermia group, birth weight, Apgar scores, and encephalopathy grade and identified an association between the absence of amplitude-integrated EEG identified seizures and better 18 month outcome (odds ratio 0.46) (52). A study of 85 term neonates with hypoxic–ischemic encephalopathy managed with therapeutic hypothermia who underwent cEEG or amplitude-integrated EEG and MRI found that on multivariate logistic regression, high seizure burden was independently associated with greater MRI injury (43).

Infants with congenital heart disease have undergone extensive study. In a cohort of 139 children

with D-transposition of the great arteries followed to adolescence, multivariable analysis found postoperative seizures as infants (electroclinical seizures or EEG-only seizures) were the medical variable most consistently associated with worse outcome, including clinically meaningful lower scores on reading and math composites, general memory index, executive function, and visuospatial testing (53). In a second cohort of 132 infants with congenital heart disease followed up at 4 years, a multivariable analysis including clinical and operative factors found that presence of postoperative seizures (which were all EEG-only seizures) was associated with worse executive function and impaired social interactions/restricted behavior (54).

Together, these findings suggest there may be a dose- dependent or threshold effect of seizures upon clinical outcomes, with high seizure burdens having clinically relevant adverse impacts. However, further study is needed to determine whether seizure identification and management improves neurodevelopmental outcomes.

Current Practice and Guidelines

A recent survey of cEEG use in the pediatric intensive care units of 61 large pediatric hospitals in North America reported that the median number of patients who underwent cEEG per month increased about 30% from 2010 to 2011. Indications for cEEG included determining whether events of unclear etiology were seizures in 100% of centers, identifying electrographic seizures in patients considered at risk (altered mental status following a convulsion, altered mental status in a patient with a known acute brain injury, and altered mental status of unknown etiology) in 90% of centers, and using cEEG as a pathway component (i.e., following resuscitation from cardiac arrest or with severe TBI) in 50% of centers (55). An international survey of neurologists and neonatologists reported monitoring of "at-risk" neonates with EEG by 24%, amplitude-integrated EEG in 24%, both in 19%, and none in 34%. Only 8% reported that seizure diagnosis was made by clinical and not EEG or amplitude-integrated EEG criteria (56).

Guidelines related to cEEG are available from the Neurocritical Care Society for children (46) and the American Clinical Neurophysiology Society for neonates (45). Both advocate for the use of cEEG for the identification of electrographic seizures in at-risk patients. The Neurocritical Care Society's status epilepticus guideline identifies at-risk patients as those with persisting altered mental status for more than 10 minutes after convulsive seizures or status epilepticus or encephalopathic children after resuscitation from cardiac arrest, with TBI, with ICH, or with unexplained encephalopathy. The guideline strongly recommends 48 hours of cEEG in comatose patients and that status epilepticus management should continue until all electrographic seizures (not just clinical seizures) are halted (46). The American Clinical Neurophysiology Society's guideline identifies at-risk neonates as those with acute neonatal encephalopathy including hypoxic–ischemic encephalopathy, cardiac or pulmonary risks for brain injury, CNS infections, neurotrauma, inborn errors of metabolism, stroke, or genetic/syndromic diseases at risk for seizures. The guideline recommends cEEG for at least 24 hours (45).

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SECTION D DIFFERENTIAL DIAGNOSIS OF EPILEPSY

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CHAPTER 40 PSYCHOGENIC NONEPILEPTIC SEIZURES

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TERMINOLOGY AND CLASSIFICATION

Psychogenic nonepileptic seizures (PNES) are time-limited, paroxysmal alterations in consciousness, motor activity, sensation, and/or cognition, with psychological underpinnings that are not associated with ictal epileptiform discharges. PNES are commonly seen in emergency rooms and across epilepsy centers and are one of the most common forms of conversion disorder. While neurologists have debated on the name for PNES, past labels, such as "hysterical fits" and "pseudoseizures," are avoided today because of the pejorative connotations of those terms (1). Some neurologists have argued that including the term "seizure" in PNES may confuse patients, families, and other caregivers, and they propose terms such as attacks, spells, episodes, or events (2). However, just as headaches can be qualified as either migraine or tension, "seizure" can be either epileptic or nonepileptic, with diagnoses made using electroencephalogram (EEG), history, and clinical judgment (3).

For some patients, it may take several visits to accept the diagnosis of PNES, especially if they have been under the impression they have had epileptic seizures for many years. Rather than imposing terms such as attacks, spells, and fits, terms that may distance patients and providers, sharing the common language of "seizure" may facilitate communication and meet the patients where they are, conceptually and psychologically. The term "psychogenic" distinguishes events from physiologic nonepileptic causes, such as syncope or alcohol withdrawal seizures, and these are not recurring, unprovoked epileptic seizures. As discussed in this chapter, accepting the diagnosis, the patients' label, as well as ownership of the illness may be important for successful treatment.

The challenge in naming and classifying PNES is not simply a territorial, semantic, or reimbursement issue, but it reflects how PNES is conceptualized. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) classifies PNES as it was in DSM-IV, a conversion disorder also termed a "functional neurologic disorder" (4). In contrast, the International Classification of Diseases-10 (ICD-10) categorizes PNES as a dissociative disorder. Conversion and dissociative disorders, though sometimes conflated under the category of "medically unexplained symptoms," have developed as distinct conceptual models that may have implications on how the illness is explained to a patient, as well as how a clinician approaches treatment (5). The concept of dissociation emerged from the psychodynamic tradition, in which the integration of thought, affect, sensory experience, and behavior is impaired by psychological trauma. Dissociative symptoms may manifest as amnesia, fugue, identity disorders, or unexplained sensory and motor behavior with change in the level of consciousness. The DSM-II subcategorized hysterical neurosis into conversion and dissociative subtypes, with the former representing neurologic symptoms (such as psychogenic paralysis, movement disorders, or seizures) and the later denoting changes in consciousness or identity (such as fugue or multiple personality disorder) (5). The DSM-III introduced the category of

somatoform disorders, which represented symptoms associated with a medical disorder that are thought to be psychologically driven. As a result, much of the discourse regarding "somatization" exists in the primary care and internal medicine literature (6). As conversion disorders began to be subsumed within the category of somatoform disorders, somatization and conversion became more prominent in the neurology literature. Conversely, this discourse of dissociative disorders became primarily restricted to the mental health literature. Consequently, the role of dissociation in illnesses such as PNES began to be underemphasized. Clinicians may not address dissociative features of PNES as much as the physical or somatic complaints of the patients.

One subtlety to approaching PNES as a somatization disorder, as opposed to a dissociative disorder, is that somatization is often understood as an unconscious impairment or limitation in the ability of patients to express or communicate emotional distress. Whether the difficulty of communication is due to cultural, developmental, or psychodynamic reasons, therapists' treatment is premised on providing patients with the communication tools to express their emotions in a healthy manner. In contrast, the approach to dissociative disorders may include preventing the triggers that lead to the trance-like states or how to reintegrate sensory systems during dissociative episodes.

Another way to understand the relationship between dissociation and somatization is across a psychological continuum. Dissociation may represent a defense mechanism in which the mind disconnects from the environment or blocks thoughts altogether, usually associated with a past or present traumatic event. In contrast, with somatization, instead of thought blocking and disengaging from the environment, emotional distress is expressed as a physical symptom (6). In spite of the common psychological substrate, the role of somatization and dissociation in PNES continues to be contested by some. Studies tend to emphasize that PNES is associated with other somatization symptoms and disorders (7–9) more than dissociative symptoms. Somatization in PNES is associated with greater seizure severity and worse outcomes independent of dissociative symptoms (10,11). In contrast, dissociative episodes may involve regressed behavior that is not consistent with seizures. Still, people argue that understanding PNES as a dissociative disorder may be useful because, theoretically, somatic symptoms may be understood as expressions of dissociating consciousness from somatosensory experience or behavior (12). Independent of the nosology discussion, an approach that has been conveyed to and readily understood by patients is that PNES are symptom manifestations of an underlying conflict or stressor. Once patients and family members grasp this concept, progress is made in addressing the underlying issues.

EPIDEMIOLOGY

The majority of studies documenting the prevalence of PNES take place in seizure monitoring units. Across centers, 20% to 40% of people admitted for evaluation of seizures are diagnosed as PNES (13–16). These numbers are similar for veteran population (16). Three incidence studies, to date, have been conducted to assess the proportion of new onset PNES in the community. The first was conducted in Iceland, which estimated, based on 1996 population data, an annual incidence of 1.4 per 100,000 in people older than 15 years (17). The study was possible because there is only one neurophysiologic service in the country; therefore, it should not be considered a community-based sample. The second study, conducted in Hamilton County, Ohio, used a similar methodology (18). Since there were only two centers with EEG capacity to evaluate people with PNES, they assumed that they would capture all (if not most) citizens of Hamilton county who experienced PNES. The primary limitation of this methodology is a potential underestimation of incidence, that is, if patients

with PNES are evaluated elsewhere or do not seek medical services. The Ohio study estimated a PNES incidence of 3.03/100,000 person-years, which is double the rate of the Iceland study. A third study prospectively identified first presentations of PNES from a population of 367,566, over 3 years. PNES were diagnosed in 68 patients, in 54 of whom the diagnosis was confirmed by video/EEG recording, indicating an incidence of 4.90/100,000/year (15). The studies demonstrated that more women were affected with PNES—73% in the Ohio study and 78.6% in the Iceland study. Also younger adults have the highest average incidence with 3.4/100,000 person-years in 15- to 24-year-olds in Iceland and 4.38/100,000 in 25- to 44-year-olds in Ohio, respectively. A door-to-door community-based study to determine the incidence and prevalence of PNES would be both resource intensive and not feasible given the requirement for video-electroencephalographic (VEEG) confirmation of events. Based on the extrapolation that the prevalence of epilepsy is 0.5% to 1%, the proportion of medically refractory epilepsy is 20% to 30%, the proportion of medically refractory people with epilepsy that are referred to epilepsy centers is 20% to 55%, and the percentage of people admitted to epilepsy centers are diagnosed with PNES is 10% to 20%, then the prevalence of PNES is estimated to be 2 to 33 per 100,000 (14).

The consistent finding that PNES occurs more commonly in women (up to three time more likely) than in men is often attributed to higher reports of sexual abuse among women (19,20). Men with PNES are more likely to report work-related problems (20) and present with more violent motor PNES (21). Younger age, poor socioeconomic status, and increased psychosocial stressors have also been reported as risk factors for PNES (22–24). Among the most studied risk factors for PNES are psychiatric comorbidity and psychological profiles. Extensively reviewed elsewhere (25,26) and based on relatively small studies (with sample sizes ranging from 20 to 85 subjects), people with PNES have relatively higher rates of depression, anxiety, and personality disorders compared to community and people with epilepsy. For instance, depressive disorders range from 13% to 60% and anxiety disorders from 10% to 70% in people with PNES. Borderline personality disorders ranged from 10% to 38% of people with PNES compared to 3% to 5% of controls with epilepsy. Psychiatric comorbidity markedly impacts quality of life (27) and should be addressed. Both neuropsychological as well as psychological profiles are limited at diagnosing PNES (10,28), but they may be useful in determining the patient's psychosocial needs, cognitive strengths and limitations, and prognosis.

DIAGNOSIS

VEEG remains the gold standard for diagnosis PNES (29). Recent studies, however, have demonstrated that key historical features in the descriptions from family members and/or significant others of witnessed events may be accurate in identifying PNES (30). As reviewed elsewhere (31–33), symptoms, signs, and semiology may help distinguish epileptic seizures (ES) from PNES; however, no one symptom or sign can definitively establish the diagnosis of PNES (33).

History

Many clinicians begin to consider PNES in the differential diagnosis when a patient is not responding to antiepileptic drugs (AEDs) or when a patient's profile or symptoms are not consistent with ES. However, many symptoms expected to be reported in ES are also reported in PNES: 59.2% people with PNES may report history of events during sleep as opposed to 47% of people with ES (34); urinary incontinence has been shown to occur in 44% of patients with PNES, as opposed to 57% with

ES (35); prodromal phenomena such as sensory auras or premonitions have been reported in 59% of patients with PNES (36); postictal confusion has been reported in 55% of PNES patients who report losing consciousness during attacks (36); and tongue biting is reported in 0% to 18% of people with PNES (37–40). Although several features of PNES, such as forced eye closure, asynchronous movements, side-to-side head movements, prolonged duration, pelvic thrusting, preserved awareness, and others influencing the ictal event, are sensitive for diagnosing PNES (Table 40.1), eyewitness reports by family and significant others have been shown to be very unreliable in identifying PNES based on these symptoms (41).

Table 40.1 Sensitivity of Identifying PNES Correctly Based on Clinical Symptoms, Signs, and Diagnostic Procedures

Clinical Indicator	Sensitivity	Reference
History		
Eye witness	25%	(41)
Preserved awareness		
Eye flutter	42%	
Others can intensify or alleviate	25%	
Patient procedure		
Hypnotic seizure induction	77%	(42)
IV saline procedure induction	91%	
Bedside assessment by clinician		
Ictal cognitive assessment	54%	(43)
Ictal semiology		
Long duration	—	
Closed eyes	52%–96%	(32,44)
Fluctuating course	47%–88%	
Asynchronous movements	9%–56%	
Side-to-side head movements	15%–36%	
Pelvic thrusting	7%–44%	
Ictal weeping	4%–37%	
Recall for period of apparent unconsciousness	63%	
Review of video (without EEG) by neurologist	87%	(45)
Review of video (without EEG) by epileptologist		
Psychological testing		
MMPI II	30%–92%	(46)
Laboratory testing		
Prolactin level (CPS, GTC)	46%, 60%	(47)
Neuroimaging		
Postictal SPECT	70%–73%	(48)

CPS, complex partial seizure; GTC, generalized tonic–clonic seizure; MMPI II, Minnesota Multiphasic Personality Inventory-2.

When shown a video of ES and PNES, neurologists are highly accurate (89%) in distinguishing the two types of seizures (45). Importantly, neurologists are accurate in diagnosing PNES by video when considering the constellation of signs. However, when attempting to make the diagnosis based on one sign on video, they are not as accurate (41). Likewise, when presented with the history alone, neurologists have a high sensitivity for ES, but specificity was only 50%, with simple partial epileptic seizures and PNES being frequently missed (15). With the nearly ubiquitous availability of

video cameras on smart phones, patients and their significant others may be able to provide the data for a clinician to help make the diagnosis. The primary limitation would be the quality of the video and the strong likelihood that only part of the PNES would be captured without the beginning of the event.

Laboratory and Neuroimaging

Use of prolactin (PRL) level has been extensively reviewed in an American Academy of Neurology (AAN) technical guideline report (47). Pooled data, of studies distinguishing both complex partial and generalized seizures from PNES, demonstrate that PRL are highly specific (95.9% to 96.3%) but not that sensitive (46.1% to 60%). PRL fluctuates with circadian rhythm, time of day, quality of sleep, and with syncope. Most studies demonstrating utility of PRL level measured baseline levels and within 30 minutes after the seizure since levels begin to attenuate within hours of the seizure. AAN guidelines suggest that PRL levels should be drawn within 20 minutes of the seizure to be most useful. Criteria for determining elevated PRL have included a 300% increase from baseline; reaching >25 ng/mL; and reaching > 32 ng/mL for females and >23 ng/mL for males. A rise in PRL level does not occur in simple partial epileptic seizures. Syncope has been shown to elevate PRL levels; therefore, PRL are likely not useful to distinguish between ES and syncope.

The majority of structural neuroimaging studies in people with PNES are within normal limits, although abnormalities are present in a significant minority of studies (49). While there is an increased interest in studying neuroimaging changes in people with somatization and dissociative disorders (50–52), including PNES (53,54), neuroimaging does not distinguish between ES and PNES. Two studies have shown that changes in interictal and postictal single photon emission computed tomography (SPECT) may be useful when semiology of PNES is atypical or VEEG is unclear (48,55).

Neurophysiology/EEG Monitoring

Several studies have demonstrated that nonspecific interictal EEG abnormalities may be seen in people with PNES that may be due to overreading of normal variants on the EEG (56), comorbid medical and psychiatric issues (such as traumatic brain injury or psychotropic medications) (57), and misdiagnosis of frontal lobe seizures (58). Criteria for VEEG diagnosis have also been debated. Research studies have varied in how many of the typical events should be captured and how to interpret interictal epileptiform activity (31). Studies vary regarding how many episodes should be captured to determine the diagnosis, whether interictal discharges rule out PNES, whether to include preictal and postictal EEG changes as part of the criteria, and the how to use psychogenic semiology in the diagnosis (31). The gold standard is to capture a PNES that is typical of the events the patient experiences in the community. The entire event should be captured, and there should be ideally no epileptiform activity on VEEG before, during, or after the event. In addition, the semiology can provide helpful information (listed in Table 40.1). The heart rate, for example, tends to accelerate relative to baseline during ES but not PNES and can distinguish between the two with a sensitivity of 83% and specificity of 96% (59). Postictal agitation and confusion are seen in both ES and PNES (60); however, PNES is distinguished from ES postictally by shallow rapid breathing as opposed to deep, heavy breathing in ES (61). Recently, the International League Against Epilepsy PNES Task Force proposed criteria for diagnostic levels of certainty for PNES to offer guidance in events that

cannot be captured by VEEG either because the technology is not available or because events are too infrequent to expect capture (Table 40.2) (30). The three criteria involve history, semiology, and EEG and levels include "Documented," "Clinically established," "Probable," and "Possible PNES."

Table 40.2 Overview of Proposed Diagnostic Levels of Certainty for PNES

Diagnostic level	History	Witnessed event/semiology	EEG
Possible	+	By witness or self-report/ description	No epileptiform activity in routine or sleep-deprived *interictal* EEG
Probable	+	By clinician who reviewed video recording or in person, showing semiology typical of PNES	No epileptiform activity in routine or sleep-deprived *interictal* EEG
Clinically established	+	By clinician experienced in diagnosis of seizure disorders (on video or in person), showing semiology typical of PNES, while not on EEG	No epileptiform activity in routine or ambulatory *ictal* EEG during a typical ictus/event in which the semiology would make ictal epileptiform EEG activity expectable during equivalent epileptic seizures
Documented	+	By clinician experienced in diagnosis of seizure disorders, showing semiology typical of PNES, while on VEEG	No epileptiform activity immediately before, during, or after ictus captured on *ictal* VEEG with typical PNES semiology

As noted in the text, additional tests may affect the certainty of the diagnosis—for instance, self-protective maneuvers or forced eye closure during unresponsiveness or normal postictal prolactin levels with convulsive seizures.

+, history characteristics consistent with PNES; EEG, electroencephalogram.

Reproduced with permission from LaFrance WC Jr, Baker GA, Duncan R, et al. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach: a report from the International League Against Epilepsy Nonepileptic Seizures Task Force. Epilepsia. 2013;54(11):2005–2018.

COURSE OF ILLNESS

Due to the delay in the diagnosis of PNES, most (if not all) people with PNES experience some stigma and restructure their lives around the diagnosis of epilepsy. Furthermore, the delay in diagnosis and treatment as epileptic seizures frequently results in unnecessary use of AEDs, incurring the risk of side effects, as well as the high cost of chronic use (16). Less commonly, patients may be inappropriately referred for neurosurgical interventions for "medically intractable epilepsy" (62). Standard medical care (SMC) at this time is limited to communicating the diagnosis of PNES, tapering AEDs in patients with PNES only and referring to a psychiatrist or psychologist for psychiatric comorbidities (63). Although a few small studies have shown marginal improvement in the frequency of PNES with only communicating the diagnosis, SMC has not shown significant improvement in depression and anxiety symptoms, quality of life measures, utilization of health care resources, dependence of state welfare programs, or employment status. Unlike people with epilepsy who have improvement in quality of life (QOL) with seizure remission (64), in the minority of patients (approximately 30%) who experience PNES remission with SMC, utilization of health care services, quality of life, anxiety, depression, somatization, and unemployment status are not better than those who continue to experience PNES (65). People who suffer from PNES die earlier than the

general population (66) and have a high rate of self-injury, as well as suicide attempts (35). Therefore, overall people with PNES have worse outcomes than people with ES. As reviewed elsewhere (67), factors that are associated with lower remission of PNES include the following: adulthood during the age of PNES onset (68), female gender (69), receiving social security benefits (70), lower education (8,71), unemployment (8,70), difficulty forming relationships (37), not accepting the diagnosis of PNES (70), people with more violent psychogenic seizure semiology (72), and higher level of psychopathology (69,73). In particular, people with delusions, paranoia, and bizarre behavior are less likely to achieve PNES control (74). Personality characteristics, including lower emotional dysregulation, inhibitedness, and compulsivity scores, are associated with better outcomes (8).

TREATMENT

Prior editions of this chapter have almost exclusively focused on PNES as a differential diagnosis. However, the emerging literature (75–77) on treatment warrants review of the increase in evidence-based therapies. Once the diagnosis of PNES is made, there are three critical phases to treatment of PNES: presentation of the diagnosis, gaining control over the symptoms, and maintenance therapy (77). Some neurologists argue that providing the diagnosis of PNES itself is (at least part of) the treatment for PNES, but as discussed SMC is associated with poor outcome. Open-labeled psychological interventions, including psychodynamically oriented, as well as cognitive behavioral therapies (CBTs) (78,79), and pilot pharmacologic clinical trials (80) have demonstrated improved outcomes. Two pilot studies of CBT for PNES focused on PNES-related trigger prevention has resulted in seizure freedom of 25% (78) and 65% (81) and a >50% reduction of seizure frequency in 76% and 81% of subjects enrolled, respectively.

Pharmacologic trials for PNES include the use of psychotropic medications and analgesics (82). In a double-blinded, placebo-controlled, 12-week clinical trial of sertraline, 38 subjects were enrolled and 26 (68%) completed the study (80). Subjects who received sertraline had a 45% reduction in seizures from baseline, compared to an 8% increase in those who received placebo. No significant difference was seen in depression, anxiety, impulsivity, somatic symptoms, QOL, and psychosocial functioning scores. This feasibility study was not powered to demonstrate efficacy, but interestingly showed improvement in seizure frequency independent of mood and anxiety symptoms. A 5-month, open-label prospective study of venlafaxine required subjects to have a comorbid DSM-IV diagnosis of an anxiety and/or unipolar depressive disorder (83). Of the 19 subjects that completed the trial, 8 were seizure free at 5 months, 15 (88%) had >50% reduction in frequency of seizures, 11 (65%) had >50% reduction in depression scores, and 7 (41%) had >50% reduction in anxiety scores. Absence of a control arm makes it difficult to determine how much of the improvement was due to the medication. A recent pilot multicenter randomized trial comparing a workbook-based psychotherapy (84), workbook psychotherapy plus SSRI, SSRI alone, and SMC revealed significant seizure reduction and improvement in comorbidities in the psychotherapy and psychotherapy plus SSRI arms and no improvement in the SMC arm (85). The study illustrates that effective treatments exist for PNES and that the current standard of treatment (usually supportive psychotherapy) is not adequate in treating patients with PNES.

CONCLUSION

Much has been learned recently about the nature and consequences of PNES, which have been documented in the medical literature for centuries. As information is increasingly available on the characteristics and treatments for PNES, neurologists, mental health providers, and other health care professionals not only should consider PNES in the differential diagnosis of paroxysms but should also actively be engaged in providing care for these patients. The risk of unnecessary AED, emergency room visits, hospital admissions, unnecessary procedures, and self-injury is exceedingly high. Clinicians may play a central role in not only diagnosing PNES but also referring patients to appropriate mental health treatment. Neurologic clinics and epilepsy centers may even consider collaborating closely with mental health professionals to develop multidisciplinary care for conversion disorders beyond PNES, such as psychogenic movement disorders or other psychosomatic complaints (86). Hope for improvement in PNES is present not only for patients and family members but also for neurologists who evaluate and care for this challenging population.

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CHAPTER 41 OTHER NONEPILEPTIC PAROXYSMAL DISORDERS

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A number of conditions cause intermittent and recurring symptoms that look like epilepsy. Although seizures must be considered in the differential diagnosis, the clinical characteristics sometimes clearly differentiate these disorders from true seizures. These so-called nonepileptic paroxysmal disorders tend to recur episodically. They must not be confused with seizures because treatment with antiepileptic drugs is usually unnecessary and unsuccessful, leading to adverse effects, and alternative etiologies may be overlooked (1–6).

For the clinician dealing with a paroxysmal disorder, the patient's age and an accurate description of the event, including the time of occurrence (during wakefulness or sleep), can lead to the correct diagnosis (7,8). Nevertheless, some nonepileptic symptoms can be present in a patient who also has epilepsy, and unusual repetitive movements can be misdiagnosed as seizures when the actual seizures have been controlled by medication. Prensky (7) classified such symptoms as unusual movements, loss of tone or consciousness, respiratory derangements, perceptual disturbances, behavior disorders, and episodic behaviors related to disease states (Table 41.1).

Table 41.1 Common Symptoms of Nonepileptiform Paroxysmal Disorders

- Unusual movement
  - Jitteriness, tremor
  - Masturbation
  - Shuddering
    - Benign sleep myoclonus
  - Startle responses
    - Paroxysmal torticollis
  - Self-stimulation
    - Head banging (rhythmic movement disorder)
    - Tics (Tourette syndrome)
    - Paroxysmal dyskinesia
  - Pseudoseizures
  - Eye movement
  - Head nodding
  - Paroxysmal tonic upgaze
- Loss of tone or consciousness
  - Syncope
  - Drop attacks
  - Narcolepsy/cataplexy
  - Attention deficit
  - Acute hemiplegia
- Respiratory derangements
  - Apnea
  - Breath holding
  - Hyperventilation
- Perceptual disturbances
  - Dizziness
  - Vertigo
  - Headache
  - Abdominal pain
- Episodic features of specific disorders
  - Ataxia
  - Tetralogy spells
  - Hydrocephalic spells
  - Cardiac arrhythmias
  - Hypoglycemia
  - Hypocalcemia
  - Periodic paralysis
  - Hyperthyroidism
  - Gastroesophageal reflux
  - Rumination
  - Drug poisoning
  - Cerebrovascular events
- Behavior disorders
  - Night terrors
  - Sleepwalking
  - Nightmares
  - Rage
  - Confusion
  - Fear
- Acute psychotic symptoms
  - Fugue
  - Phobia
  - Panic attacks
  - Hallucinations
  - Autism
- Munchausen syndrome by proxy

The following overview of nonepileptic paroxysmal disorders is organized by age, type, and time of occurrence. Psychogenic nonepileptic seizures are discussed in Chapter 40.

INFANCY

Sleep

During infancy, at least two paroxysmal behaviors may be confused with seizures: repetitive episodes of head banging while the infant is falling asleep and benign neonatal myoclonus usually occurring during sleep.

Head Banging (Rhythmic Movement Disorder)

Rhythmic movement disorders, such as repetitive motion of the head, trunk, or extremities, usually occur as a parasomnia during the transition from wakefulness to sleep or from sustained sleep (9). Head banging can last from 15 to 30 minutes as the infant drifts off to sleep and, unlike similar daytime activity, is usually not related to emotional disturbance, frustration, or anger. No abnormal electroencephalographic (EEG) findings are noted. These benign movements usually disappear within 1 year of onset, typically by the second or third year of life, without treatment (7,9).

Benign Neonatal Myoclonus

Rapid and forceful myoclonic movements may involve one extremity or many parts of the body. Occurring during sleep in early infancy, these bilateral, asynchronous, and asymmetric movements usually migrate from one muscle group to another. Unlike seizures, their rhythmic jerking is not prolonged, although clusters of these movements may occur episodically during all stages of sleep. Attacks are usually only a few minutes long but may last up to hours. Myoclonus is not stimulus sensitive, and EEG shows no epileptiform activity. The movements stop as the infant is awakened and should never be seen in a fully awake and alert state. No treatment is required, but clonazepam or other benzodiazepines have been suggested in children who demonstrate a large amount of benign myoclonic activity. The movements typically disappear over several months (10).

Wakefulness

Jitteriness

Neonates and young infants demonstrate this rapid generalized tremulousness, which in neonates may be severe enough to be mistaken for clonic seizures. The infants are alert, and the movements may be decreased by passive flexion or repositioning of the extremities. Although jitteriness may occur spontaneously, it is typically provoked or increased by stimulation. Because neonatal jitteriness may be caused by certain pathologic states, jittery newborns are more likely than normal infants to experience seizures, and their EEG tracings may show abnormalities. Central nervous system dysfunction is the suspected etiology, but hypoxic–ischemic insults, metabolic encephalopathies such as hypoglycemia and hypocalcemia, drug intoxication or withdrawal, and intracranial hemorrhage may play a role and should be ruled out, if symptoms persist. The more benign forms of jitteriness usually decrease without specific therapy. Prognosis depends on the etiology and in neonates with severe, prolonged jitteriness may be guarded. Nevertheless, in 38 full-term infants who were jittery after 6 weeks of age, the movements resolved at a mean age of 7.2 months; 92% had normal findings

on neurodevelopmental examinations at age 3 years (11). Sedative agents may be used, but their adverse effects usually increase the irritability (11,12).

Head Banging or Rolling and Body Rocking

Head banging, head rolling, and body rocking often occur in awake infants (7). In older infants, head banging may be part of a temper tantrum. Head rolling and body rocking seemingly are pleasurable forms of self-stimulation and may be related to infantile masturbation. If the infants are touched or their attention is diverted, the repetitive movements cease. They are more common in irritable, excessively active, cognitively challenged infants (7). Nevertheless, most of this activity decreases during the second year. Particularly, bothersome movements may be diminished by behavior modification techniques, but drug treatment usually is unnecessary.

Infantile Gratification Behavior (Infantile Masturbation)

Gratification behavior or infantile masturbation is a form of self-stimulation in infancy (13,14). Infantile masturbation is part of the normal sexual human development. It may mimic abdominal pain, seizures, or dyskinesias. Although infantile masturbation has been typically described in infant girls, it is also present in boys, but due to cultural reasons, episodes in boys may not be brought to the attention of health professionals.

The typical description of the events includes sitting with the legs held tightly together or straddle the bars of the crib or playpen or other toys and rock back and forth. Distracting stimuli usually stop these movements, but some children become irritable when interrupted. Events typically disappear over the period of several months. Masturbation in older children is less likely to be confused with seizure activity. In some cognitively impaired children with autism, self-stimulation can also be associated with a fugue state. Because these children are difficult to arouse during the activity, seizures are commonly suspected (15). Once the diagnosis is made, parents may be taken aback by the terminology due to social stigma associated with the term masturbation. We therefore offer gratification behavior as an alternative diagnostic term that may be accepted more easily by families.

Benign Myoclonus of Early Infancy

These myoclonic movements occur in children during wakefulness state and may resemble infantile spasms but are not associated with EEG abnormalities. Infants are usually healthy, with no evidence of neurologic deterioration. The myoclonic episodes abate without treatment after a few months (16).

Spasmodic Torticollis

Spasmodic torticollis is a disorder characterized by sudden, repetitive episodes of head tilting or turning to one side with rotation of the face to the opposite side. The episodes may last from minutes to days. During episodes, children are irritable and uncomfortable but alert and responsive. Although movements may present in a recurrent and episodic pattern, EEG findings remain normal. Nystagmus is not associated with this disorder. The etiology is unknown, although dystonia and labyrinthine imbalance have been proposed. A family history of torticollis or migraine may be present. Similar tonic or head, neck, and body rotary movements may also be seen with gastroesophageal reflux (Sandifer syndrome), but these usually last longer than spasmodic torticollis (17–20).

The differential diagnosis includes congenital, inflammatory, and neoplastic conditions of the posterior fossa, cervical cord, spine, and neck. During these conditions, the episodes of torticollis are sustained and lack the usual on-and-off variability. An evaluation is necessary, but spasmodic torticollis usually subsides without treatment during the first few years of life.

Spasmus Nutans

Head nodding, head tilt, and nystagmus comprise spasmus nutans. Head nodding or intermittent nystagmus (or both) is usually noted at 4 to 12 months of age. Interestingly, nystagmus may be more prominent in one eye. The symptoms can vary depending on position, direction of gaze, and time of day. The children are clinically alert, and although symptoms may fluctuate throughout the day, episodic alterations in level of consciousness do not occur. Spasmus nutans usually remits spontaneously within 1 or 2 years after onset but may last as long as 8 years. Minor EEG abnormalities may be noted, but classic epileptiform discharges are not associated. Because mass lesions of the optic chiasm or third ventricle have been noted in a small proportion of these infants, computed tomography or magnetic resonance imaging studies are usually recommended. It is difficult to distinguish eye movements persisting into later childhood or adulthood from congenital nystagmus (21–23).

Opsoclonus

Opsoclonus is a rare abnormality characterized by rapid, conjugate, multidirectional, oscillating eye movements that are usually continuous but may vary in intensity. Because of this variation and occasionally associated myoclonic movements, generalized or partial seizures may be suspected. The children remain responsive and alert. Opsoclonus usually implies a neurologic disorder such as ataxia myoclonus or myoclonus. Children who develop these signs early in life may have a paraneoplastic syndrome caused by an underlying neuroblastoma (24–26). The triad of opsoclonus, myoclonus, and encephalopathy is termed Kinsbourne encephalopathy (dancing eyes, dancing feet) and responds to removal of the neural crest tumor or treatment with corticosteroids or corticotropin (27). Other forms of episodic ataxia in association with nystagmus may be seen in later infancy and childhood, but rarely true opsoclonus (8).

Rumination

Rumination attacks involve hyperextension of the neck, repetitive swallowing, and protrusion of the tongue. Episodes are thought to be related to abnormal esophageal peristalsis and typically follow or accompany feeding. The child is alert but sometimes seems distressed and uncomfortable. Variable feeding techniques are helpful in this disorder, which resolves as the child matures (28).

Startle Disease or Hyperekplexia

Hyperekplexia together with stimulus-induced disorders and neuropsychiatric startle syndrome are part of the startle syndromes (Table 41.2) (29). Hyperekplexia is a rare familial disorder with autosomal dominant or autosomal recessive inheritance, but some cases are sporadic (29,30). At least five genes have been described in the context of hyperekplexia to date, and over 80% have been linked to mutations of the alpha subunit of the glycine receptor (GLRA1). Other genes include GLRB,

SLC6A5, GPHN, and ARHGEF9, while frequently no mutation can be found (30).

Table 41.2 Differential Diagnosis of Three Groups of Startle Syndromes

Hyperekplexia	Stimulus-induced disorders	Neuropsychiatric disorders
Neonatal stiffness, startle, and stiffness with startle	Nonepileptic	Startle-induced tics
Excessive startling	Without rigidity	Culture-specific syndrome
Cerebral	Paroxysmal kinesigenic dyskinesias	Latah
Cerebral palsy	Episodic ataxia	Jumping Frenchmen of Maine
Postanoxic encephalopathy	Cataplexia (narcolepsy)	Myriachit
Occlusion of posterior thalamic arteries	Reflex myoclonus	Functional startle syndromes
Posttraumatic	With rigidity	Anxiety disorder
Paraneoplastic	Stiff person syndrome	Posttraumatic stress syndrome
Multiple sclerosis and lateral sclerosis	Progressive encephalomyelitis with rigidity	
Cerebral abscess with encephalitis	Strychnine poisoning	
Brainstem	Tetanus	
Brainstem infarction	Epileptic	
Brainstem hemorrhage	Reflex epilepsy	
Brainstem encephalopathy	Progressive myoclonic epilepsy	
Pontocerebellar hypoplasia	Pyridoxine-dependent epilepsy	
Posterior fossa malformation		
Medulla compression		
Multiple system atrophy		

Modified from Bakker MJ, van Dijk JG, van den Maadenberg AM, et al. Startle syndromes. Lancet Neurol. 2006;5:513–524.

In the past, any type of exaggerated startle response was labeled hyperekplexia. It has now become clear that many of these cases may simply represent an augmented normal startle reflex (31), and we therefore reserve the term hyperekplexia for patients presenting with the three main clinical symptoms of generalized stiffness (hypertonia), excessive startle beginning at birth and a short period of generalized stiffness following the startle reflex (32). Hyperekplexia may lead to falls. Clinically, the infant becomes stiff when handled, and episodes of severe hypertonia may also present with apnea and bradycardia. At times, forced flexion of the neck or hips may interrupt episodes. Also noted, along with transient hypertonia, are falling attacks without loss of consciousness, ataxia, generalized hyperreflexia, episodic shaking of the limbs resembling clonus, and excessive startle. While the interictal electroencephalogram is normal, a spike may be associated with a startle attack. Whether this discharge represents an evoked response to the stimulus or an artifact is a subject of debate. The disorder must be distinguished from so-called startle epilepsy, in which a startle is followed by a partial or generalized seizure, which suggests a defect in inhibitory regulation of brainstem centers (33,34). The prognosis in hyperekplexia is variable (31). Seizures do not develop after this benign disorder. However, clonazepam and valproic acid have been used to treat associated startles, stiffness, jerking, and falling (35,36).

Shuddering Attacks

Shuddering attacks far exceed the normal shivering frequently seen in older infants and children. A very rapid tremor involves the head, arms, trunk, and even the legs; the upper extremities are adducted and flexed at the elbows or, less often, adducted and extended. The episodes may begin as early as 4 months of age and decrease gradually in frequency and intensity before age 10 years. Treatment with antiepileptic drugs does not modify the attacks. Except for movement artifact, results of electroencephalography are normal. While earlier reports linked shuddering attacks with early

manifestations of essential tremor (37,38), findings could not be confirmed in a more recent series (39).

Alternating Hemiplegia

Alternating hemiplegia of childhood may be confused with epilepsy because of the paroxysmal episodes of weakness, hypertonicity, or dystonia. Presenting as tonic or dystonic events, these intermittent attacks may alternate from side to side and at times progress to quadriplegia. They usually occur at least monthly and may be part of a larger neurologic syndrome in children with delayed or retarded development who also have seizures, ataxia, and choreoathetosis. Attacks begin before 18 months of age and can be precipitated by emotional factors or fatigue. The hemiplegic episodes may last minutes or hours, and recent genetic studies linked the clinical presentation with the ATP1A3 gene, which encodes a Na^+,K^+-ATPase, an ion pump responsible for maintaining sodium and potassium electrochemical gradients across the plasma membrane (40). Although anticonvulsants and typical migraine treatments are unsuccessful, flunarizine, a calcium channel blocker (5 mg/kg/day), has been reported to reduce recurrences (41,42).

Paroxysmal Tonic Upgaze

Age of onset of paroxysmal tonic upgaze is within the first year of life, with the earliest cases described at age 2 weeks, but some cases are detected during the preschool years. Episodes are described as upward, and tonic deviation of the eyes as a single symptoms or eye movement can be associated with altered movement coordination or ataxia. Events are typically brief but occasionally can last up to 30 minutes. The frequency of the events ranges from rare episodes to daily leading to consider the diagnosis of epileptic seizures. There is a predilection for boys. Neurologic assessment may be normal or may reveal hypotonia and developmental delays. Prognosis is benign with complete improvement of the symptoms before age 2 years in most cases (43).

Respiratory Derangements and Syncope

Primary breathing disorders usually occur without associated epilepsy. At times, however, respiratory symptoms may be confused with epilepsy, or, rarely, tonic stiffening, clonic jerks, or seizures may follow primary apnea (44). An electroencephalogram or polysomnogram recorded during the event may easily distinguish a respiratory abnormality associated with true seizures from one completely independent of epilepsy.

Infant Apnea or Apparent Life-Threatening Events

Apnea usually occurs during sleep and may be associated with centrally mediated hypoventilation, airway obstruction, aspiration, or congenital hypoventilation. Formerly called (near) sudden infant death syndrome, these symptoms have now been termed apparent life-threatening events. During central apnea, chest and abdominal movements decrease simultaneously with a drop in airflow. During obstructive apnea, movements of the chest or abdomen (or both) continue, but there is diminished air flow. Central apnea presumably results from a disturbance of the respiratory centers, whereas obstructive apnea is related to a peripheral blockage of airflow. Some infants may also have a mixed form of the disorder. A few jerks may occur with the apneic episodes but do not represent

epileptic myoclonus. The apnea that follows a seizure is a form of central apnea with postictal hypoventilation. Primary apnea, however, is only rarely followed by seizures (45,46).

The etiology and characteristics of apneic episodes vary among infants. Apnea of prematurity responds to treatment with xanthine derivatives. In older infants with primary central apnea, elevated cerebrospinal fluid levels of β-endorphin have been reported, and treatment with the opioid antagonist naltrexone has been successful (47). The role of home cardiopulmonary monitors is controversial. Parents should be encouraged to follow the recommendations of the American Academy of Pediatrics that healthy term infants be put to sleep on their back or side to decrease the risk of apnea and possible sudden infant death syndrome (48).

Although apnea occurs less often when the child is fully awake, it may be associated with gastroesophageal reflux (49,50). Aspiration may follow. Reflux is frequently accompanied by staring, flailing movements of the extremities or posturing of the trunk, possibly in response to the pain of acidic contents washing back into the esophagus. Gastroesophageal reflux is more common when infants are laid supine after feeding. Diagnosis is established by radiologic demonstration of reflux or by abnormal esophageal pH levels. Reflux is treated by upright positioning of the baby during and after feeding (51), thickened feedings, and the use of agents to alter sphincter tone and, in infants who do not respond to medical treatment, very rarely, Nissen fundoplication.

Cyanotic Breath-Holding Spells

Although common between the ages of 6 months and 6 years, cyanotic infant syncope (breath-holding spells) is frequently confused with tonic seizures (52). Typically precipitated by fear, frustration, or minor injury, the spells involve vigorous crying, following which the child stops breathing, often in expiration. Cyanosis occurs within several seconds, followed by loss of consciousness, limpness, and falling. Prolonged hypoxia may cause tonic stiffening or brief clonic jerking of the body. After 1 or 2 minutes of unresponsiveness, consciousness returns quickly, although the infant may be briefly tired or irritable. The crucial diagnostic point is the history of an external event, however minor, precipitating the episode. The electroencephalogram does not show interictal epileptiform discharges but may reveal slowing or suppression during the anoxic event. The pathophysiologic mechanism is not well understood, but correction of any underlying anemia may reduce the attacks (53). Children with pallid breath-holding spells have autonomic dysregulation caused by parasympathetic disturbance distinct from that found in cyanotic breath-holding (54). Although the episodes appear unpleasant for the child, they do not result in neurologic damage. Antiepileptic medication may be appropriate for the rare patients with frequent postsyncopal generalized tonic–clonic seizures triggered by the anoxia.

Pallid Syncope

Precipitated by injury or fright, sometimes trivial, pallid infant syncope occurs in response to transient cardiac asystole in infants with a hypersensitive cardioinhibitory reflex. Minimal crying, perhaps only a gasp, and no obvious apnea precede loss of consciousness. The child collapses limply and subsequently may have posturing or clonic movements before regaining consciousness after a few minutes (52,55–57). The asystolic episodes may be reproduced by ocular compression, but this procedure is risky and of uncertain clinical utility as it may lead to iatrogenic prolonged asystole and cardiac arrest. As with cyanotic breath-holding spells, the key to diagnosis is the association with precipitating events.

The long-term prognosis is benign. Most children require no treatment, although atropine has been recommended for frequent pallid attacks or those followed by generalized tonic–clonic seizures (58). A trial of the anticholinergic drug atropine sulfate 0.01 mg/kg every 24 hours in divided doses (maximum 0.4 mg/day) may increase heart rate by blocking vagal input. Atropine should not be prescribed during very hot weather because hyperpyrexia may occur.

CHILDREN

Sleep

Myoclonus

Nocturnal myoclonic movements, called "sleep starts" or "hypnic jerks" and associated with a sensation of falling, are less common in older children and adolescents than in infants (10). The subtle involuntary jerks of the extremities or the entire body occur while the child is falling asleep or being aroused. Repetitive rhythmic jerking is uncommon, although several series of jerks can occur during the night. The jerks are not associated with epileptiform activity, but a sensory-evoked response or evidence of arousal may be present on the electroencephalogram (59–62).

Periodic repetitive movements that resemble myoclonus are seen in deeper stages of sleep and may arouse the patient so that daytime drowsiness is noted. These movements are more common in rapid eye movement (REM) than in non–rapid eye movement (NREM) sleep and are clearly distinguished from epilepsy on sleep polysomnographic recordings. In very severe cases, a treatment trial with benzodiazepine may be helpful.

Hypnagogic Paroxysmal Dystonia

In hypnagogic paroxysmal dystonia, an extremely rare disorder, sleep may be briefly interrupted by seemingly severe dystonic movements of the limbs lasting a few minutes. Episodes are sometimes accompanied by prolonged vocalization. No EEG abnormality is noted. Carbamazepine may decrease the attacks. It is not clear whether some or all patients with this clinical syndrome actually have seizures arising from the supplementary motor area (60,63).

Nightmares

Nightmares occur during REM sleep and are rarely confused with seizures. Although children may be restless during the dream, they usually do not scream out, sit up, or have the marked motor symptoms, autonomic activity, and extreme sorrow seen with night terrors. Incontinence may be present, however. Remembrance of the content of nightmares may lead to a fear of sleeping alone. An electroencephalogram recorded during these events shows no abnormalities (7).

Night Terrors (Pavor Nocturnus)

Night terrors, most common in children between the ages of 5 and 12 years, begin from 30 minutes to several hours after sleep onset, usually during NREM slow-wave sleep or sleep stage N3 according to the American Academy of Sleep Medicine terminology. Diaphoretic and with dilated pupils, the

children sit up in bed, crying or screaming inconsolably for several minutes before calming down. Sleep resumes after the attack, and children do not recall the event. No treatment is recommended (64,65).

Sleepwalking

Approximately 15% of all children experience at least one episode of sleepwalking or somnambulism, which usually occurs 1 to 3 hours after sleep onset (NREM slow-wave sleep or sleep stage N3). The etiology is unknown, but a familial prevalence is noted. Mumbling and sleeptalking, the child walks about in a trance and returns to bed. Semipurposeful activity such as dressing, opening doors, eating, and touching objects during an episode of somnambulism may be confused with automatisms of complex partial seizures. The eyes are open, and the child rarely walks into objects. Amnesia follows, and no violence occurs during the event. Treatment is usually not required, except for protecting the wandering child from injuries during the night. Benzodiazepine therapy may be helpful in frequent or prolonged attacks (3,66,67).

Wakefulness

Myoclonus

In many normal, awake children, anxiety or exercise may cause an occasional isolated myoclonic jerk. Treatment is rarely necessary.

Multifocal myoclonus may occur in patients with progressive degenerative diseases or during an acute encephalopathy. It may be difficult to distinguish these movements from chorea, and these two disorders may coexist in some encephalopathic illnesses. Myoclonus persists in sleep, whereas chorea usually disappears during sleep (7).

Chorea

Usually seen as rapid jerks of the distal portions of the extremities, choreiform movements may affect muscles of the face, tongue, and proximal portions of the extremities. When associated with athetosis, chorea involves slower, more writhing movements of distal portions of the extremities. The jerks may be so fluid or continuous that they are camouflaged. Acute chorea may accompany metabolic disorders but is more likely in patients recovering from illnesses such as encephalitis. Other causes are Sydenham chorea seen in the setting of β-hemolytic streptococcal infection, drug ingestion, and mass lesions or stroke involving the basal ganglia. Treatment depends primarily on the etiology, but movements may respond to haloperidol or a benzodiazepine such as clonazepam (68,69).

Tics

Like chorea, most tics are present during wakefulness and disappear with sleep. They usually involve one or more muscle groups, are stereotyped and repetitive, and appear suddenly and intermittently. Movements may be simple or complex, rhythmic, or irregular. Facial twitches, head shaking, eye blinking, sniffling, throat clearing, and shoulder shrugging are typical, although more complex facial distortions, arm swaying, and jumping have been noted. These purposeless movements cannot be completely controlled, but they may be inhibited voluntarily for brief periods and are frequently

exacerbated by stress or startle (70–72).

In Tourette syndrome, complex vocal and motor tics are frequently associated with learning disabilities, hyperactivity, attention deficits, and compulsive behaviors. The incidence of simple and complex tics is high in relatives of these patients. The disorder varies in severity but tends to be lifelong, although it may stabilize or improve slightly in adolescence or early adulthood. Combinations of behavior therapy and medical treatment of tics and compulsive behavior are indicated. Haloperidol, pimozide, and clonidine have been used successfully for behavior control. Stimulants such as methylphenidate may initially exacerbate tics (70–72).

Paroxysmal Dyskinesias

Paroxysmal dyskinesias are rare disorders characterized by repetitive episodes of relatively severe dystonia or choreoathetosis (or both). Multiple brief attacks occur daily, precipitated by startle, stress, movement, or arousal from sleep (73). Consciousness is preserved, but discomfort is evident. Both sporadic and familial types have been described. Kinesigenic dyskinesia frequently is associated with the onset of movement as well as with prior hypoxic injury, hypoglycemia, and thyrotoxicosis. Alcohol, caffeine, excitement, stress, and fatigue may exacerbate attacks of paroxysmal dystonic choreoathetosis, a familial form of the disorder. Although the electroencephalogram displays normal findings during the episodes, the paroxysmal dystonic form responds to antiepileptic drugs such as carbamazepine (73–76).

Stereotypic Movements

Other repetitive movements have been mistaken for seizures, especially in neurologically impaired children. Stereotypy is seen in individuals with autism, sensory disabilities, intellectual disabilities, or developmental disabilities (77–79).

Donat and Wright (80) noted head shaking and nodding, lateral and vertical nystagmus, staring, tongue thrusting, chewing movements, periodic hyperventilation, tonic posturing, tics, and excessive startle reactions in these patients, many of whom had been treated unnecessarily for epilepsy.

A behavior is defined as stereotypy when "involves repetition, rigidity and invariance, as well as a tendency to be inappropriate in nature" (81). The stereotypical behaviors may be verbal or nonverbal and involve fine or gross motor movements or simple and complex movements. Behaviors can occur with and without objects (77). Some stereotypies can involve self injurious behavior (78). Other common example of stereotypies include hand flapping, body rocking, toe walking, spinning objects, sniffing, immediate and delayed echolalia, and running objects across one's peripheral vision (77). Self-stimulatory behaviors such as rhythmic hand shaking, body rocking, and head swaying, performed during apparent unawareness of surroundings, also are common in cognitively impaired children with specific neurologic diagnoses. Rett syndrome should be suspected when repetitive "hand-washing" movements are noted in retarded girls (70). Deaf or blind children frequently resort to self-stimulation such as hitting their ears or poking at their eyes or ears, which has been misidentified as epilepsy. Behavior training is frequently more successful than medication in controlling these movements (80).

Head Nodding

Head nodding or head drops may be of epileptic or nonepileptic origin. A study by Brunquell et al.

(82) showed that epileptic head drops were associated with ictal changes in facial expression and subtle myoclonic extremity movements. Rapid drops followed by slow recovery indicated seizures. When the recovery and drop phases were of similar velocity or when repetitive head bobbing occurred, nonepileptic conditions were much more common.

Staring Spells

When ordinary daydreaming or inattentive periods are repetitive and children do not respond to tactile or auditory stimulation being called, the behaviors may be classified as absence (petit mal) seizures. During innocent daydreaming, posture is maintained and automatisms do not occur. Staring spells are usually nonepileptic in normal children with normal EEG findings, when parents report preserved responsiveness to touch, body rocking, or identification without limb twitches, upward eye movements, interrupted play, or urinary incontinence (83). Children with attention deficit hyperactivity disorder sometimes have staring spells that resemble absence or complex partial seizures. Although unresponsive to verbal stimuli, these children generally become alert immediately on being touched and frequently recall what was said during the staring spell. During these spells, the electroencephalogram pattern is normal. Attention deficit hyperactivity disorder affects 3% to 10% of children and has a male predominance. Stimulants are most widely used, but other medications may be necessary to ameliorate behavior in refractory cases. Antiepileptic drugs are usually ineffective (60,84–87).

Headaches

Recurrent headaches are rarely the sole manifestation of seizures. However, postictal headaches are not uncommon, especially following a generalized convulsion. Headaches may also precede seizures. As an isolated ictal symptom, headache occurs most frequently in children with complex partial seizures (88). Children with ictal headaches experience sudden diffuse pain, often have a history of cerebral injury, derive no relief from sleep, and lack a family history of migraine. Distinguishing headache from paroxysmal recurrent migraine may be difficult in young children when the headache's throbbing unilateral nature is absent or not readily apparent. Migraine, however, is more prevalent than epilepsy. In addition, ictal electroencephalograms during migraine usually show slowing, whereas those during epilepsy demonstrate a clear paroxysmal change. Associated gastrointestinal disturbance and a strong family history of migraine help establish the appropriate diagnosis (88–94).

Epilepsy and migraine can coexist. Children with migraine have a 3% to 7% incidence of epilepsy, and as many as 20% exhibit epileptiform discharges on interictal electroencephalograms (91). Up to 60% of children with migraine obtain significant relief with antiepileptic medication (93,94). Other variants of migraine that may be confused with seizures include cyclic vomiting (abdominal pain), acute confusional states, and benign paroxysmal vertigo.

Recurrent Abdominal Pain

Recurrent abdominal pain may be associated with vomiting, pallor, or even fever and has been noted in migraine and epilepsy. Usually, these complaints indicate neither diagnosis, although some children with recurrent abdominal pain or vomiting may experience migraine later in life (7,95). About 7% to 76% of children with recurrent abdominal pain exhibit interictal paroxysmal EEG changes. Approximately 15% of these patients have a diagnosis of seizures, and more than 40% have

recurrent headaches (7). A family history of migraine is found in approximately 20% (94). Although most of these children do not respond to antiepileptic drugs, approximately 20% obtain relief from antimigraine medications such as β-blockers or tricyclic antidepressants (7,91,95).

Confusional Migraine

Migraine may present in an unusual and sometimes bizarre fashion as confusion, hyperactivity, partial or total amnesia, disorientation, impaired responsiveness, lethargy, and vomiting (96). These episodes must be distinguished from toxic or metabolic encephalopathy, encephalitis, acute psychosis, head trauma, and sepsis as well as from an ictal or postictal confusional state. Confusional migraine usually persists for several hours, less commonly for days, and spontaneously clears following sleep. The diagnosis is usually made following the episode when the patient or family reports severe headache or visual symptoms heralding the onset of the event or a history of similar events. During and soon after the episodes, an electroencephalogram may demonstrate regional slowing, a nondiagnostic finding.

Benign Paroxysmal Vertigo

Benign paroxysmal vertigo consists of brief recurrent episodes of disequilibrium of variable duration that may be misinterpreted as seizures. Lasting from minutes to hours, the attacks of vertigo occur as often as two to three times per week but rarely as infrequently as every 2 to 3 months. Tinnitus, hearing loss, and brainstem signs have been implicated as causes, but the onset is sudden, and the child is usually unable to walk. Extreme distress and nausea are noted, but the patient remains alert and responsive during attacks. Nystagmus or torticollis is frequently observed. Between attacks, examination and electroencephalography reveal normal results. A minority of children show dysfunction on vestibular testing but show no abnormalities on audiograms. A family history of migraine is common, and most of these children experience migraines later in life. No treatment is indicated because the attacks do not respond well to either antiepileptic or antimigraine medications. Benign paroxysmal vertigo usually subsides by ages 6 to 8 years (60,97,98).

Stool-Withholding Activity and Constipation

Children may have sudden interruption of activity and assume a motionless posture with slight truncal flexion and leg stiffening when experiencing discomfort from withholding stool (99). The withholding behavior, which may be mistaken for absence or tonic seizures, evolves as a way to prevent the painful passage of stool that is large and hard because of chronic constipation. At times, stool withholding occurs in the setting of a painful anal fissure. Small jerks of the limbs may be misperceived as myoclonus, and the child may have fecal incontinence. The behavior resolves with treatment of the chronic constipation.

Rage Attacks

The episodic dyscontrol syndrome, or recurrent attacks of rage following minimal provocation, may be seen in children with or without epilepsy. The behavior often seems completely out of character. Rage may be more common in hyperactive children or those with conduct and personality disorders. Similar dyscontrol and near rage have been seen following head injury with frontal or temporal lobe

lesions. Ictal rage is rare, unprovoked, and usually not directed toward an individual. Following attacks of rage and the appearance of near psychosis, the child resumes a normal state, may recall the episode, and feel remorseful. Behavior frequently can be modified during the event. Depending on the cause of the associated syndrome, β-blockers (100), stimulant drugs, and carbamazepine along with other antiepileptic drugs have been used to control outbursts (101).

Munchausen Syndrome by Proxy

Munchausen syndrome, or factitious disorder, describes a consistent simulation of illness leading to unnecessary investigations and treatments. When a parent or caregiver pursues such a deception using a child, the situation is called Munchausen syndrome by proxy. Infants may be brought to child neurologists with parental reports suggesting apnea, seizures, or cyanosis; older children may be described to have episodes of loss of consciousness, convulsions, ataxia, headache, hyperactivity, chorea, weakness, gait difficulties, or paralysis. Accompanying symptoms may include gastrointestinal disorders or a history of unusual accidents and injuries that are poorly explained and almost never observed by anyone but the parent(s) (Table 41.3). Sometimes the child also becomes persuaded of the reality of the "illness" and develops independent factitious symptoms such as psychogenic seizures.

Table 41.3 Clinical Features of Munchausen Syndrome by Proxy

Persistent and recurrent unexplained illness
Clinical signs at variance with the child's health status
Unusual or remarkable signs or symptoms
Signs and symptoms not recurring in the parent's absence
Mother or caregiver overattentive or refuses to leave the hospital
Mother or caregiver not appropriately concerned about prognosis
Lack of anticipated response of clinical syndrome
"Rare" clinical syndrome

The perpetrator is often the mother, who appears initially to be a model parent but has a pathologic need for the child to be sick (102–104). Usually young, articulate, and middle class, she has an unnatural attachment to her child, coexisting personality disorder, and somatizing behavior. The mother often has some medical training, for example, as a nurse. Families are usually dysfunctional. The parents' exaggerated and constant need for illness and medical intervention may lead to the child's death.

Treatment is similar to that of child abuse and typically involves a pediatrician, child psychiatrist, nurse, and social workers. The child is separated from the parents, and details of the history are corroborated. Medical and neurologic evaluations rule out specific disease processes. Admission of a child with paroxysmal symptoms to a video monitoring unit may help to demonstrate this behavior in both mother and child (105).

Future serious psychological disturbances are a significant possibility. Good relationships with the nonabusive father or other parent, successful short-term foster parenting before return to the mother or long-term placement with the same foster parents, long-term treatment or successful remarriage of the mother, and early adoption are associated with more favorable outcome for the

child (106).

LATE CHILDHOOD, ADOLESCENCE, AND ADULTHOOD

Wakefulness

Syncope

Syncope is common in adolescents or older children and usually can be distinguished from seizures by description. Warning signs of lightheadedness, dizziness, and visual dimming ("graying out" or "browning out," "like a curtain coming down") occur in most patients. Nausea is common before or after the event, and a feeling of heat or cold and profuse sweating are frequent accompaniments. A particular stimulus such as the sight of blood with vasovagal syncope, minor trauma, or being in a warm, crowded place often elicits the attack. Orthostatic syncope may follow prolonged standing or sudden change in posture. The family history may disclose similar events (107). Reflex syncope may be seen with coughing, swallowing, or micturition (108). Table 41.4 lists frequent causes of syncope. A few clonic jerks or incontinence occurring late in syncope complicate the picture, but a full history usually elucidates the cause (92). Physical examination frequently yields normal results, although supine and standing blood pressure measurements may implicate or rule out an orthostatic cause. There may be examination evidence of a drop in blood pressure (usually >20/10 mm Hg) within 3 minutes of standing, associated with syncope or presyncope. Sinus bradycardia on rapid standing is also highly suggestive of orthostatic hypotension. A search for arrhythmia and murmur is warranted, as cardiac causes of syncope are primarily obstructive lesions or arrhythmias not otherwise clinically evident (108,109). Syncope associated with ophthalmoplegia, retinitis pigmentosa, deafness, ataxia, or seeming myopathy mandates an urgent evaluation for heart block (Kearns–Sayre syndrome) (110).

Table 41.4 Causes of Syncope

Vasovagal	Fear
	Pain
	Unpleasant sights
Reflex	Cough
	Micturition
	Swallowing
	Carotid sinus pressure
Decreased venous return	Orthostatic
	Soldier syncope (standing at attention)
	With the Valsalva maneuver
Decreased blood volume	
No clear precipitating event	
Cardiac	Arrhythmia
	Obstructive outflow
Cerebrovascular insufficiency	
Familial	
Undetermined cause	

Electrocardiographic monitoring and echocardiography are frequently more valuable than electroencephalography in establishing the diagnosis. Tilt table testing may be helpful in this regard (111,112).

Narcolepsy and Cataplexy

Narcolepsy is a state of excessive daytime drowsiness causing rapid brief sleep, sometimes during conversation or play; the patient usually awakens refreshed. Narcolepsy also includes sleep paralysis (transient episodes of inability to move on awakening) and brief hallucinations on arousal along with cataplexy, although not all patients demonstrate the complete syndrome. Measurement of sleep latency through electroencephalogram recordings reveals the appearance of REM sleep within 10 minutes in narcoleptic patients. Narcolepsy may be treated with a stimulant drug (113–115).

Cataplexy produces a sudden loss of tone with a drop to the ground in response to an unexpected touch or emotional stimulus such as laughter. Consciousness is not lost during these brief attacks. Coexistent narcolepsy is common.

Basilar Migraine

Most common in adolescent girls, basilar migraine begins with a sudden loss of consciousness followed by severe occipital or vertex headache. Dizziness, vertigo, bilateral visual loss, and, less often, diplopia, dysarthria, and bilateral paresthesias, may occur. A history of headache or a family history of migraine is helpful in making the diagnosis. Of note, interictal paroxysmal EEG discharges may be seen in this population. Children may respond to classic migraine therapy or antiepileptic drugs (105,106,116,117). Due to vasoconstriction, ergot alkaloids and triptans are generally not recommended (89).

Tremor

An involuntary movement characterized by rhythmic oscillations of a particular part of the body, tremor, may appear at rest or with only certain movements. Consequently, it is occasionally mistaken for seizure activity, particularly when the movement is severe and proximal such as in the “wing-beating tremor” of Wilson disease or related basal ganglia disorders. Tremors disappear during sleep. Examination at rest and during activities, possibly by manipulating the affected body part while observing the tremor, usually can define the movement by varying or obliterating the tremor. The electroencephalogram is unchanged as the tremor escalates and diminishes (118).

Panic Disorders

Panic attacks may occur as acute events associated with a chronic anxiety disorder or in patients suffering from depression or schizophrenia. These attacks last for minutes to hours and are accompanied by palpitations, sweating, dizziness or vertigo, and feelings of unreality. The following symptoms also have been noted: dyspnea or smothering sensations, unsteadiness or faintness, palpitations or tachycardia, trembling or shaking, choking, nausea or abdominal distress, depersonalization or derealization, numbness or tingling, flushes or chills, chest pain or discomfort,

and fears of dying, aura, or losing control. An electroencephalogram recorded at the time of the attacks differentiates ictal fear and nonepileptic panic attacks (119).

Panic disorders involve spontaneous panic attacks and may be associated with agoraphobia. Although they may begin in adolescence, the average age at onset is in the late 20s. Psychiatric therapy is indicated (120).

Acute fugue, phobias, hallucinations, and autistic behaviors may seem to represent seizures; however, associated features and EEG findings usually distinguish these behavioral disorders from epilepsy.

DISEASE-RELATED BEHAVIORS

Several disease states include recurrent symptoms that are misdiagnosed as epilepsy. Episodes of cyanosis, dyspnea, and unconsciousness followed by a convulsion may occur in as many as 10% to 20% of children with congenital heart disease, particularly those with significant hypoxemia. In "tet" spells, young children with tetralogy of Fallot squat nearly motionless during exercise as their cardiac reserve recovers (121).

Children and adults with shunted hydrocephalus may have seizures, although these are not usual (122). Obstruction associated with the third ventricle or aqueduct may cause the bobble-head doll syndrome (two to four head oscillations per second) in mentally retarded children (123). In hydrocephalic patients treated with ventricular shunting, acute decompensation may increase seizure frequency or give rise to symptoms misdiagnosed as seizures. So-called hydrocephalic attacks, characterized by tonic, opisthotonic postures frequently associated with a generalized tremor, are caused by increased intracranial pressure and herniation. Head tilt or dystonia may also indicate increased intracranial pressure, a posterior fossa mass, or a Chiari malformation. Urgent evaluation for malfunctioning shunt or increased intracranial pressure is warranted with any of these symptoms.

The episodic nature of periodic paralysis may lead to misidentification of the symptoms as epilepsy. Familial and sporadic cases typically are associated with disorders of sodium and potassium metabolism. Acetazolamide is useful in some forms of the disorder (124).

Cerebrovascular disorders of various types and etiologies may have transient recurrent symptoms and thus may be confused with epilepsy. The exact clinical presentation of cerebrovascular disorders in both children and adults depends primarily on the size and location of the brain lesion and on the etiology of the vascular compromise (125,126). Transient ischemic attacks, episodes of ischemic neurologic deficits lasting <24 hours, are typically caused by small emboli or local hemodynamic factors that temporarily prevent adequate brain perfusion. Symptoms begin suddenly following an embolus, with the deficit reaching maximum severity almost immediately. Function returns several minutes or hours after the onset of symptoms. Symptomatology is characteristically separated into carotid artery syndromes with symptoms of middle cerebral artery, anterior cerebral, and lacunar deficits. The latter are most common in adults with long-standing hypertension and may be characterized by pure motor hemiparesis or monoparesis and isolated hemianesthesia. Vertebrobasilar syndromes, especially transient ischemic attacks, may be mistaken for epilepsy because of recurrence and duration and may present with ataxia, dysarthria, nausea, vomiting, vertigo, and even coma. Homonymous hemianopsia may result from posterior cerebral artery occlusion. The subclavian steal syndrome is associated with stenosis or occlusion of the subclavian artery proximal to the origin of the vertebral artery. Retrograde flow through the vertebral artery into the poststenotic subclavian artery may occur. Vertigo, ataxia, syncope, and visual disturbance occur intermittently

when blood is diverted into the distal subclavian artery. Vigorous exercise of the arms tends to produce symptoms. The brachial and radial pulses in the affected extremity are absent or diminished.

The etiology of cerebral embolism includes cardiopulmonary disorders, traumatic injuries to blood vessels like dissection, and congenital or inflammatory arterial disorders. Besides blood products, air emboli, foreign body embolism with pellets, needles, or talcum, or fat emboli may be noted. In adults, carotid and vertebrobasilar occlusion with or without embolization is typically associated with systemic cerebrovascular disease. In younger black patients, sickle cell disease always must be considered as an etiology of cerebrovascular symptoms. It is sometimes difficult to distinguish between transient ischemic attacks and brief seizures in these patients who have multiple areas of infarction. Because strokes may occur on the basis of both large- and small-vessel abnormalities associated with sickle cell disease, symptoms may vary.

Transient global amnesia deserves special mention as a symptom that may or may not be related to epilepsy. Multiple authors argue that it is either of vascular origin or related to seizures. Recurrent attacks may occur in up to 25% of cases. Attacks, however, last hours rather than minutes, and the most frequently observed EEG changes are small sharp spikes of questionable significance (127).

CONCLUSIONS

A variety of paroxysmal events may be confused with epilepsy. A careful medical history with description of events before, during, and after the spell; age of onset; time of occurrence; and clinical course aided by a thorough physical examination frequently clarify the nature of these episodes. Home video recordings of the episodes may be extremely helpful. The routine or specialized use of electroencephalography or polysomnography provides further characterization. Dual diagnoses are possible. Abnormal findings on neurologic examination are not uncommon in patients with nonepileptic events. Previously noted interictal EEG abnormalities should be reviewed to modify the interpretation of false-positive records (128).

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PART IV ANTIEPILEPTIC MEDICATIONS

SECTION A GENERAL PRINCIPLES OF ANTIEPILEPTIC DRUG THERAPY

CHAPTER 42 ANTIEPILEPTIC DRUG DEVELOPMENT AND EXPERIMENTAL MODELS

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ANIMAL MODELS FOR ANTIEPILEPTIC DRUG DISCOVERY

All of the currently available antiepileptic drugs (AEDs) approved for the treatment of epilepsy have been identified and developed as a result of their ability to block seizures in one or more of the available rodent seizure and epilepsy models. Since 1993, over a dozen new AEDs have been made available for patients with epilepsy. These new drugs have provided increased seizure control, appear to be better tolerated, and display fewer drug–drug interactions. Unfortunately, seizures remain uncontrolled in a substantial percentage of the patient population, and thus there continues to be a significant unmet need for the patient with refractory epilepsy. As such, efforts continue in the hope that more efficacious and safer AEDs will be identified for this population.

At the present time, a new drug for the symptomatic treatment of epilepsy, regardless of mechanism, must always demonstrate some degree of efficacy in one or more animal seizure models before it proceeds down the drug development pathway and is ultimately validated in well-controlled double-blinded randomized clinical trials. Typically, a compound will be evaluated for its ability to block convulsive seizures in models of generalized and focal seizures. This approach provides the necessary proof of concept to support the further development of a new chemical entity. However, as there remains a large population of patients who are refractory to current AEDs, new animal models of epilepsy and screening approaches are being applied in the early identification and characterization of potential AEDs. Previous reviews discuss the advantages and limitations of the various strategies in greater detail (1–3). This chapter briefly reviews the approach that is often employed in the early identification and characterization of the antiseizure profile of an investigational drug, followed by a discussion of efforts to develop new models of refractory and acquired epilepsy in the drug screening process.

In Vivo Testing

It is important to note that no single laboratory test will establish the presence or absence of anticonvulsant activity or fully predict the clinical utility of an investigational AED. Nonetheless, the animal models that have been developed and utilized since phenytoin (PHT) was first identified using the maximal electroshock (MES) seizure model (4), do possess varying degrees of face validity. Historically, the successful identification of PHT using the cat MES test by Merritt and Putnam (4) and its subsequent acceptance as an effective drug for the management of human generalized seizures

with tonic components provided the validation required to consider the MES test as a useful model of human generalized seizures with tonic–clonic components. In addition to the MES test, the subcutaneous pentylenetetrazol (sc PTZ) test, and the various forms of kindling represent two other important in vivo model systems that have played a key role over the last 40 years in the early identification and characterization of AEDs that may be useful for the treatment of generalized and focal seizures (1,5,6).

ASSESSING ADVERSE EFFECTS IN ANIMALS

For the patient with refractory epilepsy, the clinical utility of currently available AEDs is limited in a large part by a lack of efficacy at doses that do not produce dose-limiting side effects. With respect to assessing central nervous system–related adverse effects, preclinical testing includes behavioral observations, activity measurements, and models evaluating the potential impact of an AED on overt motor function. Among the latter models, the rotarod test is commonly used to quantify a therapeutic index (TI) (7). The extent to which an AED impairs the ability of an animal to remain on a rotating rod is determined at various doses. A TI can then be quantified by comparing the median toxic (TD_{50}) dose of an AED that impairs performance on the rotarod against the median effective (ED_{50}) antiseizure dose in the same species.

The validity of using normal animals in an attempt to predict adverse effects in epilepsy patients has been brought into question ever since Loscher and Honack (8) demonstrated that N-methyl-D-aspartate (NMDA) antagonists produced more ataxia, hyperactivity, and stereotypic behaviors in amygdala-kindled rats than they did in normal rats. This finding was subsequently confirmed in humans when the potential antiepileptic properties of the competitive NMDA antagonist D-CPPene was tested (9). D-CPPene was well tolerated in healthy volunteers in doses up to 2000 mg/day; whereas doses of 500 to 1000 mg/day induced severe adverse effects such as confusion, hallucination, ataxia, impaired concentration, and sedation when used as add-on therapy in eight patients with refractory complex partial epilepsy. Interestingly, similar doses of D-CPPene in healthy volunteers and epilepsy patients produced higher exposure levels in the healthy volunteers versus epilepsy patients. These results suggest that pharmacodynamic factors were responsible for the severe adverse effects observed in patients with epilepsy. The enhanced susceptibility of fully amygdala-kindled rats to the behavioral adverse effects of NMDA antagonists has also been observed with several AEDs (10). Thus, this phenomenon appears to represent a permanent reactivity specific for limbic kindling because it has not been observed after chemical kindling (11). Collectively, these findings suggest that the neuronal substrate is altered in the epileptic brain in such a way that it leads to a worsened adverse effect profile of AEDs. These findings underlie the importance of using fully limbic kindled animals (or animals with spontaneous seizures) for assessing the adverse effects of an AED. However, a highly promising AED should not necessarily be discarded because of adverse effects observed in an animal model. This information should be used to guide decisions regarding the advancement of one analog over another when testing a series of structurally related molecules.

In addition to the screening for overt motor impairments that can be used to calculate TI, a novel compound should also be assessed on the basis of off-target liabilities on behavioral and cognitive performance. Historically, many AEDs have been associated with significant adverse cognitive effects (2,3). There is now a concerted effort to develop novel treatments that can not only bring symptomatic seizure relief but also do so without conferring adverse cognitive effects either from or exacerbated by the investigational drug itself (2,12). Moreover, efforts to develop therapies that can

concurrently address the comorbidities of epilepsy are also under way. Comorbidities of epilepsy can include cognitive impairment, depression, suicidality, anxiety, attention deficits, and migraine; all of which can often be as detrimental to quality of life as the seizures themselves. In fact, comorbidities of epilepsy are one of the National Institutes of Health (NIH) Benchmark areas for research in epilepsy. Thus, drug screening and testing efforts to develop new treatments for epilepsy must also address developing treatments for comorbidities associated with epilepsy (12), and not just those that arise as side effects from AEDs. Fortunately for the epilepsy research community, many of the animal models currently available for drug screening and testing also present with behavioral and cognitive abnormalities, such as the post–status epilepticus models of temporal lobe epilepsy discussed below (13). The mouse model of Dravet syndrome also presents with autistic-like behaviors and cognitive deficits that can be rescued with low-dose treatment with clonazepam (14). Thus, future efforts in drug screening and testing should attempt to not only understand the effects of a novel compound on the seizure severity and presentation but also examine the potential for a compound to affect comorbidities present in the animal model under scrutiny (12–14). Such efforts may likely prove fruitful in the improvement of patient drug adherence, quality of life, and seizure control should an investigational compound ultimately progress to clinical use.

STRATEGIES FOR ANTIEPILEPTIC DRUG DISCOVERY

Three different approaches are routinely employed in the identification of new AEDs. These include (i) random screening of new chemical entities for anticonvulsant activity; (ii) structural modifications of existing AEDs; and (iii) rational, target-based drug discovery. Over the decades, each of these approaches has contributed to the discovery of new AEDs. Regardless of the approach by which a new drug is synthesized, the first proof-of-concept study almost always involves testing it in one or more of the animal models described above; for example, the MES, sc PTZ and/or kindling model. With the exception of levetiracetam, all of the currently available AEDs (and those currently in development) have been found to possess activity in one or more of these models. A further evaluation found levetiracetam to possess anticonvulsant properties in the amygdala-kindled rat and to display a marked and persistent ability to inhibit kindling acquisition (15–17). Levetiracetam was also found to be active in a variety of genetic animal models of epilepsy, for example, epilepsy-like mice (18), the audiogenic seizure–susceptible rat, and the Genetic Absence Epileptic Rat of Strasbourg (GAERS), a highly useful model of spike–wave seizures (19). Levetiracetam was also shown to be active in the mouse 6-Hz seizure model (20).

The ultimate development of LEV illustrates the limitations of relying solely upon the use of acute seizures evoked by MES and sc PTZ in normal animals as a valid screening procedure to identify drugs for a disease that is characterized by a chronic network hypersynchrony and spontaneous seizures. It is becoming clear that these "traditional models," such as the MES and sc PTZ tests, may only be able to identify drugs that share characteristics with other, currently available AEDs, thereby likely not providing much improvement in treating the refractory patient population (21). Thus, to usher in a new era of drug discovery, it is important to use a battery of models during random screening of new chemical entities that include animal models with (i) an acquired epilepsy, kindling-induced hyperexcitability, or alteration in seizure threshold; (ii) induced or natural mutations associated with an altered seizure threshold or spontaneous seizure expression; and (iii) new models

of pharmacoresistant epilepsy to address the needs of the therapy-resistant patient population (22). This does not imply that the acute seizure models are of little value. Fortunately for the patient with epilepsy, these models have yielded several drugs that have proven to be effective for the treatment of their seizures.

MODELS OF PHARMACORESISTANCE

The models summarized in Table 42.1 have been used successfully to identify effective therapies for human epilepsy. Clinical experience has demonstrated that they are effective for a large fraction of the patients with focal and generalized seizures. Unfortunately, as mentioned above, there still remains a substantial need for the identification of therapies for the patient with refractory seizures. To this point, one might argue that the acute models summarized in Table 42.1 are not predictive of efficacy in those patients with refractory epilepsy. Thus, identification and characterization of one or more model systems that could predict efficacy in the pharmacoresistant patient is an area of active pursuit by the epilepsy research community (2).

Table 42.1 Correlation Between Anticonvulsant Efficacy and Clinical Utility of Antiepileptic Drugs in Experimental Animal Models

Experimental model	Generalized seizures with tonic and/or clonic components	Myoclonic/ generalized absence seizures	Generalized absence seizures	Focal seizures
MES (tonic extension) (1)	CBZ, PHT, VPA, PB (FBM, GBP, LCM, LTG, PGB, RUF, TPM, ZNS) (EZG, PRL)			
Sc PTZ (clonic seizures) (1)		ESM, VPA, PB[a], BZD (FBM, GBP, PGB, RUF, TGB[a], VGB[a]) (EZG, PRL)		
Spike–wave discharges[b]			ESM, VPA, BZD (LTG, TPM, LVT)	
Electrical kindling (focal seizures)				CBZ, PHT, VPA, PB, BZD (FBM, GBP, LCM, LTG, TPM, TGB, ZNS, LVT, VGB) (EZG, PRL)
PHT-resistant kindled rat (24,25)				(LVT, GBP, TPM, FBM, LTG)
LTG-resistant kindled rat (24–26)				VPA (EZG)
6 Hz (44 mA) (20)				VPA (LVT)

BZD, benzodiazepines; CBZ, carbamazepine; ESM, ethosuximide; EZG, ezogabine; FBM, felbamate; GBP, gabapentin; LTG, lamotrigine; LVT, levetiracetam; PB, phenobarbital; PHT, phenytoin; LCM, lacosamide; PGB, pregabalin; PRL, perampanel; RUF, rufinamide; TGB, tiagabine; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide; VGB, vigabatrin.

[a]PB, TGB, and VGB block clonic seizures induced by sc PTZ but are inactive against generalized absence seizures and may exacerbate spike–wave seizures.

[b]Data summarized from GBL, GAERS, and lh/lh spike–wave models (16).

[ ], second-generation AED; ( ), third-generation AED.

At the present time, there are a number of potentially interesting model systems of therapy

resistance available. Models of "pharmacoresistant" epilepsy should meet certain criteria; that is, "pharmacoresistance" can be defined as persistent seizure activity that does not respond to monotherapy at tolerable doses with at least two currently available AEDs (3). Ideally, it can be hoped that any proposed model will lead to the identification of a new therapy that will ultimately be highly effective in humans resistant to existing AEDs. In recent years, a number of in vivo model systems have been characterized that display a phenotype consistent with pharmacoresistant epilepsy and are the subject of the discussion below. These models include the PHT-resistant kindled rat (23,24), the LTG-resistant kindled rat (25–28), the 6-Hz psychomotor seizure model of partial epilepsy (20), and models of temporal lobe epilepsy (29). All of these models have some utility when attempting to differentiate an investigational drug's antiseizure profile from existing AEDs. Moreover, more emphasis may be placed on the value of these models for screening in the future. At the present time, many investigational AEDs are routinely evaluated in the LTG-resistant kindled rat and 6-Hz mouse model (3,25,26). Because it is not known whether efficacy in any of these models will yield a drug candidate that proves to be highly effective in the patient with refractory epilepsy, a continued effort should be made to employ as many novel models as possible in the evaluation of an investigational AED.

The Lamotrigine-Resistant Kindled Rat Model

Kindling is a well-established experimental model of focal seizures with generalized components. Over the years, Loscher et al. have conducted extensive pharmacologic evaluations in the kindled rat model. They were among the first to demonstrate that AEDs were less effective against the fully expressed kindled seizure than were MES-induced generalized tonic extension seizures (23,30,31). Moreover, Loscher (23) developed the PHT-resistant model, which demonstrated that pharmacoresistant kindled rats could be effectively applied to screening novel compounds. In addition to the PHT-resistant model, the LTG-resistant kindled rat model of partial epilepsy is now available and routinely used to screen investigational compounds (29). Perhaps most important when considering the application of the LTG-resistant kindled rat model to drug screening is the observation that LTG-resistant rats are also refractory to CBZ and PHT, but not VPA or the KCNQ2 ($Kv_{7.2}$) activator EZG (25–27). In this regard, the LTG-resistant kindled rat can serve as an early model of drug-resistant epilepsy to differentiate novel AEDs from PHT, LTG, and CBZ.

The Low-Frequency (6 Hz) Electroshock Seizure Model

In many respects, the 6-Hz seizure model offers many of the same advantages of the MES test. Like the MES test, the 6-Hz seizure can be acutely evoked using standard corneal electroshock. Moreover, it is a high-throughput model and requires minimal technical expertise. The main difference between the 6-Hz and MES tests is the frequency (6 Hz vs. 50 Hz) and duration (3 seconds vs. 0.2 seconds) of the stimulation employed. The low-frequency, long-duration stimulus results in a seizure that is characterized by immobility, forelimb clonus, Straub tail, and facial automatisms and is thought to more closely model human focal seizures (20,32). The finding that LEV was found to be active at a specific stimulus intensity where other AEDs display little to no efficacy illustrates the use of the 6-Hz model as a screen for novel compounds, particularly when one considers that LEV was inactive in the acute seizure models such as the MES and sc PTZ seizure tests (7). Thus, the incorporation of a simple acute screen that would minimize the chances of "missing" a unique drug like LEV is an

important consideration when setting up a testing protocol to evaluate investigational AEDs.

Models of Temporal Lobe Epilepsy

Models of refractory mesial temporal lobe epilepsy (mTLE) are now important tools in the differentiation of investigational AEDs. A concerted effort has been made by the epilepsy research community to develop models of therapy-resistant epilepsy to identify potential treatments for the approximately 30% of patients refractory to currently available AEDs. As such, several new mTLE models are in development; any of which have the potential to provide significant clinical benefit (13,30,33). These chronic epilepsy models differ significantly from the more traditional animal models in that seizures are spontaneously evolving and not evoked. Moreover, these models fulfill an important characteristic of the ideal model system; that is, they display spontaneous recurrent seizures (13,30). For example, the post–status epilepticus rat model of mTLE, provides an investigator with the opportunity to evaluate the efficacy of a given treatment on seizure frequency, seizure type (i.e., focal or generalized), and the liability for tolerance development following chronic treatment. Unfortunately, drug trials in animal mTLE models take on another level of complexity. The trials are extremely laborious and time-consuming and require a greater level of technical expertise. As such, there have only been a few pharmacologic studies conducted to date (34–38). Having said this, the advantages of mTLE models in the ability to differentiate a given compound from the established AEDs is well worth the investment. Furthermore, acute brain sections collected from mTLE models also present with spontaneous recurrent epileptiform discharges that show varying degrees of responsiveness to drug treatment (39,40); thereby expanding the screening and testing capabilities of these epilepsy models. All of these models are being used with increasing frequency in the search for novel AEDs. Unfortunately, none of these models have been validated clinically and thus, it is too early to say whether any of them will lead to the identification of a next-generation AED. Importantly, the use of these models has led to the development of novel drug-testing protocols in animals that more closely resemble clinical protocols (30).

NEW APPROACHES TO ANTIEPILEPTIC DRUG DISCOVERY

While established models and models of pharmacoresistance will continue to provide invaluable information in the screening and identification of novel treatments for epilepsy, a substantial need remains to develop new and unique models of epilepsy that can facilitate efforts to identify the next generation of clinical treatments. With the exception of the mTLE models described above, many of the available acute seizure models are models of epileptic seizures rather than models of epilepsy. Thus, efforts to add models to the drug screening and testing repertoire should also attempt to identify models that more closely mimic the human epilepsy phenotype, rather than the seizures alone. Emerging evidence on the contributing factors underlying epileptogenesis as well as improved genetic approaches for drug screening and testing may ultimately provide previously drug-refractory patients with a palliative, if not curative, treatment.

Models of Acquired Epilepsy

Models of infection-induced or posttraumatic epilepsy are beginning to emerge as potentially useful

differentiation tools in the identification of new treatments for refractory epilepsy. Evidence suggests that inflammatory processes are up-regulated and may, in fact, be a contributing factor to epileptogenesis (41). Proinflammatory cytokines are highly expressed in various animal seizure models (38,41), and patients with epilepsy (42). Of note, human patients with viral infection–induced encephalitis who present with seizures during the acute infection period are up to 22 times more likely to develop spontaneous, unprovoked seizures than the general population (43). Therefore identifying and developing models that specifically target the pathogenic infection–induced inflammatory events contributing to epileptogenesis may ultimately prove to be useful in AED screening and testing. Additionally, identifying compounds to selectively target inflammation may be useful in posttraumatic (PTE) models of acquired epilepsies (44), as epilepsy associated with traumatic brain injury in humans is often drug refractory (45). It is also reasonable to believe that models of inflammation and acquired epilepsy will identify compounds with novel, and as yet unexplored, mechanisms of action that may prove effective in the refractory human epilepsy patient. Unfortunately, models of infection-induced seizures (s.f. (46)) and PTE models (s.f. (44)) remain largely underutilized in the early identification and characterization of investigational AEDs; moreover, much work is required to fully characterize the effects of currently available AEDs in these models. Needless to say, the availability of data from these and other emerging models with available AEDs will likely prove productive in the treatment of drug-refractory epilepsy patients.

Novel Genetic Screening Tools

Advances in our understanding at the molecular and genetic level have led to the development of vertebrate models with known genetic defects that resemble the human condition. Their availability to the general scientific community has provided greater insight into the role of various molecular targets in ictogenesis and epileptogenesis. Detailed pharmacologic characterization with existing AEDs is now possible using genetic models, such as the Scn1a+/- mouse model of Dravet syndrome (14). More recently, Baraban et al. (47,48) have pioneered drug screening and testing in the zebrafish (Danio rerio) as a potential high throughput system for identifying anticonvulsants using both chemoconvulsants and genetic mutations to model human epilepsies. The zebrafish model of Dravet syndrome (Scn1a mutants), for example, is responsive to stiripentol and valproate (47), both of which are used in the clinical treatment of Dravet's syndrome patients (49). Thus, high-throughput screening in this and other genetic, zebrafish models could provide an effective means to rapidly and cost-effectively identify potential investigational compounds for one or more of the genetic epilepsies (47), which could then be moved to more in-depth assessment in available mammalian models. Furthermore, these and other mutant animal models represent important tools for evaluating the therapeutic potential of an investigational drug in a model system that more closely approximates human genetic epilepsy. Mechanism- and target-specific drug discovery efforts in these genetic models may also likely prove useful in selectively targeting the causal pathways of human genetic epilepsies (2). To this point, genetic models will likely play an important role in efforts to develop personalized medicines for those patients with a known genetic mutation.

CONCLUSION

Currently, there are no known preventive treatments available and the treatment of epilepsy is purely symptomatic. The identification and characterization of an investigational AED relies entirely on the

use of a variety of animal seizure and epilepsy models. Those drugs that were discovered with this approach that displayed a favorable therapeutic window and showed no significant preclinical toxicity were advanced into clinical add-on epilepsy trials with patients with refractory partial seizures. Since 1993, many new therapies have been brought to the market for the treatment of epilepsy. Despite the success of this approach, as many as one in three patients with focal seizures still remain refractory to available AEDs. It is clear that there is a need to move beyond the conventional animal models and to explore other animal models and molecular targets by which neuronal hyperexcitability may be reduced. Levetiracetam demonstrated that a new therapy does not have to be effective in the traditional seizure models to be effective in the patient with epilepsy. Moreover, there is no a priori reason to believe that the truly novel AED that will demonstrate a substantial impact in the treatment of the patient with refractory epilepsy will have an anticonvulsant profile that resembles any of the available therapies, including levetiracetam. This implies that the scientist interested in developing a drug for this patient population will need to take a substantial risk when advancing a novel drug into a clinical trial. Only then will we likely find a therapy that provides the level of efficacy for which patients continue to hope.

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CHAPTER 43 MECHANISMS OF ACTION OF ANTIEPILEPTIC DRUGS

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Antiepileptic drugs (AEDs) protect against seizures through interactions with a variety of cellular targets. By affecting the functional activity of these targets, AEDs suppress abnormal hypersynchronous activity in brain circuits, leading to protection against seizures. The actions on these targets can be categorized into four broad groups: (i) modulation of voltage-gated ion channels, including sodium, calcium, and potassium channels; (ii) enhancement of GABA inhibition through effects on $GABA_A$ receptors, the GAT-1 GABA transporter, or GABA transaminase; (iii) direct modulation of synaptic release through effects on components of the release machinery, including SV2A and α2δ; and (iv) inhibition of synaptic excitation mediated by ionotropic glutamate receptors, including AMPA receptors (Table 43.1). The ultimate effects of these interactions are to modify the bursting properties of neurons and to reduce synchronization in localized neuronal ensembles. In addition, AEDs inhibit the spread of abnormal firing to distant sites. Some seizures, including typical generalized absence seizures, result from thalamocortical synchronization. AEDs effective in these seizure types interfere with the rhythm-generating mechanisms that underlie synchronized activity in the thalamocortical circuit. In this chapter, we consider each of the targets and discuss how AEDs affect the activity of these targets.

Table 43.1 Molecular Targets of Clinically Used AEDs

Molecular target	AEDs that act on target
Voltage-gated ion channels	
Voltage-gated sodium channels	Phenytoin, fosphenytoin,[a] carbamazepine, oxcarbazepine,[b] eslicarbazepine acetate,[c] lamotrigine, and lacosamide; possibly, topiramate, zonisamide, and rufinamide
Voltage-gated calcium channels	Ethosuximide
Voltage-gated potassium channels	Ezogabine
GABA inhibition	
$GABA_A$ receptors	Phenobarbital, primidone, and benzodiazepines including diazepam, lorazepam, and clonazepam; possibly, topiramate and felbamate
GAT-1 GABA transporter	Tiagabine
GABA transaminase	Vigabatrin
Synaptic release machinery	
SV2A	Levetiracetam
α2δ	Gabapentin, gabapentin enacarbil,[d] and pregabalin
Ionotropic glutamate receptors	
AMPA receptor	Perampanel
Mixed/unknown	Valproate, felbamate, topiramate, zonisamide, rufinamide, and adrenocorticotropin

[a]Fosphenytoin is a prodrug for phenytoin.

[b]Oxcarbazepine serves largely as a prodrug for licarbazepine, mainly S-licarbazepine.

[c]Eslicarbazepine acetate is a prodrug for S-licarbazepine.

[d]Gabapentin enacarbil is a prodrug for gabapentin.

Many AED targets are ion channels, most notably voltage- gated sodium and potassium channels and $GABA_A$ receptors. It is interesting to note that certain idiopathic epilepsy syndromes are believed to be the result of mutations in these same ion channels (see Chapter 4).

VOLTAGE-GATED ION CHANNELS

Voltage-Gated Sodium Channels

Voltage-gated sodium channels play an essential role in the initiation and propagation of action potentials in neurons. Neuronal depolarizations by a few millivolts, ordinarily as a result of synaptic activation of glutamate receptors (mainly AMPA receptors), activate sodium channels, causing opening of the channels and influx of sodium. The channels then inactivate within milliseconds. Influx of sodium ions during the brief time that sodium channels are open generates the depolarizing component of the action potential. Although the bulk of sodium channels inactivate, about 1% of the sodium current is noninactivating resulting in a small persistent sodium current (I_{NaP}), which is carried by the same channels as the fast transient current. I_{NaP} facilitates epileptic burst firing by reducing the threshold for action potential generation, sustaining repetitive firing, and enhancing depolarizing synaptic currents (1). Some AEDs, most notably phenytoin, inhibit I_{NaP}, which is believed to contribute to their efficacy (2).

Voltage-gated sodium channels are multimeric protein complexes, composed of a large α subunit that forms four subunit-like homologous domains (designated I to IV) and one or more smaller β subunits (3). The ion-conducting pore is contained within the α subunit, as are the elements of the channel that mediate its fundamental physiologic properties including rapid inactivation. There are nine voltage-gated sodium channels, designated $Na_v1.1$ to $Na_v1.9$. $Na_v1.2$ is the predominant form in brain neurons, but $Na_v1.1$ and $Na_v1.6$ are also expressed in the brain. Mutations in each of these channels have been associated with various genetic epilepsies (4).

AEDs that protect against seizures through an interaction with voltage-gated sodium channels are commonly referred to as “sodium channel blockers.” They are among the most frequently used drugs in the treatment of focal and primary generalized tonic–clonic seizures and include phenytoin, carbamazepine, lamotrigine, oxcarbazepine (as well as its active metabolite licarbazepine), and lacosamide. AEDs that interact with voltage-gated sodium channels exhibit a characteristic “use-dependent” blocking action so that they inhibit high-frequency trains of action potentials much more potently than they inhibit individual action potentials or firing at low frequencies. Because they also exhibit a “voltage dependence” to their blocking action, sodium channel–blocking AEDs are more potent at inhibiting action potentials that ride on a depolarized plateau potential as characteristically occurs in seizures. Thus, sodium channel–blocking AEDs preferentially inhibit seizure discharges in relation to normal ongoing neural activity. By virtue of their ability to inhibit the action potential invasion of nerve terminals, sodium channel–blocking AEDs inhibit the release of diverse

neurotransmitters including glutamate; whether this is responsible for the therapeutic activity of the drugs is uncertain (5).

The binding site on sodium channels for sodium channel–blocking AEDs is believed to overlap the binding site of local anesthetics, which is within the pore of the channel and is formed by the S6 segments of domains I, II, and IV. Sodium channel–blocking AEDs bind with higher affinity to this site when the channel is in the inactivated state, and, when such a drug is bound, the channel is stabilized in the inactivated state. When neurons are depolarized and firing rapidly, sodium channels spend a greater amount time in the inactivated state and are able to accumulate bound drug so that they become trapped in the inactivated state. This accounts for the use- and voltage-dependent blocking action that they exhibit. Phenytoin, carbamazepine, and lamotrigine are considered "classical" sodium channel–blocking AEDs. Lacosamide also is believed to exert its therapeutic effects by interacting with sodium channels (6). Unlike other sodium channel–blocking AEDs, lacosamide does not inhibit high-frequency repetitive spike firing on the time scale of 100s of milliseconds. It does, however, inhibit spike firing in long trains of spikes on the time scale of 1 to 2 seconds. It has been proposed that the very slow action of lacosamide is due to an enhancement of a distinct and poorly understood form of inactivation, referred to as "slow inactivation." However, an alternative explanation is that lacosamide binds more slowly to fast inactivated sodium channels than do the other sodium channel–blocking AEDs. In any case, the unusually slow development of block produced by lacosamide during high-frequency activity could allow lacosamide to better discriminate between seizure-like pathologic firing and normal network activity.

T-Type Voltage-Gated Calcium Channels

Low voltage-activated (T-type) calcium channels play a role in the intrinsic thalamocortical oscillations that underlie the spike-and-wave discharges of generalized absence seizures (7–9). There are three T-type Ca^{2+} channel isoforms encoded by separate genes, denoted as $Ca_v3.1$ (α1G), $Ca_v3.2$ (α1H), and $Ca_v3.3$ (α1I). All three T-type calcium channel isoforms are expressed in thalamocortical circuits (10). $Ca_v3.1$ is prominently expressed in thalamic relay neurons in the dorsal thalamus, which plays a key role in absence seizures; $Ca_v3.2$ and to a lesser extent $Ca_v3.3$ are prominently expressed in thalamic reticular neurons. All three T-type calcium channel isoforms are expressed in the cortex, with $Ca_v3.2$ mainly localized to layer V. In non-REM sleep, including during delta waves, sleep spindles, and K complexes, the thalamocortical circuit switches from a tonic to oscillatory mode of firing, but in absence epilepsy, this switching can occur inappropriately, even during wakefulness (11,12). T-type calcium channels in the thalamus and cortex contribute to the abnormal behavior of the circuit. These channels generate low-threshold spikes, leading to burst firing and oscillatory behavior (13). GABA-ergic neurons of the thalamic reticular nucleus are also critically involved in absence seizures as they hyperpolarize thalamic relay neurons, which deinactivate T-type calcium channels allowing the channels to generate burst firing and the propagation of spike-and-wave discharges in the thalamocortical circuit (14).

Ethosuximide, which is highly efficacious in the treatment of absence seizures but not other seizure types, seems to act by inhibition of T-type calcium channels in the thalamocortical circuit (15–17). At clinically relevant concentrations (20 to 40 μg/mL), some but not all investigators have observed a partial (20% to 30%) reduction of T-type calcium current by ethosuximide. However, studies with recombinant T-type calcium channels have confirmed that ethosuximide blocks all three

channel types (18). The block increases when the current is activated from more depolarized potentials and when T-type calcium channels are inactivated as especially occurs during high-frequency activation, so that the drug has selectivity for pathologic behavior in the thalamocortical circuit, which is associated with neuronal depolarization and inactivation of T-type calcium channels. Effects on other membrane currents, including I_{NaP} and calcium-activated potassium current, may contribute to the efficacy of ethosuximide in absence epilepsy (17). Remarkably, results in animal models indicate that early treatment with ethosuximide can have disease-modifying (antiepileptogenic) effects, causing a persistent reduction in seizures and mitigation of behavioral comorbidities (19,20). These actions may be caused by epigenetic modifications. A study showing that children with absence epilepsy who receive ethosuximide are more likely than those who receive valproic acid to achieve long-term remission is consistent with the disease-modifying actions observed in animal studies (21).

The efficacy of some other AEDs may also depend, at least in part, on actions at T-type calcium channels. Zonisamide, in addition to effects on voltage-activated sodium channels, may also block T-type calcium channels (11), thus accounting for its likely efficacy in absence epilepsy (22). Similarly, there is evidence that valproate, a drug of choice in absence epilepsy, may also inhibit T-type calcium channels (17).

K_V7 Voltage-Gated Potassium Channels

Voltage-gated potassium channels are a diverse and evolutionarily ancient group of ion channels that serve a variety of key functions in the nervous system. Opening of potassium channels drives the membrane potential toward a hyperpolarized level, which serves to repolarize depolarizing events (such as action potentials and synaptic potentials) and cause a generalized reduction in excitability. In 1998, the first genes for a human idiopathic epilepsy were identified (23). These genes, designated KCNQ2 and KCNQ3, encoded novel brain potassium channel subunits, $K_v7.2$ and $K_v7.3$, respectively, that are homologous to a previously identified cardiac potassium channel $K_v7.1$, encoded by KCNQ1 (LQT1). The novel brain potassium channels mediate the M-current, a potassium current that increases as the membrane potential in neurons approach action potential threshold. K_v7 channels, together with HCN (hyperpolarization-activated cyclic nucleotide-gated potassium channels) and KCa2/SK (small-conductance calcium-activated potassium channels), generate the medium after hyperpolarization, which is elicited by a burst of action potentials and serves to limit further firing (24). K_v7 potassium channels therefore contribute to spike- frequency adaptation and can be considered to serve as a "brake" on epileptic firing. The K_v7 family of potassium channels is now known to contain five members, including $K_v7.1$, which is expressed predominantly in the heart, and $K_v7.2$ to $K_v7.5$, which are expressed exclusively in the nervous system (25).

Ezogabine, which is efficacious in the treatment of partial seizures, acts as a positive modulator of the nervous system K_v7 potassium channels ($K_v7.2$ to $K_v7.5$) but does not affect the cardiac member of the family ($K_v7.1$). Of particular relevance to the antiseizure action of ezogabine is its action on the M-current, which is predominantly carried by channels composed of $K_v7.2$ and $K_v7.3$, although $K_v7.5$ alone or in combination with $K_v7.3$ also contributes (26,27). Ezogabine causes a hyperpolarizing shift in the activation of K_v7 channels such that more M-current is generated near resting potential. It also causes a change in the kinetics of single KCNQ channels to favor channel

opening, thus increasing the macroscopic M-current; ezogabine does not alter the single-channel conductance of individual K_v7 channels (28). Many K_v7 channels in the brain are believed to be $K_v7.2/K_v7.3$ heteromers, which are highly sensitive to ezogabine (EC_{50}, 1.6 μM) (27). Peak plasma levels of ezogabine range from 354 to 717 ng/mL (1.2 to 2.4 μM) (29), and plasma protein binding is 80% so that free plasma concentrations are estimated to be about 0.2 to 0.5 μM; brain concentrations are expected to be similar. Therefore, therapeutic concentrations likely only modestly potentiate the most sensitive K_v7 channels and do not affect less sensitive channels. The binding site for ezogabine in $K_v7.2/K_v7.3$ heteromers is in a pocket formed by the pore-lining S5 membrane segment of one subunit and the pore-lining S6 membrane segment of the neighboring subunit (30,31). Channel opening may expose the pocket, permitting binding of ezogabine, which stabilizes the open-channel conformation.

GABA INHIBITION

GABA, the neurotransmitter of local inhibitory interneurons, acts through $GABA_A$ receptors and $GABA_B$ receptors. $GABA_A$ receptors, which are Cys loop-type ligand-gated chloride channels, represent an important target for AEDs and will be considered here; $GABA_B$ receptors, which are heterodimeric G protein–coupled receptors that activate potassium channels and inhibit calcium channels, are distinct in structure and function from $GABA_A$ receptors and are not a target of any AED. Although only about one in five cortical neurons is GABA-ergic (32), these neurons play a critical role in controlling the firing rate and timing of principal (excitatory) neurons. In addition, they synchronize local neuronal ensembles and restrain the generation of abnormal epileptic behavior. Consequently, enhancement of GABA-ergic inhibition is a key mechanism of AED action.

$GABA_A$ Receptors

$GABA_A$ receptors are heteropentameric protein complexes localized to the postsynaptic membrane of inhibitory synapses where they mediate fast neuronal inhibition on a millisecond time scale. They are also located extrasynaptically where they respond to ambient GABA in the extracellular milieu and confer tonic (long-term) inhibition. There are 19 known $GABA_A$ receptor subunits (α1 to 6, β1 to 3, γ1 to 3, δ, ε, θ, π, and ρ1 to 3). However, the bulk (60%) of synaptic $GABA_A$ receptors are believed to have the α1β2γ2 configuration, and a considerable fraction of the remainder (15% to 20%) are α2β3γ2. Among the receptor subtypes that contribute to tonic signaling in the brain regions relevant to epilepsy are α4βxδ receptors, which are believed to mediate the tonic current in dentate granule cells and thalamocortical neurons, and α5-containing $GABA_A$ receptors in CA1 pyramidal cells (33).

Benzodiazepines, such a diazepam, lorazepam, and clonazepam, and barbiturates, such as phenobarbital, are AEDs that act on $GABA_A$ receptors as positive allosteric modulators. At higher concentration, barbiturates can directly activate $GABA_A$ receptors in the absence of GABA (34), whereas benzodiazepines cannot. Benzodiazepines are specific for synaptic $GABA_A$ receptors containing the γ2 subunit and act to allosterically modulate these receptors to increase the channel opening frequency resulting in enhanced synaptic inhibition. This confers a broad-spectrum anticonvulsant action. In most epilepsy syndromes, the specific cellular types that are involved in the

antiseizure activity of benzodiazepines are not known. However, in the case of absence epilepsy, it is believed that benzodiazepines desynchronize the thalamocortical oscillations underlying generalized spike-and-wave discharges by specific effects on α3-containing $GABA_A$ receptors in the thalamic reticular nucleus (35). Barbiturates, presumably because they are not specific for α3-containing $GABA_A$ receptors, are not active in absence epilepsy and may even aggravate absence seizures. In contrast to benzodiazepines, barbiturates do not appear to increase the frequency of GABA-induced chloride channel opening, but instead increase the channel open time. In addition to effects on $GABA_A$ receptors, barbiturates modulate other ion channel systems, including calcium and sodium channels, and these actions may contribute to therapeutic activity (36).

GAT-1 GABA Transporter

The action of neurotransmitter GABA is terminated by uptake into neurons and glial cell by membrane-bound GABA transporters, of which there are four types, termed GAT-1, BGT-1, GAT-2, and GAT-3. GAT-1 (encoded by the SLC6A1 gene), the predominant form in the forebrain (including the neocortex and hippocampus), is localized to GABA-ergic terminals as well as to glial processes near GABA synapses. Tiagabine is a highly selective inhibitor of GAT-1 in neurons and glia (37). Inhibition of GAT-1 by tiagabine suppresses the translocation of extracellular GABA into the intracellular compartment, thus raising extracellular GABA levels. Functionally, tiagabine prolongs GABA-mediated inhibitory synaptic responses, and the marked elevation in extracellular GABA it produces may lead to activation of extrasynaptic GABA receptors.

GABA Transaminase

4-Aminobutyrate aminotransferase (GABA transaminase), an enzyme that catalyzes the conversion of GABA and 2-oxoglutarate into succinic semialdehyde and glutamate, is responsible for the metabolic inactivation of GABA. Inhibition of GABA transaminase with vigabatrin (γ-vinyl GABA), an irreversible suicide inhibitor of the enzyme, leads to marked increases in brain GABA levels. Although the antiseizure action of vigabatrin is believed to reflect inactivation of GABA transaminase, how this occurs is not straightforward and does not appear to be due to an enhancement of inhibitory synaptic transmission. In contrast to the action of tiagabine, vigabatrin does not elicit larger or more prolonged $GABA_A$ receptor–mediated synaptic responses (38,39). Rather, preincubation of brain slices with vigabatrin irreversibly inhibited miniature and evoked inhibitory postsynaptic currents. Additional experiments suggested that the paradoxical effect resulted from a reduction in the GABA content of synaptic vesicles caused by GABA transaminase inhibition. In contrast to the effect on GABA-mediated synaptic transmission, vigabatrin caused an increase in nonsynaptic tonic $GABA_A$ receptor current. This steady current is believed to be mediated by the action of GABA in the extracellular milieu acting on extrasynaptic $GABA_A$ receptors. High levels of intracellular GABA cause a reversal of GABA transporters, resulting in a marked elevation in extracellular GABA, which is likely responsible for the increase in tonic $GABA_A$ receptor current. It can be concluded that vigabatrin causes divergent effects on synaptic and extrasynaptic GABA-mediated inhibition, with seizure protection resulting from a predominance of the extrasynaptic action. Interestingly, in the early period after administration of vigabatrin to animals, there is a reduction in seizure threshold, whereas the anticonvulsant actions become evident only later (40,41).

Thus, vigabatrin has a biphasic action with proconvulsant effects likely related to suppression of synaptic GABA-ergic neurotransmission and anticonvulsant effects due to spillover of GABA into the extracellular space and activation of extrasynaptic $GABA_A$ receptors. Interestingly, individuals with a rare genetic deficiency of GABA transaminase experience refractory seizures, supporting the view that inhibition of GABA transaminase is in fact the proconvulsant mechanism of vigabatrin (42).

SYNAPTIC RELEASE MACHINERY

SV2A

A variety of lines of evidence support the conclusion that SV2A, a membrane glycoprotein found in the secretory vesicles of neurons and endocrine cells and possibly immune cells, is the molecular target for levetiracetam (43,44). There is a strong correlation between the affinity of levetiracetam analogs for binding to SV2A and the potency of the analogs in several animal seizure models. Moreover, seizure protection conferred by levetiracetam and other SV2A ligands strongly correlates with the degree of SV2A occupancy in vivo. Finally, the anticonvulsant efficacy of levetiracetam but not valproate, which does not interact with SV2A, is reduced in $SV2A^{+/-}$ mice that have one copy of SV2A disrupted by gene targeting. The precise way in which binding of levetiracetam to SV2A leads to seizure protection is not understood.

Indeed, the function of SV2A itself is obscure. Among the various functions proposed are roles in calcium-dependent exocytosis, neurotransmitter loading/retention in synaptic vesicles, and synaptic vesicle priming, as well as transport of vesicle constituents. SV2A is one of three homologous of SV2 proteins that belong to the major facilitator superfamily of 12-transmembrane domain transporters. Despite substantial effort, no transport function of these proteins has been identified, although studies with protein tomography have found that SV2A can adopt two alternate conformations consistent with a transporter role (45). Interestingly, however, levetiracetam binding does not cause a large-scale conformational change in SV2A or lock a specific conformational state of the protein as would an inhibitor of transport. Apparently, the drug has a more subtle effect on the protein. Although the function of SV2A is still poorly defined, $SV2A^{-/-}$ knockout mice exhibit a lethal seizure phenotype demonstrating that SV2A in some way serves to restrain seizures.

A series of recent studies has examined the impact of levetiracetam on synaptic transmission in brain slice recordings (46). Although the drug had no effect on synaptic physiology with low-frequency activation, levetiracetam did reduce the synaptic release of both excitatory (glutamate) and inhibitory (GABA) neurotransmitters during high-frequency activation. The frequency dependence is compatible with the selective suppression of epileptic activity. Modulation of synaptic release is a common mechanism of many AEDs, including sodium channel blockers that indirectly inhibit release at both excitatory and inhibitory synapses by inhibiting action potential firing. It seems that drugs that suppress inhibition and excitation can effectively protect against seizures and they are not often proconvulsant. However, it is noteworthy that in some instances AEDs (notably phenytoin) can have proconvulsant effects.

α2δ-1

The gabapentinoids gabapentin and pregabalin act by binding to the α2δ-1 protein, which is an

accessory subunit of voltage-gated calcium channels (47,48). α2δ-1 is located heterogeneously in the brain, particularly at presynaptic sites on excitatory (glutamatergic) neurons. Dense expression is observed in areas relevant to epilepsy, including in excitatory hippocampal mossy fibers and in the neocortex and amygdala. In contrast, α2δ-1 has minimal expression in the thalamus, and it is noteworthy that gabapentinoids are not active in absence seizures, which as discussed above are dependent upon this brain structure. Four α2δ subunits have been identified, but gabapentinoids only bind to α2δ-1 and α2δ-2 owing to the presence of an RRR motif containing a critical arginine that is required for binding. Seizure protection conferred by gabapentinoids is eliminated in mice bearing a mutation in this motif (RRR mutated to RRA) in α2δ-1, demonstrating that α2δ-1 and not α2δ-2 is relevant for pharmacologic activity. Interestingly, deletion of α2δ-1 or α2δ-2 in mice is associated with absence epilepsy or enhanced seizure susceptibility (49,50).

The precise way in which binding of gabapentin and pregabalin to the α2δ-1 protein confers seizure protection is not well understood (51). Although some studies have found that the drugs inhibit calcium channel currents, most have not and it is generally believed that calcium channel inhibition is not the mechanism of action of gabapentinoids (52–54). Regardless of whether the drugs inhibit calcium channel function, they do seem to block the release of various neurotransmitters, including glutamate, and this may account for the antiseizure activity (55). There is some evidence that gabapentinoids cause internalization of calcium channels by reducing trafficking to the cell membrane (56,57). Whether this action could account for the rapid antiseizure effects of gabapentinoids in animal models is uncertain.

AMPA RECEPTORS

Perampanel is the first selective AMPA receptor antagonist approved for epilepsy treatment. Whereas $GABA_A$ receptors mediate fast synaptic inhibition, AMPA receptors are cation channels that serve as the main mediators of fast (millisecond time scale) synaptic excitation. It has been long appreciated that cascading excitation within networks of synaptically connected neurons is a key mechanism of epileptic synchronization, at least in the hippocampal CA3 region and possibly in other brain areas (58). Epileptic activity emerges from the network when GABA-mediated inhibition is deficient, and indeed chronic alterations in inhibition represent a leading hypothesis to explain some forms of epilepsy.

Fast synaptic excitation is elicited by the exocytotic release of glutamate from excitatory principal neurons, which diffuses across the synaptic cleft and interacts with ionotropic glutamate receptors (iGluRs) of the AMPA and NMDA types to generate excitatory postsynaptic potentials (EPSPs). Summation of EPSPs leads to the firing of action potentials by the postsynaptic neuron. AMPA receptors have a special role in epileptic activity as epileptic synchronization cannot occur when AMPA receptors are blocked. In contrast, kainate receptors, which are iGluRs that have a similar structure to AMPA receptors, do not have a similarly essential role as kainate receptor knockout does not interfere with seizure generation (59). NMDA receptors are thought to contribute to epileptiform activity, but the blockade of NMDA receptors is insufficient to abolish epileptiform discharges in many seizure models (60). Pharmacologic blockade of AMPA receptors has broad-spectrum anticonvulsant activity in in vitro and animal seizure models.

Perampanel is a potent noncompetitive antagonist of AMPA receptors that does not affect NMDA receptor responses and has no known affects on other ion channels or molecular targets at therapeutically relevant concentrations (61). Therapeutic blood levels are expected to result in brain

concentrations that would produce only low levels of inhibition of AMPA receptors. However, such low-level block of AMPA receptors is apparently sufficient to exert a clinical antiseizure action. Perampanel has a relatively low therapeutic window. Adverse central nervous system effects such as dizziness, irritability, and somnolence are common, particularly at higher-dose levels, emphasizing the importance of AMPA receptors in brain function.

MIXED/UNKNOWN ACTIONS

Valproate

Although valproate is one of the most valuable AEDs, the mechanism by which it protects against seizures is poorly understood. Valproate has multiple pharmacologic actions (62,63). Since it has been difficult to relate any one mechanism to the drug's broad spectrum of activity, it has been proposed that combined actions on several targets could account for its therapeutic properties. Although the actions of valproate on GABA systems are not straightforward, among the various pharmacologic effects that have been described, those related to GABA mechanisms are among the most likely to be relevant to valproate's antiseizure activity. For example, valproate increases the turnover of GABA, and this might be associated with enhanced synaptic or extrasynaptic inhibition. At high concentrations, valproate affects voltage-gated sodium channels, but recent studies in brain slice recordings have failed to provide support for sodium channel block as a relevant mechanism to explain clinical activity (64). Similarly, despite efficacy in absence epilepsy, there is little support for effects on T-type calcium channels. It is likely that valproate has pharmacologic actions relevant to its antiseizure activity that remain to be elucidated.

Felbamate

Felbamate, at concentrations within the therapeutic range, has been shown both to act as positive modulators of $GABA_A$ receptors and also to inhibit NMDA receptors (65). Felbamate potentiates GABA responses via an interaction with a site on the $GABA_A$ receptor that is distinct from the benzodiazepine recognition site. This action may be of relevance to felbamate's clinical activity. Although drugs that block NMDA receptors can exert antiseizure effects in certain animal models, there is doubt whether blockade of NMDA receptors is a useful strategy to treat epilepsy (66). Therefore, it is uncertain whether the NMDA receptor–blocking activity of felbamate is relevant to its clinical antiseizure activity.

Topiramate

As is the case for valproate and felbamate, the broad-spectrum anticonvulsant activity of topiramate is likely to result from mixed effects on several targets (67). Among topiramate's diverse pharmacologic actions, effects on voltage-activated sodium channels, $GABA_A$ receptor subtypes, AMPA or kainate receptors, and types II and IV carbonic anhydrase isoenzymes are potentially relevant to seizure protection. Unlike other AEDs, the effects on ion channels are unlikely to occur through direct modulation of channel gating. Rather, the pharmacologic actions of topiramate seem to be mediated indirectly, possibly through effects on channel phosphorylation.

The effects of topiramate on sodium channels occur at relatively low, therapeutically relevant concentrations and could be similar to the effects of other sodium channel–blocking AEDs (68). In addition to effects on fast sodium currents, topiramate, like phenytoin, blocks I_{NaP} at low concentrations. Effects of topiramate on $GABA_A$ receptors could contribute to the broad spectrum of activity of topiramate. Topiramate is not active in animal models, such as the pentylenetetrazol test, that are typically sensitive to drugs that positively modulate $GABA_A$ receptors. Nevertheless, the drug does have activity in an absence epilepsy model and can affect pentylenetetrazol threshold, which is consistent with effects on $GABA_A$ receptors. There is evidence that topiramate may preferentially modulate a subset of $GABA_A$ receptors and that drug sensitivity is dependent upon the β-subunit type (69).

Several authors have suggested that actions on fast glutamate- mediated excitatory neurotransmission could contribute to topiramate's antiseizure activity. In cultured neurons, the drug has been reported to inhibit responses to kainate, an agonist of AMPA and kainate receptors, leading to the conclusion that topiramate could be an antagonist of either AMPA or kainate receptors (70). Recently, kainate receptors have been found to be an unlikely target for an antiseizure agent (71). Whether actions of topiramate on glutamate-mediated neurotransmission contribute to its anticonvulsant activity remains to be determined.

The action of topiramate on carbonic anhydrase has been assumed not to contribute to its clinical efficacy because there is no cross-tolerance to the anticonvulsant activity of topiramate when tolerance occurs to the classical carbonic anhydrase inhibitor acetazolamide in mice. However, a recent review left open the possibility that carbonic anhydrase inhibition could, in part, play a role (67).

Zonisamide

There are some similarities between topiramate and zonisamide as they both contain a sulfur atom and both inhibit carbonic anhydrase. In addition, like topiramate, zonisamide may act on voltage-dependent sodium channels (72). Physiologic studies do not support an action on $GABA_A$ receptors. Unlike topiramate, there are reports that zonisamide can inhibit T-type voltage-gated calcium channels (73), which may account for its activity in absence epilepsy.

Rufinamide

The unique spectrum of clinical activity of rufinamide in the treatment of the Lennox–Gastaut syndrome suggests that it has a distinct mechanism of action (26). However, to date, rufinamide has only been shown to interact with voltage-gated sodium channels, and the effects are subtle. Relevant concentrations of the drug may, at least for some subunit isoforms, cause a depolarization in the activation voltage and slowing of recovery from inactivation, which would be expected to reduce neuronal excitability (74). Clearly, the effects on sodium channels cannot explain the special clinical activity of rufinamide.

Adrenocorticotropin

The mechanism of adreocorticotropin (ACTH) in the treatment of infantile spasms is not understood (75). ACTH stimulates glucocorticoid (cortisol) synthesis and release from the zona fasciculata of the

adrenal cortex. The cortisol could produce an antiinflammatory action or have some other action in the brain to influence infantile spasms. Indeed, glucocorticoids are well recognized to themselves have therapeutic activity in the treatment of infantile spasms; whether ACTH is truly superior remains to be demonstrated conclusively. One possible additional action of ACTH that could contribute to enhanced activity is stimulation of neurosteroid synthesis. In addition to its actions with respect to glucocorticoids, ACTH also stimulates deoxycorticosterone (DOC) release from the zona glomerulosa of the adrenal cortex. DOC is, in part, converted to the anticonvulsant neurosteroid tetrahydro-DOC, which is a positive allosteric modulator of $GABA_A$ receptors (76). It has been hypothesized that the tetrahydro-DOC could, at least in part, contribute to the ability of ACTH to terminate infantile spasms.

BASIS OF COMBINATIONAL TREATMENT

All clinically used AEDs protect against seizures in animal models as single agents. Studies with early AEDs suggested that the seizure protection conferred by drug combinations is simply additive (77). Since the use of more than one agent compounds the risk of side effects, these and other observations led to the recommendation that AEDs should be tried sequentially in monotherapy before combining agents. More recent experimental data suggest that combining drugs with complementary mechanisms of action might lead to synergism for efficacy (78). Observational studies of results obtained in clinical practice have shown that combining newer AEDs with different mechanisms of action may have greater effectiveness (a combination of efficacy and tolerability) than combining drugs with similar mechanisms of action (79). Consequently, an understanding of mechanism may impact clinical decision making in regard to the choice of drug combinations.

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CHAPTER 44 PHARMACOKINETICS AND DRUG INTERACTIONS

GAIL D. ANDERSON

Pharmacokinetics is the study of the effect of the body on a drug. The pharmacokinetic parameters determine the relationship between an administered dose and the concentration of the drug in the body. The main pharmacokinetic parameters include absorption, distribution, metabolism, and excretion. Table 44.1 summarizes the pharmacokinetic parameters for the most commonly used antiepileptic drugs (AEDs). Pharmacodynamics is the study of the factors that relate to the efficacy and safety of the drug and determines the relationship between concentration and effect. The relationship between pharmacokinetics and pharmacodynamics is illustrated in Table Figure 44.1.

Table 44.1 Pharmacokinetic Parameters of AEDS

AED	F (%)	V_d (L/kg)	Protein binding (%)	$T_{1/2}$ (h)	Renal (%)	Routes of elimination hepatic isozymes involved	Active metabolite
Carbamazepine	70–80	0.8–2	75	12–17	<1	CYP3A4 (major), CYP1A2, 2C8	Yes
Clobazam	87	0.9–1.4	85–93	10–30	nk	CYP2C19, 3A4	Yes
Clonazepam	90	3.2	85	22–40	<1	CYP3A4	Yes
Eslicarbazepine[a]	—	nk	30	20–24	66	UGT1A4, UGT1A9, UGT2B4, UGT2B7, UGT2B17	No
Ethosuximide	>90	0.6–0.7	0	25–60	20	CYP3A4 (major), 2E1	No
Ezogabine	60	2–3	80	6–10	20–30	UGT, NAT2	Yes
Felbamate	>90	0.7–1.0	22–25	20–23	50	UGT, CYP3A4 (20%), 2E1	No
Gabapentin	30–60	0.85	0	5–9	>90	None	No
Lacosamide	100	0.6	<15	13	40	Not identified	No
Lamotrigine	98	0.9–1.3	55	12–60	<1	UGT1A4	No
Levetiracetam	100	0.5–0.7	<10	6–8	66	Amidase	No
Oxcarbazepine	>90	nk	40–60	1–2.5	<1	Cytosolic arylketone reductase	Yes
MHD	—	0.7–0.8	33–40	8–11	20	UGT	No
Perampanel	100	1.1	95	60–130	30	CYP3A4/5, other CYPS	No
Phenobarbital	80–90	0.5–1.0	20–60	36–118	20	Glucosides, CYP2C9, 2C19, 2E1	No
Phenytoin	70–100	0.5–1.0	88–93	7–42	2	CYP2C9 (major), CYP2C19	No
Pregabalin	>90	0.5	0	5–6.5	>95	None	No
Primidone	>90	0.4–1.0	20–30	3–7	0	CYPs, isozyme not identified	Yes
Rufinamide	85	0.7	34	6–10	<2	Non–CYP-dependent hydrolysis	No
Stiripentol	25	nk	99	13	<1	UGT and CYPs, isozymes not identified	No
Tiagabine	90	1.0	96	3–8	<2	CYP3A4 (22%),	No
Topiramate	80	0.6–0.8	9–17	21	30	Not identified	No
Valproate	90	0.14–0.23	5–15	6–17	<5	β-Oxidation, UGT1A6, 1A9, 2B7, CYP2C9, 2C19	Yes
Vigabatrin	50–60	0.8	0	5–8	>90	None	No
Zonisamide	>90	0.8–1.6	40–60	27–70	35	NAT2, CYP3A4 (major), CYP2C19	No

[a]After administration of eslicarbazepine acetate.

CYP, Cytochrome P450; UGT, UDP-glucuronosyltransferase; NAT, N-acetyltransferase; nk, not known.

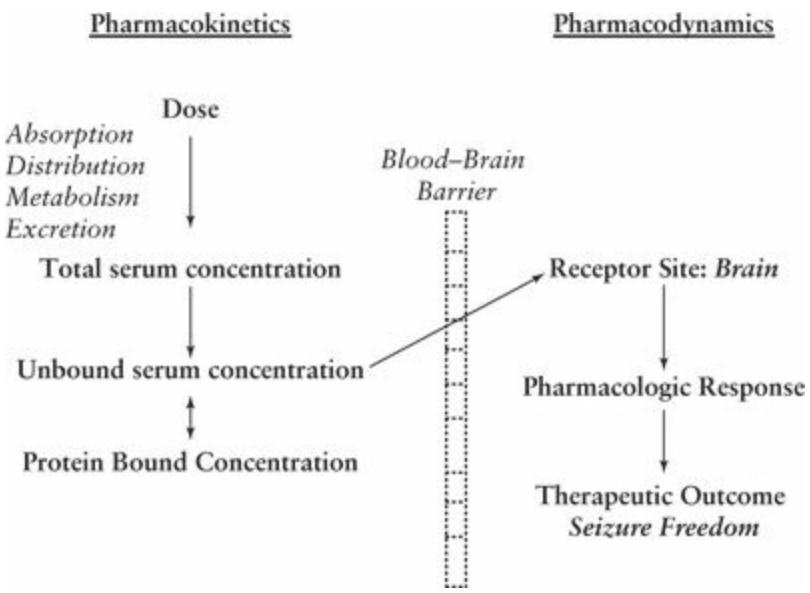

Figure 44.1. Relationship between pharmacokinetics and pharmacodynamics.

PHARMACOKINETIC PARAMETERS

Absorption

Absorption refers to the passage of the drug from its site of administration into the systemic circulation and is defined by the rate at which the drug leaves the site of administration and the extent at which it occurs. The rate of absorption is generally a first-order process, where the rate of absorption is dependent on the amount of drug. Some drugs can follow zero-order kinetics with a constant release of drug independent of the amount of drug. Bioavailability (F) is the amount of the administered drug that reaches the systemic circulation. F is dependent on the fraction absorbed through the gastrointestinal (GI) tract plus the fraction lost due to first-pass metabolism. After intravenous (IV) administration, bioavailability is equal to 1.0. Bioavailability for other non-IV formulations is determined by comparing the area under the concentration time curve (AUC) obtained after IV administration of a drug and the AUC obtained after administration by another route (i.e., oral). Most drugs are absorbed by passive diffusion in the GI tract where the rate of absorption is proportional to the drug concentration gradient across the barrier. Other drugs are absorbed by a combination of passive and active transport by proteins that can increase and/or decrease absorption depending on their location and whether they are influx or efflux transporters (1). Influx transporters that increase oral absorption include the organic anion transporters (OAT), organic cation transporters (OCT), organic anion–transporting polypeptides (OATP), peptide transporters, and large neutral amino acid transporter 1 (LAT). The oral absorption of gabapentin is dependent on active transport by the LAT (2). Conversely, efflux transporters, including P-glycoprotein (PGP), breast cancer resistance protein (BCRP), multidrug resistance proteins (MRP), and multidrug and toxin extrusion proteins (MATE), can limit drug absorption by increasing the excretion of drugs into the intestinal lumen from the systemic circulation (3). First-pass metabolism of a drug can occur in the GI tract and in the liver resulting in a decreased bioavailability. The fraction lost in the GI tract can be due to metabolism via hydrolysis, glucuronidation, sulfation, and oxidation, with cytochrome P450 3A4 (CYP3A4), the most dominant cytochrome P450 in the GI tract. Many drugs, including carbamazepine (4), are substrates of PGP and CYP3A4, both involved in decreasing oral absorption. Drugs that are high extraction ratio (ER) drugs can undergo significant first-pass liver metabolism.

Extended-release formulations are used to decrease the frequency of dosing for drugs with rapid elimination to improve convenience and compliance. For extended-release drugs, the rate-limiting step in drug elimination is the absorption rate of the drug and not the elimination rate. Use of an extended- release product can decrease the peak to trough fluctuation in serum concentrations and theoretically improve the therapeutic benefit of the drug by decreasing adverse events associated with higher peak concentrations. Other drugs are delayed release, for example, enteric-coated valproate. The enteric coating improves tolerability by decreasing absorption within the stomach and delaying absorption until the formulation reaches the intestines.

Bioequivalence is defined as chemical, when the drug meets the same chemical and physical standards; biologic, when the administered drug yields similar concentrations in blood; and therapeutic, when the drug provides equal therapeutic benefits in clinical trials. Generic drugs are chemically and biologically equivalent. Manufacturers do not have to prove therapeutic equivalence. Bioequivalence studies are single-dose, crossover studies done in healthy subjects comparing a generic product to the brand-name product. A generic product is considered bioequivalent if the mean AUC, maximum concentration (C_{max}), and the 90% confidence interval for each parameter are within 80% and 125% of the brand product. There has been a history of problems with generic versions of the older AEDs, specifically carbamazepine and phenytoin, as summarized in several reviews. Nuwer et al. (5) described three pharmacokinetic properties that predisposed the older AEDs to problems with their generic formulations: low water solubility, narrow therapeutic range, and nonlinear pharmacokinetics. The Biopharmaceutics Classification System (BCS) was designed to correlate a drug's aqueous solubility and permeability with the rate and extent of oral drug absorption (6). BCS can also provide an estimate for the likelihood of problems with generics. Drugs with high solubility and permeability are unlikely to demonstrate generic-related problems. Using the criteria, the historical problems with generic products of phenytoin and carbamazepine are predictable. The same criterion predicts that the majority of the new AEDs should not be predisposed to similar problems due to their high aqueous solubility and permeability. There have been reports from patients and neurologists of increased side effects or seizures on generic substitution (7). A recent evaluation of 141 generic AED products in 258 bioequivalence studies found that there was less than a 15% difference in the AUC and C_{max} compared to the reference product in 99% and 89% of the studies, respectively (8). The AED with the lowest solubility, oxcarbazepine, had the highest variability. In a systematic review of published 13 prospective and 7 retrospective studies, the highest quality studies (prospective, class I and II evidence), found that there was no significant difference between brand and generic formulations in safety and efficacy (9). In contrast, several retrospective studies of lower quality (class III evidence) did find a difference.

Distribution

Distribution is the process of reversible transfer of drug to and from the site of measurement. Central nervous system distribution is unique due to the blood–brain barrier (BBB). Lipid-soluble and unbound drugs have significantly higher distribution across the BBB than do water-soluble and protein-bound drugs. Both influx and efflux transport proteins alter brain distribution (3). Influx transporters involved in drug distribution include LAT, monocarboxylate transporter 1 (MCT1), and OATP. The brain uptake of gabapentin and pregabalin is dependent on the influx transporter, LAT1 (10). PGP and BRRP are the primary efflux transporters involved in transporting drugs from the brain to the blood and form an important part of the BBB. After initial reports of the overexpression of PGP

in patients with refractory epilepsy (11), it was hypothesized that increased expression of drug efflux transporters, specifically PGP and MRPs, reduce the concentration of AEDs in the brain resulting in pharmacoresistance (12). Although there is experimental evidence that phenytoin, phenobarbital, lamotrigine, and oxcarbazepine are PGP substrates, many of the other AEDs that are ineffective in refractory epilepsy are not substrates, suggesting there is not a major role of efflux transporters in pharmacoresistance (13,14).

The volume of distribution (V_d) is a measure of the apparent space in the body available to contain the drug. V_d relates the amount of drug in the body to the concentration of drug in the plasma. Therefore, the initial concentration (C_o) attained after administration of a single or bolus dose (D) is dependent on the V_d of the drug. The dose is based on either ideal or total body weight depending on the physiochemical characteristic of the drug. Lipophilic drugs will distribute into adipose tissue, and V_d will be dependent on total body weight. In contrast, for water-soluble drugs, V_d is dependent on ideal or lean body weight. V_d can be used to calculate both loading and bolus doses needed to achieve a desired concentration.

$$C_o = \frac{D}{V_d} \quad (1)$$

For the AEDs, albumin is the primary binding protein, with the exception of carbamazepine, which is bound to both albumin and alpha$_1$-acid glycoprotein (α_1-AGP). Albumin concentrations are decreased in the neonate, in the elderly, in hepatic and renal disease, during pregnancy, and after trauma. α_1-AGP is an acute-phase reactive protein and is decreased in neonates and increased in conditions of inflammation and trauma. For the majority of the drugs, protein binding is linear, and the percent unbound is a constant within the range of concentrations used clinically. Valproate is the one exception. Valproate is highly protein bound, and due to its high molar concentration, valproate saturates albumin-binding sites within the therapeutic range (15). An increase in the percent unbound as the dose increases results in measured total valproate concentrations increasing less than proportionally with increasing doses. Conversely, unbound valproate concentrations will increase linearly with increasing dose, and total valproate concentrations will no longer reflect unbound or active concentrations.

Elimination Processes

Drugs are eliminated by metabolism and/or excretion of unchanged drug by the kidneys or GI tract. Metabolism occurs predominantly in the liver with the GI, kidneys, lung and serum as other possible sites of metabolism. For the large majority of drugs, elimination is linear; the elimination rate is proportional to the amount of drug present. For drugs following linear kinetics, clearance is constant, and serum concentrations increase proportional with increasing doses. Unlike other drugs, phenytoin is unique in that its elimination is nonlinear due to saturation of metabolism within the normal dosage range. This saturation of metabolic processes results in a decreased clearance with increasing doses. For drugs like phenytoin with nonlinear elimination, serum concentrations will increase more than expected with increasing doses.

Clearance (Cl) is the most useful pharmacokinetic parameter for evaluating an elimination mechanism. It can also be used to estimate the average steady-state concentrations ($C_{ave,ss}$) attained

on multiple dosing. Physiologically, Cl is the loss of drug across an organ of elimination and is determined by the blood flow to the organ that metabolizes or eliminates the drug and the efficiency of the organ in extracting the drug. The efficiency is measured by the ER, defined as the ratio of the difference between the concentration into and out of the organ (C_{in} - C_{out}) to the concentration entering the organ (C_{in}). Cl is described in terms of the eliminating organ; hepatic clearance (Cl_H) and renal clearance (Cl_R) with total Cl determined by the sum of all the partial clearances. After multiple dosing, $C_{ave,ss}$ is dependent on the dose/interval (D/τ), Cl, and F (Eq. (2)).

$$C_{ave,ss} = \frac{F \cdot D/\tau}{Cl} \quad (2)$$

The elimination half-life ($T_{1/2}$) is the time required for the serum concentrations to decrease by 50% and is independent of dose. As shown in Eq. (3), $T_{1/2}$ is dependent on the Cl and V_d. It takes five $T_{1/2}$s to reach steady-state concentrations with multiple dosing and to eliminate greater than 95% of the drug on discontinuation.

$$T_{1/2} = \frac{0.693 \cdot V_d}{Cl} \quad (3)$$

Excretion

The renal excretion of unchanged drug and metabolites includes the processes of glomerular filtration (GFR), active tubular secretion, and passive reabsorption. The major transporter involved in renal secretion of drugs are OAT, OCT, PGP, and MRP (3). For drugs that are predominantly excreted unchanged in the urine, renal function can be assessed using the serum creatinine (SCR) to estimate creatinine clearance (CrCl) or GFR (eGRF). The Cl of creatinine is dependent on GFR and tubular secretion and is greater than GFR. The relationship between a drug's Cl and CrCl (or eGFR) can be used to estimate doses regiment needed to attain therapeutic concentrations. For most drugs that are significantly excreted unchanged in the urine, the relationship between Cl and CrCl (or eGFR) is linear with the y-intercept reflecting the nonrenal portion of the Cl. CrCl can be estimated using the Cockroft–Gault equation (16), the modified diet in renal disease (MDRD) equation (17), or the chronic kidney disease epidemiology (CKD-EPI) (18). The Cockroft–Gault equation estimates CrCl and requires knowledge of the patients' age, sex, and lean body weight (LBW). The MDRD equation was developed in 1070 patients with chronic renal failure. More recently, the CKD-EPI method was developed using a cross-sectional analysis with pooled data obtained from research studies and clinical population of 8254 patients with measured GFR. The CKD-EPI method performs better at higher GFR. The MDRD and CKD-EPI equations estimate GFR, do not require information on LBW, and also take into account ethnic differences in renal function. The majority of clinical laboratories in the United States were reporting eGFR with a measured SCR using the MDRD equation in 2008. More recently, the CKD-EPI is now used by QUEST and LabCorp, the two largest laboratory service providers in the United States (19). For the majority of the currently marketed drugs, the Cockcroft–Gault method was used to estimate renal function and to determine the relationship between CrCl and Cl (or Cl/F) to recommend dosing guidelines. As clinical laboratories are reporting eGFR, Park et al. evaluated data in the FDA database for 26 approved drugs that require renal dosage adjustment to determine if the MDRD equation could be used interchangeable with the Cockcroft–Gault (20). Only

8% of the dosage recommendations were changed to a different dosage class if the MDRD determined eGFR adjusted for BSA (20). Therefore, the eGFR can be used to guide drug dosing.

Excretion of drugs into breast milk can occur during lactation. The dose of a drug that the infant receives during breast-feeding is dependent on the amount excreted into the breast milk, the daily volume of milk ingested, and the average plasma concentrations of the mother. The physiochemical properties of a drug will determine how much of the drug will be excreted into the breast milk, including its lipophilicity and protein-binding and ionization properties. The milk-to-plasma concentration ratio has large inter- and intrasubject variability and is often not known. In contrast, protein binding is usually known, and knowledge of the protein-binding properties of a drug can provide a quick and easy tool to estimate exposure of an infant to medication from breast-feeding. Based on an extensive literature review of case reports that included infant concentrations from breast-fed infants exposed to maternal drugs (21), measurable concentrations of drug in the infant did not occur for drugs that were at least 85% protein bound, if there was no placental exposure immediately prior to or during delivery.

Metabolism

Metabolic reactions are primarily catalyzed by the cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) enzymes. However, the second- and third-generation AEDs are also metabolized by a variety of other non-CYP/UGT enzymes (Table 44.1). CYPs are a family of multiple enzymes with the individual isozymes being composed of three major families (CYP1, CYP2, and CYP3). Seven primary isozymes are involved in the hepatic metabolism of most drugs: CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. The most abundant isozyme, CYP3A4, which accounts for approximately 30% of the total hepatic CYP, has the broadest substrate specificity and is involved in the metabolism of more than 50% of all drugs. The UGTs are family of enzymes that catalyze the transfer of a glucuronic acid moiety from a donor cosubstrate UDPGA. The activity of the metabolic enzymes is dependent on genetic, physiologic, and environmental effects.

Genetic polymorphisms in the expression of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A5, UGT1A1, N-acetyltransferases (NAT2), and thiopurine S-methyltransferase (TPMT) have been identified. Poor metabolizers are homozygous for the mutant gene. Extensive metabolizers are either homozygous or heterozygous for the wild-type gene, with heterozygous carriers having intermediate metabolic activity. Ultrametabolizers have multiple copies of the gene for CYP2D6 and a promoter region polymorphism for CYP2C19 resulting in increased metabolism of CYP2D6 and CYP2C19 substrates, respectively. In addition, the predominant variants of CYP2D6 in Asian and African-American (*10 and *17, respectively) are alleles with reduced enzyme activity. Overall, there is a large interethnic variability in the proportion of poor metabolizers, intermediate metabolizers, and ultrametabolizers, which is beyond the scope of this chapter (22).

The pharmacokinetic hepatic model of elimination is a physiologically based model where hepatic clearance (Cl_H) is dependent on the unbound fraction of the drug in the blood (f_u), activity of the metabolic enzymes (Cl_{int}), and hepatic blood flow (Q_H).

$$Cl_H = \frac{Q_H \cdot (f_u \cdot Cl_{int})}{Q_H + (f_u \cdot Cl_{int})} \quad (4)$$

For low extraction ratio drugs (ER < 0.3), and $f_u \cdot Cl_{int} < Q_H$, Cl is dependent on protein binding and intrinsic clearance. For high ER drugs (ER > 0.7), $f_u \cdot Cl_{int} > Q_H$ and Cl is dependent on Q_H.

Protein Binding and Hepatic Metabolism

Protein-binding effects are only clinically significant for two different types of highly protein-bound drugs that are predominantly eliminated by hepatic elimination (23). For low ER drugs that undergo dosage adjustment by monitoring total concentrations, total concentrations will underestimate unbound or active concentrations. This has been shown for both phenytoin and valproate in the elderly (24) and in pregnant women (25,26) with epilepsy. Total concentrations decreased significantly more than unbound concentrations with decreased albumin concentrations. Adjusting doses based on total concentrations will result in higher doses of valproate and phenytoin than needed to maintain therapeutic unbound concentrations. As the teratogenicity of valproate and phenytoin has been found to be dose dependent, minimizing unnecessary dosing increases during pregnancy is desirable. Ideally, unbound concentrations should be measured. Unbound phenytoin concentrations are clinically available and should be utilized whenever possible. Valproate unbound concentrations are not routinely available to the clinician as they may be unreliable due to problems in sample collection. Patients need to be monitored based on clinical measures, that is, a change in seizure frequency and/or presence of adverse effects in the case of the AEDs.

For high ER drugs with a narrow therapeutic window and administered by nonoral routes, the AUC of unbound drug can be significantly increased and result in increased pharmacologic effect. The AUC of low ER drugs is independent of protein binding (23). Of the parenterally available AEDs, only midazolam is a high protein bound, and high ER drug.

METHODS TO DETERMINE PHARMACOKINETIC PARAMETERS

Pharmacokinetic parameters are determined using concentration time data by both compartmental and noncompartmental methods of analysis. The majority of drugs are eliminated by a first-order process, that is, the elimination rate is dependent on concentration, and serum concentration time data can be modeled using either a one-compartment or a two-compartment model. For one-compartment model, distribution is considered instantaneous, and concentrations decline exponentially with time, and a plot of log concentration versus time is linear. For a two-compartment model, the first exponential phase is primarily dependent on distribution into a peripheral compartment, and the second exponential phase is dependent on elimination after distribution is complete. The terminal elimination rate constant (β) is determined by linear regression of the log concentration time data obtained during the terminal exponential phase. The elimination half-life ($T_{1/2}$) is calculated as $0.693/\beta$. Peak serum concentration (C_{max}) and the time to peak (T_{max}) are obtained by visual inspection of the data. The AUC is calculated by the log-linear trapezoidal method. Cl is estimated by the ratio of dose to AUC. If the drug is administered orally, an apparent oral clearance (Cl/F) is defined as D/AUC as bioavailability is unknown or assumed. Renal clearance (Cl_R) is calculated as product as the fraction of the dose excreted unchanged in the urine and Cl.

PHYSIOLOGIC AND PATHOLOGIC EFFECTS ON PHARMACOKINETICS

The effect of age (27,28), pregnancy (21,29), drug interactions (30–32), renal disease (33), and/or hepatic disease (34) on AED dosing will depend on the fraction of the AED eliminated by renal and/or hepatic elimination, the metabolic isozymes involved, as well as the extent of protein binding, if therapeutic drug monitoring is involved (Table 44.1). This section provides the theoretical basis for the physiologic and pathologic effects on drug pharmacokinetics. Refer to review articles (9,13–19) and chapters on individual AEDs for more specific information.

Age

Gastric pH is increased in neonates, infants, and young children, decreasing to adult values by 2 years of age. The incidence of hypochlorhydria also increases significantly after age 70. GI motility is decreased in neonates, reaches adult levels in older infants, and then decreases in the elderly. The bioavailability of drugs given orally that are weak acids, like phenytoin and phenobarbital, may be decreased in infants, young children, and the elderly due to their higher gastric pH. In neonates and infants, the increased total body water-to-body fat ratio contributes to an increase in the V_d of hydrophilic drugs, and may require larger mg/kg loading doses of some drugs to achieve therapeutic concentrations. Albumin and α_1-AGP concentrations are decreased in the neonates and young infant. Albumin concentrations alone are decreased in the elderly resulting in decreased protein binding for highly bound drugs. The clinical significance of decreased protein binding is described above for low and high ER drugs. At birth, GFR is approximately 40 mL/min/1.73 m^2 in the full-term neonate and increases steadily to 80% to 90% of adults function by 1 year. From ages 40 to 80, kidney function declines at approximately 10% to 20% decrease per decade. Therefore, in general, weight-normalized doses of drugs excreted predominately unchanged by the kidneys need to be reduced in neonates, infants, and the elderly. In the past, there was a general assumption that all hepatic drug metabolism was increased in children compared to adults. There is now evidence that in children, hepatic metabolism can be increased or not changed compared to adults depending on metabolic pathway involved in the elimination of the drug (26). Significantly, higher weight-corrected doses are needed in children than in adults for drugs metabolized by CYP1A2, CYP2C9, and CYP3A4. In contrast, weight-corrected doses for drugs metabolized by CYP2C19, CYP2D6, NAT2, and UGT in children are similar to those in adults. In the elderly, the activity of all of the CYPs is decreased resulting in a need for decreased doses. Doses of drugs metabolized by the conjugating enzymes, NAT2 and UGT, do not need to be decreased.

Pregnancy

Despite the many physiologic changes that occur during pregnancy that could affect absorption, bioavailability does not appear to be altered. Decreased albumin and α_1-AGP concentrations during pregnancy will result in decreased protein binding for highly bound drugs. The clinical significance of decreased protein binding is described above and is important for both valproate and phenytoin, specifically. Renal clearance and the activity of the CYP3A4, CYP2D6, CYP2C9, and UGT isozymes are increased during pregnancy, and drugs eliminated by these pathways may need dosage increases

during pregnancy (25,26). In contrast, CYP1A2 and CYP2C19 activity is decreased, and drugs metabolized by these CYP isozymes may require a decrease in dosage during pregnancy (21).

Renal Disease

The effect of renal disease, in addition to declining renal function in the elderly and the immature renal function in neonates and infants, all result in decreased Cl for drugs that are predominantly excreted unchanged in the urine. For drugs with both renal and hepatic Cl, the effect of renal dysfunction is proportionate to the fraction of the Cl of the drug dependent on renal clearance. The ability to estimate renal function using SCR provides a method of determining the dose required to maintain a therapeutic effect without toxicity. In addition, to a decreased Cl, renal disease is associated with decreased albumin concentrations, which will result in decreased protein binding for highly bound drugs.

Liver Disease

Unlike renal disease, there are no specific markers of liver function that can be used to provide guidance in dosage adjustments. Liver function tests (LFTs) primarily are a measure of the extent of cell death. For example, LFTs are significantly increased in acute hepatitis; however, metabolic enzyme function is maintained, and doses of drugs eliminated by liver metabolism do not need to be altered (26,27). Conversely, acute and chronic cirrhosis results in a decreased ability to metabolize drugs due to effects on the metabolic enzymes and hepatic blood flow. The metabolic enzymes are differentially affected depending on the severity of the cirrhosis with the Cl of drugs metabolized by CYP2C19 affected first during mild liver disease (34). The activity of CYP2C19 is significantly decreased with mild liver disease and remains at a decreased level with increasing severity of disease. CYP1A2, CYP2D6, and CYP3A4 activity is also decreased in mild cirrhosis, but to a lesser extent than CYP2C19, and continues to decrease with increasing severity of disease. CYP2C9 and CYP2E1 are not significantly decreased in mild to moderate liver disease; however, the activity of the enzymes all decrease with more severe cirrhosis. The Cl of drugs metabolized by the conjugating enzymes (UGT and NAT2) is not affected until the patient reaches end-stage liver disease. End-stage liver disease also decreases the renal clearance of drugs. Decreased albumin and α_1-AGP concentrations occur due to decreased synthesis and result in increased free fractions of highly protein-bound drugs.

DRUG INTERACTIONS

Drug interactions can occur by pharmacokinetic or pharmacodynamic mechanisms. Pharmacodynamic interactions occur when the pharmacology of one agent alters the pharmacology or effect of the other drug without altering the serum concentration. Theoretically, the interaction can occur at the receptor or site of action or indirectly by affecting other physiologic mechanisms. The most commonly occurring AEDs are pharmacokinetic interactions, where one drug alters the serum concentrations of another. Pharmacokinetic interactions include hepatic enzyme induction, enzyme inhibition, and protein-binding displacement. Many of the AEDs are either specific or broad-spectrum inducers and/or inhibitors of metabolic enzymes (Table 44.2). In addition, many of the AEDs are eliminated by pathways that are affected by induction and/or inhibition by other AEDs and non-AEDs (Table 44.3).

Table 44.2 Effect of AEDs on Hepatic Metabolic Enzymes

AED	Effect	Metabolic enzyme/ transporters involved
Carbamazepine	Inducer	CYP1A2, CYP2C9, CYP2C19, CYP3A, UGT
Clonazepam	Inducer	CYP3A4, UGT
Eslicarbazepine	Inducer	CYP2C9, CYP3A4
Ethosuximide	No effect	
Ezogabine	Inducer	UGTs
Felbamate	Inducer	CYP3A4
	Inhibitor	CYP2C19, β-oxidation
Gabapentin	No effect	
Lacosamide	No Effect	
Lamotrigine	Inducer	UGT
	Inhibitor	UGT, CYP2C19
Levetiracetam	No effect	
Oxcarbazepine	Inducer	CYP3A4
	Inhibitor	CYP2C19
Perampanel	No effect	
Phenobarbital/ Primidone	Inducer	CYP1A, CYP2A6, CYP2B, CYP2C9, CYP2C19, CYP3A, UGT
Phenytoin	Inducer	CYP2C9, CYP2C19, CYP3A, UGT
Pregabalin	No effect	
Rufinamide	Inducer	CYP3A4
Stiripentol	Inhibitor	CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4
Tiagabine	No effect	
Topiramate	Inducer	CYP3A4
	Inhibitor	CYP2C19
Valproate	Inhibitor	CYP2C9, UGT, epoxide hydrolase
Vigabatrin	No effect	
Zonisamide	No effect	

CYP, Cytochrome P450; UGT, UDP-glucuronosyltransferase; NAT, N-acetyltransferase; PG, p-glycoprotein; MRP, multiresistance protein.

Table 44.3 Inducers and Inhibitors of Cytochrome P450 (CYP) isozymes and UDP-Glucuronosyltranferases (UGT) Involved in AED Metabolism[a]

Isozyme	AED substrate	Inducers[a]		Inhibitors[a]		
CYP1A2	Carbamazepine	Carbamazepine Phenobarbital Phenytoin Primidone Rifampin		Fluvoxamine		
CYP2C8	Carbamazepine	Phenobarbital				
CYP2C9	Carbamazepine Phenobarbital Phenytoin Valproate	Carbamazepine Phenobarbital Phenytoin Primidone Rifampin		Amiodarone Cimetidine Fluconazole Gemfibrozil	Miconazole Propoxyphene Sulfaphenazole Valproate	
CYP2C19	Clobazam N-Desmethylclobazam Diazepam N-Desmethyldiazepam Phenobarbital Phenytoin Valproate	Carbamazepine Phenobarbital Phenytoin Primidone Rifampin St. John's wort		Felbamate Fluoxetine Fluvoxamine Isoniazid Ticlopidine		
CYP3A4	Carbamazepine Clobazam Diazepam Eslicarbazepine Ethosuximide Perampanel Tiagabine[b]	Carbamazepine Eslicarbazepine Felbamate Oxcarbazepine Phenobarbital Phenytoin Rifampin St. John's wort Topiramate		Amprenavir Atazanavir Cimetidine Clarithromycin Danazol Darunavir Diltiazem Erythromycin	Fluconazole Grapefruit juice Indinavir Isoniazid Itraconazole Ketoconazole Miconazole Nelfinavir	Propoxyphene Quinupristin Ritonavir Saquinavir Telithromycin Troleandomycin Verapamil
UGTs	Ezogabine Lamotrigine Lorazepam MHD (oxcarbazepine) Retigabine Valproate	Carbamazepine Ertapenem[d] HRT[c] Imipenem[d] Lamotrigine Lithium[c] Lopinavir/ritonavir[c]	Meropenem[d] OCs[c] Oxcarbazepine Panipenem[d] Phenobarbital Phenytoin Primidone	Valproate		

[a]The drugs listed below have been shown to be inhibitors/inducers of the various CYP and UGT isozymes. Not all interactions have been demonstrated for all drugs. Caution should be used with concurrent therapy of known inhibitors and inducers.

[b]The fraction of the clearance associated with the pathway small; therefore, CYP3A4 inhibitors do not significantly effect tiagabine serum concentrations.

[c]Oral contraceptives (OCs), HRT (hormone replacement therapy), lithium, and lopinavir/ritonavir decrease the lamotrigine concentrations. OCs decreases the concentrations of lorazepam and valproate. The effect on retigabine has not been evaluated.

[d]The carbapenem antibiotics have only been shown to decrease valproate concentrations.

Knowledge of the specific CYP or UGT isozymes involved in the metabolism of the AEDs allows prediction of potential inhibition and induction interactions. Less is known regarding the induction and inhibition potential of the non-CYP and UGT enzymes. The extent of the drug interaction is more difficult to predict than the type of interaction. A large number of patient and drug factors will influence the extent of the induction or inhibition. Intersubject variability in the expression of the CYP and UGT isozymes will influence the fraction of the dose associated with each metabolic pathway that is inhibited.

Hepatic enzyme induction is generally the result of an increase in the amount of enzyme protein. In most cases, enzyme induction results in an increase in the rate of metabolism of the affected drug, a decrease in the serum concentration of a parent drug, and possibly a loss of clinical efficacy. If the affected drug has an active metabolite, induction can result in increased metabolite concentrations and

potentially an increase in the therapeutic effect and toxicity of the drug. Carbamazepine, phenytoin, phenobarbital, and primidone (via the phenobarbital metabolite) are broad-spectrum inducers of several CYP and UGT isozymes. Only St. John's wort and rifampin are non-AED broad-spectrum inducers (Table 44.3). Enzyme induction causes major effects on a limited number of extensively metabolized drugs (>75% metabolized) with a low therapeutic index. For the drugs listed in Table 44.4, addition or removal of a broad-spectrum inducer could result in loss of efficacy or toxicity if serum concentrations are not adjusted. Dosage adjustments of approximately 50% to 100%, with careful clinical monitoring, may be required.

Table 44.4 Drugs in Which Addition or Discontinuation of a Hepatic Enzyme Inducer Could Cause Clinically Significant Effects

Drug category	Specific drugs		
Analgesics	Alfentanil Fentanyl	Methadone Morphine	
Antidepressant drugs[a]	Amitriptyline Amoxapine Clomipramine	Desipramine Doxepin Imipramine	Nortriptyline Protriptyline Trimipramine
Antiepileptic drugs	Carbamazepine Clobazam Ethosuximide Felbamate	Lamotrigine Perampanel Phenytoin Stiripentol	Tiagabine Topiramate Valproate Zonisamide
Anti-infectious agents	Itraconazole Ketoconazole	Mebendazole Voriconazole	
Antipsychotic agents	Aripiprazole Clozapine Haloperidol	Quetiapine Risperidone	
Antiviral agents	Amprenavir Atazanavir Darunavir Delavirdine	Efavirenz Indinavir Nelfinavir Ritonavir	Saquinavir Tipranavir Zidovudine
Benzodiazepines	Alprazolam Clonazepam	Diazepam Lorazepam	Midazolam Triazolam
Calcium channel blockers	Amlodipine Bepridil Diltiazem Felodipine	Isradipine Nicardipine Nifedipine Nimodipine	Nisodipine Nitrendipine Verapamil
Cardioactive drugs	Amiodarone Digoxin	Disopyramide Procainamide	Propranolol Quinidine
Corticosteroids	Cortisone Betamethasone Dexamethasone Hydrocortisone	Methylprednisolone Prednisolone Prednisone Triamcinolone	
HMG-CoA reductase inhibitors Immunosuppressants Oral anticoagulants Oral contraceptives	Atorvastatin Cyclosporine Dicumarol Conjugated estrogens Ethinyl estradiol	Lovastatin Sirolimus Warfarin Levonorgestrel Norethindrone	Simvastatin Tacrolimus
Miscellaneous	Cyclophosphamide[b] Theophylline	Thiotepa[b] Vincristine	Imatinib

[a]Many antidepressants have active metabolites; therefore, the effect of enzyme induction on efficacy is unpredictable.

[b]Increased exposure to active metabolite is associated with increased toxicity.

The amount of enzyme induction is proportional to the dose of the inducing agent. This has been shown for phenytoin, phenobarbital, and carbamazepine. The time required for induction depends on both the time to reach steady state of the inducing agent and the rate of synthesis of new enzymes. Because induction is a gradual process, allowing time for gradual increases in the dose of the affected drug is required. The time course of deinduction is dependent on the rate of degradation of the enzyme and the time required eliminating the inducing drug. For the AEDs, the rate-limiting step in deinduction is the elimination of the inducing drug. When the inducer is removed, serum concentrations of the affected drug will increase. Serious adverse events can occur if the dose of the affected drug is not reduced. The magnitude and timing of these interactions are critical to allow clinicians to adjust doses in such a way to maintain therapeutic effect and avoid toxicity. For carbamazepine, the majority of the induction occurs within 1 week of initiation and is completed within approximately 3 weeks (35). Maximal induction occurs approximately 1 to 2 weeks after initiation phenytoin therapy corresponding to the approximately time to steady-state phenytoin concentrations (36). Theoretically, deinduction requires a similar period of time. For phenobarbital, the time course of induction and deinduction is primarily dependent on the long elimination half-life. Induction usually begins in approximately 1 week; with maximal induction occurring 2 to 3 weeks after phenobarbital therapy is initiated (37). The time course of the deinduction will follow a similar course, as phenobarbital serum concentrations decline over 2 to 3 weeks following removal of drug.

Hepatic enzyme inhibition results in a decrease in the rate of metabolism of the affected drug. Clinically, this is associated with an increased serum concentration of the affected drug and potentially an increased pharmacologic response. Enzyme inhibition can be rapidly reversible, slowly reversible, or irreversible. Rapidly reversible inhibition occurs due to competition at the enzyme site. The extent of inhibition is dependent on the dose of the inhibitor as the majority of inhibition interactions are competitive. The onset of the interaction is frequently rapid, and the extent of the interaction is highly variable. The initial effects of hepatic enzyme inhibition usually occur within 24 hours of addition of the inhibitor, but the time to maximal inhibition will depend on the time needed to achieve steady state of both the affected drug and the inhibiting drug. Irreversible or mechanism-based inhibition occurs when an inhibitor binds irreversibly to the enzyme. The time course of deinhibition is dependent not only on the elimination half-life of the inhibitor but also on the time to synthesis new metabolic enzyme. The most well-known mechanistic-based inhibitor is grapefruit juice (38).

Protein-binding displacement interactions result from the displacement of one drug with less affinity for the protein by another drug with greater affinity. Clinically significant interactions occur only with highly protein-bound drugs (>90%). For highly protein-bound drugs that are primarily eliminated by low extraction hepatic metabolism, protein-binding displacement causes a decrease in total serum concentrations of the displaced drug and no change in the unbound drug. Transient increases in unbound drug can be associated with acute toxicity. For most AEDs, total serum concentrations are used for clinical monitoring. Interpretation of total concentrations in the context of protein-binding interactions will result in dosing adjustments that will possibly lead to AED toxicity. In the case of AEDs, phenytoin and valproate are the only drugs involved in clinically important protein-binding interactions (39).

Drug interactions can also involve inhibition or induction of intestinal transporters (PGP, BCRP), inhibition of hepatic uptake transporters (OATP), and transporters involved in renal secretion (OAT, OCT, MATE, PGP) (1).

Effect of AEDs on Other Drugs

AEDs are associated with a wide range of drug interactions [for reviews, see (30–32) and the drug-specific chapters]. Carbamazepine, phenytoin, phenobarbital, and primidone (via the phenobarbital metabolite) are broad-spectrum inducers of several CYP and UGT isozymes. Stiripentol and valproate are both broad-spectrum inhibitors of a variety of metabolic isozymes. Eslicarbazepine, ezogabine, clonazepam, felbamate, lamotrigine, oxcarbazepine, rufinamide, and topiramate are inhibitors and inducers of select metabolic enzymes. Ethosuximide, gabapentin, lacosamide, levetiracetam, perampanel, pregabalin, tiagabine, vigabatrin, and zonisamide are neither inducers nor inhibitors of metabolic enzymes and do not significantly alter the serum concentrations of other drugs (Table 44.3).

Effect of Other Drugs on AEDs

The effect of other drugs on the AEDs can by and large be predicted based on their pharmacokinetic characteristics (Table 44.1), knowledge of the specific pathways of elimination, and known inducers and inhibitors (Table 44.3). Serum concentrations of AEDs that are eliminated predominantly by renal excretion of unchanged drug (gabapentin, pregabalin, and vigabatrin) are not affected by coadministration of other drugs. Serum concentrations of AEDs that are extensively metabolized by CYP and/or UGTs will be decreased in the presence of broad-spectrum and selective enzyme inducers. Serum concentrations of AEDs that are eliminated by both renal and hepatic metabolism (eslicarbazepine, felbamate, levetiracetam, oxcarbazepine, perampanel, and topiramate) will decrease less than those that are predominantly metabolized. The pharmacologic effects of a drug interaction will be more unpredictable for those AEDs with active metabolites, for example, carbamazepine and clobazam, depending on the relative effect of the interaction on parent and/or active metabolite.

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CHAPTER 45 INITIATION AND DISCONTINUATION OF ANTIEPILEPTIC DRUGS

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Over the past two decades, there has been much information about the prognosis of seizure disorders, the effects of antiepileptic drug (AED) therapy on prognosis, and the relative risks of both seizures and AED therapy. This chapter reviews the clinical decision making in initiating and discontinuing AEDs in children and adults, with particular emphasis on the data regarding the recurrence risk for seizures in different settings and the effect of AEDs on this risk. Initiating and discontinuing AED therapy are then addressed in the context of an individualized therapeutic approach that emphasizes weighing the risks and benefits of drug therapy versus both the statistical risk of another seizure and the consequences of such an event.

RECURRENCE RISK FOLLOWING A FIRST UNPROVOKED SEIZURE

To develop a rational approach to the management of individuals who present with an initial unprovoked seizure, it is necessary to have some understanding of the natural history and prognosis of the disorder in this setting. Approximately one-third to one-half of children and adults with seizures will initially present to medical attention following a single seizure (1,2). The remainder will already have a history of prior events at the time of presentation. It is the group who presents with a single seizure that is most relevant to this discussion. In accordance with the International League Against Epilepsy (ILAE) guidelines for epidemiologic research in epilepsy, a first unprovoked seizure is defined as a seizure or flurry of seizures all occurring within 24 hours in a person older than 1 month of age with no prior history of unprovoked seizures (3).

Since 1982, a number of studies have attempted to address the recurrence risk following a first unprovoked seizure using a variety of recruitment and identification techniques (4–22). The reported overall recurrence risk following a first unprovoked seizure in children and adults varies from 27% to 71%. Studies that carefully excluded those with prior seizures report recurrence risks of 27% to 52% (4–18). Higher recurrence risks are, with one exception (19), reported from studies that included subjects who already had recurrent seizures at the time of identification and who were, thus, more properly considered to have newly diagnosed epilepsy.

While there is considerable disparity in the absolute recurrence risk reported in the different studies, the time course of recurrence is remarkably similar among all studies (5). The majority of recurrences occur early, with approximately 50% of recurrences occurring within 6 months of the initial seizure and over 80% within 2 years of the initial seizure (5,13). Late recurrences are unusual,

but they have occurred up to 10 years after the initial seizure (13,14). This time course is true in studies that report both low and high recurrence risks (4,5,7–10,12–14,19–21).

A relatively small number of factors are associated with a differential recurrence risk. The most important of these are the etiology of the seizure, the electroencephalogram (EEG), and whether the first seizure occurred in wakefulness or sleep. These factors are consistent across most studies regardless of the absolute risk of recurrence reported in the individual study (4,5,7–15,18,20,21). Factors not associated with a significant change in the recurrence risk include the age of onset, the number of seizures in the first 24 hours, and the duration of the initial seizure. The absolute recurrence risks appear similar in children and adults (5), although the consequences of such a recurrence are quite different. Selected risk factors are discussed below.

Etiology

In the ILAE classification, etiology of seizures is classified as remote symptomatic, cryptogenic, or idiopathic (3). Remote symptomatic seizures are those without an immediate cause but with an identifiable prior brain injury or the presence of a static encephalopathy such as mental retardation or cerebral palsy, which are known to be associated with an increased risk of seizures. Cryptogenic seizures are those occurring in otherwise normal individuals with no clear etiology. Until recently, cryptogenic seizures were also called idiopathic. In the new classification, idiopathic is reserved for seizures occurring in the context of the presumed genetic epilepsies such as benign rolandic and childhood absence (23,24). However, much of the literature on the recurrence risk following a first unprovoked seizure lumps idiopathic and cryptogenic together as idiopathic using the original classification developed by Hauser et al. (8).

Not surprisingly, both children and adults with a remote symptomatic first seizure have higher risk of recurrence than do those with a cryptogenic first seizure. A meta-analysis of the studies published up to 1990 found that the relative risk of recurrence following a remote symptomatic first seizure was 1.8 (95% confidence interval, 1.5, 2.1) compared to those with a cryptogenic first seizure (5). Comparable findings are reported in more recent studies (13,15,21). Idiopathic first unprovoked seizures occur almost exclusively in children. Although the long-term prognosis of these children is quite favorable, the recurrence risk is actually comparable to those with a remote symptomatic first seizure (13). This is because, by definition, to meet the criteria for an idiopathic first seizure, they must have an abnormal EEG (23,24).

Electroencephalogram

The EEG is an important predictor of recurrence, particularly in cases that are not remote symptomatic and in children (5,7,8,10–13,15–18,21,25). Studies of recurrence risk following a first seizure in childhood have uniformly reported that those with an abnormal EEG have a higher recurrence risk than do those with a normal EEG (5,7,12,13,15,21,25). For this reason, the American Academy of Neurology's recently published guideline on the evaluation of children with a first unprovoked seizure considers an EEG to be a standard part of the evaluation (21). A recent guideline on the diagnostic evaluation of adults with a first seizure also recommends an EEG, though the level of evidence is not as strong as in children (26). Epileptiform abnormalities are more important than nonepileptiform ones, but any EEG abnormality increases the recurrence risk in cases that are not remote symptomatic (25). In our study, the risk of seizure recurrence within 24 months for children

with an idiopathic/cryptogenic first seizure was 25% for those with a normal EEG, 34% for those with nonepileptiform abnormalities, and 54% for those with epileptiform abnormalities (25). Whereas in our data, any clearly abnormal electroencephalographic patterns—including generalized spike and wave, focal spikes, and focal or generalized slowing—increased the risk of recurrence, Camfield et al. (7) reported that only epileptiform abnormalities substantially increase the risk of recurrence in children. Despite minor disagreements as to which electroencephalographic patterns are most significant, the EEG appears to be the most important predictor of recurrence in children with a cryptogenic/idiopathic first seizure. In addition, it is the EEG that primarily distinguishes whether a neurologically normal child with a first seizure is classified as cryptogenic or idiopathic.

In adults, the data are more controversial. The majority of studies do find an increased recurrence risk associated with an abnormal EEG (5,9,10,18), although one study failed to find a significant effect (11). Hauser et al. (8) found that generalized spike-and-wave patterns are predictive of recurrence but not focal spikes. A meta-analysis of these studies concluded that the overall data do support an association between an abnormal EEG and an increased recurrence risk in adults as well (5), although which electroencephalographic patterns besides generalized spike and wave are important remains unclear (5,9,10,18). As the recent guideline points out, an EEG is recommended not only to assess recurrence risk but also to help classify the type of epilepsy and potentially identify a specific syndrome (26).

Sleep State at Time of First Seizure

In adults, seizures that occur at night are associated with a higher recurrence risk than are those that occur in the daytime (11). In children, whose sleep patterns may include daytime naps, the association is more clearly between sleep state and recurrence risk rather than time of day (13,27). Interestingly, the association is not just because nocturnal seizures tend to occur in certain epilepsy syndromes. Thus, even children whose EEG has centrotemporal spikes and who meet the criteria for benign rolandic seizures (24) have a higher recurrence risk if the first seizure occurs during sleep than if it occurs while awake (27). Furthermore, if the first seizure occurs during sleep, there is a high likelihood that the second one, should it occur, will also occur during sleep (27). In our series, the 2-year recurrence risk was 53% for children whose initial seizure occurred during sleep compared with a 30% risk for those whose initial seizure occurred while awake (13). On multivariable analysis, etiology, the EEG, and sleep state were the major significant predictors of outcome. From a therapeutic point of view, the implication of a seizure during sleep is unclear. While the recurrence risk is higher, recurrences will tend to occur in sleep. As the major risk of a brief seizure in children or adults is that it may happen at a time or place where the impairment of consciousness will have serious consequences, the morbidity of a seizure during sleep is fairly low in both cases.

Seizure Classification

In some studies, the risk of recurrence following a first unprovoked seizure is higher in subjects with a partial seizure than in those with a generalized first seizure (5). This association is mostly found on univariate analysis and disappears once the effect of etiology and the EEG are accounted for (5,8,12,13). Partial seizures are more common in those with a remote symptomatic first seizure and in children with an abnormal EEG (12). Note that some generalized seizure types, such as absence and myoclonic, very rarely present as a first seizure and so would be excluded from studies of first

seizure (16,21). Generalized seizures that present to medical attention at the time of the first seizure are usually tonic–clonic (13).

Duration of Initial Seizure

In children, the duration of the first seizure is not associated with a differential recurrence risk. In our study, 48 (12%) of 407 children (38 cryptogenic/idiopathic, 10 remote symptomatic) presented with status epilepticus (duration longer than 30 minutes) as their first unprovoked seizure (13). The recurrence risk in these children was not different from that in children whose first seizure was briefer. However, if a recurrence did occur, it was likely to be prolonged (13,28). Of the 24 children with an initial episode of status who experienced a seizure recurrence, 5 (21%) recurred with status. Of the 147 children who presented with an initial brief seizure and experienced a seizure recurrence, only 2 (1%) recurred with status epilepticus ($P < 0.001$). In adults, there is a suggestion that a prolonged first seizure, particularly in remote symptomatic cases, is associated with a higher risk of recurrence (10).

Number of Seizures in 24 Hours

The ILAE definition of a first unprovoked seizure includes a seizure flurry occurring within 24 hours (3). Well-designed prospective studies in both children (13) and adults (29) have found no difference in recurrence risks in patients who present with a cluster of seizures in 1 day compared with those who present with a single seizure. This is not an uncommon event and occurs in about 25% of cases. The data support the epidemiologic definition of a cluster as being a single event and do not suggest an increased risk of further seizures.

Treatment Following a First Seizure

Five randomized clinical trials in children and adults examined the efficacy of treatment after a first unprovoked seizure (6,20,30–34). Two well-designed prospective studies that randomized subjects to treatment or placebo following a first unprovoked seizure found that treatment reduced the recurrence risk by approximately half (6,20,30). The larger Italian study included both children and adults (20,30). However, while recurrence risk was reduced, there was no difference in long-term outcomes between the two groups. Equal proportions were in 2-year remission after 5 years of follow-up (30). Although the authors of this study initially recommended treatment following a first seizure, once it became apparent that early treatment did not affect long-term prognosis, they changed their recommendation, suggesting that in the majority of cases, treatment should not be recommended before a second seizure occurred (30). In the more recent Multicentre Trial for Early Epilepsy and Single Seizures, immediate treatment after a first unprovoked seizure reduced the risk of recurrence from 50% to 25% but did not alter long-term outcome (34,35). In general, the accumulating evidence from a large number of studies indicates that AED therapy is effective in reducing the risk of a recurrent seizure but does not alter the underlying disorder and therefore does not change long-term prognosis (36). Based on these data and assessment of risk-to-benefit, the American Academy of Neurology has issued a practice parameter on AED therapy following a first unprovoked seizure in children and adolescents (33). This parameter recommends that (i) treatment with AEDs is not indicated for the prevention of the development of epilepsy and (ii) treatment with an AED may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the

risks of pharmacologic and psychosocial side effects. The authors rarely prescribe AEDs after a single seizure. A practice parameter addressing this issue in adults is currently under development, but the epidemiologic data and the data from randomized clinical trials are increasingly in favor of not routinely treating after a single seizure even in adults.

What Happens After Two Seizures?

Two studies in adults (9) and children (14) examined what happens after a second seizure. In adults, the recurrence risk after a second seizure is 70%, leading Hauser et al.(9) to conclude that, in adults, once a second seizure has occurred, treatment with AEDs is appropriate. In children, the recurrence risk following a second seizure is also approximately 70%. Those with a remote symptomatic etiology and those whose second seizure occurs within 6 months of the first have a higher recurrence risk (14). Interestingly, factors such as an abnormal EEG and sleep state at the time of the seizure, which help to differentiate those who only have one seizure from those who experienced a recurrence, are no longer associated with a differential risk of further seizures once a second seizure occurs (14). Despite the similarities in recurrence risk, the issue of treatment following a second seizure in children is less straightforward than in adults. Many of these children have idiopathic self-limited epilepsy syndromes, such as benign rolandic, where the need for treatment has been questioned (37–39). In addition, the frequency of seizures in this group is low, with only 25% of children who had 2 seizures experiencing 10 or more seizures over a 10-year period (14). Thus, the decision regarding treatment in children with cryptogenic/idiopathic seizures who have a second seizure must be individualized and take into account whether the seizures are part of a benign self-limited syndrome, as well as the frequency of the seizures and the relative risks and benefits of treatment.

WITHDRAWAL OF ANTIEPILEPTIC DRUGS IN THOSE WHO HAVE BEEN SEIZURE FREE ON ANTIEPILEPTIC DRUG THERAPY

AED therapy effectively controls seizures in the majority of patients with epilepsy. The preponderance of evidence indicates that most patients with epilepsy will become seizure free on AEDs within a few years of diagnosis (40–47). However, the long-term use of AEDs carries with it significant morbidity. Therefore, the issue of whether one can withdraw AEDs in patients with epilepsy after a seizure-free interval becomes important in the treatment of a vast number of patients.

A large number of prospective and retrospective studies including children, adolescents, and adults, involving thousands of subjects, have been done over the past 25 years on the question of remission and relapse rates after withdrawal of AEDs (41,48–81). A meta-analysis of the available literature reported a pooled risk of relapse of 25% at 1 year and 29% at 2 years following AED withdrawal (50).

In childhood-onset epilepsy, the majority of studies report that 60% to 75% of children and adolescents with epilepsy who have been seizure free for more than 2 to 4 years on medication will remain so after AEDs are withdrawn (48–51,57–59,61–65,67,72–75,78,80,81). Exceptionally low recurrence rates of 8% to 12% were reported in studies that limited subject entry to neurologically normal children with normal EEGs, many of whom were followed since the onset of their seizures

(66,77).

In the past, it was thought that adult-onset epilepsy had a far less favorable prognosis for remission than did childhood-onset epilepsy and that withdrawal of medications was rarely feasible in this population. Although the prognosis in adults does appear to be worse than in children, newer studies suggest that the differences are smaller than thought. Four years after onset, the majority of adults with new-onset seizures will be at least 2 years seizure free (45,46). Many adults self-discontinue their medications and are still seizure free years later (40,80). Studies of withdrawing AEDs in adults report recurrence rates of 28% to 66% (51,54,60,64,67,69,79), which is a much larger range than that reported in pediatric studies. However, it should be noted that studies that reported the lowest recurrence risks (54) limited themselves to patients followed since onset of their seizures and who had absence of other presumed risk factors. In pediatric studies, such selected populations have reported recurrence risks of <20%.

The preponderance of data at this time indicates that the recurrence risk following withdrawal of AEDs is somewhat higher in adult-onset epilepsy than in childhood-onset epilepsy with a relative risk of approximately 1.3 (50). However, much of the increased risk reported in some studies is a result of the higher risk of recurrence in adolescent-onset seizures (50,72). Selected populations of adults may have low recurrence risks. Two reports showed no differences in recurrence risks between children and adults (54,79). However, these studies have the highest reported recurrence risks for children (31% to 40%) and the lowest reported recurrence risks for adults (35% to 40%). In addition, their definition of children exceeds the usual limits of the term. In one study, 38% of the subjects had childhood onset, but this was defined as onset before 15 years of age (54). Several studies in children have reported that an age of onset older than 10 or 12 years was associated with a higher recurrence risk, presumably because this already reflects early adult-onset epilepsy (52,71–73,77).

The data on adolescents indicate that the recurrence rate is more a function of the age at onset than the age at withdrawal of medications (50,72,73). Studies of childhood-onset epilepsy that included adolescents have reported low recurrence risk (49,50,52,58,66,72,73,75,77). Studies of adolescents and adults that have primarily included adolescent-onset cases have reported recurrence rates similar to those seen in adults (50,54,64,79). One retrospective study limited to adolescents with adolescent-onset seizures reported a recurrence rate of 49% (70). A recent meta-analysis found that adolescent-onset epilepsy has a higher recurrence risk following AED withdrawal than either childhood- (relative risk, 1.79) or adult-onset (relative risk, 1.34) epilepsy (50).

When recurrences do occur after discontinuation of AEDs, they tend to occur early (50,72). The timing of recurrence is similar in studies of both children and adults and is independent of the absolute recurrence risk. Many occur as the medications are being tapered. At least half the recurrences occur within 6 months of medication withdrawal, 60% to 90% of recurrences occur within 1 year of withdrawal, and more than 85% of recurrences occur within 5 years (50,5153,55,59,63–65,67,68,70,73,74,76,80). One series in adults reported that 68% of relapses were during drug withdrawal and an additional 24% occurred during the first year after discontinuation of treatment (69). Although late recurrences do occur, they are uncommon (62,72,82). There is no secondary peak in recurrence risk years after discontinuing medications.

In analyzing recurrence risks following withdrawal of AEDs, one must also consider the recurrence risk of patients who are candidates for medication withdrawal but are maintained on AEDs. Annegers et al. (40) found a mean relapse risk of 1.6% per year in patients who were in remission for 5 or more years. Similarly, Oller-Daurella et al. (83) reported a 12.6% recurrence rate

in a group of patients who were maintained on AEDs after being in remission for 5 or more years. One large-scale, randomized trial of continued AED therapy versus slow withdrawal in 1013 patients who were seizure free for 2 or more years found a 22% recurrence rate in those maintained on medications compared with a 42% recurrence rate in those whose medications were withdrawn (68). However, after 2 years, the subsequent recurrence risks were identical, suggesting that the increased risk of recurrence attributable to AED withdrawal occurs only in the first 2 years. Late recurrences occur but are not attributable to AED withdrawal. These relapse rates must also be considered when deciding on whether to continue long-term AED therapy. Interestingly, in a 30-year follow-up study of 178 patients with epilepsy, there was a slightly higher recurrence rate in those patients who remained on AEDs, although the two groups were not randomized and were, therefore, not fully comparable (47).

RISK FACTORS FOR RECURRENCE

Clinically, it is important to identify subgroups with better or less favorable prognoses for maintaining seizure remission off medications. It is essential to quantify the significance of risk factors such as etiology, age of onset, type of seizure, and the EEG; however, different studies give very different results. A discussion of potential risk factors and their significance is presented below.

Etiology and Neurologic Status

Patients with remote symptomatic epilepsy associated with a prior neurologic insult, congenital malformation, motor handicap, brain tumor, mental retardation, progressive metabolic disease, trauma, or stroke are less likely to attain complete seizure control than are those with cryptogenic or idiopathic epilepsy (40,43,47).

Even in patients with remote symptomatic epilepsy who do attain seizure remission while on medications, current data indicate that the relapse rate after discontinuation of AEDs is higher than in those with cryptogenic seizures. In one study of 264 children and adolescents, the cumulative recurrence risk 2 years following withdrawal of medications was 26% in the cryptogenic group and 42% in the neurologically abnormal group ($P < 0.005$) (72). Despite the increased risk of recurrence in the neurologically abnormal group, the majority of this population was successfully withdrawn from AEDs. The severity of mental retardation was an additional prognostic factor within this group.

Similar results have been found in other studies (50,58,62–64). A recent study of the prognosis of epilepsy in children with cerebral palsy and epilepsy (55) found that the majority of these children did not achieve remission. However, of the 69 children who achieved a 2-year seizure remission and had their medication withdrawn, 58% remained seizure free. The type of cerebral palsy was associated with a differential risk of recurrence. With one exception (65), studies that did not find such an association either had very few (73) remote symptomatic cases or were restricted to those with cryptogenic epilepsy (54,66,69,77,79). A meta-analysis estimated the relative risk of recurrence in those with remote symptomatic epilepsy compared with cryptogenic epilepsy to be 1.55 (50). This applies to all remote symptomatic causes including both mental retardation and cerebral palsy. Within the remote symptomatic group, those with severe mental retardation have the highest recurrence risk (72).

Age

As discussed, adolescent- and adult-onset epilepsy are associated with a somewhat poorer prognosis for successful withdrawal of AED therapy (50,60,64,67,69,70,72), although selected populations may do well (54,79). The discussion that follows focuses on differences within the pediatric age group.

Many studies report that an age of onset younger than 12 years is associated with a lower recurrence risk following discontinuation of medication than is an older age of onset (49,50,52,58,64,71–73,77). This corresponds to the known higher remission rates in the younger group (40,43,84).

There is some controversy as to whether a very young age of onset of younger than 2 (58,72,84) or 3 years (57,78) may be a poor prognostic factor. Studies that include large numbers of children with remote symptomatic epilepsy have found a worse prognosis in the very young (58), whereas studies of mostly cryptogenic epilepsy have produced conflicting results (57,65,73,78). In one study that examined this question (72), 73% of the children with age of onset older than 12 years and 45% of those with age of onset younger than 2 years experienced seizure recurrence compared with 26% of those with age of onset between 2 and 12 years ($P < 0.0001$). However, the poorer prognosis in those with a very young age of onset was limited to the remote symptomatic group (72). These data are consistent with the findings of Huttenlocher et al. (85) that neurologically abnormal children with seizure onset at younger than 2 years of age had a poor prognosis for entering remission.

There are no convincing data that withdrawing AEDs during puberty are associated with a higher risk of recurrence (38,62,63,73,86). In fact, with the exception of one isolated report (82), studies on the remission of seizures and on withdrawing AEDs (40,62,63,72,73,75) do not show a reproducible pattern that correlates with puberty. The probability of attaining remission and of maintaining remission after medication withdrawal is more a function of the age of onset and the duration of the seizure disorder, without a special role for puberty.

Electroencephalogram

An abnormal interictal EEG, particularly one with epileptiform features, is often cited as a predictor of relapse after AED withdrawal (4,50,73,87,88). Results of actual studies in children and adults, however, are conflicting.

In children, a substantial number of studies found that the EEG prior to discontinuation of AEDs was an important predictor of outcome (38,41,50,58,70–73,75). Interestingly, any electroencephalographic abnormality, not just a frankly epileptiform one, was associated with an increased risk of relapse. In a study that examined specific features of the EEG, the presence of either slowing or spikes was associated with an increased risk, and the presence of both in the same patient was associated with a very high risk of recurrence (73). Two studies reported that only certain specific epileptiform patterns, such as irregular generalized spike-and-wave pattern, were associated with an increased recurrence risk following medication withdrawal (41,87).

Further evidence for the importance of the EEG as a predictor of outcome can be inferred from three large studies (49,66,77). Because these studies excluded children with abnormal EEGs and report very low recurrence risks of 8% to 12%, they provide indirect evidence for the importance of the EEG as a predictor of recurrence. However, some studies in children did not find the EEG to be predictive (52,63). The studies that did find the EEG to be predictive were mainly of children with cryptogenic seizures. In studies that specifically analyzed the relationship between the EEG and outcome in both cryptogenic and remote symptomatic cases, the EEG was a significant predictor of outcome only in the cryptogenic group (72).

The EEG prior to treatment may also have some predictive value. Certain electroencephalographic patterns are markers for specific epileptic syndromes, such as benign rolandic epilepsy, childhood absence, or juvenile myoclonic epilepsy, which are thought to have a particularly favorable or unfavorable prognosis for remaining in remission following drug withdrawal (24,38,86,89). Changes in the EEG between the onset of seizures and time of medication withdrawal may also have a prognostic value (54,73).

The number of adult studies that have examined this issue is relatively small. Callaghan et al. (54) reported that an abnormal EEG was associated with an increased risk of recurrence. However, several other adult studies reported no such association (69,79). At present, the preponderance of evidence indicates that an abnormal EEG is a predictor of recurrence in children with cryptogenic epilepsy but not in those with remote symptomatic epilepsy. In adults, the data are inconclusive but suggest that an abnormal EEG is associated with a modest increase in recurrence risk (50,51,88). Whether specific electroencephalographic patterns are associated with an increased recurrence risk is a question that requires further study.

Epilepsy Syndrome

Epilepsy syndromes are known to be associated with a differential prognosis for remission (23,24,90). Syndromes such as benign rolandic epilepsy have a particularly favorable prognosis for remission and for successfully discontinuing AEDs, even if the EEG is still abnormal (72), as EEG normalization occurs later than the clinical disappearance of seizures (23). Juvenile myoclonic epilepsy, while having a favorable prognosis for remission on medications, usually requires prolonged treatment and has a high relapse rate when medications are withdrawn (24,89). Syndromes such as Lennox–Gastaut have a poor prognosis for remission even on medications (24,47,90). Overall, patients with both idiopathic and cryptogenic epilepsy syndromes have a similar prognosis (47,72,90). Interestingly, while specific idiopathic syndromes and the various other generalized epilepsy syndromes have different prognoses, the various nonidiopathic partial epilepsies do not appear to have major differences in the relapse rate following medication withdrawal (72). Unfortunately, there is a paucity of such information as few studies of AED withdrawal provide information by epilepsy syndrome. It is clear that future studies will focus on epilepsy syndrome as a major predictor of long-term prognosis and management, both at the time of diagnosis and when in remission on medications (23,42,72,90).

Other Risk Factors

Other risk factors, such as duration of epilepsy, number of seizures, seizure type, and the medication used, have not been consistently associated with a differential risk of relapse following AED withdrawal in either children or adults.

Duration of epilepsy and number of seizures are closely interrelated. A long duration of epilepsy increases the risk of recurrence, although the magnitude of the effect is small (62,63). One study also reported that having more than 30 generalized tonic–clonic seizures was associated with a high risk of recurrence after discontinuation of therapy (58). In a community-based practice, most people are easily controlled within a short time after therapy is initiated so that these factors will rarely be important (42,46,47).

The specific AED used also has not been consistently associated with the risk of recurrence,

although one well-designed study reported an increased recurrence risk in adults who were on valproate compared with those on other AEDs (54). Note that all the published studies on AED withdrawal are reporting the results of AED withdrawal from the old AEDs (barbiturates, phenytoin, carbamazepine, valproate, and ethosuximide). The serum drug level does not seem to have a great impact on recurrence risk. Patients who have not had seizures for several years often have "subtherapeutic" levels, and few have high levels. Available studies show little or no correlation between drug level prior to discontinuation and seizure recurrence and outcome (73) or a very modest effect (58).

Seizure type has also not been consistently associated with recurrence risk, except that children with multiple seizure types have a poorer prognosis (62,63,81). The data regarding partial seizures are conflicting (50,52,54,58,62–64,67,72,73,75). Note that specific seizure types may be surrogate markers for epilepsy syndromes with a more favorable or less favorable prognosis. At this time, it is not clear that any specific seizure type is associated with an increased risk of recurrence following discontinuation of medication.

HOW LONG TO TREAT AND HOW RAPIDLY TO TAPER?

Duration of Seizure-Free Interval Prior to Attempting Withdrawal of Antiepileptic Drugs

The chances of remaining seizure free after medication withdrawal is similar whether a 2-year (49,52,54,64,72,73,75) or a 4-year seizure-free interval (58,62,63,67,72,75) is used. One study that evaluated seizure-free intervals of 1 or more years did find that a longer seizure-free period was associated with a slightly lower recurrence risk (75). However, the higher relapse rates were primarily observed in those who were withdrawn after 1 year. In general, the epidemiologic data do not support the need for treatment beyond 2 years in cases where AED withdrawal is being considered.

A few investigators attempted to withdraw AEDs in children with epilepsy after a seizure-free interval of 1 year or less (56,71,87). A meta-analysis found a pooled relative risk of 1.3 for withdrawal prior to 2 years seizure free versus 2 or more years seizure free (88). While the recurrence risks in these studies are somewhat higher than in studies that used a longer seizure-free interval, they do suggest that, in selected populations, a shorter seizure-free interval may be sufficient. The higher recurrence risks reflect the fact that when a less stringent criterion for remission is used, fewer patients are actually in long-term remission. Long-term outcomes are not adversely affected by early discontinuation (71).

Duration of Medication Taper

Once the decision to withdraw AEDs has been made, the clinician needs to decide on how quickly the medications can be withdrawn. Many clinicians have used slow tapering schedules lasting many months or even years, thinking that they would reduce the risk of recurrence. Even the randomized study from the Medical Research Council (MRC) AED Drug Withdrawal Group (67) used a relatively slow taper. There is general agreement that abrupt discontinuation of AEDs is inadvisable

in an outpatient setting and may increase the risk of seizure recurrence. Beyond that, there is much heated debate primarily based on mythology. A well-designed, prospective, randomized clinical trial has provided solid data on this issue (74). The study compared a rapid 6-week AED taper with a more gradual 9-month taper in children with epilepsy whose AEDs were being discontinued after a 2-year or longer seizure-free interval. There were no differences in recurrence risk at 2 years between the groups with short and long tapering regimens. This well-designed study should finally settle this long-standing controversy, although specific drugs, such as barbiturates and benzodiazepines, might require slightly longer tapering periods. Note that a long tapering period will not alter the recurrence risk at 2 years but may delay the recurrence and, thus, tends to prolong the period of uncertainty. Thus, a relatively short taper period is particularly important in adolescents and adults if we advise them to stop driving for 6 months to a year following AED withdrawal.

Prognosis Following Relapse

The majority of patients who relapse after medication withdrawal will become seizure-free and in remission after AEDs are restarted, although not necessarily immediately (47,71,83,91,92). The prognosis for long-term remission appears to be primarily a function of the underlying epilepsy syndrome. The MRC randomized study of medication withdrawal in children and adults found that the prognosis for seizure control after recurrence in patients with previously well-controlled seizures was no different in those who were withdrawn from AED therapy and relapsed and those who relapsed while remaining on AED therapy (92).

WITHDRAWAL OF ANTIEPILEPTIC DRUGS AFTER SUCCESSFUL RESECTIVE SURGERY

Epilepsy surgery is the treatment of choice in suitable patients with refractory epilepsy. Patients with intractable epilepsy who undergo resective surgery are considered a class 1 successful outcome if they are seizure free following surgery, whether they are on AEDs (93,94). In the past, the tendency was to maintain them on at least one AED indefinitely (94). The issue of whether and for how long patients who are seizure free following surgery need to remain on chronic AED therapy is receiving increased attention. Several retrospective studies in adults report that approximately 60% of patients with medically refractory epilepsy who become seizure free after resective surgery remain so when AEDs are withdrawn (95–97). Younger age at surgery and presence of hippocampal sclerosis on imaging were favorable predictors for seizure freedom after AED discontinuation (98–101). Factors consistently associated with a high risk of relapse include age older than 30 years at time of surgery, longer duration of epilepsy, persistent epileptiform discharges on EEG, and normal imaging preoperatively (98–101). Following neocorical resections, reported risk of relapse following medication reduction may be much higher, particularly when imaging is negative (102) Successful withdrawal of AEDs following resective surgery has also been reported in children (103,104). Generally, the risks of medication withdrawal in this population appear similar to those seen in those with remote symptomatic epilepsy in remission on medications (50,72). It, therefore, appears reasonable to consider medication withdrawal in patients who are seizure free following resective surgery (94,97,103). The prognostic factors for successful medication withdrawal are not well defined but appear to be different than for those who become seizure free with medical therapy (97). The optimal timing for medication withdrawal in this population is not clear.

In principle, one can ask, following a potentially curative procedure, why wait more than a short seizure-free interval, such as 6 months or a year, before attempting withdrawal in this population (97). Berg et al. (105) reported that many of the relapses in patients who attained at least 1-year seizure, remission occurred while reducing or eliminating the AEDs. The risk of recurrence was not higher than in those who continued AEDs (105–107). The physician should remember that while some patients may be eager to try coming off medication in the belief that they are cured (97), many may be unwilling to jeopardize their newly achieved seizure-free state (107). The decisions need to be individualized, based on the potential risks and benefits in each case and the personal preferences of the patient.

Further, well-controlled prospective studies are needed to provide rational practice guidelines to inform the clinical decision in this setting.

RISKS OF NOT TREATING OR OF DISCONTINUING ANTIEPILEPTIC DRUGS

The major risk associated with not treating after first seizure or of discontinuing AED therapy is having a seizure recurrence. The potential consequences of the seizure recurrence include both direct consequences and psychosocial impact. There is no convincing evidence that a brief seizure causes brain damage (33,39,108,109). Serious injury from a brief seizure is a relatively uncommon event usually related to the impairment of consciousness or loss of consciousness that occurred at an inopportune time or place (e.g., driving, riding a bicycle, swimming, on a stairway, cooking) (25,39,83). These are much less likely to occur in children who are usually in a supervised environment and are not driving, operating heavy machinery, or cooking. In a study of withdrawing AEDs in 264 children with epilepsy who were seizure free on medication, there were 100 recurrences (83). Of these, 2 experienced status epilepticus as their initial recurrence and have done well after reinitiation of AEDs with no long-term consequences. Five sustained an injury as a result of the initial recurrence, including 4 with lacerations and 1 with a broken arm. Thus, the rate of serious injury was quite low. Most reports of serious injuries in patients with epilepsy discuss patients with intractable epilepsy who experience injuries such as burns in the context of frequent seizures (110,111).

Status epilepticus is a concern, particularly in adults. It should be noted that the morbidity of status epilepticus in both children and adults is primarily a function of etiology, and in this clinical setting will be low (109,112–114). Furthermore, the risk of status epilepticus in this population is low and essentially limited to those who have had it before (13,28). While status epilepticus is frequently reported in patients with epilepsy who are noncompliant (112,113), the occurrence of status epilepticus in patients who are withdrawn from their AEDs after a seizure-free interval is very low (73,83). Sudden Unexplained Death in Epilepsy is of increasing concern but has not been reported in those not treated after a first seizure unless they have had many more seizures (20,25,34,115) and has not been reported in trials of discontinuation of medications in patients who are seizure free.

Some authors, most notably Reynolds, have expressed concern that, in addition to the potential for injury, the consequences of a seizure include a worse long-term prognosis, and thus, argue that treatment is indicated even after a single seizure (19,116). This view is largely based on Gower's statement that "The tendency of the disease is toward self-perpetuation; each attack facilitates the

occurrence of the next by increasing the instability of the nerve elements" (117), which became the basis for the popular notion that "seizures beget seizures." Current epidemiologic data and data from controlled clinical trials indicate that this is not the case (16,17,30,33,37,92,108,112). Studies in developing countries, where treatment delays are a result of the unavailability of AEDs, show no difference in response rate in those with many prior seizures compared with new-onset patients (37,118). Prognosis is primarily a function of the underlying epilepsy syndrome, and although treatment with AEDs does reduce the risk of subsequent seizures, it does not alter the long-term prognosis for seizure control and remission (16,30,33,37,118). The decision to treat should, therefore, be made on the grounds that the patient has had a sufficient number of events to justify initiating therapy or is at sufficiently high risk for seizure recurrence to justify continued therapy and not with the hope of somehow preventing the development of "chronic" epilepsy (33).

Although a seizure may be a dramatic and frightening event, the long-term psychosocial impact of an isolated seizure in children is minimal. In adults, the psychosocial impact can be more serious, and includes the loss of driving privileges and possible adverse effects on employment (119,120). Social stigma of seizures is also much more a concern in adolescents and adults.

RISKS OF INITIATING OR CONTINUING TREATMENT WITH ANTIEPILEPTIC DRUGS

Although effective in controlling seizures, AEDs are associated with a variety of significant side effects that must be considered when deciding to initiate or to continue treatment (Table 45.1). Physicians are generally familiar with systemic side effects, including idiosyncratic, acute, and chronic. Idiosyncratic and acute adverse events sufficient to require discontinuation of the drug occur in 15% or more of patients newly treated with an AED and need to be considered when deciding whether to initiate AED therapy. They are not generally a major concern when deciding whether to continue AEDs in patients who are seizure free as almost all those patients are on stable drug regimens without evidence of acute toxicity. Chronic toxicity is a concern in both settings. There is evidence that children may be more susceptible to chronic toxicity from AEDs (33). In the elderly, an additional concern is drug–drug interaction, as many of these patients are on multiple other medications that also are protein bound and metabolized by the cytochrome P450 system. Adverse effects on many AEDs on bone health are also of increasing concern (121).

Table 45.1 Risks and Adverse Effects of AED Therapy and of Seizures[a]

Risks of AED therapy	Risks of seizures
Systemic toxicity	Physical injury
Idiosyncratic	Loss of consciousness
Dose related	Falls
Chronic toxicity	Status epilepticus
Children and adolescents	
	Sports injuries
	Bathing/swimming: drowning
Adolescents and adults	
Teratogenicity	Driving accidents
	Bathing/shower: scalding
	Cooking injuries, burns
Higher cortical functions	
Cognitive impairment	Impairment in postictal state
Children	
Adverse effects on behavior	
Psychosocial	
Need for daily medication	Fear of subsequent seizures
Labeling as chronic illness	Loss of privacy
	Stigma of seizures
Children and adolescents	
	Restrictions on school/social activities
Adolescents and adults	
	Restrictions on driving
	Difficulties providing childcare
Economic/temporal	
Cost of medications	Time lost because of seizure and recovery
Cost/time of laboratory tests	
Cost/time of physician visits	
Adolescents and adults	
	Discrimination in employment

[a]Some adverse effects of seizures may also occur with AED therapy. Adverse effects listed by age group, such as behavioral effects and bathtub drowning, are meant to indicate the predominant age group in which they occur and do not exclude their occurrence in other age groups.

It is now recognized that AED therapy is associated with a variety of both cognitive and behavioral adverse effects (33,122). These are more common in children, and sometimes are difficult to recognize. In particular, children on medications since their preschool years may not be identified as having side effects from medications. Only when medications are stopped does it become apparent that the child's performance was impaired by the drug. Adults can also experience cognitive and behavioral adverse events from AED therapy. Increasingly, studies of new AEDs include measures of neuropsychological function to help address this issue. The reason phenobarbital is no longer considered a first-line drug in adults with epilepsy is not because of its efficacy, which is excellent, but because of the impairment of cognition and behavior associated with its use. Although other agents are less of an issue, all AEDs can have adverse effects on cognition and behavior (33,122).

For women of childbearing age, including adolescents, a discussion of the risks of treatment must include consideration of the potential teratogenicity of these compounds (123). As the major teratogenic effects usually occur in the first few weeks of gestation, often before a woman is aware that she is pregnant, the physician must always consider this issue in advance. It impacts both on the decision to initiate or withdraw AED therapy and on the choice of AED. One must also consider that

many pregnancies, particularly in adolescents, are unplanned. Furthermore, enzyme-inducing AEDs may reduce the efficacy of oral contraceptives by inducing the hepatic enzyme systems responsible for their metabolism (123). For this reason, we are reluctant to initiate AED therapy in adolescent females and are particularly aggressive in trying to withdraw them from medications after a 2-year seizure-free interval, even if their other risk factors are not favorable.

A hidden side effect of continued AED treatment is that of being labeled (see Table 45.1). People with single seizures or epilepsy who have not had a seizure in many years and are off medications are considered to be healthy both by themselves and society. Those individuals can lead normal lives with very few restrictions. Unless they choose to, they rarely need to disclose that they once had seizures. In contrast, even if a patient only had a single seizure or is seizure-free for many years, being on AED therapy implies chronic illness to both the patient and those around the patient (33,120,123). Continued use of medication requires ongoing medical care to prescribe and monitor the medication and establishes that the individual is a patient in need of treatment for a chronic condition. It also implies certain restrictions in driving and may have an adverse impact on obtaining employment and other social issues. Labeling is a problem in both children and adults. The MRC study reported that psychosocial outcomes were improved in adults who were successfully withdrawn from AED therapy (120). In children and adolescents there is the additional problem that the perception of any chronic illness adversely affects the normal psychosocial maturation process, particularly in adolescents (38,124).

COUNSELING FAMILIES

Decisions on initiating or discontinuing AEDs ultimately depend on a relative assessment of risks and benefits. These are assessed differently by physicians and by patients and their families. Therefore, providing appropriate education and counseling to the patients and their families is critical, regardless of the final therapeutic decision. Both seizures and AED therapy are associated with some risks. Even though patients with good prognostic factors have a lower risk of recurrence, this risk is not zero even if they stay on medications. Conversely, those with poor risk factors may nevertheless maintain remission off medications. The risk of adverse events from AED therapy is essentially independent of the recurrence risk and always needs to be considered, as does the psychosocial impact of both seizures and continued AED therapy. Education assists the patient and family in making an informed decision, helps them to fully participate in the plan of care, and prepares them to deal with psychosocial consequences of the diagnosis. Informed decision making by the physician, in consultation with the family, maximizes the chances of good long-term outcomes.

Patients and families need to be reassured that the risk of a serious injury or death from an isolated seizure is low. They also need to be counseled about appropriate first aid for seizures and safety information. This is a particular problem for adults, as they are more likely to engage in activities that may predispose them to injury should a seizure occur. Places of employment may or may not be accommodating to the person at risk for a seizure.

A discussion of possible restrictions on activities is also important. Parents will need to be told that most of the child's activities can be continued, although some, such as swimming, may need closer supervision. Adolescents and adults will need specific instructions regarding activities such as swimming, cooking, and driving. Counseling often allays fears and educates the patient and family on safety precautions. This reduces the chance for injury from seizures, if the patient is treated. Educational programs are available for school personnel—teachers, nurses, and students—and

information for babysitters is also readily available. Note that, in the case of the child or adult with a first seizure, this discussion is equally applicable whether one decides to initiate AED therapy, as therapy reduces, but does not eliminate, the risk of seizure recurrence.

The information provided must be individualized to both the situation and the sophistication level of the patient and the family. The family of a patient with epilepsy who is seizure free on medications should be familiar with the side effects of AED therapy and with seizures, and be able to discuss recurrence risks from withdrawing AEDs and the potential consequences. In the case of patients with a first seizure, the discussion needs to be more comprehensive, including first-aid measures in case of a recurrence, potential adverse effects of AEDs, risks of recurrence, impact on long-term prognosis of delaying therapy until after a second seizure, and restrictions on activity that will occur with or without therapy. It may be difficult to accomplish this in one session, especially in the emergency department where the circumstances may not be conducive to a calm discussion of the relative risks and benefits and where key information on recurrence risks, such as the results of the electroencephalograph or an imaging study, may not be available.

Families will usually be interested in information that will help them manage the illness or specific problems. Lengthy explanations on any one issue may be confusing and are usually not helpful. Children and adults may have fear of accidents, fear of the loss of friends, fear of taking "drugs," and other less well-defined concerns. A parent's perception of the child's disorder will be an important factor in later coping and will ultimately impact on the perception of quality of life. Adults may have to make major lifestyle changes. The practitioner's prejudices regarding treatment options will undoubtedly come into play during these discussions, but the different options need to be discussed. Although more time-consuming than issuing a prescription, this counseling is necessary for both informed decision making and for favorable long-term outcomes.

A THERAPEUTIC APPROACH

Initiating Antiepileptic Drug Therapy

In children with a first seizure, there is an emerging consensus that treatment after a first unprovoked seizure is usually not indicated (6,7,12–14,33,39,50), particularly in neurologically normal children with a brief first seizure (33). We will rarely treat a child with a first unprovoked seizure, even in the presence of risk factors such as a remote symptomatic etiology, an abnormal EEG, or a prolonged first seizure (13,14). In children with infrequent brief seizures, particularly in the context of a self-limited benign childhood epilepsy, many clinicians do not initiate AED therapy even after a second or third seizure (14,16,37–39). This is based on an assessment of the relative risks and benefits of AED therapy in children who will most likely enter remission with or without treatment and who will most likely continue to have only infrequent seizures (14). However, there is no consensus on this issue.

In adults, the decision to treat or not after a first seizure remains more controversial (9,17,30,116). However, prospective studies show lower recurrence risks than previously thought and a well-designed, prospective, randomized study demonstrated no impact on long-term prognosis from delaying therapy (30,33,36). Therefore, a growing number of clinicians are delaying initiating long-term AED therapy after a single seizure (9,17,30). This is particularly true in young adults who would be committing to long-term therapy and in women of childbearing potential. Following two seizures, the risk of further seizures is approximately 70%, and, in general, AED treatment is

indicated (9). The major exception may be a woman who wishes to have children in the immediate future and who has had two brief seizures. In this setting, there is no definite answer, and the clinician and the patient must again weigh the relative risks and benefits of initiating therapy at that time or waiting (123).

In both children and adults, a thorough evaluation of the patient, including a detailed history and neurologic examination, as well as appropriate laboratory studies, such as an electroencephalograph and an imaging study when indicated, are important (21). Of particular importance is a careful history of prior events that may be seizures (21). A substantial proportion of patients who first come to medical attention with a seizure turn out to have had prior episodes that were also seizures (1,2,12,21). This is particularly true for patients who present with a first convulsive episode and, after a careful history is taken, are found to have had prior nonconvulsive episodes of absence or complex partial seizures. These patients fall into the category of newly diagnosed epilepsy, and not first seizure, and usually need treatment.

Withdrawing Antiepileptic Drug Therapy

The question of continuing or withdrawing AED therapy in a given patient must be considered based on an analysis of the relative risks and benefits. The goal is to achieve the best possible outcome for that patient, whether the ultimate decision is to treat or not. In considering the risks of seizure recurrence, the statistical risk of relapse is only one piece of the puzzle. One must consider not only the mathematical probability of seizure recurrence but the consequences of such a recurrence. The risk of seizure recurrence following medication withdrawal in children is somewhat lower than in adults, and, in addition, there are identifiable subgroups with a particularly favorable prognosis. Adverse effects of continued AED therapy are also clearly more an issue with children than with adults, particularly adult males. However, it is in the area of potential consequences of a recurrence that the differences are most pronounced.

The adult who is driving and employed can suffer significant adverse social and economic consequences from having a seizure. In addition, an adult is more likely than is a child to have the seizure in a setting where a physical injury may occur as a result of impaired consciousness (e.g., driving, operating machinery, cooking). Therefore, a 30% risk of recurrence, which is very acceptable in most children, may be unacceptable to adults because of the more serious consequences of a recurrence. When these are taken into account, patient preferences clearly depend on age and gender, despite similar statistical risks. In the British MRC AED withdrawal study, the psychosocial outcomes of those who successfully came off AEDs were better, and the statistical risk of recurrence was similar to those seen in children (67,68). However, when other adult patients were counseled based on the results of that study, the majority chose to remain on AED therapy (119). Nevertheless, adults who are seizure free on their AEDs for 2 or more years should have the option of AED withdrawal discussed, even if the recommendation of the clinician is to remain on medications, as some patients will find the risk-to-benefit ratio favorable (119,125). Women of childbearing age are a special category, where a more aggressive approach to AED withdrawal may be indicated for reasons already discussed (123,125). Another category where a more aggressive approach should be considered is young adults of either gender with childhood-onset epilepsy who are still on medications. A chance at AED withdrawal, especially if they do not need to drive, should be considered before committing them to life-long therapy (38).

The reverse argument may be made for young children. In this group, the risk of relapse is smaller

and, depending on the degree of parental supervision, the consequences relatively minor, whereas the risks of side effects from medications are greater. It is much safer to withdraw AEDs in this environment than when the patient is an adult. The risk-to-benefit analysis favors attempting medication withdrawal even in those with a higher risk of relapse (38,56,87).

Adolescents are a special case with additional issues. Adolescents with any chronic illness tend to become noncompliant as part of adolescence. We would far rather withdraw AEDs in a controlled fashion and make the explicit contract that if a recurrence occurs both the patient and the clinician know that medications are needed, than have the adolescent drive and then become noncompliant. In adolescent women, issues of teratogenicity also need to be considered, especially as most pregnancies in this age group are unplanned. Even if immediate pregnancy is not a major concern, these young women will soon be entering their childbearing years and decision making needs to take this into account (123). On a risk-to-benefit basis, it is rational to attempt medication withdrawal at least once in adolescents, particularly young women, even if they have risk factors for recurrence. A possible exception to this discussion of adolescents is young men with juvenile myoclonic epilepsy, where there is a very high recurrence risk (24,89). This needs to be discussed with the patient. Even then, however, one attempt at withdrawal may be reasonable as the prognosis may be more variable than previously thought (24,90). In the authors' experience, the majority of adolescents who are offered the choice will choose to attempt medication withdrawal, especially if this choice is presented to them before they are driving.

The clinical data do not demonstrate any significant advantages of waiting more than 2 years before attempting AED withdrawal. The exception to this may be the child with an age-dependent epilepsy, where a longer wait may alter the recurrence risk as the underlying syndrome is more likely to be in remission. However, these are precisely the children with a favorable long-term prognosis where AED withdrawal is often successful even after a brief treatment period (37,56,72,87,88).

Once the decision to withdraw AED therapy is made, the taper should be fairly rapid, as randomized clinical studies show no advantage to a slow taper (74). A slow taper has the additional disadvantage of prolonging the period of uncertainty. In general, we taper a single AED over 4 to 6 weeks. For the patient on two AEDs, we often first taper one AED and see if the patient can be maintained on monotherapy. If the patient remains seizure free on monotherapy, then a second withdrawal is attempted with the plan of treating with monotherapy only if there is a recurrence.

CONCLUSION

Given the consequences of long-term drug therapy and its lack of effect on long-term prognosis following a first seizure, we generally do not recommend treatment following a first unprovoked seizure in either children or adults. Following a second seizure, treatment is generally indicated in adults and needs to be considered in children. In children and adolescents who are seizure free on AEDs for at least 2 years, at least one attempt should be made at medication withdrawal, even if risk factors for recurrence are present. In adults, the risk-to-benefit equation in this setting is less clear, and decisions must be individualized after discussion of the risks and benefits with the patient.

The approach presented in this chapter emphasizes that both seizures and the therapies available carry some risk and that optimal patient care requires careful balancing of these risks and benefits. Assessment of risk requires not only ascertaining the statistical risk of a seizure recurrence or of an adverse event but also the consequences of such an event. This risk-to-benefit approach is useful not only in deciding whether to initiate or discontinue AED therapy but also in other treatment decisions.

This includes deciding whether to add a second drug, to try experimental drugs or therapies such as the ketogenic diet, or to consider epilepsy surgery. In all cases, one must balance the risks and benefits of the proposed alternatives, which may change as new information becomes available. Whatever the decision, it should be made jointly by the medical providers and the patient and family after careful discussion, including not only an assessment of the risks and benefits of treatment but also an understanding that individual patients and clinicians place different values on different outcomes and on the acceptability of certain risks.

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CHAPTER 46 HORMONES, CATAMENIAL EPILEPSY, SEXUAL FUNCTION, AND REPRODUCTIVE AND BONE HEALTH IN EPILEPSY

SCOTT J. STEVENS AND CYNTHIA L. HARDEN

Steroid hormones alter neuronal excitability, and these hormones in turn can be altered by seizures, by epilepsy, and by the pharmacokinetic effects of antiepileptic medications. Steroid hormones that are neurophysiologically active and alter the seizure threshold are known as neuroactive steroids or neurosteroids.

This chapter reviews and discusses the actions of neurosteroids on cortical excitability and epilepsy, the effect of seizures and antiepileptic medications on steroid hormones, and then focuses on catamenial epilepsy and sexual function in addition to reproductive and bone health issues in people with epilepsy.

EFFECTS OF NEUROSTEROIDS ON NEURONAL EXCITABILITY

The effect of steroid hormones on neuronal excitability has been an area of translational research, studied at molecular, animal, and clinical levels. Neurosteroids can modulate neuronal excitability through nongenomic direct membrane-mediated effects or receptor-mediated effects through the indirect genomic pathway that regulates protein synthesis. The two primary female reproductive hormones, estrogen and progesterone, are neurosteroids, which have been shown to have differing effects on neuronal excitability.

Estrogen

Estrogen works through both nongenomic and genomic pathways by binding to estrogen receptors that are widely spread throughout the brain (1). In summary, estrogen has excitatory effects by facilitating kindling and lowering the electroshock seizure threshold (2,3), activating preexisting cortical epileptogenic regions (4), in addition to increasing the severity of chemically induced seizures (5,6). This is thought to be secondary to decreasing the conduction of chloride through the G-aminobutyric acid $(GABA)_A$ receptor complex and the inhibition of GABA synthesis, an inhibitory central neurotransmitter (7). It has also been shown that estradiol increases the neuronal response to glutamate, an excitatory central neurotransmitter, through agonist effects on the N-methyl-D-aspartate receptor (8). In addition to having proconvulsive properties, estrogen has also been shown to have

anticonvulsant properties. The dose, route of administration, chronic versus acute administration, and species of estrogen can determine if it is a proconvulsant or anticonvulsant (9). This finding may be useful in determining if estrogen can possibly be used as future therapy for treating patients with epilepsy.

Progesterone

Unlike estrogen, which primarily acts by decreasing chloride conduction, progesterone has been found to increase chloride conductance at the $GABA_A$ receptor complex, promoting neuroinhibition (10). This effect is modulated primarily through the action of allopregnanolone, a neuroactive progesterone metabolite. Allopregnanolone has a neuromodulatory effect similar to that of a potent benzodiazepine and is much stronger than that of phenobarbital; however, it binds to a unique $GABA_A$ receptor site (10). It is therefore believed that progesterone, mainly through the action of its metabolites, has strong anticonvulsant properties.

Progesterone has the ability to increase the electroconvulsive shock threshold and increase the threshold for chemically induced seizures (9). It has been shown in experimental models that cyclical changes in the concentrations of progesterone and allopregnanolone can predictably alter the susceptibility to seizures. However, cyclical hormonal changes likely do not fully account for seizure exacerbations in women with catamenial epilepsy (11).

Testosterone

In addition to the two neurosteroids above, testosterone also has the ability to alter the seizure threshold. Androgens are metabolized into estrogens and 5α-reduced androgens by two different enzyme pathways, and these two classes of metabolic products have opposite neuroexcitatory effects. The estrogens are derived from precursor androgens through the action of a cytochrome P450 enzyme, aromatase, and are proconvulsant as described above. In contrast, the 5α-reduced androgens act as substrates for the biosynthesis of 5α-androstane-3α-diol, an anticonvulsant molecule that is structurally similar to allopregnanolone and has similar neuromodulatory effects on the activity of the $GABA_A$ receptor (12). Additionally, two other endogenous testosterone metabolites found in men, androsterone and etiocholanolone, also have been found to have anticonvulsant properties (13).

Cortical Distribution of Neurosteroid Receptors

The differential effects of steroid hormones on neuronal excitability, endocrine function, and reproductive behavior may to some extent be explained by anatomic specificity and changes with maturation in the cortical distribution of steroid hormone receptors. Estrogen receptors are located mainly in the mesial temporal lobe (limbic cortex) and hypothalamus, while progesterone and androgen receptors are diffusely distributed throughout the brain (14). The distribution of these receptors is not static and is modified throughout development (15). These findings may partially explain why there is a variation in seizure expression with changes in age and reproductive function.

HORMONE DISTURBANCES IN EPILEPSY

Decreased libido, infertility, early menopause, and polycystic ovarian syndrome (PCOS) are found

more commonly in patients with epilepsy than in the general population (16). Epilepsy can affect steroid hormone concentrations in men and women by disrupting the hypothalamic–pituitary–gonadal axis. Additionally, certain antiepileptic drugs (AEDs) are known to alter the metabolism of reproductive hormones.

Gonadotropin-releasing hormone (GnRH) is produced in the preoptic area of the hypothalamus and is responsible for regulating the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary through pulsatile secretion. FSH promotes development of the primary ovarian follicle and secretion of estradiol in women and controls spermatogenesis in men. LH stimulates ovulation and formation of the corpus luteum in women and simulates interstitial cell secretion of androgens in men. Additionally, prolactin, which inhibits sexual behavior in both sexes and can cause impotence in men at high levels, is also under hypothalamic regulation (17).

Certain regions within the brain, especially the amygdala, have been found to have connections with the hypothalamic cells responsible for secreting GnRH, making the GnRH cell population susceptible to injury from limbic seizures. This can explain why the pulsatile secretion of LH has been found to be altered in women with certain types of seizures (18). Additionally, interictal levels of growth hormone and prolactin have been found to be elevated in many epileptic patients, with levels of prolactin increasing more than twofold after certain types of seizures (19). Seizure lateralization is important in the etiology of certain epilepsy-induced reproductive endocrine disorders. One study of women with complex partial seizures showed that those exhibiting right temporal lobe discharges were found to be more likely to have hypogonadotropic hypogonadism, while those women with left temporal lobe discharges were found more likely to have PCOS (20).

EFFECTS OF ANTIEPILEPTIC DRUGS ON REPRODUCTIVE HORMONES

AED inducers, in general, decrease concentrations of reproductive steroid hormones by increasing hepatic metabolism and inducing the production of sex hormone–binding globulin, which in turn decreases free levels of reproductive steroid hormones (21). As compared to patients taking noninducing AEDs, women taking inducing agents are found to have lower estrogen and androgen levels, while men on these agents are found to have lower testosterone levels (21). Medications that decrease the concentration of reproductive steroid hormones include phenobarbital, phenytoin, carbamazepine, primidone, topiramate, oxcarbazepine, rufinamide, and clobazam (16). Medications that have little effect on the concentrations of reproductive steroid hormones include ethosuximide, gabapentin, lamotrigine, levetiracetam, zonisamide, pregabalin, lacosamide, and retigabine (16).

Although valproate decreases free testosterone levels in men (22), testosterone levels generally rise in women taking valproate through inhibition of cytochrome P450 isoenzymes and aromatase (23,24). This is clinically important, since there is an increased incidence of PCOS is women taking valproate. Levetiracetam binds to the SV2A receptor in brain, gonadal, and endocrine tissues. It has been suggested to have a direct gonadal effect in men, increasing total testosterone levels 1 month after the onset of treatment (25). These findings with levetiracetam illustrate that the pharmacokinetic effects of AEDs may only be part of the overall explanation for the changes in hormone levels associated with these medications.

CATAMENIAL EPILEPSY

As described above, estrogen and progesterone can alter the seizure threshold. In experimental models of epilepsy, it has been found that these two hormones fluctuate throughout the course of a regular menstrual cycle, changing seizure susceptibility throughout the cycle (26). Catamenial epilepsy is the clustering of seizures in alignment with the female reproductive cycle. This phenomenon is believed to occur secondary to the properties of the neurosteroids in combination with the natural cyclic variation of their serum levels throughout the course of each menstrual cycle (27).

The Menstrual Cycle and Patterns of Catamenial Seizures

The typical average menstrual cycle is approximately 28 days and starts on the first day of menses. Ovulation takes place on day 14 and is preceded by the follicular phase on days 1 through 13. The luteal phase begins after the oocyte is released and has a fairly invariant duration of 14 days, in which the dominant follicle forms the corpus luteum, which releases progesterone. Therefore, progesterone levels, in a normal menstrual cycle, are higher during the luteal phase than during the follicular phase, then rapidly decreasing several days prior to menses.

Two predominant patterns of catamenial seizures are seen during normal ovulatory cycles, perimenstrual (C1) and periovulatory (C2), with the perimenstrual pattern being most common. Seizure frequency is linked to the ratio of serum estradiol to progesterone, with higher ratios leading to seizure clustering (27). In the normal cycle, this ratio is highest during the premenstrual period and the days preceding ovulation, and is lowest during the mid-luteal phase. The premenstrual rise in seizure frequency has been described to possibly be secondary to the rapid withdrawal of progesterone, analogous to a benzodiazepine withdrawal (28,29). The increased frequency of seizures found in the days prior to ovulation is thought to be secondary to the rapid, steep increase in serum estradiol prior to the increase in serum progesterone that occurs at ovulation (28,29). During the mid-luteal phase, serum progesterone levels are higher than those of serum estradiol, making the occurrence of seizures less likely. Anovulatory cycles are the exception to these findings, in which a rise in serum estrogen still occurs without an increase in serum progesterone (29). These relationships can be seen in Figure 46.1.

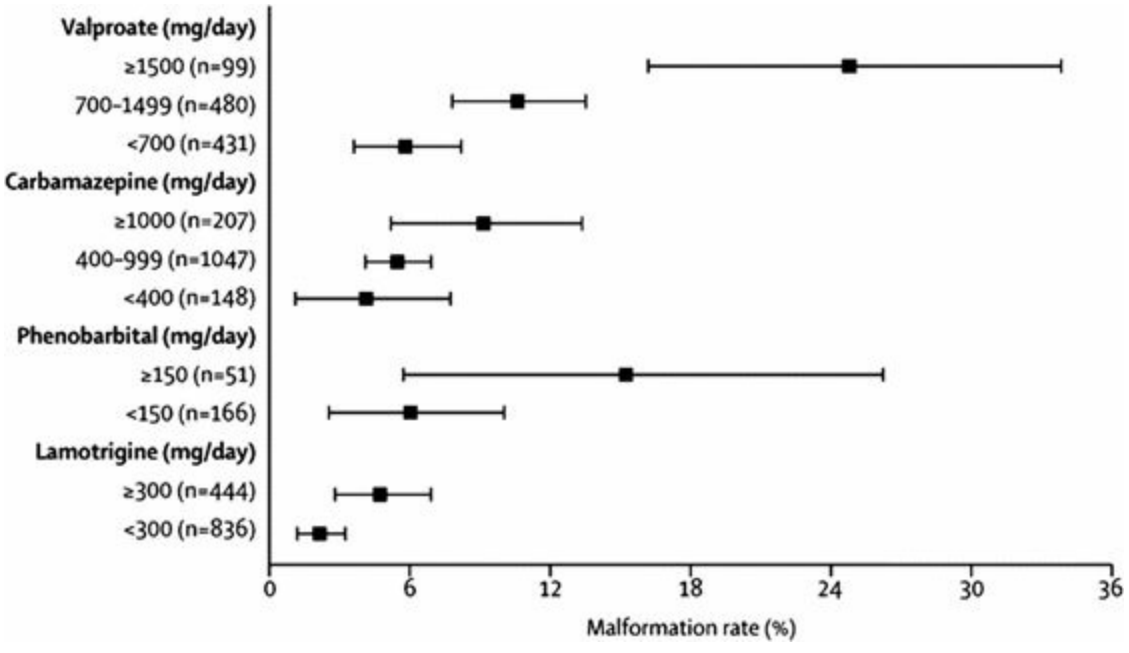

Figure 46.1. Three patterns of catamenial epilepsy: perimenstrual (C1) and periovulatory (C2) exacerbations during normal ovulatory cycles and entire second half of the cycle (C3) exacerbation during ILP cycles. F, follicular phase; L, luteal phase; M, menstruation; O, ovulation. (From Herzog AG. Catamenial epilepsy: definition, prevalence, pathophysiology and treatment. Seizure. 2008;17:151–159.)

A third pattern of catamenial seizures (C3) is seen in patients with inadequate luteal phase (ILP) cycles and occurs less frequently than the other two catamenial seizure patterns. Women with abnormal FSH secretion have decreased progesterone production secondary to poor development of the follicle and a poorly developed and functioning corpus luteum. This is known as ILP. Although ILP cycles can occasionally occur in normal women, they may also be caused by problems with the hypothalamic pituitary axis, ovarian defects, or defects in luteal cell steroidogenesis (30). ILP cycles have been shown to occur more in women with epilepsy than in healthy controls (31), which is likely related to dysfunction of inputs to the hypothalamus from ictal and interictal discharges. Estrogen levels are not affected, creating an increased estradiol/progesterone ratio and increased seizure occurrence from days 10 to 3 of the menstrual cycle (29). These findings are illustrated in Figure 46.1.

Effect of Menstrual Cyclic Antiepileptic Drug Levels on Seizure Occurrence

In addition to the pharmacodynamic effects of endogenous reproductive steroids on seizure occurrence, it has also been postulated that the pharmacokinetic effects of neurosteroids can alter the metabolism of AEDs. One study reported that phenytoin levels on day 28 in women with catamenial seizures were significantly lower than in women without cyclic exacerbations (32). However, it has also been shown in other studies that there is no relationship between neurosteroid levels and serum AED levels (32,33). In general, alterations in AED levels do not account for catamenial seizure exacerbations, while endogenous hormonal cycling has more influence.

Treatment of Catamenial Epilepsy

The first-line treatment for all patients with epilepsy is a first-line AED. However, adjunctive therapy with acetazolamide, benzodiazepines, and hormonal therapy may prove beneficial in managing patients with catamenial epilepsy. Most of the treatment interventions for women with catamenial epilepsy have been aimed at treating the premenstrual seizure exacerbations in women with regular menstrual periods (Fig. 46.2). Treatments are usually started during the second half of the menstrual cycle (days 14 to 26), starting treatment a prescribed number of days after menstrual bleeding.

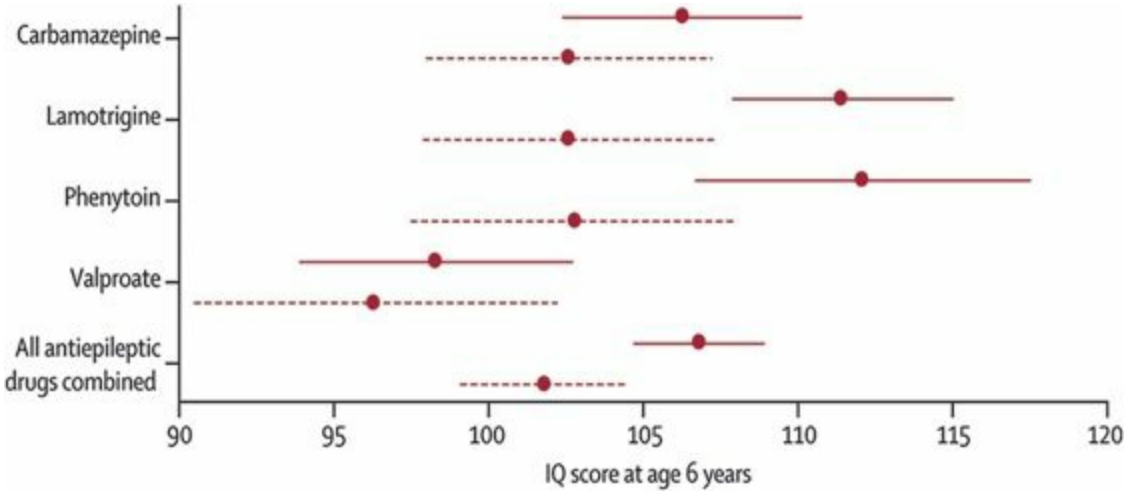

Figure 46.2. Treatment algorithm for catamenial C1 (perimenstrual) pattern of seizures. Most treatments are for focal-onset seizures in women with regular menses. C1 level 3, three times more seizures on days 25 to 3 compared with other days of the month; AEDs, antiepileptic drugs; PHT, phenytoin; IM, intramuscularly. *If menses start before day 26, start dose tapering on that day according to the same pattern of decreases. †Widely undertaken but not supported by data from randomized, controlled trails. ‡Increased risk of osteoporosis and slow return to normal fertility. (From Harden CL, Pennell PB. Neuroendocrine considerations in the treatment of men and women with epilepsy. Lancet Neurol. 2013;12:72–83.)

Although never studied in randomized trials, acetazolamide has been used in the treatment of catamenial epilepsy for over 50 years. It must be used over short periods during the menstrual cycle, since tolerance can rapidly develop to its anticonvulsant properties. It has been shown to be most effective at doses of 250 to 500 mg daily from 3 to 7 days prior to menses until day 1 of the menstrual cycle (34,35).

Benzodiazepines have also been used in women with epilepsy, with clobazam being the only formally studied treatment for catamenial seizures. Clobazam, at 20 to 30 mg/day for 10 days, starting 2 to 4 days premenstrually has been shown to reduce seizure frequency as compared to placebo (36).

In addition to the medications above, it is also reasonable to temporarily increase the dose of the patient's regular antiepileptic medication at specific times during the menstrual cycle. However, this should be avoided with phenytoin since there is a risk of toxicity associated with its nonlinear kinetics.

Since progesterone has mainly been shown to have anticonvulsant properties, it can be hypothesized that progesterone and its metabolites may be used in conjunction with current antiepileptic medications to treat women with catamenial epilepsy. Medroxyprogesterone acetate (MPA) is a synthetic progestin-only contraceptive agent that is administered every 10 to 12 weeks intramuscularly and stops the regular menstrual cycle. In patients with catamenial epilepsy, it has been shown to decrease seizure frequency by 39% at 1-year follow-up (37). However, this agent has been shown to have adverse side effects of slow return to normal fertility and increased risk of osteoporosis. Therefore, it should be considered only if catamenial exacerbations are severe and intractable to other interventions.

Although natural progesterone is not yet approved for use in the treatment of seizures, it is clear that natural progesterone could play an important role in the treatment of women with catamenial epilepsy. A small open-label study with long-term follow-up of women with catamenial seizures taking progesterone lozenges showed a significant reduction in seizure frequency when progesterone was taken during the exacerbation phase of the cycle (38). A recent randomized, double-blind, placebo-controlled multicenter clinical trial concluded that when all patients with catamenial

epilepsy were grouped together, there was no overall benefit of natural progesterone as compared to placebo (39). However, further analysis showed that progesterone was much more effective in women with at least three times or greater increase in seizure frequency during the perimenstrual phase (3 days prior to menses to 3 days after onset of menses) as compared to other days in the month (39). The degree of perimenstrual seizure exacerbation was found to be a significant predictor of response to progesterone treatment when progesterone was given as 200 mg oral lozenges twice daily on days 14 to 28, with possible taper days 26 to 28 (39). A proposed treatment algorithm of patients with seizure clustering during the perimenstrual phase is shown in Figure 46.2.

ORAL CONTRACEPTIVE AGENTS IN WOMEN WITH EPILEPSY

Oral contraceptive pills have been found in case reports to decrease seizure frequency but have not yet been systemically studied. They are, however, often used in women with epilepsy to prevent unwanted high-risk pregnancies. When these agents are used, it must be noted that they are inducers of the P450 system and may decrease the effectiveness of AEDs, which are hepatically metabolized. Furthermore, a noninducing AED should be used in combination with oral contraceptive pills when possible, to prevent increased metabolism and decreased efficacy of the contraceptive agent.

SEXUAL DYSFUNCTION AND REPRODUCTIVE HEALTH IN EPILEPSY

Sexual Dysfunction

It is important to take a detailed sexual history in all patients with a history of epilepsy. It has been shown that patients with epilepsy have a higher incidence of sexual dysfunction, mainly manifested by decreased sexual desire and potency, as compared to patients with other neurologic diseases (40). As previously discussed, there are AEDs that interact with endogenous hormones, and seizures have the ability to alter the hypothalamic–pituitary–gonadal axis. These findings, in combination with living with a perceived stigma (41) and the adverse influences of depressed mood and poor self-esteem (42), create a multifactorial etiology for sexual dysfunction in patients with epilepsy.

It is also important for the physician to bring up the topic of sexual dysfunction, since the frequency with which sexual complaints are volunteered is largely dependent on the attitude of the physician (43). When discussing sexual dysfunction, social factors, mood, hormone levels, and the effect of AEDs must all be assessed. The patient's somatic, psychological, and social well-being, as well as the dynamics of the couple and family, must all be explored (43). It must also be remembered that the sexual dysfunction may not always be secondary to epilepsy, and a full medical workup is often required as well. In addition to a complete physical and neurologic examination, patients with sexual dysfunction should undergo laboratory evaluation looking at the following serum levels: testosterone, sex hormone–binding globulin, FSH, LH, prolactin, hemoglobin A1C, and TSH. If a clear cause of sexual dysfunction cannot be elicited, urologic or gynecologic consultation may be necessary.

Vaginal dryness and dyspareunia may be treated with over-the-counter moisturizing and

lubrication products in addition to prolongation of foreplay. Phosphodiesterase inhibitors have been used in men to treat erectile dysfunction but have no effect on libido or sexual desire, which are controlled mainly by testosterone. A combination of testosterone and an aromatase inhibitor may hypothetically be beneficial in treating men with epilepsy having sexual dysfunction by increasing free serum testosterone levels and decreasing serum estradiol levels. Aromatase inhibitors in men with epilepsy have been shown to increase testosterone levels and possibly decrease seizure frequency, increase mood, and improve sexual functioning, but this combination needs to be further studies before making any definite judgments about their role in clinical practice (44,45).

Birth Rates

Population-based studies have shown that both men and women with epilepsy have lower birth rates than the general population and that adults with active epilepsy have lower birth rates in comparison to those who no longer have seizures after childhood (46,47). Decreased birth rates may be in part secondary psychosocial factors affecting patients with epilepsy such as choosing not to enter into romantic relationships or deciding not to have children. Additionally, patients with epilepsy have been shown to have decreased fertility, defined as the absence of contraception after 1 year of unprotected intercourse.

Fertility in Men with Epilepsy

Abnormal spermatogenesis may be a cause of infertility in men with epilepsy. A study of 60 men with epilepsy and 41 controls found the frequency of morphologically abnormal sperm to be significantly higher among men treated with carbamazepine, oxcarbazepine, and valproate compared the control group. Poor sperm motility was found in men taking valproate or carbamazepine, and the frequency of abnormally low sperm concentration was highest in men taking carbamazepine (22). Men treated with phenytoin have also been found to have morphologically abnormal sperm in addition to lower seminal volume, spermatozoa concentration, and total sperm count (48). However, temporal lobe epilepsy itself has also been documented to cause testicular failure independent of AED use (49). These findings indicate that both seizures and AEDs have effects on the hypothalamic–pituitary–gonadal axis in men that can impair fertility.

Fertility in Women with Epilepsy

Disturbances in the hypothalamic–pituitary–gonadal axis secondary to seizures or AEDs make women with epilepsy more likely to have early perimenopause and menopause, increased rates of anovulatory cycles, and a frequent occurrence of PCOS all of which are associated with decreased fertility (50,51). PCOS is defined as the presence of hyperandrogenism (clinical and/or biochemical), ovarian dysfunction (oligo-anovulation and/or polycystic ovaries), and the exclusion of related disorders (52). It is currently thought that PCOS is multigenic in etiology and susceptible to a variety of environmental triggers, which are as of yet unclear (53). Secondary to likely hypothalamic and pituitary dysregulation, there is elevated LH secretion and an increased ratio of LH to FSH, with produces polycystic follicles that are premature and deficient in aromatase, leading to increased serum androgen levels. The androgen is converted to estrogen by aromatase in the periphery, which feeds back to the pituitary to dysregulate normal LH secretion (54).

In addition to the effect of seizures on the hypothalamic–pituitary–gonadal axis creating an

increased risk for PCOS, it has also been shown that patients on valproate are at increased risk for the symptoms associated with PCOS (55). A recent study of women with epilepsy found that the incidence of PCOS was twice that of the general population (56). Taking valproate and younger age of seizure onset were risk factors for getting PCOS. Taking these findings into account, physicians must assess for abnormal menstrual cycles, hirsutism, acne, male pattern balding, and weight gain at each visit in women with epilepsy. Women with an early age of seizure onset, and women on valproate, should have a higher index of suspicion. If PCOS features are present, patients should be referred to an endocrinologist, gynecologist, or both for further evaluation and possible treatment. In addition, it is reasonable to consider alternative agents if valproate is part of the AED regimen.

Women with epilepsy, in addition to an increased occurrence of PCOS, also are at risk of early perimenopause and menopause, often in the late fourth decade or early fifth decade of life. A negative correlation has been reported between the age at menopause and seizure frequency, with women having frequent seizures experiencing earlier menopause (51). As in PCOS, the mechanism for this finding is likely related to hypothalamic–pituitary–gonadal axis dysfunction producing dysregulation of maturation of ovarian follicles, which leads to early loss of follicles available for ovulation.

Perimenopause and Menopause

No prospective information exists on the course of epilepsy as women progress through the transition to menopause. However, a cross-sectional study evaluated the effect of menopause and perimenopause on the course of epilepsy (57). The perimenopausal group consisted of 39 women with a history of epilepsy. Nearly two-thirds of the women reported an increase in seizure frequency during perimenopause, with those women having a history of catamenial epilepsy more likely to have increased seizures. The increase in seizure frequency during perimenopause is likely secondary to the elevation of the estrogen/progesterone ratio during this period. Evaluation of the postmenopausal women with epilepsy showed no overall direction change in seizure frequency (57). However, a history of catamenial epilepsy was significantly associated with a decrease in seizures after menopause.

Hormone Replacement Therapy

In the cross-sectional study listed above, postmenopausal was found to have an increase in seizure frequency after starting hormone replacement therapy (HRT), which usually consisted of an estrogen in combination with a synthetic progestin (57). These results prompted further investigation in the form of a double-blind, randomized, placebo-controlled trial using three study groups: women taking single-dose combination HRT (0.625 mg of conjugated equine estrogens [CEEs] plus 2.5 mg of MPA, or CEE/MPA) daily, double-dose CEE/MPA, or placebo (58). Increased seizure frequency was associated with increasing the CEE/MPA dose, suggesting that this regimen should not be used in postmenopausal women with epilepsy. Perhaps a regimen combining natural progesterone with estrogen may be alternatively considered in women requiring HRT.

BONE HEALTH IN EPILEPSY

Both men and women with epilepsy have an increased propensity to fractures due to medication side effects (e.g., ataxia and dizziness), coexisting neurologic deficits (e.g., cerebral palsy), and seizure-

related falls (59) in addition to the bone damaging effects of certain antiepileptic agents. The use of certain AEDs increases the risk of decreased bone density and abnormalities in bone metabolism. Hepatic enzyme inducers, such as phenytoin, carbamazepine, phenobarbital, and primidone, and noninducing AEDs such as valproate, are known to be associated with accelerated rate of bone loss and development of secondary osteopenia and osteoporosis with an increase in the risk for fractures (60). Limited evidence is available regarding the newer AEDs.

It is believed that the cytochrome P450 enzyme–inducing effects of certain AEDs are the main mechanism for bone disease. The enzyme induction leads to increased breakdown of vitamin D to inactive metabolites, which results in reduced calcium absorption, with secondary hyperparathyroidism, increased bone resorption and accelerated bone loss, and more rapid turnover of bone (61). These mechanisms have been postulated by the findings of decreased vitamin D and calcium levels (62,63) and increased levels of bone-specific alkaline phosphatase and makers of osteoblast and osteoclast activity (64,65). Other mechanisms for the negative impact of AEDs on bone have been hypothesized, such as direct impact on calcium absorption or on bone cells, disruption of vitamin K metabolism, changes in calcitonin secretion, and changes to the hypothalamic–pituitary–gonadal axis, which may adversely impact bone health (66).

There are not currently any official recommendations for investigating and treating bone disease in patients with epilepsy. Measuring bone mineral density with dual x-ray absorptiometry is the most sensitive predictor of fracture in patients at risk (66). FRAX is an online screening tool used to calculate a patient's risk of low bone mineral density and fracture by evaluating a patient's prior bone health history and risk factors for bone disease (66). This questionnaire, in combination with measurements of bone mineral density, can be performed on patients with long-term AED exposure, particularly if they have other risk factors for bone disease. Routine vitamin D levels can also be checked in patients treated with enzyme-inducing AEDs (60). Furthermore, antiepileptic medications associated with a negative impact on bone should be avoided in patients with risk factors for bone disease.

It has been shown that patients with epilepsy shown to have low bone mineral density who were treated with high-dose vitamin D had significant increases in bone mineral density (67). These findings suggest that epileptic patients treated with AEDs should have adequate daily intake of calcium and vitamin D and that patients taking enzyme-inducing AEDs may require higher doses of vitamin D than the recommended daily allowance and possible calcium supplementation if necessary (66).

A prospective 2-year double-blind, randomized, placebo-controlled study of male veterans with epilepsy treated with phenytoin, phenobarbital, valproate, or carbamazepine evaluated the use of the bisphosphonate, risedronate, on bone mineral density (68). The study found that the use of risedronate plus calcium and vitamin D lead to a significantly greater increase in bone mineral density at the lumbar spine as compared to placebo patients only receiving vitamin D and calcium. However, the difference in total body and proximal bilateral femoral bone mineral density between the two groups was not significant. Five new vertebral compression deformities and one nonvertebral fracture were only observed in the placebo group, but no vertebral or nonvertebral fractures were observed in the group receiving bisphosphonate treatment. However, the long-term use of bisphosphonates in the epileptic patient population has not yet been studied, and patients requiring such therapy should be referred to a bone specialist.

SUMMARY

Seizures and their treatment affect reproductive functioning and bone health in people with epilepsy. Additionally, the effects of neurosteroids on cortical excitability complicate seizure management in women with epilepsy, with estrogen increasing and progesterone decreasing seizure likelihood. Catamenial epilepsy, the clustering of seizures in alignment with the female reproductive cycle, is a phenomenon that occurs secondary to fluctuations in neurosteroid levels during specific time periods in the menstrual cycle. Although AEDs are first-line treatment for catamenial seizures, other adjunctive therapies have been studied and are used in common practice.

Patients with epilepsy also have an increased incidence of sexual dysfunction and infertility secondary to alteration of the hypothalamic–pituitary–gonadal axis by seizures and AEDs. It is important to take a detailed sexual and medical history, possibly discontinue any AEDs that may be contributing to sexual dysfunction and consult appropriate outside consolation if needed. Furthermore, it is important to council patients with epilepsy taking hormone-based contraception to use an AED that does not interact with their hormonal birth control.

There is an increased risk of osteopenia and osteoporosis in patients with epilepsy, especially if they are on an enzyme-inducing AED. Patients must be screened for low bone density and should have vitamin D levels checked. All epileptic patients treated with AEDs should have adequate daily intake of calcium and vitamin D. If bone loss is detected on routine screening, a bone specialist should be consulted.

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CHAPTER 47 TREATMENT OF EPILEPSY DURING PREGNANCY

PAGE B. PENNELL

INTRODUCTION

Medical care of adolescent and adult women with epilepsy during the childbearing years presents specific clinical challenges. When making treatment recommendations, the practitioner needs to not only consider seizure types and epilepsy syndromes, efficacy, and side effect profiles of the different antiepileptic drugs (AEDs) but also consider additional key factors when selecting which medication to prescribe. From the initial prescription and repeated at every subsequent visit, the AEDs prescribed should be considered in light of the risks of the medications during any potential pregnancy, planned or unplanned, and the potential interactions with the form of contraception used.

CONTRACEPTION

Effective contraception in women with epilepsy is essential to allow for preconception planning and to implement the measures known to improve pregnancy outcomes. However, concomitant use of AEDs and hormonal contraceptives is complicated because of the bidirectional pharmacokinetic interactions, the pharmacodynamic consequences, and the potential effects on seizure control.

The enzyme-inducing AEDs lead to rapid clearance of sex steroid hormones (SSHs) and may allow ovulation in women taking oral contraceptives (OCs) or other hormonal forms of birth control (vaginal ring, patch). Table 47.1 categorizes the different AEDs according to the degree of induction of female SSHs. This classification is derived primarily from pharmacokinetic interaction studies between the AED and OC formulations, but when direct interaction studies with OCs are not available, the categorization has to be inferred from studies with other medications that undergo hepatic clearance. Prior authors have recommended “high-dose” OCs with EIAEDs assuming enzyme induction will lower levels to what occurs with an effective lower-dose OC. A few OCs with higher doses of ethinyl estradiol (EE) and progestin remain available but are infrequently used in practice for healthy women. No direct evidence supports efficacy in this situation. The CDC Medical Eligibility Criteria for contraception classified certain AEDs (phenytoin [PHT], carbamazepine [CBZ], phenobarbital [PB], primidone [PRM], topiramate [TPM], and oxcarbazepine [OXC]) as a category 3: The risks (birth control failure) generally outweigh the benefits (1). The authors state that the use of other contraceptives should be encouraged for women who are long-term users of any of these drugs. For women on EIAEDs that cause substantial changes in SSH levels (see Table 47.1), one of the long-acting reversible contraceptives (LARCs) should be encouraged. These include a progestin implant, intramuscular medroxyprogesterone acetate, and the intrauterine devices (IUDs). The levonorgestrel IUD prevents pregnancy by local hormonally mediated changes in cervical mucus, which are not likely to be impacted by hepatic changes in p450 enzyme induction. One reassuring

prospective registry study in the United Kingdom demonstrated a pregnancy rate of 1.1 per 100 women years for 56 women using the LNG-IUD with enzyme-inducing AEDs (2).

Table 47.1 Antiepileptic Drugs: Degree of Induction of Metabolism of Hormonal Contraceptive Agents

Strong inducers[a]	Weak inducers[a]	Noninducers
Phenobarbital	Topiramate	Ethosuximide
Phenytoin	Lamotrigine	Valproate
Carbamazepine	Felbamate	Gabapentin
Primidone	Rufinamide	Clonazepam
Oxcarbazepine	Clobazam	Tiagabine
		Levetiracetam
		Zonisamide
		Pregabalin
		Vigabatrin
		Lacosamide
		Ezogabine

[a]Avoid concomitant use with the lowest dose oral contraceptive pills, and additional nonhormonal forms of contraception should be used.

PREGNANCY

Epilepsy is the most common neurologic disorder that requires continuous treatment during pregnancy, and AEDs are one of the most frequent chronic teratogen exposures. Approximately one-half million women with epilepsy are of childbearing age in the United States, and 3 to 5 births per 1000 will be to women with epilepsy (3). However, it is estimated that the total number of children in the United States exposed in utero to AEDs is substantially greater with the emergence of AED use for other illnesses including headache, chronic pain, and mood disorders.

Treatment during pregnancy is a precarious balancing act between the teratogenic risks of AEDs and maintaining maternal seizure control. However, pregnancy registries and more intensive observational studies have provided key data that allow us to lower the risk for the developing fetus to rates closer to the general population. These findings should be key considerations when counseling and treating adolescents and women with epilepsy during their reproductive years (3–5).

MAJOR CONGENITAL MALFORMATIONS

Offspring of women with epilepsy on AEDs are at an increased risk for major congenital malformations (MCMs) and minor anomalies. Minor anomalies are defined as structural deviations from the norm that do not constitute a threat to health. Minor anomalies affect 6% to 20% of infants born to women with epilepsy, approximately 2.5-fold the rate of the general population. Although not of direct health consequence, the finding of a minor anomaly should lead to enhanced vigilance about the child's health and neurodevelopment.

Major congenital malformations (MCMs) are defined as an abnormality of an essential anatomical structure present at birth that interferes significantly with function and/or requires major intervention. The reported MCM rates in the general population vary between 1.6% and 3.2%, and women with a history of epilepsy but on no AEDs show similar MCM rates. The average MCM rates

among all AED exposures vary between 3.1% and 9%, or approximately two- to threefold higher than the general population (3,6).

The MCMs most commonly reported following in utero AED exposure include congenital heart disease, cleft lip/palate, urogenital defects, skeletal defects, and neural tube defects. The abnormal neural tube closure usually occurs between the 3rd and 4th weeks of gestation. By the time most women realize they are pregnant, it is too late to make medication adjustments to avoid malformations (Table 47.2).

Table 47.2 Relative Timing and Developmental Pathology of Certain Major Congenital Malformations

Tissues	Malformations	Postconceptional age
CNS	Neural tube defect	28 d
Heart	Ventricular septal defect	42 d
Face	Cleft lip	36 d
	Cleft maxillary palate	47–70 d

AED Monotherapies

The information we have gained regarding specific AEDs and risk for MCMs has increased dramatically over the last two decades. Data obtained from large, prospective pregnancy registries from different parts of the world have demonstrated remarkably consistent findings for many of the AEDs. The 2009 AAN Practice Parameter updates on "Management issues for women with epilepsy—focus on pregnancy" (3) led to many important conclusions about intrauterine first-trimester exposure and risk for MCMs: (i) It is highly probable that valproic acid (VPA) exposure has higher risk of MCMs compared to CBZ and possible compared to PHT or lamotrigine (LTG). (ii) Compared to untreated women with epilepsy (WWE) it is probable that VPA as part of polytherapy and possible that VPA as monotherapy contribute to the development of MCMs. (iii) It is probable that AED polytherapy as compared to monotherapy regimens contributes to the development of MCMs. (iv) CBZ probably does not substantially increase the risk of MCMs in the offspring of WWE. (v) There is probably a relationship between the doses of VPA and of LTG and the risk of development of MCMs in the offspring of WWE. Additionally, for specific types of MCMS, findings included the following: (i) PHT possibly contributes to the risk of cleft palate, (ii) CBZ possibly contributes to the risk of posterior cleft palate, (iii) VPA probably contributes to neural tube defects and facial clefts and possibly contributes to hypospadias, and (iv) PB possibly contributes to cardiac malformations.

Since this evidence-based review of the literature, several large prospective pregnancy registries scattered across different regions of the world continue to provide valuable information. They reveal a very consistent pattern of amplified risk for the development of MCM in pregnancies exposed to VPA. The registries have also provided updated information on additional AEDs that further refines our ability to lower the teratogenicity risk in women with epilepsy.

The UK Epilepsy and Pregnancy Register reported on findings with TPM use in 178 live births (7). Although the confidence intervals were wide, this preliminary information noted an MCM rate of 4.8% for monotherapy use and even higher for use of TPM as polytherapy. They also noted a particularly higher rate of oral clefts, approximately 11 times their background rate, and a high rate of hypospadias. The risk of oral clefts with TPM has been replicated in other studies (8).

Using data from the National Birth Defects Prevention Study, Werler et al. (9) reported that increased risks were observed for VPA and neural tube defects (OR, 9.7; 95% CI, 3.4 to 27.5), oral clefts (OR, 4.4; 95% CI, 1.6 to 12.2), heart defects (OR, 2.0; 95% CI, 0.78 to 5.3), and hypospadias (OR, 2.4; 95% CI, 0.62 to 9.0). Increased risks were observed for CBZ and neural tube defects (OR, 5.0; 95% CI, 1.9 to 12.7). Similarly, the European Surveillance of Congenital Anomalies (EUROCAT) antiepileptic-study database, which is derived from population-based congenital anomaly registries, also reported significantly increased risks for VPA monotherapy and spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis (10). Spina bifida was the only specific MCM associated with CBZ monotherapy compared with no AEDs (OR, 2.6; 95% CI, 1.2 to 5.3), but the risk was smaller than for VPA (11,12).

The North American AED Pregnancy Registry released findings comparing the risk of MCMs among infants exposed to different AED monotherapies during the first trimester, as well as to an unexposed reference group (13). The LTG monotherapy group was chosen as the exposed reference group for the other AEDs because of a low MCM rate and tight confidence intervals (2.0% [95% CI, 1.4 to 2.8]). Table 47.3 in this article can serve as a particularly instructive tool during the preconceptional counseling phase of women with epilepsy, with detailed information on many of the AEDs with sample size and calculation of confidence intervals for the risk numbers presented. Additional analysis included the risk of MCM by average daily VPA dose during the first trimester and confirms prior reports of a dose-related risk for VPA and MCM. However, the upper limit of the confidence intervals for the lowest VPA daily dosage group (<500 mg) reached over 7%, and this is an uncommon dose range to maintain seizure control.

Table 47.3 Risk of major congenital malformations identified among infants who had been exposed to a specific AED monotherapy regimen during the first trimester and relative risk of MCMs compared to both unexposed and to lamotrigine groups: North America Pregnancy Registry 1997–2011

	Unexposed[a]	LTG	CBZ	PHT	LEV	TPM	VPA	PB	OXC	GBP	ZNS	CLZ
MCM[b] % 95% CI	1.1 (0.37–2.6)	2.0 (1.4–2.8)	3.0 (2.1–4.2)	2.9 (1.5–5.0)	2.4 (1.2–4.3)	4.2 (2.4–6.8)	9.3 (6.4–13.0)	5.5 (2.8–9.7)	2.2 (0.6–5.5)	0.7 (0.02–3.8)	0 (0.0–3.3)	3.1 (0.4–10.8)
RR to unexposed 95% CI	Reference	1.8 (0.7–4.6)	2.7 (1.0–7.0)	2.6 (0.9–7.4)	2.2 (0.8–6.4)	3.8 (1.4–10.6)	9.0 (3.4–23.3)	5.1 (1.8–14.9)	2.0 (0.5–7.4)	0.6 (0.07–5.2)	NA NA	2.8 (0.5–14.8)
RR to LTG 95% CI		Reference	1.5 (0.9–2.5)	1.5 (0.7–2.9)	1.2 (0.6–2.5)	2.2 (1.2–4.0)	5.1 (3.0–8.5)	2.9 (1.4–5.8)	1.1 (0.4–3.2)	0.3 (0.05–2.5)	NA NA	1.6 (0.4–6.8)

[a]The unexposed internal comparison group were pregnant women not taking an AED, who were recruited from among the friends and family members of the enrolled women taking an AED.

[b]Diagnosed during pregnancy or before 12 wks after birth. Confirmed by review of medical records.

AED, antiepileptic drug; MCM, major congenital malformations; RR, relative risk; CI, confidence interval; LTG, lamotrigine; CBZ, carbamazepine; PHT, phenytoin; LEV, levetiracetam; TPM, topiramate; VPA, valproate; PB, phenobarbital; OXC, oxcarbazepine; GBP, gabapentin; ZNS, zonisamide; CLZ, clonazepam.

Adapted from Hernández-Díaz S, Smith CR, Shen A, et al.; North American AED Pregnancy Registry; North American AED Pregnancy Registry. Comparative safety of antiepileptic drugs during pregnancy. Neurology. 2012;78(21):1692–1699.

Hernandez-Diaz et al. (13) also examined the frequency of specific MCMs for each AED and reported that VPA was associated with an increased risk of hypospadias, neural tube defects, and cardiovascular malformations; PB was associated with an increased risk of cardiovascular malformations; and the risk of oral clefts was higher among infants exposed to PB, VPA, and TPM,

consistent with previous reports.

The UK and Ireland Epilepsy and Pregnancy Registers combined results for first-trimester exposure to levetiracetam (LEV) with outcome data for 304 monotherapy pregnancies and 367 polytherapy pregnancies (14). The MCM rate in the LEV monotherapy group was 0.70% (95% confidence interval [CI], 0.19% to 2.51%) and in the polytherapy group was 5.56% (95% CI, 3.54% to 8.56%); the MCM rate in the polytherapy group was lower when LEV was given with LTG (1.77%; 95% CI, 0.49% to 6.22%) than when given with VPA (6.90%; 95% CI, 1.91% to 21.96%) or CBZ (9.38%; 95% CI, 4.37% to 18.98%).

A recent report from the European and International Registry of Antiepileptic Drugs and Pregnancy (EURAP) confirmed that in addition to the type of AED, dose of the AED at conception also affects rates of MCMs (15). MCM rates in pregnancies exposed to CBZ, LTG, VPA, and PB were analyzed by dose at time of conception (not throughout the first trimester or entire pregnancy). The lowest rates of MCMs occurred with LTG < 300 mg/day (2.0%; 95% CI, 1.19 to 3.24), and this group was used as the comparator group. Risks of MCMs were higher with VPA and PB at all doses and with CBZ at >400 mg/day. Additionally, an increase in MCM rates was observed with increasing doses for all of the four AEDs (Fig. 47.1).

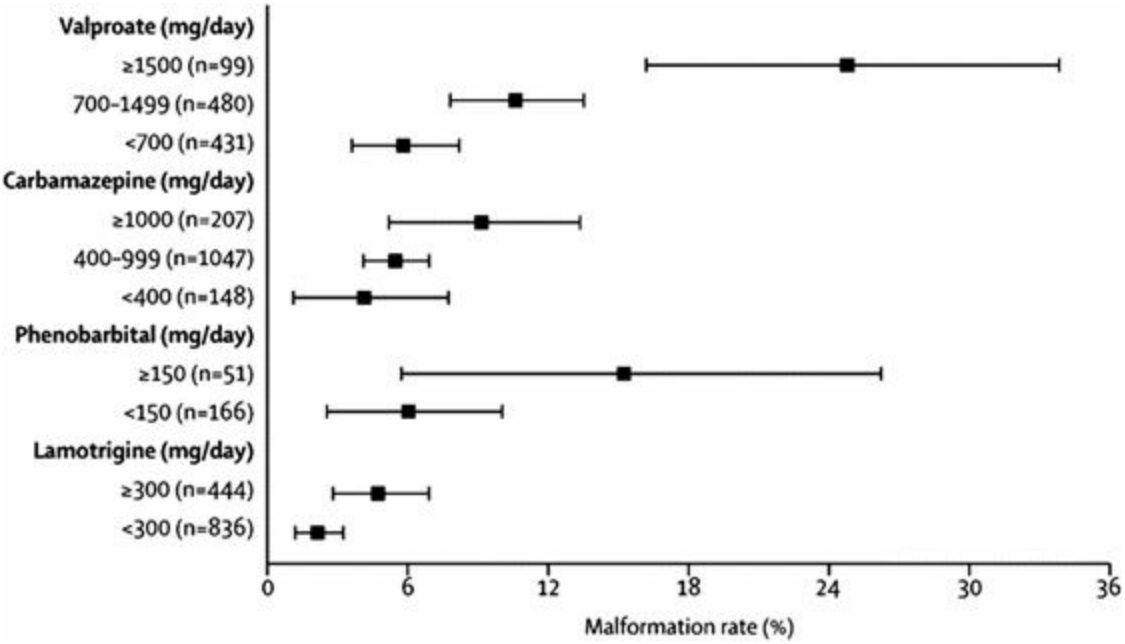

Figure 47.1. Rates of major congenital malformations at 1 year after birth in relation to exposure to AED monotherapy according to data from the International Registry of Antiepileptic Drugs and Pregnancy. Bars represent 95% confidence interval. (From Tomson T, Battino D, Bonizzoni E, et al.; for the EURAP study group. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol. 2011;10(7):609–617.)

Recent data support the concern that the amount of fetal exposure to an AED is important, as well as the type of AED. Therefore, reduction of the dose prior to conception while maintaining seizure control can further reduce the risk of structural teratogenicity. Determining the women's individual target concentration preconception can be a valuable tool for therapeutic drug monitoring during pregnancy (see below).

AED Polytherapy

The rates of MCMs have been reported as higher across several studies for women on AED

polytherapy compared to AED monotherapy regimens (3). These results led to the recommendation that AED monotherapy is preferred to polytherapy during pregnancy and should be achieved during the preconception planning phase (3). However, Holmes et al. (16) reported that data from the North American AED Pregnancy Registry suggest that not all AED polytherapy combinations are alike. Concentrating on LTG or CBZ as polytherapy, both AEDs had relatively modest rates for MCMs if the polytherapy combination was with any AED other than VPA. The MCM rates were 9.1% for LTG plus VPA (OR, 5.0; 95% CI, 1.5 to 14.0 compared with LTG monotherapy) but only 2.9% for LTG with any other AED (1.5; 0.7 to 3.0); likewise, the risks were 15.4% for CBZ plus VPA (OR, 6.2; 95% CI, 2.0 to 16.5 compared with CBZ monotherapy) and 2.5% for CBZ plus any other AED (0.8; 0.3 to 1.9).

NEURODEVELOPMENTAL OUTCOMES

Studies investigating cognitive outcome in children of women with epilepsy report an increased risk of mental deficiency (3,17). Verbal scores on neuropsychometric measures may be selectively more involved. A variety of factors contribute to the cognitive problems of children of mothers with epilepsy, but AEDs appear to play a major role. Factors other than specific AED use that have been associated with cognitive impairment include seizures, a high number of minor anomalies, major malformations, decreased maternal education, impaired maternal–child relations, and maternal focal seizure disorder (17). It is possible that these risk factors are not only additive but synergistic.

The 2009 AAN Practice Parameter Updates reported the following conclusions about in utero exposure (throughout the entire pregnancy) and risk for poor cognitive outcomes (3): (i) cognition is probably not reduced in children of untreated WWE, (ii) CBZ probably does not increase poor cognitive outcomes compared to unexposed controls, (iii) monotherapy exposure to VPA probably reduces cognitive outcomes, (iv) monotherapy exposure to PHT or PB possibly reduces cognitive outcomes, and (v) AED polytherapy exposure probably reduces cognitive outcomes as compared to AED monotherapy.

Since the 2009 AAN Practice Parameter update, several notable reports have contributed to our understanding of the various contributors to adverse neurodevelopmental outcomes and the pattern seen. The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study was a prospective, observational, multicenter study in the United States and United Kingdom and assessed the neurodevelopmental effects of in utero exposure to four monotherapy groups (CBZ, VPA, PHT, and LTG) (18). The primary outcome was intelligence quotient (IQ) at age 6 years, adjusted for maternal IQ, AED type, AED-standardized dose, gestational age at birth, and use of periconceptional folate. Primary analysis included 305 mothers and 311 children, with 224 children completing the 6-year follow-up. Multivariate analysis demonstrated that the VPA-exposed children had lower age-6 IQ compared to CBZ, LTG, or PHT, and they did poorly on several specific measures. High doses of VPA were negatively correlated with IQ, verbal ability, nonverbal ability, memory, and executive function, while the other AEDs did not have a dose effect. Interestingly, mean IQs were higher in the children of mothers who took periconceptional folic acid (Fig. 47.2). This key evidence of a beneficial effect of supplemental folic acid taken prior to and early in pregnancy in women with epilepsy on AEDs supports the recommendation that all women of childbearing age should be encouraged to take supplemental folic acid given the high unplanned pregnancy rate.

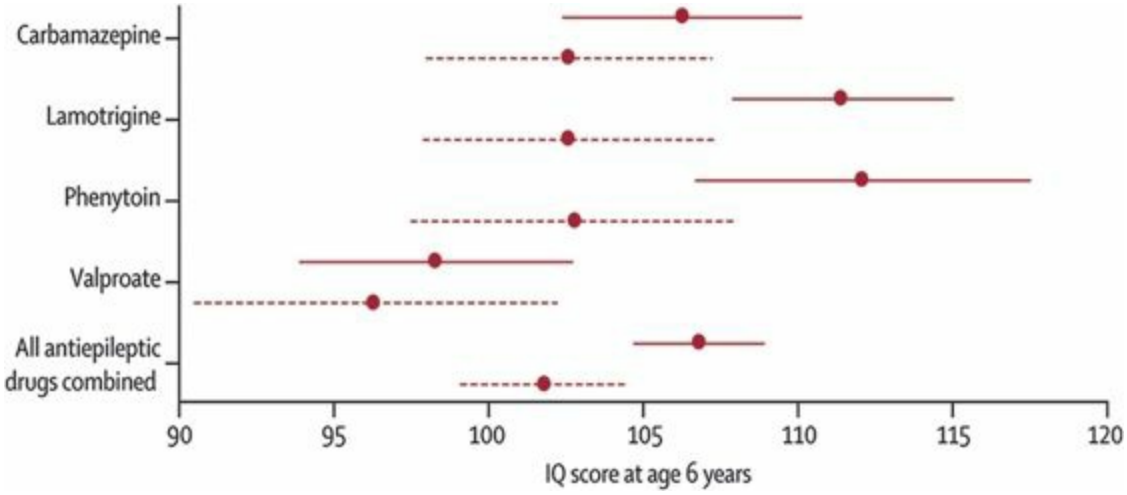

Figure 47.2. Child IQ at 6 years of age, by exposure to maternal AED use and periconceptional folate. Mean (95% confidence intervals) are shown for folate (solid lines) and no folate (dashed lines). (IQ, intelligence quotient.) (From Meador KJ, Baker GA, Browning N, et al.; for the NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013;12(3):244–252.)

The neurodevelopment research group from Liverpool and Manchester also reported that children assessed at age 6 years who were exposed to VPA in utero had a higher prevalence of neurodevelopmental disorders (19). Multiple logistic regression analysis revealed that the children born to WWE and exposed to VPA monotherapy and VPA polytherapy were, respectively, six times (aOR, 6.05; 95% CI, 1.65 to 24.53; P = 0.007) and 10 times (aOR, 9.97; 95% CI, 1.82 to 49.40; P = 0.005) more likely to be diagnosed with a neurodevelopmental disorder than controls. Moreover, autism spectrum disorder (ASD) was the most frequent diagnosis for the VPA-exposed children.

A population-based study from Denmark found that in the 508 children exposed to VPA, an absolute risk for ASD of 4.42% (95% CI, 2.59% to 7.46) (adjusted HR, 2.9 [95% CI, 1.7 to 4.9]) and an absolute risk for childhood autism of 2.50% (95% CI, 1.30% to 4.81%) (adjusted HR, 5.2 [95% CI, 2.7 to 10.0]) (20). When restricting the cohort to the children born to women with epilepsy, risks were similarly elevated in those children exposed to VPA but not with other AED exposures.

The Norwegian Mother and Child Cohort Study evaluated reports from mothers of their child's motor development, language, social skills, and autistic traits with use of standardized screening tools at 18 months and 36 months of age (21). The AED-exposed children had increased risk of abnormal score for gross motor skills, sentence skills, and autistic traits. Limitations include small sample size at very young ages to assess neurodevelopment, with very small individual AED groups, lack of use of diagnostic testing and criteria, and lack of screening for intellectual disabilities in the children or even in the mothers. Follow-up studies are needed to confirm if increased risks for these traits exist across a variety of AED exposures.

Neurodevelopmental outcomes for LEV have recently been published. The Liverpool and Manchester Neurodevelopment Group with the United Kingdom Epilepsy and Pregnancy Registry reported on the neurodevelopmental outcomes of children exposed in utero to LEV compared to control children and children exposed in utero to VPA (22). Testing of the children occurred at ages 36 to 54 months. After adjusting for confounding variables, children exposed to VPA in utero scored lower on measures of gross motor skills, comprehension language abilities, and expressive language abilities compared to children exposed in utero to LEV. Children exposed to LEV in utero did not differ from the unexposed control children.

In summary, if a prescriber chooses to place an adolescent or adult woman of childbearing age on

VPA, he/she is putting her potential children at a substantially greater risk for MCMs, lower IQ, and ASD.

NEONATAL COMPLICATIONS

Recent reports suggest that there may be increased risk for other neonatal complications for offspring of women with epilepsy on AEDs. Findings from the 2009 AAN/AES Practice Parameter Update concluded the following (3): (i) neonates of WWE taking AEDs probably have an increased risk of being small for gestational age (SGA) of about twice the expected rate and (ii) neonates of WWE possibly have an increased risk of a 1-minute Apgar score of <7 of about twice the expected rate. Since this parameter was released, a study from Taiwan reported that seizures in mothers with epilepsy during pregnancy were independently associated with approximately a 1.5-fold increased risk for preterm delivery or infants being born SGA (23). A secondary analysis of the neonatal outcomes from the NEAD cohort reported that adverse neonatal outcome risks may differ between the AEDs; the odds ratio for SGA was higher for the VPA and CBZ groups, and reduced 1-minute Apgar scores occurred more frequently in the PHT and VPA groups (24).

The North American AED Pregnancy Registry reported that prenatal exposure to TPM or ZNS was associated with higher risk for SGA births compared to prenatal exposure to LTG (25). The prevalence of SGA was 6.8% for LTG, 12.2% for ZNS (RR, 1.6; 95% CI, 0.9 to 2.8), and 17.9% for TPM (RR, 2.4; 95% CI, 1.8 to 3.3). Similar results were found when a group of unexposed newborns was used as the reference.

SEIZURES DURING PREGNANCY

The effect of pregnancy on seizure frequency is variable. Approximately 20% to 33% of patients will have an increase in their seizures, 7% to 25% will have a decrease in seizures, and 50% to 83% will experience no significant change. EURAP reported on a large but selective cohort of WWE entering pregnancy on monotherapy (26). Two-thirds of women remained seizure free throughout pregnancy, and women with genetic generalized epilepsies were more likely to remain seizure free than women with localization-related epilepsies. The physiologic changes and psychosocial adjustments that accompany pregnancy can alter seizure frequency, including changes in sex hormone concentrations, changes in AED metabolism, sleep deprivation, and new stresses. Noncompliance with medications is common during pregnancy and is in large part due to the strong message that any drugs during pregnancy are harmful to the fetus. Teratogenic effects of AEDs are well described, but risks to the fetus are often exaggerated or misrepresented. Proper education about the risks of AEDs versus the risks of seizures can be very helpful in assuring compliance during pregnancy.

The risk of seizures to the fetus should be discussed thoroughly with the patient and other family members. Generalized tonic–clonic convulsions can cause maternal and fetal hypoxia and acidosis, fetal heart rate decelerations, and miscarriages and still births. Nonconvulsive seizures can cause trauma, which can result in ruptured fetal membranes with an increased risk of infection, premature labor, and even fetal death. In addition to the physical risks of seizures to the developing fetus, reemergence of seizures in a woman who had previously experienced seizure control can be devastating. Besides the immediate risk to herself and the fetus, the loss of the ability to drive legally can have remarkable psychosocial effects.

AED MANAGEMENT DURING PREGNANCY

Maintaining seizure stability during pregnancy is dependent on maintaining therapeutic concentrations of the baseline AED. The target concentration should be individually determined, ideally in the preconception phase, for each woman according to her epilepsy history and prior seizure control relative to AED concentrations. During pregnancy, management of the AED dosing becomes complex and requires a more intensive approach than during nonpregnant stages. Clearance of most of the AEDs increases during pregnancy, resulting in a decrease in serum concentrations (Table 47.4) (4,27). Several physiologic factors contribute to the decline in AED levels during pregnancy: induction of the hepatic microsomal enzymes by the increased SSHs, increased volume of distribution, decreased concentration of the binding proteins albumin and alpha-1-acid-glycoprotein, increased renal blood flow, and alterations in drug absorption.

Table 47.4 Alterations of AED Clearance and/or Concentrations During Pregnancy: Summary of Class I, II, and III Studies (4,27)

AED	Reported increases in clearance	Reported decreases in total concentrations	Reported changes in free AED or metabolites
PHT	19%–150%	60%–70%	Free PHT clearance increased in TM3 by 25%; free PHT concentration decreased by 16%–40% in TM3
CBZ	–11% to +27%	0%–12%	No change
PB	60%	55%	Decrease in free PB concentration by 50%
PRM	Inconsistent	Inconsistent	Decrease in derived PB concentrations, with lower PB/PRM ratios
VPA	Increased by TM2 and TM3		No change in clearance of free VPA; free fraction increased by TM2 and TM3
ESX	Inconsistent	Inconsistent	
LTG	65%–230%, substantial interindividual variability		89% increase in clearance of free LTG
OXC		MHD and active moiety decreased by 36%–61%	
LEV	243%	60% by TM3	

AED, antiepileptic drug; TM, trimester; PHT, phenytoin; CBZ, carbamazepine; PRM, primidone; PB, phenobarbital; VPA, valproic acid; ESX, ethosuximide; LTG, lamotrigine; OXC, oxcarbazepine; MHD, monohydroxy derivative of oxcarbazepine; LEV, levetiracetam.

From Pennell PB, Hovinga CA. Antiepileptic drug therapy in pregnancy I: gestation-induced effects on AED pharmacokinetics. Int Rev Neurobiol. 2008;83:227–240.

The 2009 AAN/AES Practice Parameter Update concluded the following: Pregnancy probably causes an increase in the clearance and a decrease in the concentration of LTG, PHT, and to a lesser extent CBZ and possibly decreases the level of LEV and the active OXC metabolite, the monohydroxy derivative (4).

The magnitude of the enhanced clearance of LTG during pregnancy exceeds that described for

many of the older AEDs, because it is primarily eliminated via hepatic glucuronidation. This elimination pathway appears particularly susceptible to activation during pregnancy, due to direct effects of rising SSH levels. In the prospective EURAP registry, pregnancies on LTG monotherapy were less likely to be seizure free (58.2%), had a greater likelihood of deterioration in seizure control from the first to the second or third trimesters (19.9%), and were more likely to require an increase in drug load (26). Pennell et al. (28) reported findings from a class I prospective, observational study of 53 pregnancies in 53 women, using 305 samples throughout preconception baseline, pregnancy, and postpartum. Both LTG free and total clearance were increased during all three trimesters, with peaks of 94% (total) and 89% (free) in the third trimester. This study also examined therapeutic drug monitoring and seizure frequency, and changes in LTG dosing to avoid postpartum toxicity. The authors reported that seizure frequency significantly increased when the LTG level decreased to 65% of the preconceptional individualized target LTG concentration. This finding supports the recommendation to monitor levels of LTG and possibly other AEDs for which the levels decrease during pregnancy. A retrospective analysis of pregnant women on a variety of AEDs also demonstrated that seizures worsened significantly during the second trimester when the AED concentration fell by greater than 35% from the preconception baseline concentration (29).

The importance of individual therapeutic drug monitoring for LTG during pregnancy is underscored by a model-based analysis of LTG clearance changes during pregnancy (30). Two subpopulations were identified; 23% of women had only a minimal increase in clearance throughout pregnancy, while 77% of women exhibited a 10-fold higher rate of gestational age–associated increase in clearance. It is probable that the differences are related to different pharmacogenomic profiles (e.g., UGT1A4), but further studies need to be completed. The authors also commented that based on the model, postpartum doses should be tapered to preconception dose ranges within 3 weeks of delivery.

Previous studies on LTG noted a rapid decrease in LTG clearance during the early postpartum period with reports of symptomatic toxicity. Pennell et al. (28) examined the effectiveness of using an empiric postpartum taper schedule for LTG, with steady decreases in dosing at postpartum days 3, 7, and 10, with return to preconception dose or preconception dose plus 50 mg to help counteract the effects of sleep deprivation. Patients were assessed for symptoms of LTG toxicity (dizziness, imbalance, and blurred or double vision). Nonadherence to the standard taper schedule was associated with significantly higher risk of experiencing postpartum toxicity. Most of the other AED levels gradually increase after delivery and plateau by 10 weeks postpartum. The exact time course is not as well established for the other AEDs, but AED doses should be adjusted and/or levels should be followed during the postpartum period.

BREAST-FEEDING

Most infants of women with epilepsy can successfully breast-feed without complications. The concentrations of the different AEDs in breast milk are considerably less than those in maternal serum (Table 47.5). The infant's serum concentration is determined by this factor as well as the AED elimination half-life in neonates (31). A detailed study of excretion of lamotrigine into breast milk, infant serum concentrations, and infant laboratory studies demonstrated safety of women on LTG breast-feeding (32). The benefits of breast-feeding are believed to outweigh the small risk of adverse effects of AEDs. This recommendation needs to be balanced with consideration of minimizing sleep disruption. A common compromise is to elicit the help of family members and friends to provide one

or two bottle feedings per 24 hours of either formula or pumped breast milk and allow the mother at least one stretch of uninterrupted sleep.

Table 47.5 Antiepileptic Drug Exposure Through Breast Milk (4,30)

AEDs	Breast milk/maternal concentration	Adult half-life	Neonate half-life
CBZ	0.36–0.41	8–25	8–36
PHT	0.06–0.19	12–15	15–105
PB	0.36–0.46	75–125	100–500
ESX	0.86–1.36	32–60	32–38
PRM	0.72	4–12	7–60
VPA	0.01–0.1	6–20	30–60
LTG	0.5–0.77	30	—
ZNS	0.41–0.93	63	61–109
TPM	0.86	21	24
GBP	0.7–1.3	7–9	14
OXC	0.5–0.65	19.3	17–22
LEV	0.8–1.3	6–8	16–18

AED, antiepileptic drug; CBZ, carbamazepine; PHT, phenytoin; PB, phenobarbital; ESX, ethosuximide; PRM, primidone; VPA, valproic acid; LTG, lamotrigine; TPM, topiramate; ZNS, zonisamide; OXC, oxcarbazepine; LEV, levetiracetam.

From Hovinga CA, Pennell PB. Antiepileptic drug therapy in pregnancy II: fetal and neonatal exposure. Int Rev Neurobiol. 2008;83:241–258.

Recent data from the NEAD cohort that included mothers on PHT, LTG, VPA, or CBZ monotherapy actually demonstrated a benefit to breast-feeding (33). Meador et al. compared the age-6 IQ between children who breast-fed (43%) to those who did not. Adjusted IQ was actually higher by 4 points for children who were breast-fed versus those who were not, and verbal ability measures were also higher in the breast-fed children. The improved neurodevelopmental outcomes in the NEAD children that were breast-fed support the recommendation to breast-feed despite continued exposure to AEDs via breast milk.

SUMMARY

Improving maternal and fetal outcomes for women with epilepsy involves effective preconceptional counseling and preparation. The importance of planned pregnancies with effective birth control should be emphasized, with consideration of the interactions described in this chapter. LARC methods are preferred for many women with epilepsy. The consistent findings of increased risk for MCMs and neurodevelopmental deficits with VPA use during pregnancy should enter into the physician's daily treatment decisions, as well as the newer findings of differential risks between types and doses of the other AEDs. Figure 47.3 summarizes the author's interpretation of the available data at the time of authorship. The risk profiles include data about MCMs and neurodevelopmental outcomes when available, with consideration of the range of relative risks reported from multiple studies, number of subjects studied, and confidence intervals. The AEDs that are omitted do not have enough reported monotherapy data to be included. These risk profiles will likely change as new data become available. Folic acid supplementation should be encouraged in all women of childbearing age on any AED. Maintaining seizure control during pregnancy is important, and therapeutic drug monitoring of serum AED levels can help achieve that goal, especially for AEDs that undergo substantial pregnancy-associated changes in clearance. Knowledge and appreciation of

these key principles enhance our ability to make informed treatment recommendations that not only provide favorable seizure control but also improved maternal and child outcomes.

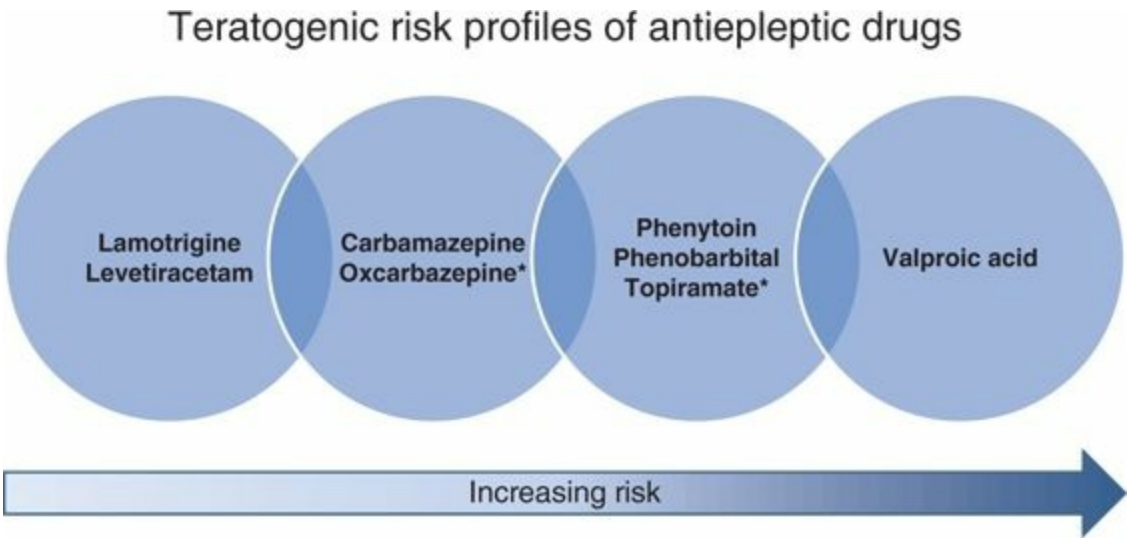

Figure 47.3. Summary of relative teratogenic risk profiles of antiepileptic drugs, based on available data at the time of authorship. The risk profiles include data about major congenital malformations and neurodevelopmental outcomes when available, with consideration of the range of relative risks reported from multiple studies, number of subjects studied, and confidence intervals. (*, Neurodevelopmental outcomes are not yet known.)

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CHAPTER 48 INDIVIDUAL APPROACH TO LABORATORY MONITORING OF ANTIEPILEPTIC DRUGS

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INTRODUCTION

Antiepileptic drugs (AEDs) are the mainstay of treatment of patients with epilepsy. However, because treatment is prophylactic and efficacy is not readily measured since seizures occur at irregular intervals and sometimes drug toxicity is difficult to distinguish from the underlying epilepsy, AED therapeutic drug monitoring (TDM) has provided an invaluable surrogate marker so as to help individualize treatment. Indeed, AED TDM is defined as the measurement and the clinical use of drug concentrations (levels) in serum or plasma but increasingly in saliva, to adjust the individual drug dosage and schedule to each patient's individual therapeutic requirement.

Epilepsy, in addition, has specific features that make it particularly amenable to AED TDM, namely, it begins predominantly in early life; it is a chronic condition that often lasts for years, decades, or for a lifetime; the majority of patients require long-term therapy, and 30% of patients require long-term polytherapy (1); and during transition from childhood, adolescence, adulthood, and old age, there are significant changes in a patient's physiologic and pathologic state, including hepatic, renal, and other diseases resulting in changing and altered AED pharmacokinetic characteristics and thus individualization of AED dosage is of paramount importance (2). Those AED blood concentrations that reflect patient pharmacokinetic variability (due, for example, to age, gender, metabolic capacity, comorbidities) provide an invaluable surrogate marker for patient management (3,4).

TERMINOLOGY AND DEFINITIONS

New terminology and definitions for TDM of AEDs have been suggested on behalf of the International League Against Epilepsy (3). Terms such as "reference ranges," "therapeutic ranges," "optimal ranges," "target ranges," and "target concentrations" have been used interchangeably, often with different meanings. Clear definitions are therefore important.

The Concept of an AED Reference Range

Two separate terms are now recommended to define drug concentration ranges in relation to their clinical effects. The "reference range" can be defined as a range of drug concentrations and based on a variable number of studies, which is quoted by a laboratory and specifies a lower limit below which a therapeutic response is relatively unlikely to occur and an upper limit above which toxicity is

relatively likely to occur. The reference range is therefore not a "therapeutic range," which is associated with the best response in a given patient. The therapeutic range will vary between different patients and can therefore only be determined for the individual patient. Thus, the term "individual therapeutic concentration" is recommended for use (3,5).

Reference ranges have been quoted for the first-generation AEDs (carbamazepine, phenytoin, phenobarbital, and valproic acid) for many years and are often used rigorously to guide TDM and patient care. However, it is rarely noted that these ranges are based on limited data in highly selected patients. For example for phenytoin, which probably has the best-documented relationship between serum concentrations and clinical effect, its generally quoted range of 10 to 20 mg/L (40 to 79 μmol/L) is constructed from various studies (6–11). Buchthal et al. (6), in their study of 80 patients with at least one "grand mal" seizure per week, found that only 6 out of 24 (25%) improved at serum phenytoin concentrations below 10 mg/L, 21 out of 27 patients (77%) improved at concentrations above 10 mg/L, and the majority of patients with concentrations above 30 mg/L experienced adverse effects. The study of Kutt et al. (7) helped to further define the upper limit of the range in that nystagmus was observed in all their patients with serum phenytoin concentrations above 20 mg/L, ataxia was observed at phenytoin concentrations above 30 mg/L, and occurred in all patients at concentrations above 40 mg/L. A subsequent prospective study of 32 outpatients with "grand mal" seizures gave further support to the quoted therapeutic range (8). However, these early studies were all conducted in patients with severe epilepsy and frequent generalized tonic–clonic seizure; patients with newly diagnosed and perhaps easier to treat epilepsy were excluded. Indeed, Schmidt et al. (9,10) subsequently demonstrated that not only does the severity of the epilepsy influences which serum concentration is needed to obtain seizure control but also the seizure type. That one-third of previously untreated patients with newly diagnosed epilepsy were controlled with phenytoin concentrations below the usually recommended range (11) has seriously challenged the value of the lower limit of the therapeutic range, and it is being increasingly recognized that there is a considerable individual variation in what is the optimal serum phenytoin concentration and this applies to all AEDs.

For the second- and third-generation AEDs, reference values are available (Table 48.1), and these values are based on Phase II and Phase III clinical trials population data as recently highlighted by the newest AED perampanel whereby robust pharmacokinetic/pharmacodynamic data have been used to define its reference range (12).

Table 48.1 Some Pharmacokinetic Characteristics and Reference Ranges of AEDs

Drug	Time to peak concentration (hours)	Time to steady state (days)	Half-life monotherapy, adults (hours)	Half-life AED + enzyme inducers (hours)	Half-life monotherapy, children (hours)	Half-life monotherapy, elderly (hours)	Serum protein binding (%)	Reference range (mg/L)	Reference range (μmol/L)	Active metabolite
Carbamazepine	4–8[a]	2–4	8–20[b]	5–12[b]	10–13[b]	30–50[b]	75	4–12	17–51	Carbamazepine–epoxide
Clobazam	1–3	2–7	10–30	<30	~16	30–48	85	0.03–0.3	0.1–1.0	
N-Desmethyl clobazam	___	7–10	36–46	___	___	___	___	0.02–0.07	1.0–10.5	*N*-Desmethyl clobazam
Clonazepam	1–4	2–10	17–56	12–46	22–33	___	86	0.02–0.07	0.60–0.22	
Eslicarbazepine acetate[c]	2–3	4–5	20–24	13–20	___	___	30	3–35	12–139	Eslicarbazepine also known as 10-hydroxycarbazepine
Ethosuximide	1–4	8–12	40–60	20–40	30–40	___	0	40–100	283–708	
Felbamate	2–6	3–5	16–22	10–18	___	___	25	30–60	126–252	
Gabapentin	2–3	1–2	5–9[b]	5–9[b]	___	___	0	2–20	12–117	
Lacosamide	1–2	2–3	12–16	___	___	___	<30	10–20	40–80	
Lamotrigine	1–3	3–7	15–35 (+valproic acid = 30–90)	8–20 (+valproic acid = 15–35)	___	___	55	3–15	10–59	
Levetiracetam	1–2	1–2	6–8	5–8	5–6	10–11	0	12–46	70–270	
Oxcarbazepine[c]	4–6	2–3	8–15	7–12	___	___	40	3–35	12–139	10-Hydroxycarbazepine
Perampanel	0.25–2	14	52–129	25	___	___	95	0.05–0.4	0.14–1.14	
Phenobarbital	2–4	15–29	70–140	50–160	63–69	___	55	10–40	43–172	
Phenytoin	1–12	6–21	30–100[b]	30–100[b]	30–100[b]	___	90	10–20	40–79	
Pregabalin	1–2	1–2	5–7	5–7	___	___	0	2–8	13–50	
Primidone	2–6	2–4	7–22	3–12	5–11	___	10	5–10	23–46	Phenobarbital
Retigabine	0.5–2	1–2	7–11	___	___	9–14	80	NE	NE	
Rufinamide	3–6	1–2	6–10	4–7	___	___	35	30–40	126–168	
Stiripentol	1–2	7	4–13[b]	___	___	___	99	4–22	17–94	
Tiagabine	0.5–2	1–2	5–9	2–4	___	___	96	0.02–0.2	0.05–0.53[c]	
Topiramate	2–4	4–5	20–30	10–15	13–20	___	15	5–20	15–59	
Valproic acid	3–7[d]	2–4	12–16[b]	5–9[b]	8–13[b]	___	90[d]	50–100	346–693	
Vigabatrin	1–2	1–2	5–8	5–8	___	___	0	2–36	6–279	
Zonisamide	2–5	10–15	50–70	25–35	___	___	40	10–40	47–188	

[a]Conventional tablets.

[b]Concentration dependent.

[c]Values refer to pharmacologically active metabolite eslicarbazepine/10-hydroxycarbazepine.

[d]Enteric-coated tablets.

NE, not established.

The Individual Therapeutic Concentrations

Despite the shortcomings of present reference ranges, TDM may be useful by employing the concept of "individual therapeutic concentrations" using intraindividual comparisons of drug serum concentrations (3,5). The drug concentration at which a patient has an optimal effect will serve as the individual reference for comparison if future treatment failures should occur and to check if the change in the clinical status of the patient is related to pharmacokinetic alterations or not. The concept of the individual therapeutic concentration may therefore be helpful even without a well-defined reference range. The basis for TDM will rely on a relationship between drug serum concentration and clinical effect in the individual patient, depending on the mechanism of drug action and possible influence by pharmacologically active metabolites and pharmacokinetic intraindividual variability. Thus, an optimal AED treatment can be best guided by identifying the "individual therapeutic concentration" (3,5).

IMPACT OF TDM ON CLINICAL OUTCOME

Although studies of the impact of TDM on treatment outcome in terms of optimum seizure control are scarce (12–15), two randomized studies comparing treatment outcome with or without the use of TDM have been reported (14,15). Neither study, however, provided evidence for the usefulness of routine monitoring of AEDs in the general epilepsy population, which, however, does not argue

against the value of TDM in special situations and clinical indications.

CLINICAL INDICATIONS FOR MONITORING ANTIEPILEPTIC DRUGS

Traditionally, TDM has been applied to the older first-generation AEDs (carbamazepine, phenytoin, phenobarbital primidone, and valproic acid), primarily because not only do they exhibit substantial interpatient pharmacokinetic variability but also they have narrow therapeutic indices. Nevertheless, TDM is increasingly being used to individualize treatment with the various new second- (vigabatrin, lamotrigine, gabapentin, pregabalin, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide) and third-generation (lacosamide, retigabine, eslicarbazepine acetate, and perampanel) AEDs and also for the orphan AEDs (stiripentol and rufinamide), and the indications for monitoring are exactly the same for all AEDs (Table 48.2) (3,4,16). Some key pharmacokinetic characteristics that impact on TDM and the reference ranges for the various AEDs are shown in Table 48.1. Indications for AED TDM are discussed in the following sections.

Table 48.2 Clinical Indications for Monitoring Antiepileptic Drugs

Reasons for TDM	Possible clinical consequence
When a drug therapy is initiated, or when a dose change occurs	To determine the serum concentration for a particular dose so as to guide therapy. To confirm that the degree of serum concentration change is reflective of the dose change; this is particularly important for AEDs that exhibit nonlinear pharmacokinetics
When the desired therapeutic outcome is achieved	To establish the "individual therapeutic concentration" of a given AED
Suspected nonadherence	Serum concentrations will reveal whether or not drug adherence is occurring
Therapeutic failure	To establish whether a lack of efficacy may be due to too low dose/serum concentration or indeed a too high dose/serum concentration that may produce a paradoxical worsening of seizures
When adverse effects occur	To confirm whether the serum concentration is high and is therefore the probable cause of drug toxicity
Individual variations between dose and serum concentrations	Pharmacogenetic variability, ethnicity, age, pharmacoresistance, concurrent illness, organ function (liver, kidneys) and pharmacokinetics are among factors that contribute to interindividual variability
Pharmacokinetic variability in special patient populations	Children, pregnant women, and the elderly require different dose requirements due to alteration in AED pharmacokinetics
Pharmacokinetic interactions	Pharmacokinetic interactions are common in epilepsy and result in increases or decreases in AED serum concentrations with potential exacerbation of adverse effects or seizure breakthrough, respectively
The emergency situation: drug overdose status epilepticus	To guide when the AED dose should be reinstated so as to maintain seizure control To determine whether drug nonadherence has occurred and to guide dosage regimen so as to control seizures

Drug Interactions

Pharmacokinetic interactions with AEDs represent a major indication for AED TDM. These interactions involve changes in serum concentrations consequent to changes in metabolism, principally due to enzyme induction or inhibition and are well described (17–22). Enzyme induction can result in a decrease in serum concentrations and potentially seizure breakthrough while enzyme inhibition can result in increased serum concentrations and potentially neurologic toxicity. Typically, enzyme induction completes within 14 to 21 days, and thus TDM should be undertaken after this period has elapsed. The maximum consequence of enzyme inhibition interactions, whereby new steady-state serum concentrations are achieved, is directly dependent on the half-life of the inhibited drug and typically occurs 4–6 half-lives after the inhibiting drug is coprescribed. Thus, TDM can be readily used to characterize the time course and magnitude of these interactions and make dosage adjustments as necessary.

For most patients, seizure freedom is readily achieved by use of AED monotherapy. However, 30% of patients require polytherapy AEDs (the use of two or more AEDs), and it is these patients that are susceptible to pharmacokinetic AED versus AED interactions. Being aware of which AEDs have a propensity to cause pharmacokinetic interactions and to choose those that do not interact or have minimal propensity to interact, along with knowledge of the mechanism of interaction, is important (22). Thus carbamazepine, phenytoin, phenobarbital, and primidone are potent enzyme inducers, while valproate is a potent enzyme inhibitor, and they may affect the serum concentration of other AEDs (17). In contrast, gabapentin, levetiracetam, lacosamide, pregabalin, and vigabatrin are not likely to be involved in pharmacokinetic interactions due to the fact that they do not undergo metabolism via cytochrome P450 (CYP) or uridine glucuronyl transferase (UGT)-mediated metabolism and instead are excreted renally.

Interactions between AEDs and other drugs used to treat concurrent pathologies are also important and similarly require TDM so as to individualize treatment. These include analgesics, antimicrobials, antineoplastic agents, cardioactive drugs, immunosuppressants, psychotropic drugs, and steroids, including oral contraceptives (18,21,23).

Regarding oral contraceptives, the estrogen component enhances metabolism via UGTs so that AEDs (lamotrigine, oxcarbazepine, and valproate) whose metabolism is via this enzyme system experience decreases in serum concentrations, in some patients by up to 50% (24,25). Conversely, many AEDs (carbamazepine, phenytoin, and phenobarbital) enhance the metabolism of oral contraceptives and compromise contraceptive control.

It should be remembered that when an interacting drug is withdrawn, the interaction will go in reverse, and therefore it is important to reverse any dosage adjustments made accordingly and is best guided by TDM. Finally, identification of pharmacodynamic interactions can similarly benefit from TDM because any change in the clinical status of a patient (seizure exacerbation or increased adverse effects) that is not associated with a change in serum AED concentration is concluded by default as a pharmacodynamic interaction.

Special Patient Populations

Children and Adolescents

Children differ from the adult population due to rapid changes in pharmacokinetics during infancy and early childhood, due to physiologic alterations early in life. For most AEDs studied in youngest children, the elimination half-life is reduced because the clearance is high, especially from 6 months of age and to about 6 years of age. The volume of distribution may also differ (2,4,26). The clinical consequence is that children will need a higher dosage per kilogram of body weight than in older children or adults. This pharmacokinetic variability in children makes it difficult to predict optimal doses and serum concentrations, and thus, TDM is particularly helpful in these patients.

Pregnant Women

In pregnant women, rapid changes in pharmacokinetics are expected as a consequence of various physiologic changes including decreased absorption, altered distribution, decreased protein binding, increased metabolism due to increased enzyme capacity in the liver CYP isoenzymes and UGTs, and increased drug excretion (4,27,28). During this period, TDM is particularly helpful in patient management. For highly protein-bound drugs, management may best be guided by measurement of unbound concentrations (29). Significant pharmacokinetic changes have been recorded for lamotrigine, with an increase in clearance of 50% to 330%, with the most pronounced effect occurring in late pregnancy (28–32). Levetiracetam plasma concentrations can decrease by 60% in the third trimester compared to baseline (33). The metabolism of oxcarbazepine also increases during pregnancy due to enhanced glucuronidation, as the concentrations of the most active enantiomer (S-(+)-10-hydroxycarbazepine) metabolite is increased 1.5- to 13-fold after delivery. Serum concentrations of topiramate also appear to decline gradually throughout pregnancy. The mechanisms are not known, but increased glomerular filtration may play a major role (33,34). Other AEDs that are associated with decreases in serum concentrations during pregnancy and that may benefit from TDM so as to optimize therapy include felbamate, gabapentin, pregabalin, tiagabine, vigabatrin, and zonisamide (28,35,36).

Elderly

The oral clearance of almost all AEDs is reduced in the elderly. Reductions of 10% to 90% have been observed but are most often in the range of 30% to 50% (2). The elderly, with increased morbidity, exhibit pronounced physiologic alterations that affect the pharmacokinetic characteristics of AEDs namely decreased absorption, altered distribution, decreased capacity of metabolizing enzymes, decreased blood flow to eliminating organs, and impaired hepatic and renal function. Additionally, age-related changes in pharmacodynamics and an increased likelihood of drug interactions, because of treatment of concomitant comorbidities, affect the efficacy and safety not only of AEDs but also of concomitant therapy. TDM can guide attainment of targeted concentrations and maintaining these concentrations over time, especially as comedications are added or discontinued. For highly protein-bound AEDs, measurement of unbound concentrations may be indicated. Interpretation of drug concentrations in the elderly should also take into account the fact that the elderly may show increased pharmacodynamic sensitivity to AEDs, and therefore, therapeutic and toxic effects may develop at relatively low concentrations. Thus, interpretation of drug concentration measurements should be interpreted more cautiously.

Hepatic and Renal Disease

Most AEDs are metabolized by the liver, and thus, hepatic disease may alter their clearance (4). In addition, as the liver is the source of many proteins, serum protein binding may also be affected. Studies evaluating serum AED concentrations during hepatic illness are sparse, and there is no test that will predict the degree of change in clearance. Thus, in any person with hepatic disease, AED TDM should be undertaken, and for highly bound AEDs, free concentration monitoring may better guide treatment.

Renal function is of special importance for drugs eliminated in part or primarily by renal excretion, such as primidone, pregabalin, gabapentin, levetiracetam, lacosamide, and vigabatrin (4). Creatinine clearance is a useful measure of renal function, but the measurement of AED serum concentrations can provide better guidance to adjust doses. Also, because many AEDs are efficiently removed during dialysis, AED TDM can also help guide the replacement dosages needed so as to maintain optimum seizure control. For highly bound drugs, free serum concentrations increase significantly in patients with renal disease, and therefore, treatment may be best guided by monitoring free serum concentrations.

Adherence (Compliance)

Nonadherence is a major problem in the treatment of epilepsy as it compromises seizure control. Indeed, the nonadherence rate in children and adults with epilepsy has been determined to be of the order of 33% to 39% (37,38). In the elderly, suboptimal adherence such as underdosing, overdosing, missed doses, or makeup doses is well recognized and alters serum AED concentrations and, potentially, clinical response (39). TDM is useful in identifying nonadherence, but it should be remembered that TDM can only identify short-term nonadherence and not long-term or intermittent nonadherence.

What to Measure

Serum or plasma is the matrix of choice for AED TDM. However, for many AEDs, saliva is a well-validated alternative matrix since concentrations in saliva reflect the pharmacologically relevant serum unbound drug concentrations as recently reviewed by Patsalos and Berry (40). Saliva sampling is simple and noninvasive, multiple serial samples can be readily collected, and it can be undertaken by patients themselves or by their caregivers and is particularly useful in children who often dislike or fear venipuncture. Saliva AED concentrations, however, can be affected by the sampling conditions and by contamination of mucus and the presence of residual drug and food in the mouth. Under well-controlled conditions, saliva AED concentrations can be used to individualize AED treatment and can be particularly useful in clinical settings whereby protein binding is altered for highly protein-bound AEDs (3,40).

Sampling Time

Routinely, the sampling time for individual patients should be standardized so as to have comparable results. It should be remembered, however, that the references ranges are based on trough concentrations (41,42). Samples should be drawn at steady state, which occurs at 4–6 half-lives after starting treatment or a dose adjustment. The ideal sampling time for all AEDs is after an overnight fast and just before ingestion of the morning dose (trough concentrations). Sampling just before the next scheduled dose is also useful. In the outpatient setting, the morning dose can be postponed for at

most 1 hour; however, overall, it is best that sampling time in relation to dose ingestion is recorded so as to better interpret the results. If toxic symptoms present, sampling should occur at time the patient is experiencing adverse effects so as to determine whether indeed the symptoms are drug related.

CONCLUSIONS

AED TDM is a useful tool to optimize and individualize the treatment of patients with epilepsy because it provides important information so as to guide dosage adjustment in patients with unexpected treatment outcomes and in specific age groups (children and the elderly) where the clinical assessment of treatment effects may be particularly difficult. This is in part due to the characteristics of epilepsy and also because of the pharmacokinetic variability of AEDs. The relative value of TDM will depend on the characteristics of the AED, and all the new AEDs have properties that suggest a role for TDM. For most AEDs, reference ranges have been reported, which define the serum concentrations at which most patients are expected to exhibit an optimal clinical response. However, because of individual variation, many patients may require serum concentrations outside the reference ranges, and thus, patient management is best guided by determination of the "individual therapeutic concentration," which is defined as the drug concentration at which an individual achieves seizure freedom or optimum seizure control with tolerable adverse effects.

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CHAPTER 49 GENETIC INFLUENCES ON RESPONSES TO DRUGS USED TO TREAT EPILEPSY

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CHAPTER OBJECTIVES

The goal of this chapter is to provide an update on the major topics in antiepilepsy drug (AED) pharmacogenetics. Introductory sections provide background for understanding drug response as a complex trait, describe factors that have limited the clinical application of basic research findings, address elements of common genetic variation, and discuss the concept of genetic association as related to general pharmacology. The main body of the chapter is intended to assess the current state of the field of AED pharmacogenetics by reviewing the major genes that have been documented to have variation that impacts the clinical effects of AEDs. The chapter concludes with a summary and look ahead to future research directions.

INTRODUCTION

Pharmacogenetics is the field of biomedical science that is concerned with the relationship between variability in DNA sequence and variability in response to specific drugs or classes of drugs (1). The ultimate goal of pharmacogenetics is to individualize drug therapy based upon analysis of specific gene variants or other genetic biomarkers that can predict the best possible clinical outcome. However, there are a very limited number of accepted biomarkers for responses to antiepileptic drugs (AEDs) (2,3), and thus, this goal has yet to be achieved. Therapeutic response to drug administration is a highly complex trait (4) that depends not only upon variability in the genome but also upon variability in the environment (5) including factors such as smoking, diet, and coadministered medications. Pharmacogenetic studies of various classes of drugs estimate modest heritability for drug effects (6). Importantly, the influence of environmental factors that affect drug responses hinders identification of genetic factors, and inadequate control of the environment has contributed to the slow progress in the field of AED pharmacogenetics. Nonetheless, given the large fraction of epilepsy patients who do not derive adequate therapeutic benefit from currently available medications, and the potential for individual genetic variation to play a role in this pharmacoresistance (7), great effort continues to be expended on studying the correlation between the effects of AEDs and genetic polymorphisms and on attempting to identify specific genetic markers that will guide the therapeutic decision-making process.

Apart from environmental factors, several constraints in the design of studies to evaluate influences of genetics on response to AEDs can be identified as obstacles in the field. One is related to the relatively small magnitude of effect of individual genetic variants. Complex phenotypes, including those involving responses to AEDs, are recognized to involve multiple genes each with a partial effect on overall phenotype (8–10). This makes the identification of any one causative polymorphism highly challenging, particularly in the setting of uncontrolled environmental factors. Another is lack of a standardized means to quantify therapeutic benefit in terms of seizure reduction, one that is specifically designed for pharmacogenetic studies. A set of guidelines for classifying pharmacoresistance was recently codified by the International League Against Epilepsy (11); however, these guidelines have not been adopted by all laboratories, and they were generally not followed in conduct of the large body of earlier work. A third major obstacle is related to the clinical heterogeneity of epilepsy and the lack of information on the seizure phenotypes of patients included in some notable studies (12). It is possible that genetic influences on pharmacoresistance vary according to epilepsy subtype, and studies that combine different subtypes may introduce confounding variables. A related issue involves the selection of patients with regard to specific drug treatments. Many

studies include patients treated with a variety of drugs (13), referring to the phenotype of "multidrug resistance," and whereas there are some common biologic mechanisms among clinically effective AEDs (14), the genes involved in determining therapeutic responsiveness or resistance may be at least in part drug specific. Thus, it is possible that genetic effects are masked by resulting "noise" in studies that do not parse patients by specific AED. Another critical factor that has limited AED pharmacogenetic studies, although not unique to AEDs, is the relatively small size of patient populations and lack of statistical power. On the other hand, positive results in some studies may be questioned because of failure to correct for multiple statistical testing or population stratification. These factors and others have so far limited the clinical application of AED pharmacogenetic research. Whereas a variety of factors have been identified as obstacles, an area that has pushed the field forward has been genetic technology and advances in nucleic acid analysis. The ability to acquire a vast amount of genetic information from any individual rapidly and economically is already having a major impact in the field of medicine and is bound to have even greater importance in the future, particularly as related to pharmacogenetics.

GENETIC VARIATION AND GENETIC ANALYSIS

Shown in Table 49.1 are several types of structural variants that are commonly observed in human chromosomal DNA including single-base deletions, insertions, and substitutions, the latter representing the largest class DNA variation in the human genome (15). However, while any of these types of variants may impact the function of a gene product relevant to drug action, single-base substitutions, more commonly known as single nucleotide polymorphisms (SNPs), are the largest source of genetic variation between individuals and are likely most relevant to pharmacogenetics (16,17). The development of SNPs and SNP marker maps allows essentially any gene to be surveyed for variants that are associated with a phenotype. The typical experimental design for a pharmacogenetic study is analogous to the familiar "case–control" genetic association study, and it involves direct comparison of SNP genotypes for genes of interest between drug "responders," patients who derive a therapeutic benefit from drug therapy, and drug "nonresponders", those who do not (18). An important extension of this research approach involves comparison of haplotypes, or sets of SNP genotypes, at linked loci; this may help to distinguish whether a particular SNP is in itself functional or whether it is a surrogate for other tightly linked variants (19). Broad application of this strategy in genome-wide association studies has also become technically feasible and is now accelerating the pace of discovery in pharmacogenetics (20). On the horizon are targeted, whole-exome and whole-genome next generation DNA sequencing strategies that will facilitate the highest possible level of personalized drug treatment (21,22).

Table 49.1 Common Forms of DNA Variants Relevant to AED Pharmacology[a]

Variant	Description
Missense	Exonic single nucleotide substitution; produces protein amino acid substitution
Nonsense	Exonic single nucleotide substitution; creates premature translation stop codon
Splice site	Intronic single nucleotide substitution; adds or removes splice site; alters transcript exon composition
Regulatory	Single or polynucleotide insertion, deletion, or substitution in 3′ or 5′ untranslated region; alters gene expression level
Frameshift	Exonic insertion or deletion; changes protein amino acid sequence

[a]Genetic effects on pharmacology arise due to the influence of variation in the DNA sequence of genes encoding proteins that are therapeutic drug targets as well as proteins that are involved with the absorption, metabolism, distribution, and excretion of drugs.

DRUG RESPONDERS AND NONRESPONDERS

In pharmacogenetic studies of AEDs that address end points related to therapeutic benefit, determining which patients are "responders" and which are "nonresponders" is a critical and controversial issue. The assignment of patients to one of these groups will obviously have a major impact on results; however, inspection of the literature reveals substantial variability in the definition of these two response categories. Establishing which patients have derived clinical benefit from treatment, and which have not, is highly dependent upon the criteria utilized for assessment, and therefore, it is imperative for research teams to adopt uniform standards for valid comparison and confirmation of results. Recently, guidelines for defining resistance to AEDs were proposed by the International League Against Epilepsy (11). Epilepsy is recommended being classified as drug resistant if there is continued expression of seizures following a trial of at least two drugs (in monotherapy or polytherapy) that were appropriately selected for the type of epilepsy exhibited, correctly administered, and well tolerated. Conversely, drug responsiveness is defined as freedom from seizures for the period of at least 1 year, or three times longer than the previous interparoxysmal period (whichever is longer). Such guidelines have been proposed previously (23) and have led to more consistency in recent studies; however, strict adherence to these criteria will be required as the field moves toward large multicenter studies that combine patient data collected in diverse settings.

SEIZURE AND AED PHENOTYPES

Currently, there are no widely accepted standards for categorizing seizures in pharmacogenetic studies, a factor that has led to some confusion in the literature and has hindered progress. Whereas detailed seizure phenotypes are clearly important and can be highly informative (24), it is difficult to standardize and implement clinical research protocols that involve intensive collection of seizure data, especially in outpatient or primary care settings. On the other hand, self-reporting of seizure history by patients is also a major detriment to AED pharmacogenetic studies, even when data are basic, such as the number and duration of seizures. Similarly, qualitative ratings of seizure type

and/or severity, while possibly amenable to reliable assessment in certain clinical settings (25), are prone to significant nonspecific variability in ambulatory settings and in multicenter studies. Outcomes that are based upon complete seizure freedom may be more objective and less prone to reporting error; however, this strict criterion may reduce the number of responsive patients below practical limits of inclusion for robust studies. It is necessary to develop novel approaches to the challenges associated with establishing valid seizure response variables in AED pharmacogenetic studies, such as automation of EEG trait characterization (26), possibly with personal EEG devices that are more portable, are less obtrusive, and offer the possibility of remote data capture (27,28). Thus, while the limitations of AED pharmacogenetic studies have been known for some time, many studies are retrospective, utilizing preexisting AED response data from electronic or analog patient records that are often incomplete, lacking in detail, and prone to error. These factors must be taken into account both when designing new studies and when reviewing previous studies.

Because all drugs have multiple effects, including AEDs, multiple responses can be monitored and dissected genetically in pharmacogenetic studies. These responses are not limited to abrogation of seizures but may also include aspects of general pharmacology as well as biochemical, physiologic, or behavioral side effects of the drugs. Detailed phenotyping of patient responses to drug therapy may ultimately help to adopt standardized criteria for evaluating the relationship between genetic variability and AED effects. Additionally, since the effects of genetic variability may not be the same for all response end points, there is significant value added to studies that provide a high level of clinical information related to therapy, including data on seizure semiology, blood drug levels, metabolites, and drug interactions among others. In general, clinically relevant responses in epilepsy patients are tied to the pharmacology of AEDs. Two main categories of end points cover the range of responses that may be monitored in individual subjects, pharmacokinetic and pharmacodynamic. This classical distinction in the field of pharmacology represents a useful framework within which to ask questions about pharmacogenetics, and it is used here to organize discussion of relevant molecules.

PHARMACOKINETICS

The current state of the field of pharmacogenetics of AEDs is related in large part to genetic association studies in which statistical relationships are sought between clinical outcome variables and common polymorphisms in genes whose protein products are involved in pharmacokinetic processes. There are four basic sets of processes that constitute pharmacokinetics: (i) modalities by which drugs are administered to patients; (ii) the physiologic means by which they are distributed throughout the body and delivered to specific organs, tissues, and cells; (iii) the enzymatic pathways via which they are metabolized; and (iv) the mechanisms used to eliminate them and their metabolites from the body. There are many endogenous molecules that interact with drugs and that play specific roles in these pharmacokinetic processes; close coordination of the function of these molecules is critical for drugs to exert therapeutic effects. Sometimes underemphasized are the complexities associated with statistical analysis and modeling of pharmacokinetic processes for AEDs (29).

From the perspective of AED pharmacogenetics, the most studied endogenous molecules relevant to pharmacokinetics are drug transport proteins and drug-metabolizing enzymes. In general, these molecules play major roles in determining drug efficacy, time course of effect, and toxicity. Transporter proteins and enzymes that mediate drug biotransformation are from families in which members may be highly polymorphic and have similar or overlapping functions. The relative role of a

particular drug transport protein is dependent upon the specific AED and the expression level of the transport protein at the target brain site, which, in the case of epilepsy, may vary from patient to patient. Similarly, drug biotransformation may be shunted down alternative metabolic pathways based on substrate concentration or the activity levels of individual enzymes in different patients. Although some part of the difference between patients in drug transport and drug metabolism is a result of environmental influences, such as diet, exercise, and smoking (30), a substantial component is also a result of genetic variability, and studies suggest that both genetically mediated overexpression of cellular drug efflux pumps (31) and altered activity of polymorphic drug-metabolizing enzymes (32) may have a clinically relevant impact on the outcome of treatment with AEDs.

DRUG TRANSPORTERS

The processes of drug absorption, distribution, and excretion involve numerous transport proteins that are expressed on various cell types in many organs and tissues including vasculature, small intestine, brain, liver, and kidney. Several families of drug transport proteins potentially relevant to AED therapy have been identified; however, there is controversy regarding the role of specific molecules and their substrate specificity. This controversy stems in part from the many closely related members of protein transport families, tissue-specific expression of isoforms, species differences, and differences in assay parameters, all of which hinder the interpretation of data (33,34). These factors and others have prevented full elucidation of the role of drug transport proteins in the absorption, distribution, and elimination of AEDs in humans.

ATP-Binding Cassette Proteins

ATP-binding cassette (ABC) proteins are ATPase-dependent membrane transporters that mediate drug efflux from various types of cells including epithelium, endothelium, glial cells, and neurons (35). In the intestine, ABC transporters promote the excretion of drugs into the lumen (36) and could theoretically affect bioavailability of orally administered AEDs by inhibiting their absorption into the bloodstream. In endothelial cells of cerebrovasculature and choroid plexus, ABC transporters could extrude drugs absorbed from the blood and potentially restrict access to the brain (37). They are recognized as a factor of very high potential impact with regard to pharmacoresistance in epilepsy (38).

Although there is considerable evidence to support the concept that ABC transporters are relevant to the pharmacology of AEDs, studies on the substrate specificity of these transporters have yielded conflicting results with regard to their interactions with individual drugs. Analysis of prior work suggests that of currently available AEDs, phenytoin, phenobarbital, oxcarbazepine, and lamotrigine are highly likely to serve as substrates for ABC transport proteins (39,40). There is also evidence that levetiracetam, carbamazepine, felbamate, topiramate, valproate, and gabapentin interact with ABC transporters although there are conflicting data on these agents (39,40). Overall, this work has helped in the formulation of the hypothesis that high levels of transporter expression in epithelial cells lining the gastrointestinal tract and/or in endothelial cells constituting the blood–brain barrier contribute to pharmacoresistant epilepsy and has led directly to efforts to use transport inhibitors to increase penetration of AEDs into the brain (41).

Studies in animal models (42) and in humans with pharmacoresistant epilepsy (43) suggest that recurrent seizure activity increases expression of ABC transporter expression; however, the effects of

AED treatment on the expression of P-glycoprotein (44,45), the major ABC transport protein (46), complicate interpretation of results in human studies. It is also possible that interindividual differences in baseline expression or function of transporter proteins are involved in determining which patients will respond to a given medication. Positive genetic association between ABC gene variants and AED effects would represent strong evidence for a functional relationship and could be used to establish genotype-specific treatment guidelines that would optimize therapeutic drug regiments. Studies to date have focused on two members of the ABC transporter gene family: ABCB1 and ABCC2.

ABCB1

ABCB1, also known as MDR1 (multidrug resistance gene 1), encodes P-glycoprotein, a 1280 amino acid residue product (46). C3435T (rs1045642) is a common SNP in exon 26 of the ABCB1 gene with a minor allele frequency that shows significant ethnic differences (47). It is a synonymous polymorphism predicting an isoleucine residue in the intracellular C-terminal segment of the protein, and it may be the most comprehensively studied variant in AED pharmacogenetics. The functional effect of this variation is manifest as a change in protein folding due to the differential rate of protein synthesis caused by usage of an alternate codon (AUU for the T allele and AUA for the C allele) resulting in altered drug transport properties (48). As more P-glycoprotein is produced, specific tRNA species become depleted, and the role of alternative codon usage may be more critical (48). Thus, there is strong rationale for considering this variant as a potential factor in AED pharmacogenetics. Two other exonic SNPs in ABCB1 that have also been the focus of multiple studies are C1236T in exon 12 and G2677T/A in exon 21. The latter SNP is nonsynonymous and predicts a change from an alanine residue (G) to a threonine (T) or serine (A).

Studies designed to assess the role of C3435T and other ABCB1 SNPs in therapeutic responses to AEDs have been numerous and conflicting with nearly as many reporting positive associations as negative associations. A summary of these studies is shown in Table 49.2. Notably, among positive reports for C3435T, there is also discordance with regard to the allele or genotype associated with drug resistance. Early studies in Caucasian populations suggested that drug resistance was associated with the CC genotype (12) or with haplotypes containing the C allele (50). In contrast, the TT genotype was associated with drug resistance in Asian patients with epilepsy (57,63). Such ethnic differences suggested that C3435T may be linked to other ABCB1 polymorphisms that influence AED responses. Subsequent reports have revealed that the T allele and TT genotype may also be associated with drug resistance in Caucasian epilepsy patients (87) and the C allele and CC genotype may be associated with drug resistance in Asian patients with epilepsy (92). This suggests a potentially complex influence of ABCB1 genetic variability that requires further research to fully elucidate.

Table 49.2 Summary of ABCB1 Association Studies Related to AED Treatment Outcome

Author	Year	Population	Reference	SNPs	Association result[a]
Siddiqui et al.	2003	Caucasian; Asian	(12)	C3435T	CC genotype associated with drug resistance
Tan et al.	2004	Caucasian	(49)	C3435T	Negative
Zimprich et al.	2004	Caucasian	(50)	C1236T, G2677T/A, C3435T	Haplotype including C3435T associated with drug responsiveness
Soranzo et al.	2004	CEPH Families	(51)	Three intronic SNPs	Negative
Sills et al.	2005	Caucasian	(52)	C3435T	Negative
Hung et al.	2005	Han Chinese	(53)	C1236T, G2677T/A, C3435T	Haplotypes CGC, TGC, and TTT (for C1236T, G2677T, and C3435T) associated with drug resistance
Leschziner et al.	2006	Caucasian	(54)	C1236T, G2677T, C3435T	Negative
Kim et al.	2006	Korean	(55)	C3435T	Negative
Kim et al.	2006	Korean	(56)	C1236T, G2677T, C3435T	Negative
Seo et al.	2006	Japanese	(57)	T-129C, C1236T, G2677T/A, C3435T	T allele and TT genotype at C3435T and TT genotype at G2677T/A associated with drug resistance; haplotypes
Leschziner et al.	2007	Caucasian	(58)	C1236T, G2677T, C3435T	Negative
Shahwan et al.	2007	Caucasian	(59)	C3435T; 8 tagging SNPs	Negative
Chen et al.	2007	Han Chinese	(60)	C3435T	Negative
Ebid et al.	2007	Egyptian	(61)	C3435T	C allele associated with drug resistance
Hung et al.	2007	Han Chinese	(62)	C1236T, G2677T/A, C3435T	T allele at both G2677T and C3435T and their interaction term associated with drug resistance
Kwan et al.	2007	Han Chinese	(63)	C3435T	TT genotype associated with drug resistance
Simon et al.	2007	Caucasian	(64)	T-129C, C1236T, G2677T/A, C3435T	2677T allele associated with low plasma phenytoin levels
Dericioglu et al.	2008	Turkish	(65)	C3435T	Negative
Ozgon et al.	2008	Turkish	(66)	C3435T	Negative
Basic et al.	2008	Croatian	(67)	C3435T	CC genotype associated with low CSF/serum phenobarbital ratio and with drug resistance
Szoeke et al.	2009	Caucasian	(68)	C3435T	Negative
von Stülpnagel et al.	2009	Caucasian	(69)	C1236T, G2677T/A, C3435T	Negative

Author	Year	Population	Reference	SNPs	Association result[a]
Lakhan et al.	2009	Indian	(70)	C1236T, G2677T, C3435T	Negative
Vahab et al.	2009	Indian	(71)	C1236T, G2677T/A, C3435T	Negative
Kim et al.	2009	Korean	(72)		Negative
Kwan et al.	2009	Han Chinese	(73)	C3435T, G2677T/A	C3435T, 2677G/T/A and haplotypes associated with drug resistance only in males with focal epilepsy
Grover et al.	2010	Indian	(74)	C1236T, G2677T/A, C3435T	Negative
Maleki et al.	2010	Iranian	(75)	T129C, T1236C	1236 CC and CT genotypes associated with resistance; 129 CT genotype associated with responsiveness
Sánchez et al.	2010	Spanish	(76)	G2677T/A, C3435T	3435TT or 2677TT lower risk drug resistance than CC or GG; symptomatic epilepsies 3435CT or TT lower-risk drug resistance than CC
Meng et al.	2011	Chinese	(77)	C3435T	Negative
Haerian et al.	2011	Chinese, Indian, Malaysian	(78)	C1236T, G2677T/A, C3435T	Negative
Haerian et al.	2011	Chinese, Indian, Malaysian	(79)	C1236T, G2677T/A, C3435T	Negative
Dong et al.	2011	Han Chinese	(80)	C1236T, G2677T/A, C3435T	Negative
Haerian et al.	2011	Chinese, Indian, Malaysian	(81)	C3435T, 117+4196T>C	C3435T C allele associated with resistance to CBZ and VPA males with cryptogenic epilepsy; 117+4196T>C T allele associated with resistance to CBZ and VPA in females with symptomatic epilepsy
Kumari et al.	2011	Indian	(82)	G2677T/A	A allele associated with drug resistance
Sayyah et al.	2011	Iranian	(83)	C3435T	CC genotype associated with drug resistance in adult females
Hung et al.	2012	Han Chinese	(84)		Negative
Hung et al.	2012	Han Chinese	(85)	C1236T, G2677T/A, C3435T	C1236T, G2677T/A associated with phenytoin concentration/ dose ratio
Ponnala et al.	2012	Indian	(86)	C3435T	T allele and CT and TT genotypes associated with drug resistance.
Sterjev et al.	2012	Macedonian	(87)	C3435T	CT and TT genotypes associated with drug resistance
Lovrić et al.	2012	Croatian	(88)	C1236T, G2677T/A, C3435T	Associated with lamotrigine serum concentrations
Emich-Widera et al.	2013	Not Specified	(89)	C3435T	Negative
Seven et al.	2013	Turkish	(90)	C3435T, G2677T/A	Children; Negative
Shaheen et al.	2013	Indian	(91)	C3435T	TT genotype associated with drug resistance
Subenthiran et al.	2013	Malaysian	(92)	C3435T, G2677T/A	3435TT and 2677TT genotypes associated with response to CBZ; GCGC haplotype associate with resistance
Puranik	2013		(93)		Associated with carbamazepine clearance

[a]Association results are based on the significance of the P-value in the original publication. "Negative" refers to a P-value that was determined to be statistically not significant.

The large number of studies on the influence of C3435T and other ABCB1 SNPs on AED responses in epilepsy patients has spawned several meta-analyses permitting an increase in statistical power and helping to address issues associated with multiple testing artifacts. An early meta-analysis (94) combined data from over 1000 patients but failed to demonstrate a statistically significant association of C3435T with multidrug resistance. The next published meta-analysis also focused specifically on C3435T, involved 11 studies including over 3300 drug refractory and 1600 drug-responsive epilepsy patients (95), and it also obtained negative results both with and without segregation of studies by country of origin. A third meta-analysis included 22 studies (96), and it too was negative irrespective of segregation of ethnic subgroups. This latter study conducted a separate analysis including only reports meeting the International League Against Epilepsy's recommendation for drug resistance, but this was also negative. A subsequent update of this latter meta-analysis included 25 studies and examined 3-SNP haplotypes in addition to C3435T genotypes and allele frequencies (81), but again no positive association was documented. Thus, despite a number of provocative literature reports, based upon the outcome of several meta-analyses, the impact of ABCB1 genotype on AED response is unclear. The addition of new studies to the literature since the time of the last meta-analysis, both positive (79,82,83,86,87,91,92) and negative (77,78,85,89,90), provides impetus for another combined meta-analysis and a reassessment of the impact of ABCB1 genetic variation on therapeutic response to AEDs. However, it is likely that inadequate control of variables including diet, smoking, exercise, epilepsy subtype, and issues related to polypharmacy such as inclusion of drugs that may not be substrates for the ABCB1 transporter will continue to have a negative impact on such attempts.

With regard to pharmacokinetic end points, several studies have attempted to correlate ABCB1 genotypes with levels of AEDs. A study in European patients showed that low plasma levels of both phenytoin and carbamazepine are associated with the T allele of G2677T SNP but not with SNPs at positions 129, 1236, or 3425 (64). A subsequent study of Han Chinese epilepsy patients on phenytoin monotherapy reported that ABCB1 genotypes at C1236T, G2677T, or C3435T had no clear effect on maintenance dose or plasma drug levels (85). An earlier study involving a 6-month trial of phenobarbital monotherapy in Croatian epilepsy patients reported that whereas there was no effect of ABCB1 polymorphisms at G2677T or C3435T on serum drug levels, patients with the CC genotype had significantly lower CSF drug levels and significantly more seizures than patients with CT or TT genotypes (67). On the other hand, a recent study in Croatian patients showed that the CC genotype of the C1236T SNP was associated with high plasma lamotrigine levels compared to TT and CT patients; no effect of genotype at either C3435T or G2677T/A was observed (88). Steady-state and dose-corrected lamotrigine concentrations were also shown to be significantly associated with C1236T as well as with G2677T, and the 3-SNP haplotype 1236C–2677G–3435C was associated with significantly higher lamotrigine plasma levels compared to several other common haplotypes, although a complicating aspect of the study is that the majority of the patients were taking multiple AEDs in addition to lamotrigine (88). Overall, while there is some suggestion that ABCB1 genotypes are involved in shaping clinically relevant parameters of AED pharmacokinetics, it is not yet possible to develop a clear picture of which SNPs are most relevant and which AEDs are affected.

ABCC1 and ABCC2

ABCC1 encodes multidrug resistance–associated protein 1 (MRP1), a 1522 amino acid residue drug transporter protein (97). ABCC1 is ubiquitously expressed and its substrate specificity overlaps with

that of ABCB1 (98). While this gene has been shown to be highly polymorphic (99), no clinically significant associations have been recognized. ABCC2 encodes multidrug resistance–associated protein 2 (MRP2, ABCC2), a 1545 amino acid residue protein that also may be involved in the transport of AEDs (98,100) and is up-regulated in the brain tissues of patients with epilepsy, similar to ABCB1 (101–104). In an early study, no association between the ABCC2 genotypes or haplotypes, and responsiveness to AEDs was observed in nearly 300 Japanese epilepsy patients (105). Subsequently, it was shown that carriers of the putatively low-expression 24T variant were significantly overrepresented among nonresponders, a finding that was confirmed by comparing young responders with adult drug-refractory patients (106). Following this, it was reported that carriers of the nonsynonymous polymorphism, G1249A (V417I, rs2273697), were more frequent among responders, and the allele was more prevalent among the subgroup of patients receiving carbamazepine or oxcarbazepine, but not in patients receiving other AEDs (107). In another study, ABCC2 C-24T (exon 1) and C3972T (exon 10) polymorphisms and one ABCC2 haplotype were associated with multidrug pharmacoresistance (108). Evidence for clinical relevance of the nonsynonymous G1249A (V417I) variant comes from a study reporting that presence of the A allele is an independent determinant of adverse neurologic effects caused by carbamazepine (109). Functional experiments using an ATPase assay in conjunction with flow cytometry indicated that carbamazepine was a substrate of MRP2 and that the 417I variation selectively reduced carbamazepine transport across the cell membrane (109). However, not all studies of ABCC2 have been positive. In a study of drug-resistant and drug-responsive Han Chinese epilepsy patients, no statistically significant genotype or haplotype associations were detected following analysis of 25 tagging SNPs from ABCC2, ABCC5, and ABCG2 genes (110). Similarly, a recent study did not identify any significant association between genetic polymorphisms of the C-24T and G1249A of ABCC2 or any combined effect in response to AED treatment and development of drug resistance in patients with partial complex epilepsy (111).

Thus, as is the case with ABCB1, numerous genetic association analyses between common ABCC2 polymorphism and response to AEDs have been reported; however, as described above, results are conflicting and difficult to interpret clearly. In attempts to integrate available data and support this line of investigation, two meta-analyses have recently been undertaken. One analyzed the effect of the G1249A (V417I) polymorphism in 6 published studies, involving 2213 patients (1100 patients with drug-resistant epilepsy and 1113 controls with drug-responsive epilepsy) and showed that variant genotypes were associated with a significantly decreased risk of AED resistance (112). A stratified analysis by ethnicity showed similar findings for Caucasians in an additive model again suggesting that the ABCC2 G1249A polymorphism is significantly associated with a decreased risk of AED resistance (112). The other meta-analysis involved 8 studies that included 1294 responders and 1529 nonresponders, and it analyzed all the commonly reported variants that included C-24T, G1249A (V417I), and C3972T (I1324I) (113). Although preliminary analyses showed an overall significant association of high activity promoter variant C-24T, the T allele being associated with beneficial therapeutic response to AEDs, the association was lost after testing for multiple corrections. Thus, taken together, results of the two meta-analyses suggest a possible role of the ABCC2 transporter variants in altered drug response in patients with epilepsy; however, the genetic mechanism underlying this effect is unclear, and the magnitude of its influence in determining overall response to AEDs, if any, remains to be elucidated.

SLC3A2 and SLC7A5

Another protein complex documented to affect to membrane flux of AEDs is the large neutral amino acid transporter, also called L-amino acid transporter or system L, a heterodimer encoded by the genes SLC3A2 and SLC7A5 (114,115). Although there is evidence to support a role for system L in the absorption of pregabalin and gabapentin (116,117), data on the role of genetic variation in this system with regard to individual differences in drug effects in general are sparse (118).

SLC22A4

SLC22A4 encodes the organic cation transporter 1 (OCTN1) and may be involved in the absorption and excretion of certain cationic drugs. Gabapentin is an AED that does not undergo extensive metabolism and whose absorption and renal elimination appear to involve membrane transporters. To test the hypothesis that variation in SLC22A4 plays a role in gabapentin pharmacokinetics, the common variant L503F was analyzed in relation to gabapentin clearance (119). Results showed that in subjects homozygous for the variant phenylalanine allele, gabapentin renal clearance approximates the glomerular filtration rate, whereas in subjects homozygous for the wild-type leucine allele, gabapentin undergoes net secretion in the kidney. This finding was supported by in vitro studies showing that OCTN1 facilitates the Na^+-independent transport of gabapentin and that the OCTN1 phenylalanine variant is deficient in gabapentin transport activity (119). It was concluded that OCTN1 contributes to active tubular secretion of gabapentin and that this effect may be diminished or absent in individuals carrying the OCTN1 phenylalanine variant. The results of this study underscore the clinical relevance of genetic variation in renal drug transporters with regard to active drug secretion and suggest it may be involved in explaining interpatient variability observed regarding the effects of certain AEDs including gabapentin.

DRUG-METABOLIZING ENZYMES

Biotransformation of AEDs is diverse and involves a host of different enzyme proteins (120). Genetic effects are observed as a result of the many drug-metabolizing enzymes that are products of polymorphic genes (121), and it is important to note that these polymorphisms exhibit significant ethnic differences (122). Drug metabolism is generally recognized to proceed in two phases. Phase I reactions involve the cytochrome P450 (CYP) family of mixed function oxidases. Although numerous CYP family members have been identified (http://www.cypalleles.ki.se/), only four (CYP1, CYP2, CYP3, and CYP4) are involved in drug metabolism. CYP enzymes mediate a wide array of reactions involving both xenobiotics and endogenous substrates alike. They incorporate one atom of molecular oxygen into the substrate and the other atom into water. In general, phase 1 reactions involve the addition of a functional group, which is then used as a site of conjugation in phase 2 reactions.

With respect to phase 1 drug metabolism, the most common reaction involving CYP enzymes is hydroxylation (123). The highly polymorphic nature of the CYP gene family has functional relevance with regard to the pharmacology and clinical use of many AEDs. Most AEDs undergo phase 1 metabolism including phenytoin, phenobarbital, carbamazepine, valproate, diazepam, ethosuximide, zonisamide, felbamate, and tiagabine (124,125). In some cases, phase 1 metabolism activates AEDs and contributes to therapeutic or toxic effects (126). Other AEDs are metabolized primarily by non-CYP mechanisms or undergo phase II metabolism directly including lacosamide, rufinamide,

topiramate, and vigabatrin (127). Levetiracetam and gabapentin are excreted mostly unchanged in the urine.

Phase 2 metabolism involves various conjugation reactions that increase hydrophilicity and facilitate renal excretion of a drug or phase 1 drug metabolite. Among the common endogenous molecules conjugated to xenobiotics are acetyl and sulfate moieties, glucuronic acid, glycine, and glutathione (123). The enzymes that are involved in conjugating these endogenous compounds to exogenous drug substrates represent another level of potential genetic influence since functional polymorphisms are also known to exist in all the major phase 2 enzyme systems including N-acetyltransferases, sulfatases, glucuronidases, and glutathione synthetase. There is evidence that some of these variants are relevant to the pharmacology of AEDs.

Table 49.3 shows a summary of polymorphic drug- metabolizing enzymes studied in relation to the pharmacology of AEDs. For the most part, pharmacogenetic studies of drug-metabolizing enzymes for AEDs have focused on pharmacokinetic phenotypes such as the influence of variants on the relationship between dosage and plasma levels. Variants of phase 1 enzymes with impaired activity are often associated with higher plasma levels. In a number of studies, this has been related to increased drug toxicity and a requirement for dosage reduction. Studies of the influence of genetic variation in AED-metabolizing enzymes on therapeutic responses to AEDs are less frequent and the results less clear with regard to clinical relevance. Following are key genes whose variation has been suggested to be most relevant to the pharmacology of AEDs.

Table 49.3 Summary of Reported Associations Between Variation in Genes for Drug Metabolism Enzymes and AED Treatment Endpoints

Gene	AED[a]	Association result	Reference
CYP2C19	PHT	Variant alleles associated with maximal elimination rate	(128–130)
		Variant allele associated with decreased elimination Km and lower p-HPPH/PHT ratios	(131)
		Variant allele associated with higher plasma levels	(64,67,78,85,88,89,97–127,132–138)
		Haplotype associated with drug resistance	(90)
	PBN	Total clearance significantly decreased in homozygous variant	(139)
	CLB	Variant alleles associated with decreased clearance and higher plasma N-CLB/CLB dose ratios	(134–136)
	PB	No association with PB clearance, volume of distribution or plasma level	(140)
	ZNS	Variant alleles associated with decreased clearance	(141)
	VPA	Variant alleles associated with decreased clearance	(137)
CYP2C9	PHT	Variant allele associated with decreased elimination rate	(129,130)
		Variant allele associated with decreased V_{max} of elimination and decreased p-HPPH/PHT ratios	(131)
		Promoter variant associated with decreased clearance	(142)
		Variant allele associated with decreased dose requirement	(85,143–145)
		Variant allele associated with higher plasma levels	(85,138,146,147)
		Promoter variant associated with dose requirement	(148)
		Variant allele and haplotype associated with drug resistance	(90)
	VPA	No association of variants with levels of hepatotoxic 4-diene-VPA	(149)
		Variant *3 allele associated with higher plasma VPA	(150)
		Variant alleles associated with reduced clearance	(151)
	MULTI	Variant alleles associated with multidrug resistance	(82)
	PB	Variant allele associated with decreased clearance	(152)
CYP2A6	VPA	Variant *4 allele associated with higher plasma VPA	(150)
CYP2B6	VPA	Variant allele associated with higher plasma VPA	(150)
CYP3A4	CBZ	Variant allele associated with altered clearance	(93)
CYP3A5	CBZ	Variant allele associated with higher steady-state level	(153)
EPHX1	CBZ	Variant allele associated with altered metabolite ratios	(93)
		Variant allele associated with maintenance dose	(154)
		Variant allele associated with higher plasma levels	(155)
NAT2	CLZ	Variant alleles associated with lower V_{max} for formation of acetylated metabolite in vitro	(156)

Gene	AED[a]	Association result	Reference
	PHT	Variant alleles associated with increased half-life, decreased clearance, toxicity	(157)
POR	CLB	Variant genotype associated with increased clearance	(134)
UGT1A3	VPA	Variant allele associated with low trough plasma level	(158)
UGT1A4	LTG	Variant allele associated with low serum levels	(159)
UGT1A6	VPA	Variant allele associated with low concentration–dose ratio	(160,161)
UGT2B7	VPA	Variant allele associated with decreased clearance	(13)
		Variant allele associated with low concentration–dose ratio	(160)
		Variant allele associated with low serum level	(162)
	LTG	Variant promoter allele associated with low concentration–dose ratio	(163)

[a]PHT, phenytoin; PBN, pentobarbitone; CLB, clobazam; PB, phenobarbital; ZNS, zonisamide; VPA, valproate acid; MULTI, polypharmacy; CBZ, carbamazepine; CLZ, clonazepam; LTG, lamotrigine.

CYP2C19

The CYP2C family is the most extensively studied enzyme system in relation to AEDs. It is a large gene family that is highly expressed in the liver, and its various isoforms exhibit numerous polymorphisms including some that are functional and that are clinically relevant to drug biotransformation. CYP2C19 was the first isoform to gain prominence with regard to its potential for pharmacogenetic relevance. Initial studies showed that variants of the CYP2C19 gene had a significant influence on the metabolism of the AED mephenytoin (132,133). Since that time, a role for CYP2C19 variants in the effects of other AEDs has been suggested. For example, the ratio of the plasma concentration of the active metabolite of clozaban, N-desmethylclobazam, to the administered dose of clozaban (the so-called CD ratio) is significantly greater in patients harboring CYP2C19 variants (134,135). In a related study, the concomitant use of hepatic enzyme inducers (phenytoin and carbamazepine) reduced the CD ratio of clozaban independent of CYP2C19 genotype; however, ratios for N-desmethylclobazam were only elevated in patients harboring variant alleles (136). This latter study showed that when the cutoff value of the CD ratio for N-desmethylclobazam was set at 10.0 (μg/mL)/(mg/kg) for predicting the CYP2C19 variant status, the sensitivity and specificity were 94.4% and 95.7%, respectively (136). Screening tests such as this which allow better management of AED polypharmacy have high potential clinical utility.

Epilepsy patients who harbor CYP2C19 variants have been reported to have significantly reduced clearance of several other AEDs including phenytoin and diazepam. Although phenytoin is primarily metabolized by CYP2C9, a number of studies have suggested that epilepsy patients with CYP2C19 low-activity ("poor metabolizer") variants may have significantly decreased clearance (128–130,137,138), a significantly higher CD ratio (85) and a significantly lower ratio of plasma metabolite to parent drug level (131). With respect to diazepam, CYP2C19 catalyzes N-demethylation and 3-hydroxylation reactions, both of which generate therapeutically active compounds (164). CYP2C19 variants increase plasma elimination half-lives of diazepam, and its metabolites and the clearance of diazepam was significantly lower in individuals harboring variant alleles (165). Clearance of zonisamide has also been shown to be lower in CYP2C19 variant carriers

(141) as has clearance of valproic acid (137). One study that examined the relationship between CYP2C19 genotypes and the plasma level, volume of distribution and clearance of phenobarbital was negative (140).

Although there are notable ethnic differences in the frequency of CYP2C19 variant alleles, the wild-type or extensive metabolizer phenotype predominates in all populations so far studied (122). CYP2C19 variant alleles are more frequent in Asian populations (13% to 23%) compared to whites and African Americans (1% to 6%) (166). The main defective allele, CYP2C19*2, occurs in 30% of Chinese and between 15% and 17% in Caucasian and African American populations. CYP2C19*3 occurs in about 5% of individuals of Chinese descent and is very rare in Caucasians (167). Although CYP2C19*2 and CYP2C19*3 alleles together explain essentially all poor metabolizers of Asian descent, it only explains about 80% of Caucasian poor metabolizers (168). Thus, additional variants await discovery in this population, and in the interim such variants may be a cause of "idiosyncratic" reactions.

CYP2C9

CYP2C9 is the primary enzyme responsible for the metabolism of phenytoin. Of the many CYP2C9 alleles identified, the wild-type allele encodes an enzyme with the highest activity; variants encode enzymes with reduced activities that confer "poor metabolizer" phenotypes (169–171). CYP2C9 variants thus have been associated with a number of pharmacokinetic parameters including high plasma or serum level (138,143,146,147), reduced clearance (129,130,144,172) and lower dose requirement (85,143–145) compared to patients who carry only wild-type alleles. In one study, the mean maximal drug elimination rate was 40% lower in patients harboring CYP2C9 variants (131).

A major implication of CYP2C9 variants that substantially decrease the rate of phenytoin metabolism and elimination is related to the possibility of drug accumulation and toxicity. Several studies have investigated the relationship between CYP2C9 variants and adverse reactions to phenytoin, particularly neurologic signs such as weakness, lethargy, motor incoordination, slurred speech, cognitive disturbance, and memory loss. Early case reports of phenytoin-treated patients harboring known (173) or novel (174) variants highlighted this potential problem. Subsequently, a study of nearly 300 epilepsy patients treated with phenytoin showed that there was a significantly greater frequency of CYP2C9 variants in the 20% of the patients who exhibited neurotoxic effects compared to the 80% who did not (175). This report was confirmed by others showing an association between phenytoin toxicity and CYP2C9 variants in large patient populations (176,177). Taken together, these reports document the clinical relevance of CYP2C9 variants with regard to dose-related nonspecific neurologic toxicity induced by phenytoin. A more specific abnormal neurologic phenotype associated with long-term phenytoin treatment is cerebellar atrophy, and a recent study has shown that this effect is also related to CYP2C9 gene variants (178). Interestingly, two other recent studies have reported protective effects of CYP2C9 variants in epilepsy patients treated with phenytoin, one showing reduced risk for atherosclerosis (179) and another showing increased bone mineral density (180).

The AEDs valproate and phenobarbital may also be substrates for CYP2C9, and they too have been studied in relation to genotype. In a population of Japanese epilepsy patients, phenobarbital clearance was shown to be reduced by nearly one-half in those carrying CYP2C9 variants (152). CYP2C9 variants are also reported to be associated with higher valproate plasma levels (150) and decreased valproate clearance (137) but have no effect on production of the hepatotoxic 2,4-diene

valproate metabolite (149). All of these studies suggest a broad influence of CYP2C9 variants on AED pharmacology.

In addition to effects on AED pharmacokinetics, CYP2C9 polymorphisms have also been studied in relation to multidrug resistance. One study showed a marginally significant difference between drug-responsive and drug-resistant patients for frequency of the CYP2C9*3 variant (A1075C) (82). A subsequent study confirmed the association between CYP2C9*3 and drug resistance and also demonstrated an association with haplotypes containing variants for both CYP2C9 and CYP2C19 (90). It is noteworthy that positive results were obtained in the above studies despite patients having been treated with multiple AEDs, some of which are not substrates for CYP2C9 or CYP2C19.

CYP3A

The CYP3A family has several members relevant to the metabolism of AEDs. CYP3A4 is one of the most prominent members of the hepatic microsomal P450 system (181) and is involved in the metabolism of many diverse drugs (182). AED substrates for this enzyme and the closely related CYP3A5 include carbamazepine, tiagabine, and felbamate. Zonisamide is metabolized mostly by the CYP3A4 and CYP3A5 but also by CYP3A7 (183). Valproate is metabolized by CYP3A1 (184).

Pharmacogenetic studies involving CYP3A variants have been conducted in regard to the pharmacology of carbamazepine primarily because this family is involved in the formation of the 10,11-epoxide, a major carbamazepine metabolite. In one study, steady-state plasma levels of carbamazepine were higher in patients harboring the CYP3A5*3 variant (153). In another study, clearance of carbamazepine was reduced in patients harboring the CYP3A4*1B variant (93). These results suggest that CYP3A variants are functional and may affect the use of carbamazepine. However, effects of CYP3A4 genotype on carbamazepine levels are not observed in all studies (155), and no relationship is observed between CYP3A4 genotype, carbamazepine pharmacokinetics, and therapeutic response (155). A study investigating a possible relationship between CYP3A4 genotype and the pharmacokinetics of zonisamide also reported negative results (164).

EPHX1

EPHX1 encodes human microsomal epoxide hydrolase, a major phase 1 enzyme involved in the detoxification of aromatic drug molecules. This enzyme catalyzes the conversion of epoxides to less toxic dihydrodiols that subsequently can be conjugated with glucuronic acid or glutathione and excreted in phase 2. In the case of carbamazepine, 10,11-CBZ-epoxide is further deactivated by the action of epoxide hydrolase to give inactive 10,11-CBZ-diol that is excreted as a glucuronide. Several AED pharmacogenetic studies of EPHX1 have been reported on patients treated with carbamazepine. In one study, a multivariate model that included patient age and genotypes for SNPs T337C and A416G revealed a significant association with carbamazepine maintenance dose (154). In another study, EPHX1 SNPs were associated with greater CBZ-10,11-trans dihydrodiol:CBZ 10-11 epoxide ratios (93). However, while studies continue to confirm that EPHX1 A416G affects carbamazepine levels, there is a lack of association with drug resistance (155). In addition to carbamazepine, another AED whose metabolism involves the action of epoxide hydrolase is phenytoin (185). In a study focused on the fetal toxicity of phenytoin, maternal EPHX1 Y113H and H139R variants were associated with congenital malformations whereas the Y113/H139 haplotype was protective (186).

UGT1A and UGT2B

UGT1A and UGT2B, along with UGT2A, are genes that encode isoforms of the enzyme uridine 5′-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase, UGT), a glycosyltransferase that catalyzes the transfer of the glucuronic acid component of UDP-glucuronic acid to a small hydrophobic molecule (187). Such glucuronidation reactions are critical elements of phase 2 drug metabolism (123,188). Extensive genetic variation exists in the UGT1A and UGT2B genes (189,190), and since several AEDs use the UGT pathway, this variation is beginning to be examined in regards to AED pharmacotherapy.

Glucuronidation pathways involving UGT enzymes are particularly important for valproate and lamotrigine. One study showed that trough plasma levels of valproate were lower in patients carrying the UGT1A3*5 variant (158). Another study examined pediatric patients with background CYP2C9*1/*1 genotypes undergoing AED polypharmacy and showed that valproate plasma levels were lower in those who were homozygous CC for the UGT2B7 C161T variant (13). Analysis of a set of six candidate genes relevant to valproate pharmacology identified UGT2B7 as a functionally important gene showing a significant association between dosage (mg/kg/day) and the UGT1A6 T19G, A541G, and A552C variants, carriers of which exhibited a lower valproate CD ratio and thus were observed to require higher drug doses to achieve a therapeutic effect (160). A subsequent study refined this observation reporting that patients who were double heterozygotes at nucleotide variants T19G, A541G, and A552C in UGT1A6 exhibited lower plasma valproate levels and required higher valproate doses (161). Finally, a recent study of A268G and G211T in the UGT2B7 gene showed that the plasma valproate concentration in patients homozygous AA for A268G was significantly higher than that of patients who were GG (162). Similar positive associations have been reported between UGT genes and pharmacokinetic parameters for lamotrigine, an AED that is metabolized predominantly by glucuronidation. The major inactive urinary metabolites are a 2-N-glucuronide (76%) and a 5-N-glucuronide (10%). Thus, in one study that looked at the relationship between lamotrigine CD ratios and UGT2B7, a significant association was found with a 5′UTR promoter SNP suggesting that increased expression of glucuronidation enzymes results in increased clearance and lower levels (163). Another study examined two SNPs predicting amino acid substitutions in UGT1A4, P24T, and L48V and reported that serum levels of lamotrigine in nonsmoking patients undergoing monotherapy who carried a valine residue at position 48 were 52% lower compared to nonsmoking monotherapy patients who were homozygous for the wild-type leucine allele (159). Together, these results confirm an important effect of genetic variation in phase 2 drug-metabolizing systems on the pharmacology of certain AEDs.

NAT2

The NAT2 gene encodes an N-acetyltransferase isozyme that functions to both activate and deactivate certain arylamine and hydrazine drugs. Variation in this gene is responsible for the N-acetylation polymorphism in which human populations segregate into rapid, intermediate, and slow acetylator phenotypes (191). N-acetylation is not recognized to play a major role in the metabolism of AEDs however there are some acetylation pathways involving metabolites of clonazepam and to a lesser extent phenytoin. One study on phenytoin reported that a poor metabolizer phenotype with increased drug half-life, decreased clearance and signs of toxicity were associated with the presence of the *5A (C481T) and *5C (A803G) variants (157). A study of patients treated with clonazepam showed that the presence of *5B and *6A variant alleles was associated with a 20-fold lower rate of 7-

aminoclonazepam acetylation in vitro (156). These studies confirm that variant NAT2 alleles can significantly impact AED pharmacokinetics and may have clinical relevance.

ADVERSE REACTIONS

Genetic influences on adverse reactions to certain AEDs have been suggested for a number of years (192), and now there is growing evidence for such effects in several realms. Whereas some common AED side effects and general toxicity are associated with genetic variation in metabolic or transport systems as described in preceding sections of this chapter, there are some reported variations that predispose or cause specific and often severe adverse drug reactions. In one study, a significant association was reported between the glutathione S-transferase M1 null allele and carbamazepine hepatotoxicity (193). Hepatotoxicity is potentially more problematic and severe during treatment with valproate and several studies have investigated genetic links with phenotypes reflecting liver injury or dysfunction such as elevation of transaminase levels. One study reported an association between valproate-induced hepatotoxicity and a nonsynonymous SNP predicting the variant V16A in superoxide dismutase type 2 (194). Another study discovered an even stronger association with the nonsynonymous Q1236H in POLG, the gene encoding the mitochondrial DNA polymerase γ (195). Mutations in POLG cause Alpers–Huttenlocher syndrome, a neurometabolic disorder associated with an increased risk of developing fatal valproate hepatotoxicity (196), which served as a clue to facilitate the discovery of the important influence of the common polymorphism Q1236H in other cases of severe valproate hepatotoxicity (195). Another valproate adverse phenotype examined, although in patients with bipolar disease, is a metabolic syndrome involving altered plasma leptin and lipid levels (197). This study analyzed a C825T variant of the gene GNB3, which was previously linked to metabolic abnormalities, and reported a strong association between T allele carriers and a lower risk for valproate-induced metabolic abnormalities (197). Several other genes are notable for their role in severe adverse drug reactions are methylenetetrahydrofolate reductase (MTHFR) and HLA-B, and these are discussed in the following sections.

MTHFR

One of the first potentially clinically significant discoveries involved a variant in the MTHFR gene, C677T, which was reported to be an independent predictor of hyperhomocysteinemia patients treated with phenytoin or carbamazepine (198). This study led to the conclusion that patients with a TT genotype have a higher folate requirement to maintain normal levels of homocysteine and folic acid. The results of subsequent studies were equivocal however (199–202), with the most recent study reporting no relationship between homocystinuria and polymorphisms in any genes associated with homocysteine metabolism (203). Thus, the relationship between genetic variation in the MTHFR gene and folate requirements remains unclear.

HLA-B*1502

AED-induced immune-mediated hypersensitivity reactions often involve dermatologic disorders ranging from mild rash to toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS), potentially fatal conditions characterized by severe skin lesions over the entire body (204,205). Drugs whose chemical structure involves an aromatic ring such as carbamazepine, phenytoin,

lamotrigine, and phenobarbital are most likely to cause exaggerated adverse reactions (206,207). Ability to reliably screen patients for hypersensitivity to AEDs prior to initiation of therapy would be a major therapeutic advance.

New insight into carbamazepine-induced SJS was gained 10 years ago with the discovery of its strong relationship to the HLA-B*1502 allele (208). The initial observation was extended in a larger population of patients and whereas the strength of the association between HLA-B*1502 and carbamazepine-induced TEN/SJS increased further, it was shown that this allele was not associated with other carbamazepine-induced cutaneous side effects such as maculopapular eruption or hypersensitivity syndrome (209). At the same time, it was discovered that Caucasian patients with carbamazepine-induced TEN/SJS do not harbor the HLA-B*1502 allele (210,211). This is consistent with the vanishingly low frequency of this allele in most parts of the world (212), and thus, the link between HLA-B*1502 and CBZ-induced SJS is viewed primarily as an issue in treating individuals having descended from certain regions of Asia where the allele is more common. Subsequently, it was demonstrated that the association between HLA-B*1502 and carbamazepine-induced SJS in some Asian populations could be extended to the drugs phenytoin and lamotrigine (213). Following this was a report of a significant association between HLA-B*1502 and phenytoin- and carbamazepine- induced SJS/TEN in a patient group from Thailand (214), the first positive result in a non-Chinese population, and another report showing that HLA-B*1502 was not associated with carbamazepine-induced SJS/TEN in patients of Japanese ancestry (215). Based on the positive reports, the U.S. Food and Drug Administration added a warning to the label of carbamazepine that recommends screening for HLA-B*1502 in patients of certain Asian ancestry prior to initiating treatment with carbamazepine (216). However, carbamazepine-induced SJS/TEN was subsequently linked to HLA-B*1502 in additional patient populations such as one from India (217).

Aside from HLA-B*1502, there is evidence for other HLA alleles to be associated with AED-induced SJS/TEN in non-Chinese patient populations. For example, HLA-B*5901(218) and HLA-B*1511 (219) as well as HLA-A31, HLA-A11, and HLA-B51 (220) are candidate markers for susceptibility to carbamazepine-induced SJS and other adverse cutaneous reactions involving carbamazepine in Japanese patients. In addition, a study in patients of Northern European ancestry revealed that the presence of the HLA-A*3101 allele was associated with a fivefold increase in the risk for carbamazepine-induced hypersensitivity reactions, including SJS and maculopapular eruption (221). Korean patients appear to be at risk from both HLA-B*1511 and HLA-B*3101, but not from HLA-B*1502 (222). Most recently, a systematic review and meta-analysis involving 20 studies determined HLA-A*3101 and HLA-B*1502 as risk markers and HLA-B*4001 as a protective marker for susceptibility to cutaneous adverse drug reactions when comparing intolerant with tolerant patients (223). Furthermore, stratification by clinical outcome showed HLA-B*1502 and HLA-B*1511 as risk markers and HLA-A*2402 as a protective marker for bullous lesions in the Asians, whereas HLA-A*3101 was observed to be a universal risk marker for all cutaneous adverse drug reactions and HLA-B*4001 observed to be a protective marker specifically in Chinese populations (223).

PHARMACODYNAMICS

There are numerous drugs currently approved to treat epilepsy, but there are substantially fewer proven mechanisms of AED action, and there is considerable overlap between mechanisms of available drugs (14). Table 49.4 lists many of the standard and novel AEDs and their primary

therapeutic target. Polymorphisms in the genes that encode these targets may impact the action and effects of AEDs. The most common mechanism of AED action involves inhibition of voltage-dependent sodium channels. SCN1A is the gene that encodes the major subunit of the primary neuronal voltage-dependent sodium channel, Na(V)1.1, and thus, considerable attention has been given to genetic variation in SCN1A with regard to polymorphisms that may affect the action and efficacy of AEDs as a general class. Pharmacogenetic studies of AED targets other than SCN1A and related sodium channel subunit genes have been relatively sparse.

Table 49.4 Primary Targets for Common Antiepilepsy Drugs[a]

Antiepilepsy drug	Primary therapeutic target
Acetazolamide	Carbonic anhydrase
Carbamazepine	Voltage-dependent sodium channel
Benzodiazepines	GABA-A receptor
Ethosuximide	T-type calcium channel
Felbamate	Voltage-dependent sodium channel, NMDA glutamate receptor
Gabapentin	α2δ subunit L-type calcium channel
Lamotrigine	Voltage-dependent sodium channel
Levetiracetam	SV2A synaptic vesicle protein
Phenytoin	Voltage-dependent sodium channel
Pregabalin	α2δ subunit L-type calcium channel
Retigabine	KCNQ potassium channel
Tiagabine	GABA transporter, glutamate receptor
Topiramate	Voltage-dependent sodium channel, AMPA/kainate glutamate receptor
Valproate	Voltage-dependent sodium channel; T-type calcium channel; GABA transaminase
Vigabatrin	GABA transaminase
Zonisamide	Voltage-dependent sodium channel

[a]Based on information from reference Porter RJ, Dhir A, Macdonald RL, et al. Mechanisms of action of antiseizure drugs. Handb Clin Neurol 2012;108:663–681.

SCN1A

Detailed study of the SCN1A gene led to the discovery of an intronic polymorphism that disrupts the consensus sequence of the 5′ splice donor site of a highly conserved alternative exon (5N), affects the proportion of the alternative transcripts in individuals with a history of epilepsy, and was reported to be significantly associated with maximum doses in regular usage of both carbamazepine and phenytoin (145). This polymorphism is identified as IVS5-91 G>A (rs3812718); however, data on rs3812718 are sometimes described as a C/T SNP (alleles complemented to the “plus” DNA strand) such that the original publication reported that the T allele is associated with an increased

maintenance dose of phenytoin in epilepsy patients as compared to allele C and that the TT genotype is associated with increased dose of carbamazepine compared to CC genotype (145). The C/T polymorphism is located in the 5′ splice donor site of a highly conserved, alternatively spliced fetally expressed exon, and the major allele (T or A) disrupts the consensus sequence of the so-called 5N fetal exon, possibly reducing the expression of this exon relative to the so-called 5A adult exon (145). In a follow-up study, genotypes TT and CT were shown to be weakly associated with higher maintenance doses of both phenytoin and carbamazepine as compared to genotype CC; however, this relationship did not withstand correction for multiple statistical testing (224), suggesting the need for additional independent studies.

The IVS5-91 G>A variant has subsequently been studied in relation to AED effects by several other laboratories. Initial attempts at independent replication were conflicting, with a lack of association reported between IVS5-91G>A and carbamazepine maintenance doses in one study (225) and a significant association reported between the CC genotype and resistance to carbamazepine in another study (151). In a subsequent study, lack of association was reported between the C allele and response to carbamazepine or oxcarbazepine in patients treated for epilepsy (226). However, in a more recent study of patients who reached a stable maintenance dose of carbamazepine (dosage not changed for at least 1 year) under good compliance and good seizure control, the TT genotype was significantly associated with increased dose of carbamazepine and decreased concentration–dose ratio compared to CC and CT genotypes (84). A similar positive result was reported in a study of the relationship between this variant and phenytoin pharmacokinetics showing a significant association with concentration–dose ratios covaried by age, gender, and epilepsy type (85).

Other recent reports have also been confirmatory. In a study of carbamazepine tolerability assessed over 2 years by retention rates (the proportion of patients who continued to take carbamazepine over the preceding 3 months), CC and CT genotypes were associated with increased tolerability and increased therapeutic response compared to TT genotype (227). And in a companion study, patients with the CC and CT genotypes had a higher retention rate than those with the TT genotype, with the TT genotype also shown to be a significant predictor of nonretention defined as termination of carbamazepine monotherapy (due to drug allergy, CNS effects, or inadequate seizure control) before the end of the 12-month study period (228). On the other hand, a very recent, multicenter study reported that, after 1000 permutation testing for each marker or haplotype and Bonferroni correction, the T allele was not associated with response to carbamazepine or valproic acid, a result confirmed in a follow-up meta-analysis of over 1300 drug-resistant and 1100 drug-responsive epilepsy patients in which drug response was defined as complete seizure freedom for at least 1 year during monotherapy treatment, and drug resistance was defined as any seizure occurring within a 1-year period of treatment (229). A number of other negative reports have also recently been published between IVS5-91 G>A and resistance to carbamazepine (155,230). Thus overall, there are significant conflicts in the literature with regard to the influence of SCN1A IVS5-91G>A, and the clinical relevance of this variant remains to be established.

Functional evidence to support a role for IVS5-91 G>A in differential responsiveness to AEDs has also been reported. For example, Na(V)1.1-5N (i.e., fetal exon) channels exhibited enhanced tonic block and enhanced use-dependent block by both phenytoin and lamotrigine compared to Na(V)1.1-5A (i.e., adult exon) channels (231). Phenytoin and lamotrigine also induced shifts in steady-state inactivation and recovery from fast inactivation for both splice isoforms; however, no splice isoform differences were observed for channel inhibition by carbamazepine, suggesting that Na(V)1.1 channels containing exon 5N, which are decreased in proportion to 5A channels in

individuals carrying the major A (T) allele of IVS5-91 G>A (145), are more sensitive to the commonly used AEDs phenytoin and lamotrigine, but not to carbamazepine (231). On the other hand, functional evidence for an effect of IVS5-91 G>A on carbamazepine comes from a very recent in vivo study in humans in which the effects of the rs3812718 genotype were assessed on cortical excitability at baseline and after administration of carbamazepine (232). Paired-pulse transcranial magnetic stimulation was applied in 92 healthy volunteers with the homozygous genotypes AA (TT) or GG (CC) of rs3812718 at baseline and after administration of 400 mg of carbamazepine or placebo in a double-blind, randomized, crossover design with results showing that the GG (CC) genotype was associated with a higher carbamazepine-induced increase in the duration of the "cortical silent period" as compared to AA, reflecting a genetic influence on GABAergic inhibition by cortical interneurons (232) and suggesting that GG individuals are more sensitive to the effects of carbamazepine. These provocative findings create impetus to further examine the potential pharmacogenetic impact of IVS5-91 G>A on AED action and therapeutic effects.

In addition to IVS5-91 G>A in SCN1A, several other SCN1A variants have been studied in relation to AEDs including A3184G (rs2298771), which predicts an A1056T amino acid substitution. In an initial investigation, this SNP was shown to be without effect on a multidrug resistance phenotype (233); however, a follow-up revealed that the proportion of AA genotype carriers exhibiting seizure freedom was significantly higher than that of AG plus GG genotype carriers (227,228). A SNP in SCN1B has also been studied in regard to multidrug resistance and was reported to have an effect in a gene-by-gene interaction model involving variants in SCN2A (234).

SCN2A and SCN3A

Other sodium channel subunit genes whose variation has been investigated in relation to AEDs include SCN2A and SCN3A. One potentially relevant variant in SCN2A is rs17183814, a nonsynonymous SNP, G61478A, that predicts an R19K amino acid substitution. In one study, the A allele was associated with resistance to carbamazepine, phenobarbital, phenytoin, or valproic acid as compared to the G allele although the statistical significance did not withstand correction for multiple testing (233). Subsequently, a follow-up study by the same authors reported that the A allele was associated with lack of therapeutic response to carbamazepine, phenytoin, and valproic acid (82). A recent independent study that also included a meta-analysis was unable to confirm prior results (229), suggesting additional research is required on this variant. Another SCN2A variant that has been studied in relation to AEDs is the intronic SNP IVS7-32A>G or rs2304016. In a study examining therapeutic responses to AEDs, it was reported that the A allele is associated with lack of therapeutic response to carbamazepine, lamotrigine, oxcarbazepine, phenytoin, and topiramate compared to the G allele, a result that was confirmed in a haplotype analysis (235). The SNP is located within the putative splicing branch site for splicing exons 7 and 9; thus, PCR of reverse-transcribed RNA from blood or brain of patients with different IVS7-32A>G genotypes was performed using primers in exons 7 and 9, but results showed no skipping of exon 8, and real-time PCR showed no difference in SCN2A mRNA levels among genotypes (235) leaving the mechanism underlying the putative pharmacogenetic effect of this SCN2A variant in question.

GABA-Related AED Target Genes

GABRA1 is a gene that encodes a primary subunit of the GABA-A receptor, a direct or indirect

target of multiple AEDs, and 6136171A>G (rs2290732) is a polymorphism in the 3′-untranslated region that has potential pharmacogenetic relevance. In a 2-year study of genetic influences on carbamazepine tolerability in which the phenotype was measured as the proportion of patients who continued to take the drug for seizures over the previous 3 months, results showed patients with the AA plus AG genotypes had significantly greater retention rates than patients with the GG genotype (227,228), suggesting that AA and AG patients better tolerated carbamazepine and obtained greater therapeutic benefit. Another GABA-related target gene that has been studied is SLC6A11, which encodes GAT3, an astrocytic–neuronal GABA transport protein. Distribution of alleles and genotypes of a synonymous SNP, C1572T, C524C, were analyzed in multidrug resistance epilepsy patients, and a significant association was reported between the resistance phenotype and both the T allele and CT/TT genotypes, a result that was confirmed in a replication arm of the study (236), suggesting that SLC6A11 (GAT3) C1572T may be one of the contributing factors with an effect on AED pharmacoresistance.

Other AED Target Genes

Despite the critical relationship between glutamatergic neurotransmission and seizures, there are surprisingly few published AED pharmacogenetics studies on genes in pathways involving glutamate. In one accessible report, the G allele of a 5′ promoter SNP -2000G>T in the NMDA glutamate receptor subunit gene GRIN2B (rs1019385) was associated with lower valproate dosages, and the GG genotype was associated with lower valproate dosages and also a higher CD ratio (160). Other potential effects of genetic variation on glutamatergic synapses are unknown. Another neurotransmitter-related gene that has been studied in relation to AEDs is SLC6A4, the gene encoding the serotonin transporter protein 5-HTT with a single report showing that responsiveness to ACTH in pediatric patients being treated for infantile spasms was higher in patients homozygous for a common 44 base pair insertion polymorphism (237), although the relevance of this finding is not readily apparent given the relatively distant relationship between the action of ACTH and serotonin pathways in the brain. A study with better biologic plausibility examined the association between the effect of ACTH in patients with infantile spasms and variation in MCR2, the gene that encodes the melanocortin 2 receptor, and reported that a 4-SNP promoter haplotype with functional effects on receptor expression in vitro was associated with a good therapeutic response to ACTH (238). One additional study of note was designed based on the hypothesis that inflammatory processes play a role in epilepsy, and it examined variation in genes encoding molecules in the cytokine pathway. Thus, analysis of SNPs in IL-1β, TNF-α, and IL-6 showed that IL-6 G174C (rs1800795) was significantly associated with seizure frequency and drug refractory epilepsy (239) helping to reinforce the concept that genetic variability within the inflammasome may be relevant to epilepsy and to interindividual differences in the therapeutic effects of AEDs.

SUMMARY AND FUTURE PERSPECTIVE

The field of AED pharmacogenetics continues to advance knowledge regarding the gene variants and related mechanisms that contribute to differences between patients in both therapeutic and adverse effects of AEDs; however, the utility of this information in routine clinical practice remains limited. With regard to adverse effects, the discovery of the relationship between specific HLA alleles and rare severe adverse skin reactions caused by some AEDs is an area of high medical relevance and

stands as probably the most important achievement in AED pharmacogenetics to date. Thus, HLA-B*1502 has high predictive value and is considered a validated biomarker for carbamazepine-induced SJS (3). This allele should be screened for in individuals of Asian descent prior to instituting treatment with standard AEDs including carbamazepine, phenytoin, valproate, or lamotrigine. Continued work on HLA alleles in other populations will ultimately lead to discoveries of similarly high impact and, in the long term, better understanding of the mechanism underlying these hypersensitivity reactions will help in the design of safer medications.

The other area of major clinical relevance for AED pharmacogenetics is polymorphic drug metabolism. There are numerous polymorphisms in gene families for both phase 1 and phase 2 biotransformation enzymes that have functional effects, and there is strong evidence that several of these have a measurable influence on pharmacokinetics of specific AEDs. In some cases, this information has been translated into dosing guidelines (145); however, these are not firmly established. CYP2C9 and CYP2C19 encode polymorphic cytochrome P450 oxidase isoforms that are well documented to metabolize several conventional AEDs and low-activity variants (i.e., "poor metabolizers"), while exhibiting significant ethnic differences in frequency, are not uncommon. Nonetheless, the relatively modest overall effect of these variants likely contributes to the fact that alleles of this polymorphic enzyme system are not regarded as validated biomarkers for the effects of AEDs (3).

Whereas the metabolic enzymes for many AEDs have been established, the role of ABC transporter proteins is less clear. Thus, not only are the reported effects of genetic variation in the genes ABCB1 and ABCC2 highly tentative, role of ABC transporters themselves in the absorption, distribution, and elimination of AEDs remains to be fully elucidated. For this reason and others, variant alleles of genes encoding ABC transporter proteins are not considered to be validated biomarkers for AED treatment (3). New approaches using human brain imaging promise to allow greater insight into the role of P-glycoprotein transport of AEDs and may lead to discoveries that could eventually inform routine treatment decisions.

Whereas pharmacokinetic aspects of AED therapy have shown a number of promising genetic leads with regards to refinement of treatment protocols, only the SCN1A gene has shown the potential to provide similarly useful information from a pharmacodynamic perspective. However, even in the case of SCN1A, the validity of the intronic polymorphism IVS5-91G>A as a biomarker for treatment response remains to be established. Recent functional evidence for an effect of this variant in human brain as determined by imaging will fortify resolve to further study this variant and document, or disprove, its clinical relevance. Currently, there are no other major AED targets known whose genetic variability has a significant impact on treatment regimens.

Overall, while there is clear evidence that genetic variation can have a significant influence on the effects of AEDs, the perceived value and use of genetic testing in routine therapy is currently limited; however, this is not different than the situation for many other therapeutic classes of drugs. Drug response is a complex trait determined by many diverse factors in the genome (and the environment), and although each is likely to have only a minor effect individually, they have a cumulative impact and contribute to interpatient variability, offering insight into ways to refine therapy. Considering the extent to which therapeutic responses are determined by plasma levels, a rational approach seems to develop algorithms based on combinations of variants that can predict AED CD ratios and other pharmacokinetic parameters. In one study, integrated analysis of polymorphisms in several candidate genes using logistic regression revealed that variants in CYP2C9 and ABCB1 explained 15% of the variability in phenytoin plasma levels in a group of healthy

individuals and also had predictive value in a clinical practice setting involving epilepsy patients (240). Building additional validated genetic influences into such regression models and using other newer methods of statistical analysis will permit better clinical control of critical factors that can be modulated to optimize treatment plans for every patient individually. This is the ultimate goal of pharmacogenetics, but one that still remains at a considerable distance.

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SECTION B SPECIFIC ANTIEPILEPTIC MEDICATIONS AND OTHER THERAPIES

ASSOCIATE EDITOR: BARRY E. GIDAL

CHAPTER 50 BENZODIAZEPINES

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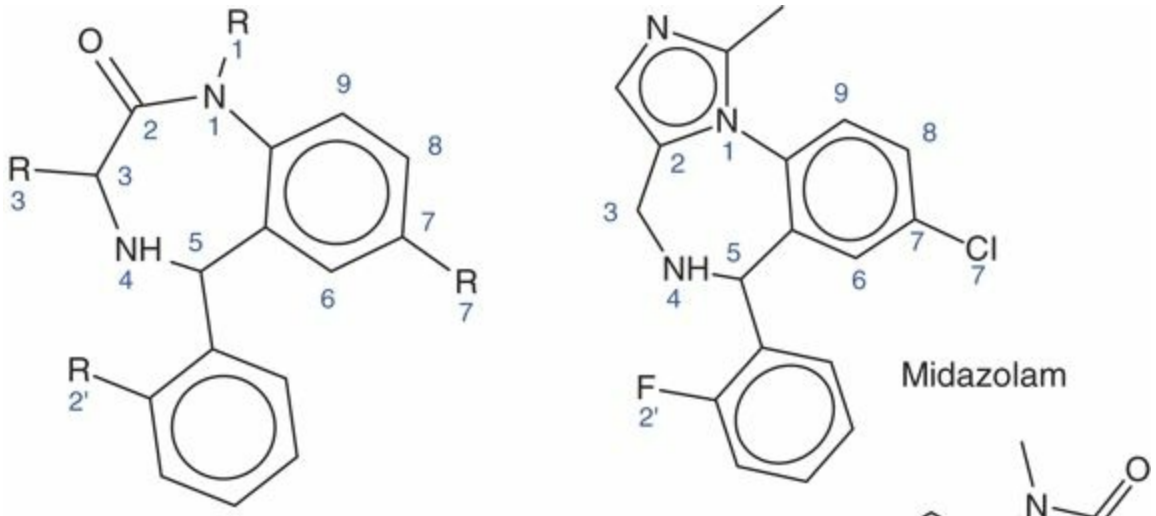
INTRODUCTION

Benzodiazepines (BZs) were developed in the 1950s from a class of heterocyclic compounds known since 1933 (1,2). Chlordiazepoxide was introduced as an anxiolytic agent in 1960, followed by diazepam (3) and nitrazepam (4). The BZs soon became the most widely prescribed drugs in the United States. Gastaut et al. (5) first used diazepam to treat status epilepticus in humans in 1965. Clonazepam was introduced in the 1970s primarily as an antiseizure drug (ASD) (6), and clobazam, a 1,5-BZ, was later developed as an ASD with reduced sedative effects (7). However, only a few BZs have been approved for acute or chronic use as ASDs in the United States.

The site of action of the BZs was clarified by the discovery of high-affinity, saturable BZ binding to a central nervous system (CNS) receptor (8,9). The BZs were also shown to enhance inhibitory neurotransmission mediated by γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter of the mammalian brain (10). Subsequent studies confirmed that the brain BZ receptor was in fact a binding site on the $GABA_A$ receptor, where the BZs act as positive allosteric modulators (11).

CHEMISTRY AND MECHANISM OF ACTION

The BZ structure is based on a benzene ring fused to a seven- member ring containing two nitrogens, usually in the 1 and 4 positions (1,4 BZs), commonly with an aryl group attached at the 5 position (Fig. 50.1). An exception to this pattern is clobazam, a 1,5-BZ with antiepileptic properties and fewer sedative effects (7,12). Some agents (e.g., midazolam and flumazenil) have fused R1 and R2 substituents, creating further ring complexity.



Drug	R1	R3	R7	R2'
Diazepam	CH_3	H_2	Cl	H
Lorazepam	H	H, OH	Cl	Cl
Clonazepam	H	H_2	NO_2	Cl
Nitrazepam	H	H_2	NO_2	H
Clorazepate	H	COOH	Cl	H

Figure 50.1. Structure of the 1,4-benzodiazepines. Substituents at the named sites are given in the table for diazepam, lorazepam, clonazepam, nitrazepam, and clorazepate. Midazolam with its fused R1 ring is shown separately. Clobazam is a 1,5 benzodiazepine.

BZ potency correlates with binding affinity at the BZ site on neuronal $GABA_A$ receptors (Table 50.1) (14,15). An electron-withdrawing group at the 7 position increases receptor-binding affinity (Table 16) and potency, and all useful anticonvulsant BZs have this feature. A methyl group on the position-1 nitrogen (as in diazepam and clobazam) increases binding affinity and potency, as does a halogen at the 2′ position on the aryl group. A hydroxyl group at position 3 (as in lorazepam) decreases potency and binding affinity.

Table 50.1 Antiseizure Activity, Motor Impairment, and Receptor Binding of Some BZs

BZ	ED_{50} to suppress clonus in kindled rats, mg/kg[a]	ED_{50} for ataxia, mg/kg[a]	IC_{50} to inhibit [^{3}H] flunitrazepam-specific binding, nM[b]
Clobazam	2.8	13.2	870
Diazepam	0.4	1.5	78
Clonazepam	0.09	0.9	16
7-amino-clonazepam	>40	—	195

[a]Dose required to inhibit forelimb clonus or to cause ataxia in 50% of amygdala-kindled rats (data from Tietz EI, Rosenberg HC, Chiu TH. A comparison of the anticonvulsant effects of 1,4- and 1,5-benzodiazepines in the amygdala-kindled rat and their effects on motor function. Epilepsy Res. 1989;3:31–40.; (13), except 7-amino-clonazepam data (HC Rosenberg, EI Tietz, and TH Chiu; unpublished data, 1987).

[b]Concentration required to displace 50% of 2 nM [^{3}H]flunitrazepam specifically bound to rat cerebral cortical membranes (EI Tietz, TH Chiu, and HC Rosenberg; unpublished data, 1990).

BZ activity at the $GABA_A$ receptor is a function of the drug's affinity for the BZ binding site and

its intrinsic allosteric effect on the $GABA_A$ receptor. The efficacy of individual compounds varies widely. Most BZ ASDs are full agonists that maximally enhance $GABA_A$ receptor activity. Competitive antagonists bind to the BZ site but do not affect $GABA_A$ receptor function. The BZ antagonist, flumazenil, is used to reverse sedation induced by BZs in anesthesia (17,18) and to treat BZ overdose (19). Several "partial agonists" at the BZ binding site have been characterized, including abecarnil (20), imidazenil (21), and bretazenil (22). Although less effective than full agonists like diazepam, these drugs have demonstrated anticonvulsant efficacy in animal models and appear less prone to the development of tolerance (23,24). Still other compounds, notably the beta-carbolines, behave as "inverse agonists" at the BZ site and inhibit GABA binding or GABA-evoked currents (25). These agents can induce convulsive seizures or anxiety (25,26) and have no clinical utility.

Anticonvulsant Activity

BZs are effective against most experimental seizure types, but there are large differences between individual drugs in their potency, efficacy, and other clinical effects (27). BZs are particularly effective against seizures induced by pentylenetetrazol (28) but are less effective against tonic seizures in the maximal electroshock model (29). BZs also slow the development of kindling (30). The dose ratio between clinical efficacy and adverse effects varies between specific agents. For example, the diazepam dose for blocking pentylenetetrazol seizures is 1% of that necessary to abolish the righting response; for clonazepam, the ratio is <0.02%, suggesting a wider therapeutic window.

BZ Actions at the $GABA_A$ Receptor

In 1977, a high-affinity, saturable binding site for BZs was discovered on CNS neuronal membranes (8,9,14). BZ receptor binding was "coupled" to GABA binding (31), which led to the idea of a "$GABA_A$ receptor complex" incorporating binding sites for GABA, the BZs, and barbiturates and a ligand-gated chloride channel. Later, it became clear that BZs and GABA bind to sites on a single pentameric channel. Electrophysiologic studies demonstrated that BZs increased the amplitude of GABA-mediated inhibitory postsynaptic potentials (IPSPs) (10) by increasing the opening frequency of the GABA-gated chloride channel (32); this was later confirmed with single-channel studies (33).

In whole-cell patch clamp recordings of isolated CNS neurons, BZs alone produce no $GABA_A$ receptor current. Increasing BZ concentrations enhance GABA currents evoked by a low GABA concentration (Fig. 50.2A, C). This enhancement results from an effect of BZs to increase the affinity of GABA at the GABA binding site, which produces a leftward shift of the concentration–response curve for GABA (34) (Fig. 50.2B). There is no change in the kinetics of channel gating (33). The BZs increase the current produced by low GABA concentrations but not by high (millimolar) synaptic concentrations at which receptor binding is saturated (35). Thus, BZs do not usually increase the amplitude of miniature inhibitory postsynaptic currents (mIPSCs) from individual synapses. So, how do they increase GABA currents? By increasing the binding affinity of GABA for the receptor (see Fig. 50.2B), BZs slow the dissociation of GABA from the receptor, which prolongs the mIPSC decay phase (36,37). Prolongation of the mIPSC increases the likelihood of temporal and spatial summation of multiple synaptic inputs, which in turn increases the amplitude of stimulus-evoked polysynaptic IPSCs (Fig. 50.2D). The BZs thus increase the inhibitory "tone" of GABA-ergic synapses, which

reduces the hypersynchronous firing of neuron populations that underlies seizures (38).

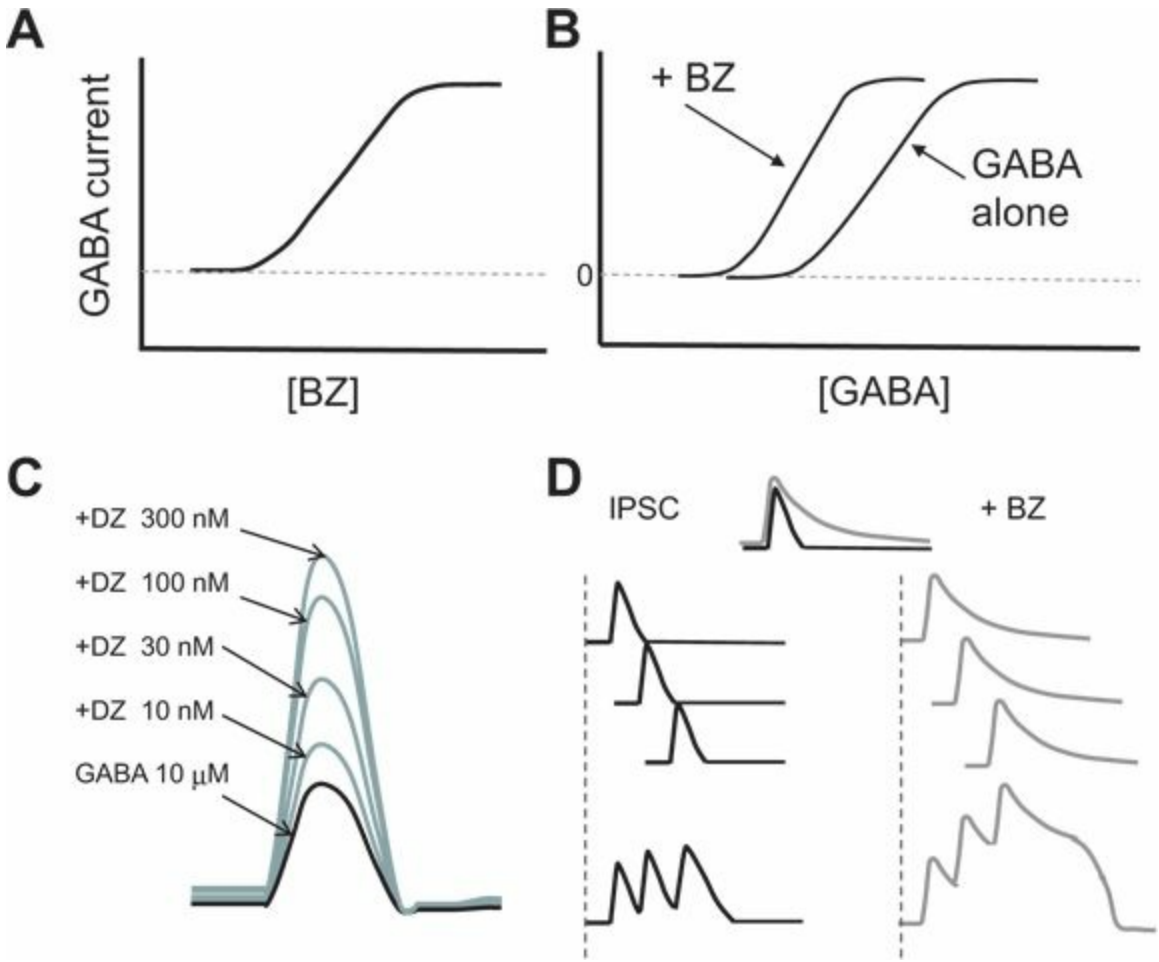


Figure 50.2. Effects of BZs on $GABA_A$ receptor currents. **A:** Increasing BZ concentration with a single low concentration of GABA evokes progressively larger currents, as shown in **(C)** for increasing diazepam (DZ) concentrations (mock data). **B:** Addition of a single BZ concentration to increasing GABA concentrations shifts the concentration–response curve for GABA to the left, indicating increased affinity for GABA at the receptor but no increase in maximal current. The BZs have no effect in the absence of GABA. **D:** The increased GABA affinity prolongs the IPSC decay phase (gray), resulting in increased temporal and spatial summation to produce larger polysynaptic currents (mock data).

Molecular Biology of $GABA_A$ Receptors

$GABA_A$ receptors are pharmacologically complex, with binding sites for BZs; barbiturates; neurosteroids; general anesthetics; the novel anticonvulsant, loreclezole; and the convulsant toxins, picrotoxin and bicuculline. Protein subunits from seven different subunit families (39) assemble to form pentameric (40) transmembrane chloride channels (Fig. 50.3). In mammals, 16 subunit subtypes have been cloned, including 6 α, 3 β, and 3 γ subtypes, as well as δ, π , ε, and θ, and there are alternatively spliced variants of the β2 and γ2 subtypes (39). Though thousands of subunit compositions are possible, expression is regulated by region and cell type (41) and also developmentally controlled (42), reducing the number of possible isoforms in specific brain regions and individual neurons. The most common $GABA_A$ receptor has a presumed stoichiometry of two α1, two β2, and a single γ2 subunit; the δ subunit may in some cases substitute for γ, particularly when receptors are expressed extrasynaptically. The subunits are arranged around a central water-filled pore, which opens to conduct Cl^- ions when GABA is bound (see Fig. 50.3). Studies of recombinant receptors have shown that individual subunit subtypes confer different sensitivities to $GABA_A$

receptor modulators, including BZs (43), loreclezole (44), and zinc ions (45).

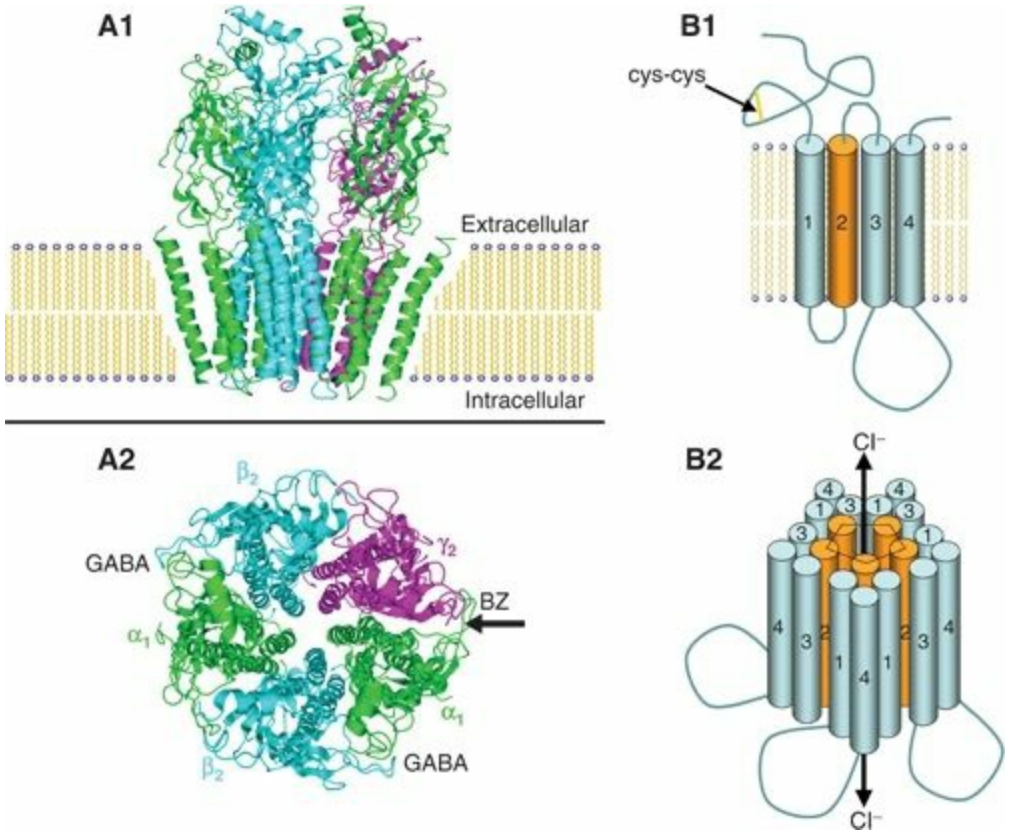


Figure 50.3. Model of a $GABA_A$ receptor in the plasma membrane. **A:** A space-filling model of the pentamer in side view (**A1**) and top view (**A2**) based on the high sequence homology with the nicotinic acetylcholine receptor. There are with two binding sites for GABA, between α and β subunits, and one for BZs, between the alpha and gamma subunits (arrow). **B:** A schematic view shows the topology of each subunit with a large extracellular loop containing a cysteine loop (**B1**) and four transmembrane domains from which the second forms the lining of the chloride ion channel. Binding of GABA allows the channel to open and conduct Cl^- ions **(B2)**, resulting in the fast inhibitory postsynaptic potential (IPSP)

$GABA_A$ Receptor Subunits and BZ Pharmacology

BZ augmentation of $GABA_A$ receptor currents requires a γ subunit, and the selectivity of BZ responsiveness is determined by which α subunits are present (46). The BZ binding site is located in a cleft between the extracellular amino termini of these two subunits. The α1 subunit results in a receptor with high affinity for the hypnotic, zolpidem, defining the "BZ-1" (or Ω1) receptor type (47). The α2 and α3 subunits result in receptors with moderate zolpidem affinity, termed BZ-2 receptors. $GABA_A$ receptors with the α5 subunit and/or the γ3 subunit are sensitive to diazepam, but far less so to zolpidem, and are termed BZ-3 receptors. $GABA_A$ receptors with the α4 or α6 subunits are insensitive to most BZs (46).

The $GABA_A$ receptor subunit composition determines not only the affinity for particular BZs but also the clinical/behavioral effects of the BZ at that specific receptor subtype. The role of the α subunits in BZ pharmacology was revealed by the discovery of a single histidine (H) residue found in all BZ-sensitive α subunits (H101 in the rat α1 subunit) but not in the BZ-insensitive α4 or α6 subunits, which instead have a charged arginine (R) residue. This H residue was discovered in a strain of "alcohol-nontolerant" rats, which were found to have a spontaneous point mutation in the α6 subunit (R100Q) that made their α6-containing $GABA_A$Rs (found mostly in the cerebellum) diazepam

sensitive. Since alcohol appears to enhance $GABA_AR$ function via the BZ site (39), the abnormally BZ-responsive receptors in the cerebellum resulted in ataxia and intolerance to these agents (48). Mutation of R100 to H in α6 dramatically increased BZ binding in this normally insensitive subunit, while mutation of H101 to R in α1 reduced BZ sensitivity (49). BZ-insensitive α subunit mutations were subsequently "knocked in" to identify BZ actions at receptors containing that subunit. In homozygous α1(H101R) knock-in mice, the anxiolytic effect was intact, but BZs were not protective against pentylenetetrazol-induced convulsions and did not produce sedation or amnesia, suggesting that binding to the (wild type) α1 subunit is responsible for sedative, amnestic, and antiseizure actions (50). Moreover, the α1-selective sedative–hypnotic, zolpidem, showed no sedative effect in α1(H101R) mice (51). Unfortunately, these findings underscore the association between sedation and antiseizure efficacy at α1-containing $GABA_ARs$. Similarly, the anxiolytic (52) and myorelaxant (53) properties of BZs appear to derive from α2- and α3-containing $GABA_ARs$, while the α5 subunit was critical for amnestic effects (54). BZs may also have a true analgesic effect independent of their sedative and anxiolytic actions, associated with the α2 and α3 more than α5 subunits (55). Since there is no evidence of biophysically distinct effects of BZs on receptors composed of different α subunits, the different behavioral effects are likely due to the brain regions and neuronal populations expressing specific $GABA_AR$ isoforms. New α2/α3 subunit–selective BZs appear to have anxiolytic activity without causing sedation (56). Development of nonsedating antiseizure BZs that do not induce tolerance (57) may also be possible.

$GABA_A$ Receptors and Epilepsy

The anticonvulsant properties of BZs are likely related to the prominent role of $GABA_A$ receptors in epilepsy. The evidence linking epilepsy with dysfunction of GABA-ergic inhibition is substantial (38). $GABA_A$ receptors are the target not only of the BZs but of other ASDs including the barbiturates and, indirectly, of two agents that increase GABA concentration at the synapse, tiagabine and vigabatrin (38). Several animal models of epilepsy have demonstrated altered $GABA_A$ receptor number or function (38,58). Moreover, genetic or acquired changes in the composition or structure of the transmembrane protein subunits that make up $GABA_A$ receptors can result in epilepsy. $GABA_A$ receptor subunit expression is altered in the hippocampi of experimental animals with recurrent seizures (59) and in patients with temporal lobe epilepsy (60,61). Reduced expression of the $GABA_AR$ γ2 subunit in rats using an antisense oligonucleotide to block translation of endogenous γ2 mRNA led to spontaneous electrographic seizures that evolved into limbic status epilepticus (62). In humans, Angelman syndrome, a neurodevelopmental disorder associated with severe mental retardation and epilepsy, is linked to a deletion mutation on chromosome 15q11-13 (63) in a region encoding the $GABA_A$ receptor β3 subunit (64). In addition, two mutations in the γ2 subunit that impair $GABA_A$ receptor function (65), K289M (66) and R43Q (67), have been linked to a human syndrome of childhood absence epilepsy and febrile seizures, and a loss-of-function mutation in the α1 subunit was found in a family with autosomal dominant juvenile myoclonic epilepsy (68). The R43Q mutation in the γ2 subunit reduces BZ sensitivity (69) by altering $GABA_A$ receptor assembly (70) and trapping the receptor in the endoplasmic reticulum (71). The relative positions of these and several other epilepsy-causing mutations are shown schematically on a "generic" $GABA_A$ receptor subunit in Fig. 50.4, along with the sites of action for several $GABA_A$ receptor subunit–associated

ASDs (72).

Other BZ Actions

With a few caveats (26), the BZs derive their anticonvulsant properties from their specific interaction with $GABA_A$ receptors. At doses used to treat status epilepticus, BZs can also inhibit voltage-gated sodium (73) and calcium channels (74) and can increase GABA levels in cerebrospinal fluid (75). However, it should be noted that the BZs have no interaction with the G protein–linked $GABA_B$ receptor, which can either suppress voltage-gated Ca^{2+} channels or activate inward rectifying K^+ channels (76).

The BZs also bind to the "peripheral BZ receptor" (PBR) (77), an 18-kDa protein in the outer mitochondrial membrane that functions as part of the mitochondrial permeability transition pore involved in cholesterol transport (77), apoptosis, and regulation of mitochondrial function (78). Although the PBR is widely expressed throughout the body, its expression in the CNS is restricted to ependymal cells and glia (79); hence, it is unlikely that the PBR is involved in the antiseizure properties of the BZs, though it may explain the neuroprotective properties of some BZs (80,81).

Excitatory $GABA_A$ Currents

BZ enhancement of $GABA_A$ receptor function may not always be anticonvulsant or even inhibitory. Early in CNS development, neurons express the $Na^+/K^+/Cl^-$ cotransporter, NKCC1, rather than the K^+/Cl^- cotransporter, KCC2, which is expressed in adult neurons. NKCC1 increases intracellular Cl^- resulting in a depolarizing Cl^- reversal potential, while KCC2 exports Cl^- yielding the hyperpolarizing Cl^- reversal potential found in adult neurons (82). As a result, activation of $GABA_A$ receptor channels can be excitatory during early development (83) and play a trophic role in neuronal migration and connectivity (84,85), but this may also contribute to epileptogenesis (86). In fact, endogenous GABA appears to be proconvulsant in early postnatal rat hippocampal slices, as $GABA_A$ antagonists blocked epileptiform activity induced by depolarization with high external $[K^+]$ (87). However, BZ anticonvulsant efficacy appears to be intact, likely because persistent opening of GABA channels (in the presence of BZs) may reduce the depolarizing chloride reversal potential, resulting in "shunt" inhibition, or alternatively, subthreshold GABA-evoked depolarization may inactivate sodium channels and prevent action potential firing (88). The current through $GABA_A$ receptor channels can also be altered by changes in intracellular bicarbonate, $[HCO_3^-]$ (82), which, like Cl^-, can flow through the channel (89). Changes in $[HCO_3^-]$ may underlie reduced synaptic GABA currents during development of BZ tolerance (90). Depolarizing $GABA_A$ currents may also be a source of interictal spike activity, as observed in epileptic subiculum neurons in brain slices of hippocampi removed from patients with temporal lobe epilepsy (91). Changes in the GABA current reversal potential might also explain why diazepam may be less effective in children with epileptic encephalopathies (92) and rarely can cause status epilepticus in patients with the Lennox–Gastaut syndrome (93).

ABSORPTION, DISTRIBUTION, AND

METABOLISM

The major anticonvulsant role of the BZs is in the treatment of status epilepticus (SE) and seizure clusters, for which they represent first-line therapy, preferably administered intravenously (IV) (94). In very young children, this may be difficult or impossible, necessitating administration via rectal (95–100), intraosseous (101), buccal (102,103), or nasal (104–106) routes. With IV administration, the main factor in a drug's effectiveness for SE is the rate at which it crosses the blood–brain barrier (BBB). The BZs are highly lipophilic and cross the BBB rapidly (107), though this varies more than 50-fold between agents (108) and is fastest for the most lipophilic agents, such as diazepam. Protein binding also correlates with lipophilicity and is high for most BZs, up to nearly 99% for diazepam. The BZs are fully absorbed after oral ingestion.

Despite generally long plasma half-lives, most BZs are relatively "short-acting" after administration of a single dose due to a similarly rapid distribution from the brain and vascular compartments to peripheral tissues (109,110). BZ pharmacokinetics are best fit by a two-compartment model: high levels occur rapidly in the brain and other well-perfused organs and then decline rapidly with an initial brief half-life due to distribution into peripheral tissues and lipid stores, followed by a much slower elimination half-life related to enzymatic metabolism and excretion. For example, the elimination half-life of diazepam ranges from 20 to 54 hours (111), but the duration of action after a single IV injection is only 1 hour, with peak brain concentrations present for only 20 to 30 minutes (112).

The BZs are metabolized in the liver by cytochrome P450 enzymes, particularly CYP3A4 and CYP2C19, with relatively little enzyme induction. The presence of biologically active metabolites (e.g., nordazepam, a metabolite of diazepam) can significantly prolong the biologic half-lives of some BZs. Elimination may be prolonged by enterohepatic circulation, particularly in the elderly. Most BZs cross the placenta and are secreted into breast milk. A schematic of BZ metabolic pathways is shown in Figure 50.5. The biotransformation and pharmacokinetics of the BZs have been extensively reviewed (115–117) and will be presented in more detail for the individual agents below.

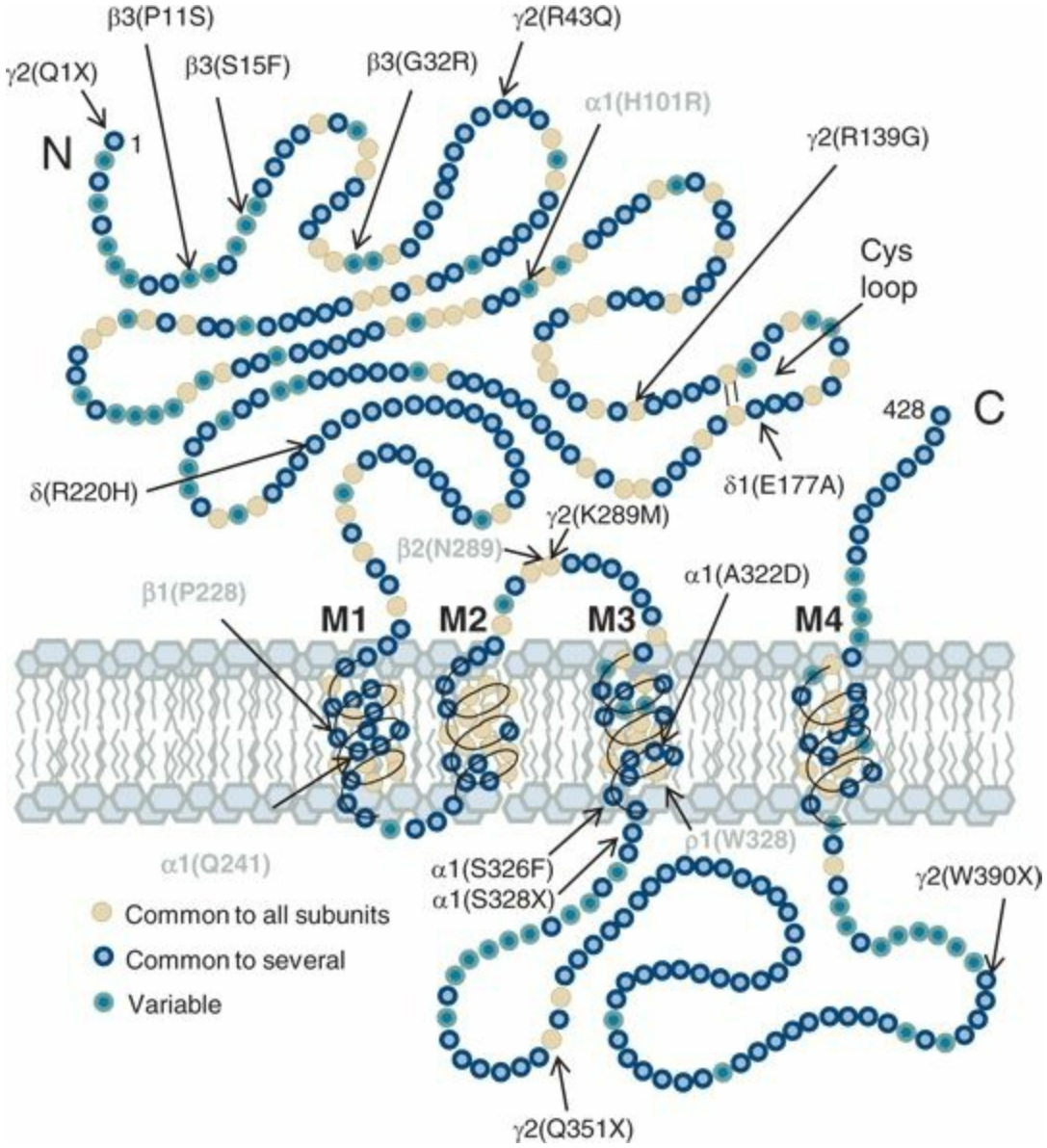


Figure 50.4. Model of a prototype $GABA_AR$ subunit (based on α1 subunit diagram from Olsen RW, Tobin AJ. Molecular biology of GABAA receptors. FASEB J. 1990;4:1469–1480.) showing approximate locations of point mutations associated with generalized epilepsies (see also Macdonald RL, Kang JQ, Gallagher MJ. GABAA receptor subunit mutations and genetic epilepsies. In: Noebels JL, Avoli MB, Rogawski MA, Olsen RW, Delgado-Escueta AV, editors. Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th edition. Bethesda (MD): 2012) in black and point mutations associated with ASD sites of action (see text for details).

DRUG INTERACTIONS

BZs interact with other drugs more prominently through pharmacodynamic than pharmacokinetic mechanisms. They do not significantly affect plasma protein binding or metabolism of other drugs. CNS depression is increased when BZs are given in conjunction with other CNS-depressant drugs (118). Pharmacokinetic interactions with other anticonvulsants are infrequent and inconsistent, with the exception of phenobarbital. Diazepam enhances phenobarbital elimination (119), and phenobarbital increases clearance (120) and lowers plasma levels of clonazepam (121). Clobazam increases the 10,11-epoxide metabolite of carbamazepine (122). Valproate reduces diazepam protein binding, increasing free drug levels (123), and enhances diazepam's CNS effects (119). Other ASDs may augment metabolism and clearance of N-desmethyldiazepam derived from clorazepate (124). Inhibitors of CYP3A4, including erythromycin, clarithromycin, ritonavir, itraconazole, ketoconazole, nefazodone, and grapefruit juice, can slow BZ metabolism (125). Cimetidine decreases the clearance

of diazepam (126,127) and nitrazepam (128). Rifampin increases the clearance and shortens the half-life of nitrazepam (129). Lorazepam half-life is markedly increased by probenecid (130).

ANTISEIZURE EFFICACY

Status Epilepticus

Status epilepticus is associated with significant morbidity and mortality (131,132) and requires emergent medical treatment to avoid neuronal damage and its neurologic consequences (133,134). The BZs have become agents of choice for initial therapy due to their rapid onset, proven efficacy (135), and lower risk of cardiotoxicity or respiratory depression compared to the barbiturates (136). The role of BZs in status epilepticus has been confirmed in several well-controlled clinical trials, including the multicenter, double-blind VA Cooperative Status Epilepticus Trial (137).

Lorazepam and diazepam were compared for treatment of status epilepticus in a double-blind study of 78 adults with epilepsy (135). Intravenous lorazepam (4 mg) stopped status epilepticus in 78% of patients and diazepam (10 mg) in 58% after the first injection; both had similar efficacy (89% and 76%, respectively) after the second injection. An open-label, prospective, randomized trial compared lorazepam (0.05 to 0.1 mg/kg) and diazepam (0.3 to 0.4 mg/kg) in children with acute convulsions, including convulsive status epilepticus (138). Lorazepam was more effective ($P < 0.01$) after the first dose and apparently safer than diazepam. A meta-analysis of 11 randomized controlled trials with 2017 participants found that lorazepam was better than either diazepam or phenytoin alone for reducing risk of seizure continuation (139). A population-based study of 182 children with convulsive status epilepticus showed that IV lorazepam was 3.7 times more likely than rectal diazepam to terminate seizures (140). Lorazepam's superiority may be due to its longer duration of action, based on a longer distribution half-life (see Lorazepam: Pharmacokinetics).

Lorazepam has largely replaced diazepam as the agent of choice for prehospital treatment of status epilepticus. A prehospital trial of lorazepam and diazepam found that status epilepticus had terminated by arrival at the emergency department in 59.1% of patients treated with lorazepam (2 mg), compared to 42.6% of patients treated with diazepam (5 mg) and 21.1% of patients given placebo (141). Rates of circulatory or ventilatory complications for lorazepam and diazepam were similar (10.6% and 10.3%, respectively) and lower than that of placebo (22.5%), confirming the safety of BZ treatment in this setting. However, patients treated with >30% more than the standard therapeutic BZ doses were more likely to require intubation for airway protection and had significantly longer hospitalizations (2 weeks vs. 1 week) (142).

Early treatment of status epilepticus increases the probability of seizure termination (141), likely because prolonged seizures lower $GABA_A$ receptor sensitivity to BZs (143). Reduction in $GABA_A$ receptor BZ sensitivity can occur within minutes in status epilepticus (144,145) and may be responsible in part for both the persistent epileptic state and its refractoriness to treatment. Refractoriness to BZs may be mediated by N-methyl-D-aspartate (NMDA) receptor mechanisms, as NMDA antagonists improve the response to diazepam in late pilocarpine-induced status epilepticus (146). These findings suggest a possible strategy for treatment of late, BZ-refractory status epilepticus with combinations of a BZ and an NMDA receptor antagonist such as the dissociative general anesthetic, ketamine. Efficacy of combined diazepam and ketamine has been demonstrated in a rat model of status epilepticus (147). A recent nonrandomized trial of oral ketamine for refractory

nonconvulsive status epilepticus in children showed efficacy in five of five cases (148). Treatment protocols involving NMDA antagonists have been suggested (149,150), but such approaches will require validation in controlled clinical trials.

Both lorazepam and diazepam have been approved by the U.S. Food and Drug Administration (USFDA) for treatment of status epilepticus in adults; diazepam has also been approved in children older than 30 days. Parenteral preparations of other BZs, including midazolam, flunitrazepam, and clonazepam, expand the possibilities for BZ treatment of status epilepticus. However, parenteral clonazepam is currently available only in Germany and the UK, and flunitrazepam is not available in the USA. Alternative routes of administration, including intramuscular (IM) injection and intranasal (104,105), buccal (102), endotracheal (151,152), or rectal (100,153,154) instillation, also rapidly produce therapeutic levels and have demonstrated efficacy against status epilepticus or seizure clusters.

Acute Repetitive Seizures

The availability of alternative methods of BZ administration increases the therapeutic options for treatment of acute repetitive seizures. Individual agents can be selected for specific clinical situations. For example, repeated seizures in a patient rapidly tapered off anticonvulsants for inpatient epilepsy monitoring could be treated with diazepam (rather than lorazepam) since its shorter peak duration of action may be less likely to suppress seizure activity needed later for localization of seizure onset. In the case of serial seizures, the need for high drug levels immediately is less urgent, and the ease of administration by family or allied health workers becomes important. Diazepam rectal gel is effective in preventing subsequent seizures during seizure clusters (153–155) and can reduce the frequency of emergency department visits (96). Buccal (156,157) and intranasal (158) routes may be equally effective and more acceptable (159). Table 50.2 compares the clinical and pharmacologic properties of the BZs used for acute seizures.

Table 50.2 Clinical Pharmacology of BZs Used for Acute Seizures

	Diazepam		Lorazepam		Midazolam		Clonazepam
Characteristic	IV	Rectal	IV[a]	Buccal[a]	IV[a]	IM[a]	IV[b]
Bolus dose (mg)	10–20	0.5–1/kg	4	2–4	0.125–0.15/kg	0.2/kg	0.01–0.09/kg
Infusion rate	8 mg/h	—	—	—	0.15–0.2 mg/kg/h	—	—
Minimum effective concentration	500 ng/mL	NA	30 ng/mL	NA	NA	NA	30 ng/mL
Onset of effect (min)	<1	2–6	<2	NA	<2	2–30	<1
Peak effect (min)	3–15	10–120	30	NA	10–50	25 ± 23	NA
Duration of effect	<20 min	NA	>360 min	NA	<50 min	20–120 min	24 h
Protein bound (%)	96–97	96–97	85–93	85–93	95 ± 2	95 ± 2	86 ± 5
Volume of distribution, (L/kg)	133	133	12	12	NA	NA	NA
Distribution half-life	0.96–2.2 h	NA	2–3 h	NA	5.7 ± 2.4 min	NA	NA
Elimination half-life (h)	36 ± 4.9	36 ± 4.9	14.1	14.1	1.9 ± 0.6	1.9 ± 0.6	20–80

[a]Not approved by the USFDA for seizures.

[b]Not available in the United States.

NA, not available.

Chronic Treatment of Epilepsy

Although the use of BZs in chronic treatment of epilepsy is limited by sedation and the development of tolerance, BZs may have specific therapeutic indications, such as adjunctive treatment of myoclonic and other generalized seizure types or in conjunction with comorbid anxiety disorders. For example, lorazepam improved control of seizures associated with psychological stressors (160). Intermittent use of BZs when seizure thresholds are transiently reduced may be the ideal strategy for these ASDs. Not only are they suited pharmacokinetically for such applications, but short-term use may avoid the development of tolerance. For example, catamenial seizures improved with intermittent administration of clobazam (161). ASD efficacy for specific indications will be discussed with the individual agents below.

TOLERANCE AND DEPENDENCE

BZ Tolerance

Chronic BZ treatment is associated with tolerance, a decrease in sedative or anticonvulsant properties, and dependence, the need for continued drug to prevent a withdrawal syndrome (162). The development of tolerance is a significant clinical problem, requiring escalation of drug doses and increasing the risk of withdrawal seizures. Chronic treatment with BZs can also reduce their subsequent effectiveness in acute conditions (163), rendering them less useful for treatment of status epilepticus. In animal studies, tolerance develops proportionally to agonist efficacy. BZ partial agonists develop much less tolerance than full agonists, and the antagonist flumazenil causes no tolerance-related changes in receptor number or function (24). Tolerance to one BZ with a particular regimen may not induce tolerance to a different BZ, suggesting drug-specific interactions of each agent at BZ receptor sites on specific $GABA_A$ receptor subunit combinations (164). The duration of tolerance also varies between BZs (165). Several studies of tolerance have noted changes in $GABA_A$ receptor subunit expression (166–168) as well as functional changes (169,170); however, such changes are dependent not only on the drug and dosage but also on the duration and method of drug administration, all of which contribute to chronic BZ receptor occupancy that predisposes to tolerance. Measurements of tolerance also depend on the animal seizure model and the behavioral tests used to assess BZ clinical properties (171).

Physical Dependence

Abrupt cessation of prolonged BZ therapy can result in withdrawal symptoms, including restlessness and agitation, anxiety, loss of appetite, nausea, lethargy, dizziness, headache, palpitations, irritability, confusion, and, in some cases, seizures. The short-acting antagonist, flumazenil, precipitated a withdrawal syndrome in subjects given chronic low-dose diazepam (mean dose 11.2 mg/day) for an average of 4.6 years (172). Four of 13 patients developed panic attacks. A short-lived withdrawal syndrome was elicited by IV flumazenil following 7, 14, or 28 days of oral diazepam (15 mg/70 kg) administration to healthy volunteers (173). There is debate whether withdrawal symptoms, such as heightened anxiety, might represent rebound of existing symptoms to a level greater than that before treatment and whether withdrawal anxiety can result in relapse to the previous state of anxiety (174). BZ prescription misuse has been ascribed to patients' efforts to alleviate withdrawal symptoms,

which can lead to a drug dependence syndrome (175,176). BZ self-administration is enhanced in long-term therapeutic users suddenly switched to placebo relative to those whose dose was tapered gradually (177).

Changes in $GABA_A$ receptors related to tolerance might be assumed to underlie withdrawal symptoms and physical dependence (178,179). Yet, evidence from animal models suggests that enhancement of excitatory systems in a variety of brain regions (180) may underlie anxiety behavior (181–183) and increased seizure activity (183). Enhanced glutamatergic neurotransmission involves a selective increase in GluR1-containing alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (183–185), which correlates with increased anxiety-like behavior (181). Such neuroplastic changes in the hippocampus are similar to those found with long-term potentiation (LTP) (186). LTP depends on AMPA receptor–mediated depolarization and subsequent relief of the Mg^{2+} block from NMDA receptors, allowing Ca^{2+} entry, which in turn activates kinases resulting in persistent enhancement of GluA1 AMPA receptors. In contrast, for BZ withdrawal, the calcium signal that mediates enhancement of GluA1 AMPA receptors enters through voltage-gated calcium channels (VGCCs) (181,182). In fact, VGCC currents double during chronic BZ treatment and withdrawal, and anxiety can be alleviated by prior administration of the VGCC antagonist, nimodipine (182). The increased anxiety and other symptoms abate over time, associated with downregulation of NMDA receptors (181,187,188), which may serve as a natural brake on withdrawal symptoms.

ADVERSE EVENTS

With acute treatment of status epilepticus, the primary adverse effects are respiratory and cardiovascular depression (135,189). For IV infusions, the propylene glycol solvent contributes to toxicity (190). Other toxic effects such as sedation and amnesia are of relatively little consequence in this setting and difficult to distinguish from the effects of status epilepticus itself. However, sedation after termination of convulsive status epilepticus often necessitates EEG evaluation to ensure that convulsive seizures have not been converted to nonconvulsive status epilepticus. When BZs have been administered in conjunction with other CNS-active drugs such as phenobarbital, respiratory and cardiovascular toxicity may be enhanced (118). In patients with Lennox–Gastaut syndrome, parenterally administered BZs can induce tonic status epilepticus, though this is rare (191). Thrombophlebitis may occur (192), and intra-arterial injection may produce tissue necrosis (193).

With chronic use, all of the BZs induce similar untoward effects including sedation and drowsiness, lightheadedness, ataxia, cognitive slowing and confusion, and anterograde amnesia. Other effects include weakness, headache, blurred vision, vertigo, nausea and vomiting, GI distress, and diarrhea. Joint aches, chest pains, and incontinence occur more rarely (108). The risk of tolerance, dependence, and abuse is significant but low in patients prescribed these agents for appropriate indications (110,194). Abrupt withdrawal of the BZs has been associated with convulsions, worsening of insomnia, psychosis, and delirium tremens in nonepileptic individuals using diazepam, clonazepam, clorazepate, or nitrazepam (195,196). The incidence of allergic, hepatotoxic, or hematologic reactions to the BZs is extremely low. The BZs can sometimes increase the frequency of seizures in epileptic patients. Specific adverse effects will be discussed with the individual agents below.

INDIVIDUAL BZS

Diazepam, lorazepam, and midazolam are used predominantly for short-term indications including status epilepticus, serial seizures, and episodes of lower seizure threshold. Clonazepam, clorazepate, clobazam, and nitrazepam are used more commonly for treatment of chronic epilepsy.

Diazepam

Diazepam, the first BZ used in the treatment of epilepsy (5), became a standard initial therapy for status epilepticus in adults and children (135), though its primary role has been usurped by lorazepam (137,141). Diazepam is available in both oral and parenteral preparations. The classification of rectal diazepam as an orphan drug in 1993 allowed the development of rectal diazepam gel (Diastat).

Diazepam and other BZs induce an increase in β-frequency activity and slowing of the background on EEG, which can be quantified by spectral analysis (197). The pattern of EEG changes may be of prognostic value in seizure control; 88% of patients (29/33) whose EEG responded to diazepam with loss of abnormal activity or emergence of fast (β-frequency) activity had a good prognosis (seizure free or 50% seizure reduction) (198).

Absorption, Distribution, and Metabolism

Diazepam is highly lipophilic, which allows rapid entry into the brain but also results in rapid subsequent redistribution into peripheral tissues. It is extensively bound to plasma proteins (90% to 99%) (199). The volume of distribution is 1.1 L/kg. Plasma concentration declines rapidly during the distribution phase with an initial half-life ($t_{1/2\alpha}$) of 1 hour (200). Diazepam undergoes demethylation to desmethyldiazepam (DMD, nordazepam), a metabolite with anticonvulsant activity and a long half-life (>20 hours), followed by slow hydroxylation to oxazepam, which is also active (see Fig. 50.5) (201). Small amounts of temazepam are also formed by 3-hydroxylation of diazepam. The hydroxylated metabolites are conjugated with glucuronic acid in the liver (202) followed by renal excretion (201) with an elimination half-life ($t_{1/2\beta}$) of 24 to 48 hours (119,200). Diazepam treatment causes modest induction of cytochrome P450 type 2B (203). There is little evidence of enterohepatic circulation (204), but diazepam may be secreted in the gastric juices resulting in enterogastric circulation (205). Like most BZs, diazepam crosses the placenta and is excreted in breast milk (108,200).

Adverse Effects and Drug Interactions

Diazepam can produce respiratory depression (206), which may be exacerbated by postictal CNS depression and necessitate ventilatory support (207). Sedative effects, including inattention and drowsiness, occur at plasma levels of about 200 ng/mL (208), the same level needed to suppress spikes (209) and maintain control of status epilepticus in acute studies (119). Drowsiness, fatigue, amnesia, ataxia, and falls are more prominent in the elderly. Intravenous diazepam can cause thrombophlebitis and lactic acidosis (due to the propylene glycol vehicle) (192,210). Rare paradoxical responses include increased seizure frequency, muscle spasms, or status epilepticus (125). An idiosyncratic allergic interstitial nephritis has also been reported (211). Other rare adverse events include cardiac arrhythmias, hepatotoxicity, gynecomastia, blurred vision and diplopia, neutropenia or thrombocytopenia, rash and urticaria, and anaphylaxis (212). There is potential for abuse, though it is rare in patients prescribed diazepam for appropriate indications (110). The

teratogenicity of diazepam is uncertain, but diazepam taken during the first trimester has been associated with oral clefts (213). Diazepam may also amplify the teratogenic potential of valproic acid (214).

Diazepam enhances the elimination of phenobarbital (119), likely due to induction of cytochrome P450 (203). Valproic acid displaces diazepam bound to plasma proteins, leading to increased free diazepam and associated increased sedation (123).

Clinical Applications

Status Epilepticus.

Diazepam is effective initial therapy in both convulsive and nonconvulsive status epilepticus (137). It may be particularly effective in generalized absence status epilepticus, with 93% of patients initially controlled (215). In the same early study, diazepam also controlled 89% of generalized convulsions, 88% of simple motor seizures, and 75% of complex partial status epilepticus. These numbers are higher than those observed in the VA Cooperative Status Epilepticus Trial (137), possibly due to differences in patient populations.

Diazepam is typically administered initially as a single IV bolus of 10 to 20 mg (119). A 20-mg bolus given at a rate of 2 mg/minute stopped convulsions in 33% of patients within 3 minutes and in 80% within 5 minutes (216), but a single injection often does not produce lasting control, due to its short duration of action, and may be less effective when status results from acute CNS disease or structural brain lesions (115). Strategies to avoid this problem have included giving subsequent 5 to 10 mg IV doses every few hours, following diazepam with a longer-lasting anticonvulsant (e.g., phenytoin (137)), or continuous IV diazepam. Repeated dosing results in a decrease in apparent volume of distribution and clearance; hence, subsequent doses should be tapered to prevent toxicity (217). Diazepam (100 mg in 500 mL of 5% dextrose in water) infused at 40 mL/hour delivers 20 mg/hour (94) and may be suitable to obtain a serum level in the range of 200 to 800 ng/mL; 500 ng/mL appears to be effective for termination of status epilepticus (119,218). Complete suppression of 3 Hz spike and wave required 600 to 2000 ng/mL (219). Continuous infusion has been used in patients hypersensitive to anticonvulsants (220). Diazepam is absorbed onto polyvinyl chloride bags, with a reduction in bioavailability of 50% after 8 hours (221), which should be taken into account if a chronic infusion of diazepam for status epilepticus is contemplated. As noted above, the efficacy of BZs decreases with duration of status epilepticus (143); hence, higher levels or alternative treatments may be necessary if seizures are refractory.

Pediatric Status Epilepticus.

The initial recommended IV diazepam dose in children is 0.1 to 0.3 mg/kg IV by slow bolus (<5 mg/minute) repeating every 15 minutes for two doses, with a maximum of 5 mg in infants and 15 mg in older children (222). If IV administration is not possible, a diazepam solution (0.5 to 1 mg/kg), placed 3 to 6 cm into the rectum, has been effective (97). Continuous IV diazepam infusion (0.01 to 0.03 mg/kg/min) controlled seizures in 86% of pediatric patients in status epilepticus (49/57) within an average of 40 minutes (223). Hypotension occurred in 1 patient (2%), respiratory depression in 6 patients (12%), and death in 7 patients (14%). A meta-analysis of 111 pediatric patients (1 month to 18 years) with refractory generalized convulsive status epilepticus, treated with diazepam, midazolam, thiopental, pentobarbital, or isoflurane, suggested that diazepam was less effective as

continuous therapy than the other agents (86% vs. 100%) after stratifying for etiology of status epilepticus (224). However, all of the patients receiving diazepam were from one region (India), and none received continuous EEG monitoring, suggesting that differences in location or details of care may have been contributory. Mortality was 20% in symptomatic cases and 4% in idiopathic cases and was less frequent in midazolam-treated patients.

Although IV administration is preferable, rectal administration of diazepam rapidly produces effective drug levels (225) and safely aborts status epilepticus in pediatric patients (95,99). In children found to be in electrographic status epilepticus during EEG monitoring, rectal diazepam stopped paroxysmal activity in 58% of cases (226). Rectal diazepam was particularly effective in patients with electrical status epilepticus during sleep and less effective in patients with hypsarrhythmia. Intraosseous injection is a viable alternative in children of suitable age when IV access is not available (101).

Febrile Convulsions.

Rectal diazepam is effective in aborting febrile and nonfebrile seizures in the home setting (96). While the concept of chronic prophylaxis for childhood febrile convulsions has long been in disrepute, it has not been clear whether there was benefit to short-term seizure prophylaxis during fever. A prospective trial randomized 289 children in Denmark to intermittent prophylaxis (diazepam at fever) or no prophylaxis (diazepam at seizure) and assessed neurologic outcome; motor, cognitive, and scholastic achievement; and likelihood of future seizures 12 years later (227). There were no differences in these measures, suggesting that short-term prophylaxis is probably not necessary. Moreover, the incidence of respiratory depression in children treated with IV and/or rectal diazepam is fairly high, with 9% showing decreased respiratory rate or oxygen saturation in one study (207).

Acute Repetitive Seizures.

In a large-scale multicenter open- label trial of rectal diazepam gel (Diastat) in 149 patients older than 2 years, 77% of diazepam administrations resulted in no further seizures for the ensuing 12 hours (154). There was no loss of effectiveness with more frequent (>8) doses, suggesting that tolerance did not reduce the effectiveness of diazepam under these conditions. Sedation occurred in 17%. Diazepam rectal gel was also useful against serial seizures in adult patients with refractory epilepsy (100,153), with 0.5 mg/kg found to be an effective dose (98). Intramuscular diazepam injection may also be suitable for prophylaxis of serial seizures, but absorption is not rapid enough to be effective against status epilepticus. Intranasal diazepam administration is another alternative in this setting. In healthy human volunteers, peak serum concentrations of diazepam (2 mg) after intranasal administration occurred after 18 ± 11 minutes with bioavailability of about 50% (104). A pharmacodynamic effect was seen at 5 minutes.

Chronic Epilepsies.

Periodic courses of diazepam have been proposed as therapy for several chronic conditions, including West syndrome, Lennox–Gastaut syndrome, Landau–Kleffner syndrome, and electrical status epilepticus during sleep (228). Oral diazepam (0.5 to 0.75 mg/kg/d) administered in cycles of 3 weeks duration was beneficial in interrupting electrical status epilepticus and improved neuropsychological function in some cases.

Lorazepam

Lorazepam (see Fig. 50.1) has greater potency and a longer duration of action than diazepam and has become the agent of choice for initial treatment of status epilepticus in adults (132). Lorazepam is also less likely to produce significant respiratory depression (138). It is available in both oral and parenteral preparations.

Pharmacokinetics

Lorazepam is rapidly absorbed but less bioavailable after oral administration due to first-pass biotransformation in the liver (229). Peak plasma levels occur 90 to 120 minutes after oral dosing (230). Lorazepam is about 90% protein bound, with CSF levels approximately equivalent to free serum levels (231). Sleep spindles in EEG recordings were observed within 30 seconds to 4 minutes after IV lorazepam (232), though peak brain concentrations and maximal EEG effect did not occur until 30 minutes (233). The volume of distribution is about 1.8 L/kg (233). After a single IV injection, plasma levels decrease initially due to tissue distribution with a half-life ($t_{1/2\alpha}$) of 2 to 3 hours. The minimal effective plasma concentration for control of status epilepticus was 30 ng/mL (234); after IV injection of 5 mg, plasma levels remain above that level for about 18 hours (235). Sedation, amnesia, and anxiolysis occur at plasma levels between 10 and 30 ng/mL (230).

Lorazepam is metabolized in the liver via glucuronidation at the 3-hydroxy group (236) and then excreted by the kidneys (237) (see Fig. 50.4). The half-life for elimination ($t_{1/2\beta}$) is in the 8 to 25 hours range (mean 15 hours) and is the same for oral administration (238).

Adverse Effects and Drug Interactions

Sedation, dizziness, vertigo, weakness, and unsteadiness are relatively common, with disorientation, depression, headache, sleep disturbances, agitation or restlessness, emotional disturbances, hallucinations, and delirium less common (239). Psychomotor impairment, dysarthria, and anterograde amnesia have also been observed. Lorazepam (0.2 mg orally) impaired driving more than a blood alcohol level of 0.5 mg% (240). Mild respiratory depression sometimes occurs, particularly with the first IV dose (241). Rare adverse events include neutropenia. A paradoxical effect was observed in a patient with Lennox–Gastaut syndrome in which lorazepam precipitated tonic seizures (242). Abuse liability is relatively low. Although lorazepam is in USFDA pregnancy category D, of unknown teratogenic potential, short-term use in treatment of status epilepticus may be of lifesaving benefit and likely to outweigh the uncertain risks. Sudden discontinuation after chronic use has caused withdrawal seizures (243).

Valproic acid increased plasma concentrations of lorazepam (244) and decreased lorazepam clearance by 40% (245), apparently by inhibiting hepatic glucuronidation. Lorazepam does not affect valproic acid levels (244). Probenecid increased the half-life of lorazepam by inhibiting glucuronidation, resulting in toxicity in patients on long-term therapy (130).

Clinical Applications

Status Epilepticus.

The recommended IV dose of lorazepam for status epilepticus is 0.1 mg/kg (up to a maximum of 4

mg) administered at 2 mg/minute, with repeat doses after 10 to 15 minutes if necessary (137). Although lorazepam is less lipophilic than diazepam, it crosses the BBB readily. Onset of action occurred within 3 minutes, with control of status epilepticus in 89% of episodes within 10 minutes (135). In another study, all 10 patients with generalized convulsive status epilepticus had seizures controlled with IV lorazepam (mean 4 mg), but 9 of 11 patients with complex partial status epilepticus experienced problems, including respiratory depression (246). Other studies have shown response rates of 80% (115) and 92% (241). Similar success rates were achieved with simple partial status epilepticus (163,241). As noted above, the VA Cooperative Status Epilepticus Trial demonstrated superiority of lorazepam (0.1 mg/kg) over phenytoin (18 mg/kg) in response rate to initial therapy (64.9% vs. 43.6%), with slightly better results for lorazepam than diazepam (0.15 mg/kg) (137). Intravenous lorazepam (4 mg) was effective against post–anoxic myoclonic status epilepticus after cardiac arrest in six patients (247). However, continuous EEG monitoring during lorazepam treatment is advisable, as electroclinical dissociation (electrographic seizures despite cessation of convulsive activity) has been observed.

Pediatric Status Epilepticus.

The usual IV lorazepam dose in pediatric status epilepticus is 0.05 mg/kg, repeated twice at intervals of 15 to 20 minutes (138,163). This regimen terminated seizure activity in 81% of 31 children aged 2 to 18 (241). In a prospective randomized trial of 178 children, lorazepam (0.1 mg/kg) had the same efficacy (100%) as diazepam (0.2 mg/kg) plus phenytoin (18 mg/kg), with similar rates of respiratory depression (about 5%) (248). A retrospective study found that lorazepam (0.1 mg/kg in children and 0.07 mg/kg in adolescents) was most effective in partial status epilepticus, terminating seizures in 90% of cases (163). Prior treatment of status epilepticus with phenytoin, phenobarbital, or diazepam did not alter the effectiveness of lorazepam, though chronic BZ treatment with clonazepam or clorazepate significantly reduced the effectiveness of lorazepam in status epilepticus (163), indicating tolerance. Respiratory depression, when observed, occurred after the first injection.

Lorazepam was effective in neonatal seizures refractory to phenobarbital and/or phenytoin in several small studies. In seven neonates (gestational ages 30 to 43 weeks) treated with IV lorazepam (0.05 mg/kg), seizures were controlled within 5 minutes in all seven patients, with no recurrence in five, and at least 8 hours of control in the remaining two patients (249). No respiratory depression or other adverse effects were reported. In another small series, status epilepticus in six of seven neonates was terminated with lorazepam (0.05 to 0.14 mg/kg) (250).

Pediatric Serial Seizures.

Sublingual lorazepam (1 to 4 mg) was effective against serial seizures in 80% (8/10) and partially effective in 20% (2/10) of children, with onset of clinical effect within 15 minutes in most cases (251).

Alcohol Withdrawal Seizures.

Lorazepam (2 mg) administered after a witnessed ethanol withdrawal seizure prevented a second seizure better than placebo (3% vs. 24%) and may be the agent of choice in this setting (252). Duration of withdrawal symptoms was shorter with lorazepam than with chlordiazepoxide (253).

Chronic Epilepsy.

Lorazepam was effective as adjunctive treatment of complex partial seizures, with an optimal dose of 5 mg/day after slow upward titration from 1 mg twice daily (189). Therapeutic levels were in the range of 20 to 30 ng/mL. However, long-term treatment with lorazepam is likely to result in tolerance and is not generally recommended (254).

Midazolam

Midazolam (see Fig. 50.1) is widely used for induction of anesthesia and as a preanesthetic agent. It is three to four times as potent as diazepam. Midazolam has gained popularity in acute treatment of status epilepticus by either IV or IM use, though its short duration of action necessitates continuous IV maintenance or subsequent therapy with an additional anticonvulsant. Midazolam (10 mg) IM injection reduced interictal spike frequency in EEG recordings as well as IV diazepam (20 mg) (255), and this route provides a valuable alternative when IV access is unavailable.

Pharmacokinetics

Midazolam is water soluble, but at physiologic pH, a conformational change in the BZ ring makes it lipid soluble (256). Serum midazolam levels after IV administration were best fit by a two-compartment model, with an initial tissue distribution phase ($t_{1/2\alpha}$ of 5.7 minutes) and an elimination phase ($t_{1/2\beta}$ of 1.9 hour) (200). After IV administration in eight healthy adult volunteers, mean plasma concentration for a half-maximal increase in β-frequency activity on EEG recording was 276 μmol/L (257). With an IM injection, peak serum concentration occurred after 25 minutes (258). After oral administration, 44% of the dose was bioavailable (200), while intranasal midazolam bioavailability ranged from 50% (259) to 83% (260). Bioavailability after rectal administration was 52% (261) and 74.5% after buccal administration (102). Midazolam is 95% protein bound, with a volume of distribution of 1.1 L/kg and a half-life in the range of 1.9 (200,262) to 2.8 hours (258). The clearance rate was 6.6 mL/min/kg, with 56% urinary excretion. The pharmacokinetics of midazolam is altered in children and critically ill patients. In children aged 1 to 5 years, administration of midazolam (0.2 mg/kg) by intranasal or IV route resulted in a similar elimination half-life, 2.2 hours for intranasal and 2.4 hours for IV administration (263). In critically ill neonates, the elimination half-life after IV administration was 12.0 hours (264). In adult ICU patients, the volume of distribution (3.1 L/kg) and elimination half-life (5.4 hours) were significantly greater than in healthy volunteers (0.9 L/kg and 2.3 hours, respectively) (265) though clearance was not significantly different (6.3 vs. 4.9 mL/min/kg for patients and volunteers, respectively).

Midazolam is metabolized rapidly by α-hydroxylation of the methyl group on the fused imidazo ring (Figs. 50.1 and 50.5) (256). This metabolite is biologically active but is eliminated by hepatic glucuronidation, with an elimination half-life of about 1 hour (266).

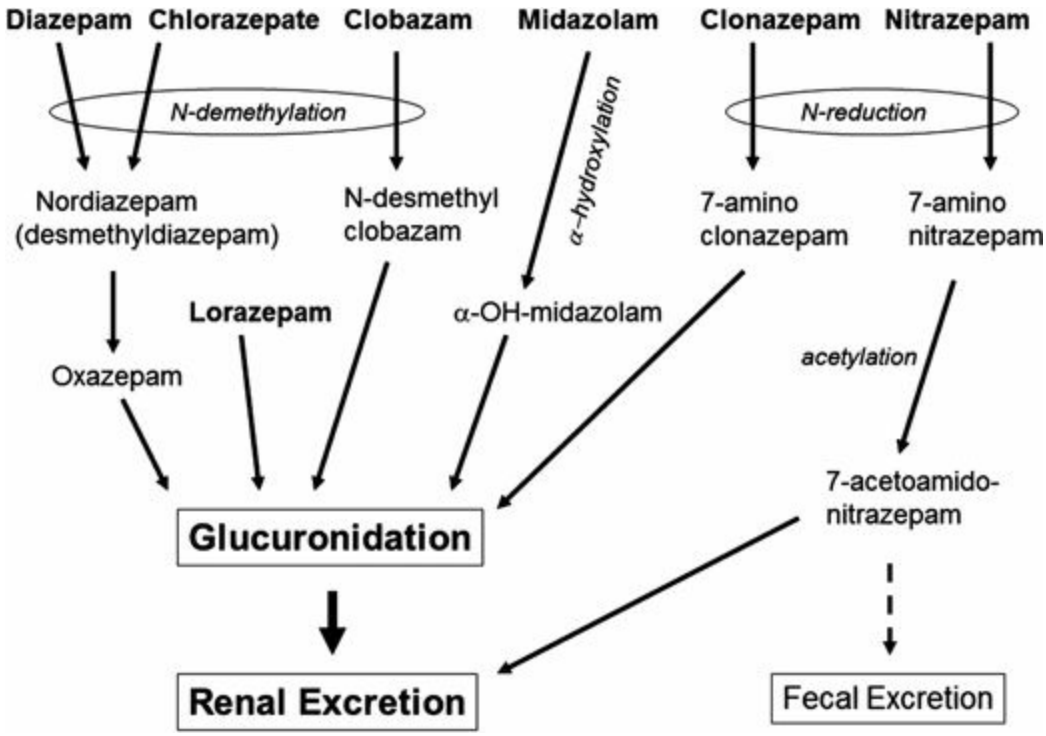


Figure 50.5. Hepatic metabolism of the antiseizure BZs.

Adverse Effects and Drug Interactions

Dose-dependent sedation with midazolam may be prolonged after continuous infusion despite its short half-life (267). Retrograde amnesia, euphoria, confusion, and dysarthria also occur. Midazolam syrup has been associated with respiratory depression and arrest and should only be given where resuscitative drugs, equipment, and experienced personnel are immediately available. Paradoxical reactions (agitation, tremor, involuntary movements, hyperactivity, combativeness) occur in about 2%, and seizures and nystagmus in about 1%. Midazolam syrup is associated with nausea (8%) and vomiting (4%), but these are far less common with IV administration. Hypotension and decreased cardiac output likely result from peripheral vasodilatation (256). Sudden discontinuation after long-term use can result in withdrawal seizures (268). Midazolam is in USFDA pregnancy risk category D.

Erythromycin prolongs the half-life of midazolam to 10 to 20 hours (269). Phenytoin and carbamazepine reduce the bioavailability of oral midazolam by inducing cytochrome P450, which enhances first-pass hepatic metabolism (270).

Clinical Applications

Status Epilepticus.

For refractory status epilepticus, IV midazolam 0.2 mg/kg by slow bolus injection followed by 0.75 to 10 μg/kg/min maintenance infusion has been recommended (132,271). Midazolam suppresses respiratory drive, so patients must be intubated and mechanically ventilated. Typically, infusion is maintained for 24 hours and then slowly tapered during continuous EEG monitoring; if seizure activity returns, midazolam infusion is resumed for additional 12-hour periods. Tolerance may develop, and doses up to 2 mg/kg/h have been required for seizure control (270). Advantages of midazolam over other BZs include rapid onset of action, ease of administration and titration (with the possibility of initial IM injection (272)), good efficacy, and lack of serious adverse effects (271).

Continuous IV infusion of midazolam was effective for treatment of refractory status epilepticus, terminating seizures within 100 seconds in seven patients who had failed treatment with diazepam, lorazepam, and phenytoin with or without phenobarbital (273). Intramuscular midazolam has been used successfully for status epilepticus in several small series, with an effective dose of 0.2 mg/kg (272,274).

Pediatric Status Epilepticus.

Midazolam is also safe and effective in pediatric status epilepticus. In a retrospective study of unprovoked refractory convulsive status epilepticus in epileptic children 1 to 15 years old, repeated bolus midazolam (0.1 mg/kg every 5 minutes) controlled 89% of the episodes after three doses, with infrequent adverse events (respiratory depression, 13%) (275). In another study, midazolam (0.15 mg/kg bolus followed by 1 to 5 μg/kg/min infusion), either alone or with concomitant phenytoin or phenobarbital, controlled status epilepticus in 19 of 20 children (mean age 4 years) (276). In a series of 8 pediatric patients (age 17 days to 16 years) with refractory status epilepticus treated with prolonged (>48 hours) midazolam coma, the average dose for seizure cessation was 14 μg/kg/min and mean duration of therapy was 192 hours; one patient could not be successfully weaned and died after 4 weeks (277). In a similar series of 20 children (mean age 4 years), midazolam was well tolerated and stopped seizures in 95% of patients (278). Intravenous midazolam was safe and effective as first-line therapy in 15 of 16 episodes of status epilepticus in 10 children (20 months to 16 years), using a loading dose of 0.1 to 0.3 mg/kg followed by average infusion of 2.7 μg/kg/min for 12 hours to 6 days (279). It was also effective as a second-, third-, or fourth-line drug, with seizure control in 34 of 38 status epilepticus episodes. In neonates (1 to 9 days, 30 to 41 weeks gestational age), midazolam (0.1 to 0.4 mg/kg/h) controlled overt seizures refractory to high-dose phenobarbital in six patients within 1 hour (280); electrographic seizures continued in two of the six for another 12 hours. Midazolam was tolerated well by neonates, with no change in pulse or blood pressure and no adverse reactions.

Febrile Seizures.

In a prospective, randomized study of 47 children, intranasal midazolam was as effective as IV diazepam for controlling prolonged febrile convulsions, with shorter mean time to starting treatment and shorter time for controlling seizures (3.5 vs. 5.5 minutes) (106).

Pediatric Acute Repetitive Seizures.

A study comparing IM midazolam to IV diazepam in children with seizures lasting longer than 10 minutes found similar efficacy between these agents, though patients in the midazolam group received medication sooner and seizures ended sooner (281). Intranasal midazolam was rapidly effective (158,282), and parents preferred it over rectal diazepam due to faster action and the ability to give it in public (158). In a prospective randomized trial comparing rectal diazepam (0.3 mg/kg) to intranasal midazolam (0.2 mg/kg), mean time from drug administration to cessation of seizure was less in the midazolam group, and mean respiratory rate and oxygen saturation were lower in the diazepam group (159). A randomized trial in children (aged 5 to 19 years) with the Lennox–Gastaut syndrome or other symptomatic generalized epilepsies showed that midazolam (10 mg in 2 mL) administered to the buccal mucosa stopped 75% of seizures, compared to 59% of seizures stopped by rectal diazepam (10 mg) (103). The time to end of seizure was not different between groups, and no

cardiorespiratory adverse events occurred. Intrabuccal and intranasal midazolam are thus viable routes of administration in this patient population. A randomized, double-blind, placebo-controlled trial of intranasal midazolam for seizure clusters in children over age 14 and adults to age 65 (ARTEMIS I, Upsher-Smith, NCT01390220) is in progress.

Clonazepam

Clonazepam (see Fig. 50.1) is used primarily as an anticonvulsant for treatment of both acute seizures and chronic epilepsy. It is effective in several types of status epilepticus (283), but in the United States, clonazepam is available only as an oral preparation.

Pharmacokinetics

The initial distribution half-life after IV injection has not been studied. Clonazepam is 81% to 98% absorbed after oral administration, with peak plasma levels occurring in 1 to 4 hours (6). It is highly lipid soluble with somewhat lower plasma protein binding (86%) than diazepam (108). The volume of distribution is 1.5 to 4.4 L/kg (6), which is greater than that of diazepam or lorazepam. Clonazepam is primarily metabolized to an inactive product, 7-amino-clonazepam, which is conjugated to glucuronide and excreted by the kidneys (6) (see Fig. 50.5). Plasma half-lives were similar in single- and multiple-dose studies, with ranges of 18.7 to 39 hours and 31 to 42 hours, respectively, suggesting relatively little hepatic enzyme induction (6). An intranasal formulation with superior delivery of drug to brain has been developed (284).

Adverse Effects and Drug Interactions

Drowsiness and lethargy occur in about 50% of adult patients initially, but tolerance to these symptoms develops with continued administration (285). Drowsiness was seen in up to 85% of children treated with clonazepam and, along with other side effects, necessitated termination of the drug in 27% of patients (6). Respiratory and cardiovascular depression can occur with IV use. Nystagmus is fairly common; incoordination, ataxia, hypotonia, dysarthria, and dizziness are less frequent. Behavior disturbances including aggression, hyperactivity, and paranoia can be seen in up to 12% of children (286). Seizure frequency is sometimes increased by clonazepam, and seizures (287) or status epilepticus (288) can occur upon abrupt withdrawal. Increased salivary and bronchial secretions, anorexia, or hyperphagia can also occur. A “burning mouth syndrome” with painful oral dysesthesias has been described (289).

Clinical Applications

Status Epilepticus.

Intravenous injection of 0.01 to 0.09 mg/kg terminates status epilepticus in most cases (6). A single 1 mg dose controlled various types of status epilepticus in 80% of adult patients (290). Both IV and oral clonazepam were effective treatments for status epilepticus in children (283,291). The minimum effective plasma level of clonazepam for control of convulsive status epilepticus was 30 ng/mL (115). In children and adults with absence status epilepticus, clonazepam (1 to 4 mg) was effective in 83.3% (292). Dissolving clonazepam into a droplet of propylene glycol followed by buccal

administration achieved therapeutic levels in 10 to 15 minutes and might be a strategy for treating serial seizures (293). An open label study comparing clonazepam and lorazepam for status epilepticus in 50 adults with various epilepsies found similar efficacy (68% and 69%) (294). A single site retrospective study in Germany found clonazepam more effective in terminating generalized convulsive status epilepticus than other ASDs (295). However, neither diazepam nor clonazepam was found to be effective for status epilepticus in another study of 55 patients with symptomatic generalized epilepsy, primarily Lennox–Gastaut syndrome (290).

Pediatric Status Epilepticus.

An IV 0.25 mg bolus of clonazepam, repeated as needed up to 0.75 mg, terminated status epilepticus in 17 of 17 children (2 weeks to 15 years old) (283). Doses ranged from 0.01 to 0.09 mg/kg; the mean clonazepam level was 185 ng/mL at 10 minutes after seizure termination and 43 ng/mL at 30 minutes.

Chronic Epilepsy.

The dose for chronic therapy in children is 0.01 to 0.02 mg/kg/d; in adults, it may range up to 8 mg/day in two to three divided doses. Good control of absence seizures was obtained at plasma levels of 13 to 72 ng/mL (291). However, correlation between plasma clonazepam levels and efficacy is relatively poor (6,296) due to the development of tolerance to antiseizure effects (297). Children require relatively higher doses than adults due to a higher clearance rate. Because of rapid absorption and elimination, children should receive the total daily dose in thirds (6). Clonazepam can be safely discontinued with dosage reduction of 0.04 mg/kg/wk (298).

Severe Childhood Epilepsies.

Although clonazepam is effective against a wide variety of seizure types, side effects limit its use to the most difficult epileptic conditions. Clonazepam produced lasting improvement in 5 of 24 patients with infantile spasms and in 3 of 13 patients with Lennox–Gastaut syndrome at doses of 0.1 to 0.3 mg/kg/d (299). Similarly, complete seizure control was achieved in about one-third of 42 cases of infantile spasms and 37 cases of Lennox–Gastaut syndrome (300).

Myoclonic Seizures.

Clonazepam is effective in various myoclonic seizure disorders including myoclonic–atonic seizures (301), myoclonic seizures (302), Unverricht–Lundborg myoclonic epilepsy (303), and intention myoclonus (304). Other conditions reported to respond to clonazepam include hyperekplexia (305), acute intermittent porphyria (306), epilepsy with continuous spike and wave during slow-wave sleep (307), and neonatal seizures (308).

Clorazepate

Clorazepate (see Fig. 50.1) is used as adjunctive treatment of seizure disorders, anxiety, and alcohol withdrawal. Its role in epilepsy is limited to adjunctive therapy of refractory generalized or partial seizure disorders, particularly in the setting of comorbid anxiety disorders.

Pharmacokinetics

Clorazepate is a prodrug for nordiazepam (N-desmethyldiazepam, DMD), the major active metabolite of diazepam (see Fig. 50.5). Nonenzymatic decarboxylation at position 3 occurs at gastric pH, with 90% of clorazepate converted to DMD in <10 minutes. Decarboxylation of absorbed clorazepate continues more slowly in the blood. DMD is responsible for most of clorazepate's antiseizure effect. Clorazepate is 100% bioavailable by the IM route (309) and 91% (as DMD) by oral ingestion (310). Clorazepate and DMD are 97% to 98% protein bound. The time to peak DMD concentration is 0.7 to 1.5 hours, with peak response in 1 to 2.5 hours (311). Volume of distribution ranged from 0.9 to 1.5 L/kg and was greater in the elderly and in obese subjects (312). The elimination half-life of clorazepate is 2.3 hours, but the half-life of DMD is about 46 hours (313), longer in elderly males and neonates (314). DMD is then hydroxylated to oxazepam (see Fig. 50.5), which is then conjugated to glucuronic acid in the liver (202) and excreted by the kidneys with an elimination half-life of 1 to 2 days (119). As with diazepam, drugs and conditions that alter hepatic metabolism can dramatically affect the metabolism and clearance of clorazepate, DMD, and oxazepam.

Adverse Effects and Drug Interactions

Clorazepate is reportedly less sedating than other BZ anticonvulsants, although sedation is still its most common side effect (315). Dizziness, ataxia, nervousness, and confusion are less commonly seen. Memory problems, difficulty in concentration, irritability, and depression also occur, particularly in association with primidone (316). Paradoxical akathisia has been reported in two patients with history of head trauma and seizure disorders (317). Personality changes with aggressive behavior, irritability, rage, or depression have been described (318), though some have attributed these changes to the underlying temporal lobe epilepsy (319). Hepatotoxicity (320) and transient skin rashes have also been reported. Withdrawal symptoms after chronic use include nervousness, insomnia, irritability, diarrhea, muscle aches, and memory impairment. Clorazepate is in USFDA pregnancy category D; major malformations were reported in one infant born to a mother who took clorazepate during the first trimester (321).

Clinical Applications

The recommended initial dose for adjunctive treatment is 7.5 mg three times daily (0.3 mg/kg/d), with slow increases as required, to a maximal daily dose of 90 mg (about 1 mg/kg/d) in adults and up to 3 mg/kg/d in children (315). Rapid absorption and conversion to DMD require divided dosing to avoid toxicity, despite the long elimination half-life (124). A sustained release preparation delivers 22.5 mg in a single daily dose (Tranxene-SD). Plasma DMD levels of 0.5 to 1.9 mg/mL may represent the therapeutic range (200).

Clorazepate has been used primarily as add-on therapy. It was ineffective as monotherapy but improved seizure control as adjunctive therapy in 59 patients with various seizure disorders (322). Other studies have found limited effectiveness (323) or drowsiness at effective doses (324). Clorazepate was no more effective than phenobarbital as an adjunct to phenytoin treatment, but patients preferred clorazepate (325). Clorazepate controlled refractory generalized seizures in 11 children (age 3 to 17 years), though seizures recurred in 3, likely due to tolerance (326). However, clorazepate's long half-life, slow-release formulation, and slow induction of tolerance may make it more useful than some other BZs for chronic treatment of epilepsy (254).

Clobazam

Despite the possible development of tolerance, clobazam (8-chloro-5-methyl-1-phenyl-1,5-benzodiazepine-2,4-dione) has become the most widely used BZ for the long-term treatment of epilepsy because of its effectiveness and relatively low tendency to produce sedation (327). In post–temporal lobectomy patients, clobazam is the third most common anticonvulsant employed after carbamazepine and phenytoin (328). Clobazam has primarily been used as add-on therapy, though the Canadian Study Group for Childhood Epilepsy (329) has found it effective as monotherapy in children. In 2011, it was approved in the United States for adjunctive treatment of seizures associated with Lennox–Gastaut syndrome.

Pharmacokinetics

Clobazam is the only 1,5-BZ in clinical use as an anticonvulsant. Clobazam has a relatively low binding affinity and a correspondingly low potency (see Table 50.1). It is well absorbed, with peak concentrations in 1 to 4 hours, highly lipid soluble, and 85% protein bound. N-desmethylclobazam, the major metabolite, is the primary anticonvulsant component in patients undergoing long-term therapy. The mean elimination half-life is 18 hours for clobazam and 42 hours for N-desmethylclobazam. Clobazam induces hepatic enzymes, leading to more rapid conversion to N-desmethylclobazam with long-term treatment (330). Plasma levels of clobazam and N-desmethylclobazam correlated with both therapeutic effect and toxicity, but therapeutic levels have not been established, likely due to presence of the active metabolite and the development of tolerance (331).

Adverse Effects and Drug Interactions

Clobazam may have fewer or milder side effects than other BZs at equipotent doses (7,332,333). Levels of the metabolite, N-desmethylclobazam, correlated with side effects (334). In epileptic patients, the predominant side effects of clobazam are drowsiness and fatigue (330). Of 23 open-label studies of clobazam, ataxia was described in 4, dizziness in 19, and vertigo in 2 studies (330). Memory disturbance, aggressiveness, dysphoria, and illusional and psychotic symptoms occur relatively infrequently. Clobazam has been associated with blurred vision. Negative myoclonus (asterixis, sudden brief loss of tone) has been observed when clobazam was added to carbamazepine (335). Tolerance occurred in 48% of Lennox–Gastaut syndrome patients treated with clobazam (336) as seen with the 1,4-BZs (57). Increased seizure activity can occur with discontinuation of the drug (337).

Clinical Applications

Clobazam doses range from 10 to 50 mg/day, with most studies using 10 to 30 mg/day in one or two doses. In the Canadian Clobazam Cooperative Group trial of 877 patients, the average dose in adults was 30.8 mg, while the average dose for children was 0.86 mg/kg (338).

Clobazam is effective against all seizure types (339), but the benefits may be short-lived. In the Canadian Clobazam Cooperative Study, more than 40% of patients with a single seizure type had a 50% or greater reduction in seizure frequency, and 60% of patients with multiple seizure types had improvement in at least one type of seizure (338). About a third developed drowsiness as a side

effect, but this was severe enough to cause discontinuation in only 11%. About 9% discontinued due to recurrence of seizures, which was thought to represent tolerance. In a randomized, double-blind study of clobazam as adjunctive therapy for drop seizures in Lennox–Gastaut syndrome, clobazam provided a significant, dose-related reduction in drop seizure rates, with non–drop seizures also reduced; adverse effects were rare and mild (340). Clobazam may be particularly effective in the Lennox–Gastaut syndrome (327), but tolerance prevents it from being the drug of first choice for most epilepsies (330). In a large prospective US study of 251 refractory patients prescribed adjunctive clobazam (5 to 60 mg/day, mean 23.9 mg/day), 7 patients (11.3%) became seizure free for at least 6 months after introduction of clobazam, and the 1-year retention rate was 61% (341). An indirect comparison of clobazam to other ASDs found that clobazam had greater efficacy for seizures of all types and drop attacks (atonic seizures) (336). An economic analysis found that clobazam was cost-effective due to the reduction in emergency care needed for drop attacks (342). Clobazam was effective when used intermittently in catamenial epilepsy, as tolerance to the anticonvulsant effect was apparently avoided (161). It has also been shown safe and effective in the treatment of epileptic encephalopathies of childhood (343) though its ability to suppress EEG spike-and-wave activity has caused confusion in the diagnosis of electrical status epilepticus during sleep (344).

Despite reports of rapid development of tolerance, the Canadian Clobazam Cooperative Study (338) reported that 40% to 50% of patients remained on clobazam for 4 years or longer. Patients who had a seizure reduction exceeding 75% when clobazam was added were likely to sustain this response if their epilepsy was not long-standing and had a known cause (345).

Nitrazepam

Nitrazepam (see Fig. 50.1) has been used as a hypnotic and anticonvulsant, with benefit against infantile spasms, and as adjunctive therapy for severe generalized epilepsies of childhood. Nitrazepam may be particularly effective against myoclonic seizures.

Pharmacokinetics

Oral bioavailability is about 78% (346), with peak concentration occurring in 1.4 hours (347). Nitrazepam is 85% to 88% protein bound (348) and has a volume of distribution of 2.4 L/kg in healthy young adults, higher in the elderly and in women (346). Nitrazepam is metabolized in the liver to an inactive product (see Fig. 50.5) (349). It does not induce its own metabolism. A portion is apparently bound in tissues for prolonged periods (350). Metabolism is slowed in patients with hypothyroidism (351) and obesity (352).

Adverse Effects and Drug Interactions

Like other BZs, nitrazepam can produce disorientation, confusion, and drowsiness, particularly in elderly patients (348). Vivid nightmares have occurred at the onset of therapy (353). Drooling and aspiration have occurred in children (354,355), apparently caused by impaired swallowing (355), though this did not occur at doses <0.8 mg/kg/d (355). Respiratory depression has occurred in elderly patients (356). Increased seizure frequency and new seizure types are sometimes seen (357). Tolerance can develop with chronic use, and withdrawal symptoms have occurred (195,358,359).

Nitrazepam is in USFDA pregnancy category C. Infants born to mothers on nitrazepam late in pregnancy have been somnolent, floppy, poorly responsive, and required tube feeding but recovered

in several days (360). Among 43 pregnant women who took overdoses of nitrazepam in suicide attempts, 30% of births were associated with congenital abnormalities (361). Like other BZs, nitrazepam is associated with increased teratogenic risk, particularly oral clefts (213).

Nitrazepam therapy increased the risk of death in young patients with intractable epilepsy. In a retrospective analysis of 302 patients treated with nitrazepam, 21 patients died, 14 of whom were taking nitrazepam at time of death (362). In patients younger than 3.4 years, the death rate was 3.98 per 100 patient-years, compared with 0.26 deaths per 100 patient-years in patients not taking nitrazepam. Nitrazepam had a slight protective effect in patients older than 3.4 years. It should therefore be used with extreme caution if at all in children younger than 4 years.

Clinical Applications

Nitrazepam is not available for clinical use in the United States. The usual daily dose is 1 mg/kg for children and 0.5 mg/kg for adults. Initial doses of 1 to 6 mg daily, with gradual increases up to 60 mg daily, have been used in treatment of pediatric seizure disorders (363–365). In children, satisfactory seizure control was associated with a mean plasma concentration of 114 ng/mL (348); levels above 220 ng/mL were more likely to be toxic. Nitrazepam (0.25 to 0.5 mg/kg/d, in t.i.d. dosing during fever) was effective in prophylaxis of febrile convulsions (366).

Nitrazepam was particularly effective for infantile spasms, myoclonic seizures, and the Lennox–Gastaut syndrome (363,365,367). In 52 patients (1 to 24 months) with infantile spasms and hypsarrhythmia on EEG, nitrazepam (0.2 to 0.4 mg/kg/d in two divided doses) and adrenocorticotrophic hormone (ACTH, 40 U IM daily) were similar in efficacy and incidence of adverse effects (368). Both regimens resulted in 75% to 100% reduction in seizure frequency in 50% to 60% of patients. Twenty children (4 to 28 months) with infantile spasms or early Lennox–Gastaut syndrome were treated with nitrazepam (median dose 1.5 mg/kg/d); of these, five had complete cessation of seizures, seven had >50% seizure reduction, and eight had no response (369). Twelve children experienced pooling of oral secretions and 6 developed sedation, but no serious side effects were reported.

Flumazenil: Potential Uses in Epilepsy

The BZ antagonist, flumazenil, has been used primarily to reverse BZ-induced sedation (17,18) but may also have benefit in reversing hepatic coma (370,371) in patients who had no prior exposure to BZs. Ammonia and manganese activate mitochondrial benzodiazepine receptors leading to increased production of neuroactive steroids, some of which (e.g., allopregnanolone, THDOC) enhance inhibitory neurotransmission via allosteric modulation of the $GABA_A$ receptor (372,373). The reversal of hepatic coma has bolstered arguments for an endogenous BZ ligand or "endozepine," which could be displaced by flumazenil (374,375). An endogenous "diazepam-binding inhibitor" (DBI) peptide has been characterized (376), though its role in inhibitory neurotransmission remains unclear. Endogenous potentiation of GABA-ergic synaptic transmission and responses to GABA uncaging in thalamic reticular nucleus (nRT) neurons was absent in nm1054 mice, in which the DBI gene is deleted (377). Viral transduction of DBI into nRT was sufficient to rescue the endogenous potentiation of GABA-ergic transmission in these mice. Hence, DBI may function as an endogenous inhibitory neuromodulator, possibly increased in the setting of hepatic encephalopathy.

Flumazenil may be of use in epilepsy by reversing tolerance and may also have intrinsic

antiepileptic effects. Brief exposure to flumazenil can reverse tolerance-related changes in $GABA_A$ receptor function (378,379) and subunit expression (380). Flumazenil has been used with modest success to treat BZ dependence (381). The concept of using intermittent low doses of flumazenil to reverse BZ anticonvulsant tolerance has been explored in humans (382). Three patients with daily seizures who had become tolerant to clonazepam (1 mg b.i.d.) were treated with a single IV dose of flumazenil (1.5 mg, corresponding to 55% receptor occupancy), resulting in a mild withdrawal syndrome (shivering) lasting 30 minutes, followed by seizure freedom for 6 to 21 days (mean 13 days). Refinement of this approach may allow more extensive use of the BZs in the chronic treatment of epilepsy. Curiously, flumazenil itself has shown anticonvulsant efficacy in some animal models, possibly due to partial agonism at high doses (383,384) or antagonism of an endogenous proconvulsant (382). Flumazenil also reduced epileptiform discharges in rat hippocampal slices (385) and slowed the development of kindling (386). Flumazenil (0.75 to 15 mg) suppressed focal epileptiform activity in six patients with partial (temporal lobe) seizures but had no effect on generalized spike-and-wave activity in six patients with generalized seizures (387). Several small studies have suggested possible benefit as an ASD in humans (387,388). In 9 of 11 previously untreated patients with epilepsy, oral flumazenil (10 mg one to three times daily) caused a 50% to 75% reduction in seizure frequency, and 9 of 16 patients experienced 50% to 75% reduction in seizure frequency when flumazenil was added as an adjunctive anticonvulsant (389). Flumazenil's ability to prevent interictal epileptiform discharges on EEG was similar to that of diazepam (382,390).

Flumazenil can precipitate seizures, particularly in the setting of hepatic encephalopathy, in BZ-dependent patients, or in patients who have ingested multiple agents in overdose (e.g., tricyclic antidepressants) (391). The ability of flumazenil to induce seizures in patients previously treated with BZs has been used to precipitate partial seizures during inpatient epilepsy monitoring to localize seizure onset (392), though that practice is controversial. In addition, [^{11}C]flumazenil has been used diagnostically in positron emission tomography studies to demonstrate regions of neuronal loss associated with epilepsy (393–395) and may be useful in localizing the seizure focus in patients with dual pathology (396) and to define the epileptogenic zone (397).

FUTURE DIRECTIONS: NEW STRATEGIES FOR THE BZS

Partial BZ agonists (abecarnil, bretazenil, imidazenil) may retain anticonvulsant efficacy but be less prone to the development of tolerance. The utility of these agents in human epilepsy has not been adequately explored. Combination therapy using a full agonist with a partial agonist or antagonist (flumazenil), or intermittent use during periods of higher seizure risk (e.g., catamenial epilepsy), might prevent the development of tolerance and provide new strategies for BZ use. Novel routes of administration via the nasal, buccal, or rectal mucosa provide less invasive means to use BZs acutely in the outpatient setting. Another novel approach involves using BZs in a device capable of detecting seizure discharges and injecting the drug at the onset of seizure activity, locally onto the epileptic focus, into the cerebral ventricles, or systemically. A model for this type of device in rats showed a decrease in seizure frequency and duration when diazepam rather than vehicle was injected onto a bicuculline-created seizure focus (398). Such approaches may increase the future role of BZs in the treatment of status epilepticus, serial seizures, and epilepsy.

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CHAPTER 51 CARBAMAZEPINE, OXCARBAZEPINE, AND ESLICARBAZEPINE

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Carbamazepine (CBZ) is one of the most often prescribed drugs worldwide for the treatment of neurologic disorders. CBZ is considered an efficacious agent for the treatment of focal and generalized tonic–clonic seizures in children and adults, with an excellent side effect profile (1).

Oxcarbazepine (OXC), the 10-keto analog of CBZ, has been used largely as an alternative for CBZ because of its more favorable pharmacologic and adverse event profiles. It is effectively a prodrug for licarbazepine, which exhibits effects similar to CBZ but avoids metabolism into carbamazepine-10,11-epoxide, which is believed to add to the toxicity of CBZ.

It was felt that there might still be room for improvement, however, since licarbazepine exists in two enantiomeric forms, yet only the S-enantiomer appears to contribute to anticonvulsant activity. This prompted the development of eslicarbazepine acetate (ESL), which is metabolized directly to S-licarbazepine, without loss to the R-enantiomer.

CHEMISTRY AND MECHANISM OF ACTION

CBZ is an iminodibenzyl derivative. Both CBZ and OXC are tricyclic anticonvulsant agents that are structurally similar to antidepressants. However, unlike the tricyclic antidepressants, CBZ and OXC are neutral substances because of their carbamoyl side chains (Fig. 51.1).

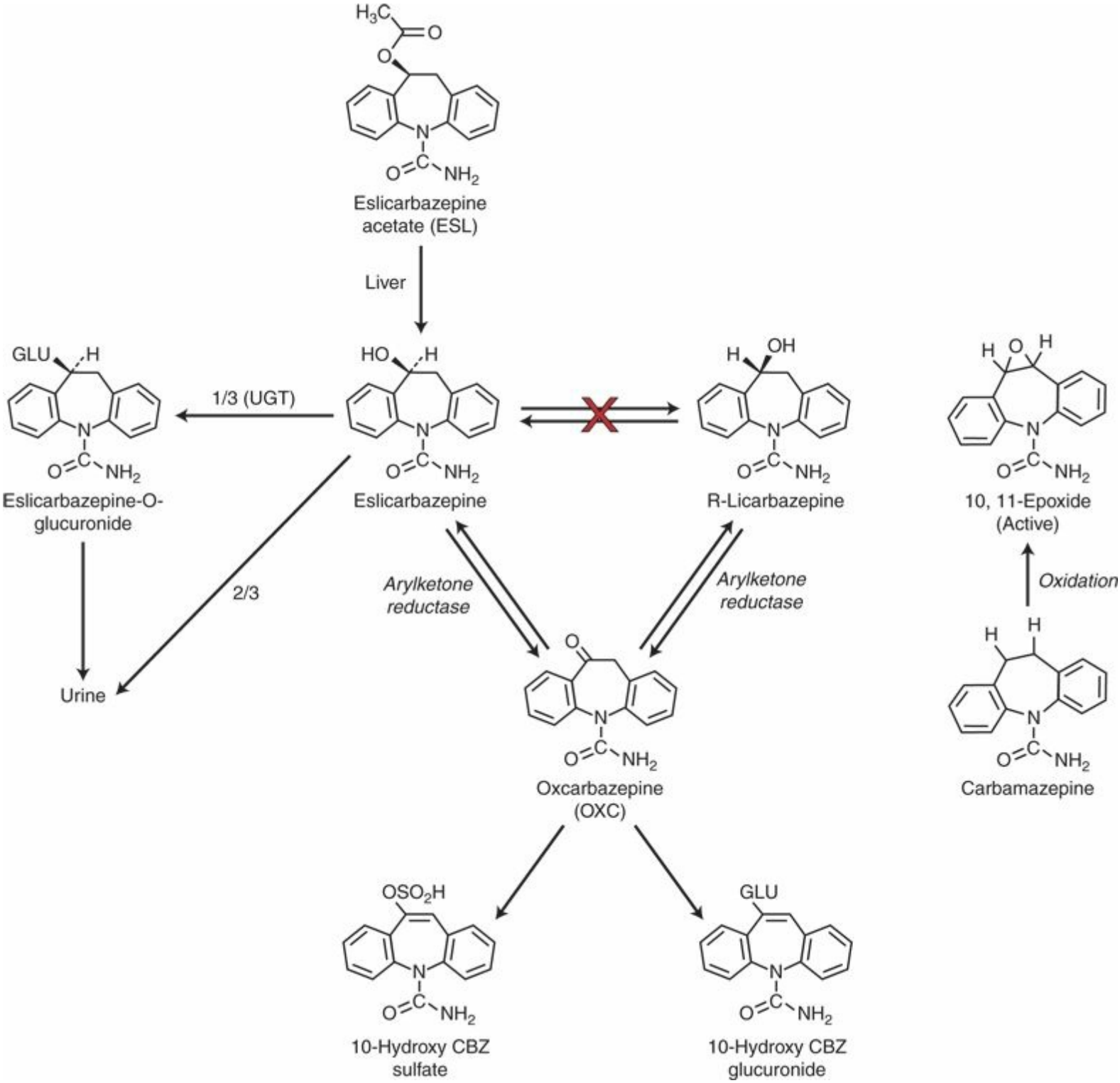

Figure 51.1. Chemical structure and main first-step metabolic pathways of oxcarbazepine and carbamazepine, and their active metabolites, MHD and CBZ-10,11-eproxide (CBZ-E).

OXC as a prodrug is rapidly and completely metabolized to R- and S-licarbazepine, which together are sometimes referred to as the monohydroxy derivative of oxcarbazepine (MHD). CBZ and OXC (and also their active metabolites—CBZ epoxide and MHD) share many known actions of antiepileptic drugs (AEDs). They produce blockade of voltage-dependent ionic membrane conductance (especially sodium, potassium, and calcium), resulting in stabilization of hyperexcited neural membranes and synaptic actions of such neurotransmitters as γ-aminobutyric acid (GABA), glutamate, purine, monoamine, N-methyl-D-aspartate, and acetylcholine receptors; the effect is diminution of propagation of synaptic impulses (2). There are subtle differences in the mechanisms of

action of CBZ and OXC. For instance, MHD blocks N-type calcium channels, whereas CBZ blocks L-type (3). ESL, being converted into the active enantiomer of MHD (S-licarbazepine), is presumed to act in the same manner as does OXC. One recent study found that ESL maintains its effect on Na^+-channel currents even in mice who lack the B subunit of the channel, in sharp contrast to CBZ; this effect is also seen with lacosamide, and raises the possibility that ESL may have at least some effects that are distinct from CBZ (4).

Circulating MHD exists as a racemic mixture composed of S-licarbazepine and R-licarbazepine. There appear to be potentially important differences in pharmacologic activity between these two enantiomers. For example, the affinity of R-licarbazepine appears to be about fourfold greater for voltage-gated sodium channels when in the resting state (vs. inactive state) as compared to S-licarbazepine. In addition, R-licarbazepine may block voltage-gated potassium channels (Kv7.2 currents), whereas S-licarbazepine does not. Finally, administration of eslicarbazepine was shown to inhibit acquisition of kindling in mice, whereas R-licarbazepine administration did not (5).

CARBAMAZEPINE

Absorption and Distribution

CBZ is absorbed from the gastrointestinal tract slowly, with an estimated bioavailability of about 80% to 90%. The bioavailability of the agent is similar for all formulations—that is, tablets, solution, oral suspension, chewable tablets, and extended-release tablets/capsules. However, some studies have demonstrated the advantages in reducing serum level fluctuation with controlled-release forms of CBZ. Peak plasma concentration with chronic dosing is 3 to 4 hours. CBZ is a lipophilic compound that crosses the blood–brain barrier readily and is rapidly distributed to various organs, including fetal tissues and amniotic fluid as well as breast milk (6). Pharmacokinetic parameters are shown in Table 51.1 (7–9).

Table 51.1 Pharmacokinetic Parameters of CBZ, OXC, and MHD (7–9)

	F (%)	T_{max} (h)	V_d (L/kg)	Protein binding (%)	$t_{1/2}$ (h)	T_{ss} (d)	Therapeutic range (μg/L)	Dose (mg/kg/d)
CBZ	75–85	4–12	0.8–1.9	70–80	5–20	20–30	3–12	10–30
OXC	>95	1–2	—	—	2	—	—	10–50
MHD	—	3–5	0.75	40	8–15	2	8–20	—

CBZ, carbamazepine; OXC, oxcarbazepine; MHD, monohydroxy derivative; F, bioavailability; T_{max}, time interval between ingestion and maximum serum concentration; V_d, volume of distribution; protein binding, fraction to serum protein; $t_{1/2}$, elimination half-life; T_{SS}, steady state; therapeutic range, therapeutic range of serum concentration.

Metabolism

CBZ clearance is accomplished almost entirely via hepatic metabolism (9). The major pathways of CBZ biotransformation, consecutively or as parallel reactions, are the epoxide–diol pathway, aromatic hydroxylation, and conjugation. Metabolites from these major routes account for 80% to 90% of total urinary radioactivity. The main metabolites found in urine are due 40% to oxidation of the 10,11 double bond of the azepine rings, 25% to hydroxylation of the six-membered aromatic rings,

15% to direct N-glucuronidation at the carbamoyl side chain, and 5% to substitution of the six-membered rings with sulfur-containing groups. CBZ is oxidized by the cytochrome P450 system (CYP3A4 and CYP2C8 isoforms) to CBZ-10,11-epoxide (CBZ-E), which is considered the most important product of CBZ metabolism (see Fig. 51.1). CBZ-E is an active metabolite that may contribute to rash and other side effects associated with CBZ use. CBZ induces the activity of CYP3A4, with the metabolic clearance of CBZ-E nearly doubled in induced patients (6).

CBZ leads to autoinduction, which increases clearance (double in monotherapy), shortens serum half-life, and decreases serum concentrations. This process takes approximately 2 to 6 weeks to occur (6).

CBZ-E is hydrolyzed via the microsomal enzyme epoxide hydrolase to trans-10,11-dihydroxy-10,11-dihydrocarbamazepine (trans-CBZ-diol). The diol is excreted in the urine and accounts for 35% of a CBZ dose and is considered to be inactive. Another, somewhat less important metabolic pathway of CBZ is the hydroxylation at different positions of the six-membered aromatic rings. The third most important step in CBZ biotransformation is conjugation reactions. CBZ may be directly conjugated with glucuronic acid. Direct N-glucuronidation of CBZ and its metabolites depends on microsomal uridine diphosphate glucuronosyltransferase (UDPGT). Additionally, CBZ and its phenolic metabolites can be conjugated with sulfuric acid (6).

Drug Interactions

CBZ has a narrow therapeutic range, and plasma concentrations are often maximized to the upper limit of tolerance. As a low-clearance drug, CBZ is sensitive to enzyme induction or inhibition, especially by the large number of agents that induce or inhibit CYP3A4 isoenzymes. Drugs that inhibit CYPA34 increase plasma concentrations of CBZ.

CBZ, like phenytoin (PHT) and phenobarbital (PB), is a broad and potent inducer of the CYP450 isozyme system including CYP3A4, CYP2C9, CYP2C19, and CYP1A2 as well as UDP-glucuronyl transferase (UGT). As a result, the metabolism of other agents, including both AEDs, and numerous other non-AED medications is increased (10). Polytherapy with CBZ can therefore result in unpredictable plasma concentrations and, potentially, clinical effect of other medications. Pharmacokinetic interactions among CBZ, OXC, and AEDs are shown in Table 51.2 (7,11).

Table 51.2 Pharmacokinetic Interactions Among CBZ, OXC, and other AEDs (7,11)

	Effects of the addition of						
On levels of	CBZ	PHT	PB	PRM	VPA	OXC	ZNS
CBZ	↓	↓	↓	↓	↑E	↑E	↑E
OXC	↓	↓	↓	↓			

Note: Ethosuximide, felbamate, lamotrigine, gabapentin, tiagabine, pregabalin, levetiracetam, and vigabatrin addition do not affect level of OXC.

CBZ, carbamazepine; OXC, oxcarbazepine; PHT, phenytoin; PB, phenobarbital; PRM, primidone; VPA, valproate; ZNS, zonisamide; E, CBZ epoxide.

While neurologists tend to pay most attention to the effect of CBZ on other AEDs, the number of other drugs whose metabolism is induced by CBZ is vast; these include cancer chemotherapy, psychotropics, antibiotics, antithrombotic agents, antihypertensives, HMG-CoA reductase inhibitors,

immunosuppressants, and many more besides (11). The number of these is so extensive, in fact, that a full discussion of these is beyond the scope of this chapter, and the reader is referred to other sources for more detail (9).

These interactions can have a profound effect on the care of other health conditions aside from the patient's epilepsy, some of which are worth highlighting. The effectiveness of hormonal contraceptives, independent of preparation (oral, subcutaneous, intrauterine, implant, or injectable), is reduced by CBZ administration. Midcycle spotting or bleeding is a sign that ovulation has not been suppressed (10). Some practitioners believe that oral contraceptives should contain ≥50 μg of estrogen in the setting of CBZ treatment to overcome the induction, but there is a lack of good evidence to support this, so in view of the potential consequences, others take the view that OCP and CBZ should simply not be used together. Agents used for HIV infection are significantly reduced in level, and likely in efficacy, by concomitant use of enzyme-inducing AEDs, including CBZ; this is of such importance that it has generated a formal recommendation that the inducing drugs should be avoided when possible in HIV-infected patient (13). Warfarin metabolism is substantially induced by CBZ treatment, necessitating higher doses. With warfarin, and indeed all other concomitant hepatically metabolized drugs, discontinuation of CBZ will result in higher circulating levels of the other agent due to deinduction; this may result in drug toxicity. Factors pertaining to drug interaction constitute a major issue with CBZ treatment and need to be kept in mind whenever it is prescribed; the use of newer agents without such interactions avoids such complications and may be preferable in a wide range of clinical circumstances.

Efficacy

The efficacy of CBZ in patients with epilepsy was first demonstrated in the early 1960s (14). The agent continues to be a first-line treatment for patients with focal seizures.

Randomized, Monotherapy, Controlled Trials: CBZ Versus Other Agents

Most studies have demonstrated no difference in efficacy between CBZ and PHT as monotherapy for adults and children with epilepsy (14). No difference in efficacy was reported in trials comparing CBZ and PB in children. The second Veterans Administration (VA) Cooperative Study (15), a multicenter, randomized, double-blind, parallel-group trial, compared CBZ with valproate (VPA) for the treatment of 480 adults with complex partial (n = 206) or secondarily generalized (n = 274) seizures. The patient population comprised recently diagnosed, AED-naïve patients with epilepsy, as well as those who were being suboptimally treated. In patients with tonic–clonic seizures, there was no difference in efficacy between the two agents. However, CBZ appeared more efficacious than VPA for the treatment of patients with partial seizures, according to several outcome measures: number of seizures, seizure rate, seizure score, and time to first seizure. Other studies did not reveal any significant differences between CBZ and VPA in adults or children (14).

Large Trials Comparing Several AEDs with CBZ

The first VA study was a double-blind, comparative study of monotherapy with PB, PHT, primidone (PRM), and CBZ in 622 adults with partial and secondarily generalized tonic–clonic seizures (16). CBZ was found to be similarly as effective as PB, PHT, and PRM in controlling secondarily generalized tonic–clonic seizures. However, CBZ was more effective than barbiturates for the

treatment of partial seizures, whether simple or complex. No difference was found between CBZ and PHT.

Other studies in the United Kingdom (14) did not demonstrate any difference between CBZ and PB, PHT, or VPA. However, the patients from the United Kingdom had been recently diagnosed with epilepsy, whereas half of the patients in the VA trials had been previously treated. Nevertheless, the large number of patients with complex partial seizures in the VA studies may provide the power to detect statistically significant differences. Because of the above-mentioned data, CBZ has been considered a first-line AED for the treatment of focal and generalized tonic–clonic seizures and is used as an active control in trials of all new compounds.

A multicentric class I study (17) of 593 elderly subjects with newly diagnosed seizures, comparing gabapentin (GBP), lamotrigine (LTG), and CBZ, concluded that there were no significant differences in the seizure-free rate at 12 months, but the main limiting factor in patient retention was adverse drug reactions. Patients taking LTG or GBP did better than those taking CBZ. Seizure control was similar among the groups. Based on the findings, the authors proposed that LTG and GBP should be considered as initial therapy for older patients with newly diagnosed seizures.

CBZ has been tested against almost all new AEDs in monotherapy trials. The majority of these studies have shown no difference in efficacy between CBZ and LTG in adults, adolescents, and children, OXC (14), or topiramate (TPM) in children and adults (18). CBZ was significantly more efficacious than were vigabatrin (VGB) (19), remacemide (20), and probably GBP (21). Some studies have suggested that GBP, LTG, VGB, and OXC are better tolerated than is CBZ.

There are several methodologic limitations in many trials, with some satisfying regulatory agencies but not necessarily guaranteeing clinical use. Most studies are either undertaken with insufficient numbers of patients to demonstrate significant differences, or else the follow-up is relatively short, considering the seizure-free period, for a true improvement in quality of life to be realized.

An important study comparing CBZ and levetiracetam did not show difference in the efficacy and effectiveness between these AEDs (22).

The available data suggest that CBZ is as effective as any of the other AEDs that have been investigated. More studies that assess the economic impact of epilepsy treatment are warranted to compare several therapies.

According to the evidence-based analysis of the AED efficacy and effectiveness as initial monotherapy for adults with focal seizures, CBZ was considered a level A recommendation (23). Based on the same guidelines, CBZ is not a level A, but a level C recommendation for elderly patients with focal epilepsy.

Adverse Events

Accurate determination of adverse events has been a limitation in several AED trials. Systematic active questioning of patients has revealed a completely different picture of a spontaneously self-reporting adverse event. Although up to 50% of patients treated with CBZ experience adverse events, only 5% to 10% need to discontinue therapy (24,25).

Neurotoxicity

Most adverse events associated with CBZ use involve the central nervous system (CNS) and are mild, transient, and dose related; severe idiosyncratic reactions occur rarely. The most common

adverse events are nausea, gastrointestinal discomfort, headache, dizziness, incoordination, vertigo, sedation, diplopia or blurred vision, nystagmus, tremor, and ataxia. Adverse events are similar in children and more common in elderly patients (24,25).

As with most AEDs, CBZ may cause several psychic disturbances, including asthenia, restlessness, insomnia, agitation, anxiety, and psychotic reactions. Neuropsychological adverse events associated with nontoxic, chronic CBZ use are generally minimal. Some investigators believe that the use of a sustained-release preparation may be advantageous in both children and adults (25).

Movement disorders, including dystonia, choreoathetosis, and tics, are associated with the use of CBZ, possibly with toxic plasma levels of the agent.

Hypersensitivity Reactions

The incidence of rash with CBZ use is approximately 10% (16,26). CBZ causes the anticonvulsant hypersensitivity syndrome (AHS), characterized by fever, skin rash, and internal organ involvement (26,27). AHS is associated with the aromatic AEDs—that is, PHT, PB, PRM, CBZ, and LTG. AHS begins within 2 to 8 weeks after AED therapy initiation; the reaction usually starts with low- or high-grade fever, and over the next 1 or 2 days, a cutaneous reaction, lymphadenopathy, and pharyngitis may develop. Involvement of various internal organs may occur, resulting in hepatic, hematologic, renal, or pulmonary impairment. The most prominent manifestations are hepatitis, eosinophilia, blood dyscrasias, and nephritis. The most common cutaneous manifestation is an exanthema with or without pruritus. Rarely, severe skin reactions may occur, such as erythema multiforme, Stevens–Johnson syndrome, and toxic epidermal necrolysis (26). It is important for the management of the patient to be aware of acute cross-reactivity, which may be as high as 70% to 80% among CBZ, PHT, and PB (25,27). VPA is considered a safe, acute alternative for the treatment of patients with AHS. Systemic corticosteroids are usually required for full recovery (27).

Systemic lupus erythematosus may be induced by CBZ. Symptoms generally appear 6 to 12 months after initiation of therapy. Discontinuation of CBZ usually leads to disappearance of the symptoms. Hair loss associated with CBZ use has been reported. Myocarditis has been described as a manifestation of CBZ hypersensitivity (25).

Hematologic and Hepatic Effects

Transient leukopenia occurs within the first 3 months of treatment in 10% to 20% of patients taking CBZ. Persistent leukopenia, which is seen in 2% of patients, reverses with discontinuation of CBZ treatment (25). In the VA study, only one patient had a transient, clinically significant neutropenia (<1000 cells/mm^3) associated with CBZ use, and the treatment was not discontinued (16). Isolated thrombocytopenia associated with CBZ treatment has been described at a rate of 0.9 per 100,000. Aplastic anemia and agranulocytosis have been reported in association with the use of CBZ (9,24). Data from a population-based case–control study demonstrated that the risk of developing these reactions is five to eight times greater than in the general population (9).

Hepatic enzymes may be elevated in patients receiving CBZ treatment—mostly mild elevations with no clinical significance. Rarely, CBZ hepatotoxicity can be a serious adverse event that leads to death. Cases in pediatric patients are probably less common than in adults (24). Cardiac arrhythmias have also been associated with CBZ use (25).

Metabolic Effects

Because of its potent enzyme-inducing properties, CBZ has extensive effects upon metabolism owing to the involvement of CYP450 and other similar enzymes in many endogenous metabolic processes (28). CBZ is well established to increase serum cholesterol by an average of about 25 mg/dL; it also substantially increases lipoprotein(a), doubles C-reactive protein, and may increase homocysteine as well (29–31). All of these would be expected to increase the risk of ischemic vascular disease.

Over the past several years, bone health impairment and increased risk of fractures have been associated with epilepsy and AEDs, including CBZ, both in children and in adults. There is clear evidence that CBZ decreases 25-hydroxyvitamin D levels by about 25% to 30%, accompanied by increases in markers of bone turnover (12). Because of this, many authors recommend vitamin D and calcium supplementation. Nevertheless, there is no evidence-based guidance about the efficacy of dietary supplements or the appropriate amount to be used (32,33). It is also unclear whether CBZ actually reduces bone density or increases fracture risk, with the evidence being mixed on that score (34–37).

The effect of CBZ on metabolism of testosterone, pituitary responsiveness to gonadotropin-releasing hormones, prolactin, follicle-stimulating hormone, and luteinizing hormone have been studied, although the clinical relevance of the findings has not been thoroughly elucidated (25,38). CBZ has been repeatedly shown to reduce bioactive testosterone, but not total testosterone, apparently via induction of sex hormone–binding globulin. While sizable, the clinical impact of this testosterone decrease is uncertain, with contradictory evidence regarding its effects on male sexual function (39).

Although thyroid function tests may be abnormal due to CBZ use, treated patients remain clinically euthyroid. Because of the induction effect of CBZ on the metabolism of thyroid hormones, hypothyroid patients may require higher doses of T_4 to maintain euthyroid states (25).

Hyponatremia is an adverse event seen commonly by CBZ treatment. The risk for hyponatremia increases in proportion to the dose CBZ and age of the patient; it is unusual in children (25). Clinical significant hyponatremia, usually defined as sodium ≤125, is quite rare.

Weight gain is an occasional side effect associated with the use of CBZ, although it is nowhere near as pronounced as with VPA use (25)—typically in the range of 2 to 4 kg.

Teratogenic and Postnatal Effects

As with other established AEDs, CBZ exhibits teratogenic effects. CBZ exposure has also been associated with neural tube defects and major congenital malformations in monotherapy (40). Polytherapy with two or more agents significantly elevates the teratogenic risk. Despite uncertainty about the efficacy of periconceptional folate supplementation in women with epilepsy, most authors recommend its use at the same dosage as that recommended for the general population: 0.4 to 0.6 mg/day. Women taking CBZ should have prenatal diagnostic ultrasonography to detect any congenital malformations. The overall risk for CBZ causing major congenital malformation appears relatively low. Breast-feeding is considered safe for women being treated with CBZ.

A fetal AED exposure study revealed that CBZ is safer than VPA when cognitive outcomes at age 6 years are concerned (41). The North American AED Pregnancy Registry (40) assessed the safety of AEDs during pregnancy. The risk of major malformations was 3.0% for CBZ and 2.0% for lamotrigine, showing that CBZ is one of the safest AEDs during pregnancy (40). Nevertheless, when

efficacy is concerned, pregnancies exposed to lamotrigine were less likely to be seizure free than were pregnancies exposed to CBZ (42).

Clinical Use

CBZ is one of the agents of choice for the treatment of structural–metabolic and unknown cause focal epilepsies, as well as for generalized tonic–clonic seizures. CBZ is available as 100-mg chewable tablets; 200-mg tablets; and 100-mg, 200-mg, and 400-mg extended-release tablets for oral administration. CBZ is also available as a 100-mg/5 mL (60 mg/mL) oral suspension (9). Doses must be adjusted individually because of great variability in different epileptic syndromes and intra- and interindividual responses.

CBZ treatment should be initiated with 100 to 200 mg/day in adults and children >12 years of age. Increments up to an initial target dose of 400 to 800 mg (10 mg/kg) in adults (60 to 80 kg) (14,15,22) and changes at weekly intervals are preferred. Risk for AHS or rash is higher with rapid titration. Newly diagnosed patients usually require lower doses than those with chronic epilepsy.

For children under 6 years of age, CBZ treatment should be initiated with 10 to 20 mg/kg/day, with a twice-daily or thrice-daily regimen. Doses can be increased at weekly intervals to achieve doses below 35 mg/kg. If a satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the therapeutic range (9).

Maintenance dosage should be adjusted to the minimum effective level, usually 400 to 1200 mg daily in adults. Dosage generally should not exceed 1000 mg daily in children 12 to 15 years of age and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances (9). If seizures cannot be controlled, doses should be gradually increased by 100- or 200-mg increments until either control is achieved or unacceptable adverse events appear.

Although plasma level monitoring is a useful tool for the clinician, it has no definitive value. It is necessary to push the CBZ dose to the maximum clinically tolerated dose, independent of plasma level, in uncontrolled patients. Plasma level monitoring may be useful in the range of 4 to 12 mg/L (14). The dosage interval depends both on the severity of the epilepsy and on the difficulty with control. Most responsive patients, such as those newly diagnosed, need modest doses twice daily. If higher doses are necessary, however, toxicity may be avoided by taking CBZ three times per day. Two or three times per day provides similar levels, with fluctuations of 57% ± 20% and 56% ± 29%, respectively. In children, the interdose variation was 21% for patients receiving CBZ sustained-release and 41% for those treated with standard CBZ preparation. Children metabolize CBZ faster than do adults and thus may need higher doses. Elderly patients retain their sensitivity to dose-dependent autoinduction and heteroinduction by CBZ, but their metabolism rates remain considerably lower than those observed in matched controls. As a result, elderly individuals will require a lower dosage to achieve serum concentrations comparable to those found in nonelderly adults (14). In patients receiving doses that approximate the maximal tolerated doses, the use of sustained-release formulations of CBZ twice daily may minimize dose fluctuations and may help to adequately control seizures (25). On the other hand, a recent review does not confirm or refute the superiority of the sustained-release formulation with respect of seizure frequency in patients with newly diagnosed epilepsy. This study showed a trend for sustained-release CBZ to be associated with fewer adverse events when compared to immediate-release CBZ (43).

Precautions and Contraindications

CBZ should not be used in patients with a known hypersensitivity to any tricyclic antidepressant or to OXC. Use of CBZ can worsen some epileptic conditions by aggravating preexisting seizures or by leading to new seizure types, particularly absence and myoclonic seizures. An increase in the number of generalized seizures has been documented in children (14).

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis and Stevens–Johnson syndrome, have been reported with CBZ treatment. The risk of these events is higher in patients with a particular human leukocyte antigen (HLA) allele: HLA-B* 1502. This allele occurs almost exclusively in patients with Asian ancestry. The U.S. FDA (44) has recommended genetic screening for the HLA-B* 1502 allele in patients of Asian ethnicity before starting CBZ therapy.

Aplastic anemia and agranulocytosis have been reported in association with CBZ treatment. Patient with history of adverse hematologic reaction to any drug may be particularly at risk of bone marrow depression (9).

OXCARBAZEPINE

Absorption, Distribution, and Metabolism

Orally administered OXC is rapidly and almost completely absorbed, with absorption being largely unaffected by food. As discussed earlier, the pharmacologic effect of OXC in humans is exerted predominantly through its main metabolite, MHD, which is a racemic mixture of R(-) and S(+) enantiomers. This metabolic pathway accounts for its unique pharmacokinetic and pharmacodynamic profile (45,46) (see Fig. 51.1). OXC undergoes rapid and extensive metabolism via ketoreduction to MHD. Oral absorption of OXC is extensive (>95%) and rapid. At steady state, peak concentrations of MHD are seen within about 2 to 4 hours following drug ingestion. The half-life of OXC is 1 to 3.7 hours, and the half-life of MHD is 8 to 10 hours. As a lipophilic compound, MHD is widely distributed throughout the body and easily crosses the blood–brain barrier (47). The plasma protein binding of MHD is approximately 40%, which is less than that of CBZ (70% to 90%). Steady state is achieved after three to four doses. At steady state, the pharmacokinetics of OXC is linear over the dose range of 300 to 2400 mg/day (48). After oral administration of ^{14}C-labeled MHD, most of the dose is excreted in the urine within 6 days after dosing, <1% as unchanged drug (46). As with most AEDs, placental transfer of OXC appears to occur.

Drug Interactions

OXC exhibits no enzyme autoinduction and has a moderate potential for heteroinduction. Induction of the cytochrome P450 system is less pronounced with OXC than with CBZ (46,48). Therefore, polytherapy is much simpler with OXC. Levels of the MHD are not significantly modified by felbamate, LTG, PHT, or VPA (49). CBZ and PB may decrease levels of MHD, so dosage adjustments may be necessary (48).

Whereas CBZ induces many cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4), OXC is a weak inhibitor of CYP2C19 and a weak inducer of CYP3A4. Since CYP2C19 is involved in PHT metabolism, OXC may increase plasma levels of PHT. As the CYP3A subfamily is responsible for the metabolism of estrogens, oral contraceptive levels may be lower in patients receiving OXC therapy (49). The same precautions used with CBZ therapy apply to OXC therapy,

relative to coadministration with hormonal contraceptives.

Efficacy

Monotherapy

Most studies found OXC to be efficacious as monotherapy for patients with focal and generalized tonic–clonic seizures. OXC has a similar efficacy to CBZ, but with a more favorable tolerability profile (50).

In two large, similarly designed trials of previously untreated patients with recently diagnosed epilepsy, OXC was as effective as PHT (51) and VPA (52). A total of 287 adult patients with either focal or generalized tonic–clonic seizures were randomized in a double-blind, parallel-group comparison of OXC and PHT (51). In the efficacy analyses, no statistically significant differences were found between the treatment groups. Seventy patients (59.3%) in the OXC group and 69 (58%) in the PHT group were seizure free during the 48-week maintenance period (47). In the comparison of OXC and VPA (52), 249 adult patients with either focal or generalized seizures were randomized. As with OXC and PHT, no statistically significant differences were found between the treatment groups in the efficacy analyses. Sixty patients (56.6%) in the OXC group and 57 (53.8%) in the VPA group were seizure free during the 48 weeks of maintenance treatment (52).

A multicenter, double-blind, randomized, parallel-group trial compared the efficacy of two different doses of OXC as monotherapy in a refractory epilepsy patient population. In the intent-to-treat analysis, 12% of patients in the higher-dose (2400 mg/day) OXC group were seizure free, compared with 0% in the lower-dose (300 mg/day) OXC group (53).

In another monotherapy trial, OXC was compared with placebo in a double-blind, randomized, two-arm, and parallel-group design in hospitalized patients with refractory focal and generalized seizures. Both primary and secondary efficacy variables showed a statistically significant effect in favor of OXC (54).

In children and adolescents with newly diagnosed epilepsy, a double-blind, controlled clinical trial of OXC versus PHT showed that OXC was comparable to PHT in terms of efficacy, but had significant advantages over PHT in terms of tolerability and treatment retention (55). A total of 193 patients 5 to 18 years of age with either focal or generalized tonic–clonic seizures were enrolled. In the efficacy analyses, no statistically significant differences were found between the treatment groups. Forty-nine patients (61%) in the OXC group and 46 (60%) in the PHT group were seizure free during the 48-week maintenance period (55).

A long-term extension phase of two multicenter, randomized, double-blind, controlled trials (51,55) showed that the estimated seizure-free rate after 52 weeks on open follow-up was 67.2% with OXC and 62.2% with PHT. These 2-year studies revealed that the majority of patients were seizure free, suggesting an improvement in seizure control during the 2nd year of OXC monotherapy.

Adjunctive Therapy

Several adjunctive studies have shown that patients treated with OXC experienced a significantly greater reduction in focal seizure frequency than those treated with placebo (48).

Adverse Events

Monotherapy

The main adverse events associated with OXC treatment are CNS-related effects, gastrointestinal symptoms, and idiosyncratic reactions (50–56). The most common adverse events are somnolence, headache, dizziness, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait, and rash.

When OXC was compared with placebo (54), most adverse events with OXC were mild or moderate in intensity and similar to those with placebo. Adverse events reported at some time during the trial by ≥5% of all treated patients were headache, nausea, dizziness, pruritus, somnolence, diplopia, vomiting, fatigue, constipation, dyspepsia, and insomnia. Each of these adverse events occurred with greater frequency in the OXC treatment group. Three patients in the OXC group discontinued treatment prematurely—one for a transient rash, one for postictal psychosis, and one for an administrative reason. Two patients discontinued prematurely from the placebo group, both for administrative reasons.

The trial that compared OXC with PHT (51) showed that the number of premature discontinuations due to adverse experiences with OXC was significantly lower than that with PHT. Five of 143 patients in the OXC group discontinued treatment because of tolerability reasons—rash in one case, pregnancy in one case, an astrocytoma not previously diagnosed in one case, a suicide attempt with OXC intoxication in one case, and gastrointestinal discomfort combined with depression/anxiety in one case. Sixteen of 144 patients in the PHT group discontinued treatment because of tolerability reasons—rash in 10 cases, hirsutism/gum hypertrophy in 5 cases, and cerebellar symptoms/sedation in the last case. Somnolence, headache, dizziness, nausea, and rash occurred in ≥10% of the patients in both groups. Gum hyperplasia, tremor, diplopia, acne, nervousness, and nystagmus occurred in <10% of the patients in both groups (51). When differences in the incidence of adverse events were apparent between the groups, these were nearly all in favor of OXC therapy.

The comparison of OXC and VPA in 249 adults revealed no statistically significant difference between treatment groups with respect to the total number of premature discontinuations or those due to adverse events. The most frequent reason for withdrawal due to adverse events in the OXC group was allergic reaction with skin symptoms (6 patients); in the VPA group, it was hair loss (4 patients). The most common adverse events considered to have a causal relationship to the trial treatment were somnolence, weight increase, fatigue, headache, alopecia, dizziness, nausea, tremor, abdominal pain, impaired concentration, increased appetite, and diarrhea. When differences in incidence existed between the groups, these generally favored OXC treatment. Abnormally low plasma sodium levels were reported in two OXC-treated patients. Both patients were asymptomatic with respect to their low plasma sodium levels, and neither discontinued treatment prematurely (52).

In another study of OXC monotherapy for focal seizures, most of the adverse events were transient and rated as mild to moderate in intensity (53).

The trial that compared the efficacy and safety of OXC with that of PHT in 193 children and adolescents (55) found that two patients in the OXC group and 14 patients in the PHT group discontinued treatment prematurely for tolerability reasons. The number of premature discontinuations due to adverse events was statistically significantly lower in the OXC group than in the PHT group. Moreover, the odds of an individual discontinuing prematurely were almost twice as high in the PHT group. Based on the findings of this trial, the authors concluded that OXC has significant advantages

over PHT in terms of tolerability and treatment retention.

OXC therapy in elderly patients (≥65 years of age) seems as safe as treatment in younger adults. The four most common adverse events experienced by elderly patients were vomiting (19%), dizziness (17%), nausea (17%), and somnolence (15%). Three of 52 patients developed an asymptomatic hyponatremia, with at least one patient's serum sodium level <125 mequiv./L (56).

Adjunctive Therapy

The study that evaluated the safety of a broad OXC dosage as adjunctive therapy in patients with uncontrolled focal seizures (56) found that the most common adverse events were related to the nervous and digestive systems. Rapid and fixed titration to high doses was associated with an increased risk for adverse events, which could potentially be reduced by adjusting concomitant AEDs and using a slower, flexible OXC titration schedule.

The trial that compared the safety of OXC with placebo as adjunctive therapy in children with inadequately controlled focal seizures (56) found that 91% of the OXC group and 82% of the placebo group reported at least one adverse event. Vomiting, somnolence, dizziness, and nausea occurred more frequently in the OXC-treated group. The majority of these adverse events were mild to moderate in severity. The incidence of rash was 4% in the OXC group and 5% in the placebo group. Fourteen patients (10%) in the OXC group and 4 patients (3%) in the placebo group discontinued treatment prematurely because of adverse events. The most common reasons for discontinuation in the OXC group were adverse events involving the digestive system (primarily nausea and vomiting), which occurred in 5 patients, and rash (maculopapular and erythematous), which occurred in 4 patients.

Hyponatremia

Hyponatremia is usually defined as a serum sodium level <135 mequiv./L. Clinically significant hyponatremia (sodium level <125 mequiv./L) has been observed in 2.5% of OXC-treated patients in 14 controlled trials (48). Acute symptoms of hyponatremia include headache, nausea, vomiting, tremor, delirium, seizures, and decerebrate posturing, whereas chronic symptoms include anorexia, cramps, personality changes, gait disturbance, stupor, nausea, and vomiting (48). The 14 trials that evaluated 1966 patients showed that hyponatremia increased with age, from 0% at <6 years and 0.5% at <18 years to 3.4% between 18 and 64 years and 7.3% at >65 years (48,56,57). OXC-induced hyponatremia has not been attributable to the syndrome of inappropriate secretion of antidiuretic hormone. Possible mechanisms include a direct effect of OXC on the renal collecting tubules or an enhancement of their responsiveness to circulating antidiuretic hormone. Although hyponatremia has been reported, it is only rarely accompanied by clinical symptomatology and rarely leads to OXC discontinuation. The degree of hyponatremia seems to be related to the dose of OXC. Rapid titration may be another risk factor (57).

Other Potential Adverse Events

An analysis of 29 trials involving 2191 patients treated with OXC for up to 11.5 months showed no clinically significant weight changes in the OXC group compared with the placebo group (58). However, the authors have seen patients with weight gain that reversed with OXC substitution. This information is also described in very few other clinical trials (48).

OXC in monotherapy or combination therapy has no effect on blood pressure and electrocardiograms (48).

A few studies have evaluated the teratogenicity of OXC. The risk associated with OXC monotherapy in a recent study was 2.2% (40).

OXC does not appear to affect cognitive function in healthy volunteers or adults with newly diagnosed epilepsy. The cognitive effects of the agent in children and adolescents have not been systematically studied (59).

OXC, like CBZ, has been reported to aggravate some seizures in children (60). Clinical and EEG monitoring may be important, especially in patients who do not show adequate response to OXC.

Clinical Use

OXC is indicated for use as monotherapy or adjunctive therapy in the treatment of focal and generalized tonic–clonic seizures in adults and children 4 to 16 years of age and as adjunctive therapy in the treatment of focal seizures in children 2 to 16 years of age. OXC is available as 150-mg, 300-mg, and 600-mg film-coated tablets for oral administration. OXC is also available as a 300-mg/5 mL (60 mg/mL) oral suspension (48). It can be taken with or without food. An extended-release once-daily oral preparation became available in 2013 with 150-mg, 300-mg, and 600-mg tablets (61).

In adults, treatment with OXC monotherapy should be initiated at a dose of 300 to 600 mg/day. Increases at weekly intervals are advisable and titration should be planned according to the clinical condition of the patient, since slow and gradual initiation of therapy minimizes side effects. In the case of frequent seizures, the interval may be shortened (e.g., every 2nd day). Another option to achieve rapid therapeutic level of MHD can be a single loading dosage of 30 mg/kg (62). This study showed that oral loading of OXC is an effective and well-tolerated method for rapidly achieving therapeutic level of MHD.

The recommended monotherapy dosage is 600 to 1200 mg/day in two divided doses. OXC dosages range from 600 to 3000 mg/day. As adjunctive therapy, treatment with OXC should be initiated at a dose of 600 mg/day, administered as a twice-daily regimen. The recommended dosage for adjunctive therapy is 1200 mg/day or higher, if needed, which may be increased at weekly intervals. In controlled trials, most patients were not able to tolerate a 2400 mg/day dose, mainly due to CNS side effects (48).

In children, treatment should be initiated at a daily dose of 8 to 10 mg/kg administered as a twice-daily regimen. The target maintenance dose of OXC should be achieved over 2 weeks and is dependent upon the patient's weight (900 mg/day for 20 to 29 kg, 1200 mg/day for 29.1 to 39 kg, and 1800 mg/day for >39 kg). For patients under 20 kg, a starting dose of 16 to 20 mg/kg may be considered. The maximum maintenance dose should be achieved over 2 to 4 weeks and should not exceed 60 mg/kg/day in a twice-a-day regimen (48). The pharmacokinetics of OXC are similar in older children (>13 years of age) and adults. However, younger children (<13 years of age) have an increased clearance compared with older children and adults. Therefore, the OXC dose per body weight may be up to twice that of adults for children 2 to <4 years of age and 50% higher than the adult dose for children 4 to <12 years of age (48).

A multicentric study has shown improvement in the quality of life in patients with focal seizures after conversion to OXC monotherapy (63).

Therapeutic drug monitoring is claimed to be of little or no value with OXC because of the linear pharmacokinetics of the agent, although measuring drug levels is undoubtedly useful for

individualization of treatment in selected cases in a particular clinical setting. The plasma concentration associated with antiepileptic effect was reported to be 5 to 50 mg/L (46).

It is believed that there is no need to monitor sodium levels regularly in asymptomatic patients, unless there are special risks, such as in patients taking high doses or diuretics and in the elderly individuals. OXC is not a drug of first choice for the elderly patients (57).

ESLICARBAZEPINE

Pharmacology

In the acetate form in which it is marketed, ESL is essentially completely converted from the acetate form to eslicarbazepine proper by first-pass hydrolysis, with oral bioavailability of over 90% and peak plasma concentrations occurring 1 to 4 hours post dose. As discussed previously, it is the S-enantiomer that is believed to be primarily responsible for the anticonvulsant activity of either OXC or ESL. Protein binding of ESL is under 40%. The drug exhibits linear pharmacokinetics throughout the clinical dose range. The apparent volume of distribution for an average (70 kg) person was calculated as 61 L. Metabolites, including glucuronides of OXC and R-licarbazepine, account for only 9% of systemic exposure. Unlike CBZ, there is no autoinduction of metabolism, with elimination half-life ranging from 13 to 20 hours and remaining stable with chronic dosing. Excretion is renal, with eslicarbazepine and its glucuronide accounting for 90% of this and minor metabolites for the remainder.

The pharmacokinetics of ESL are similar in the elderly to the younger population, and the drug is not affected by mild or moderate hepatic dysfunction. Renal function has a substantial impact, however, with exposure increasing 60% to 100% and 150% for mild, moderate, and severe renal failure, respectively, leading to a formal recommendation that doses for the latter two groups should be halved.

Efficacy

A preliminary trial to assess the most appropriate dosing regimen for ESL (64) arrived at a very surprising result: not only was once-daily dosing fully effective, but twice-daily dosing (between 200 and 600 mg BID) failed to separate from placebo using the primary outcome measure.

As a consequence of this, the subsequent pivotal phase III adjunctive therapy trials were all done using once-daily dosing of ESL in adult patients with focal epilepsy. The first of these tested doses of 400, 800, and 1200 mg daily, with the result that the low dose did not separate from placebo, while the middle and higher doses were clearly effective in reducing seizure frequency; using the primary outcome measure, percentage reduction in seizures, there was essentially no difference in efficacy between those two doses (65). A second study, also using the same three doses in a once-daily fashion, produced very similar results, with the 400-mg dose not significantly effective and the 800-mg and 1200-mg doses significantly and equally effective (66). The third study utilized only the two higher doses, each of which resulted in a significant decrease in seizure frequency of about 40% (compared to 17% in the placebo group) (67).

Interestingly, the most common concomitant AED used in the population in these three studies was CBZ, and in at least two of the trials, analyses suggested no difference in efficacy when comparing patients taking ESL with CBZ to those taking ESL with other AEDs (65,66). All trials excluded

patients taking OXC. As is typical of regulatory trials, all of these were of relatively short duration (12 weeks); open-label extensions were performed, though those are uncontrolled and thus of uncertain value. A metaanalysis of these four trials found that the responder rate (chance of achieving a ≥50% reduction in seizures) was 36%, nearly double the rate in the placebo group, while the chance of seizure freedom over the trial was about 7%, three times higher than the placebo group (68).

Adverse Effects

Similar to OXC, side effects with ESL are almost entirely CNS-related: symptoms such as dizziness, somnolence, headache, diplopia, vertigo, and cognitive impairment were those most commonly reported in studies. The aforementioned metaanalysis of ESL trials found that the three adverse effects seen with drug significantly more often than with placebo were dizziness, nausea, and diplopia, each occurring about three times more commonly with ESL treatment than with placebo. Based upon the drug's mechanism of action, and clinical experience, one would expect that these effects would be more common when ESL is used with another sodium channel–blocking agent (e.g., CBZ, PHT, lamotrigine, lacosamide). Like all newer-generation AEDs, ESL carries a warning regarding suicidal thoughts and behavior based upon an FDA metaanalysis that clinicians in the field consider dubious at best.

Hyponatremia, seen sometimes with CBZ and frequently with OXC, occurs more rarely during ESL treatment, with clinically significant hyponatremia ($Na^+ \leq 125$) occurring in only 1% to 1.5% of patients. Elevations of liver function tests have been reported, though not hepatic failure. Again, like its cousins, ESL can cause serious allergic reactions, including Stevens–Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), and angioedema with anaphylaxis. Patients who have had an allergic reaction to CBZ or OXC should not be treated with ESL owing to the great similarity in structure between these agents and the potential for a dangerous reaction.

Total ESL exposure, as measured by the area under the time–concentration curve (AUC), is reduced by about a third in the presence of the enzyme-inducing AEDs PHT, CBZ, or PB. This is presumably due to induction of the UGT enzymes, which mediate glucuronidation of ESL. A higher dose of ESL may be necessary as a consequence (bearing in mind, with the former two agents, the potential for synergistic toxicity due to sodium channel blockade).

ESL appears to inhibit CYP2C19, which is prominently involved in the metabolism of PHT. PHT peak concentrations (C_{max}) and area under the curve (AUC) increased by about a third when ESL was given concomitantly. This may necessitate a PHT dose decrease; monitor levels and adjust accordingly. The drug reduces the AUC for topiramate by a modest amount (15% to 20%), but this may not be clinically important. The drug has no effect on other AEDs studied, including CBZ, PHT, PB, VPA, gabapentin, levetiracetam, lamotrigine, or clobazam.

As with its cousins CBZ and OXC, the potential for induction of CYP450 and other metabolic enzymes led to drug interaction studies. The good news is that ESL has no effect on metformin, digoxin, or warfarin (based upon coagulation parameters in the treated patients). The bad news is that, like its aforementioned relatives, ESL appears to significantly increase metabolism of the active components of oral contraceptives in a dose-dependent fashion, with the estrogen affected at the 800 mg ESL dose (decrease in AUC by 30%) and both the estrogen and progestin impacted at the 1200-mg ESL dose (AUC decrease by about 40%) (69). While some have advocated for the use of higher-dose contraceptive pills to overcome what is presumably due to CYP450 enzyme induction, there is

no convincing evidence for this, and in view of the serious potential consequences, this author's policy has always been to insist that a patient obtain either a new AED or a new contraceptive method.

There is somewhat more mixed news in the form of ESL's interaction with simvastatin. Plasma exposure to simvastatin is reduced by 50% to 60% in the presence of ESL, and the active metabolite of the simvastatin is reduced by 40% to 50%, presumably due to induction of CYP3A4 (69). However, a recent abstract suggested that, despite this, there seemed to be no effect on patients' lipid levels (70). Thus, the clinical impact of this interaction remains to be determined.

Clinical Use

ESL is presently approved for add-on treatment of focal epilepsy in patients age 18 and older. There are virtually no data regarding its use in children. Its similarity to CBZ and OXC would suggest that it is unlikely to be effective for generalized epilepsies and in fact could exacerbate them, as CBZ is known to do. The drug is not indicated to be used in combination with OXC because the studies did not include any OXC-treated patients.

The drug is manufactured in 200-mg, 400-mg, 600-mg, and 800-mg tablets, with all but the 400-mg tablet being scored. The formally approved titration schedule entails simply starting at 400 mg once daily and increasing to 800 mg daily in a week. As the 400-mg dose was not demonstrated effective in the trials, and 1200-mg showed little to no increased efficacy over the 800-mg dose (and a higher incidence of adverse effects), a dose of 800 mg daily seems the only reasonable target. Increase to 1200 mg daily may be considered if efficacy is inadequate and there are no tolerability issues, though it will take time to amass the clinical experience to determine if this is worthwhile.

Use of the drug is not affected by mild to moderate hepatic impairment (severe hepatic disease has not been studied). Renal insufficiency does have an impact, however, and both the initial and target doses should be halved in patients with moderate to severe renal impairment.

Pending more extensive clinical experience, it would seem prudent to prioritize the use of ESL with drugs that do not act on the sodium channel rather, as this might reduce the incidence of side effects. Further time and clinical data will be needed to ascertain this, as well as to ascertain whether the drug might have a place as early monotherapy for focal epilepsy.

CARBAMAZEPINE VERSUS OXCARBAZEPINE VERSUS ESLICARBAZEPINE

CBZ and OXC are among the most efficacious AEDs available. The literature suggests that CBZ and OXC do not differ in terms of seizure control efficacy. However, OXC has a better safety profile, including its association with fewer severe adverse events, such as idiosyncratic reactions, aplastic anemia, and agranulocytosis. Except for sodium monitoring under special circumstances with OXC treatment, laboratory monitoring of drug levels is not necessary. The OXC pharmacokinetic profile is also better than that of CBZ, with lack of autoinduction, low protein binding, and minimal drug interactions, except with contraceptive use. OXC does not appear to change endogenous hormonal levels—though it likely induces the metabolism of vitamin D (71)—and OXC also does not appear to affect serum lipids (72). These considerations suggest OXC should be considered one of the first-line treatment options for patients with focal seizures. According to the ILAE guidelines, OXC was considered a level A recommendation for efficacy and effectiveness as initial monotherapy for

children with focal seizures (23).

In some cases, a decision may be made to switch a patient from CBZ to OXC. This can either be done gradually or with a more abrupt changeover. Typically, the conversion ratio for similar efficacy is on the order of 1:1.5.

ESL is quite new as of this writing, and more clinical study and clinical experience will be needed to determine its appropriate place in epilepsy treatment algorithms. Both its efficacy and its tolerability relative to CBZ or OXC remain unassessed. ESL seems not to affect serum lipids [Sunovion, data on file], and it may have the more limited drug interaction profile of OXC, thus representing an improvement over CBZ with its diffuse metabolic effects. When comparing ESL to OXC, the former's once-daily dosing surely represents an advance with regard to convenience and compliance, and the reduced incidence of hyponatremia relative to OXC is also a clear improvement. Whether this or other considerations are sufficient to justify the difference in cost between patented ESL and generically available OXC remains to be determined. The imminent availability of once-daily sustained-release forms of OXC makes this calculus even more complex.

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CHAPTER 52 ETHOSUXIMIDE

ANDRES M. KANNER AND RAMSES RIBOT

INTRODUCTION

Ethosuximide (ETS) is one of the first-generation antiepileptic drugs (AEDs) that, despite the advent of several new AEDs, continues to maintain its position as a first-line treatment of absence seizures. Its narrow therapeutic profile has limited its use to the treatment of childhood absence epilepsy. Some studies have also suggested a potential therapeutic effect in epileptic negative myoclonus (1) and encephalopathy with status epilepticus during sleep (ESES) (2,3). In addition, data from several experimental animal models of pain suggest that ETS may have potential analgesic properties. Despite its 52-year existence in the market, additional research continues to further elucidate the mechanisms of action of this AED. The purpose of this chapter is to review the latest experimental and clinical data of ETS.

HISTORICAL BACKGROUND

The development of ETS was a response to the need in the 1950s to develop a more effective, safer, and better-tolerated anticonvulsant for the treatment of absence seizures (4). Introduced in the 1940s, trimethadione and its analog paramethadione were the first anticonvulsants to demonstrate efficacy against absence seizures, but they were associated with significant toxicity (5– 8). These toxicity issues spurred the discovery and testing in the 1950s of the succinimide family of anticonvulsants (ETS, methsuximide, and phensuximide) (8). Of the succinimides, ETS had the greatest efficacy and least toxicity when used against absence seizures (8). Because of this combination of efficacy and safety, ETS has been considered as first-line therapy for absence seizures since its introduction in 1958 (9,10).

CHEMISTRY

ETS (2-ethyl-2-methylsuccinimide), with a molecular mass of 141.2, is a chiral compound containing a five-member ring, with two negatively charged carbonyl oxygen atoms with a ring nitrogen between them and one asymmetric carbon atom (11,12) (Fig. 52.1). Its chemical characteristics include a melting point of 64°C to 65°C, a weakly acidic pK_a of 9.3, and a partition coefficient of 9 (chloroform-to-water; pH 7) (12). ETS is freely soluble in ethanol and water (solubility, 190 mg/5 mL) (10). Being a white crystalline material, ETS is used clinically as a racemate and is commercially available in 250-mg capsules or 250 mg/5 mL of syrup (9,11).

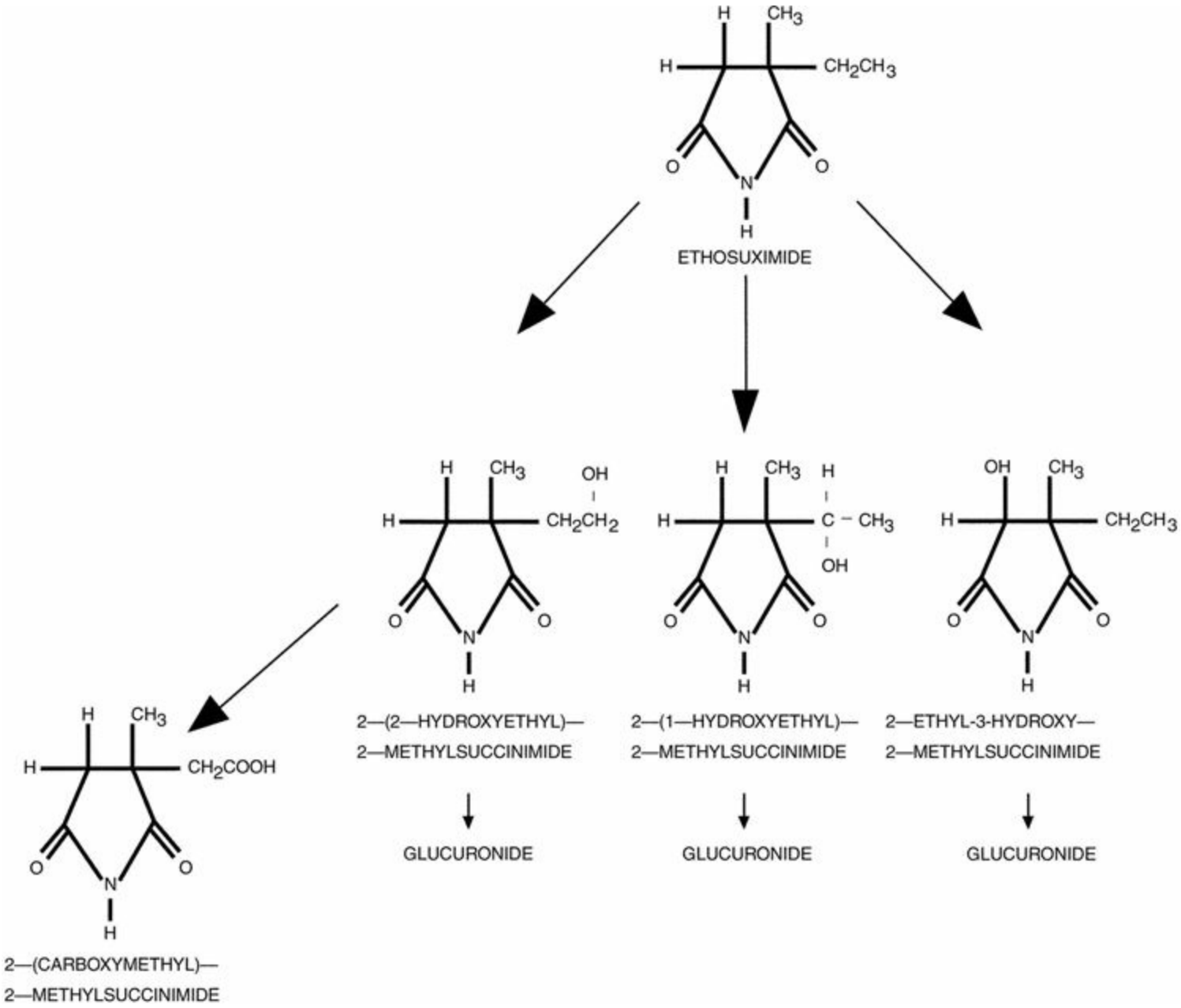

Figure 52.1. Structure and biotransformation pathways of ethosuximide. (From Pisani F, Meir B. Ethosuximide: chemistry biotransformation. In: Levy R, Mattson R, Meldrum B, eds. Antiepileptic Drugs. 4th ed. New York : Raven Press; 1995:655–658, with permission.)

MECHANISM OF ACTION

As stated above, in addition to its antiepileptic effect, ETS appears to have an analgesic effect.

Antiepileptic Effects

The presumed mechanism of action against absence seizures is reduction of low-threshold T-type calcium currents in thalamic neurons (13,14). The spontaneous pacemaker oscillatory activity of thalamocortical neurons involves low-threshold T-type calcium currents (15). These oscillatory currents are considered to be the generators of the 3-Hz spike-and-wave rhythms in patients with absence epilepsy (15). Voltage-dependent blockade of the low-threshold, T-type calcium current was demonstrated at clinically relevant ETS concentrations in thalamic neurons isolated from rats and guinea pigs (13,14,16). ETS does not alter gating of these T-type Ca^{2+} channels (8,14). Combining

these findings, it is proposed that ETS's effect on low-threshold, T-type calcium currents in thalamocortical neurons prevents the "synchronized firing associated with spike–wave discharges" (13).

In addition to the effects on voltage-dependent Ca^{2+} currents of the thalamus, studies have investigated the impact of ETS on GABA, on persistent Na^+ and sustained K^+ currents in cortical and thalamic neurons, and on G protein–activated inwardly rectifying K^+ channels. Here are some of the data.

The genetic absence epilepsy rats from Strasbourg (GAERS) have been identified as one of the ideal animal models of absence epilepsy (17). In this animal model, the frequency of spike-and-wave discharges is high with one-third of recorded EEG presenting as seizure activity. The use of ETS has been effective in stopping such epileptic activity (18). On this model, Polack and Sharpier conducted simultaneous in vivo electrocorticographic and intracellular recordings from the cortical focus of the GAER in which ETS had been administered at therapeutic concentration. The cessation of seizures mediated by ETS correlated with a recovery, in the hyperactive focus neurons, of physiologic values of membrane potential, firing rate, and pattern, thus converting the ictogenic cortical neurons into normal neurons (19). The impact of ETS on GABA was also investigated in this animal model by various investigators all of who recognize a pivotal pathogenic role of excess GABA in absence epilepsy (20). In one study, ETS was shown to reduce GABA concentration in the primary motor cortex of GAERS (21), confirming the findings from a previous study (18). The antiabsence effect of ETS has also been associated with an enhancement of synaptic inhibition of glutamate and GABA release (22).

Using a different animal model of absence epilepsy (WAG/Rij rats), investigators demonstrated the initiation of epileptic activity in the somatosensory cortex (23). Furthermore, the effect of infusion of ETS into thalamic nuclei (ventrobasal and reticular nuclei) was significantly lower than that seen with its infusion in the somatosensory cortex. The potential effect of ETS on GABA was also suggested in a study using a mouse with a mutation in the gamma2 subunit of the GABA receptor. Such mutation has been identified in childhood absence epilepsy and febrile seizures. Tan et al. developed a mouse model with a gamma2-subunit point mutation (R43Q) in a large Australian family. ETS blocked the 6- to 7-Hz spike-and-wave discharges and clinical events consisting of behavioral arrest recorded in mice heterogeneous for the mutation (24).

In cortical tissue, at concentrations significantly greater than those used for anticonvulsant effect, ETS inhibits Na^+, K^+-adenosine triphosphatase (Na^+, K^+-ATPase) activity (25– 29). Yet, one in vitro study suggested that ETS lowers the persistent Na^+- and Ca^{2+}-activated K^+ currents of layer V cortical pyramidal and thalamic relay neurons of rats and cats, but has no effect on the transient Na^+ current (30).

G protein–activated inwardly rectifying K^+ channels (GIRK) have been found to play an important role in the regulation of neuronal excitability (31). Using the Xenopus oocyte expression assay, Kobayashi et al. (31) demonstrated that ETS inhibited GIRK at clinically relevant concentrations and in a concentration- and time-dependent manner, but such inhibition was voltage independent during each voltage pulse.

Blumenfeld et al. demonstrated that an early treatment with ETS suppressed the development of absence seizures in WAG/Rij rats, through the blockade of changes in the expression of ion channels Nav1.1, Nav1.6, and HCN1. More importantly, ETS prevented seizure occurrence during its administration from age p21 to 5 months and even after its discontinuation (up to the age 8 months).

This model illustrates how early treatment during development may provide a new strategy for preventing epilepsy in susceptible animals (32). Similar findings were published by Russo et al., who used ETS or levetiracetam (LEV) in WAG/Rij rats approximately 3.5 months, starting before seizure onset (at age 1.5 months). In that study, both drugs reduced the development of absence seizures, thus exhibiting antiepileptogenic effects in this specific animal model. This antiepileptogenic effect of ETS is thought to be possibly linked to changes in Na^+ and HCN1 channel expression (33). In the GAERS model, Dezsi et al. randomized these rats to chronic therapy with either ETS or water from 3 to 22 weeks of age, followed by tap water for all rats for an additional 12 weeks. These investigators assessed the impact of ETS on the expression of key components of the epigenetic molecular machinery, the DNA methyltransferase enzymes. GAERS randomized to ETS exhibited a significant reduction in seizure occurrence during the treatment phase and for a 12-week posttreatment period. In addition, ETS treatment was associated with increased expression of DNA methyltransferase enzyme messenger RNA in the cortex. These data again suggest that chronic treatment with ETS can yield disease-modifying effects in the GAERS model of GGE, with antiepileptogenic effects against absence seizures through epigenetic modifications of cellular mechanism of this type of epilepsy (34).

Analgesic Effects

T-type Ca^{2+} channels appear to be important targets for treating persistent pain syndromes. Accordingly, various animal models of pain have suggested a potential analgesic effect of ETS (see section Efficacy).

Other Calcium Channel Antagonistic Properties

Based on the postulated idea that T-type calcium channel antagonists may effectively suppress tremor, Handforth et al. (35) found that five T-type calcium antagonists, including ETS, suppress tremor in two animal tremor models. It is possible that ethosuxamide's action on Na and K channel may have contributed to this effect. These findings open the possibility of ETS as a suitable target for developing new therapeutic strategies for treating tremor. However, this antitremor effect was not replicated in the parkinsonian tremor model in rats. No clear explanation was found for this finding given antitremor effect of similar calcium channel blockers with high transitivity to the brain such as zonisamide (36).

PHARMACOKINETICS

Implications of Racemic Mixture

ETS has always been used clinically as a racemate. It is theoretically possible that the two enantiomers could demonstrate different pharmacokinetic parameters or anticonvulsant effects. In rats, ETS's disposition is nonstereoselective (12). In chiral gas chromatographic analysis of enantiomer concentrations in plasma samples obtained for routine monitoring, 33 patients demonstrated that the enantiomer ratio was close to unity, and there was little interindividual variability (37). This implies that the disposition of ETS in humans is nonstereoselective and that measurement of total ETS for therapeutic monitoring is reasonable and appropriate (12,38). A small study (three pregnancies in two women taking ETS) demonstrated that the nonstereoselective

disposition was unaffected by pregnancy, placental transfer, or passage into breast milk (38).

ABSORPTION

In rats, dogs, and monkeys, absorption is rapid, with nearly complete oral bioavailability in dogs (88% to 95%) and monkeys (93% to 97.5%) (39–44). In children and adults, absorption is considered to be rapid and nearly complete (90% to 95%), even though no intravenous formulation can be used as a reference standard to determine absolute bioavailability in humans (4,43,45,46). Absorption is reported to remain efficient over multiple administrations (43). In two single-dose capsule administration studies, three volunteers given a single 1-g oral dose and four healthy adults given a 0.5-g oral dose, peak ETS plasma concentrations were reached between 1 and 4 hours after administration (44,46,47). A separate study with five institutionalized children that compared capsules and syrup demonstrated peak plasma concentrations within 3 to 7 hours with either formulation (10,43–45,48). The syrup had a faster absorption rate than the capsules, but the two formulations were bioequivalent (9,10,43–45,48).

DISTRIBUTION

Tissue Distribution

In rats, ETS distributes evenly to the brain, plasma, and other tissues, except for adipose tissue (in which steady-state concentrations are approximately one-third of those reached in plasma) (43). ETS crosses the placenta in rats (44,49) and, in dog and rat studies, readily passed through the blood–brain barrier (39,44). In dogs, the plasma–to–cerebrospinal fluid (CSF) ratio was 1.01 ± 0.15, with an estimated half-life of entry into the CSF at about 4 to 5 minutes (39,43,44,50). In one study in rats, the whole brain to plasma ETS concentrations ratio was near unity, whereas a second study in rats found uniform distribution in four discrete brain areas (cerebral cortex, cerebellum, midbrain, and pons medulla) (42,44). However, a third study in rats receiving a single intraperitoneal (I.P.) dose of 50 mg/kg found a decrease in brain-to-plasma concentrations over time, suggesting that ETS may be actively transported out of the rat brain (43,51).

In humans, ETS homogeneously distributes throughout the body (9). Saliva, tears, and CSF concentrations are similar to plasma concentrations (43,44,52–57). In three studies (involving 6, 15, and 19 patients), the respective correlations between saliva and serum concentrations were R = 0.99, R = 0.99, and R = 0.74 (55–57). A fourth study, which examined concentrations in paired parotid saliva and plasma samples from 10 patients, showed the average saliva-to-plasma ratio to be 1.04, which appeared constant over the measured time intervals (54). In light of these results, multiple studies have concluded that saliva can be used in lieu of plasma for therapeutic monitoring of ETS (44,52,54–58).

ETS crosses the placenta in humans and has been detected in cord serum and amniotic fluid at concentrations of 104% and 111% of maternal serum concentrations, respectively (9,59). In two separate reports, ETS was detected in either the urine or plasma of a newborn of a woman receiving long-term therapy (44,60,61). The serum concentration in the newborn was similar to that in the mother (43,61). ETS is excreted in the breast milk of mothers receiving long-term therapy (43). In multiple studies, the average breast milk–to–maternal serum concentration ratio ranged from 0.8 to

0.94 (43,61–64). The ETS serum concentration of breast-feeding infants of mothers given long-term therapy was 30% to 50% of their mothers' serum concentration (43,63,64). The American Academy of Pediatrics, however, considers ETS to be usually compatible with breast-feeding (65).

Volume of Distribution and Protein Building

The apparent volume of distribution in rats, dogs, and rhesus monkeys ranges from 0.7 to 0.8 L/kg (39,40,43,66). In humans, ETS's apparent volume of distribution is 0.62 to 0.65 L/kg in adults and 0.69 L/kg in children, implying distribution through total body water (9,43,45,46,53).

ETS protein binding is 0% to 10% in humans, dogs, and rats (37,43,45,48,52,67).

METABOLISM AND EXCRETION

Animals

Metabolism is the main method of ETS elimination in animals. In rhesus monkeys and rats, the drug and its metabolites are excreted predominantly by the kidney, with only a small proportion recovered in the feces (43,49). Unchanged ETS accounts for only 12% of urinary recovery in rats (68).

In rats, biotransformation is catalyzed predominantly by hepatic cytochrome P450 (CYP)3A isoenzymes, with possible minor contributions by CYP2E, CYP2B, and CYP2C isoenzymes (12,43,65,69,70,71). These CYP enzymes are inducible, and autoinduction has been reported in rats (43,65). The major metabolite in rats and monkeys is 2-(1-hydroxyethyl)-2-methylsuccinimide, and the two minor metabolites are 2-ethyl-3-hydroxy-2-methyl-succinimide and 2-(2-hydroxyethyl)-2-methylsuccinimide (43,72). ETS provided complete protection against pentylenetetrazol-induced clonic seizures in mice at a dose of 125 mg/kg; in contrast, the major metabolite demonstrated "no significant anticonvulsant activity" (72).

Elimination appears to follow first-order kinetics in animals, except in dogs, in which Michaelis–Menten kinetics may apply (39,43,72). Studies of single- and multiple-dose ETS administration in monkeys have demonstrated comparable elimination half-life and total body clearance (9,40,41). In animals, elimination half-lives range from 1 hour in mice to 9 to 26 hours in rats and 11 to 25 hours in dogs (39,43,72). Steady-state plasma concentrations are significantly higher in the morning than in the evening in rhesus monkeys receiving intravenous ETS at a constant rate. These fluctuations may result from circadian changes in ETS-metabolizing enzymes (43,72,73).

Humans

As in animals, metabolism is the main method of ETS elimination in humans. ETS undergoes extensive hepatic oxidative biotransformation (80% to 90%) to pharmacologically inactive metabolites. Although most of the remaining drug is excreted unchanged in the urine, small amounts of unchanged ETS can be recovered from bile and feces (74). ETS oxidation is catalyzed mainly by enzymes of the CYP3A subfamily (9). In vitro studies with humanized heterologous CYP microsomal systems showed that ETS is primarily oxidized by CYP3A4, with CYP2E1 playing a minor role in its metabolism (75).

The major metabolite recovered from human urine in patients receiving ETS is 2-(1-hydroxyethyl)-2-methylsuccinimide, of which at least 40% is excreted as a glucuronide conjugate

(12,75). Two other metabolites recovered (often as a glucuronide conjugate) from human urine are 2-ethyl-3-hydroxy-2-methylsuccinimide and 2-(2-hydroxyethyl)-2-methylsuccinimide. The latter metabolite can undergo subsequent metabolism by the hepatic mixed-function oxidase system to form the fourth major metabolite, 2-carboxymethyl- 2-methylsuccinimide (12,72,75) (see Fig. 52.1).

In humans, ETS's elimination follows first-order kinetics. Total body clearance in adults averages 0.01 L/kg/h (46) and in two children was 0.016 and 0.013 L/kg/h (45). This is significantly lower than hepatic plasma flow (0.9 L/kg/h) implying that ETS does not undergo a significant first-pass effect and that drug clearance is not blood flow limited (43,44). Total body clearance has been reported to decrease slightly after repeated dosing (43). ETS does not induce hepatic microsomal CYP enzymes or the uridine diphosphate glucuronosyltransferase (UDPGT) system (67,76,77). In humans, in contrast to rats, autoinduction does not occur (77,78).

In general, ETS has a long elimination half-life that varies with age. Its mean half-life in adults reportedly ranges from 40 to 60 hours, compared with 30 to 40 hours in children (45–47,53,72,78–81). Large variations have been observed in pediatric studies, with half-lives ranging from 15 to 68 hours (44,72,79). In neonates, half-lives ranging from 32 to 41 hours have been reported (61,63). The time to reach steady-state concentration after a dosage change is 6 to 7 days for children and 12 days for adults (9,82). ETS clearance is reported to be lower in women than men (83). Dose size and repeated dosing do not affect the elimination half-life (53,79).

The effects of liver and renal disease on ETS elimination have not been formally studied (43). It would seem that liver disease would impair ETS elimination because of the drug's substantial hepatic oxidative metabolism, whereas renal disease would have much less impact on ETS elimination (43). Hemodialysis can readily remove ETS. One report estimated that approximately 50% of the body's ETS was removed over a 6-hour dialysis interval and that the drug's half-life dropped to 3 to 4 hours during dialysis (43,84). In a separate case report, peritoneal dialysis decreased ETS concentrations in a child taking ETS and phenobarbital (85).

DRUG INTERACTIONS

Interactions with Other Antiepileptic Drugs

ETS's lack of effect on either the hepatic microsomal CYP enzymes or the UDPGT system, along with negligible protein binding, indicates a low potential for drug interactions (67,82). Most investigators conclude that ETS therapy does not have a clinically significant effect on the pharmacokinetics of phenytoin, phenobarbital, or carbamazepine, despite scattered reports of some changes in phenytoin or phenobarbital concentrations when ETS is used in combination with phenytoin or primidone (9,86–93). There is no alteration in the plasma protein binding of carbamazepine or phenytoin when ETS is used concomitantly, nor is there a change in the formation of phenobarbital from primidone (94). One study reported a significant decrease in valproic acid (VPA) serum concentration after the addition of ETS (120.0 ± 20.1 μg/mL before ETS vs. 87.0 ± 13.1 μg/mL during cotherapy with ETS; $P < 0.01$). After cessation of ETS, VPA levels rose to 36.7%. The mechanism underlying this observed effect is unknown (95).

In a review of the available literature, Czuczwar et al. (96) suggested a potential anticonvulsant synergy between ETS and valproic acid. In another study that investigated the interactions between several AEDs in suppressing pentylenetetrazole-induced clonic seizures in mice by the use of type II

isobolographic analysis, the combinations of VPA and ETS with LEV at the fixed ratio of 1:2 were found to have a supra-additive (synergistic) effect in suppressing seizures, while VPA and ETS with LEV (1:1, 2:1, and 4:1) were additive. Of note, ETS was found to significantly reduce brain LEV concentrations, and ETS and LEV have been suggested by some authors (97).

In contrast, because of ETS's extensive hepatic oxidative metabolism by CYP isoenzymes, concomitant therapy with enzyme-inducing AEDs would be predicted to increase ETS's total clearance (93). ETS's clearance is significantly accelerated (leading to a drop in the serum concentration) when the drug is used concurrently with phenobarbital, phenytoin, or carbamazepine (67,93,98–101). In one study, discontinuation of concomitant carbamazepine therapy increased ETS plasma concentrations by 48% (102). The magnitude of this effect may vary considerably among patients (98).

The effect of concomitant therapy with VPA on the pharmacokinetics of ETS is variable, with studies showing increases, decreases, or no change in ETS clearance (67,78,81,90,103–105). Some investigators postulate that VPA may inhibit the metabolism of ETS, leading to an increase in the plasma ETS concentration (106).

Whenever an AED–ETS interaction could occur, serum concentration and clinical response of both AEDs should be monitored. No formal pharmacokinetic interaction studies have examined potential ETS interactions with felbamate, gabapentin, lamotrigine (LTG), tiagabine, topiramate, oxcarbazepine, levetiracetam, or zonisamide.

Interactions with Nonantiepileptic Drugs

The clearance of ETS is substantially increased when it is used in combination with rifampin, an inducer of CYP3A isoenzymes (100). In contrast, concomitant use with isoniazid, a potent inhibitor of CYP isoenzymes, resulted in increased ETS serum concentrations and psychotic behaviors (107).

EFFICACY

Antiepileptic Effects

Animal Models

ETS exhibits very different efficacy profiles in the two major traditional animal models of epilepsy—the maximal electroshock test (MES) and the pentylenetetrazol seizure test. The MES is used to identify agents able to prevent the spread of seizures and has been hypothesized to identify agents effective against partial-onset and generalized tonic–clonic seizures (8,108). ETS was ineffective against MES-induced tonic seizures, except at anesthetic doses (8,108–110), but ETS blocked clonic seizures produced by subcutaneously administered pentylenetetrazol or bicuculline (8,108,110,111). These chemically induced seizure models are hypothesized to identify agents that raise the seizure threshold and may be effective against absence seizures. ETS's activity profile suggests that the drug exerts its anticonvulsant effects by raising the seizure threshold rather than by blocking the spread of seizures, and it predicts efficacy against absence rather than partial-onset or generalized tonic–clonic seizures.

ETS demonstrated activity against spontaneously occurring absence seizures in three other animal

models (mutant tottering mice, Wistar rats, and spontaneously epileptic rats) (112–114), as well as activity against spike–wave seizures induced by systemic administration of α-hydroxybutyrate (108,115,116).

Humans

Monotherapy Trials.

The efficacy of ETS as an effective monotherapy against childhood absence epilepsy had been taken for granted for many years, following two studies conducted in the 1970s strongly suggesting the efficacy of ETS in childhood absence epilepsy (117,118). Efficacy against typical partial seizures was examined in a study with a well-constructed method for patient selection and assessment. Each patient's absence seizure was required to meet a predetermined clinical definition and be witnessed by the principal investigator. Seizure frequency was then assessed by five separate measures: the ward's staff observation, trained observer's observation, mother's observation, physician's observation (including during patient hyperventilation), and standardized video-electroencephalographic (video-EEG) recording. These measures were combined into a "seizure index" (117). Thirty-seven patients were enrolled. By the eighth week of treatment, 19% (7 of 37 patients) were seizure free, with a 100% reduction in seizure index. Overall, during ETS therapy, 49% (18 of 37) of patients demonstrated at least a 90% reduction in seizures, and 95% (35 of 37) had a 50% or more reduction. The full antiabsence effect occurred within a week for any given ETS dose. Plasma ETS concentrations ranged from 16.6 to 104.0 μg/mL (doses of 6.5 to 36.7 mg/kg) and, on the basis of the seizure index, the investigators suggest that the optimal ETS plasma concentrations in this study were 40 to 100 μg/mL (117).

The second major study was a prospective, longitudinal, open-label investigation that used therapeutic drug monitoring to maximize clinical response (118). Seventy patients were enrolled; 54% (38 of 70) were female, with ages ranging from 4 to 28 years (median, 12 years). Thirty-eight patients (54%) had only absence seizures. The remaining patients had either absence seizures with tonic–clonic seizures (30%) or absence seizures, and one or more other generalized seizure types (16%). Approximately 50% of the patients were taking other AEDs in addition to ETS. Patients received between 9.4 and 73.5 mg/kg/d of ETS and were evaluated at 6-month intervals. Introduction of ETS therapy completely controlled seizures in 47% (33 of 70) of the patients. None of these patients had plasma ETS concentrations below 30 μg/mL; only 9% were below 40 μg/mL (119). During the next 2.5 years, attempts were made to achieve plasma ETS concentrations above 40 μg/mL in the remaining 53% (37 of 70) of patients with uncontrolled absence seizures. Improved compliance and higher dosages led to significantly higher ETS plasma concentrations in 19 patients, 10 of whom became seizure free. At the 2.5-year follow-up, 61% (43 of 70) of the group was seizure-free. In these patients, ETS's effectiveness persisted over the next 2.5 years of follow-up (total, 5 years). In contrast, ETS was not able to control absence seizures in patients with both absence seizures and tonic–clonic seizures who were receiving combination AED therapy (118).

Three randomized, controlled, prospective trials have compared ETS and VPA as monotherapy for absence seizures (119–121), and a Cochrane Review reexamined the results (122). A parallel, open study enrolled 28 drug-naive patients, between 4 and 15 years of age, who had typical absence seizures, and followed them up for a mean of 3 years (range, 18 months to 4 years) (119). The relative risk (RR) estimate with 95% confidence interval (CI) for seizure freedom (RR < 1 favors

ETS) was 0.70 (95% CI, 0.32 to 1.51); the RR estimate for 50% or more reduction in seizure frequency was 1.02 (95% CI, 0.70 to 1.48). The outcomes were confirmed by 6-hour telemetry and clinical observation. Although no difference was apparent for either outcome, the CIs were wide; the possibility of important differences could not be excluded, and equivalence of ETS and VPA could not be inferred (119,122).

Another trial of similar design enrolled 20 patients between 5 and 8 years of age whose simple absence seizures had begun <6 months before (120). Follow-up lasted for 1 to 2 years, and outcomes were confirmed by clinical observation and EEG. Again, wide CIs and the possibility of important differences precluded confirmation of equivalence of ETS and VPA. All patients achieved at least a 50% reduction in seizure frequency (120,122).

A double-blind, crossover study used a complex response–conditional design and recruited 45 patients between 4 and 18 years of age (123). The enrollment included both treatment-naive patients and those with drug-resistant disease. Some had only absence seizures; others had other seizure types as well. In the first phase of this trial, patients were assigned to receive either ETS with placebo VPA or VPA with placebo ETS for 6 weeks. Responders continued with the randomized drug for a further 6 weeks. This group included treatment-naive patients who became seizure free and previously treated patients who had an 80% or more reduction in seizure frequency. Nonresponders and those with adverse effects were crossed over to the alternative treatment and followed up for another 6 weeks. No differences emerged between therapies, but the CIs were wide, and equivalence could not be inferred. The reduction in seizure frequency, determined by a 12-hour video-EEG telemetry, was 100% for the drug-naive group and 80% for the drug-resistant group.

Yet, the efficacy of ETS as a "first-line treatment" was demonstrated in an initial 16- to 20-week, multicenter, randomized, double-blind, controlled study that compared the efficacy and tolerability of ETS, VPA, and LTG given as monotherapy in 446 children with Childhood Absence Epilepsy (123). At the end of the 16- to 20-week period, ETS and VPA yielded comparable seizure freedom rates (53% and 58%, respectively) compared to 29% for LTG. Yet, attentional problems were more frequent with VPA (49%) than ETS (33%). On the other hand, discontinuation related to adverse events failed to differ among the three AEDs.

The study was continued for 12 months, by which time 37% of all enrolled subjects were free from treatment failure (no seizures, no significant adverse event leading to discontinuation), with rates for ETS and VPA continuing to be comparable (45% and 44%, respectively) and higher than that for LTG (21%) (124). More children on LTG discontinued because of poor efficacy, while 42% of the 115 children discontinuing due to adverse events was among those on VPA. The higher rate of attentional dysfunction identified at 16 to 20 weeks in children on VPA compared with those on ETS and LTG continued to be present at 12 months. The last new AED guidelines of the International League Against Epilepsy recognized that the data proving efficacy/effectiveness evidence as initial monotherapy for CAE met the criterion for a level A evidence (125).

In a retrospectively study of 128 children with CAE at the Seoul National University Hospital, investigators compared the seizure-free rate and the retention rate observed during 2 years of treatment (126). After 3 months, children on ETS were more likely to achieve seizure freedom (84%) than those on VPA (62%) and LTG (53%), but this difference disappeared at 9 and 12 months (ETS, 77%; VPA, 83%; and LTG, 64%). Furthermore, the drug AEDs failed to differ in retention rate throughout the whole treatment period and adverse event rates (ETS, 25%; VPA, 29%; and LTG, 14%); this study suggested that the onset of efficacy was faster for ETS compared with VPA or LTG.

ETS in Polytherapy.

Combination therapy with ETS and VPA for absence seizures resistant to either drug alone was reported in one open-label study of five patients (127), and many investigators subsequently recommended this combination for patients with absence seizures resistant to monotherapy (10,48,82,128). Similarly, ETS in patients with both absence and tonic–clonic seizures should be combined with another AED effective against tonic–clonic seizures, such as VPA, carbamazepine, or phenytoin (10,82,128). Despite being reported as "highly effective" against atypical absence seizures (82,128), ETS is almost always used as part of combination therapy for patients with atypical absence seizures because of the high incidence of coexisting seizure types (10).

ETS has been found to be useful in the prevention and treatment of absence status epilepticus at serum concentrations >120 μg/mL (129,130), and there are anecdotal reports of effectiveness in severe myoclonic epilepsy in infancy (131), childhood epileptic encephalopathy (Lennox–Gastaut syndrome) (7,132), juvenile myoclonic epilepsy (133,134), epilepsy with myoclonic absences (134), eyelid myoclonia with absences (134), photosensitive seizures (135), gelastic seizures (48,136), frontal absence seizures (137), epilepsy in Angelman syndrome (138), nonconvulsive status epilepticus in mucopolysaccharidosis type II (139), and nonconvulsive seizures after brain injury (140). No controlled studies have investigated ETS's effectiveness against simple partial, complex partial, or partial secondarily generalized tonic–clonic seizures.

Epileptic negative myoclonus consists of an interruption of tonic muscle activity, which is time locked to an epileptic EEG abnormality, without evidence of an antecedent positive myoclonia in the agonist–antagonist muscles (1). It can be identified in various types of seizure disorders, including idiopathic, cryptogenic, and symptomatic epileptic disorders. It has been suggested that ETS may be effective in epileptic negative myoclonus associated with childhood idiopathic partial epilepsy. Capovilla et al. (141) reported a remission of the motor disorder in nine patients after the addition of ETS to other AEDs. Furthermore, Oguni et al. (142) reported total remission of epileptic negative myoclonus in 6 of 10 patients with the use of ETS.

ETS has been used in the treatment of encephalopathy with status ESES or continuous spikes and waves during slow sleep syndrome. In a recent retrospective study with these syndromes, ETS was reported to yield a favorable response when given in combination with other drugs and steroids (2,3). Accordingly, these findings remain equivocal.

Analgesic Effects

Animal Models

Barton et al. (143) investigated the effect of ETS in acute and persistent nociceptive tests in the rat. Intraperitoneal administration of ETS reversed capsaicin-induced mechanical hyperalgesia in a dose-dependent manner. In addition, ETS produced antinociceptive effects in the rat tail-flick reflex test and displayed significant analgesic effects in both early- and late-phase formalin-induced behaviors. Similar findings were reported by Shannon et al. (144). Of note, in this study, ETS increased the doses of pentylenetetrazol required to produce both first twitch and clonic seizures, thus showing that the analgesic effects can be obtained at doses that yield an anticonvulsant effect.

Todorovic et al. injected ETS intradermally into peripheral receptive fields of sensory neurons in the hind paws of adult rats and studied pain perception using the model of acute thermal nociception;

ETS induced dose-dependent analgesia in the injected paw but not in the contralateral (noninjected) paw (145). These findings suggest an analgesic effect mediated at peripheral nerve endings of rat sensory neurons.

Flatters and Bennett demonstrated the analgesic properties of ETS in an animal model using male Sprague Dawley rats, to which four I.P. injections of 2 mg/kg paclitaxel were administered on alternate days (146). Paclitaxel is a chemotherapeutic agent known to produce neuropathic pain and sensory abnormalities in patients treated with this agent both during therapy and after its discontinuation. The development of mechanical and cold allodynia/hyperalgesia was demonstrated with behavioral assessment using von Frey filaments and acetone. ETS administered by I.P. route at doses of 450 mg/kg yielded a near complete remission of mechanical allodynia/hyperalgesia. No tolerance of the analgesic effect was found following repetitive dosing with I.P. ETS at doses of 100 or 300 mg/kg daily for 3 days. Furthermore, I.P. administration of ETS at doses of 300 mg/kg also reversed paclitaxel-induced cold allodynia and vincristine-induced mechanical allodynia/hyperalgesia. Of note, paclitaxel-induced pain was resistant to opioid therapy. Similar results were suggested by Hamidi et al. (147) also in the Sprague Dawley rats, using the chronic constriction injury model of neuropathic pain with ETS blocking tactile and thermal hypersensitivity and potentiating the analgesic effects of morphine in neuropathic pain conditions and behavioral responses.

Finally, Wang and Thompson demonstrated an analgesic effect of ETS in an animal model of central pain syndrome (148). These investigators created unilateral electrolytic or demyelinating lesions in the spinothalamic tract of the spinal cord of rats resulting in thermal hyperalgesia and mechanical allodynia in all four paws that were attenuated significantly with the administration of ETS. Clearly, ETS appears to have analgesic properties in various animal models of pain.

Human Studies

There have been no open or controlled studies that have investigated the analgesic efficacy of ETS in humans.

ADVERSE EFFECTS

Effects That Depend on Concentration

The incidence of adverse effects due to ETS in initial published reports in 1952, 1958, and 1961 was very low, ranging from 1% to 9%; subsequent studies have indicated an incidence ranging from 31% to 44% (118,149–155). Most adverse effects depend on concentration and are related to the primary and secondary pharmacologic effects of the drug. These reactions are usually predictable, dose dependent, and host independent; they resolve with dose reduction (156,157).

The most common ETS concentration-dependent adverse effects involve the gastrointestinal system and include nausea (the most common), abdominal discomfort, anorexia, vomiting, and diarrhea (4,10,48,149,150,158). Between 20% and 33% of children experience these symptoms, usually at the onset of therapy (48,158). Symptoms are considered mild and respond promptly to dose reduction (48,149,150,158). Techniques to reduce the symptoms include dividing the total daily dose and administering the smaller doses at mealtime (9).

Central nervous system (CNS)-related adverse events (e.g., drowsiness) are the second most

common form of ETS concentration-dependent adverse events. Drowsiness usually occurs at the onset of therapy and responds promptly to dose reduction (9,149,150,158). Other CNS-related adverse events include insomnia, nervousness (12% of children), dizziness, hiccups, lethargy, fatigue, ataxia, and behavior changes (e.g., aggression, euphoria, irritability, hyperactivity) (10,158). A direct relationship between ETS therapy and these reported behavioral changes is not certain, because poor methodology (e.g., lack of reliable methods for objectively measuring behavior changes, confounding variable of polypharmacy, and lack of serum AED measurements) makes analysis of existing reports difficult at best (149,150).

Few trials have examined the potential cognitive effects of ETS in a controlled fashion, accounting for confounding variables such as plasma concentrations, underlying mental retardation, concomitant AEDs, or seizure type. In one early report, psychometric testing of 25 children receiving ETS for various seizure types revealed memory, speech, and emotional disturbances (159). However, no plasma concentrations were measured, all the patients were also taking barbiturates; 60% of the cohort had intelligence quotient (IQ) scores below 83; and no matched control group was used (159). In a cohort of children without epilepsy but with learning disorders, and 14- and 6-Hz positive spikes on EEG recording, administration of ETS significantly improved verbal and full-scale IQ scores, without changing motor performance or personality test scores (160).

In a well-designed study, psychometric performance improved significantly over 8 weeks of ETS therapy in 17 (46%) of 37 children with absence seizures (119). This improvement was significantly greater than that of a control group tested in the same fashion over the same interval. Only 25% of the study group had IQ scores below 83, and only 32% were receiving other AEDs.

Dreifuss (149,150) reported a probable dose-dependent, ETS-related granulocytopenia that often resolves with dose reduction without the need to terminate therapy. Distinction between this probable adverse event and ETS-associated idiosyncratic bone marrow depression (see section Idiosyncratic Reactions) is critical. Careful clinical and laboratory monitoring are essential in making this decision.

Effects That Do Not Depend on Concentration

Some ETS adverse effects do not appear to be concentration dependent, but are also not idiosyncratic reactions in the usual sense. Headaches, reported in 14% of children, may not respond to dose reduction and may persist (9,149,150,158,161).

Episodes of psychotic behavior (i.e., anxiety, depression, visual hallucinations, auditory hallucinations, intermittent impairment of consciousness, and mania) have been noted with ETS (149,162–166) and are most likely in young adults with a history of mental disorders (9,149). The acute psychotic episodes appeared after ETS-induced seizure control with associated EEG improvement, and they resolved when ETS was stopped and seizures returned, illustrating the phenomenon of forced normalization (9,149). Psychotic symptoms have recurred when ETS was restarted in patients with previous ETS-related psychotic episodes (149). This forced normalization reaction is not dose dependent and, among all antiabsence AEDs, occurs with highest frequency with ETS (9,167).

Most studies find no evidence of ETS-associated seizure exacerbation (118,149,153,168,169); however, scattered reports describe exacerbation of myoclonic and absence seizures and transformation of absence into “grand mal” seizures in patients receiving ETS (149,151,170). Dreifuss considered this exacerbation effect to be a consequence of the high incidence of generalized

tonic–clonic seizures in patients with absences seizures, coupled with ETS's lack of efficacy against generalized tonic–clonic seizures (149). Furthermore, Anyanwu et al. reported a case of conversion of typical absence to Rolandic spikes after treatment with ETS. However, it is not clear if this represents the simultaneous presence of these two common childhood idiopathic epilepsies as a continuum or a drug-induced conversion (171).

Calcium channel blockers, including ETS, have been shown to negatively affect spermatogenesis and steroidogenesis in the prepubertal mouse testis. Lee et al. showed a significant reduction in body weight, testis size/weight, and sperm production when feeding ETS and nifedipine to prepubertal male mice for 20 days at dosages below maximum tolerated. The authors suggest these drugs must be used with caution due to its potential adverse side effects on male infertility (172). There have been no human studies or reports, however.

Idiosyncratic Reactions

Idiosyncratic drug reactions are unpredictable, dose-independent, host-dependent reactions that are not associated with the known pharmacologic effects of the drug; they can be serious and life threatening. Preclinical animal toxicologic testing may not detect these reactions, and often they cannot be reproduced in animal models (156,157). In general, the skin is the most commonly affected site, followed by the formed elements of the blood and liver and, to a lesser extent, the nervous system and kidneys (156,173). These reactions may be organ specific or may manifest with generalized nonspecific symptoms, such as lymphadenopathy, arthralgias, eosinophilia, and fever (156,174). Idiosyncratic reactions are believed to result from toxic metabolites that cause injury directly or indirectly (i.e., through an immunologic response or free radical-mediated process) (175).

ETS has been associated to various degrees with a wide array of idiosyncratic reactions (149,150,158,176), including allergic dermatitis, rash, erythema multiforme, Stevens–Johnson syndrome (177), systemic lupus erythematosus (178–180), lupus–scleroderma syndrome (181), a lupus-like syndrome (182), blood dyscrasias (aplastic anemia, agranulocytosis) (118,155,168,183–190), dyskinesia (191,192), akathisia (191), autoimmune thyroiditis (193), and diminished renal allograft survival (194).

Mild cutaneous reactions, including allergic dermatitis and rash, are the most common ETS-associated idiosyncratic reactions. They frequently resolve with withdrawal of the drug, but some patients may require steroid therapy. Patients who develop Stevens–Johnson syndrome, a potentially life-threatening condition, require more aggressive in-hospital therapy.

The symptoms of the lupus-like syndrome are described as fever, malar rash, arthritis, lymphadenopathy and, on occasion, pleural effusions, myocarditis, and pericarditis (149). After discontinuation of ETS, these patients usually fully recover, but the recovery may be prolonged (149).

The manifestations of ETS-associated blood dyscrasias range from thrombocytopenia to pancytopenia and aplastic anemia (118,155,168,183–188). Between 1958 and 1994, only eight cases of ETS-associated aplastic anemia were reported, with onsets of 6 weeks to 8 months after initiation of therapy (187). Six patients were receiving polypharmacy; five were taking phenytoin or ethotoin in combination with ETS (187). Despite therapy, five of the eight patients died (118,155,168,183–188).

Long-Term Effects

Adverse effects resulting from long-term therapy are related to the cumulative dose (156,157). Severe

bradykinesia and parkinsonian syndrome have been reported after several years of ETS treatment (154,195).

Delayed Effects

In mice, ETS exhibits considerably less teratogenic effect than carbamazepine, phenytoin, phenobarbital, or primidone (196). In humans, because ETS is predominantly indicated for absence seizures, which frequently remit before child-bearing years, little is known about the risks that maternal use poses to the fetus (149). Not enough data are available to accurately assess the teratogenic effect of ETS in humans.

CLINICAL USE

Indications

ETS is regarded as effective first-line monotherapy against typical absence seizures. ETS may be the first choice in children younger than 10 years old with absence epilepsy, but as adolescence approaches and the risk of generalized tonic–clonic seizures increases, VPA clearly becomes the drug of choice in males (197). Because of the potential serious teratogenic effects of VPA and its negative impact on reproduction functions, LTG should be considered as an alternative in woman. In addition, ETS as adjunctive therapy may be beneficial for patients whose absence seizures are not controlled by VPA or LTG monotherapy, patients with both absence and tonic–clonic seizures, and patients with atypical absence seizures (10,48,82,125,197). No evidence supports a role for ETS as monotherapy or adjunctive therapy in patients with only simple partial, complex partial, or partial secondarily generalized tonic–clonic seizures.

Starting and Stopping

A common starting dosage for children is 10 to 15 mg/kg/d with subsequent titration to clinical response (9,10). Maintenance dosages frequently range from 15 to 40 mg/kg/d (82). In older children and adults, therapy can begin at 250 mg/day and increase by 250-mg increments until the desired clinical response is reached. The interval between dosage changes for older children and adults varies from 3 days (10) to every 12 to 15 days (9). Common maintenance doses for older children and in adults are 750 to 1500 mg/day (9,10). In elderly patients, titration should involve smaller increments with longer intervals between changes (10). After a dosage change, steady-state concentration is reached in 6 to 7 days in children and 12 days in adults (9,82). ETS can be administered once, twice, or even thrice daily (with meals) for maximum seizure control with minimum adverse effects (9,10).

If intolerable side effects without seizure control or 2 or more years' freedom from absence seizures occur, discontinuation may be warranted, with gradual reduction over 4 to 8 weeks (9,10). If necessary, abrupt discontinuation is probably safe because of ETS's long half-life (10).

Monitoring

ETS should always be titrated to maximal seizure control with minimal side effects. The generally

accepted therapeutic range is 40 to 100 µg/mL (9,10); some patients with refractory seizures or absence status may need serum concentrations up to 150 µg/mL (10). Monitoring ETS's serum concentration may help to identify noncompliance and aid in maximizing seizure control (119).

There is no evidence that monitoring of blood count values during therapy anticipates the drug's idiosyncratic hematologic reactions. Patients must alert their physicians immediately if fever, sore throat, and cutaneous or other hemorrhages occur (149). However, one recommendation for monitoring is that "periodic blood counts be performed at no greater than monthly intervals for the duration of treatment with ETS and that the dosage be reduced or the drug discontinued should the total white blood cell count fall below 3500 or the proportion of granulocytes below 25% of the total white blood cell count" (149).

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CHAPTER 53 EZOGABINE (RETIGABINE)

SCOTT MINTZER

INTRODUCTION

Ezogabine was first developed as a new agent for the treatment of focal seizures under the name retigabine, and then the appellation was changed in the United States to avoid confusion with the antiparkinsonian agent rotigotine. As an allosteric modulator of KCNQ2-5 potassium channels, ezogabine is believed to take advantage of a mechanism of action that had not previously been leveraged by other antiepileptic medications.

PHARMACOLOGY

Ezogabine is a structurally novel compound (Fig. 53.1) consisting of two aromatic rings—one with a fluorine atom and the other with a carbamic acid ethyl ester side chain, linked by an amino group between them, carrying the chemical name N-[2-amino-4-(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester. It is a white, odorless, tasteless powder, insoluble in water at room temperature except in highly acidic environments, but somewhat more soluble in organic solvents.

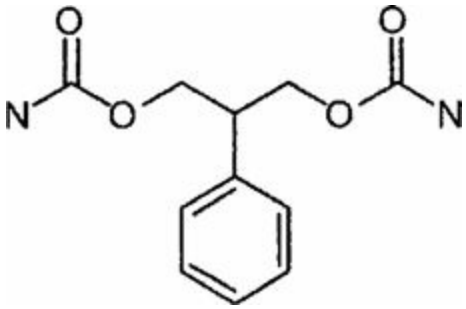

Figure 53.1. Chemical structure of ezogabine/retigabine.

Interest in the drug began with a compound called flupirtine, developed in Europe as an analgesic but demonstrating some modest anticonvulsant activity (1). An attempt was made to modify this molecule to maximize the latter effect, resulting in the development of retigabine/ezogabine. Early evidence of preclinical efficacy in animal models of epilepsy was rapidly followed by mechanistic studies that first excluded traditional epilepsy pharmacologic targets as sites of action and then revealed evidence that the drug acted as an opener of neuronal potassium channels (2,3). The discovery and cloning of the KCNQ-type potassium channels and their link to epilepsy (4) led subsequently to the discovery that ezogabine has potent effects on this channel family (2) and thus recognition that the compound was clearly acting via a heretofore undescribed mechanism. While one may establish that a compound reduces seizures and that it has certain pharmacologic properties, there may still be no definitive basis to connect the latter to the former. In the case of ezogabine, both the physiologic activity of the drug and the connection to seizure predisposition are clear enough that

it is widely believed that its true mechanism of anticonvulsant action is established.

Ezogabine's primary activity is as an allosteric modulator of KCNQ2-5 potassium channels. This type of channel is assembled from four subunits, which may be the same type or two different types. The predominant type of KCNQ channel in the brain includes both subunits 2 and 3, called KCNQ 2/3, and ezogabine has greater affinity for this one than it does for channels that include KCNQ4 or KCNQ5 subunits. KCNQ channels are also present in nonneurologic tissues, but ezogabine has no effect on KCNQ1, the type found in cardiac tissue, which presumably explains the drug's lack of cardiac effects (2). When it binds to the allosteric modulation site on the channel, it reduces the threshold for the channel to open and keeps the channel open three to four times longer, resulting in greater potassium efflux from the neuron and more negative membrane potential (i.e., hyperpolarization), which reduces action potential generation and retards the development of synchronous electrical discharges (i.e., seizures).

Confirmation of the importance of KCNQ2/3 in epilepsy comes from the observations that loss-of-function mutations in the genes coding for these subunits are strongly associated with the syndrome of benign familial neonatal convulsions (4) and that even modest reductions in the expression of these genes results in an epileptic diathesis (5). These findings, the impact of potassium channel opening on neuronal physiology, and the lack of effect on other molecular targets of epilepsy at physiologic doses all make it likely that the allosteric modulation of brain potassium channels is the true source of ezogabine's anticonvulsant activity.

PHARMACOKINETICS AND DRUG INTERACTIONS

Ezogabine is rapidly absorbed, with peak plasma concentrations being reached in about 1.5 hours, and has an oral bioavailability of about 60% (6). High-fat foods delay absorption somewhat and can increase the maximum concentration reached just over a third but do not affect overall extent of absorption, so that the drug can be given without respect to meals. Concomitant ingestion with alcohol may increase ezogabine peak concentrations and overall systemic exposure by 20% to 30%. Ezogabine is 80% protein bound in serum, with a volume of distribution of 2 to 3 L/kg. Ezogabine has an elimination half-life of about 7 hours in patients with normal renal function.

About 60% of a dose of ezogabine is metabolized, mainly by hepatic glucuronidation and to a lesser extent by acetylation, mostly to inactive metabolites but also to an N-acetyl metabolite (called NAMR, where the R stands for retigabine) that possesses some modest antiepileptic activity. Ezogabine is metabolized by UGT1A1 and UGT1A9 to form two distinct N-glucuronides. Multiple UDP-glucuronosyltransferases appear to be involved in the metabolism of ezogabine and include UGT1A1, 1A4, and 1A9, while acetylation is mediated by NAT2 (7). The cytochrome P450 isozyme system does not participate in its metabolism. Renal excretion accounts for about 36% of an oral dose of the parent molecule and 18% of NAMR.

Ezogabine neither inhibits nor induces the major CYP450 enzymes involved in drug metabolism, so as expected, it has no effect on the metabolism of other antiepileptic drugs (AEDs) with the exception that it causes an increase of approximately 20% in lamotrigine clearance; both the mechanism for, and the clinical significance of, this effect remain unknown. The drug has no effect on oral contraceptives (or vice versa). Coadministration of carbamazepine or phenytoin results in about a one-third increase in clearance and a corresponding one-third decrease in the area under the curve

for ezogabine, engendering a formal recommendation that a higher dose should be considered in this clinical circumstance. Curiously, phenobarbital, which like the two aforementioned agents is a potent UDP-glucuronyltransferase (UGT) inducer, does not affect ezogabine at all nor do any other anticonvulsants, including valproate.

Ezogabine is neither a substrate for nor an inhibitor of P-glycoprotein, although renal clearance of digoxin (a P-glycoprotein substrate) was reduced by NAMR in a concentration-dependent manner, suggesting that this metabolite is a modest P-glycoprotein inhibitor.

EFFICACY

Demonstration of ezogabine's efficacy has come in the form of three pivotal trials, each done for adjunctive treatment of focal epilepsy in a randomized, double-blind, placebo-controlled fashion. The first of these was a dose-finding study in patients aged 16 years and over, with three different treatment arms consisting of ezogabine at total daily doses of 600, 900, or 1200 mg (8). The lower dose did not separate from placebo, while the 900- and 1200-mg doses did, using either the Food and Drug Administration–preferred percent seizure reduction or the European Medicines Agency–requested 50% responder rate as the outcome. The former measure showed a steady increase with increasing dose (−13.1% for placebo vs. −23.4%, −29.3%, and −35.2%, respectively), while the latter measure showed no real change between the 900- and 1200-mg doses (31.6% and 33.0%, respectively, vs. 15.6% in the placebo group).

Two further placebo-controlled trials were performed in comparable populations, one comparing the 600- and 900-mg doses to placebo and one comparing the 1200-mg dose to placebo. The former study (9) showed dose–response efficacy, this time with both doses significantly superior to placebo using either percent seizure reduction (−27.9% and −39.9%, respectively, vs. −15.9% with placebo) or 50% responder rate (38.6% and 47.0%, respectively, vs. 18.9% with placebo). The latter study had similar placebo outcome rates, and outcomes with 1200 mg daily were comparable to those seen using 900 mg in the other trial (44.3% seizure reduction, 44.4% responder rate) (10). These results are in the range seen with other compounds in phase III trials for focal epilepsy. Seizure-free rates in all arms of both of these trials were minimal (2% to 4.7%), likewise in keeping with results seen with other drugs in the highly treatment-resistant clinical epilepsy trial population.

A combined analysis of the data from all three of the aforementioned trials was subsequently published (11), confirming that all three doses were effective, there was a moderate increase in efficacy with the step-up in dose from 600 to 900 mg, and that there was only modest evidence of further efficacy at 1200 mg when compared to 900 mg. The difference between the higher two doses was greater when efficacy was examined during the maintenance phase, rather than throughout the entire double-blind phase, suggesting that a gradual titration period exhibiting less efficacy may have contributed to obscuring some of the difference between the higher doses. None of the pivotal studies performed subanalyses of different seizure types, so extant data must be assumed to apply broadly to the category of focal seizures with or without secondary generalization.

ADVERSE EFFECTS

Most of the adverse effects of ezogabine that emerged from clinical trials were central nervous system related (11). The most common of these were dizziness, somnolence, fatigue, ataxia, dysarthria, and confusion (along with other forms of cognitive impairment). All of these showed a

clear and continuous increase in incidence with increasing dose, indicating that they were true effects of the drug. Tremor was also seen at higher doses, and this was observed consistently in the pivotal trials. There was no evidence of adverse behavioral effects. There may be a modest and dose-dependent tendency to produce some weight gain, with significant (≥7% of body weight) gain seen in 11% (low or medium dose) and 18% (high dose) of patients (compared to 1% in the placebo group). Like all newer-generation AEDs, ezogabine carries a warning regarding the risk of suicidal thoughts and behavior derived from the results of an FDA meta-analysis.

Ezogabine has been associated with two serious adverse effects, including urinary retention and retinal and cutaneous discoloration. Researchers were alerted to the possibility of urinary complications during clinical trials, because the KCNQ2/3-type potassium channel, the type most commonly found in the brain and impacted by the drug, is also found quite prominently in the bladder. In the placebo-controlled trials, urinary complications were categorized as urinary retention, urinary hesitation, and dysuria, and they occurred in 0.9%, 2.2%, and 2.3% of ezogabine-treated patients, respectively (compared to 0.5%, 0.9%, and 0.7% of patients on placebo). When data from the placebo-controlled trials and the open-label extensions were combined, 29 of 1365 patients, or 2.1%, developed urinary retention, generally within the first 6 months of treatment but sometimes later. Five of these 29 patients required bladder catheterization, and 2 of them developed hydronephrosis, with 1 of these developing renal failure with spontaneous resolution following drug withdrawal. Of the five, one had spontaneous resolution of the urinary retention, but one patient continued to require intermittent self-catheterization even after discontinuation of ezogabine; of note, this patient had a prior history of drug-induced urinary retention. Ezogabine-induced urinary retention showed no gender bias, and the relative risk for urinary side effects relative to placebo was elevated only for those taking the 1200-mg dose, with no apparent increased risk for those taking 900 or 600 mg daily (12).

As an accessory urinary issue, crystals of an unknown, bilirubin-like substance were observed in 15% of ezogabine-treated patients in clinical trials, but they were not actually made of bilirubin, and there is no clear evidence that the drug is associated with nephrolithiasis at present.

The other serious adverse effect, described in a “black box” warning on the label, is that of retinal and cutaneous discoloration. This was publicly documented by the FDA in April 2013, 1 year after the drug was released to the market. This adverse effect may be divided into two forms. The first consists of skin discoloration, usually bluish in color, most commonly of the lips or nail beds, but also seen less often in the eyes (sclera, conjunctiva, eyelids), the face, the palate, or the legs. It was found in 6.3% of 605 patients as of the FDA’s original report. The second form, the subject of the formal warning, consists of pigmentary deposits on the retina. This is assumed to be related to the skin deposits, though they are not always seen together. The retinal abnormality resembles that seen in retinal pigment dystrophies—conditions that cause functional retinal damage—and the first patients observed to have this were thought to have retinal dystrophy until subsequent spontaneous reports made it apparent that this was an adverse drug reaction. Some of the patients with these deposits had less than normal visual acuity, but none of these had acuity documented prior to initiation of ezogabine therapy, and given the high prevalence of abnormal vision, it remains unclear whether or not the deposits were themselves productive of visual compromise.

The large majority of patients with discoloration of the skin or retina had been on ezogabine for 2 years or more, and in a group of patients taking ezogabine for about 4 years, one-third of those who had ophthalmic examinations were found to have retinal deposits. However, at least one patient developed skin discoloration after only 10 months’ exposure to the drug. Because the functional

impact of the retinal findings is unclear, and because it is unclear whether the retinal (or skin) changes are reversible with discontinuation of the drug, the FDA has formally recommended that patients should undergo ophthalmologic screening before starting ezogabine and subsequently every 6 months.

CLINICAL USE

Ezogabine is indicated for adjunctive treatment of focal seizures in patients aged 18 years and over. Because of concerns over the potential impact of retinal pigment deposits, its indication is specifically for those patients who have failed to respond sufficiently to other agents.

The drug comes in 50-, 200-, 300-, and 400-mg tablets; the former should be used for initial titration and the larger sizes for maintenance therapy at the target dose. Ezogabine must be dosed on a TID schedule (13). It is initiated at 100 mg TID, with weekly increases of 50 mg TID up to the target dose of 200 to 300 mg TID. It is formally approved for dosing up to 400 mg TID, but given only moderate evidence of increased efficacy at that dose, with a clear-cut worsening in tolerability, this dose should probably not be an initial therapeutic target. For those with moderate or severe renal or hepatic impairment, and for the elderly, a modified dosing regimen is recommended, beginning with 50 mg TID and increasing by 50 mg TID each week to a maximum of 200 to 250 mg TID. There is no information on the drug in pregnancy.

Ezogabine was given a designation as a Schedule V–controlled substance due to the occurrence of euphoric mood in a minority of substance abusers who were given the drug in testing. This designation is shared by pregabalin and lacosamide, drugs that some clinicians believe to have low abuse potential.

As mentioned previously, baseline and semiannual ophthalmic exams are now mandated when using the drug, and because of concerns about potential retinal toxicity, it is formally recommended that the drug be discontinued if there is insufficient benefit from its use. These recommendations are reminiscent of those for vigabatrin, which also may cause visual toxicity but can be effective for children with infantile spasms (14). If it is found that the retinal toxicity from ezogabine adheres to a certain subgroup that could be screened prior to initiation of treatment, then this would also be advantageous.

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CHAPTER 54 FELBAMATE

EDWARD FAUGHT

HISTORICAL BACKGROUND

Felbamate (FBM) is historically significant as the first of a new generation of antiepileptic drugs (AEDs) introduced in the 1990s. It was synthesized in the 1950s as one of a series of dicarbamates. Meprobamate, another drug in this series, was marketed as one of the first nonbarbiturate tranquilizers. FBM has no tranquilizing action and found no immediate clinical use. In the 1970s, it was submitted to the National Institutes of Health (NIH) AED-screening program. After impressive results in animal seizure models (1), FBM entered human clinical trials in 1985 (2–6). It was only modestly effective as adjunctive therapy for refractory partial-onset (focal) seizures, but results of later monotherapy trials were very positive (7,8). In the United States, FBM was approved for both adjunctive and monotherapy use for partial-onset seizures in 1993. Dangerous side effects were not anticipated based on the experience of 2100 patients enrolled in clinical trials, but in 1994, FBM was linked to cases of aplastic anemia and liver failure (9), and prescription numbers plummeted. FBM remains available for patients with refractory seizures who respond poorly to other medications. Patients on long-term therapy are often quite loyal to the drug, citing its nonsedating quality. An estimated 6000 to 10,000 patients are currently taking FBM in the United States (Gever L, personal communication, 2013).

CHEMISTRY AND MECHANISMS OF ACTION

Chemistry

FBM (2 phenyl-1,3-propanediol dicarbamate, molecular weight 238.24) differs from meprobamate by having a phenyl group, rather than an aliphatic chain, at the 2-carbon position (Fig. 54.1). It is lipophilic and relatively insoluble in water (10).

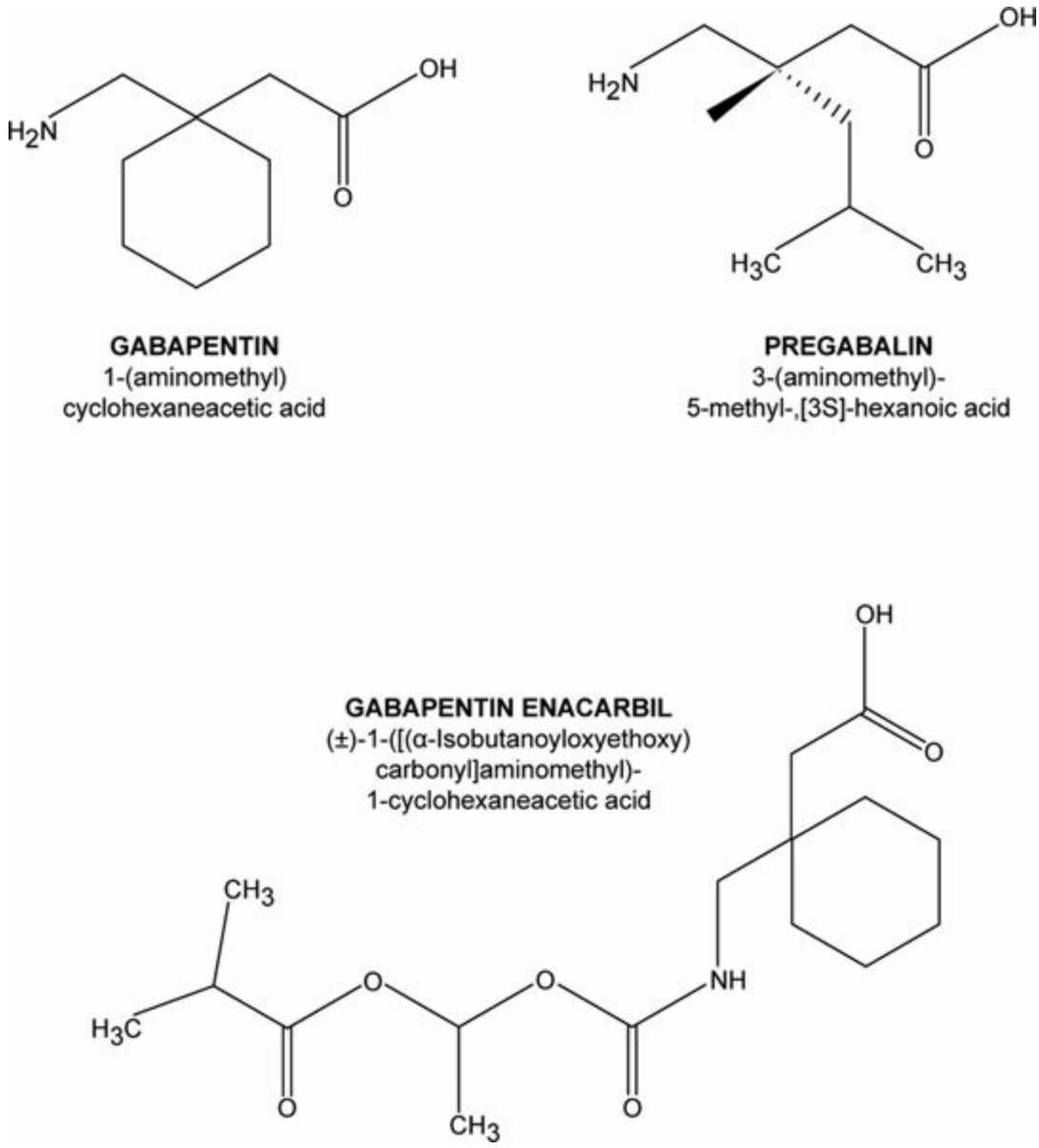

Figure 54.1. Structure of felbamate.

Antiepileptic Profile in Animals

FBM displayed high protective indices (toxic $dose_{50}$/effective $dose_{50}$) against the tonic phase of both maximal electroshock seizures (MES) and subcutaneous pentylenetetrazol-induced seizures in rodents (1). It is effective in amygdala-kindled, phenytoin (PHT)-resistant rats (11).

Mechanisms of Action

FBM binds to open ion channels of the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor (12) and may also modulate NMDA receptor function by binding to an associated strychnine-insensitive glycine receptor (13). These actions inhibit sodium and calcium excitatory currents. The NMDA effect of FBM is unique among available AEDs. Binding is more specific to receptors containing the N2RB subunit of the glutamate receptor (14,15). Subtype specificity may account for the lack of serious neurobehavioral complications and impairment of learning, which might be expected of NMDA receptor blockers (16).

FBM may also affect non–NMDA-type glutamate channels (17), voltage-gated sodium channels

(17), high-threshold voltage-sensitive calcium currents (18), and GABA-mediated chloride current inhibition (19).

The antiglutamatergic mechanism may imply neuroprotective effects: FBM reduced neuronal damage in a rat model of hypoxia–ischemia (20), protected CA1 hippocampal neurons from apoptosis in a gerbil ischemia model (21), and exhibited neuroprotective effects in a rat model of status epilepticus (22).

ABSORPTION, DISTRIBUTION, AND METABOLISM

FBM is well absorbed; more than 90% of ^{14}C-labeled FBM, or its metabolites, is recovered in urine and feces after oral administration (23). The rate and extent of absorption are not affected by food or antacids (24). Protein binding in human plasma is low, 22% to 25% (23). FBM readily crosses the blood–brain barrier (25).

Of the absorbed FBM dose, 30% to 50% is excreted in the urine unchanged (23). The remainder —more if there is renal insufficiency—is metabolized by the liver, utilizing CYP3A4 and CYP2E1 isozymes (23). Clearance in children is up to 40% higher in comparison to adults (26) but does not decrease significantly in the elderly (27).

In humans, FBM exhibits linear first-order kinetics over a dose range of 1200 to 6000 mg/day (28). Peak plasma concentration is reached 3 hours after an oral dose (23). Monotherapy with FBM 3600 mg/day produced a mean trough plasma level of 78.4 μg/mL (range, 23.7 to 136.6 μg/mL) in one study (7) and a mean (±standard deviation) level of 65 (±23) μg/mL after 112 days in another (8).

The mean terminal elimination half-life of 20 hours (range, 13 to 23 hours) in monotherapy decreases to 13 to 14 hours in the presence of phenytoin (PHT) or carbamazepine (CBZ) (3). The apparent volume of distribution is 0.8 L/kg (3,29). Steady-state plasma levels are achieved in 4 days (29).

EFFICACY

FBM is approved for use in the United States as either adjunctive therapy or monotherapy for patients older than 14 years of age with partial seizures, with or without generalization, and as adjunctive therapy for patients of any age with Lennox–Gastaut syndrome and its component seizure types (29).

Partial-Onset Seizures

Early clinical studies of FBM employed standard adjunctive trial designs. Adding FBM to CBZ (4,5) or to PHT (4) in outpatient trials produced modest reductions in seizure frequency. An adjunctive therapy trial among patients in an inpatient seizure monitoring unit produced a more encouraging result (6). The primary end point was time to occurrence of a fourth seizure or 29 days, whichever came first. Of patients randomized to adjunctive placebo, 88% had a fourth seizure, compared to 46% taking adjunctive FBM ($P = 0.03$) (6). Nevertheless, the authors of a Cochrane review concluded that there is “no reliable evidence to support the use of FBM as an add-on therapy in patients with refractory partial-onset epilepsy” (30). A flaw in this conclusion is that CBZ and PHT strongly induce the metabolism of FBM, and it is possible that suboptimal FBM concentrations were achieved

in those three trials (4–6). The efficacy of FBM when added to newer non–enzyme-inducing drugs has not been tested in humans, although a synergistic effect with levetiracetam was shown in a mouse MES model (31).

In 1988, new monotherapy designs for AED trials were proposed in a workshop sponsored by the NIH (32). Clinical investigators of FBM were the first to use these designs. The presurgical design was repeated as a monotherapy trial, and results suggested good efficacy (33). In two outpatient monotherapy trials, standard therapy was withdrawn over 28 days, while FBM 3600 mg/day or valproate (VPA) 15 mg/kg/day was substituted (7,8). The VPA control requires explanation: it was a compromise between a placebo control, considered unsafe, and a flexible dose active control, which could have reduced the chance of detecting a difference (34). This design has been criticized as violating the concept of equipoise, but 15 mg/kg/day is the recommended starting dose for VPA. Therefore, patients were randomized to a drug with unknown efficacy—FBM—or to the recommended initial dose of a drug with proven efficacy for their seizure type—VPA. The end point, "escape" (treatment failure), was defined individually for each patient according to predetermined criteria, including doubling of seizure frequency during any 2-day or 30-day period compared to the pretreatment baseline. Patients were removed from the trial at once if one of the end points were met. Patients taking low-dose VPA met escape criteria more often than did FBM-treated patients (86% vs. 14%, respectively, of 42 patients in the single-center study (7); 78% vs. 40%, respectively, of 95 patients in the multicenter study (8). Experience with partial-onset seizures in children is limited.

Lennox–Gastaut Syndrome and Other Seizure Types

FBM 45 mg/kg/day was used as adjunctive therapy, most often as an adjunct to valproate, in a multicenter, double-blind, controlled trial of 73 patients with a diagnosis of Lennox–Gastaut syndrome (35). Atonic seizures (drop attacks) were reduced by 34% and all seizures by 19%, versus a 9% decrease and a 4% increase, respectively, with placebo. During a 12-month, open-label follow-up, seizure frequency decreased by 50% with adjunctive FBM, compared to 15% with adjunctive placebo (36).

Infantile spasms may respond (37). Among 38 children with severe intractable epilepsies (22 Lennox–Gastaut syndrome, 6 Doose syndrome, and 10 other syndromes), FBM rendered 16% seizure free and 63% experienced a reduction of >50% in seizure frequency (38). Children younger than 4 years of age with various seizure types have sometimes responded well (39).

DRUG INTERACTIONS

Skillful use of FBM requires knowledge of several drug interactions. Primary references for these interactions are available from a review article (40). Clinically significant interactions are summarized in Table 54.1. FBM often acts as an enzyme inhibitor, especially of the cytochrome P450 2C19 isozyme. FBM therefore increases serum levels of many other drugs, including phenobarbital, PHT, and warfarin. FBM raises VPA levels by inhibiting its beta oxidation. Typical clinical toxicities of concomitant drugs, such as ataxia with PHT, may occur when FBM is added. The FBM/CBZ interaction is unusual: when FBM is added to CBZ, levels of CBZ decrease by 20% to 30%, but CBZ epoxide (CBZ-E) levels increase by 50% to 60%. The increase in CBZ-E can cause clinical toxicity such as dizziness, diplopia, or headache.

Table 54.1 Interactions of Felbamate with Other AEDS

	Effect of felbamate on other AEDs		Effect of other AEDs on felbamate
	AED change in concentration (%)	Recommended dose adjustment (%)	Change in concentration (%)
Phenytoin	↑ (30–50)	↓ (20–33)	↓ (32)
Carbamazepine (total)	↓ (30)	↓ (20–33)	↓ (38)
Carbamazepine (epoxide)	↑ (50–60)	—	—
Valproate	↑ (25–50)	↓ (20–33)	↔ (Variable, 53)
Phenobarbital	↑ (24)	↓ (25)	↓ (27)
Gabapentin	—	—	↑ (37)

AEDs, antiepileptic drugs.

In contrast, enzyme-inducing drugs may lower effective FBM serum levels by enhancing its metabolism via CYP2E1 and CYP3A4 pathways. This effect is pronounced for PB, CBZ, and PHT, which lower FBM levels by 27%, 32%, and 38%, respectively (40).

Oddly, CYP3A4 inhibitors such as erythromycin have little effect on FBM metabolism. VPA, however, does inhibit the metabolism of FBM, though the extent is not clear from the limited data. A nonmetabolic effect of gabapentin (GPN) in raising FBM serum levels is thought to be due to an interaction at the renal excretion level: GPN can increase FBM elimination half-life by 46% (40).

ADVERSE EFFECTS

Common Adverse Effects

The overall dropout rate attributed to adverse effects in clinical trials was 12% (29), a figure not dissimilar to that seen in clinical trials of other new AEDs. Gastrointestinal disturbances, headache, anorexia, and insomnia are common (7,8,29). Weight loss is most likely over the first year of use, then may stabilize (29). Dizziness, diplopia, and ataxia were more common in adjunctive therapy than with monotherapy (4,5,7,8) and thus may have been related to pharmacokinetic elevations in PHT and CBZ-E levels.

Monotherapy is better tolerated. Among 366 adults receiving monotherapy, 4.1% experienced nausea, 3.6% insomnia, 3% anorexia, 2% to 5% dizziness, and 2% weight loss (7,8,33). Administering FBM in three daily doses after meals may reduce stomachache.

FBM has a stimulant effect in many patients. This is a major advantage in comparison to other AEDs, but it may be associated with insomnia, irritability, and behavioral changes. Giving the largest dose in the morning may help insomnia. At 3% to 4%, the incidence of rash was no higher than placebo in clinical trials (29). Two children experienced involuntary dyskinetic movements (41). There is one report of a kidney stone (42).

Dose-Limiting Effects

Doses in clinical trials were limited to 3600 mg/day for adults and 45 mg/kg/day for children. Some patients cannot achieve these doses without side effects, especially in adjunctive therapy. Higher doses are sometimes well tolerated: among 50 patients stabilized on 3600 mg/day whose dose was raised to 4200 to 7200 mg/day (mean 5412 mg/day, mean serum concentration 110 mg/L), 32%

developed new or increased side effects, but only 15% required dose reductions (43). The most common dose-limiting effects in this group were dizziness, ataxia, and nausea.

Aplastic Anemia

FBM can cause aplastic anemia. In 1994, 33 cases were reported to the FDA (9,44,45). Another case was reported in 2000 and a questionable one in 2007 (29). There have been 14 fatalities. Detailed review of the first 31 cases according to International Agranulocytosis and Aplastic Anemia Study criteria revealed that 23 (74%) met criteria for a diagnosis of aplastic anemia (44). Six others had preexisting blood dyscrasias or systemic lupus erythematosus. Of the 23 confirmed cases, FBM was implicated as the most likely cause in 14; others had other plausible causes, usually other medications known to cause aplastic anemia.

Based on a 1997 estimate of 110,000 patients exposed, this yields a most probable incidence of 127 per million (1/8000 cases), compared with a population rate of 2 per million per year, with a worse-case incidence of 300 per million (44). By comparison, estimates for CBZ range from 5 to 39 per million per year (44). All FBM-related aplastic anemia cases were diagnosed within 1 year of starting the drug, two-thirds within 6 months (45). This suggests that the risk drops substantially after 1 year.

Patients developing aplastic anemia were more likely to have histories of blood dyscrasias, especially cytopenia, autoimmune disorders, and rashes, or significant toxicities with previous drugs (45,46). It seems best to avoid FBM in such patients. FBM may be safer for children; only one child, a postpubescent 14-year-old, has been affected (29).

Liver Failure

Among patients taking FBM for 25 to 959 days, 18 reported cases of liver failure resulted in 9 fatalities (45,46). Of these 18, 8 cases may have been caused by other factor: 5 with status epilepticus and 1 case each of hepatitis A, acetaminophen poisoning, and severe hypotension. Using population exposure estimates, this implies a risk of about 1 per 10,000 patient exposures.

Mechanisms of Toxicity

The mechanism by which FBM causes bone marrow and liver toxicity is unknown, but the formation of a toxic metabolite that triggers an immune reaction is suspected. The second step in FBM metabolism is formation of 3-carbamoyl-2-phenylpropionaldehyde (CBMA) (47). CBMA is then metabolized by three competing pathways, one of which leads to the formation of 2-phenylpropenal, also known as atropaldehyde (47). Atropaldehyde is cytotoxic and immunogenic, and it may be that individuals who form more of this compound on a genetic basis are more at risk. The aldehyde undergoes beta-elimination to 2-phenylpropenal, another known toxic compound (48). Since atropaldehyde is detoxified by glutathione, and glutathione stores are depleted by acetaminophen, it seems prudent to advise patients on FBM therapy not to take acetaminophen, although this notion is theoretical. There may be other mechanisms for blood toxicity. Both FBM and metabolites can cause apoptosis of bone marrow progenitor cells in vitro (49). Fluorofelbamate, a potent antiepileptic compound that is not metabolized to atropaldehyde, has been proposed as a safer alternative to FBM (50), and other carbamate derivatives of FBM show promise as anticonvulsant agents (51). However, it will be difficult to conduct human trials of these drugs without very thorough reassurance from

animal safety studies.

CLINICAL USE

Patient Selection

Because of the low but definite risk of serious blood or liver reactions, FBM should not be used as initial therapy or when an effective alternative can be found. Patients with focal seizures refractory to several drugs, especially with both severe epilepsy and drug sedative side effects, may be considered for treatment. A Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society have formulated practice guidelines (52) (Table 54.2). All patients or their caretakers must be able to report side effects reliably, comply with blood testing, and understand potential risks and benefits.

Table 54.2 Recommendations for Use of Felbamate

A. Patients for whom risk-to-benefit ratio supports use because there is class I evidence of benefit
   1. Patients with Lennox–Gastaut syndrome >4 y of age who are unresponsive to primary AEDs
   2. Intractable partial seizures in patients >18 y of age who have failed standard AEDs at therapeutic levels (monotherapy data indicate a better risk-to-benefit ratio for FBM used as monotherapy)
   3. Patients taking FBM >18 mo

B. Patients for whom the current risk-to-benefit assessment does not support the use of FBM
   1. New-onset epilepsy in adults or children
   2. Patients who have experienced significant prior hematologic adverse events
   3. Patients in whom follow-up and compliance will not allow careful monitoring
   4. Patients unable to discuss risks to benefits (i.e., those with mental retardation, developmental disability) and for whom no parent or legal guardian is available to provide consent

C. Patients in whom risk-to-benefit ratio is unclear and based on case reports and expert opinion (class III) only, but under certain circumstances, depending on the nature and severity of the patient's seizure disorder, FBM use may be appropriate
   1. Children with intractable partial epilepsy
   2. Patients with other generalized epilepsies unresponsive to primary agents
   3. Patients who experience unacceptable sedative or cognitive side effects with traditional AEDs
   4. Patients with Lennox–Gastaut syndrome <4 y of age who are unresponsive to other AEDs

Adapted from French J, Smith M, Faught E, et al. Practice advisory: the use of felbamate in the treatment of patients with intractable epilepsy. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society . Neurology. 1999;52:1540–1546, with permission.

Dosage

Both children and adults may be started on FBM 15 mg/kg/day in three divided doses, taken after meals, with increases to 30 mg/kg/day and 45 mg/kg/day at 2-week intervals (29). Therefore, the starting dose for adults is about 600 mg twice a day. However, starting with 300 to 400 mg twice a day (one 400-mg tablet or half 600-mg tablet) is better tolerated, then doses can be increased more slowly at about 10 mg/kg/day every 2 weeks. It is important to remember that FBM is generally an enzyme inhibitor and doses of other drugs may need to be decreased to avoid toxicity. For example, ataxia when it is added to PHT and headache and dizziness when it is added to CBZ are to be expected, and the proper course of action is to reduce the baseline drug. This effect can be verified by measuring levels of the baseline drug or CBZ epoxide in the case of CBZ. FBM is more effective and better tolerated as monotherapy, and if initial encouraging results are obtained, consideration should be given to reduction or withdrawal of concomitant drugs. Nevertheless, if seizure freedom without

toxicity is achieved with polytherapy, it is certainly reasonable to defer further dose changes. The target adult dose is 3600 mg/day; the target pediatric dose is 45 mg/kg/day. If no definite improvement is seen at this dose, FBM should be tapered back down gradually over 4 to 6 weeks and stopped. There is no reason to expose a patient to therapy longer than a few months in the absence of benefit, since shorter therapy durations, at least up to a year, may reduce the risk of dangerous side effects. Higher mg per kg doses may be necessary for younger children, in whom clearance is increased (26). Because of the many drug interactions, FBM serum levels during polytherapy may also be useful. The average therapeutic range for FBM is reported to be 50 to 110 mg/L, similar to valproate (53).

Monitoring for Adverse Effects

Patients with aplastic anemia from any cause may have symptoms before laboratory confirmation (54). Patients should be advised to watch for early symptoms, especially unusual fatigue, pallor, dyspnea, easy bruising, or bleeding. Nausea, vomiting, or jaundice may be indicative of hepatic problems. The manufacturer recommends blood counts and liver function tests, but the frequency is not mandated (29). However, neither patient surveillance nor periodic blood testing may detect adverse events early enough to prevent serious illness or death. A reasonable schedule is a baseline blood count and liver function panel before FBM is started, followed by monthly testing for the first 6 months then every 2 months for the second 6 months. Experience has shown that patients comply poorly with more frequent blood tests. The diminishing risk after 1 year implies that less frequent testing is acceptable, perhaps every 3 months during the second year, then only if symptoms develop thereafter. There is no evidence that lower doses are safer. Since most serious reactions began 3 to 12 months after initiation of FBM, consideration should be given to withdrawing it if no benefit occurs after a few months (44). There are no published guidelines for how much change in blood parameters should mandate FBM discontinuation. FBM should be withdrawn at once if a precipitous drop in white or red blood cells or platelets occurs, or perhaps if two of the three cell lines drops below the laboratory lower limit of normal. It may be acceptable to monitor a drop of a single cell line, perhaps with weekly blood counts, so long as the cell count itself is within a safe range. It is even harder to know what change in liver function parameters should lead to discontinuation. It is probably reasonable for the clinician to follow his or her usual practice for other hepatically metabolized drugs. Of course, a steady trend downward in blood counts or upward trend in liver function tests even within the normal range may be enough to support a decision to stop.

Managing Adverse Effects

The first question to ask is whether adverse effects are from FBM itself or from the pharmacokinetic or pharmacodynamic effects on the concomitant drugs. Common FBM-specific effects may include insomnia, gastrointestinal distress, weight loss, and headache. Insomnia can be moderated by giving a larger dose earlier in the day, or giving a dose right at bedtime, so that the maximal concentration occurs after sleep is achieved. An hypnotic may be necessary. Otherwise FBM should be given after meals to reduce GI effects. Weight loss is usually only a problem in thin individuals, especially in patients with cognitive problems who cannot increase their caloric intake voluntarily. Headache usually requires an FBM dose reduction.

Withdrawal from Felbamate

Dramatic increases in seizure frequency and even status epilepticus can occur with rapid withdrawal from FBM (55). Remember that as the dose of FBM is reduced, levels of PHT, PB, and valproate will also decrease. Surveillance for hematologic and hepatic effects should be continued for 6 months after FBM therapy ends, because damage to bone marrow stem cells may not be manifested immediately in peripheral blood counts. If a quick reduction in FBM is necessary because of hematologic or hepatic concerns, then either a simultaneous increase in a concomitant AED or a bridge treatment with a benzodiazepine should be considered.

SUMMARY

FBM can be dramatically effective, especially as monotherapy for focal seizures. Many patients report improved alertness when switched from other drugs. Nevertheless, serious toxicities preclude its use except in those patients who do not achieve complete seizure control with safer agents. Safety may be improved by avoiding FBM use in patients with autoimmune diseases, previous histories of significant cytopenia, or serious drug reactions. The combined risk for serious bone marrow or hepatic toxicity is about 1 per 5000 patients, and for death perhaps 1 in 10,000, with nearly all of the risk coming during the first year. These dangers are almost certainly less than the dangers of poor seizure control.

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CHAPTER 55 GABAPENTIN AND PREGABALIN

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Gabapentin (1-[aminomethyl]cyclohexaneacetic acid; Neurontin) and pregabalin (3-[aminomethyl]-5-methyl-,[3S]- hexanoic acid; Lyrica) are 3-substituted analogues of γ-aminobutyric acid (GABA), constituting a class of compounds known as "gabapentinoids" (Fig. 55.1). Related to this class is gabapentin enacarbil ((±)-1-([(α-isobutanoyloxyethoxy)carbonyl]aminomethyl)-1-cyclohexaneacetic acid; Horizant), an acyloxyalkylcarbamate analogue and a prodrug of gabapentin (see Fig. 55.1).

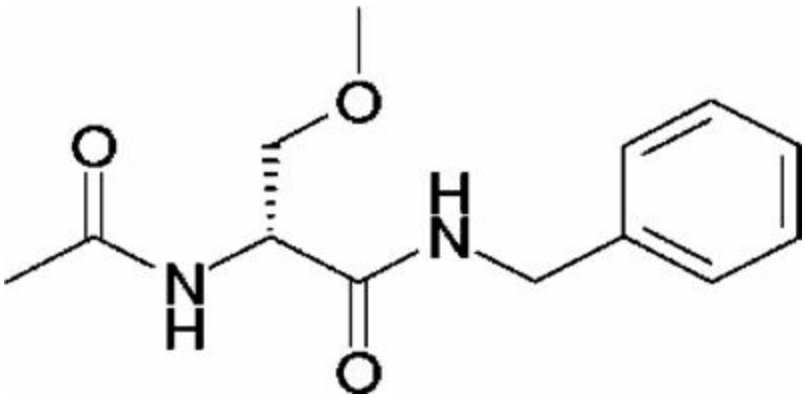

Figure 55.1. Chemical structure of gabapentin, pregabalin, and gabapentin enacarbil.

The mechanism of action of gabapentinoids differs from that of other antiepileptic drugs (AEDs). Contrary to initial belief, they do not interact with GABA receptors. Rather, compelling evidence suggests that they bind to the α_2-δ subunit of the P-, Q-, and N-type voltage-gated calcium channels (1,2). The binding affinity of pregabalin for the α_2-δ subunit is six times greater than that of gabapentin (3). The functional consequences of binding to this site are yet to be fully elucidated. These may involve allosteric modulation of calcium channels (4), or inhibition of trafficking and expression of calcium channels at the presynaptic membrane (5). In any case, the ensuing effect appears to be a decrease in presynaptic calcium influx, which leads to a reduction in calcium-dependent release of neurotransmitters, such as glutamate, noradrenaline, serotonin, acetylcholine, substance P, and calcitonin gene–related peptide, from nerve terminals (6).

GABAPENTIN

Chemistry

Gabapentin is a highly water-soluble, bitter-tasting, white crystalline substance with a molecular weight of 171.34 g/mol. At 25°C, it has two pK_a values at 3.68 and 10.70. At physiologic pH, it is a

zwitterion—a neutral molecule with both negative and positive charges (7). In this latter form, gabapentin is recognized by the L-amino acid transport system, which mediates its transport across the gut wall, the blood–brain barrier, and cell membranes (7,8).

Pharmacokinetics

Absorption

Gabapentin is absorbed predominantly in the small intestine, where the L-amino acid transport system is concentrated (9). Absorption in the colon is poor (10).

Gabapentin exhibits dose-dependent pharmacokinetics because its oral bioavailability decreases with increasing doses (11). Oral bioavailability is approximately 60% after a 300-mg dose, but only approximately 40% after a 600-mg dose and approximately 35% at a dose of 1600 mg t.i.d. at steady state (7). Peak serum concentrations typically occur 2 to 3 hours postdose (7,9), and steady state is achieved in 1to 2 days (7). Although in phase I pharmacokinetic studies serum concentrations of gabapentin increased linearly up 1800 mg/day (12), further rises in serum concentrations were less than dose proportional at doses between 1900 and 4800 mg/day (12). A nonlinear increase in serum concentrations of gabapentin with increasing doses was also noted in clinical trials (12). Overall, these findings are consistent with the saturability of the L-amino acid transport system involved in the gastrointestinal absorption of the drug (11,13).

Absorption of gabapentin varies considerably between patients (14), resulting in substantial interindividual variations in serum concentrations (13), which may contribute to differences in dose requirements. Within subjects, however, pharmacokinetic variability appears to be relatively low (13).

No dose adjustments are required when the drug is administered with food, as this has a negligible impact on gabapentin absorption (9).

Distribution

Gabapentin is not bound to plasma proteins (15). The volume of distribution is approximately 60 L or 0.65 to 1.04 L/kg (7). Gabapentin crosses the blood–brain barrier via the L-amino acid transport system. Cerebrospinal fluid (CSF) concentrations are 5% to 35% of that of plasma (15), and after a single dose continue to rise for hours after peak serum concentrations are attained.

Elimination

Gabapentin is not metabolized in humans and is eliminated unchanged in the urine (15,16). The elimination half-life of gabapentin is 5 to 9 hours in individuals with normal renal function (17). It is unknown whether gabapentin elimination is dependent on a tubular reabsorption process. However, cimetidine (an inhibitor of renal tubular secretion) decreases gabapentin clearance by approximately 12%, suggesting that a tubular secretion process could be involved in the elimination of the drug (18).

Special Populations

Gabapentin clearance is higher in children than in adults. It is greatest in younger children, with those under 5 years of age requiring approximately 30% higher doses than do children aged 5 to 12 years

(19). Gabapentin serum concentrations are higher in the elderly than in nonelderly adults receiving the same dose, a finding that is consistent with the physiologic decline in renal function (20).

Gabapentin clearance is decreased in patients with renal failure (especially in those requiring hemodialysis), potentially resulting in severe drug toxicity if appropriate dose adjustments are not made (21). Dose recommendations for different degrees of renal impairment are available in the drug information sheet (22).

New Formulations

To overcome the problems of gabapentin having a short half-life and a saturable mechanism of absorption, an extended- release formulation (Gralise) has been developed, which uses gastric-retentive technology to release gabapentin slowly over approximately 10 hours (23). This may attenuate the saturation of the L-amino acid transport system, thus enhancing and prolonging the absorption of the drug, particularly at higher doses, compared to the traditional formulation (24). Absorption of the extended-release formulation is substantially improved by food (23). Extended-release gabapentin has been found to be effective in the treatment of postherpetic neuralgia (23), but no controlled trials with this formulation have been reported as yet in patients with epilepsy.

Another agent developed to improve gabapentin absorption is gabapentin enacarbil, a prodrug of gabapentin (25). Gabapentin enacarbil is absorbed in the small and large intestine via the monocarboxylate transporter type 1 and the sodium-dependent multivitamin transporter (25). Absorption of gabapentin enacarbil is not saturable nor dose dependent, and it is improved by food. Gabapentin enacarbil is rapidly converted to gabapentin by nonspecific carboxylesterases in enterocytes and, to a lesser extent, in the liver (25). Serum concentrations of the intact prodrug are transient and represent ≤2% of those of gabapentin. The disposition of gabapentin derived from gabapentin enacarbil is similar to that of gabapentin administered as such. Gabapentin enacarbil is effective in the treatment of moderate–severe primary restless legs syndrome and postherpetic neuralgia, but no controlled studies with this agent have been reported as yet in patients with epilepsy.

Drug Interactions

Gabapentin has not been reported to cause or be a target for clinically relevant drug interactions. This is attributable to the fact that gabapentin is not bound to plasma proteins, is not metabolized, and does not induce or inhibit enzymes involved in the metabolism of other drugs (7,9).

Antacids containing aluminum or magnesium can reduce gabapentin bioavailability by approximately 20% (7), but the clinical relevance of this interaction is uncertain (7). In any case, it is generally recommended that administration of antacids and gabapentin be separated by ≥2 hours.

Efficacy

Adjunctive Therapy in Epilepsy

Adults.

Five randomized, double-blind, placebo-controlled trials demonstrated the efficacy of gabapentin as

adjunctive therapy in adults with refractory partial seizures (26–30) (Table 55.1). In these studies, 600 to 1800 mg/day of gabapentin (in three divided doses) were investigated over approximately 3 months. Titration was 2 to 3 days, except for one study (26) in which the target dose was reached over a 2-week period. The proportion of patients attaining a ≥50% reduction in seizure frequency compared to baseline (responder rates) varied between 12.5% and 33% (vs. 6.7% and 16.7% with placebo), with higher doses being associated with higher responder rates. Open-label studies (31–33) and case series (34,35) have suggested additional benefit at even higher doses (up to 6400 mg/day).

Table 55.1 Randomized Placebo-Controlled Trials of Gabapentin as Adjunctive Therapy in Adults with Drug-Resistant Partial Seizures

		Arms				
Study[a]	No. of subjects assessed (total)	Doses (mg/day)[b]	No of subjects assessed	Mean R Ratio	Responder rate (%)	Median decrease in seizure frequency (%)
UK Gabapentin study group (1990) (26)	113 (127)	1200	52	−0.192**	25*	29.2
		Placebo	61	−0.06	9.8	12.5
Sivenius et al. (1991) (27)	43 (36)	900	16	n/r	12.5	25.0
		1200	9	n/r	33	57*
		Placebo	18	n/r	16.7	16.7
US Gabapentin study group (1993) (28)	288 (306)	600	49	−0.151**	18.4	24.3
		1200	91	−0.118*	17.6	20
		1800	53	−0.233***	26.4**	31.9
		Placebo	95	−0.025	8.4	5.9
Anhut et al. (1994) (29)	245 (272)	900	94	−0.136**	22.9*	21.8
		1200	50	−0.157**	28**	17.8
		Placebo	96	−0.025	10.1	0.3
Yamauchi et al. (2006) (30)	190 (209)	1200	80	−0.144**	16.3	21.2
		1800	35	−0.160**	20	27.9
		Placebo	75	−0.037	6.7	9.7

[a]All studies consisted of a 12-wk baseline period, followed by a 12-wk treatment period. The only exception was the UK Gabapentin study group (26), in which the 12-week baseline was followed by a 14-week treatment period.[b]In three divided doses.
*P < 0.05,**P < 0.01 and ***P < 0.001 for comparisons with placebo.
n/r, not reported; R Ratio = (T − B)/(T + B), where T is the seizure frequency during treatment and B is the seizure frequency during baseline. Therefore, negative values indicate a reduction in the number of seizures during treatment, whereas positive values indicate an increase; Responder rate, proportion of patients with ≥50% reduction in seizure frequency.

A 14-week, double-blind, placebo-controlled trial evaluated the efficacy of gabapentin as add-on therapy for refractory generalized seizures in patients with idiopathic or symptomatic generalized epilepsy (37). A total of 129 patients with a mean age of approximately 30 years (range: 13 to 62) were randomized to placebo or 1200 mg/day of gabapentin. No significant differences were found between the two groups in terms of seizure outcome. The lack of effect on seizure outcome may be a result of the relatively low dose of gabapentin used in the study.

Children.

A 12-week, randomized, double-blind, placebo- controlled trial of 247 patients provided evidence for the efficacy of gabapentin as adjunctive therapy for refractory partial seizures in children aged 3

to 12 years (38). The target dose was 25 to 35 mg/kg/day. Children receiving gabapentin had a median reduction of 35% in the frequency of complex partial seizures (vs. 12% in the placebo group) and 28% in the frequency of secondarily generalized seizures (vs. a 13% increase in the placebo group). Higher daily doses (up to 78 mg/kg/day) have been used in open-label studies, but do not appear to be associated with increased efficacy (39).

The efficacy of gabapentin (40 mg/kg/day) as add-on treatment for refractory partial seizures in very young patients has been investigated in a 3-day, randomized, double-blind, placebo-controlled trial in 76 patients aged 1 to 36 months (40). Although there was a reduction in seizure frequency in the gabapentin arm versus a worsening in patients receiving placebo, differences did not reach statistical significance.

Monotherapy in Epilepsy

Adults.

The efficacy of gabapentin as monotherapy for refractory partial seizures has been evaluated in two randomized double-blind trials (41,42). One study compared 300 and 3600 mg/day over an 8-day period in 82 hospitalized patients whose medications had been discontinued for seizure monitoring (41). Time to meet exit criteria primarily related to lack of efficacy (the primary outcome variable) was significantly longer and completion rate was significantly higher in the 3600 mg/day arm. In the second study, 275 patients were randomized to 600, 1200, or 2400 mg/day and then underwent gradual discontinuation of their concomitant AEDs (42). Duration of the double-blind treatment phase was 26 weeks (2 weeks of gabapentin add-on therapy; 8 weeks of gradual discontinuation of concomitant AEDs; and 16 weeks of gabapentin monotherapy). Outcome measures, including time to exit, completion rate, and mean time on monotherapy, did not differ across the three groups. Overall, completion rate was only 20%.

Several studies assessed the efficacy of gabapentin monotherapy in adults with newly diagnosed seizures. Chadwick et al. (43) randomized 275 patients with newly diagnosed epilepsy to one of three masked doses of gabapentin (300, 900 or 1800 mg/day) or an open-label fixed dose of immediate-release carbamazepine (600 mg/day). After titration (7 days for gabapentin, 21 days for carbamazepine), patients entered a 24-week evaluation phase. Completion rate was 37% in the carbamazepine arm and 25%, 39% and 38% in patients receiving 300, 900 and 1800 mg/day, respectively. Although the completion rate for 900 and 1800 mg/day of gabapentin was similar to that of carbamazepine, more patients in the two gabapentin groups (40% and 43%, respectively) exited the study due to seizure occurrence compared to the carbamazepine group (30%). Conversely, the withdrawal rate because of adverse events was higher with carbamazepine compared to gabapentin 900 and 1800 mg/day (24% vs. 4% and 14%, respectively). In a 30-week, randomized, double-blind study, Brodie et al. (44) compared 1200 to 3600 mg/day of gabapentin to 100 to 300 mg/day of lamotrigine in 309 patients with newly diagnosed partial or generalized epilepsy. No between-group differences were found across several outcome measures. However, since many patients had only a few seizures in the ≥12 months prior to enrollment (median seizure number at study entry: 3 for the gabapentin group and 4 for the lamotrigine group), a period >30 weeks would have been desirable to obtain a more robust assessment of comparative efficacy. In an open-label trial (45), 1721 patients for whom carbamazepine was deemed to be preferable to valproate as initial treatment were randomized to carbamazepine (100 to 2000 mg/day), gabapentin (300 to 4800 mg/day), lamotrigine

(20 to 800 mg/day), topiramate (25 to 600 mg/day), and oxcarbazepine (300 to 2850 mg/day), and followed for up to 6 years. Most patients (82%) had newly diagnosed seizures, but patients who had previously received suboptimal treatment or who had relapsed after discontinuation of effective therapy were also included. Time to treatment failure, one of two primary endpoints, was significantly better with lamotrigine compared to gabapentin (hazard ratio 0.65 [95% CI 0.52–0.80]). Time to 12-month remission, the other primary endpoint, significantly favored carbamazepine over gabapentin (0.75 [0.63–0.90]).

A randomized, double-blind, parallel study compared gabapentin (target dose: 1500 mg/day), lamotrigine (150 mg/day), and immediate-release carbamazepine (600 mg/day) in 593 elderly patients (mean age 72 years) with newly diagnosed seizures (36). Patients were followed for up to 2 years. Doses could be optimized on the basis of clinical response. Although carbamazepine was the most efficacious agent, significantly more patients in the lamotrigine and gabapentin groups (55.8% and 49%, respectively) remained in the trial for 12 months, the primary outcome measure, compared to the carbamazepine group (35.5%; $P < 0.0001$ for lamotrigine and $P = 0.008$ for gabapentin vs. carbamazepine). This was largely attributable to the fact that carbamazepine was associated with higher withdrawal rates due to adverse events (31% vs. 12.6% for lamotrigine and 21.6% for gabapentin; $P = 0.001$).

Children.

The efficacy of gabapentin (9.7 to 19.1 mg/kg/day) in newly diagnosed childhood absence epilepsy has been investigated in two identical 2-week, randomized, double-blind, placebo-controlled trials including 33 children aged 4 to 12 years (46). Gabapentin did not significantly improve or worsen seizure frequency compared to placebo.

A double-blind study suggested that gabapentin monotherapy may be efficacious in benign childhood epilepsy with centrotemporal spikes (47). A total of 225 patients aged 4 to 13 years were randomized to gabapentin (30 mg/kg/day) or placebo for 34 weeks. In preliminary analyses, time to treatment failure was significantly longer with gabapentin compared to placebo. The estimated completion rate was 57% in the gabapentin arm and 44% in the placebo arm. These preliminary data, however, have not been followed by a final report.

Nonepilepsy Indications

There is evidence from randomized, double-blind, placebo- controlled trials that gabapentin is effective in the treatment of neuropathic pain disorders, particularly postherpetic neuralgia (48). Other conditions for which gabapentin may be useful include restless legs syndrome, anxiety disorders, and postoperative pain (49–51).

Adverse Effects

Gabapentin is generally well tolerated. In early trials, dropout rates due to adverse events were <10% in patients receiving gabapentin. Its adverse effects typically involve the central nervous system (CNS), such as drowsiness, fatigue, dizziness and ataxia (Table 55.2), tend to be mild to moderate in severity, often appear in the first few days of therapy, and may resolve within 2 to 3 weeks (13). These effects do not display a clear dose–response relationship (31,33) (see Table 55.2), with some individuals not tolerating even small doses of the drug (33).

Table 55.2 Most Common Treatment-Emergent Adverse Events in a Placebo-Controlled Trial of Gabapentin Versus a Placebo-Controlled Trial of Pregabalin

	US Gabapentin study group (1993) (28)				French et al. (2003) (52)				
		Gabapentin (mg/day)				Pregabalin (mg/day)			
Adverse event	Placebo (n = 98)	600 (n = 53)	1200 (n = 101)	1800 (n = 54)	Placebo (n = 100)	50 (n = 88)	150 (n = 86)	300 (n = 90)	600 (n = 89)
Somnolence	12.2%	7.5%	35.6%	20.4%	11%	10.2%	17.4%	17.8%	28.1%
Dizziness	9.2%	24.5%	24.8%	18.5%	9%	9.1%	16.3%	31.1%	42.7%
Ataxia	11.2%	11.3%	25.7%	18.5%	3%	3.4%	10.5%	10.0%	14.6%
Accidental injury	—	—	—	—	5%	14.8%	5.8%	11.1%	12.4%
Nystagmus	13.3%	9.4%	16.8%	16.7%	—	—	—	—	—
Asthenia	—	—	—	—	8%	5.7%	8.1%	12.2%	10.1%
Headache	12.2%	18.9%	8.9%	20.4%	13%	6.8%	9.3%	5.6%	5.6%
Tremor	9.2%	7.5%	14.9%	13%	3%	3.4%	3.5%	6.7%	11.2%
Fatigue	7.1%	11.3%	10.9%	13%	—	—	—	—	—
Withdrawal due to adverse events	1%	5.7%	2%	3.7%	5%	6.8%	1.2%	14.4%	23.6%

Note that, for both gabapentin and pregabalin, adverse events mainly involve the CNS. However, while gabapentin adverse events do not clearly display a dose-dependent relationship, those emerging during pregabalin therapy appear to be largely dose related.

A relatively common complication of gabapentin therapy is weight gain. DeToledo et al. (53) reviewed changes in body weight in 44 patients with refractory seizures receiving gabapentin for ≥12 months. Twenty-eight patients were taking doses of >3000 mg/day. Overall, 10 patients gained >10% of their initial weight, 15 patients gained 5% to 10%, 16 patients had no change, and 3 patients lost 5% to 10%. Gabapentin-induced weight gain appears to be dose related. In a 6-month open-label study of gabapentin add-on therapy for refractory partial seizures, weight gain was observed in 8%, 6.3%, 9.7%, and 15.2% of patients receiving 1200, 1600, 2000, and 2400 mg/day, respectively (31).

Gabapentin can cause peripheral edema, particularly at higher doses. In a pooled analysis of three randomized, double-blind, placebo-controlled studies of gabapentin in postherpetic neuralgia, the incidence of peripheral edema was 1.6%, 1.4%, and 7.5% in patients receiving placebo (n = 245), <1800 mg/day (n = 358), and ≥1800 mg/day (n = 321) of gabapentin, respectively (54). The edema resolves with discontinuation of therapy.

Movement disorders have been observed with gabapentin (55). There are several reports of gabapentin-induced myoclonus, for which individuals with preexisting myoclonus, severe chronic static encephalopathy, or renal failure appear to be at higher risk (56,57).

A few reports suggest that, in children and individuals with intellectual disabilities, gabapentin may induce behavioral problems, such as hyperactivity and aggression (51).

Serious idiosyncratic reactions are extremely uncommon during gabapentin therapy, and the potential for causing hypersensitivity reactions is much lower with gabapentin compared to some other AEDs, such as carbamazepine, phenytoin, and lamotrigine (58,59). Of note, three reports suggested that gabapentin may cause rhabdomyolysis (60–62).

There is sparse information on the fetal risks in gabapentin-exposed pregnancies (Table 55.3). As reflected by the large confidence intervals in Table 55.3, the number of exposed cases in each study is too small to allow meaningful conclusions about the teratogenic potential of gabapentin. In a recent prospective study (63), rates of major malformations in the offspring were 4.1% among 223 pregnancies exposed to gabapentin compared to 2.5% among 223 pregnancies exposed to agents considered nonteratogenic (e.g., acetaminophen or antibiotics). Gabapentin-exposed pregnancies were associated with lower rates of live births (76.2% vs. 90%, P < 0.001), and higher rates of therapeutic abortions (13% vs. 2.2%, P < 0.001), preterm births (10.5% vs. 3.9%, P = 0.019), low

birth weight (8.1% vs. 4%, P = 0.033), and admissions to neonatal intensive care unit/special care nursery (38% vs. 2.9%, P < 0.001). However, because no distinction was made between monotherapy and polytherapy, and pregnancy outcomes with other AEDs for comparison are missing, these findings are difficult to interpret.

Table 55.3 Rates of Major Congenital Malformations After Exposure to Gabapentin Monotherapy in Different Prospective Studies

Study	Number of exposed pregnancies	Number of malformations	Rate (95% CI)
Montouris (2003) (64)	17	1	5.9% (1.0%–26.7%)
Morrow et al. (2006) (65)	31	1	3.2% (0.6%–16.2%)
Tomson et al. (2011) (66)	23	0	—
Hernandez-Diaz et al. (2012) (67)	145	1	0.7% (0.1%–3.8%)
Fujii et al. (2013) (63)	36	0	—
Total	*252*	*3*	*1.2% (0.4%–4.3%)*

Inclusion criteria and methods of assessment (including duration of follow-up postnatally) differed across studies.
CI, confidence interval.

Place in Current Therapy

Gabapentin has been approved in several countries for adjunctive therapy and monotherapy use in partial seizures, as well as for the treatment of neuropathic pain. In the United States, it has received Food and Drug Administration (FDA) approval for adjunctive therapy in the treatment of partial seizures in patients aged ≥3 years, and for the management of postherpetic neuralgia in adults.

In the Neurontin U.S. Physician Prescribing Information (68), the recommended starting dose for patients with epilepsy aged >12 years is 300 mg t.i.d. However, if a rapid response is required, starting doses up to 3600 mg/day can be well tolerated. The effective dose range of Neurontin is given as 900 to 1800 mg/day (68). However, postmarketing experience suggests additional benefit with further dose increases, up to 3600 mg/day.

In children with epilepsy aged 3 to 12 years, the recommended starting dose is 10 to 15 mg/kg/day in three divided doses, which can be increased to the effective dose over a period of approximately 3 days (68). The effective dose of Neurontin is stated as 25 to 35 mg/kg/day in children aged 5 to 12 years, and 40 mg/kg/day in children aged 3 and 4 years (68).

Neither the extended-release formulation of gabapentin nor gabapentin enacarbil is indicated for the treatment of epilepsy. Extended-release gabapentin has received FDA approval for the treatment of postherpetic neuralgia in adults. Gabapentin enacarbil is FDA approved for the treatment of moderate–severe primary restless legs syndrome in adults, and postherpetic neuralgia in adults.

In the Gralise Prescribing Information (69), the recommended starting dose of extended-release gabapentin is 300 mg once daily, which should be increased to a 1800-mg once-daily dose over 15 days (69). Extended-release gabapentin should be taken with the evening meal. In the Horizant Prescribing Information (25), the recommended dose of gabapentin enacarbil is 600 mg once daily at 5 PM for the treatment of restless legs syndrome. For the treatment of postherpetic neuralgia, the recommended dose is 600 mg once daily for 3 days, which should be increased to 600 mg twice daily

beginning on day 4 (25). When discontinuing gabapentin enacarbil, tapering is not necessary in patients taking ≤600 mg/day (25). In patients with postherpetic neuralgia taking 600 mg twice daily, the dose of gabapentin enacarbil should be reduced to 600 mg once daily for 1 week prior to discontinuation to reduce the risk of withdrawal seizure (25).

In summary, gabapentin is a safe and well-tolerated agent, which displays a wide therapeutic window and no clinically relevant drug interactions. It is also suitable for rapid titration, with little or no significant risk for serious toxicity. Although well-designed head-to-head comparative studies are lacking, gabapentin is generally considered less efficacious than other AEDs for the treatment of partial seizures, possibly due to incomplete bioavailability especially at the high doses. There is no evidence of gabapentin being efficacious in generalized epilepsies. The extended-release formulations of gabapentin and gabapentin enacarbil have yet to be investigated in patients with epilepsy.

PREGABALIN

Chemistry

Pregabalin is a white to off-white crystalline substance with a molecular weight of 159.23 g/mol. It has two pK_a, 4.2 and 10.6, corresponding to the carboxylic acid and the amine groups, respectively (see Fig. 55.1). It is freely soluble in water and in basic and acidic aqueous solutions (70).

Pharmacokinetics

Absorption

Like gabapentin, pregabalin is absorbed in the small intestine by the L-amino acid transport system (9,71). Unlike gabapentin, which shows dose-dependent pharmacokinetics due to saturable absorption, pregabalin exhibits linear absorption pharmacokinetics within the therapeutic dose range (9,70). This can be explained by the fact that pregabalin is used clinically at much lower doses compared to gabapentin, and also by differences in regional distribution and sodium dependence between the pregabalin and gabapentin carriers (72). In addition, mechanisms other than the L-amino acid transport system may be involved in the absorption of pregabalin, and contribute to the >90% oral bioavailability across the effective dose range (9). Peak serum concentrations occur approximately 1 hour after oral intake, and steady state is achieved 1 to 2 days after repeated dosing. Food delays peak serum concentrations but does not affect total drug absorption (73).

Distribution

Pregabalin does not bind to plasma proteins, and it has a volume of distribution of approximately 0.5 L/kg. Pregabalin crosses the blood–brain barrier via the L-amino acid transport system. Peak CSF concentrations occur 8 hours postdose, and decrease at a slower rate compared to plasma (9).

Elimination

Pregabalin undergoes negligible metabolism (<2% of the dose) and is eliminated virtually unchanged

in the urine (70,71). Its elimination half-life is 5 to 7 hours in people with normal renal function (70). Pregabalin renal clearance (67.0 to 80.9 mL/min) has been found to be lower than the glomerular filtration rate, suggesting that tubular reabsorption may be involved in the renal clearance of the drug (9).

Special Populations

Pregabalin clearance is decreased in patients with impaired renal function. This decrease is directly proportional to the reduction in creatinine clearance (CL_{Cr}) (71). A 50% reduction in pregabalin daily dose is recommended in patients with CL_{Cr} between 30 and 60 mL/min compared to those with CL_{Cr} greater than 60 mL/min. Daily doses should be further reduced by 50% for each additional 50% decrease in CL_{Cr} (74). Since pregabalin is highly cleared by hemodialysis, supplemental doses may be required for patients on chronic hemodialysis treatment after each dialysis session to maintain unaltered drug serum concentrations (74).

Preliminary observations suggest that pregabalin clearance may be also reduced in the elderly (75), a finding that can be explained by the physiologic age-related decline in renal function (76).

Drug Interactions

Since pregabalin is not bound to plasma proteins, does not influence the activity of drug metabolizing enzymes, and is not itself significantly metabolized (71), its potential for clinically relevant drug interactions is very low. In regulatory trials, pregabalin did not alter serum concentrations of concomitantly administered carbamazepine, lamotrigine, phenobarbital, phenytoin, tiagabine, topiramate, and valproic acid (77). Evidence also exists that pregabalin pharmacokinetics are not affected by several comedications, including other AEDs, oral contraceptives, oral hypoglycemics, diuretics, and insulin (78). In one study, however, comedication with enzyme-inducing AEDs was associated with moderately lower pregabalin serum concentrations compared to comedication with noninducers (75).

Pregabalin may worsen the cognitive and motor dysfunction caused by oxycodone, and potentiate the CNS effects of ethanol and lorazepam (79).

Efficacy

Adjunctive Therapy in Epilepsy

Adults.

Six randomized, double-blind, placebo-controlled trials involving 2009 patients demonstrated the efficacy of pregabalin as adjunctive therapy in adults with refractory partial seizures (52,80–84) (Table 55.4). In these studies, pregabalin doses of 50 to 600 mg/day were investigated over 12 to 17 weeks; titration was 1 to 8 days, except for one study (82) in which the target dose was reached over a 2-week period. The first three studies were designed to assess dose–response relationships by using a fixed-dose regimen (52,80,81). Doses of 150, 300, and 600 mg/day were found to be superior to placebo in reducing seizure frequency, whereas 50 mg/day was not effective (see Table 55.4). Twice-daily and three times daily dosing schedules displayed similar effectiveness. The fourth and

fifth studies differed from the earlier trials in that they tested a flexible-dose regimen of 150 to 600 mg/day (82,83). In both studies, pregabalin therapy was associated with a significantly greater reduction in seizure frequency compared to placebo (see Table 55.4). The sixth study randomized 434 patients to pregabalin (300/600 mg/day), lamotrigine (300/400 mg/day), or placebo for 17 weeks of double-blind treatment divided in two phases (84). Phase I consisted of 11 weeks starting with titration (1-week for pregabalin, 5-week for lamotrigine) and concluding with doses of both AEDs fixed at 300 mg/day. Phase II was an additional 6 weeks in which patients who had seizures during phase I received a higher dose of their assigned AED (pregabalin: 600 mg/day, up-titrated over 1 week; lamotrigine: 400 mg/day, no titration). Patients who were seizure free during phase I were maintained on their assigned AED at the original dose. During phase I, there were no significant differences in efficacy measures across the three groups. Over the entire 17-week treatment period, however, pregabalin was associated with a greater reduction in seizure frequency and higher responder rates compared to placebo. Responder rates, but not seizure frequency reduction, also significantly favored pregabalin over lamotrigine (see Table 55.4).

Table 55.4 Randomized Placebo-Controlled Trials of Pregabalin as Adjunctive Therapy in Adults with Drug-Resistant Partial Seizures

		Arms				
Study[a]	No. of subjects assessed (total)	Doses (mg/day)	No. of subjects assessed	Mean R Ratio	Responder rate (%)	Median change in seizure frequency (%)
French et al. (2003) (52)	453 (455)	50[b]	88	−6	15	n/r
		150[b]	86	−21***	31**	n/r
		300[b]	90	−28***	40***	n/r
		600[b]	89	−37***	51***	n/r
		Placebo[b]	100	−4	14	n/r
Arroyo et al. (2004) (80)	287 (288)	150[c]	99	−11.5***	14.1	−16.5
		600[c]	92	−31.4***	43.5***	−42.6
		Placebo[c]	96	0.9	6.2	1.3
Beydoun et al. (2005) (81)	312 (313)	600[b]	103	−28.4***	43***	−35.6
		600[c]	111	−36.1***	49***	−48.1
		Placebo[c]	98	0.6	9	0.8
Elger et al. (2005) (82)	341 (341)	150–600[b]	131	−21.5**	31.3**	n/r
		600[b]	137	−32.7***	45.3**	n/r
		Placebo[b]	73	−5.6	11	n/r
Lee et al. (2009) (83)	178 (178)	150–600[b]	119	−35.8*	46.2	−48.2*
		Placebo[b]	59	−23.2	32.2	−32.4
Baulac et al. (2010) (84)	434 (434)	300–600	152	−16.5***	35.5**[d]	n/r
		Lamotrigine (300–400)	141	−12.3	24.1	n/r
		Placebo	141	−7.7	21.4	n/r

[a]Three studies [French et al. (52), Arroyo et al. (80), Beydoun et al. (81)] consisted of a 8-wk baseline period, followed by a 12-wk treatment period. Two studies [Elger et al. (82), Lee et al. (83)] consisted of a 6-wk baseline, followed by a 12-wk treatment period. The study by Baulac et al. (84) was characterized by a 6-wk baseline, followed by a 17-wk treatment period.[b]In two divided doses.[c]In three divided doses.[d]$P < 0.05$ for comparisons with lamotrigine.*$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ for comparisons with placebo. n/r, not reported; R Ratio = $[(T - B)/(T + B)] \times 100$, where T is the seizure frequency during treatment and B is the seizure frequency during baseline. Therefore, negative values indicate a reduction in the number of seizures during treatment, whereas positive values indicate an increase; Responder rate, proportion of patients with ≥50% reduction in seizure frequency.

Open-label studies suggest that the clinical response to pregabalin is sustained over time (70,85). In a pooled analysis of six long-term, open-label, adjunctive therapy studies involving 2061 patients, the mean percentage reduction in 28-day seizure frequency remained relatively stable over time (25% to 40%), with 43% of all patients exhibiting a ≥50% reduction in seizure frequency during the last 3 months of treatment (85). However, these results must be interpreted with caution due to the high number of patients who discontinued treatment (n = 1304), with responders being more likely to remain in the study than nonresponders. These studies also allowed for changes in concomitant agents, which might have contributed to the apparent sustained effect of pregabalin on seizure control.

Children.

A prospective, open-label, uncontrolled study evaluated the efficacy and safety of pregabalin (150 to 300 mg/day) as adjunctive therapy in 19 children aged 4 to 15 years with severe refractory epilepsy (86). Over a follow-up of 3 to 6 months, one patient became seizure free, and seven attained a >50% reduction in seizure frequency. Of note, pregabalin was withdrawn in five patients due to lack of efficacy, and in two due to worsening of myoclonic seizures.

Large company-sponsored trials assessing the effectiveness of pregabalin as add-on therapy in pediatric patients with partial and generalized seizures are currently under way.

Monotherapy in Epilepsy

Adults.

The efficacy of pregabalin as monotherapy for refractory partial seizures has been evaluated in two randomized double-blind trials (87,88). One study compared 600 mg/day of pregabalin and 300 mg/day of gabapentin over an 8-day period in 93 hospitalized patients whose AEDs had been discontinued for seizure monitoring (87). There was a nonsignificant trend towards a longer median time to meet exit criteria primarily related to lack of efficacy (primary outcome variable) in the pregabalin group compared to the gabapentin group (191 hours vs. 88 hours, P = 0.08). Completion rate was higher in the pregabalin arm (57.7% vs. 23.5%, P = 0.003). The second study was based on a historical-controlled conversion to monotherapy design (88). Pregabalin doses of 150 and 600 mg/day were compared over a 20-week double-blind phase, comprising an 8-week conversion period (during which the pregabalin dose was escalated and the concomitant AEDs discontinued) and a 12-week monotherapy period. The trial was stopped early after an interim analysis on 134 patients showed that efficacy in the 600 mg/day group (primary study endpoint) could already be established based on predefined exit criteria.

In a recent randomized, double-blind, noninferiority trial, Kwan et al. (89) compared pregabalin and lamotrigine monotherapy in 660 patients with newly diagnosed partial seizures. Initial target doses were 150 mg/day for pregabalin and 100 mg/day for lamotrigine, which could be increased as needed during a 52-week assessment period to a maximum of 600 and 500 mg/day, respectively. Fewer patients became seizure free for ≥6 continuous months (primary study endpoint) with pregabalin compared to lamotrigine (52% vs. 68%; differences in proportion: −0.16 [95% CI −0.24 to −0.09]). Secondary efficacy endpoints, including time to exit due to lack of efficacy, time to first seizure, and time to 6-month seizure freedom, also favored lamotrigine over pregabalin. The authors speculated that these findings might have been at least in part attributable to the choice of the initial target dose of pregabalin (150 mg/day), possibly too low for this type of epilepsy population.

Children.

There are no data on the efficacy of pregabalin monotherapy in children with epilepsy.

Nonepilepsy Indications

Data from randomized, double-blind, placebo-controlled trials indicate that pregabalin is effective in neuropathic pain disorders (90), particularly postherpetic neuralgia and painful diabetic neuropathy (91). Pregabalin has also shown efficacy in fibromyalgia (92), generalized anxiety disorder, and social anxiety disorder (51).

Adverse Effects

Similarly to gabapentin, adverse effects of pregabalin typically involve the CNS, such as dizziness, ataxia, and drowsiness; usually appear in the first days of treatment; are generally mild to moderate in severity; and may abate with continued therapy (2 to 7 weeks). As opposed to gabapentin, these effects exhibit a definite dose-dependent relationship (see Table 55.2) (93). In a pooled analysis of four randomized, double-blind, placebo- controlled studies of pregabalin in refractory partial seizures (94), discontinuation rates due to adverse events were 6.9%, 5.9%, 14.4%, and 24.2% in patients receiving 50 mg/day (n = 88), 150 mg/day (n = 187), 300 mg/day (n = 90), and 600 mg/day (n = 321) of pregabalin, respectively (vs. 6.3% in 294 patients receiving placebo).

Weight gain is also a common complication of pregabalin therapy. In regulatory trials, an increase of ≥7% over baseline body weight was found in 9% of patients taking pregabalin and 2% of patients receiving placebo (95). Weight gain appeared to be dose related. The proportion of patients experiencing a ≥7% increase in body weight was 4.9% at 150 mg/day, 6.7% at 300 mg/day, and 20.4% at 600 mg/day (70). Very few patients (0.3%) discontinued pregabalin due to weight gain (95). In a pooled analysis of six long-term, open-label, adjunctive therapy studies involving 2061 patients, the estimated weight gain at 1 year from starting pregabalin treatment was 5.2 kg (85). In a randomized controlled trial, extended clinical counseling was found to be ineffective in preventing pregabalin-induced weight gain (96).

Peripheral edema may occur in up 20% of patients taking pregabalin (97), and appears to be more common in neuropathic pain compared to epilepsy (94). Sexual dysfunction, including erectile dysfunction, decreased libido, and anorgasmia, has been associated with pregabalin therapy (98). A few reports suggest that pregabalin may induce myoclonus (99).

Pregabalin has been associated with negative effects on mood. In a recent single-center study, 24 of 402 (6%) patients treated with pregabalin discontinued the drug because of psychiatric adverse events, including depression, low mood, and mood swings (100).

A number of reports have suggested that pregabalin might have a potential for abuse and addiction, with individuals with a previous history of substance dependence being at higher risk (95).

To date, there is no adequate information on the teratogenic potential of pregabalin in women with epilepsy. Pregabalin has teratogenic effects in rats at very high doses (1250 to 2500 mg/kg), which are much higher than those used in humans (94).

Place in Current Therapy

Pregabalin has received FDA approval as adjunctive therapy in adults with partial seizures. It has

also been approved for the treatment of fibromyalgia, postherpetic neuralgia, and neuropathic pain associated with diabetic peripheral neuropathy and spinal cord injury. In other countries, pregabalin is also indicated for the management of generalized anxiety disorder (9). Because of its potential for abuse, pregabalin has been classified as a Schedule V controlled substance by the U.S. Drug Enforcement Administration (95).

In the Lyrica U.S. Physician Prescribing Information (95), the recommended starting dose for adults with partial seizures is 150 mg/day (75 mg b.i.d. or 50 mg t.i.d). However, clinical experience suggests that, in patients prone to developing AED-related CNS toxicity, a starting dose of 50 to 75 mg/day may be preferable, with up-titration to 150 mg/day over a period of 2 to 4 weeks (94). The effective dose range of Lyrica is given as 150 to 600 mg/day.

In summary, like gabapentin, pregabalin displays absence of hepatic metabolism, minimal potential for clinically relevant drug interactions, protective activity against partial-onset seizures, and efficacy in some nonepilepsy indications, including neuropathic pain. Unlike gabapentin, however, pregabalin exhibits linear pharmacokinetics and complete bioavailability at all clinically used doses, resulting in perceived greater antiseizure efficacy but also greater propensity to cause adverse effects at the upper portion of the approved dose range. The value of pregabalin relative to other AEDs remains to be elucidated in well-designed head-to-head comparative trials.

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CHAPTER 56 LACOSAMIDE

RAJ D. SHETH

HISTORICAL BACKGROUND

Lacosamide (Vimpat; previously harkoseride) is the R-enantiomer of 2-acetamido N-benzyl-3-methoxypropionamide (Fig. 56.1). Lacosamide is a recently approved antiepileptic medication for adjunctive therapy for patients 17 years and older with partial complex seizures. Formulations as a tablet, a syrup, and an intravenous injection are available. The drug was initially developed by Harris LLC with preclinical trials conducted by Schwartz Pharma and subsequently acquired by UCB Pharma. Although it was specifically synthesized as an antiepileptic medication, as with many newer agents, it was found to have additional pharmacologic properties including a role in the alleviation of pain associated with diabetic neuropathy. Preclinical development suggests neuroprotection in animal models of seizures as well as in status epilepticus models. Most studies have examined activity in the maximal electroshock-induced seizure test used in rodents. Human randomized controlled trials have shown lacosamide to have efficacy as an adjunctive therapy in patients 17 years and older with partial-onset seizures; however, efficacy in other epilepsy syndromes is being investigated.

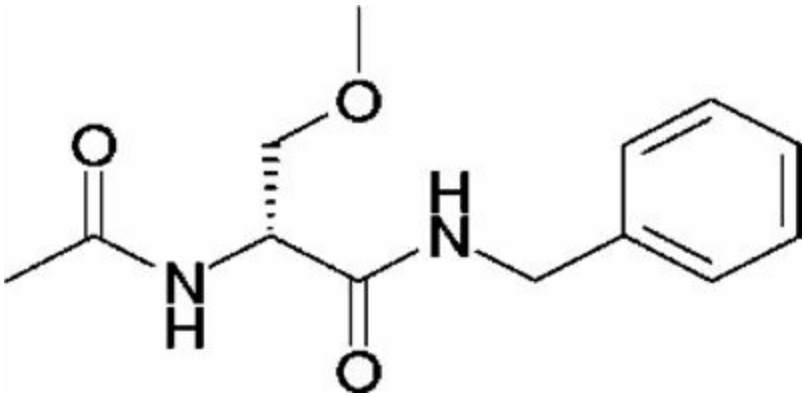

Figure 56.1. Structure of lacosamide ($C_{13}H_{18}N_2O_3$).

GENERAL CHARACTERISTICS

Lacosamide belongs to a class of functionalized amino acids that were specifically designed to have potential anticonvulsant properties (see Fig. 56.1). It is a light yellow crystalline powder that is soluble in phosphate-buffered saline (pH of 7.5 at 25°C) and has a chemical formula of $C_{13}H_{18}N_2O_3$.

METABOLISM

Almost 40% of lacosamide is excreted unchanged in the urine. A further 30% is metabolized by demethylation to the pharmacologically inactive O-desmethyl metabolite that is excreted in the urine (1). In addition, a polar fraction (approximately 20% of the dose) is also excreted into urine after

both oral and intravenous administration. Small amounts of further metabolites representing 0.5% to 2% of the dose are also found in urine. Cytochrome P450 (CYP) 2C19 is involved in the demethylation of lacosamide. The relative contribution of other CYP isoforms to lacosamide metabolism is currently not clear.

Given the large portion that is renally excreted, adjustment with moderate-to-severe renal failure is needed. With mild-to-moderate renal impairment, there is no need for dosage adjustment. It should be noted that hemodialysis clears over half of serum lacosamide. Accordingly, dose supplementation after hemodialysis should be considered (2). In patients with mild-to-moderate renal impairment dosage adjustment does not appear to be needed.

This study examined, population-based pharmacokinetics of lacosamide in adults with partial-onset seizures. A total of 2370 lacosamide plasma concentrations were examined using nonlinear mixed-effect modeling in two phase 3, double-blind, multicenter, randomized, parallel-group, placebo-controlled trials where subjects received 200, 400, or 600 mg/day lacosamide in divided doses twice daily (3). As a class, inducer antiepileptic medications increased clearance by approximately 36%. Individually, coadministration of the CYP inducers carbamazepine or phenytoin resulted in an approximate decrease in area under the curve by 20%, and coadministration of phenobarbital yielded an approximate 30% decrease. The observed effect of inducer antiepileptic medications on lacosamide exposure was modest. Accordingly, this finding result is unlikely to be clinically significant when adding lacosamide to an existing treatment regimen. Furthermore, no significant change in lacosamide PK was seen in CYP2C19 poor metabolizers or following comedication with omeprazole.

MECHANISM OF ACTION

Animal Models

Lacosamide has a dual mechanism of action, both of which appear novel and operational across a wide variety of animal seizure models when administered intraperitoneally in a dosage range of 1 to 30 mg/kg (4). Animal models where lacosamide has had antiseizure activity demonstrated include mice with audiogenic seizures and maximal electroshock and N-methly-D-aspartate–induced seizures (5).

Lacosamide appears to have two main mechanisms of actions. The primary mechanism of action appears to be selective enhancing the slow inactivation of voltage-gated sodium channels without interfering with fast inactivation. Slow inactivation of sodium channels is an endogenous mechanism whereby neurons reduce ectopic hyperactivity and may represent an effective mechanism to selectively reduce ictal hyperactivity without altering physiologic function (6). Lacosamide, unlike carbamazepine, lamotrigine, and phenytoin, did not produce frequency-dependent facilitation of block of 3 seconds, 10-Hz pulse stimulation train. The slow inactivation voltage curve was shifted in the hyperpolarizing direction and significantly promoted the shift of channels to the slow inactivated state without impairing rate of recovery. Such modulation of neuronal activity may underlie lacosamide's therapeutic activity in the management of pain (5).

Lacosamide is highly potent in acute status epilepticus models. In rats, it has been shown to have the potential for disease modification that may be CRMP-2 dependent (7). Inhibition of CRMP-2 was thought to render the medication effective both as a traditional antiepileptogenic agent and having

efficacy in acute seizures. However, lacosamide binding to CRMP-2 has been questioned (8).

Early preclinical electrophysiologic studies have demonstrated that lacosamide targets voltage-gated sodium channels and acts by specifically enhancing slow inactivation without affecting fast inactivation of the channel (9). Initial preclinical investigations (8,10) suggested that lacosamide might have an additional mode of action by binding to the collapsin response mediator protein 2 (CRMP-2). However, Wolff et al. (8) demonstrated that there is currently no experimental evidence to support direct binding between lacosamide and CRMP-2.

Male rats rendered in self-sustaining EEG and clinical status epilepticus treated with early (10 minutes) or delayed (40 minutes) lacosamide showed dose-dependent and potent reduction in both the frequency of seizures and the cumulative duration of seizures. Early treatment with lacosamide resulted in a dose-dependent reduction of the number of spontaneous recurrent seizures of up to 70%. Late treatment with lacosamide resulted in a 50% reduction in the frequency of spontaneous recurrence. The number of seizure-free animals increased from 0% in the untreated group to 65% in the highest-dose groups. Protection of hippocampal structures within 72 hours following induction of status epilepticus was greatly enhanced. It is not clear if this mechanism is operational in humans.

Lacosamide was also evaluated in a comprehensive preclinical toxicology and pharmacology program (10) conducted in mice, rats, rabbits, and dogs. These studies found lacosamide to be well tolerated; either no or only minor side effects were observed in safety studies involving the central nervous, respiratory, gastrointestinal, and renal systems, and in three animal models, there was no indication of abuse liability. Long-term, repeated-dose toxicity studies demonstrated that after either IV or oral lacosamide administration, adverse events were reversible and consisted mostly of exaggerated pharmacodynamic effects on the central nervous system. No genotoxic or carcinogenic effects were observed in vivo, and lacosamide showed a favorable profile in reproductive and developmental animal studies (11).

CLINICAL STUDIES

Lacosamide has been studied in two clinical settings: (i) in patients 17 years or older with partial seizures as an adjunctive agent and (ii) in pain associated with diabetic neuropathy. Dose ranges that were tested in these situations are between 200 and 600 mg/day (Table 56.1), following indications from initial trials of efficacy between 100 and 600 mg/day.

Table 56.1 Change in Seizure Frequency per 28 Days During the First 2 Weeks of Lacosamide Exposure

Randomized treatment group	Reduction over placebo (%)	*P*-value
First week of exposure to LCM (LCM 100 mg/day)		
LCM 200-mg/day group	17.6	0.031
LCM 400-mg/day group	21.2	0.002
Second week of exposure to LCM (LCM 200 mg/day)		
LCM 200-mg/day group	25.3	0.001
LCM 400-mg/day group	18.3	0.007

RANDOMIZED CONTROLLED TRIALS IN

EPILEPSY

A total of three randomized controlled trials in adults with partial complex epilepsy where lacosamide was used as an adjunctive have been completed to date. All three used similar randomization with double-blind parallel-group design in a 12-week dose escalation with target 100 mg/day increments followed by a 12-week maintenance period.

Ben-Menachem et al. (12,13) in a multicenter, international, double-blind, placebo-controlled, randomized, dose–response study, involving 418 adults with refractory partial epilepsy, demonstrated significant efficacy at doses of 400 and 600 mg/day. At these dosages, compared to placebo, median seizure frequency was reduced 40%, with 49% of patients experiencing a 50% or greater reduction in seizure frequency. A dose–adverse effects relationship was seen with doses of 600 mg/day most consistently associated with the highest adverse event rate. In these studies, adverse effects included common neurologic symptoms, including nausea, headache, ataxia, fatigue, and diplopia. Serious adverse effects resulting in medication withdrawal occurred in <1% of all patients. Adverse effects resulting in withdrawal most frequently consisted of exacerbation of convulsive seizures and intolerable dizziness. Lacosamide appeared to be neutral on its effect on body weight. Importantly, there was no change in the serum concentrations of coadministered anticonvulsants. When lacosamide is added to other sodium channel agents, there is an additive effect on experienced adverse effects (14,15). Furthermore, rapid titration to high doses of lacosamide with simultaneous tapering of other sodium channel AEDs was associated with a marked reduction in adverse events when compared to that reported for fixed doses of concomitant AEDs (14,15).

Dose-Range Study

Dose-finding studies are critically important in the clinical development of a new drug. They help define the no-effect, mean effective, and maximal effective doses and determine a potentially optimal therapeutic dose range. In a pooled post hoc review of 1294 patients treated in three placebo-controlled, double-blind, international clinical trials evaluating the efficacy and safety of adjunctive lacosamide (200 to 600 mg/day) in adults ≥17 years with partial-onset seizures with or without secondary generalization, Chung et al. (16) found consistent seizure reduction for lacosamide dosages 400 and 600 mg/day. Dosage with 200 mg/day produced a variable effect, although pooled data suggested that 200 mg/day was efficacious compared to placebo. Lacosamide 400 mg/day added to between 1 and 3 other antiepileptic medications in 466 patients with intractable epilepsy in phases 2 and 3 double-blind placebo-controlled studies was examined to understand medication efficacy (17). Lacosamide was added to carbamazepine (33%), lamotrigine (33%), levetiracetam (30%), valproate (23%), topiramate (23%), and oxcarbazepine (17%). Median percent reduction over 28 days in seizure frequency from baseline was 36.8% for lacosamide 400 mg/day versus 18.4% for placebo. Lacosamide showed a similar magnitude of reduction versus placebo regardless of which combination of antiepileptic medication regimens it was added to. Importantly, efficacy was demonstrated whether lacosamide was added to a sodium channel–blocking AED or to an AED with other mechanisms of action. This suggests an independent additive efficacy in excess of that provided by preexisting antiepileptic medication to which lacosamide was added.

The time of onset of efficacy is an important consideration in the choice of antiepileptic medication. Lacosamide appears to have an early onset of efficacy against seizures. Secondary analysis of lacosamide in a pooled analysis of three Phase 2 and Phase 3 trials demonstrated efficacy

in the early weeks after addition (18).

Lacosamide in fixed doses of 200, 400, or 600 mg/day was used in these pooled data. Titration was started at 100 mg/day during the initial week of lacosamide exposure, followed by weekly titration in 100 mg increments to the assigned target dose. After the first week of lacosamide exposure to 100 mg/day, the percent reduction of seizures over placebo was 17.9% ($P < 0.01$) and only slightly improved to 20.4% by the second week when patients were receiving 200 mg/day. Post hoc pooled analysis showed an early onset of efficacy starting at a dose of 100 mg/day in the first week and increasingly modestly after that for patients where lacosamide was added to their antiepileptic medication regimen. Thus, efficacy can be expected in the first week or two following initiation of adjunctive lacosamide. Prospective trials are required to confirm these findings.

Clinical use suggest that lacosamide be initiated as an adjunctive at 50 mg twice daily with subsequent dose increases on a weekly basis to a target dose of 200 to 400 mg/day in adults with partial epilepsy. The availability of a parenteral formulation has the potential to be useful in the management of acute seizures, although studies in status epilepticus are still to be performed. Studies in other populations, including pediatrics and the elderly, are needed to further define the therapeutic spectrum of lacosamide.

Recently, 5-year open-label long-term safety and efficacy follow-up has been studied. Efficacy based on retention of lacosamide exposure was reported for >1, >2, >3, or >4 years as being 75%, 63%, 54%, and 29%, respectively. Primary reasons for discontinuation were lack of efficacy (26%) and adverse events (11%). Common treatment-emergent adverse effects were similar to currently reported adverse effects with dizziness, headache, contusion, nausea, convulsion, nasopharyngitis, fall, vomiting, and diplopia being most common. Of patients exposed to lacosamide ≥2 years, 3.1% remained seizure-free for a period ≥2 years (23).

Studies in Diabetic Neuropathy

At least three randomized placebo-controlled double-blind trials have been completed to test the efficacy of lacosamide in diabetic neuropathy–related pain. Lacosamide appears to be effective in doses up to 400 mg/day. However, doses of 600 mg/day were not associated with further increments in efficacy and were generally less well tolerated (20).

ABSORPTION, DISTRIBUTION, AND METABOLISM

The pharmacokinetic properties of lacosamide include a fast rate of absorption, little metabolism with cytochrome P450 isoenzymes with about 20% metabolized via CYP2C19, limited effect of age and gender on plasma levels, and low potential for drug–drug interactions (21).

Oral administration of lacosamide results in rapid and near complete absorption with minimal first-pass effects (22). Bioavailability after oral administration approaches 100%, with peak plasma concentration being reached after 30 minutes to 4 hours following oral administration. Dose to plasma concentrations are linear with low intra- and intersubject variability. Food appears to have a no influence on lacosamide's absorption with oral bioavailability reaching 100% (23). Escalating dose administration orally results in near linear increases in serum concentration. Lacosamide administered in a 300-mg single dose following consumption of a high fat diet did not influence its serum concentration. Lacosamide has an apparent volume of distribution of about 40 to 60 L (0.5 to

0.8 L/kg) and has a low plasma protein binding, with <15% of serum lacosamide being bound to plasma protein. Distribution in placenta and breast milk and distribution in children have not been examined.

INTERACTIONS WITH OTHER DRUGS

Given the pharmacokinetic properties, the probability of drug–drug interactions with lacosamide treatment is likely to be low (13,24). When used at therapeutic concentrations, lacosamide did not have a significant effect on the cytochrome P450 enzyme system. Human hepatocyte showed no potential to induce cytochrome P450 isoforms including 1A2, 2B6, 2C9, 2C19, and 3A4. At 30 times higher than "therapeutic" human plasma concentrations, lacosamide exerted a 60% inhibition of CYP2C19 function. The dosage at which this inhibition would be expected is unlikely to be routinely achieved in the treatment of human epilepsy.

Twenty-three patients had a baseline median of 4 seizures per month with persisting partial-onset seizures, despite previous treatment with an average of 6.8 AEDs. Mean decreases in monthly seizure frequency were as follows: 3 months, 49.9% ($P = 0.011$); 6 months, 55.4% ($P = 0.010$); 9 months, 60.8% ($P = 0.002$); and 12 months, 58.2% ($P = 0.011$). Most adverse events were mild CNS-related symptoms and occurred transiently only during titration—there was no significant relationship ($\chi^2 < 1.5$, $P > 0.1$) between lacosamide dose and the presence of side effects at 3, 6, 9, or 12 months. Drug-resistant patients rapidly titrated to high doses of lacosamide with simultaneous tapering of traditional sodium channel AEDs had marked reduction in CNS-related adverse events compared with patients treated in three previous pivotal trials that used fixed doses of concomitant AEDs.

Coadministration of lacosamide 400 mg/day did not alter the pharmacokinetics of warfarin 25 mg or anticoagulation. These results suggest that there is no need for dose adjustment of warfarin when coadministered with lacosamide (14,15).

ADVERSE EFFECTS

Animal Toxicology

Single as well as 3-, 6-, and 12-month repeated-dose studies in mice, rats, and dogs did not demonstrate adverse effects that persisted after discontinuation of lacosamide. Signs of dose-related toxicity, typically seen with other antiepileptic medication, including ataxia, tremor, and reduced motility, occurred. At high doses, paradoxical convulsions were observed. This supratherapeutic effect was similar to that described for phenytoin, gabapentin, and carbamazepine.

Clinical Adverse Effects

Adverse events were evaluated in 944 subjects randomized to receive either lacosamide 200 mg/day (n = 270), 400 mg/day (n = 471), or 600 mg/day (n = 203) or placebo (n = 364) (10). A dose–adverse effect relationship was seen for frequently reported nervous system and gastrointestinal adverse effects. All patients were on between 1 and 3 other concomitantly administered antiepileptic drugs, including carbamazepine (35%), lamotrigine (31%), levetiracetam (29%), valproate (24%), topiramate (22%), oxcarbazepine (18%), and phenytoin (14%).

Frequently reported treatment-emergent adverse events are shown in Table 56.2. Other adverse

events including peripheral edema (1%), weight gain (1%), memory impairment (2%), pancreatitis (0.1%), and psychotic disorders (0.2%) were low and generally similar to placebo. Clinically relevant changes in observed laboratory parameters, ECGs, vital signs, or body weight measurements were not seen, although there was a small, dose-related increase in PR interval. Generally, lacosamide was well tolerated when combined with up to three concomitant antiepileptic medications. Lacosamide has been FDA approved in the United States as a class V controlled substance. All AEDs have a labeling from the FDA as class V agents since 2008. The increased risk of suicidal thoughts or behavior was generally consistent among antiepileptic medication despite varying mechanisms of action and across a range of indications including epilepsy. Accordingly, the Federal Drug Administration has required that all AEDs carry the label warning of the risk used for any indication.

Table 56.2 Most Common Treatment-Emergent Adverse Effects (≥2%) Resulting in Early Discontinuation

Adverse effects	Placebo (n = 364) (%)	LCM 200 mg/day (n = 270) (%)	LCM 400 mg/day (n = 471) (%)
Dizziness	0.3	0.4	4.2
Vomiting	0.3	0.4	2.3
Diplopia	0.3	1.5	2.1

Cardiac conduction disturbances, including atrial fibrillation and atrioventricular block, have been reported in patients receiving lacosamide for epilepsy. This is a particular concern when lacosamide used to treat diabetic neuropathy due to the higher cardiac comorbidity associated with diabetes (25).

Intravenous Administration

Intravenous administration of lacosamide was studied in a multicenter, double-blind, double-dummy, randomized, inpatient trial evaluating the safety, tolerability, and pharmacokinetics as replacement for oral lacosamide (9). This study utilized patients from an open-label extension trial of oral lacosamide and randomized to either intravenous lacosamide and oral placebo or intravenous placebo and oral lacosamide. Infusions occurred over either 30- or 60-minute time periods. Treatment-emergent adverse events were mild and included dizziness, headache, back pain, somnolence, and injection site pain and were similar to oral lacosamide. There were no significant cardiac/hemodynamic adverse effects noted, and there does not appear to be the need for special monitoring of cardiovascular function. Efficacy of the intravenous formulation in partial complex seizures or status epilepticus has not been studied. There have not been clinical trials evaluating lacosamide for status epilepticus. This is not surprising given the very recent availability of an intravenous formulation. Given lacosamide's pharmacokinetic profile, a 1:1 substitution of intravenous to oral dosage has been approved by the Federal Drug Administration. Optimum effective dosage in adults is 200 to 400 mg/day suggesting similar-type dosages for intravenous formulation. Case reports of usage in adults with status epilepticus have reported the use of 200 mg administered intravenously over 30 minutes with a subsequent repeat in 30 minutes. However, such recommendations need to be substantiated by carefully designed clinical studies.

Recent studies (26) have safely administered 200 and 300 mg of lacosamide intravenously over 15 minutes in patients with partial-onset seizures.

Infusion with 400 mg loading was less well tolerated due to a higher frequency of adverse events that were similar to that for oral dosing.

CONCLUSIONS

Lacosamide is a novel anticonvulsant with a favorable pharmacokinetic profile including low protein binding, a long half-life, and good bioavailability that is not affected by food intake. Furthermore, the lack of induction or inhibition of the hepatocyte CYP family renders a low potential for clinically significant drug–drug interactions. Weight neutrality and absent skin rashes, at least in limited studies, are favorable features. Efficacy from pooled analysis indicates target doses of 200 to 400 mg/day are likely to have optimum effect with an acceptable and low adverse effect rate. Clinical use in adults with partial epilepsy suggests that lacosamide be initiated as an adjunctive at 50 mg twice daily with subsequent dose increases on a weekly basis to a target dose of 200 mg/day. Dizziness is the most common adverse event, followed by gastrointestinal disturbances such as nausea and vomiting. The availability of a parenteral formulation has the potential to be useful in the management of acute seizures, although studies in status epilepticus are still to be performed. Studies in other populations, including pediatrics and the elderly, are also needed to further define the therapeutic spectrum of lacosamide in these populations.

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CHAPTER 57 LAMOTRIGINE

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CHEMISTRY AND MECHANISM OF ACTION

Lamotrigine is a phenyltriazine, tertiary amine derivative (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, MW = 256.09), which is poorly soluble in water or alcohol. A primary cellular mechanism of action for lamotrigine is voltage- and use-dependent blockade of neuronal sodium channels, that is, greater blockade during repetitive activation (1–7). Lamotrigine blockade of sodium channels activated from depolarized membrane potentials occurs at lower concentrations than those required to elicit blockade from a hyperpolarized membrane and occurs at clinically achievable concentrations (6). A potential binding site within the sodium channel pore has been identified, and lamotrigine appears to stabilize the inactivated state of the sodium channel (8).

In addition to sodium channels, lamotrigine produces dose-dependent inhibition of high-voltage–activated Ca^{++} currents, possibly through inhibition of presynaptic N- and P/Q-type calcium channels (9,10). Despite its apparent clinical activity in human absence seizures, lamotrigine does not appear to inhibit low-voltage currents mediated by T-type calcium channels. Although these actions are mechanistically similar to those of phenytoin, important differences do exist between these agents. Veratrine-evoked release of both glutamate and GABA is inhibited by phenytoin. At similar concentrations, however, lamotrigine is twice as effective in inhibiting the release of glutamate as compared to GABA (11). Release of excitatory amino acid neurotransmitters such as glutamate and aspartate is blocked during sustained repetitive firing. Animal models also suggest that lamotrigine inhibits ischemia-induced release of excitatory neurotransmitters (12–15). Inhibition of nitric oxide release (16) and serotonin uptake (17) may also modestly contribute to lamotrigine's action in both epilepsy and affective disorders. Lamotrigine appears to display only modest inhibition of potassium channels. Similarly, lamotrigine is only a weak inhibitor of 5-HT uptake in humans or rodents (17). Lamotrigine is not an N-methyl-D-aspartate receptor antagonist (18), nor does it displace other ligands for this receptor complex (CNQX, CGS, TCHP). Furthermore, lamotrigine does not appear to alter either plasma or brain GABA concentrations in humans (19,20). Most likely, the antiepileptic actions and clinical spectrum of lamotrigine can be predominantly explained by the combination of both sodium and calcium (N, P/Q) channel inhibition.

Lamotrigine is effective in preventing maximal electroshock seizures in mice with potency and duration that are similar to phenytoin and carbamazepine (21). In contrast to its clinical efficacy for absence seizures, lamotrigine does not prevent pentylenetetrazole-induced clonus, which is a model of absence seizures (21). Lamotrigine is active in suppressing photically evoked after-discharges and photoconvulsive responses (22) and has demonstrated activity in the genetic epilepsy-prone rat (23). Lamotrigine has also demonstrated efficacy in the electrically induced electroencephalogram after-discharge model (24). While lamotrigine does not prevent the development of cortical kindling in rats, it does attenuate kindled seizures in a dose-dependent manner (24–26).

ABSORPTION, DISTRIBUTION, AND METABOLISM

Lamotrigine is an orally administered drug and is available in a variety of dosage strengths, and also including dispersible tablets and extended-release tablets. Bioequivalence has been established between these various product formulations. Lamotrigine is completely absorbed, with a bioavailability of 98% (27,28). Peak serum concentrations are achieved within 1 to 3 hours following oral administration (29–31). Lamotrigine displays linear oral absorption, with proportionality observed following doses up to 700 mg (32–34). A secondary peak in serum concentration may occur between 4 to 6 hours following either oral or parenteral administration, suggesting enterohepatic recycling. Food does not significantly affect drug absorption (35).

The extended-release formulation of lamotrigine that is marketed as Lamictal XR has an enteric coating and a modified-release core. A small aperture is drilled through the coating, allowing for a gradual dissolution rate over approximately 12 to 15 hours. Pharmacokinetic studies in patients with epilepsy (36) have demonstrated that this extended-release formulation is bioequivalent to the immediate-release brand product, when patients are converted from twice-daily branded lamotrigine (Lamictal) to once-daily Lamictal XR. In this study, peak-to-trough fluctuations for once-daily Lamictal XR were less than twice-daily immediate-release Lamictal, particularly in those patients receiving a concomitant enzyme-inducing antiepileptic drug (AED). Simulation studies suggest that lamotrigine serum concentrations may remain more stable following a missed dose with the XR, once-daily formulation as compared to twice-daily administration of the IR product in the same setting. This same study suggested that doubling the dose after a missed dose for either XR or IR formulation would not be expected to result in excessively high peak serum concentrations (37).

Lamotrigine is also systemically absorbed following rectal administration, although mean AUC (area under plasma concentration-time curve) are approximately 50% of corresponding oral administration values (38,39).

Lamotrigine is only moderately bound to plasma proteins with approximately 56% bound, and this is constant over a concentration range of at least 1 to 10 μg/mL (32). In vitro studies have demonstrated that lamotrigine protein binding is unaffected by phenytoin, phenobarbital, carbamazepine, and valproate (32). Lamotrigine volume of distribution is independent of dose and ranges between 0.9 and 1.2 L/kg in healthy volunteers (14,40). Recent data suggest that lamotrigine distribution into the brain may be mediated, at least in part by a specific influx transporter, OCT1. Whether this may result in clinically meaningful drug interactions (i.e., inhibitors of OCT1) is still unclear (41). In contrast, lamotrigine does not appear to be a substrate for multidrug resistance–associated proteins that have been implicated in treatment-resistant epilepsy (42).

In humans, lamotrigine is extensively hepatically metabolized by UDP-glucuronyltransferase (UGT 1A4, UGT 2B7) (43). Glucuronide conjugation can occur at both heterocyclic nitrogen atoms to form a quaternary amine glucuronide (44). In healthy volunteers, 70% of a single dose was recovered in the urine (32), with the 5-N and 2-N-glucuronide metabolite accounting for 90% of the recovered dose. This glucuronide metabolite is pharmacologically inactive. Genetic polymorphisms in one or both of these UGT isozymes may contribute to the observed interindividual variability seen with this agent (45,46). Renal elimination of unchanged drug accounts for a minor fraction of administered dose (<10%).

When given as monotherapy in adults, lamotrigine elimination half-life is approximately 24 to 29

hours. Oral clearance averages 0.35 to 0.59 mL/min/kg (47). Lamotrigine clearance is higher in children and lower in the elderly as compared to young adults. The concentration/dose ratio of lamotrigine was approximately 30% to 50% lower in young children (3 to 6 years) versus that seen in older children (7 to 15 years) or young adults (48). Mean lamotrigine oral clearance was 0.64 mL/kg/min and elimination half-life was 32 hours, in 12 children (ages 4 to 11 years) receiving monotherapy (49). Advancing age has modest effects upon lamotrigine clearance and half-life. In a group of elderly volunteers (ages 65 to 76 years), lamotrigine clearance was 37% lower than a group of young adults (ages 26 to 38 years) (31). In another study, lamotrigine clearance in older adults (55 to 92 years) was been found to be 22% lower than in younger adults (16 to 36 years) (50).

Evidence demonstrates that lamotrigine undergoes autoinduction. Population analysis of sparse data obtained retrospectively from 163 monotherapy patients demonstrates a 17% increase in clearance over a 48-week period (51). As lamotrigine initiation usually involves gradual dose escalation, this modest degree of autoinduction is not clinically meaningful.

Hepatic disease, depending upon severity, can influence lamotrigine pharmacokinetics, and patients with Child–Pugh scores of 5 to 6 (B) or 7 to 9 (C) requiring dosage reductions of 50% to 75%, respectively (52). No significant differences in the plasma clearance of lamotrigine have been noted in patients with chronic renal failure (53). Approximately 17% of a lamotrigine dose may be removed by hemodialysis, with a corresponding reduction in half-life to about 13 hours (54).

The apparent oral clearance of lamotrigine does not appear to significantly differ between men and women overall (51). However, the magnitude of alterations in lamotrigine concentrations exceeds that described for many of the older AEDs, perhaps due to sex hormone–mediated activation of UDP-glucuronyltransferase (55,56). Supporting this possibility is the observation that lamotrigine clearance may transiently decrease during menopause (57). Moreover, lamotrigine oral clearance may be markedly (>65%) increased during pregnancy, with changes being most evident during the second and third trimester.

In association with this change, women treated with lamotrigine may experience increased seizure frequency due to decreased serum concentrations. Data from Pennell et al. (58) indicated that lamotrigine total and unbound oral clearance were increased during all three trimesters, with peaks of 94% (total) and 89% (unbound) in the third trimester. In this study population, seizure frequency significantly increased when the lamotrigine serum concentration decreased to 65% of the individualized, preconceptional value. Lamotrigine oral clearance appears to return to baseline values during the early postpartum period, which necessitates further dose modifications soon after delivery (59). In that, these changes in oral clearance may result in reduced serum concentrations and possibly increased seizures during pregnancy, monitoring lamotrigine serum concentrations before, during, and immediately after pregnancy is clearly prudent (60).

A well-defined serum concentration–effect range for lamotrigine has yet to be conclusively established (61), and individual patients may respond to a wide range of concentrations. A target range of 4 to 14 μg/mL has been suggested by some investigators for patients with epilepsy (62,63). Use of serum concentration data may aid in the interpretation of drug interactions and adherence issues. Given ongoing concerns regarding the interchangeability of various generic formulations of this drug (64,65), additional monitoring of serum concentrations both before and following generic substitution would also seem prudent.

DRUG INTERACTIONS

Effect of Other Drugs on Lamotrigine

Comedication with Hepatic Enzyme–Inducing AEDs

Lamotrigine displays substantial interpatient variability in plasma clearance; a phenomenon that can largely be explained by the presence or absence of concomitant drug therapy (66,67). Lamotrigine elimination half-life is reduced by approximately 50% ($t_{1/2}$ about 12 to 15 hours) in the presence of UGT-inducing drugs, such as carbamazepine, phenobarbital, primidone, and phenytoin (22). While the effect of adding an enzyme inducer to a regimen containing lamotrigine is well recognized, an important clinical question involves deinduction, following the removal of a concomitant inducer such as phenytoin or carbamazepine. In a recent pharmacokinetic analysis of lamotrigine serum concentration data derived from the pivotal conversion-to-monotherapy trial (68), Anderson et al. found that mean lamotrigine serum concentrations increased by approximately 100% following the withdrawal of concomitant phenytoin treatment, the increase was only 50% to 75% following the withdrawal of concomitant carbamazepine treatment. Importantly, these data suggested that lamotrigine concentrations did not significantly change (increase) until the concomitant enzyme-inducing drug was completely removed, and concentrations of either phenytoin or carbamazepine approached zero (69).

There do not appear to be any significant interactions between lamotrigine and newer AEDs such as topiramate, felbamate, gabapentin, pregabalin, zonisamide, vigabatrin, or levetiracetam, lacosamide or perampanel. Modest reductions (approximately 30%) in lamotrigine serum concentrations have been noted in patients receiving concomitant oxcarbazepine (70–73) and eslicarbazepine (approximately 14%) (74). Comedication with ezogabine (retigabine) also seems to result in a modest 20% reduction in lamotrigine serum concentrations (75).

Comedication with Valproate

As lamotrigine does not undergo cytochrome P450–dependent metabolism, only drugs that inhibit UGTs, such as valproate, will decrease lamotrigine clearance and result in increased serum concentrations. Valproate can markedly reduce lamotrigine clearance and prolong elimination half-life by about 60 hours (76). Pharmacokinetic studies in adult volunteers have suggested that the maximal theoretical inhibition of lamotrigine clearance by valproate is approximately 65%, with 50% of maximal inhibition occurring at valproate plasma concentrations of approximately 5 to 6 μg/mL. Maximal theoretical inhibition appears to occur at valproate concentrations of approximately 50 μg/mL. These data suggest that valproate-mediated inhibition of lamotrigine begins at very low valproate doses (e.g., 125 to 250 mg/day), with maximal inhibition occurring at valproate doses of approximately 500 mg/day (77).

While earlier studies suggested that concurrent treatment with lamotrigine may result in modestly decreased valproate serum concentrations, this is unlikely to be of clinical significance (78,79).

Effect of Lamotrigine upon Other Drugs

Lamotrigine does not induce or inhibit the mixed-function oxidase system (cytochrome P450 isozymes). In addition, lamotrigine is not extensively bound to plasma proteins. These properties would predict lamotrigine to have a low incidence of causing pharmacokinetic interactions. Addition

of lamotrigine does not alter serum concentrations of phenytoin, phenobarbital, primidone, carbamazepine, or carbamazepine epoxide (47,54,80,81). Lamotrigine does not appear to significantly alter hormone concentrations in female volunteers taking oral contraceptives (OCs) (82).

Effect of NonAEDs on Lamotrigine

Daily doses of acetaminophen, a drug that is 55% eliminated by glucuronide conjugation, but not an inducer of UGT, unexpectedly increased lamotrigine clearance. Occasional use of acetaminophen would not be expected to alter lamotrigine pharmacokinetics (83). One anecdotal report has suggested a potential interaction between the serotonin-selective reuptake inhibitor sertraline and lamotrigine, with lamotrigine serum concentrations increasing following the addition of the antidepressant (84); however, changes in lamotrigine concentrations are likely to be modest and are unlikely to be relevant in most patients (85).

While lamotrigine does not alter the pharmacokinetics of OC medications, clinical reports have indicated that concomitant treatment with combined OCs may decrease lamotrigine serum concentrations, possibly due to induction of UGT by ethinyl estradiol (86–88). The addition of an OC-containing ethinyl estradiol may decrease lamotrigine serum concentrations by as much as 30% to 50%. Importantly, this interaction dissipates quite rapidly during the pill-free week and within 1 week following discontinuation of OC.

EFFICACY

Lamotrigine is indicated by the United States Food and Drug Administration (FDA) as adjunctive therapy for patients ≥2 years of age with

- Partial seizures
- Primary generalized tonic–clonic (PGTC) seizures
- Generalized seizures of Lennox–Gastaut syndrome

Lamotrigine is indicated by the FDA for conversion to monotherapy for patients ≥16 years of age with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as a single AED. Although data from several clinical trials suggest utility, lamotrigine has not yet received FDA approval as initial monotherapy.

The extended-release formulation of lamotrigine is indicated by the FDA for patients ≥13 years as

- Adjunctive therapy for PGTC seizures and partial-onset seizures with or without secondary generalization
- Conversion to monotherapy for partial seizures being treated with a single AED

Adjunctive Therapy for Partial Seizures

Seven premarketing multicenter, double-blind, placebo-controlled add-on trials supported the efficacy of lamotrigine as adjunctive treatment for partial seizures in adults (89). The study with the highest dose (500 mg) (90) demonstrated a mean reduction in seizure frequency of 36% compared to baseline. Seizure frequency was reduced by greater than 50% in about one-quarter of these patients. The placebo group had an 8% reduction in seizure frequency relative to baseline. These studies

supported the initial approval for the indication of lamotrigine as adjunctive therapy for partial seizures in persons 16 years and older. A subsequent pediatric trial demonstrated efficacy over placebo in 201 children from 40 sites in the United States and France and supported an FDA indication for children who are at least 2 years old (91).

Naritoku et al. (92) confirmed that once-daily, extended- release lamotrigine was effective as adjunctive treatment in patients (13 years and older) with partial seizures, many of whom had tried multiple other AEDs without seizure control. In this study, the percentage of patients with at least a 50% reduction in seizure frequency was significantly greater than placebo (42% vs. 24%, $P = 0.0037$).

Monotherapy for Partial Seizures

Efficacy as monotherapy in partial seizures has been shown by several trials, including a multicenter, double-blind randomized trial comparing 500 mg of lamotrigine to an active control of 1000 mg of valproate (68) and a conversion-to-monotherapy study using an historical control group (93). The primary end point for the active control study was proportion of patients exiting the trial according to a criterion of doubling of greatest 2-day or 1-month seizure rates observed in the baseline period. With this primary end point, 56% of patients taking lamotrigine completed the trial compared to 20% receiving low-dose valproate. In the historical control study, exit rates for participants were less than the aggregated exit rates for pseudoplacebo groups in eight completed conversion-to-monotherapy trials. Lamotrigine has been shown to have equivalent efficacy to immediate-release carbamazepine (94) and phenytoin (95) in double-blind, randomized clinical studies of recent-onset epilepsy in adults. Similarly, lamotrigine was shown to have comparable effectiveness when compared to controlled- release carbamazepine in newly diagnosed elderly patients with epilepsy (96).

The SANAD trial (97), which was an unblinded, randomized effectiveness trial conducted in the United Kingdom, suggested that lamotrigine was at least as effective as carbamazepine in patients with newly diagnosed partial seizures. Patients treated with lamotrigine were found to have a significantly longer time to treatment failure than either gabapentin or topiramate.

Lennox–Gastaut Syndrome in Children

A large ($n = 169$) multicenter, double-blind, randomized add-on trial of lamotrigine demonstrated efficacy of lamotrigine for the treatment of major motor seizures in children and young adults with Lennox–Gastaut syndrome (98). The age range for the study was 2 to 25 years. The target dose of lamotrigine was 15 mg/kg for patients not taking valproate and 5 mg/kg for those taking valproate. Major motor seizures, defined as atonic, tonic, major myoclonic, and tonic–clinic, were reduced by 32% compared to baseline. The placebo group had only a 9% reduction in major motor seizures. This study supported the FDA indication for major motor seizures in Lennox–Gastaut syndrome in adults and children. Other studies have supported the efficacy of lamotrigine in Lennox–Gastaut syndrome (99–101).

Other Generalized Epilepsy Syndromes

Although lamotrigine has not received FDA approval for the indication of treatment of childhood absence epilepsy and juvenile myoclonic epilepsy, several studies have identified effectiveness for the seizures of these syndromes (102–106). A double-blind, randomized, placebo-controlled

"responder- enriched" study of recently diagnosed typical absence seizures that confirmed seizure frequency by 24-hour EEG and hyperventilation EEG found that 62% of patients were seizure free compared to 21% in the placebo group (106). Glauser et al. (107), however, have reported that in children with newly diagnosed childhood absence, treatment with either valproate or ethosuximide was more efficacious when compared to treatment with lamotrigine. This result was obtained at both 16 weeks and 12 months of treatment (108). Another double-blind, placebo-controlled, add-on crossover study of treatment-resistant generalized epilepsy demonstrated that lamotrigine significantly reduced seizures that had not been controlled by other AEDs; 25% of the sample became seizure free (102). A small case series suggested that myoclonus may worsen with lamotrigine treatment in some patients with generalized epilepsy (109).

Data from Biton et al (110) suggest that lamotrigine is effective as adjunctive therapy for PGTC seizures. In a double-blind placebo-controlled trial, where lamotrigine was added to patients with recurrent PGTC seizures and concurrently receiving one or two background AEDs, seizure frequency was reduced by approximately 66% (vs. 34% in the placebo arm). Seventy-two percent of patients treated with lamotrigine (vs. 49% of placebo) experienced a 50% reduction in seizures. Importantly, no serious adverse events, nor aggravation of other seizure types, was noted. Efficacy and tolerability of once-daily adjunctive administration of the XR formulation has also been demonstrated, with statistical separation from placebo occurring as early as 1 week (111).

In an unblinded, randomized effectiveness trial, Marson et al. (112) found that in patients with idiopathic generalized seizures, initial treatment with valproate was significantly better with respect to time to 12-month remission than with lamotrigine; however, no significant differences were seen for time to treatment failure between these two treatments. Similarly, long-term seizure freedom in patients with juvenile myoclonic epilepsy has been reported to be comparable in patients randomized to receive lamotrigine or valproate (113). While these data are certainly useful, the decision as to which agent should be considered drug of the first choice will likely still depend on patient-specific characteristics, such as gender, pregnancy, weight gain, etc.

SAFETY AND TOLERABILITY

Similar to efficacy, the safety profile of lamotrigine has been defined by numerous clinical studies. Of the adverse effects reported with lamotrigine, rash has received the most attention (114,115). The pathologic mechanism is not known, but a genetic basis and an association between certain HLA alleles are suspected, but not as of yet confirmed (116–118). A cross-reactivity for rash with other antiepileptic medications, especially carbamazepine and phenytoin, appears to be present (119).

The incidence of serious rash associated with hospitalization and discontinuation of lamotrigine in the pediatric population was assessed in a prospectively followed cohort of pediatric patients (2 to 16 years of age) with epilepsy receiving adjunctive therapy. In these patients, the incidence of serious rash was approximately 0.8%. In the adult population, serious rash associated with lamotrigine occurred in 0.3%. Interestingly, the clinical trials of lamotrigine for adults with bipolar disorder identified a rash rate of 0.08% in those receiving lamotrigine as initial monotherapy and 0.13% in those who receiving lamotrigine as adjunctive therapy. When compared to either carbamazepine or phenytoin as monotherapy for new-onset epilepsy, lamotrigine monotherapy for new-onset epilepsy had an equivalent rash rate (94,95).

In general, the risk for serious rash appears to be increased either when lamotrigine is initiated at a high starting dose or when the dosage is rapidly escalated (115). Attention and adherence to FDA-

approved dosage and titration schedules are clearly warranted. There is also evidence that the combination of valproate and lamotrigine may increase the risk of serious rash in both pediatric and adult patients.

The most common central nervous system and systemic adverse effects reported with lamotrigine conversion and monotherapy are shown in Table 57.1. Some adverse events are related to pharmacodynamic interactions, which occur most commonly with carbamazepine. Several double-blind, randomized monotherapy studies indicate that lamotrigine causes significantly less sedation or cognitive adverse effects than several other AEDs (68,94,95,120). Steiner et al. (95) reported that 28% of patients reported sleepiness while taking phenytoin, compared to 7% ($P < 0.05$) with lamotrigine. Brodie et al. (94) also found less sedation compared to carbamazepine (12% vs. 22%, $P < 0.05$), and more patients withdrew from the study due to adverse events on carbamazepine (15% vs. 27%). However, a randomized, double-blind comparison study of lamotrigine and carbamazepine for new-onset epilepsy in the elderly (aged 65 to 90 years old) found no significant difference in most quality of life and adverse effects measures (121). The one significant difference was a decrease in dysphoria for those taking lamotrigine. When compared to levetiracetam, lamotrigine did not have a significant difference in efficacy or tolerability in a prospective, randomized, open-label monotherapy study of patients with newly diagnosed focal or generalized epilepsy (122).

Table 57.1 Most Common Adverse Events in Pivotal Trial (n = 156) of Lamotrigine (500 mg/d) as Monotherapy Compared to Active Control Valproate (1000 mg/d) (82)

	Transition phase		Monotherapy phase	
	Lamotrigine (500 mg)	Low-dose valproate	Lamotrigine	Low-dose valproate
Dizziness	20%	23%	7%	0%
Nausea	16%	19%	7%	2%
Headache	13%	13%	7%	14%
Asthenia	12%	13%	2%	0%
Coordination abnormality	12%	0%	7%	0%
Vomiting	11%	9%	9%	0%
Rash	11%	8%	2%	2%
Somnolence	8%	14%	0%	2%
Tremor	7%	10%	5%	7%
Dyspepsia	0%	14%	7%	2%

Other studies have also suggested that lamotrigine has a favorable psychotropic profile and may improve mood in some patients (123–125). This observation is potentially confounded by decreased sedations and improved concentration after converting from less well-tolerated antiepileptic medications (126), but available evidence supports that lamotrigine can improve mood or even protect against adverse mood effects of other medications. For example, Mula et al. reported that concomitant treatment with lamotrigine was associated with reduced rates of adverse psychiatric reactions to levetiracetam (127) or topiramate (128).

Recently, an association between lamotrigine use and aseptic meningitis has been reported. While the mechanism underlying this relatively rare adverse effect is unclear, clinicians should consider this is cases of culture-negative meningitis (129).

Teratogenicity is another consideration in an assessment of safety. Data derived from rodents as well as human ex vivo placental perfusion studies suggest that lamotrigine easily and rapidly crosses

the placenta (40). Comparison of lamotrigine serum concentration in maternal and umbilical cord blood has identified a median infant-to-mother concentration ratio of 0.9 (SD 0.2) (130). A direct comparison of the effect of lamotrigine on the fetus has been found to be lower than valproate and similar to carbamazepine with an odds ratio of 1.48 (95% CI 0.47, 4.69) (131). Data from the Australian Pregnancy Registry suggest a malformation rate of 5.2% in women receiving lamotrigine monotherapy and, further, failed to find dose-dependent increase in risk (132). A large population-based registry identified a 2.2% major congenital malformation rate from a first-trimester exposure group that included 1558 women (133). This registry lacked an internal control group, which precludes an odds ratio calculation, but the rate is similar to the general population. This registry also failed to detect an increased frequency of major malformations with increased lamotrigine dose. However, a higher rate of 3.2% also has been observed, and lamotrigine has not been found to be without teratogenic potential (134,135). Lamotrigine is present in maternal milk at potentially clinically significant concentrations (136).

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CHAPTER 58 LEVETIRACETAM

JOSEPH I. SIRVEN, KATHERINE H. NOE, AND MATTHEW T. HOERTH

Levetiracetam (LEV) is a novel antiepileptic drug (AED) approved in 2000 by the U.S. Food and Drug Administration (FDA) as adjunctive therapy for patients with partial epilepsy, myoclonic seizures, and primary generalized tonic–clonic seizures. The compound was developed as a derivative of the nosotropic agent piracetam, with a wide spectrum of anticonvulsant effects in animal models of various types of epileptic seizures (1). It is chemically unrelated to existing AEDs. In addition to its unique chemical structure, LEV has a distinct mechanism of action and a favorable pharmacokinetic and safety profile, making it an attractive therapy for seizure management.

CHEMISTRY

LEV is a single enantiomer (−)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide with a molecular weight of 170.21 (1,2). The structural formula of the agent is shown in Figure 58.1. The drug is a white to off-white crystalline powder with a faint odor and bitter taste. It is very soluble in water (104.0 g/100 mL), freely soluble in chloroform and in methanol, and soluble in ethanol. It is much less soluble to insoluble in acetonitrile and n-hexane. LEV tablets contain LEV and the inactive ingredients silicon dioxide, cornstarch, methylcellulose, magnesium stearate, polyethylene glycol 4000, and coloring agents. LEV is supplied for clinical use in regular and extended-release tablets and as an oral and intravenous solution (2).

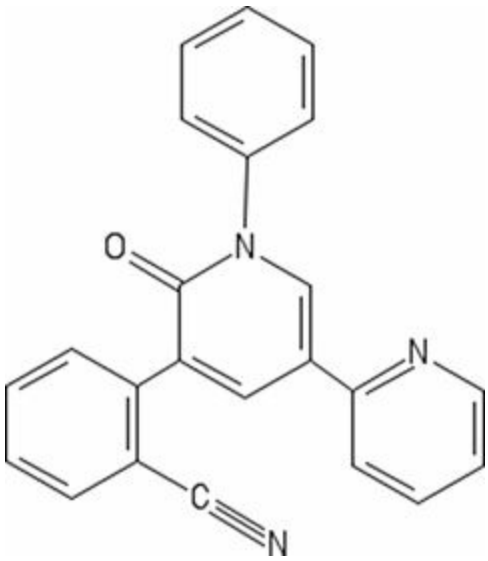

Figure 58.1. The chemical structure of LEV.

MECHANISM OF ACTION

Prior to undergoing standardized AED testing by the National Institutes of Health, LEV was found to

have antiepileptic properties. In contrast to previously approved AEDs, LEV lacked conventional modulation of the acute seizure model (maximum electroshock seizure test and pentylenetetrazol), suggesting a novel mechanism of action (3–5). Moreover, LEV displays unique potent protection against kindled seizures in both mice and rats during kindling models (3,4). In comparative tests with established AEDs in a number of animal models of epileptic seizures, LEV displays potent protection in a broad range of animal models of chronic epilepsy, including partial and primary generalized seizures (5).

The mechanisms by which LEV exerts its AED effect are still not fully defined. Initial investigations of classic AED targets such as neuronal voltage-gated sodium, T-type calcium currents, or gamma-aminobutyric acid A receptors did not demonstrate sufficient action to account for the effectiveness of the drug (6,7). Subsequently, LEV was determined to have a unique central nervous system–binding site, synaptic vesicle protein 2A (SV2A) (8,9). SV2A is a component of secretory vesicle membranes and has been shown to mediate calcium-dependent vesicular neurotransmitter release (10–12). Binding affinity for SV2A has been shown to correlate with antiepileptic potency in animal models of audiogenic, partial, and generalized seizures (9,13). However, the mechanism by which binding of LEV to SV2A results in antiseizure activity is not yet known. This is a focus of ongoing research, given the potential importance of SV2A as a target for development of new antiepileptic agents.

ABSORPTION, DISTRIBUTION, AND METABOLISM

Overview

LEV is rapidly and almost completely absorbed following oral administration. The pharmacokinetics is linear and time invariant, with low individual variability (14). LEV is not protein bound (<10%), and its volume of distribution is close to the volume of intracellular and extracellular water (14,15). Sixty-six percent of the dose is unchanged as it is excreted renally (14). The major metabolic profile of LEV is an enzymatic hydrolysis of the acetamide group (14,15). LEV is not liver cytochrome P450 dependent (14). Its metabolites have no known pharmacologic activity and are renally excreted. The plasma half-life of LEV across studies is approximately 6 to 8 hours. The effects of the agent are increased in the elderly (primarily due to impaired renal clearance) and in patients with renal impairment (14,15).

Absorption and Distribution

Absorption of LEV is rapid, with peak plasma concentrations occurring about 1 hour following oral administration. Oral bioavailability is 100%, with no effect from ingestion of food. Linear pharmacokinetics characterizes LEV over a dose range of 500 to 5000 mg. Steady state is achieved after 2 days of multiple twice-daily dosing. LEV is <10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein-binding sites are unlikely (14,15).

Metabolism and Elimination

LEV is not extensively metabolized in humans with the major metabolic pathway of enzymatic hydrolysis of the acetamide group, which produces the pharmacologically inactive carboxylic acid metabolite. There is no dependency on P450 cytochrome liver metabolism (14,15).

LEV is eliminated by renal excretion as unchanged drug, which represents 66% of the administered dose (14). The total body clearance is 0.96 mL/min/kg, and the renal clearance is 0.6 mL/min/kg (14,15). The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. Elimination is correlated with creatinine clearance (CrCl) (14).

Special Populations

Pediatrics

The pharmacokinetics of LEV has been evaluated in children 6 to 12 years of age following single 20-mg/kg doses. The apparent clearance of LEV was approximately 40% higher in children than in adults. The half-life in children is 4 to 8 hours, compared with approximately 7 hours in adults. The maximum concentration of drug (C_{max}) and area under the curve (AUC) values are comparable to those in adults. There is no correlation between age and clearance among pediatric patients (15).

Elderly

In older adults, total body clearance decreased by 38%, and the half-life was 2.5 hours longer compared with healthy adults (14).

Renal Impairment

Total body clearance of LEV is reduced in patients with impaired renal function by 40% in those with mild renal impairment (CrCl 50 to 80 mL/min), 50% in those with moderate impairment (CrCl 30 to 50 mL/min), and 60% in those with severe renal impairment (CrCl < 30 mL/min). In patients with end-stage renal disease, total body clearance decreased by 70% compared with those with normal renal function. About 50% of LEV is removed during a standard 4-hour hemodialysis procedure. Thus, dosage should be reduced in patients with impaired renal function, and supplemental doses should be given after hemodialysis (14).

Hepatic Impairment

The pharmacokinetics of LEV is unchanged in individuals with hepatic impairment. No dose adjustment is needed in patients with hepatic impairment (14).

DRUG INTERACTIONS

In vitro data on metabolic interactions indicate that LEV is unlikely to produce or be affected by pharmacokinetic interactions. Minimal plasma protein binding makes interactions due to competition for protein-binding sites unlikely (16). Potential pharmacokinetic interactions were assessed, but none were reported in clinical pharmacokinetic studies with phenytoin, warfarin, digoxin, and oral

contraceptives (17–20). Analysis of Phase 3 studies also revealed no pharmacokinetic interactions with other AEDs, such as phenytoin, carbamazepine, valproic acid, and phenobarbital (17,21).

EFFICACY

Partial-Onset Seizures

The effectiveness of LEV as adjunctive therapy in adults was established in three multicenter, randomized, double-blind, placebo-controlled clinical trials in patients with refractory partial-onset seizures with or without secondary generalization (22–24). Patients (N = 904) were randomized to one of four treatment arms: placebo, LEV 1000 mg, LEV 2000 mg, or LEV 3000 mg/day. Responder rates (50% or more reduction in seizure frequency compared with baseline) of 37.1% and 20.8%, respectively, were reported for 1000-mg/day doses for studies 1 and 2. At 2000 mg/day, a responder rate of 35.2% was reported; responder rates of 39.6% and 39.4%, respectively, were noted for 3000 mg/day (22–24). All of the response rates were statistically significant when all three LEV treatment arms were compared with placebo. Complete seizure freedom was reported to be 2% at 1000 mg and 6.7% at 3000 mg/day (22–24).

An interesting finding in study 1 was the rapid onset of efficacy of LEV (22). A significant reduction in weekly seizure frequency compared with that of the baseline period was observed during the first 2 weeks of the titration period, indicating that the agent has a rapid clinical effect at an initial dose (22). Open-label community trials confirmed the results noted in the pivotal trials, with efficacy achieved in patients at a dose of only 500 mg b.i.d. (25).

Four published studies have demonstrated the sustained efficacy of LEV as add-on epilepsy therapy for a period of at least 12 months and for as long as 54 months. The long-term tolerability of the agent is similar to that seen in the short-term, placebo-controlled trials (26–31).

Myoclonic Seizures

The effectiveness of LEV as adjunctive therapy in patients 12 years of age or older with juvenile myoclonic epilepsy (JME) experiencing myoclonic seizures was established after one multicenter, randomized, double-blind, placebo-controlled study (32). One hundred twenty-two patients were randomized to either placebo or LEV at a target dose of 3000 mg/day. A total of 58.3% of the LEV group responded (>50% reduction from baseline in myoclonic seizure days per week) versus 23.3% of those in the placebo arm; 25% of those treated with LEV were seizure free.

Primary Generalized Tonic–Clonic Seizures

LEV was evaluated for efficacy as adjunctive therapy in patients with idiopathic generalized epilepsy experiencing primary generalized tonic–clonic seizures by one randomized controlled multicenter trial (33). One hundred sixty-four subjects aged 4 to 65 years were randomized to either placebo or a LEV dose of 3000 mg/day or 60 mg/kg/day for children, added to one or two baseline AEDs. 77.2% of the LEV-treated group had a >50% reduction in GTC frequency versus 45.2% in the placebo arm. More subjects in the LEV arm were also seizure free (34.2% vs. 10.7%) during the evaluation period.

Monotherapy

Individuals with refractory partial epilepsy who completed a multicenter, double-blind, placebo-controlled parallel group with LEV 3000 mg/day were eligible for a monotherapy trial (24). Forty-nine patients entered the monotherapy arm. The median percent reduction in partial seizures was 73.8%, with a 50% responder rate of 59.2%. Nine patients (18.4%) remained seizure free on monotherapy (24).

In a multicenter, noninferiority comparison trial conducted in newly diagnosed patients with epilepsy, LEV was compared to controlled-release carbamazepine as initial treatment. At 1 year, seizure outcomes were similar, with 56.6% of patients randomized to LEV (N = 288) and 58.5% of patients receiving controlled-release carbamazepine (N = 291) were seizure free. Withdrawal rates due to treatment-emergent adverse events were 14.4% with LEV and 19.2% for those treated with controlled-release carbamazepine (34). LEV is not currently FDA approved as initial monotherapy.

Pediatrics

LEV has been evaluated in partial-onset seizures in children with epilepsy. One randomized, double-blind, placebo-controlled study was performed in North America with 60 sites and 198 pediatric patients between the ages of 4 to 16 years of age (35). Patients were randomized to placebo or to a dose of 20 mg/kg/day in two divided doses to a target dose of 60 mg/kg/day. The results showed a responder rate of 44.6% and a 26.8% reduction in weekly partial-onset seizures. A comparative trial was recently performed comparing LEV versus carbamazepine monotherapy for partial epilepsy in children <16 years of age. LEV was shown to have equal efficacy to carbamazepine (36).

Two open-label trials have been conducted to assess the efficacy and safety of LEV in children with partial seizures (15,37). Twenty-three children 6 to 12 years of age with treatment-resistant partial-onset seizures who were receiving one standard AED were eligible (32). Seizure frequency in these children was evaluated and compared with a 4-week baseline seizure frequency, using a 6-week titration to a target dose of 40 mg/kg/day. Twelve children (52%) responded (50% seizure reduction), with two patients remaining seizure free during the entire study period (37).

A small randomized trial of LEV versus placebo for children and adolescents with newly diagnosed absence epilepsy found no statistically significant response with short-term use (38).

Status Epilepticus

The availability of an intravenous formulation of LEV that can be infused relatively quickly without hemodynamic side effect has led to multiple case series reported in the literature. Ten of the highest quality studies were identified and systematically reviewed, which included a total of 334 patients. Of the patients reported, 279 were treated with LEV after the administration of a benzodiazepine, while the remaining 55 were treated as initial therapy. The definition of efficacy varied between the reviewed studies and ranged between 44% and 94%. No serious adverse effects were reported. The most common side effect noted was somnolence in up to 40%. Caution should be used when attempting to generalize these data, since none of these studies were controlled trials and 8 of the 10 studies were retrospective. Also, due to the design of these studies, many of these patients had relative contraindications to traditional therapies (39).

Subsequent to the systematic review, a larger randomized prospective open label trial of 79 patients in convulsive status epilepticus was published comparing LEV 20 mg/kg infused over 15

minutes to lorazepam and 0.1 mg/kg over 2 to 3 minutes. Primary end point was the cessation of seizure activity by 30 minutes. There was no statistical difference between the two groups for first-line therapy (LEV 79.8% vs. lorazepam 78.2%). Also, there was no statistical difference in response when crossed over to second-line therapy, seizure recurrence in 24 hours, and seizure freedom at 24 hours (40). From these initial data, a prospective randomized multicenter trials are planned to determine the effectiveness of LEV and other therapies in benzodiazepine refractory status epilepticus (41). LEV is not currently FDA approved for the indication of status epilepticus.

ADVERSE EVENTS

Central Nervous System

Three main types of CNS adverse effects are associated with LEV use: fatigue, coordination difficulties, and behavioral problems (22–24,37). In the three pivotal clinical trials, 14.7% of patients reported fatigue, whereas 3.4% had coordination problems. Coordination difficulties included ataxia, abnormal gait, and incoordination. Dose reduction improved these symptoms. Fatigue and coordination problems occurred most frequently within the first 4 weeks of treatment. Of patients treated with LEV, 13% reported such behavioral symptoms as agitation, hostility, anxiety, apathy, emotional lability, depersonalization, and depression (Table 58.1). Most of these symptoms occurred within 4 weeks of drug initiation (22–24). Dose reduction was associated with improvement in these behavioral problems, with only 0.8% of treated patients requiring hospitalization. In the open-label trial of children, there were no differences between adverse events reported in this population and those reported in adults (42).

Table 58.1 Neurologic and Psychiatric Adverse Effects of LEV

Neurologic effect	Reported incidence in placebo-controlled trials in adults
Somnolence	14.8%
Vertigo	3%
Agitation	6% (pediatric trials)
Nervousness	4%
Depression	6.7%
Irritability	7%
Suicidal ideation	0.5%
Anxiety	2%

Other Systemic Adverse Events

Table 58.2 illustrates systemic adverse effects that have been reported in clinical trials with LEV. The most frequently reported adverse events included asthenia, somnolence, and dizziness, which occurred predominantly during the first 4 weeks of treatment. In 15% of patients treated with LEV, somnolence was most often associated with discontinuation or dose reduction, followed by breakthrough seizures or dizziness (22–24).

Table 58.2 Adverse Effects of LEV: Systemic

Body system	Adverse effects
Cardiac	No effect
Dermatologic	Minimal rash potential
Gastrointestinal	No significant effect
Hematologic	Minor decreases in hemoglobin, red blood cell count, and white blood cell (WBC) count No patients required treatment discontinuation because of these effects
Hepatic	No meaningful changes in liver function tests
Infectious	Pharyngitis, rhinitis with no relationship to WBC count
Pulmonary	No effect

Pregnancy

Data from prospective observational pregnancy registries to date suggest that use of monotherapy LEV during the first trimester of pregnancy carries a relatively low risk for major congenital malformations (43–46). To date, in utero exposure to LEV has not been shown to adversely impact early-life cognitive development (46). Maternal serum LEV levels can fall significantly during pregnancy, so that monitoring of blood levels to guide dosing during gestation and in the postpartum period should be considered (47). LEV is excreted into breast milk, but serum drug levels in a small sample of breast-fed infants were shown to be low (47).

CLINICAL USE

The recommended dosage of LEV is between 1000 and 3000 mg/day in two divided doses (2). Although in some studies there was a tendency toward greater response with higher doses, a consistent increase in response with increased dose has not been reported. Indeed, some older adults may respond to a dose as low as 500 mg/day (48). Dosage should guide titration to clinical response.

LEV should be introduced gradually at 250 to 500 mg b.i.d. in adults, in order to reduce the potential for side effects and to identify the minimum effective dose. Increases of 250 to 500 mg/day at 1- to 2-week intervals are recommended. If behavioral symptoms occur, reducing the dose may be beneficial. Although LEV has a rapid onset of effect, dose escalation that is too rapid could lead to adverse effects. A therapeutic serum concentration has not been established for LEV. Dosage should be guided by clinical response. LEV may be ideally suited for individuals with seizures who are hepatically compromised or are taking multiple medications.

For adjunctive treatment of partial-onset seizures and primary generalized seizures, children from age 4 to 16 years should be initiated with a daily dose of 20 mg/kg in two divided doses (2). The daily dose can be increased every 2 weeks by increments of 20 mg/kg to a target dose of 60 mg/kg/day. In children 12 years of age or older with myoclonic seizures, treatment should be initiated with a dose of 1000 mg/day given as b.i.d. doses. The target maximum dose is 3000 mg/day (2).

OTHER PREPARATIONS

Extended-Release Formulation

There is an extended-release preparation of oral LEV based on matrix pill technology available. The bioavailability of Keppra XR tablets is similar to that of immediate-release LEV. Similarly, no differences exist between extended-release formulations and immediate-release LEV with regard to metabolism or renal excretion. Extended-release LEV is different than immediate-release LEV in that the time to peak plasma concentrations is about 3 hours longer with extended-release LEV than with immediate-release LEV. Single administration of two 500-mg extended-release LEV tablets once a day produces comparable maximal plasma concentration and AUC plots as one 500-mg immediate-release LEV taken twice daily. There are no tablet skeletons/shells seen in the stool.

Extended-release LEV was evaluated for efficacy as adjunctive therapy in one multicenter, double-blind, randomized, placebo-controlled study in patients with refractory partial seizures (49). Patients were randomized to placebo versus two 500-mg tablets of extended-release LEV. When compared to placebo, median reduction in seizure frequency for the extended-release group was 46.1% versus 33.4% ($P = 0.038$) for placebo during the 12-week treatment period. A subsequent meta-analysis of 555 patients over 16 years old comparing side effects from extended and immediate-release formulations demonstrated statistically significant less headaches favoring those treated with extended-release LEV. Trends toward less somnolence, dizziness, nervousness, anxiety, and depression were also reported but not statistically significant (50). The manufacturer suggests that treatment should be initiated as adjunctive therapy for partial seizures with a dose of 1000 mg once daily with dosage adjusted in increments of 1000 mg every 2 weeks to a maximum recommended dose of 3000 mg/day. There are no data for the use of extended-release LEV in myoclonic seizures, primary generalized epilepsy, and children. This formulation can be taken with or without food but must be swallowed whole and should not be crushed or chewed.

Intravenous Preparation

An intravenous formulation of LEV is available for adult patients 16 years and older when oral administration is temporarily not feasible (51–53). This preparation does not have an indication for seizure emergencies (2). Intravenous LEV and oral LEV result in equivalent pharmacokinetic parameters when IV LEV is administered as a 15-minute infusion. Its distribution, metabolism, and elimination are no different than oral LEV. In fact, intravenous LEV is almost interchangeable with oral LEV. In switching from oral LEV to intravenous LEV, the total daily dosage of medication should be equivalent. The manufacturer suggests that the total daily dose of LEV be administered as a 15-minute infusion following dilution in 100 mL of a compatible diluent. There is no evidence to suggest that a loading dose is necessary. Compatible diluents include sodium chloride (0.9%), lactated Ringer solution, and dextrose (5%).

CONCLUSION

LEV is a highly efficacious broad spectrum agent that can be used for a number of seizure types including partial seizures, myoclonic seizures of JME, and generalized tonic–clonic seizures of primary generalized epilepsy in both adults and children. LEV has linear and predictable pharmacokinetics, renal metabolism with few drug interactions, and multiple dosing preparations. These pharmacologic characteristics reduce the need for frequent serum therapeutic monitoring and allow the agent to be utilized in a variety of clinical settings. Although LEV has few adverse effects,

its main drawback is concerns relating to its behavioral side effects. These effects can be mitigated by patient education and surveillance.

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CHAPTER 59 PERAMPANEL

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Perampanel is a selective, noncompetitive AMPA receptor antagonist that has recently been approved in both Europe and the United States as adjunctive treatment of localization-related epilepsy (Fig. 59.1) (1,2).

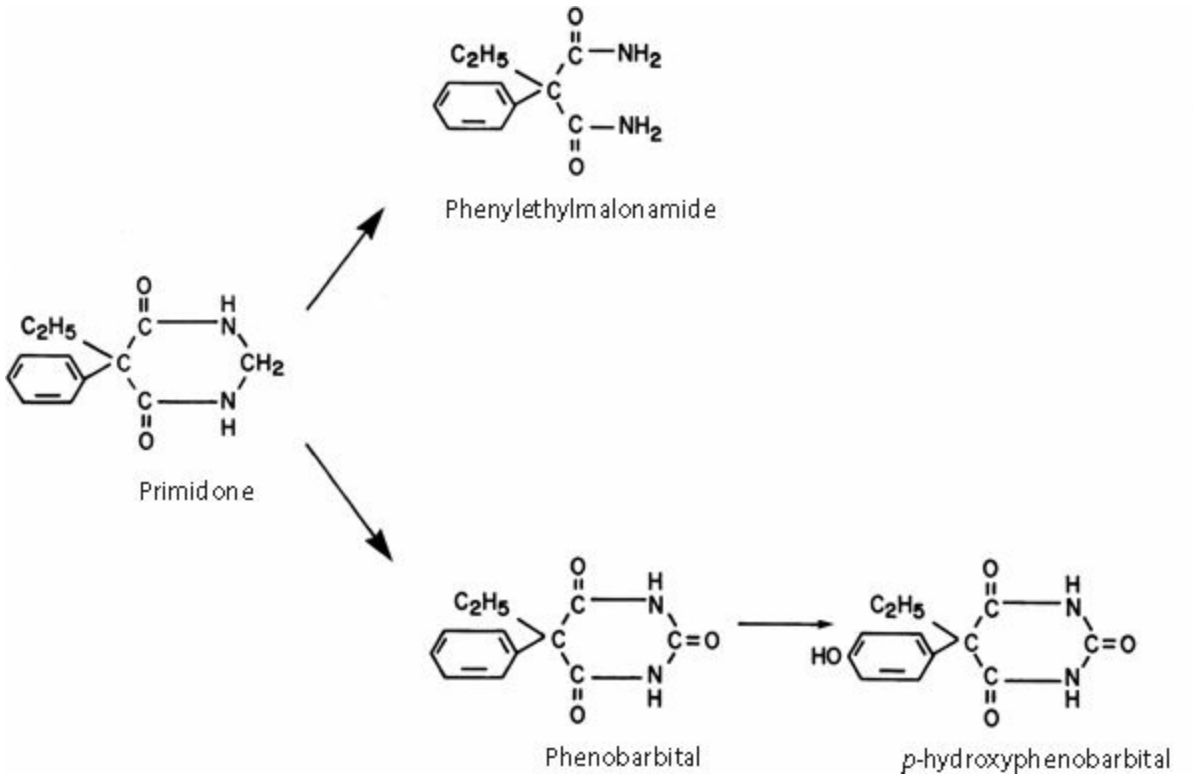

Figure 59.1. 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate, M.W. 349.38 (perampanel).

PERAMPANEL PHARMACOLOGY

Glutamate is the major excitatory neurotransmitter in the CNS. Fast glutaminergic transmission is mediated predominantly by NMDA and AMPA receptors within the CNS. In vitro studies suggest that selective blockade of NMDA receptors has only minimal effect on hippocampal epileptiform activity, while AMPA receptors are quite important in initiating epileptiform discharges and mediating epileptic synchronization (3). AMPA receptors are glutamate-gated ion channels that are formed as tetramers of protein subunits. These receptors are widely distributed throughout the CNS and are found both in the postsynaptic membrane of excitatory neurons and in inhibitory interneurons as well.

Glutamate receptor antagonists have been evaluated to treat a variety of neurologic disorders, including hypoxic injury, amyotrophic lateral sclerosis, Parkinson disease, and epilepsy. NMDA receptor antagonists, however, produced unacceptable CNS depression. NMDA receptor gating is also necessary for induction of long-term potentiation, which is likely an important cellular process in memory formation. Blockade of NMDA receptors can abolish long-term potentiation and has been

found to impair memory formation. In contrast, selective blockade of AMPA receptors does not appear to interfere with long-term potentiation, and animal studies suggest no impairment in memory formation, even at higher doses (4).

Based upon the growing understanding of the importance of AMPA receptors, a number of early competitive antagonists were developed. The quinoxalinediones such as CNQX demonstrated poor in vivo response due to lack of penetration across the blood–brain barrier. Subsequent analogs such as NBQX showed improved permeability and demonstrated in vivo anticonvulsant response in a number of seizure models.

Talampanel, a 2,3-benzodiazepine, is a selective noncompetitive AMPA antagonist that demonstrated good CNS penetration but only had modest potency. Although showing initial promise for treating localization-related epilepsy and ALS, this compound was not effective for treating malignant gliomas and was not further developed (5).

Perampanel—2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2 dihydropyridin-3-yl)benzonitrile hydrate (4:3) or benzonitrile, 2-(1′,6′-dihydro-6′-oxo-1′-phenyl[2,3′-bipyridin]-5′-yl)—was discovered via high-throughput screening program using [3H]AMPA-binding assay to find selective competitive displacers at the glutamate recognition site in rat cortical neurons (3,6,7). Perampanel was shown to inhibit AMPA-induced responses in a noncompetitive manner in cultured rat neurons, with little to no inhibition of NMDA receptors (6).

In keeping with in vitro observations, perampanel demonstrated efficacy in a variety of animal seizure models, including audiogenic seizures in DBA/2 mice, as well as maximal electroshock, pentylenetetrazol, and 6-Hz tests (7). Interestingly, this spectrum of efficacy across diverse seizure models differentiates perampanel (from a mechanistic perspective) from more traditional sodium channel–blocking AEDs, which are relatively inactive in 6 Hz or pentylenetetrazole models (6). Perampanel was not active, however, in the WAG/Rij rodent model of absence seizures (7).

PERAMPANEL PHARMACOKINETICS AND DRUG INTERACTIONS

Perampanel pharmacokinetics in humans has been delineated in 14 phase I studies in single doses ranging from 0.2 to 12 mg and in chronic once-daily doses ranging between 1 and 12 mg/day (8). Following oral administration, perampanel is rapidly and essentially completely absorbed with a median time to maximal peak concentration of 0.75 hours (0.5 to 1 hours). Perampanel does not appear to be a substrate for xenobiotic efflux transporters such as P-glycoprotein or breast cancer resistance protein (6). When given with food, perampanel absorption is slowed (t_{max} 3 hours later in fed vs. fasted state), and resulting maximal peak concentrations are reduced by about 28%, but the overall extent of drug absorption is not significantly altered. Perampanel absorption is linear, and plasma concentrations are dose proportional. Perampanel is approximately 95% bound to plasma proteins, and its binding appears to be linear. Following oral administration, perampanel displays an initial decline in plasma concentrations over 12 hours, with a long elimination phase. Perampanel terminal elimination half-life has been reported to range between 53 and 136 hours, with an average half-life of about 100 hours in the noninduced subject.

Perampanel is extensively metabolized via CYP3A4, with the main metabolic pathway being oxidation at the pyridine, benzene, or benzonitrile rings and subsequent glucuronide conjugation. Although several metabolites have some activity at AMPA receptors, their potency is much weaker

than the parent molecule, and their contributions to clinical activity in patients are likely minimal (6).

Consistent with its long elimination half-life, accumulation was evident with multiple-dose administration, and perampanel concentrations at steady state were substantially higher than after a single dose. Renal elimination of perampanel is minimal, with <0.12% of an administered dose eliminated unchanged in urine. In subjects with mild (Child–Pugh A) and moderate (Child–Pugh B) hepatic impairment, unbound systemic exposure was 1.8- to 3.3-fold higher, and half-life of perampanel was approximately twofold longer than that in healthy subjects.

Perampanel oral clearance is significantly influenced by the presence of concomitant enzyme inducing AEDs, such as phenytoin, oxcarbazepine, or carbamazepine, which can increase perampanel oral clearance by about two- to threefold. While concomitant administration will reduce perampanel elimination half-life, it is still sufficiently long enough to support once-daily dosing. Pharmacokinetic/pharmacodynamic analyses showed that increased steady-state perampanel plasma concentrations were related to decreased seizure frequency and increased probability of achieving ≥50% reduction in seizure frequency (9). This association between plasma concentration and improved clinical response was seen in patients enrolled in the clinical trials irrespective of whether or not they were receiving an enzyme-inducing AED (10). Although there was no apparent effect of enzyme inducers on the concentration–response curve, the dose–response curve may be shifted due to patients receiving concomitant enzyme-inducing medications having lower perampanel concentrations. Patients receiving inducing medications may require higher maintenance doses of perampanel than do noninduced patients.

Perampanel has few other pharmacokinetic interactions. Data derived from the clinical trials suggest that topiramate concentrations may be increased by 20% and oxcarbazepine concentrations increased by 35% (9). Perampanel 12 mg/day decreased levonorgestrel concentrations by 40%, and patients may require additional nonhormonal forms of contraception while taking perampanel. In that perampanel is extensively metabolized by CYP3A4, it is likely that inhibition of this isozyme will result in potentially meaningful changes in perampanel pharmacokinetics. Given its long elimination half-life, however, changes in perampanel plasma concentration in the presence of a strong CYP3A4 inhibitor, such as ketoconazole, are not likely to be evident in the short term but might develop slowly after chronic administration (11). Therapeutic plasma concentrations have not been established for perampanel, though the effective dose range of 4 to 12 mg/day was associated with a range in plasma concentrations of approximately 200 to 800 ng/mL (9). A pharmacokinetic/efficacy model of phase III study data showed expected effects of AED inducers in reducing median perampanel concentration (median Cavss approximately 200 and 300 ng/mL for perampanel 8 and 12 mg/day doses with inducers and 550 and 700 ng/mL for 8 and 12 mg/day perampanel doses without inducers). Predicted reductions in seizure frequency corresponded to increasing concentrations across these concentration ranges (12). Similarly, data are still insufficient to determine a “toxic” plasma level; however, analysis of the phase 3 data suggests that the incidence of certain adverse effects such as dizziness, somnolence, euphoric mood, irritability, gait disturbance, dysarthria, and weight increase did appear to increase at higher perampanel plasma concentrations (9).

CLINICAL EFFICACY

Perampanel was not effective in treating multiple sclerosis, Parkinson disease, or migraine prophylaxis when tested at low 0.5- to 4-mg/day doses. Two phase IIa studies showed, however, that most patients with localization-related seizures tolerated much higher doses of perampanel, and

clinical development was done using 2- to 12-mg/day doses. A placebo-controlled "maximum tolerated dose" trial showed that nearly all patients with epilepsy tolerated 4-mg/day doses when given once a day or divided twice a day. In a subsequent dose-escalation trial, the majority of patients tolerated perampanel 8 mg/day; dose-limiting side effects—usually dizziness and somnolence—became more common at perampanel doses of 10 to 12 mg/day (13).

Subsequent epilepsy trials evaluated perampanel doses of 2 to 12 mg/day (compared with placebo), with the largest number of patients treated with 8-mg/day doses. The efficacy, safety, and tolerability of perampanel for treating localization-related seizures were evaluated in three large global trials and in several extension studies (Fig. 59.2) (14–18). Patients were adults and adolescents (≥12 years) with highly treatment-resistant epilepsy (≥4 or more seizures per month despite >80% taking two or three concomitant AEDs). In these pivotal dose-ranging trials, treatment with perampanel 4 mg/day, but not 2 mg/day, was effective and established the lower effective dose range for the medication. Doses of 8 and 12 mg/day were effective compared with placebo, but patients had only small increases in efficacy with 12 mg/day compared with 8 mg/day. A large proportion of patients treated with 12 mg/day had CNS-related adverse events, demonstrating an upper effective dose range. Responder rates (>50% seizure reduction) in the three pooled pivotal trials were 28.5% for 4-mg/day, 35.3% for 8-mg/day, and 35.0% for 12-mg/day doses (compared with placebo, 19.3%) (18). Reductions in patients' median seizure frequency were similar: 23.3% for 4-mg, 28.8% for 8-mg, and 27.2% for 12-mg dose groups. One of the pivotal trials included several study sites in Latin America with unusually high placebo responses (15). The results from these sites were included in the primary efficacy analysis but were removed for several of the sensitivity analyses. Perampanel was tested in a large number of countries and ethnicities (Europe, the Middle East, South Africa, Southeast Asia, China, and North and South America), with similar overall treatment responses across various regions and ethnicities.

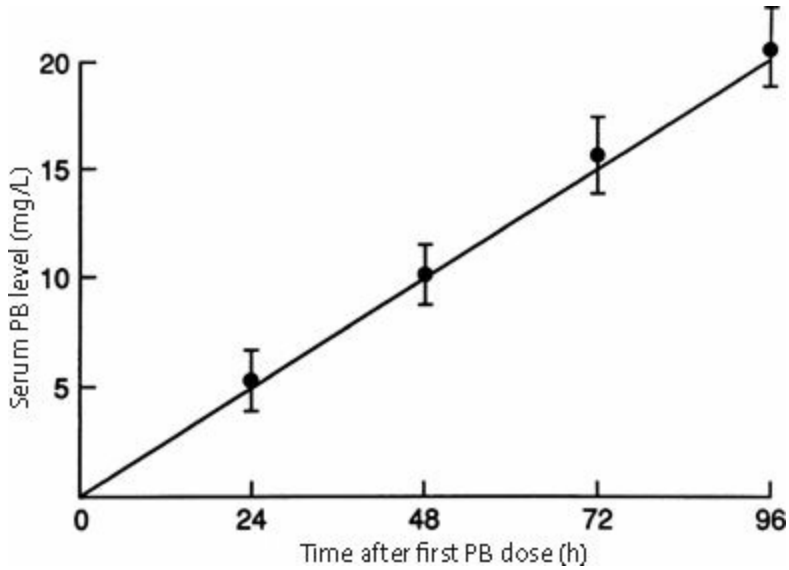

Figure 59.2. Efficacy of perampanel: proportions of 50%, 75%, and 100% responders (ITT analysis of pooled data for all partial seizure types). (Data from Steinhoff BJ, Ben-Menachem E, Ryvlin P, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies [published online ahead of print May 10, 2013]. Epilepsia. 2013;54(8):1481–1489.)

Important secondary efficacy end points showed possible benefits for some patients taking the higher 8- to 12-mg/day doses. The proportion of patients with ≥75% reduction in seizure frequency during perampanel treatment was 12.2% for 4 mg/day, 17.4% for 8 mg/day, and 16.9% for 12-

mg/day. The proportion of seizure-free patients for study completers in the pooled pivotal trial data was 1% for placebo compared to 4.4%, 3.5%, and 4.1% for 4-, 8-, and 12-mg doses, respectively (18). Secondary generalized seizures (for patients with this seizure type) decreased by 62.9% during treatment with 8 mg/day and 53.3% with 12-mg/day treatment (18). During 1 to 4 years of open treatment and follow-up, slightly more than 50% of patients continued perampanel treatment, with few patients discontinuing due to adverse events (3.9% dizziness and 1.3% irritability). Patients' continuing treatment appeared to have stable treatment responses appeared to be sustained (17). Early postmarketing experience using perampanel in Germany has shown similar responses (19).

TOLERABILITY AND SAFETY OF PERAMPANEL

Postdose sedation with perampanel coincides with brief plasma concentration peaks that occur 0.5 to 2 hours after dosing (t_{max}); symptoms of somnolence, however, were successfully alleviated in clinical trials by bedtime dosing with the once-a-day medication. The most common adverse events in adjunctive treatment trials were CNS-related symptoms similar to other AEDs—dizziness, drowsiness, blurred vision, and imbalance (Table 59.1). These symptoms were more common at higher doses, for example, 16% of patients reported dizziness with 4-mg/day treatment compared with 32% with 8-mg/day and 43% with 12-mg/day treatment (18). These symptoms were often transient during dose titration, and most patients successfully tolerated forced titration to 8- to 12-mg/day doses (median 10 mg/day) during conversion to open treatment in extension trials (17,20).

Table 59.1 Incidence of Common Side Effects (>5% of Patients) During Adjunctive Perampanel Treatment: Pooled Analysis

		Perampanel treatment groups			
Adverse event, *n* (%)	Placebo (*n* = 442)	2 mg (*n* = 180)	4 mg (*n* = 172)	8 mg (*n* = 431)	12 mg (*n* = 255)
Any treatment-emergent adverse event	294 (66.5)	111 (61.7)	111 (64.5)	350 (81.2)	227 (89.0)
Dizziness	40 (9.0)	18 (10.0)	28 (16.3)	137 (31.8)	109 (42.7)
Somnolence	32 (7.2)	22 (12.2)	16 (9.3)	67 (15.5)	45 (17.6)
Headache	50 (11.3)	16 (8.9)	19 (11.0)	49 (11.4)	34 (13.3)
Fatigue	21 (4.8)	8 (4.4)	13 (7.6)	36 (8.4)	31 (12.2)
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)
Nausea	20 (4.5)	4 (2.2)	5 (2.9)	25 (5.8)	20 (7.8)
Fall	15 (3.4)	2 (1.1)	3 (1.7)	22 (5.1)	26 (10.2)
Nasopharyngitis	18 (4.1)	7 (3.9)	9 (5.2)	23 (5.3)	11 (4.3)
Upper respiratory tract infection	12 (2.7)	11 (6.1)	6 (3.5)	14 (3.2)	10 (3.9)
Ataxia	0 (0.0)	0 (0.0)	1 (0.6)	14 (3.2)	21 (8.2)
Balance disorder	2 (0.5)	0 (0.0)	0 (0.0)	22 (5.1)	8 (3.1)

Data derived from Steinhoff BJ, Ben-Menachem E, Ryvlin P, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies [published online ahead of print May 10, 2013]. Epilepsia. 2013;54(8):1481–1489.

Special adverse events reported during clinical trials were unexplained falling, particularly in the elderly and psychiatric symptoms. Perampanel labeling includes a warning for possible psychiatric symptoms: aggression, hostility, unusual changes in mood, personality, or behavior, and other behavioral symptoms such as homicidal ideation and threats. Overall, serious psychiatric symptoms occurred in 1.2% of patients taking perampanel during controlled studies (compared to 0.9% during

placebo treatment) and in 3.9% of patients during long-term open treatment. The incidence for serious adverse events of homicidal ideation and/or threat was <0.1% (6 out of 4368 perampanel-treated patients); symptoms were usually associated with lethargy and somnolence, and most patients had prior histories of homicidal thoughts or mood or behavioral disorders. Aggression was reported in 1.6% of patients treated with perampanel and 0.5% receiving placebo. Psychiatric symptoms such as anger and irritability were most common during titration to high doses (10 to 12 mg/day) and generally occurred within 6 weeks of treatment. Several patients had these symptoms when perampanel was combined with alcohol. This suggests patients should be monitored for psychiatric symptoms, such as anger and irritability, during dose titration and particularly when perampanel is increased to high doses.

Systemic complications of perampanel treatment were rare and not increased compared with placebo. Patients experienced a small increase in weight (mean 1.1 kg compared with 0.3 kg with placebo treatment) though 46% of all patients were overweight or obese at study entry. No unusual laboratory changes or safety concerns were observed during 1 to 4 years of exposure in extension trials (17,20). Perampanel treatment did not produce significant ECG change with no QTc interval changes during treatment with up to 12 mg/day. Rashes were uncommon, occurring in 1.8% of patients treated with perampanel compared with 0.9% to 2.2% for placebo; three patients had AED-hypersensitivity reactions (1). Perampanel studies evaluated patients aged 12 to 77 years; only 28 patients were aged >65 years (1,21). Patients from a large number of regions and ethnicities were exposed with similar efficacy and safety findings during treatment.

Abuse Potential of Perampanel

Regulatory agencies in the United States have recently listed a number of newer AEDs as having possible abuse potential based on studies in drug-seeking individuals coupled with supportive evidence from clinical trial adverse event reporting and rodent reinforcement data. Clobazam and lacosamide received Schedule IV registration similar to alprazolam; while perampanel has a Schedule III listing similar to ketamine. Perampanel abuse potential studies tested therapeutic (8 mg) and supratherapeutic (24 and 36 mg) doses; drug-seeking individuals reported higher positive and sedative effects with these doses than placebo (22). Perampanel 24- and 36-mg doses were associated with drug "liking" scores similar to alprazolam and ketamine. The U.S. DEA concluded that abuse of perampanel could lead to moderate or low physical dependence or high psychological dependence. There has been, however, no evidence of psychological or physician dependence in patients enrolled in perampanel clinical trials for treatment of epilepsy (1).

PERAMPANEL DOSING

Currently, European and U.S. regulatory agencies recommend two approaches to manage the initial dosing, and dose escalation for patients receiving perampanel, based upon the presence or absence of concomitant enzyme-inducing AEDs. FDA prescribing information recommends a starting dosage of 2 mg/day (preferentially given at bedtime) for those taking a non–enzyme-inducing AED and 4 mg/day for patients taking enzyme-inducing AEDs (EIAEDs). Perampanel doses should be increased gradually, in 2 mg/day weekly increments, to a maximum dose of 4 to 12 mg/day based on clinical response and tolerability. In elderly patients, dosage increases should be slower still, with increases no more frequently than every 2 weeks. In Europe, the EMA recommends initiation of treatment with

PER at 2 mg/day, irrespective of concomitant EIAEDs.

In most patients, perampanel doses should be titrated based on clinical response and tolerability to a maintenance dose of 4 to 8 mg/day. Depending on an individual's clinical response and tolerability at a dose of 8 mg/day, some patients may require 12 mg/day. Again, consideration should be given as to the potential pharmacokinetic impact of enzyme-inducing medications.

In addition to drug-interaction considerations when initiating perampanel, patients need to be monitored for "deinduction" effects and potential rise in perampanel concentrations upon discontinuation of enzyme-inducing medications.

Perampanel was markedly effective in reducing primary generalized tonic clonic seizures in a recent placebo-controlled adjunctive therapy trial of 164 patients aged 12 years and older. In this treatment-resistant group of patients, perampanel decreased tonic clonic seizure frequency and improved responder rates. The safety profile was similar to previous trials; though, psychiatric adverse effects were similar across perampanel and placebo treatment groups. An exploratory analysis of perampanel effects on absence seizures is planned.

CONCLUSION

Perampanel is a first-in-class, selective noncompetitive AMPA receptor antagonist shown to be effective as adjunctive treatment for partial-onset seizures and for treating primary generalized tonic clonic seizures. Additional studies are examining efficacy and tolerability for treating children with localization-related epilepsy and effectiveness for treating seizures in patients with Lennox–Gastaut Syndrome.

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CHAPTER 60 PHENOBARBITAL AND PRIMIDONE

MARK C. SPITZ, JACQUELYN L. BAINBRIDGE, AND PEI SHIEEN WONG

HISTORICAL BACKGROUND

Although its use has been decreasing, phenobarbital (PB) is still a major antiepileptic drug (AED). PB has been prescribed for the treatment of epilepsy since 1912, following serendipitous findings of seizure improvement in epilepsy patients by a German psychiatrist, Alfred Hauptmann, who originally intended it for sedative purposes (1). At the 10th European Congress on Epileptology in 2012, a special Centenary Symposium was held to commemorate the first 100 years of PB (2). Interestingly, in the 20th century, PB was prescribed using a weight-based measurement, the grain (gr), which was referenced to a "grain of wheat." When a prescription was written for PB, it would be in grains. One grain was equivalent to approximately 65 mg of PB (or by today's standards, one 60 mg tablet = 1 gr). Although PB is associated with more sedative and behavioral side effects than are most other AEDs, it has relatively low systemic toxicity, a conveniently long half-life, can be administered intravenously and intramuscularly, is effective in patients with status epilepticus and in neonates, and is inexpensive.

Primidone (PRM) has been in clinical use since its synthesis in 1952 (3). Often referred to as a barbiturate, PRM does not strictly belong in this class; its pyrimidine ring contains only two carbonyl groups, compared with the three groups of barbituric acid (Fig. 60.1). The remainder of its structure is identical to that of PB. Therapeutically, however, PRM is appropriately considered a barbiturate, as its effect can be attributed predominantly to PB derived through hepatic biotransformation. This metabolic transformation has made it impossible to establish whether therapy with PRM differs clinically from that with PB or whether PRM is a PB prodrug. Complicating this issue is the experimental demonstration of independent antiepileptic activity for the other main metabolite of PRM, phenylethylmalonamide (PEMA) (see Fig. 60.1), as well as the clinical benefits derived from PRM in essential tremor not seen with PB.

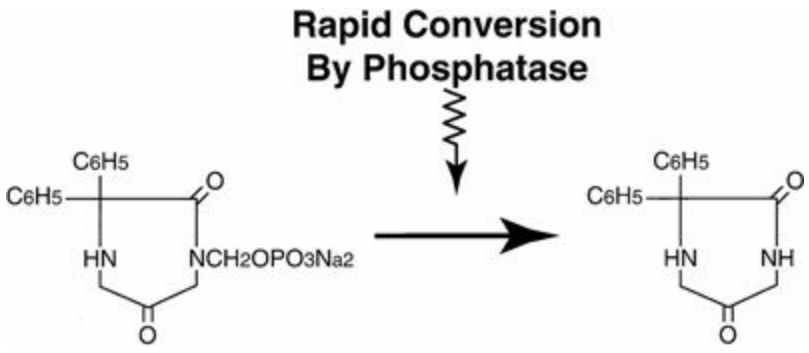

Figure 60.1. Structural formulas of PRM and its main metabolites.

CHEMISTRY AND MECHANISM OF ACTION

Phenobarbital

Chemically, PB is 5-ethyl-5-phenylbarbituric acid (see Fig. 60.1). The molecular weight is 232.23, and the conversion factor from milligrams to micromoles is 4.31 (1 mg/L = 4.31 μmol/L). The sodium salt of PB is water soluble. PB in its free acid form is a white crystalline powder soluble in organic solvents, but with limited water and lipid solubility; it is a weak acid with a pK_a of 7.3.

Many actions of PB at the cellular level have been described. Although it is not certain which are responsible for seizure protection, the available evidence seems to favor enhancement of γ-aminobutyric acid (GABA) inhibition (4). In animal models, PB protects against electroshock-induced seizures. Unlike phenytoin, carbamazepine, and PRM, PB also protects against seizures induced by chemical convulsants, such as pentylenetetrazol. In normal animals, PB raises the threshold and shortens the duration of afterdischarges elicited by electrical stimulation (5). Like other barbiturates, PB enhances postsynaptic $GABA_A$ receptor–mediated chloride (Cl^-) currents by prolonging the opening of the Cl^- ionophore (6). Increased flow of Cl^- into the cell decreases excitability. Presynaptically, PB can cause a concentration-dependent reduction of calcium (Ca^{2+})-dependent action potentials (7), which may contribute to seizure protection at higher therapeutic levels and, especially, to sedative and anesthetic effects.

Primidone

Chemically, PRM is 5-ethyldihydro-5-phenyl-4,6(1-H,5H) pyrimidinedione. The molecular weight is 218.264, and the conversion factor from milligrams to micromoles is 4.59 (1 mg/L = 4.59 μmol/L). PRM is very poorly soluble in water, somewhat soluble in ethanol, and virtually insoluble in organic solvents.

The basic anticonvulsant action of PRM has been studied in mouse neurons in cell culture (8). PRM was compared with PB for its effect on amino acid responses and on sustained, high-frequency firing. In contrast to PB, PRM had no effect on postsynaptic GABA and glutamate responses at concentrations up to 50 μg/mL. However, both agents limited sustained, high-frequency, repetitive firing at relatively high concentrations (>50 μg/mL). Together, PRM and PB limited sustained high-frequency, repetitive firing at clinically relevant concentrations (12 and 20 μg/mL, respectively). The authors concluded that PRM and PB may act synergistically to reduce sustained, high-frequency, repetitive firing.

All the evidence regarding the individual antiepileptic properties of PRM and PB has been demonstrated in experiments with animals whose seizures were provoked (9–12). Because the metabolites accumulate a few hours after administration of the first dose, possible long-term protection by PRM alone against spontaneously occurring seizures cannot be assessed in humans. The anticonvulsant potency of PRM against maximal electroshock-induced seizures is similar to that of PB, but unlike PB, PRM was ineffective against chemically induced seizures caused by pentylenetetrazol or bicuculline (11). Thus, the experimental anticonvulsant spectrum of PRM differs from that of PB and is similar to that of carbamazepine and phenytoin. Therefore, PRM and PB may be two different AEDs with different mechanisms of action.

On the basis of brain concentrations in mice, PRM appears to be 2.5 times less neurotoxic than

PB, with a superior therapeutic index (11). When PB and PRM were administered together in single-dose experiments in mice (13), their anticonvulsant activity was supra-additive (potentiated), and their neurotoxic effect was infra-additive. A PB–PRM brain concentration ratio of 1:1 provided the best therapeutic index. This ratio is not usually seen in patients, especially those taking PRM combined with enzyme-inducing drugs such as phenytoin or carbamazepine. If PRM is different from or even better than PB for the treatment of epilepsy, its different effect would be likely only when the PRM concentration equals or exceeds the PB concentration. Such a ratio is achieved only rarely with PRM monotherapy and almost never when PRM is added to phenytoin or carbamazepine, or combined with PB. The results of pharmacodynamic interactions between PRM and PB in mice were confirmed by experiments in amygdala-kindled rats. After single doses, the anticonvulsant effect of PB was potentiated by PRM, whereas side effects of PB, such as ataxia and muscle relaxation, were not increased by combined treatment with PRM (14).

In rats (15) and mice (11,12), PEMA had relatively weak anticonvulsant activity of its own. On the basis of brain concentrations in mice (11), PEMA was 16 times less potent than was PB in seizure protection and 8 times less potent in neurotoxic effects, but it potentiated the anticonvulsant (13,15) and neurotoxic effects (13) of PB. When this is interpreted together with the blood levels encountered in clinical practice, PEMA does not appear to significantly add to the antiepileptic effect or neurotoxicity of PRM therapy.

ABSORPTION, DISTRIBUTION, AND METABOLISM

Phenobarbital

Most formulations of PB contain sodium salt because of good aqueous solubility. The absolute bioavailability of oral preparations and intramuscular (IM) injection of PB is usually >90% (16,17). Accumulation half-life for the IM route (0.73 hours) was comparable to that to the oral route (0.64 hours). Time to peak concentration is usually 2 to 4 hours. In newborns, peak PB plasma levels after oral administration may be reached later than after IM administration (18). A parenteral solution of PB administered rectally has a bioavailability of 89%, compared with that of IM administration (19); average time to peak concentration was 4.4 hours.

PB is not highly bound to serum proteins (45%). Protein binding of PB is lower during pregnancy and in newborns, with a bound fraction between 30% and 40% in pregnant women and their infant offspring (20). Reported values for the volume of distribution vary. Following IV administration, average values were 0.54 L/kg in adult volunteers and 0.61 L/kg in adult patients with epilepsy (17), both well within the reported range. The volume of distribution of PB approached 1.0 L/kg in newborns (21).

PB is eliminated by both hepatic metabolism and renal excretion of the unchanged drug. An average of 20% to 25% of PB is eliminated unchanged by the kidneys in adults, with large interindividual variability (22,23). The two main metabolites of PB are p-hydroxyphenobarbital (PBOH) (see Fig. 60.1) and phenobarbital N-glucoside. At steady state, approximately 20% to 30% of the PB dose is transformed into PBOH by CYP2C9 (major), CYP2C19, and CYP2E1 (minor), approximately 50% of which is then conjugated to glucuronic acid (22–24). Nitrogen glucosidation, another relevant pathway of PB metabolism, accounts for 25% to 30% of total PB disposition (25).

Other identified metabolites of PB represent a very low percentage of the total elimination.

The elimination of PB from serum follows first-order kinetics. The half-life of PB is age dependent. It is usually well above 100 hours in newborns (26) and averages 148 hours in asphyxiated newborns (27). During the neonatal period, PB elimination accelerates markedly; thereafter, half-lives are very short, with average values of 63 hours during the first year of life and 69 hours between the ages of 1 and 5 years (28). Half-lives in adults range between 80 and 100 hours, and no evidence of autoinduction of PB metabolism has been demonstrated (17).

Primidone

PRM is supplied as 50- and 250-mg tablets and as syrup (1 mL = 50 mg); extremely low solubility precludes parenteral administration. After oral ingestion of tablets, the time to peak serum concentrations in adult patients with epilepsy was 2.7 (29) and 3.2 hours (30), respectively, and 4 to 6 hours after single-dose administration in children (31). In the same study, an average of 92% of the dose (range, 72% to 123%) was excreted in the urine as unchanged PRM and metabolites, probably indicating complete oral bioavailability. Concomitant administration of acetazolamide reduced the oral absorption of PRM (32). One generic preparation was found to have a lower bioavailability than did the trademark product (33).

The volume of distribution of PRM ranged from 0.54 L/kg following acute intoxication (34) to 0.86 L/kg (35). The volume of distribution of PEMA after its oral administration was 0.69 L/kg (36). In human plasma, protein binding of both PRM and PEMA was <10% (15,30,36). Brain concentrations of PRM were found to be lower than simultaneous plasma concentrations in mice (11,12) and in rats (10). In patients undergoing surgery for intractable epilepsy, one group of investigators found an average brain-to-plasma ratio of 87% (37). In another report (12) of six patients whose mean plasma PRM concentration was 6.3 μg/mL, brain concentrations ranged between nondetectable and 2.2 μg/g. Brain concentrations of PEMA in mice ranged between 77% and 93% of the plasma levels (11,12). In humans, the cerebrospinal fluid–plasma ratio for PRM ranged from 0.8 to 1.13 (30,37,38), which is similar to human saliva-to-plasma ratios (39) and which is consistent with the high free fraction of plasma PRM.

The elimination half-life of PRM varies, mainly because of enzymatic induction by comedication. In adults receiving long-term PRM monotherapy, the elimination half-life ranged from 10 to 15 hours (40–42). Therapy with additional AEDs was associated with values of 6.5 and 8.3 hours (29,30,41,42). In 12 children (4 treated with PRM monotherapy, 8 treated with PRM and phenytoin), half-lives ranged from 4.5 to 11 hours (mean, 8.7 hours) (31). In newborns, however, the average PRM half-life was 23 hours (range, 8 to 80 hours) (43), which was associated with a limited biotransformation to the metabolites (44).

After oral ingestion of PEMA itself, the half-life of PRM was 15.7 hours (36). The elimination rate of PEMA cannot be determined accurately in patients taking PRM because the liver produces PEMA as long as PRM is measurable in the blood.

Because two metabolites of PRM accumulate after repeated administration of the agent and because both have independent anticonvulsant activity, an understanding of the qualitative and quantitative aspects of PRM metabolism is needed before any rational clinical use of this drug can be undertaken. Although relative efficacy and relative toxicity of PRM and its metabolites have been studied acutely in animals (11,13), similar investigations are virtually impossible in humans because the three compounds are always present simultaneously during long-term therapy.

Figure 60.1 shows the relevant metabolic pathways for PRM. The first metabolite of PRM to be identified, PEMA was found initially in rats (45) and thereafter in every species studied. PB and PBOH were discovered only 4 years later, in 1956 (46), and toxic reactions attributed to the derived PB were first reported in 1958 (47). Other metabolites of PRM, with either negligible or nondetectable blood levels during long-term therapy, have no practical significance. Numerous clinical studies have discussed the quantitative aspects of the biotransformation of PRM to PB and PEMA. A comparison of the ratios of PB serum levels to dose during long-term PB therapy and during long-term PRM therapy in the same patients demonstrated that 24.5% of the PRM dose is converted to PB (48). This is in accordance with the report that average PRM doses (in mg/kg/day) required to maintain a given PB level are about five times higher than the equivalent PB doses (49). The extent of PRM biotransformation and the ratios of the blood levels of PRM and its metabolites are very sensitive to interactions with other AEDs and are discussed separately. (See Table 60.1 for a summary of pharmacokinetics of PB and PRM)

INTERACTIONS WITH OTHER AGENTS

Phenobarbital

Most of the interactions of PB reflect its status as an enzymatic inducer that accelerates the biotransformation of some AEDs, as well as other agents. No clinically significant interaction with PB has been reported that involves absorption. Significant interactions involving displacement from serum proteins do not occur as PB is only 55% protein bound in serum. Clinically, the most significant interaction affecting PB levels is the inhibition of PB elimination by valproate (50). Seen in the majority of patients, the extent of this interaction is variable. As a result, the increase in PB concentration can reach 100%, often necessitating dosage adjustments. The concentrations of PB derived from PRM are equally affected by valproate.

In the great majority of interactions, PB affects levels of other agents. Levels of valproate (51) and carbamazepine (52) are often reduced by the addition of PB. Levels of the active metabolite of carbamazepine, the 10,11-epoxide, are less affected or may even increase, and the epoxide–carbamazepine ratio is usually higher in the presence of PB. Relative to the metabolism of phenytoin, PB appears to cause both enzymatic induction and competitive inhibition. The two effects tend to balance out in patients, and dosage adjustments of phenytoin are seldom necessary (53). PB significantly increases the clearance of lamotrigine (54), as well as that of ethosuximide, felbamate, topiramate, zonisamide, tiagabine (55), and rufinamide (56). Clobazam clearance does not appear to be affected by PB (57). Those AEDs that are predominantly cleared by renal elimination (e.g., levetiracetam, pregabalin, lacosamide) do not appear to interact with PB.

PB induces the metabolism of many agents besides AEDs, which may require closer monitoring and dosage adjustments. Some examples of drugs susceptible to this interaction include theophylline (58), warfarin (59), and steroids, including those contained in oral contraceptives, leading to breakthrough bleeding and contraceptive failure (60). Combined oral contraceptive preparations containing at least 50 μg of ethinyl estradiol have been recommended for some women taking PB (61,62). Of note, preparations with this higher content of ethinyl estradiol are currently indicated only for use in emergency contraception. This should only be explored when other methods of birth control are not feasible. Alternatives can be considered, such as intrauterine devices or medroxyprogesterone

acetate injection, which is extensively metabolized on first pass through the liver, and concentrations are theoretically not affected by additional hepatic enzyme induction (63). However, as a conservative measure, the injection should be given more frequently (every 10 weeks instead of the usual 12 weeks) to ensure contraceptive efficacy. The use of the progesterone-only pill, progesterone implant, vaginal ring, and contraceptive patch are not recommended in women taking enzyme-inducing AEDs, unless combined with a barrier device. Regardless of which method is chosen, it is essential that the conversation between the patient and the practitioner, documenting a pregnancy or contraceptive plan, should appear frequently in the electronic medical records in women of childbearing potential.

Primidone

PRM is the cause, as well as the object, of numerous pharmacokinetic interactions (Table 60.1) (64). Because PB is invariably present during long-term PRM treatment, all of the effects of PB on other agents can be expected with PRM. The degree of enzymatic induction by other AEDs causes the extent of PRM biotransformation to vary among patients. Most reports describe enzymatic induction of the conversion of PRM to PB; some note inhibition. These interactions change not only the blood levels of PRM, PB, and PEMA relative to the PRM dose but also the ratios among the three substances. Phenytoin, a known potent inducer (41,65–67), causes the most extensive acceleration of PRM conversion, leading to a decrease in the PRM–PB serum concentration ratio. The rate of PRM biotransformation is slower with carbamazepine (41,64), which may also inhibit the conversion of PRM to PB, causing an increase in the PRM–PB serum concentration ratio (68). Table 60.2 summarizes the effect of comedication with phenytoin, carbamazepine, or both on the concentration-to-dose ratios and on the relative concentration ratios of PRM, PB, and PEMA (69). At the same daily dose of PRM, concomitant phenytoin or carbamazepine reduced the morning trough levels of PRM by about 50% and increased PB levels by about 160%. Thus, when patients receive concomitant phenytoin or carbamazepine, the average PRM dose required to maintain a given PB level is about 1.6 times lower than that with PRM monotherapy. Because derived PB is the product of enzymatic conversion and not the substrate, this difference is the opposite of what is usually seen with inducing interactions, which typically require an increased dose to maintain the same therapeutic drug level. With PRM, such an increase in metabolism often yields PB levels associated with toxic reactions.

Table 60.1 Pharmacokinetic Parameters of PB (17–21), PRM (29–31,34,35,40–42), and PEMA (36)

	F (%)	T_{max} (h)	Age group	V_d (L/kg)	Protein binding (%)	$T_{1/2}$ (h)	Cl (L/h/kg)
PB	90–100 (O) 90 (R)	2–4 (O) <2 (R)	Adults Children Neonates	0.61 0.63 0.96	51 51 37	96 69 111	0.0056 0.0082 0.0047
PRM	92	2.7–3.2	Adults Children Neonates	0.54–0.86 — —	<10	10–15 (MT) 6.5–8.3 (CM) 4.5–11 23	0.0355 (MT) 0.0521 (CM)
PEMA	—	—		0.86	<10	16.7	39.1

PB, phenobarbital; PRM, primidone; PEMA, phenylethylmalonamide.
O, oral; R, rectal; MT, monotherapy; CM, comedications.

Table 60.2 Serum Concentration: PRM Dose Ratios and Serum Concentration Ratios of PRM, PB, and PEMA at Steady State[a]

		Serum concentration: PRM dose[b]			Serum concentration ratio[b]	
	No. of patients	PRM	PB	PEMA	PB/PRM	PEMA/PRM
Monotherapy	10	0.78 ±0.25	1.47 ±0.53	0.64 ±0.39	1.65 ±0.74	0.70 ±0.36
Comedications[c]	53	0.40 ±0.15	2.40 ±0.98	0.75 ±0.42	5.83 ±2.62	1.71 ±0.75

[a]All blood samples were drawn before the first morning dose in hospitalized patients.

[b]Mean ± standard deviation (SD), PRM dose in mg/kg/d, serum levels in mg/L.

[c]Combination therapy included phenytoin or carbamazepine, or both.

PRM, primidone; PB, phenobarbital; PEMA, phenylethylmalonamide.

From Bourgeois BFD. Primidone. In: Resor SR, Kutt H, eds. Medical Treatment of Epilepsy. New York: Marcel Dekker; 1992:371–378.

Table 60.2 also shows that the PB–PRM concentration ratio in a morning predose blood sample was more than three times higher in patients taking phenytoin or carbamazepine in addition to PRM (5.83 vs. 1.65, respectively). This means that at a PRM level of 10 mg/L, the corresponding average PB level would be 16.5 mg/L in a patient receiving PRM monotherapy, but 58.3 mg/L in a patient also taking phenytoin or carbamazepine.

Different effects of valproate on PRM kinetics have been described. In one study (70), transient elevations of PRM levels were observed after the addition of valproate; however, in general, no consistent changes in PRM or PB levels have been detected.

In all patients receiving long-term PRM therapy, the PB level is almost always higher than the PRM level. Attempts have been made to elevate the PRM level in relation to the PB level to obtain a greater therapeutic effect from PRM itself. Adding nicotinamide to the drug regimen (68) could achieve such a change in ratio, but the necessary doses may cause gastrointestinal side effects and hepatotoxic reactions. The antituberculosis drug isoniazid also markedly inhibits PRM biotransformation, producing relatively high PRM levels relative to PB levels (71).

EFFICACY

PB shows varying degree of efficacy against every seizure type, except absence seizures, but is used mainly for the treatment of generalized convulsive seizures and partial seizures. In a large-scale, controlled comparison of 622 adults with partial and secondarily generalized tonic–clonic seizures (72), phenytoin, carbamazepine, PB, and PRM were equally effective in achieving complete control. Compared to carbamazepine, PB and PRM controlled partial seizures in a lower percentage of patients. Evidence-based comparison of PB with phenytoin (73) and with carbamazepine (74) revealed no overall difference in seizure control, but PB was more likely to be withdrawn than the other two agents, presumably because of side effects. In children, PB was as effective as carbamazepine for up to 1 year in the treatment of partial seizures (39). In a randomized study of previously untreated children, PB, phenytoin, carbamazepine, and valproate were compared (75). After 6 of the first 10 children randomized to PB discontinued treatment mainly because of behavioral side effects, PB was eliminated from the study for ethical reasons. Generalized myoclonic seizures

and, in particular, juvenile myoclonic epilepsy (76) also respond to PB, although it is not an agent of first choice.

As a major agent in the treatment of patients with convulsive status epilepticus, PB is a reasonable next-line option if seizures persist following administration of a benzodiazepine and phenytoin (77,78). In patients with status epilepticus, PB was as effective as a combination of diazepam and phenytoin (79). The main disadvantages associated with its use are respiratory depression and hypotension. Very high doses of PB have been recommended for the treatment of refractory status epilepticus in children (80,81). This approach controlled seizures when no limits were imposed relative to maximum dose, and serum levels of 70 to 344 mg/L were achieved (80). In this series, most patients were initially intubated but recovered good spontaneous respiration despite persistently high PB levels; hypotension was uncommon.

PB is the agent of first choice in newborns with any type of seizure, with control achieved in about one-third of the infants (21,82,83). An efficacy rate of 85% against various neonatal seizures was noted with loading doses of up to 40 mg/kg (84). In a recent study, newborns with seizures were randomized to initial treatment with PB or phenytoin (85). There was no difference in the percentage of neonates in whom seizure control was achieved with PB (43%) and with phenytoin (45%).

PB has been the most widely used agent for chronic prophylaxis of febrile seizures, with efficacy demonstrated at levels higher than 15 mg/L (86,87). Failure of prophylaxis was often due to noncompliance with the regimen and subtherapeutic levels at the time of seizure recurrence. However, such treatment is now rarely considered, for several reasons: improved understanding of the benign nature of simple febrile seizures; the efficacy of intermittent short-term use of rectal or oral diazepam therapy (88–90); and reservations about the possible detrimental effect on cognitive function (91,92).

Neurologic side effects have prevented PRM from becoming an agent of first choice for the treatment of any seizure type. Indications are similar to those for PB, except for the treatment of status epilepticus and neonatal seizures (PRM is not available in a parenteral formulation). PRM is effective against generalized tonic–clonic seizures and juvenile myoclonic epilepsy (93,94). However, other agents such as levetiracetam, lamotrigine, topiramate, zonisamide, and valproate have demonstrated efficacy and tolerability as first-line therapy (95) for the latter condition. The clinical efficacy of PRM and PB has been compared in various studies. Several demonstrated no superiority of PRM but did establish noninferiority (48,95,96). In one crossover study (97), the efficacy of PRM and PB was compared sequentially in the same patients. Similar PB levels were maintained during both therapies, and PRM was found to be slightly more effective than PB against generalized tonic–clonic seizures.

In partial and secondarily generalized seizures, PRM use was associated with the same degree of seizure control as PB, phenytoin or carbamazepine (98,99); however, the percentage of treatment failures was highest with PRM because of an increased incidence of side effects early on in treatment (72). PRM is rarely indicated for management of any type of seizure other than partial and secondarily generalized seizures. In particular, the agent has little or no place in the treatment of generalized epilepsies encountered in childhood, such as absence epilepsy and Lennox–Gastaut syndrome. Although some potential use has been demonstrated in the treatment of neonatal seizures (44), PRM is rarely used for this indication. PRM is contraindicated in any patient with a previous allergic, severe idiosyncratic reaction to PRM or to PB, and patients with hepatic porphyria. If indicated, the choice between PB and PRM may depend on individual factors. After PB has failed, PRM may still be tried. However, selecting PRM before PB may save one therapeutic step, based on

the assumption that PB is unlikely to be effective if maximal tolerated doses of PRM have not controlled seizures.

ADVERSE EFFECTS

Among AEDs, PB and PRM are more likely to cause dose-related neurotoxic reactions, yet serious systemic side effects are rare. These agents invariably produce sedation and drowsiness at high doses in adults, whereas children often experience paradoxical behavioral side effects, mainly hyperactivity, aggressiveness, and insomnia, even at levels in the therapeutic range (<15 mg/L) (87). Sedation, usually present at relatively low levels during the first few days of treatment, subsides over time as tolerance to this effect develops. Sedation or somnolence reappears only at high therapeutic or supratherapeutic levels, usually >30 mg/L. As dose levels increase further, neurologic toxicity appears, characterized by dysarthria, ataxia, incoordination, and nystagmus. Movement disorders, such as dyskinesia, may be induced by PB, but they are rare (100). Like other AEDs, PB can exacerbate seizures or induce de novo seizures (101).

Depression has been attributed to both PB (102,103) and PRM therapy (104). Although its effect may have been overemphasized, double-blind, controlled studies have confirmed that PB affects cognitive abilities even at levels in the therapeutic range. Children treated with PB had lower memory and concentration scores than those receiving placebo, and these differences correlated significantly with plasma levels (105). Double-blind comparisons of PB-treated children versus untreated children (91,106) or valproate-treated children (107) demonstrated subtle but significantly lower intelligence quotient (IQ) scores in the PB groups. In an intention-to-treat analysis comparing children treated with PB or placebo for febrile seizures, the average IQ score was 8.4 points lower with PB (91) and remained 5.2 points lower 6 months after discontinuation of PB. Some differences persisted 3 to 5 years later (92).

Allergic rashes and hypersensitivity reactions are relatively rare with PB and PRM treatment (108), but cross-reactivity with CBZ and PHY has been established (109). Hematologic toxicity is quite rare with PB or with PRM (110,111). Like phenytoin and carbamazepine, PB can exacerbate acute intermittent porphyria (112) and cause osteoporosis, decreased bone mineral density, and increased risk of fracture, presumably through accelerated vitamin D metabolism (113–115). Vitamin K–deficient hemorrhagic disease in newborns of mothers treated with PB (116) can be prevented by administration of vitamin K to the mother before delivery. Connective tissue disorders associated with long-term PB therapy are well known (117) and have recently received renewed attention. These include Dupuytren contractures, plantar fibromatosis, heel and knuckle pads, frozen shoulder, and diffuse joint pain (118). Connective tissue disorders are an unusual side effect in children.

Like every AED, PB has been known to increase the risk for minor and major malformations in the offspring of mothers who were chronically exposed during pregnancy. Assessment of the specific risk for a given agent in clinical studies has been complicated by polytherapy and the underlying risk for malformation due to maternal epilepsy (119). A recent study using data from the North American AED Pregnancy Registry evaluated the relative safety of different AEDs used as monotherapy in pregnant women during the first trimester. PB was reported to be associated with a higher risk of major malformation when compared to lamotrigine (RR 2.9, 95% CI 1.4–5.8). It was also associated with a higher risk of cardiac defects and oral clefts (120). Like valproate and phenytoin, PB may be associated with reduced cognitive outcome in the child (121). Folic acid supplementation taken at 5 to 12 weeks of amenorrhea may decrease the risk of anomalies (122). Evidence that PB increases the

risk for any type of tumor development in humans is lacking (123).

Acute and chronic toxic PRM reactions can be distinguished clearly from one another, but long-term PRM side effects are difficult to separate from those associated with derived PB. Because the ratio of PRM to PB varies, toxic side effects may occur at different PRM concentrations. Reliable evidence that long-term PRM side effects and potential teratogenic effects differ from those with comparable PB therapy is lacking. Ventriculoseptal defects, microcephaly, and poor somatic development (124) have been described in the offspring of women taking PRM, although no specific teratogenic pattern has been attributed to the agent.

The acute initial toxicity clearly differentiates PRM from PB. Even after a low initial dose of PRM, some patients experience transient side effects—usually drowsiness, dizziness, ataxia, nausea, and vomiting (71)—that are so debilitating they may be reluctant to take a second dose. Because this acute toxic reaction occurs before PB or PEMA is detected in the blood, it must be associated with PRM itself. Much larger doses of PRM are later tolerated by the same patients during long-term therapy, arguing for the development of tolerance to PRM probably within hours to days. The ratio of clinical toxicity score to serum PRM levels, determined in a group of patients receiving their first PRM dose (125), decreased significantly as early as 6 hours after the ingestion of drug. PB probably produces a cross-tolerance to this acute PRM toxicity and possibly to the anti-seizure activity, because patients on long-term PB therapy are less likely to experience the same degree of toxicity on first exposure to PRM (125–127).

CLINICAL USE

On the basis of its relative efficacy and toxicity profile, PB is no longer used as a first-line treatment for any seizure type, except for neonatal seizures. PB remains an agent of second or third choice for the treatment of generalized convulsive seizures and partial seizures at any age and is prescribed widely for infants because it is easier to use and is associated with less systemic toxicity than several other AEDs.

In adults, the daily maintenance dose of PB, between 1.5 and 4 mg/kg, achieves steady-state levels within the recommended therapeutic range of 15 to 40 mg/L. Because of its long elimination half-life and slow accumulation, the full maintenance dose can be administered on the first treatment day. Steady-state plasma level is attained only after 2 to 3 weeks. The daily maintenance dose of PB in children varies between 2 and 8 mg/kg; doses >8 mg/kg may be necessary in some infants to achieve high therapeutic levels. The dose is roughly inversely proportional to the child's age: 2 months to 1 year, 4 to 11 mg/kg/day; 1 to 3 years, 3 to 7 mg/kg/day; and 3 to 6 years, 2 to 5 mg/kg/day (128). Given the long half-life of PB, dividing the daily dose of the agent into two or more doses appears unnecessary, even in children (129). Close monitoring of plasma levels and dosage reductions may be necessary in patients with advanced renal disease (130) and cirrhosis (131).

The IV loading dose of PB for the treatment of status epilepticus varies between 10 and 30 mg/kg; 15 to 20 mg/kg is most common. The rate of administration should not exceed 100 mg/min (2 mg/kg/min in children weighing <40 kg). PB penetrates the brain relatively slowly. Although full equilibrium is not reached for as long as 1 hour, therapeutic brain concentrations are reached within 3 minutes (132). The initial loading dose of 15 to 20 mg/kg in newborns is similar to the dose in children and adults and will achieve a plasma level of about 20 mg/L. This level can usually be maintained in newborns with a dose of 3 to 4 mg/kg/day (133). However, loading doses up to 40 mg/kg have been used in some situations (84).

PRM should be used alone or in combination with a noninducing drug, such as gabapentin, lamotrigine, topiramate, tiagabine, zonisamide, levetiracetam, vigabatrin, or a benzodiazepine. An inducing drug will shift the PRM–PB ratio to such an extent that the clinically effective component is solely PB. Similarly, prescribing PRM and PB simultaneously for the same patient is not justified. A low starting dose is more important with PRM than with most other AEDs because of the occurrence of transient, but severe, neurotoxic reactions. A first dose of one-half tablet (125 mg) at bedtime is often well-tolerated, but some patients initially need as little as one-quarter tablet (62.5 mg). The dose can then be increased every 3 days as tolerated, to a final daily maintenance dose of 10 to 20 mg/kg. Maintenance doses are 15 to 25 mg/kg/day in newborns, 10 to 25 mg/kg/day in infants, and 10 to 20 mg/kg/day in children.

A schedule that allows rapid advancement to the full maintenance dose of PRM was devised (134) based on the idea that PB produces cross-tolerance to the effects of PRM. After initial administration of PB, the dose is titrated as rapidly as tolerated to achieve a serum level up to 20 mg/L; abrupt switch to the full maintenance dose of PRM follows. Experimentation revealed that most adult patients tolerate the following regimen: 3 mg/kg of PB orally on day 1 (two doses of 1.5 mg/kg each, 12 hours apart); 3.5 mg/kg on day 2; 4 mg/kg on day 3; and 5 mg/kg on day 4 (Fig. 60.2). On day 5, the patient can receive a full PRM maintenance dose of 12.5 to 20 mg/kg, without significant toxicity. This beneficial effect of PB pretreatment on initial PRM toxicity has been confirmed in a more recent study (135).

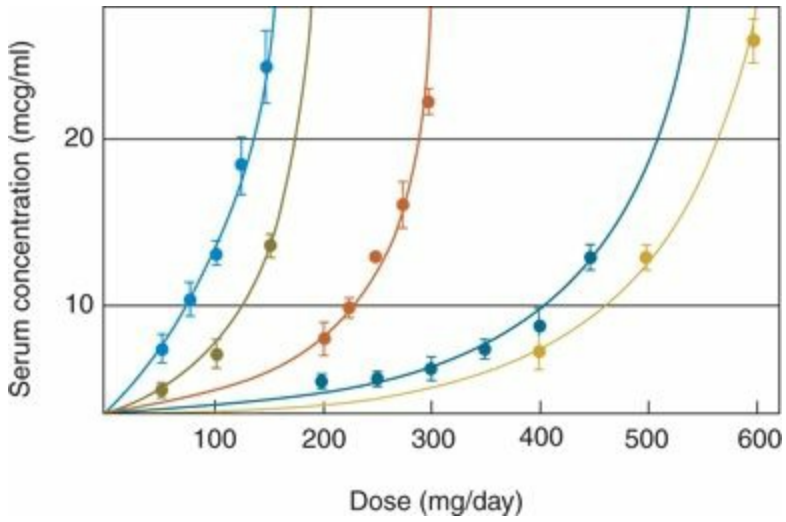

Figure 60.2. Phenobarbital (PB) loading dose over 4 days for rapid introduction of PRM. The PB values represent the average of 11 patients with standard deviation (vertical bars). The solid straight line connects the corresponding predicted values (5, 10, 15, and 20 mg/L). (Courtesy of Bourgeois BFD, unpublished data, 1991.)

PRM monotherapy at a daily dose of 20 mg/kg will achieve PB levels of 30 mg/L (see Table 60.2). Steady-state PB levels will be reached only after 2 to 3 weeks at the same PRM dose. In patients comedicated with carbamazepine or phenytoin, the same PB level will be achieved with an average PRM dose of 10 to 15 mg/kg/day. As with most AEDs, average dosage requirements may be higher in children and lower in the elderly. Because of the relatively short half-life of PRM, usual recommendations call for dividing the daily dose into three doses, although the need to do so has never been documented. If blood levels are used to adjust the PRM dose, then PB rather than PRM levels are preferred, because at the usual concentration ratios, the side effects from a high PB level are more likely to limit further dosage increases. Although a therapeutic range of 3 to 12 mg/L has been suggested for PRM (136), monitoring PRM levels or PEMA is of little help in clinical practice.

After long-term administration, PB and PRM should always be discontinued gradually over several weeks. Barbiturates and benzodiazepines are the AEDs most commonly associated with withdrawal seizures on rapid discontinuation. This phenomenon is due to pharmacodynamic mechanisms that cause a state of rebound hyperexcitability when the amount of the drug decreases in the brain, resulting in a lower seizure threshold, and predisposing the patient to more severe than usual seizures or even to status epilepticus. The phenomenon is unrelated to pharmacokinetics, and the fact that PB has a long elimination half-life does not preclude the need for very gradual withdrawal. Since patients treated with PRM are also chronically exposed to PB, the same caution should be exercised when discontinuing PRM therapy. Unless there is a specific reason to proceed faster, it is appropriate to taper the PB or PRM dose linearly over 3 to 6 months, with reductions each month.

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CHAPTER 61 PHENYTOIN AND FOSPHENYTOIN

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HISTORICAL BACKGROUND

Phenytoin

From the second half of the 19th century until 1938, the antiepileptic effect of commonly used medications (bromides and phenobarbital) was attributed to their sedative effects (1). The landmark work of Merritt and Putnam in 1937 and 1938 demonstrated that the antiepileptic potential of drugs could be tested in animals, the anticonvulsant effect and sedative effects could be separated, and anticonvulsant activity could be achieved without sedation (2,3). Phenytoin (compared with bromides and phenobarbital) showed the greatest anticonvulsant potency with the least hypnotic activity in the cat model they devised, which compared a drug's ability to change the seizure threshold with its sedative effects.

In a subsequent series of articles, Merritt and Putnam (4) demonstrated that phenytoin was effective in humans; the first clinical trial of phenytoin in epilepsy documented freedom from seizures in 50% of 142 patients with refractory disease. This trial showed, for the first time, that a drug effective against seizures in experimental animals could be successfully used in humans. In fact, Merritt and Putnam's electroconvulsive test in animals remains the most reliable experimental indicator of antiepileptic drug (AED) efficacy in tonic–clonic and partial seizures in humans. A follow-up study described effectiveness in complex partial seizures, with or without secondarily generalized tonic–clonic seizures, but not in absence seizures (5). Today, phenytoin remains one of the world's most widely prescribed AEDs and is on the WHO essential medicines list (6).

Fosphenytoin

Because phenytoin is poorly soluble in water, parenteral phenytoin sodium has been formulated as an aqueous vehicle containing propylene glycol, ethanol, and sodium hydroxide, adjusted to a pH of 12. Unfortunately, parenteral phenytoin sodium is associated with cardiovascular complications and phlebitis (7,8). First synthesized in 1973, fosphenytoin was developed as a water-soluble phenytoin prodrug that might reduce the risks of the cardiovascular complications and phlebitis from parenteral phenytoin administration (9).

CHEMISTRY AND MECHANISM OF ACTION

Phenytoin

Phenytoin is commercially available as the free acid and the sodium salt. The molecular weight is 252.26 for the free acid and 274.25 for the sodium salt. A weak organic acid, phenytoin is poorly soluble in water. The apparent dissociation constant (pK_a) ranges from 8.1 to 9.2 and requires an alkaline solution to achieve solubility in high concentrations. As a result, parenteral phenytoin sodium must be formulated as an aqueous vehicle containing 40% propylene glycol and 10% ethanol in water for injection, adjusted to a pH of 12 with sodium hydroxide (9–11).

Phenytoin affects ion conductance, sodium–potassium adenosine triphosphatase activity, various enzyme systems, synaptic transmission, posttetanic potentiation, neurotransmitter release, and cyclic nucleotide metabolism (12). Despite these numerous sites of action, the major anticonvulsant mechanism of action is believed to be the drug's effect on the sodium channel. Phenytoin blocks membrane channels through which sodium moves from the outside to the inside of the neuron during depolarization, suppressing the sustained repetitive firing that results from presynaptic stimulation (12–14).

Fosphenytoin

Fosphenytoin, a phenytoin prodrug, is the disodium phosphate ester of 3-hydroxymethyl-5,5-diphenylhydantoin (molecular weight 406.24) (Fig. 61.1). Following conversion, 1.5 mg of fosphenytoin sodium yields 1 mg of phenytoin sodium. To avoid confusion, fosphenytoin (Cerebyx) is packaged as milligram phenytoin sodium equivalents (mg PE). Thus, 100 mg of parenteral phenytoin sodium (Dilantin) and 100 mg PE of parenteral fosphenytoin sodium (Cerebyx) have equal molar amounts of phenytoin sodium.

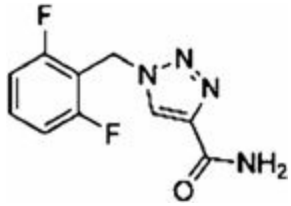

Figure 62.1. Structural formulas of fosphenytoin (**left**) and phenytoin (**right**).

Fosphenytoin's phosphate ester group on the basic phenytoin molecule significantly increases solubility. The water solubility of fosphenytoin at 37°C is 75,000 µg/mL, compared with 20.5 µg/mL for phenytoin (9). Thus, fosphenytoin is freely soluble in aqueous solutions and can be formulated without organic solvents (15). Fosphenytoin is formulated as a ready-mix solution of 50 mg PE/mL in water for injection, USP, and tromethamine, USP (Tris) buffer adjusted to pH 8.6 to 9.0 with either hydrochloric acid, NF, or sodium hydroxide, NF (16). Fosphenytoin itself has no known anticonvulsant activity and derives its utility from its rapid and total conversion to phenytoin (15,16).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Phenytoin

Absorption

Phenytoin is available in various formulations for both oral and parenteral use (Table 61.1) as phenytoin sodium or phenytoin acid. Both the rate and extent of absorption may differ among the formulations, leading to clinically significant alterations in serum concentrations when switching among products. The chewable tablet and liquid suspension are phenytoin acid and contain 100% phenytoin, whereas all other formulations are phenytoin sodium and only contain 92% phenytoin. Switching between formulations can result in significant changes in pharmacokinetics.

Table 61.1 Formulations of Phenytoin and Fosphenytoin

Formulation	Preparation	Strength	Acid or salt	Amount of drug	Prompt or extended
Dilantin Kapseals	Capsule	30 mg	Sodium salt	27.6 mg	Extended
Dilantin Kapseals	Capsule	100 mg	Sodium salt	92 mg	Extended
Dilantin Infatabs	Chewable tablet	50 mg	Free acid	50 mg	Prompt
Dilantin-125 suspension	Suspension	125 mg/5 mL	Free acid	125 mg/mL	Prompt
Phenytek	Capsule	200 mg	Sodium salt	184 mg	Extended
Phenytek	Capsule	300 mg	Sodium salt	276 mg	Extended
Phenytoin (generic)	Capsule	30 mg	Sodium salt	27.6 mg	Prompt and extended
Phenytoin (generic)[a]	Capsule	100 mg	Sodium salt	92 mg	Prompt and extended
Phenytoin (generic)	Suspension	125 mg/5 mL	Free acid	125 mg/mL	Prompt
Phenytoin (generic)	Injectable solution	50 mg/mL	Sodium salt	46 mg/mL	
Fosphenytoin	Injectable solution	50 mg PE/mL	Disodium salt	46 mg PE/mL	

[a]The prompt-release generic phenytoin 100-mg capsules are not bioequivalent to Dilantin 100-mg Kapseals. The extended-release generic phenytoin 100-mg capsules are considered bioequivalent. The prescriber should be cautious when writing prescriptions.

The rate and extent of absorption of phenytoin from its site of entrance depends on pK_a and lipid solubility, the pH of the medium in which it is dissolved, solubility in the medium, and concentration. These factors are frequently altered by the presence of foods or drugs in the intestinal tract and by the formulations. Little phenytoin is absorbed in the stomach because the drug is insoluble in the acidic pH of gastric juice (about 2.0), even though it is in its nonionized form in the stomach. Absorption occurs primarily in the duodenum, where the higher pH increases the solubility of phenytoin. Absorption from the jejunum and ileum is slower than from the duodenum and is poor from the colon (17,18).

In humans, the rate of absorption is variable and prolonged (19,20) and significantly influenced by the rate of elimination (21). Because dissolution is the rate-limiting process in the absorption of phenytoin, any factor that affects dissolution or solubility will affect absorption. After oral administration of a single dose, peak blood drug levels are generally reached between 4 and 8 hours later (range, 3 to 12 hours) (22,23). In patients ingesting massive amounts of phenytoin, absorption may continue for as long as 60 hours (24). Relative bioavailability increases with age, suggesting an age-dependent effect on drug absorption (25). In newborns and infants up to 3 months old, phenytoin is absorbed slowly and incompletely after both oral and intramuscular administration (26); absorption in older infants and children is similar to that in adults. Stable isotope tracer doses have been used to assess the bioavailability of phenytoin (27,28).

After intramuscular administration, phenytoin is absorbed slowly, as poor water solubility leads to precipitation of drug at the injection site, forming almost a depot repository (20). This prolonged absorption and pain on administration mandate use of the intravenous route if parenteral administration is required.

The reported bioavailability of rectally administered phenytoin sodium is approximately 25% (29).

Absorption of Generic Preparations

Several generic phenytoin preparations have been approved by the Food and Drug Administration and are available in the United States; however, they are not equivalent owing to differences in their rate of absorption. Most of the generic products are not rated as bioequivalent to brand name Dilantin because of their rapid ("prompt") absorption profile. Steady-state concentrations of the prompt formulation have been found to be higher than those of the brand extended-release form (30), lower (31,32), or not different (33). Thus, when stable concentrations are desirable, an extended-release profile is preferred. In 1998, a 100-mg generic extended-release product (manufactured by Mylan Pharmaceuticals) was approved as bioequivalent to Dilantin Kapseals 100 mg.

In contrast, the generic prompt-release formulation is useful when rapid serum concentrations are desired, such as with an oral loading dose. Prompt-release phenytoin administered in three divided doses of 6 mg/kg every 3 hours reaches maximal concentrations almost 4 hours sooner than does the brand name extended-release form given according to the same regimen (34).

Distribution

Protein Binding.

Phenytoin is approximately 90% bound to plasma proteins, primarily albumin, in most healthy, ambulatory patients. Only the unbound (free) portion is pharmacologically active because protein-bound drug cannot cross the blood–brain barrier. Because unbound phenytoin distributes passively between plasma and cerebrospinal fluid, concentrations are the same in both sites (35), and the unbound plasma concentration can be used to estimate the cerebrospinal fluid concentration (18).

The percentage of binding (70% to 95%) depends on albumin concentration and coexisting medications or illnesses. Low serum albumin, renal failure, or concomitant medications that displace phenytoin from protein-binding sites increase the risk for changes in protein binding. Both exogenous (other highly protein-bound medications) and endogenous (increased bilirubin) substances can compete for binding sites and increase unbound phenytoin concentrations. Valproic acid significantly alters phenytoin binding to serum albumin, whereas phenobarbital, ethosuximide, diazepam, carbamazepine, and folic acid do not (36). Binding is decreased in uremia (84.2%), hepatic disease, and acquired immunodeficiency syndrome (18); in renal dysfunction, it is most apparent at creatinine clearances below 25 mL/min (37). In patients with uremia who undergo renal transplantation, binding returns to normal when renal function recovers (38).

Volume of Distribution.

Phenytoin is distributed freely in the body with an average volume of distribution in humans of 0.78 L/kg (18). The volume of distribution after single intravenous doses (9.4 to 21.3 mg/kg) in children declines with age and ranges from 1 to 1.5 L/kg below the age of 5 years and from 0.6 to 0.8 L/kg above the age of 8 years (39). At the pH of plasma, phenytoin exists predominantly in the nonionized form, thus allowing rapid movement across cell membranes by nonionic diffusion. The volume of distribution, which correlates with body weight (40), is larger in morbidly obese patients, who may

require large loading doses to achieve therapeutic concentrations (41,42).

Metabolism

In humans, the major pathway of phenytoin elimination (approximately 80%) is 4′-hydroxylation to form 5-(4′-hydroxyphenyl)-5-phenylhydantoin (4′-HPPH). This reaction is mediated mainly by the cytochrome P450 (CYP) enzyme CYP2C9 and to a lesser extent by CYP2C19 (43,44). Approximately 10% of phenytoin is eliminated to a dihydrodiol, and another 10% is metabolized to 5-(3-hydroxyphenyl)-5-phenylhydantoin (3′,4′-diHPPH) (10,43,45). An arene oxide, which precedes the formation of these compounds, has been implicated in the toxicity and teratogenicity of phenytoin; however, its transient presence in patients with normally functioning arene oxide detoxification systems is unlikely to account for many of the toxic reactions (46,47).

Because phenytoin has nonlinear pharmacokinetics, a narrow therapeutic index, and a concentration-related toxicity profile, small changes in CYP2C9 activity may be clinically significant. Of the more than 50 CYP2C9 alleles identified to date, the most common, designated as CYP2C9*1A, is considered the wild-type allele (48,49). Individuals homozygous for the wild-type allele are called extensive metabolizers. Studies in various populations demonstrated that the CYP2C9*2, CYP2C9*3, CYP2C9*4, and CYP2C9*6 alleles are important in vivo determinants of phenytoin disposition (50–59). Individuals with at least one of these variant alleles are called poor metabolizers and have a reduced ability to metabolize phenytoin. They may require lower-than-average phenytoin doses to decrease the incidence of concentration-dependent adverse effects (54,60).

While two-thirds of Caucasians possess the wild-type allele, one-third are heterozygous for the CYP2C9*2 or CYP2C9*3 allele (61). These two variant alleles are much less prevalent in African Americans and Asians, with more than 95% of these groups expressing the wild-type genotype (61). A study in a Black Beninese population demonstrated that CYP2C9 alleles *5, *6, *8, and *11 were associated with decreased phenytoin metabolism (62). The allele CYP2C9*13 was identified in the Chinese population and found to be associated with reduced plasma clearance of drugs that are substrates for CYP2C9 (63). A clear association between the newer discovered alleles and an altered phenytoin metabolism has not yet been demonstrated. Odani et al. (50) observed a decrease of approximately 30% in the maximal rate of phenytoin elimination in Japanese heterozygous for CYP2C9*3 compared with those homozygous for the wild-type allele. Moreover, the mean phenytoin maintenance dose leading to a therapeutic serum concentration was significantly lower in patients with CYP2C9 allelic variants (199 ± 42.5 mg/day) than in those with the wild-type allele (314 ± 61.2 mg/day; $P < 0.01$) (54). A case report of a heterozygous CYP2C9*3 allele carrier described excessive phenytoin concentrations relative to the doses taken; a toxic level (32.6 μg/mL) was reached despite a modest dose (187.5 mg/day). The patient showed signs of central nervous system intoxication, ataxia, and diplopia (55).

The activity of CYP2C9 alone, however, does not fully explain the large interindividual variability in the clinical pharmacokinetics and reported drug interactions of phenytoin (64). More than 30 CYP2C19 alleles have been described to date (48). CYP2C19*2 to CYP2C19*8 are inactive and are responsible for the poor metabolizer phenotype. The CYP2C19*17 variant has been associated with ultrarapid drug metabolism for two of its substrates, omeprazole and escitalopram, which might imply increased risk of therapeutic failure (65,66).

The majority of all populations studied have the CYP2C19 extensive metabolizer phenotype

involving the wild-type CYP2C19*1 allele. The frequency of CYP2C19 poor metabolizers is much higher in Asians (13% to 23%) than in Caucasians and African Americans (1% to 6%) (67). The CYP2C19*2 and CYP2C19*3 mutations are responsible for most of the CYP2C19 poor metabolizers. CYP2C19*2, the main defective allele, occurs with a frequency of 30% in the Chinese population, approximately 15% in Caucasians, and approximately 17% in African Americans. The CYP2C19*3 variant affects approximately 5% of Chinese, and is almost nonexistent in Caucasians (68). Together, the CYP2C19*2 and CYP2C19*3 alleles can explain all Asian and approximately 80% of Caucasian poor metabolizers (69).

Because the contribution of CYP2C19 to the metabolism of phenytoin increases with an increase in drug concentration, CYP2C19 may be important when CYP2C9 is saturated. The reported differences in K_m values for CYP2C9-catalyzed and CYP2C19-catalyzed phenytoin hydroxylation (5.5 μmol/L vs. 71.4 μmol/L) suggest that CYP2C9 is likely to become saturated at phenytoin therapeutic concentrations of 10 to 20 μg/mL (40 to 80 μmol/L) (70). This mechanism explains the increased risk of toxic reactions with the coadministration of CYP2C19 inhibitors such as ticlopidine or isoniazid. The 1% to 2% of Caucasian poor metabolizers for both CYP2C9 and CYP2C19 are particularly susceptible to phenytoin's adverse effects (71). Dosage adjustments based on the CYP2C9 and CYP2C19 genotypes may decrease the risk of concentration-dependent adverse effects in allelic variant carriers, particularly at the beginning of therapy.

A Japanese epilepsy study (50) noted an approximate decrease of 14% in the maximum metabolic rate in patients with CYP2C19 variants compared with those with the extensive metabolizer phenotype. In another Japanese study (51), the predicted plasma concentrations with a phenytoin dose of 5 mg/kg/day were 18.7, 22.8, and 28.8 μg/mL in CYP2C19 homozygous extensive metabolizers, heterozygous extensive metabolizers, and poor metabolizers, respectively. Although the effect of CYP2C polymorphisms on the pharmacokinetic parameters has been reported, caution is advised when estimating the usefulness of genotyping the CYP2C subfamily for the determination of phenytoin dosage regimens. There are other factors, such as concurrent drug treatment and many environmental factors, that may overwhelm the significance of genotyping in clinical practice (72,73).

Enzyme saturation kinetics lead to phenytoin plasma concentrations increasing nonproportionally with changes in dose (Fig. 61.2) (74). The relationship between dose and concentration can be expressed by the Michaelis–Menten equation:

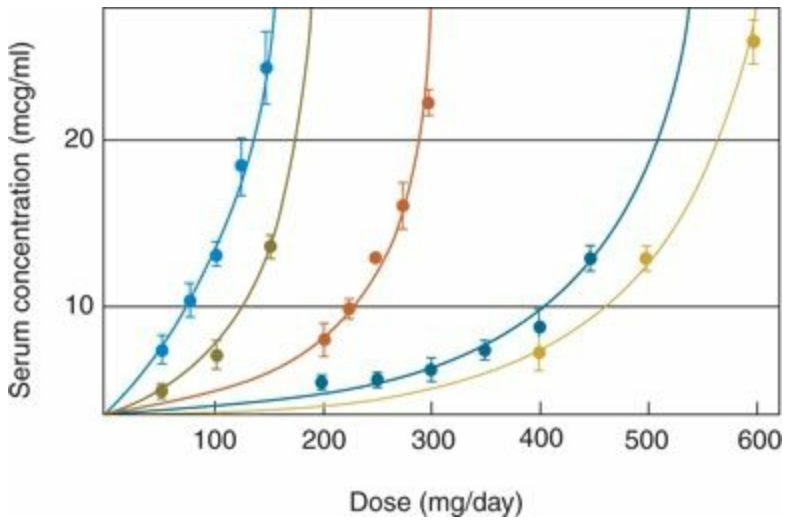

Figure 61.2. Relationship between serum phenytoin concentration and daily dose in five patients. Each point represents the mean (±SD) of three to eight measurements at steady state. The curves were fitted by computer through use of the Michaelis–Menten

equation. (From Richens A, Dunlop A. Serum phenytoin levels in the management of epilepsy. Lancet. 1975;2:247–248.)

$$\text{Dose}(\text{mg}/\text{day}) = \frac{V_{max} C_{ss}}{K_m + C_{ss}}$$

where V_{max} is the maximal rate of drug metabolism, C_{ss} the steady-state serum concentration, and K_m the concentration at which V_{max} is half-maximal. The mean apparent phenytoin K_m in adults 20 to 39 years old is 5.7 µg/mL (range, 1.5 to 20.7 µg/mL); the mean V_{max} is 7.5 mg/kg/day (75). In most patients, phenytoin exhibits nonlinear pharmacokinetics because the usual therapeutic plasma concentrations exceed the usual K_m. Concomitant illnesses (76) or medications, pregnancy (77,78), genetic makeup (79–81), and age can significantly affect V_{max} or K_m (or both). Children have higher V_{max} values, but similar K_m values, compared with adults (82–84); elderly individuals have lower V_{max} values (mean, 6.0 mg/kg/day) (75).

Excretion

Up to 95% of phenytoin is excreted in urine and feces as metabolites, with 5% or less of unchanged phenytoin excreted in urine. Phenytoin is also excreted in breast milk (85). Some investigators have suggested that phenytoin enhances its own elimination through enzyme induction (86).

Fosphenytoin

Absorption and Bioavailability

Fosphenytoin can be administered either intravenously or intramuscularly. The values for the area under the plasma total phenytoin and free phenytoin concentration versus time curves, after either intravenous or intramuscular administration of fosphenytoin, are almost identical to that for intravenous phenytoin sodium, indicating complete bioavailability by either route (9). These findings are based on studies involving single-dose intravenous and intramuscular administration to drug-free volunteers and single-dose intravenous administration to patients with therapeutic plasma phenytoin concentrations (9,87,88).

Because oral absorption of phenytoin can be erratic and unpredictable, switching to intravenous dosing can result in increased concentrations due to all medication being systemically available. Dosage adjustment is not usually necessary when fosphenytoin is used for up to 1 week, although a phenytoin plasma concentration should be checked after longer periods of administration.

Distribution

Protein Binding.

Fosphenytoin is highly bound (95% to 99%) to serum albumin in a nonlinear fashion (9). This protein binding is not affected by prior diazepam administration (89). However, in the presence of fosphenytoin, phenytoin is displaced from binding sites, rapidly increasing unbound phenytoin concentrations as a function of plasma fosphenytoin concentration. This displacement is accentuated by fosphenytoin doses of at least 15 mg PE/kg delivered at rates of 50 to 150 mg PE/min. As plasma

fosphenytoin concentrations decline, phenytoin protein binding returns to normal. There is little displacement of phenytoin after intramuscular administration of fosphenytoin (9).

Volume of Distribution.

Fosphenytoin's volume of distribution is reported to be 0.13 L/kg in patients receiving 1200 mg PE fosphenytoin at 150 mg PE/minute. At lower doses and slower infusion rates, the volume of distribution is lower, 2.6 L, or approximately 0.04 L/kg for a 70-kg human (9,87,90). Fosphenytoin, a very polar molecule, achieves a rapid equilibrium between plasma and associated tissues (90).

Metabolism

After intravenous or intramuscular administration, the phosphate group of fosphenytoin is cleaved by ubiquitous nonspecific phosphatases to produce active phenytoin. The half-life of this conversion is approximately 8 to 18 minutes, is complete in a little more than an hour, and is independent of age, dose, or infusion rate (9,16,91–93). The tissue phosphatases responsible for this conversion are present at all ages; age, plasma phenytoin or fosphenytoin concentrations, and other medications do not alter their activity. The conversion of fosphenytoin to phenytoin is slightly faster in patients with hepatic or renal disease, consistent with decreased binding of fosphenytoin to plasma proteins and increased fraction of unbound fosphenytoin resulting from hypoproteinemia in these diseases (91). In addition, fosphenytoin's phosphate load of 0.0037 mmol phosphate/mg PE fosphenytoin should be considered in patients with severe renal impairment (16).

Excretion

A clinically insignificant amount of fosphenytoin (0% to 4% of a dose) is excreted renally (93).

PLASMA DRUG CONCENTRATIONS

Phenytoin

Most laboratories and textbooks assume a therapeutic range for phenytoin of 10 to 20 μg/mL, which clinical experience and literature have called into question. Seizures have been controlled with concentrations lower than 10 μg/mL (94), although at times, more than 20 μg/mL is needed (95). This variability in seizure control may be due to the underlying disorder, the seizure type, or genetic determinants (95). In one study (96), 51% of patients achieved complete control at concentrations either below or above that range. No significant association was evident between the serum phenytoin concentration and any measures of efficacy or toxicity.

The generally established therapeutic range for phenytoin of 10 to 20 μg/mL includes both bound and unbound drugs. As 10% is normally unbound, the equivalent unbound therapeutic range is 1 to 2 μg/mL. The extent of protein binding varies little with phenytoin plasma concentration. Total phenytoin concentrations that are below the normal range can be associated with unbound phenytoin concentrations in the therapeutic range. For example, if a patient has a subtherapeutic total phenytoin concentration of 5 μg/mL but an unbound fraction of 20%, the equivalent unbound phenytoin concentration is 1 μg/mL, which is in the "therapeutic" range. Thus, patients at high risk for altered protein binding may respond to clinically subtherapeutic total concentrations and may not tolerate

total serum concentrations within the therapeutic range. If such patients experience toxic reactions despite therapeutic concentrations, measurement of unbound concentrations may be warranted. Total phenytoin concentrations may be a misleading test in developing countries, where hypoalbuminemia is highly prevalent (97).

Among the methods that predict total phenytoin concentrations in the face of reduced albumin levels, the best documented is the Sheiner–Tozer method (98,99):

$$C_n = C_o / (0.2 \quad \text{Alb} + 0.1)$$

where C_o is the measured total phenytoin concentration (milligrams/liter), Alb is albumin concentration (grams/deciliter), and C_n is the total phenytoin concentration that would have been observed with normal albumin concentrations.

Fosphenytoin

Measurement of fosphenytoin levels does not provide clinically useful information for patient care but rather has been utilized only in clinical research settings. Fosphenytoin may interfere with the ability of common laboratory immunoanalytic techniques, such as TDx/TDxFLx (fluorescence polarization) and Emit 2000 (enzyme multiplication), to measure phenytoin levels, because of cross-reactivity resulting in an artificially elevated phenytoin concentration value. Waiting until all of the fosphenytoin to phenytoin conversion has occurred (approximately 2 hours after intravenous fosphenytoin administration or 4 hours after intramuscular fosphenytoin administration) before attempting to measure a patient's phenytoin concentrations is recommended (9).

A pharmacokinetic meta-analysis of plasma total and free phenytoin concentration from seven clinical trials involving neurosurgical patients, patients with status epilepticus, patients with stroke, and healthy volunteers demonstrated that fosphenytoin loading doses of 15 to 20 mg PE/kg administered either intravenously or intramuscularly consistently resulted in total phenytoin plasma concentrations of 10 μg/mL or more and free phenytoin concentrations of 1 μg/mL or more. These therapeutic plasma phenytoin concentrations were reached in most subjects within 10 minutes, if rapid intravenous fosphenytoin dosing (≥100 mg PE/min) was used, or within 30 minutes, if slower intravenous (<100 mg PE/min) or intramuscular fosphenytoin dosing was used (100).

DRUG INTERACTIONS

Phenytoin

Phenytoin can affect, and be affected by, a number of medications (Table 61.2) (101). Because new medications are regularly being approved for patient use, it is important to regularly utilize drug interaction databases to identify and design a plan to monitor potential interactions. Although these drug interactions do not preclude concomitant administration, they signal the need for more frequent determination of serum concentrations, increased monitoring for the appearance of side effects, and, if appropriate, changes in dose. Patient-specific factors, such as genetic makeup, previous exposure to other compounds, and susceptibility to the clinical outcomes of the interaction, govern the extent and clinical significance of any drug interaction. In addition, a drug may act as an inhibitor in one patient and an inducer in another (e.g., phenobarbital's effect on phenytoin).

Table 61.2 Bidirectional Interactions Between Phenytoin and Other AEDs

Specific drug	Effect of AED on phenytoin concentration	Mechanism of AED effect	Effect of phenytoin on AED concentration	Mechanism of phenytoin effect
Carbamazepine	↑↓	CYP2C19 induction	↓↓	CYP3A4 induction
Ethosuximide	«		↓↓	CYP3A4 induction
Eslicarbazepine	↑	CYP2C19 inhibition	↓	UDPGT induction
Ezogabine	«		↓	Unknown
Felbamate	↑↑	CYP2C19 inhibition	↓↓	CYP3A4 induction
Fosphenytoin	↑ Free phenytoin	Protein-binding displacement	«	
Gabapentin	«		«	
Lacosamide	«		«	
Lamotrigine	«		↓↓	UDPGT induction
Levetiracetam	«		«	
Oxcarbazepine	↑	CYP2C19 inhibition	↓ MHD	Unknown
Perampanel	«		↓↓	CYP3A4 induction
Phenobarbital	↑↓	CYP2C9 and CYP2C19 induction	↑	Unclear
Pregabalin	«		«	
Rufinamide	↑	Unknown	↓	Unknown
Stiripentol	↑	CYP2C9 and 2C19 inhibition	↓	Unclear
Topiramate	↑	CYP2C19 inhibition	↓↓	Unknown
Tiagabine	«		↓↓	CYP3A4 induction
Valproic acid	↓/« or ↑ Free phenytoin	Protein-binding displacement and CYP2C9 inhibition	↓↓	CYP2C9 and CYP2C19 induction
Vigabatrin	↓	Unknown	«	
Zonisamide	«		↓↓	CYP3A4 induction

↑↓, Variable; ↑, minor increase; ↓, minor decrease; ↑↑, important increase; ↓↓, important decrease; «, no change; MHD, monohydroxy derivative; UDPGT, uridine diphosphate glucuronyltransferase.

Interactions can affect any of the four primary pharmacokinetic phases. A drug that affects absorption most likely will decrease phenytoin serum concentration. For example, administration of phenytoin with a continuous high-calorie, liquid complete-nutrition formula through nasogastric tube feedings causes a decrease in phenytoin serum concentrations from a mean of 9.8 to 2.72 µg/mL at the same dose (102).

Drugs that affect protein binding increase the percentage of unbound phenytoin, usually with no change in the unbound concentration and with a decrease in the total concentration. Valproic acid displaces phenytoin from protein-binding sites. When valproic acid is added to a phenytoin regimen, total phenytoin concentrations decrease, free fraction increases, and free concentrations either stay the same or increase slightly. The following equation may be used to measure unbound phenytoin concentration in a patient receiving this combination (103,104):

$$\text{Free PHT} = \left[0.095 + 0.001(\text{VPA})\right]\text{PHT}$$

where PHT is phenytoin and VPA is valproic acid. Metabolic interactions usually cause either enzyme induction or inhibition. Phenytoin is a significant liver enzyme inducer and is highly likely to cause many drug interactions (105). Addition of an inducer decreases phenytoin concentrations; addition of an inhibitor increases them. The order of addition or deletion is important. An inducer added to another compound may lead to decrease in the serum concentration of the preexisting drug; however, if that same drug is added to the inducer, the interaction would have a less noticeable clinical significance because nothing has changed—the added drug would simply require a higher dose. When an enzyme-inducing drug is removed from a regimen, the concentration of the remaining compound is likely to increase (106).

Fosphenytoin

As described above, in the presence of fosphenytoin, phenytoin is displaced from binding sites, rapidly increasing unbound phenytoin concentrations as a function of plasma fosphenytoin concentration (9).

EFFICACY AND CLINICAL USE

Phenytoin

Phenytoin is effective in the abortive treatment of acute seizures (including acute repetitive seizures and status epilepticus) or as chronic maintenance therapy to prevent seizure recurrence. Phenytoin is considered effective against partial-onset seizures and primary generalized tonic–clonic seizures (107,108); however, there is no convincing evidence that it is effective against absence, clonic, myoclonic, tonic, or atonic seizures. Phenytoin is not recommended for infantile spasms, Lennox–Gastaut syndrome, or primary generalized epilepsy syndromes such as childhood absence or juvenile myoclonic epilepsy.

Acute Seizures (Acute Repetitive Seizures and Status Epilepticus)

Multiple open-label series have indicated that patients with acute repetitive seizures or status epilepticus respond promptly to intravenous administration of phenytoin (109). In 60% to 80% of patients, a response was noted within 20 minutes after the initiation of an infusion (110,111). In one pediatric study (112), loading doses produced a complete or partial effect in 30 of 35 patients. The youngest children had lower concentrations and responded less favorably than did the older children.

For rapid increase in drug concentration, phenytoin doses of 15 to 20 mg/kg are used (113,114). Doses of 18 mg/kg increase phenytoin serum concentrations by approximately 23 μg/mL in adults being treated for acute seizures (115); in children with status epilepticus, similar or higher doses have been administered (112). The intravenous route is used during status epilepticus. In less acute situations, oral administration is appropriate, but the loading dose is divided into three or four doses, given 2 to 3 hours apart to improve bioavailability and rate of absorption (116–118).

When given intravenously to adults, phenytoin should be diluted in normal saline (not in dextrose 5% in water); the infusion should not exceed 50 mg/min and should be injected directly into a large vein through a large-gauge needle or intravenous catheter. The intramuscular route is not recommended owing to the drugs slow and erratic absorption, as well as painful local reactions likely associated with crystallization at the injection site. If, however, no other routes of administration are available, intramuscular doses 50% higher than oral doses may be needed to maintain plasma concentrations (119–121). Adjustments in dosage and monitoring of serum levels may be necessary on switching from one route to another. Therapeutic levels of phenytoin administered rectally have not been maintained in patients with seizures (122).

Partial-Onset and Generalized Tonic–Clonic Seizures

Multiple studies have compared the efficacy and tolerability of phenytoin with those of other AEDs

(including carbamazepine, phenobarbital, primidone, valproic acid, lamotrigine, topiramate, and oxcarbazepine) in the treatment of partial-onset and generalized tonic–clonic seizures.

In the first Veterans Administration Cooperative Study (123), 622 adults were randomly assigned to treatment with phenytoin, carbamazepine, phenobarbital, or primidone and remained on therapy unless unacceptable toxic reactions or lack of efficacy was evident. Carbamazepine and phenytoin were more effective and had greater tolerability over time compared with primidone and phenobarbital in the treatment of complex partial seizures. All four AEDs were equally effective as monotherapy for generalized tonic–clonic seizures. Carbamazepine and phenytoin produced the highest rates of success, as defined by retention in the study (Fig. 61.3), and were recommended as "drugs of first-choice for single-drug therapy of adults with partial or generalized tonic–clonic seizures or with both."

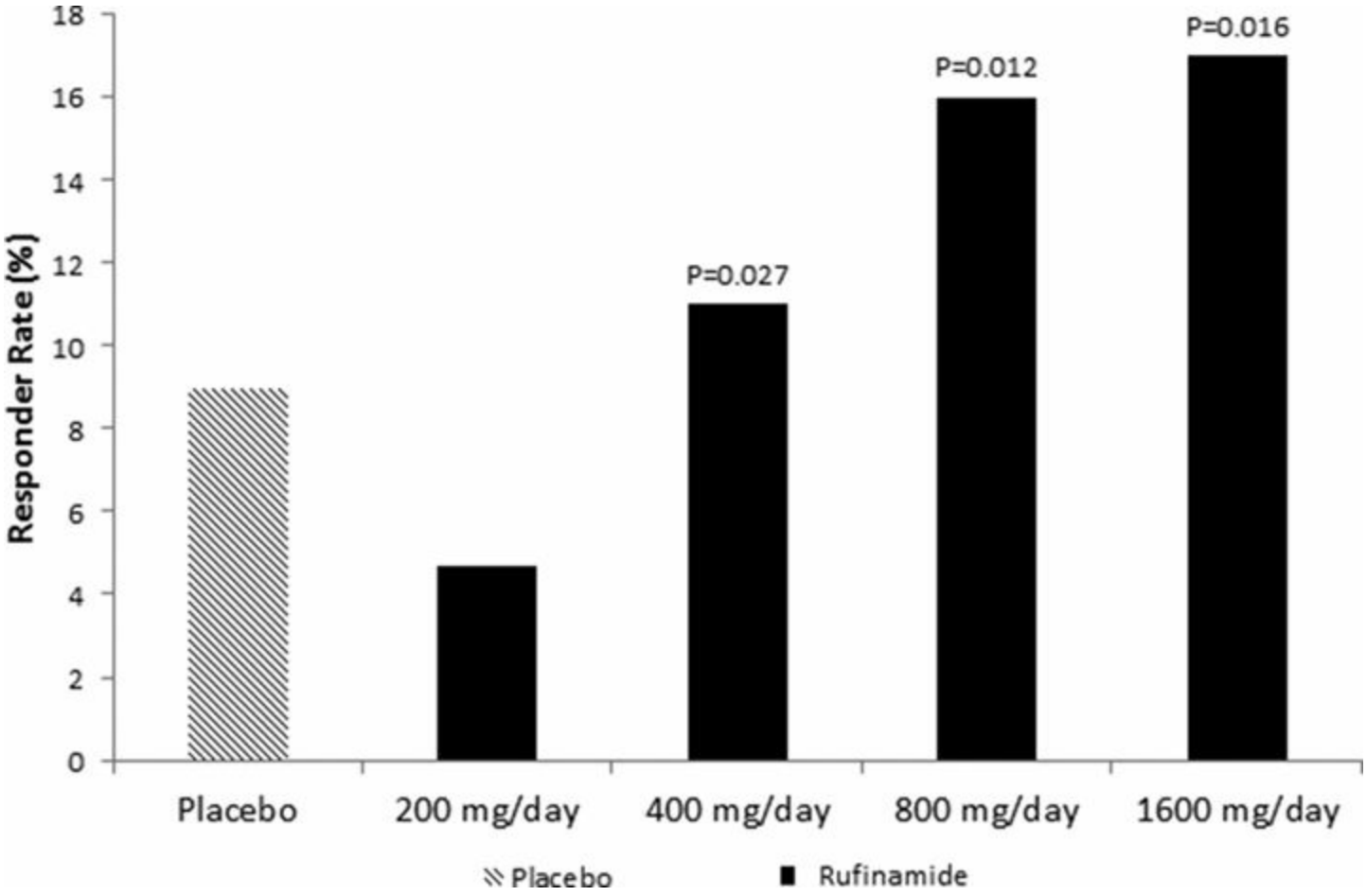

Figure 61.3. Cumulative percentage of patients remaining in the study during 36 months of follow-up. There were 275 patients at 12 months, 164 at 24 months, and 97 at 36 months. (From Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. N Engl J Med. 1985;313:145–151.)

In several other comparative trials, phenytoin was as effective as carbamazepine and valproic acid, with similar potential to cause major side effects (108,124–126). No significant differences in efficacy were found among the four drugs at 1, 2, or 3 years of follow-up. The incidence of unacceptable side effects necessitating withdrawal from treatment was 10% (127).

In children, one study compared the efficacy and toxicity of phenytoin, phenobarbital, carbamazepine, and valproate as monotherapy in children with newly diagnosed epilepsy (128). There were no differences in efficacy between the drugs. Nine percent of the children had adverse effects requiring withdrawal. Patients on phenobarbital were more likely to withdraw because of

intolerable side effects, compared to those on the other drugs. There was no significant difference in the rate of withdrawal between the other drugs (128).

A number of studies comparing phenytoin to newer AEDs have been conducted. Two studies compared the efficacy and tolerability of oxcarbazepine and phenytoin monotherapy in patients with recent-onset partial seizures or generalized tonic–clonic seizures (129,130). The first study (129) involved 287 adults and adolescents, aged 15 to 91 years, demonstrated no difference in the proportion of seizure-free patients during the 48 weeks of maintenance between the oxcarbazepine group (59%) and the phenytoin group (58%). The second trial (130), in 193 children and adolescents, aged 5 to 17 years, also showed no difference in the proportion of seizure-free patients during the 48-week maintenance period between the oxcarbazepine group (61%) and the phenytoin group (60%). Lamotrigine and phenytoin monotherapy were compared in a study of patients with newly diagnosed untreated partial-onset seizures or generalized tonic–clonic seizures (131). No between-treatment difference in efficacy was detected on the basis of percentages of patients remaining on each treatment arm, those remaining seizure free during the last 24 and 40 weeks of the study, and times to first seizure after the initial 6 weeks of treatment (dose-titration period). Topiramate and phenytoin monotherapy were compared in a study of patients with new-onset epilepsy or epilepsy relapse (132). The duration of the study was short (28 days), and there was no statistical difference to time to first seizure between medications. The rate of side effects was similar, but the rate of study discontinuation due to side effects was higher in the phenytoin arm.

No monotherapy trials have compared phenytoin with felbamate, gabapentin, tiagabine, zonisamide, or levetiracetam in the treatment of partial-onset or generalized tonic–clonic seizures.

The International League Against Epilepsy elaborated an evidence-based guideline for AED efficacy and effectiveness as initial monotherapy for different epileptic seizures and syndromes (133). The guideline concluded that based on available efficacy and effectiveness evidence alone, phenytoin and carbamazepine were efficacious or effective as initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures (with the highest level of evidence, level A). The findings in children was not that robust, and therefore, based on available efficacy and effectiveness evidence alone, phenytoin, carbamazepine, phenobarbital, topiramate, and valproate were possibly efficacious or effective as initial monotherapy for children with newly diagnosed or untreated partial-onset seizures (level C). Similarly, phenytoin, carbamazepine, phenobarbital, oxcarbazepine, lamotrigine, topiramate, and valproate were found to be possibly efficacious or effective as initial monotherapy for adults with generalized tonic–clonic seizures (level C). In children with generalized tonic–clonic seizures, phenytoin, carbamazepine, phenobarbital, topiramate, and valproate were possibly efficacious or effective (level C).

For phenytoin maintenance therapy, the nonlinear pharmacokinetics and wide interindividual variability in metabolism and absorption necessitate individualized regimens. The typical initial dose of 300 mg/day results in concentrations between 10 and 20 μg/mL in fewer than 30% of patients, and more than 57% will achieve concentrations below 10 μg/mL (99). Doses of 6 to 8 mg/kg will produce concentrations between 10 and 20 μg/mL in approximately 45% of otherwise healthy patients, less than 10 μg/mL in 35%, and more than 20 μg/mL in 20% (99). Thereafter, adjustments should be based on clinical response, increasing dosage for lack of seizure control or lowering dosage for concentration-dependent toxic reactions.

Privitera (134) proposed the following guidelines based on initial plasma concentration: increase dosage by 100 mg/day for an initial plasma concentration of less than 7 μg/mL; increase dosage by 50 mg/day for concentrations from 7 to 12 μg/mL; increase dosage by 30 mg/day for concentrations

greater than 12 μg/mL. This formula was tested in 129 dosage increases of 50 or 100 mg in 77 patients. All 53 increases that were within the guidelines produced plasma concentrations less than 25 μg/mL, whereas 36% of the increases that exceeded the guidelines produced plasma concentrations greater than 25 μg/mL (134).

Accurate predictions of phenytoin plasma concentrations cannot be accomplished with the Michaelis–Menten equation unless patient-specific values for V_{max} and K_m are obtainable, which is rarely possible in clinical situations. When at least some clinical data are available, numerous methods can assist in estimating an individual patient's dose (135–138) to achieve predetermined serum concentrations (139,140). The nonlinear pharmacokinetics of phenytoin not only leads to nonproportional changes in serum concentration with changes in dose but also increase the apparent elimination half-life with higher concentrations. Thus, patients with "high" concentrations exhibit smaller peak–trough variability and require a longer time to achieve steady state. For most patients whose concentrations are within the therapeutic range, the peak–trough remains relatively unaffected, and steady state is reached in approximately 1 to 2 weeks. Thus, any changes in dose will require 1 to 2 weeks to achieve maximum effect. Patients receiving prompt-release phenytoin products and those with low serum concentrations and rapid phenytoin metabolism (e.g., children or patients with relatively high dose requirements) are at high risk for large peak–trough variability and often need multiple daily doses to prevent wide fluctuations in clinical response.

Children require higher milligrams per kilogram daily doses, whereas the elderly should be started on 2 to 3 mg/kg/day and doses increased carefully. Elderly patients have demonstrated fluctuating concentrations despite no change in dose or other medications. An adjustment of dose may not be necessary if the patient is tolerating their current dose and is not having seizures (141). Concomitant illnesses can alter phenytoin pharmacokinetics and, consequently, dosage requirements. Critically ill patients may require plasmapheresis, continuous ambulatory peritoneal dialysis, or hemofiltration. Plasmapheresis does not appear to remove a significant amount of phenytoin (142); continuous ambulatory peritoneal dialysis may not either (143). In contrast, continuous hemofiltration at a high ultrafiltration rate may remove significant amounts of phenytoin in patients with renal failure with significant protein-binding changes (144). Pregnancy may necessitate an increase in phenytoin dose, especially during the third trimester (77,78).

Neonatal Seizures

Phenytoin and phenobarbital monotherapy were compared in a randomized trial of 59 neonates with seizures confirmed by electroencephalography (145). Seizures were controlled in 43% of the phenobarbital group and in 45% of the phenytoin group. Monotherapy or subsequent duotherapy controlled seizures in 59% of the neonates. The authors concluded that both drugs were "equally but incompletely effective as anticonvulsants in neonates."

In a sample of practice in major U.S. pediatric hospitals, 6099 infants with neonatal seizures were identified over 62 months. As expected, the most common treatment for neonatal seizures was phenobarbital, which was given to 76% of all infants in the study (range, 56% to 89%, $P < 0.001$) and 97% of the infants who received a nonbenzodiazepine AED (range, 92% to 100%). Overall, 80% of the neonates treated with phenobarbital did not receive any other nonbenzodiazepine AEDs. Phenytoin was the second most commonly used nonbenzodiazepine AED, but it was usually used in combination with another AED. It was used to treat 16% of all neonates diagnosed with neonatal seizures (range, 8% to 36%, $P < 0.001$) and 20% of the neonates who received a nonbenzodiazepine

AED (range, 12% to 42%, P < 0.001). Phenytoin was used without phenobarbital in only 11% of these neonates and was used without any other nonbenzodiazepine AEDs in only 83 infants overall (8%). Phenytoin was started at least 1 day after phenobarbital 46% of the time, started on the same day as phenobarbital 32% of the time, and started at least 1 day before phenobarbital 11% of the time (146).

Prophylaxis

Phenytoin is often used following neurosurgical procedures and cerebrovascular accidents. A randomized, double-blind trial compared the efficacy, tolerability, and impact on quality of life and cognitive functioning of anticonvulsant prophylaxis with phenytoin versus valproate in 100 patients following craniotomy (147). Fourteen patients (seven in each group) experienced postoperative seizures. No major between-treatment differences emerged in efficacy, tolerability, impact on quality of life, or cognitive functioning (147). A double-blind comparison of phenytoin or carbamazepine with no treatment after supratentorial craniotomy noted no significant differences but a higher incidence of side effects in the treated group (148). Thus, prophylactic anticonvulsants cannot be recommended routinely after this type of procedure.

The efficacy of phenytoin in the prevention of posttraumatic seizures was studied in a randomized, double-blind trial of 404 patients with serious head trauma (149). Patients received a phenytoin-loading dose within 24 hours of injury; free phenytoin serum levels were maintained in a range from 0.75 to 1.5 μg/mL. From the time of drug loading to day 7, significantly fewer seizures occurred in the phenytoin group than in the placebo group (3.6% vs. 14.2%, P < 0.001). No benefit was seen in the phenytoin group after day 8, however, leading to the conclusion that phenytoin had an early suppressive effect, but not a true prophylactic effect, on seizures, and that it reduced the incidence of seizures only during the first week after injury. In a secondary analysis of this study (150), no significant difference in mortality was found between patients assigned to phenytoin and those assigned to placebo. In a randomized, double-blind, placebo-controlled trial in children with moderate to severe blunt head injury, phenytoin did not prevent posttraumatic seizures within 48 hours of the trauma (151).

Fosphenytoin

Fosphenytoin itself has no known anticonvulsant activity; it derives its utility from its rapid and total conversion to phenytoin (15,16).

The two main situations in which fosphenytoin are used are during status epilepticus, or as a temporary substitute for oral phenytoin in a nonemergency hospital situation, such as in a patient undergoing a neurosurgical procedure. Fosphenytoin can be diluted in a variety of vehicles, such as dextrose 5% and 10%, lactated Ringer solution, and mannitol 20% (152).

Fosphenytoin (rather than phenytoin) has become part of the standard-of-care treatment protocols for convulsive status epilepticus in adults and children in many U.S. hospitals. It is preferred to phenytoin because of better tolerability at the infusion site, lack of cardiovascular complications, and overall ease of administration (153). For the treatment of convulsive status epilepticus, a fosphenytoin "loading dose" of 15 to 20 mg PE/kg can be given intravenously, with an infusion rate of at least 100 mg PE/min and up to 150 mg PE/min. The dose should be adjusted in patients who have hepatic impairment or hypoalbuminemia. For the prophylaxis of seizures in neurosurgical patients, a single nonemergency loading dose is given either intravenously or intramuscularly. The dose is

usually 10 to 20 mg PE/kg, with an intravenous infusion rate of up to 150 mg PE/min.

Fosphenytoin (given either intravenously or intramuscularly) is useful as a temporary substitute for oral phenytoin when the patient is unable to take oral medications. In this situation, the fosphenytoin dose and frequency would be the same as the patient's oral phenytoin dose and frequency.

Although now generic, fosphenytoin is more expensive than phenytoin (154). A number of studies and editorials have reported pharmacoeconomic comparisons between fosphenytoin and intravenous phenytoin (117,154–156). The overall cost of patient care with intravenous fosphenytoin was less than with intravenous phenytoin in an emergency department setting (156). Substitution of intravenous fosphenytoin for intravenous phenytoin was associated with reduced "adverse events at a reasonable increase in total hospital costs" in a second study (155). An editorial suggested that pharmacoeconomic decisions should be based on outcome cost, not acquisition costs (154). Overall, in terms of cost-effectiveness, studies in the past decade showed that despite higher acquisition cost, use of intravenous fosphenytoin appeared to be at least equivalent to, if not better than, intravenous phenytoin. However, two studies (117,157) have challenged this impression. The administration of intravenous fosphenytoin to adults in an emergency department did not significantly decrease the incidence of drug-related adverse effects or decrease the length of stay in the emergency department compared with the use of intravenous phenytoin. This result suggests that intravenous fosphenytoin may not be more cost-effective than is intravenous phenytoin.

ADVERSE EFFECTS

Phenytoin

Concentration-Dependent Effects

The most common concentration-dependent phenytoin side effects are related to the central nervous system and consist of nystagmus, ataxia, incoordination (158,159), diplopia (vestibulo-oculo-cerebellar syndrome), and drowsiness. Some patients may experience prominent side effects at concentrations in the lower end of the therapeutic range, while others may be free of complaints despite elevated drug concentrations. These effects are reversible with appropriate adjustments in dose. Although small decreases may completely alleviate complaints, significant dose alterations may dramatically decrease serum concentrations, leading to a recurrence of seizures. Nausea, vomiting, and epigastric pain are often improved by dividing the dose or taking it with meals (or both).

Symptoms noted at serum phenytoin concentrations higher than 30 μg/mL include dysarthria, far-lateral nystagmus, movement disorders (usually choreoathetosis and orofacial dyskinesia), exacerbation of seizures, external ophthalmoplegia, or encephalopathy (including lethargy, delirium, "psychosis," stupor, and coma) (93,159–164).

Reports of the effect of phenytoin on cognitive function vary, depending on the type of patients, presence or absence of concomitant AEDs, measurement instruments, and comparative drugs. In general, however, effects appear modest when serum concentrations are kept within standard therapeutic ranges, and polypharmacy is avoided (165,166). Unfortunately, patients taking phenytoin may suffer from cognitive side effects even when these guidelines are followed (167).

Idiosyncratic Reactions

Phenytoin's idiosyncratic reactions are proposed to result from the formation of a reactive metabolite (an arene oxide) that either directly (owing to deficiencies in detoxification resulting from inadequate epoxide hydrolase activity) or indirectly (through an immune response or free radical–mediated injury) causes cell, tissue, or organ injury and, at times, death (168).

The most common idiosyncratic reaction is rash, which may occur in up to 8.5% of patients, particularly children and adolescents (169–171). The in vivo and in vitro cross-reactivity between phenytoin, phenobarbital, and carbamazepine is as high as 70% to 80% (172). A recent study on cross-sensitivity of skin rashes among commonly used AEDs (n = 1875) found evidence of specific cross-sensitivity between carbamazepine and phenytoin (173). The phenytoin rash rate in patients who also had a rash to carbamazepine (n = 59) was 57.6%, which was significantly higher compared to the phenytoin rash rate in patients with rashes to any other AEDs (38.8%; $P < 0.0016$) (173). The rate of cross-sensitivity between phenytoin and other AEDs (phenobarbital, lamotrigine, oxcarbazepine, and zonisamide) was not as high as with carbamazepine (173). A more severe dermatologic idiosyncratic reaction is the "hypersensitivity syndrome" (172). In a series of 38 affected patients, the most common manifestations were rash, fever, lymphadenopathy, eosinophilia, abnormal liver function test results, blood dyscrasias, serum sickness, renal failure, and polymyositis. Symptoms usually occur within the first 3 months of therapy (174).

Other reported idiosyncratic reactions include Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis, aplastic anemia, hepatitis, pseudolymphoma, and a lupus-like reaction (159). Recent data suggest a possible association between HLA-B*1052 and phenytoin-induced SJS (175,176). The human leukocyte antigen allele, HLA-B*1502, occurs almost exclusively in patients with ancestry across broad areas of Asia, including Han Chinese, Filipinos, Malaysians, South Asian Indians, and Thais. A study from Hong Kong reported that HLA-B*1052 was associated with SJS in a patient who started phenytoin within 8 weeks prior to the development of the cutaneous reaction, and in whom no other causes for the reaction were found (175). More recently, a Thai study reported a significant association between HLA-B*1052 and SJS in four patients on phenytoin ($P = 0.005$). One of the four patients, who developed phenytoin-induced SJS, was tolerant to carbamazepine. The authors concluded that while HLA-B*1052 may be necessary, it is not sufficient to cause SJS from phenytoin in the Thai population (176).

Adverse Effects with Long-Term Therapy

Long-term administration of phenytoin has been associated with gingival hyperplasia (177,178), hirsutism, acne, and rash. The exact incidence of gingival hyperplasia attributable to phenytoin is not known (178); reports range from 13% of patients attending general medical practices (179) to about 40% of patients taking phenytoin long term in a community-based cross-sectional study in Ferrara, Northern Italy (180). In the latter report, younger age and poorer oral hygiene seemed to predispose to the severest level of gingival involvement (180). Hyperplasia regresses after discontinuation of phenytoin (181,182).

Cerebellar atrophy has been reported after long-term (183,184) and acute use (185) of high doses, although whether the true etiologic agent was phenytoin or the seizures is unclear (186,187); single photon emission computed tomography scans may be a means for early detection (186).

Among other effects of long-term phenytoin therapy are alterations in laboratory values, including reduction in bone mineral density (188), low folate levels (93), macrocytosis (93), and decreases in

levels of carnitine (189), low-density lipoprotein cholesterol, and apolipoprotein B (190). Levels of prolactin (191) and apolipoprotein A and A1 (190) increase, as does high-density lipoprotein cholesterol, although at doses of 100 mg/day, this lipid fraction was unchanged (192). Phenytoin may decrease levels of free testosterone and enhance its conversion to estradiol (193).

Changes in thyroid hormones have been reported (194). The thyroxine (T_4) and free T_4 index, total T_4 and triiodothyronine (T_3), free T_4, and free T_3 all decrease. Increases in serum levels of thyroid-stimulating hormone (195,196) may involve protein-binding displacement and induction of cellular metabolism (197). Phenytoin therapy may suppress immunoglobulin (Ig) production, leading to decreases in IgG (198,199) and IgA (198,200). Panhypoglobulinemia was reported in one patient infected with the human immunodeficiency virus (201). It is unclear whether these changes are a direct result of phenytoin or epilepsy (198) or if they occur with any drug with arene oxide intermediates (198,202).

Teratogenicity

"Fetal hydantoin syndrome" was described in 1975 and consisted of growth retardation, microcephaly, mental retardation, and numerous "minor" congenital anomalies (171,203). However, "fetal anticonvulsant syndrome" has replaced this term because the malformations are seen in children of mothers taking a wide variety of AEDs. Although there is agreement that anticonvulsant polypharmacy and folic acid deficiency increase the risk of malformation (204), the absolute and relative teratogenicity of phenytoin is not completely known. One study showed an increased risk for cleft palate in the offspring with phenytoin use during pregnancy (205).

Four recent studies described the pregnancy outcomes of women with epilepsy taking AEDs; one focused on fetal malformations (206) and the other three on the neurocognitive outcome for AED exposure in utero (207–209). The North American AED Pregnancy Registry reported the risk of major malformations in infants exposed to phenytoin monotherapy in the first trimester based on 416 infants as compared to 1562 infants exposed to lamotrigine. The risk was not significantly increased (206). The Neurodevelopmental Effect of Antiepileptic Drugs (NEAD) study is an ongoing prospective observational study that recently reported on the cognitive outcome at ages 3 (207), 4.5 (208), and 6 years (209), in 311 children born to mothers who were taking a single AED during pregnancy. The age 6 study included 225 children, and on average, the IQ of children exposed to phenytoin (n = 40) was 11 points better than the ones exposed to valproate (95% CI, 5 to 16; P = 0.0004) but not different than the ones exposed to carbamazepine or lamotrigine (P = 0.99) (209).

Intravenous Administration

Administration of parenteral phenytoin solution is associated with local reactions, including pain and burning at the infusion site, phlebitis, and vessel cording (7,11,210). Extravasation can lead to phlebitis, chemical cellulitis, or frank necrosis (8). A unique effect of unknown etiology, purple glove syndrome (211,212), begins with discoloration and progresses to a petechial rash; severe cases may require surgical intervention. In one report (213), 9 of 152 patients (5.9%) receiving intravenous phenytoin developed purple glove syndrome.

Intravenously administered phenytoin can also lead to cardiovascular complications, such as hypotension, atrial and ventricular conduction depression, and ventricular fibrillation (7). The major risk factors for these complications include preexisting disease, advanced age, and rapid infusion

(7,210). In patients without cardiovascular disease, phenytoin can be administered at 40 to 50 mg/min (214). Rates should not exceed 25 mg/min in patients with arteriosclerotic cardiovascular disease (215).

Fosphenytoin

Concentration-Dependent Effects

Intravenous fosphenytoin infusion has a favorable side effect profile (11,216,217). The local reactions associated with administration of parenteral phenytoin solution (infusion site pain, phlebitis, and vessel cording) occur significantly less often with fosphenytoin (11). Pain at the site of fosphenytoin infusion is rare, but 48.9% of patients reported pruritus or tingling (without rash) in the perianal region, elsewhere on the trunk, or on the back of the head (217). Pruritus or tingling appears soon after an infusion starts, abates rapidly when the infusion stops, and can be reduced or abolished by slowing the infusion. Decreases in systolic and diastolic blood pressure have been observed, but the changes were judged to be clinically insignificant and did not require cessation of the infusion (218). Cardiac arrhythmias have not been noted (218). Dizziness, somnolence, and ataxia were observed with a frequency similar to that after phenytoin infusion (218).

Adverse effects have been even less notable after intramuscular fosphenytoin injection (219–221). Mild local irritation occurred in only 5% of 60 patients who received intramuscular loading doses, even though the volume of injected solution was usually 15 to 20 mL (mean, 17.8 mg/PE/kg or 1359.8 mg PE total) (220).

Idiosyncratic Reactions, Long-Term Adverse Reactions, Teratogenicity

No idiosyncratic reactions are associated specifically with fosphenytoin. As fosphenytoin is used only on a short-term basis, data about long-term adverse reactions are lacking. There are also no data on possible teratogenic effects with fosphenytoin.

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CHAPTER 62 RUFINAMIDE

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INTRODUCTION

Rufinamide was identified as a potential antiepilepsy drug (AED) by Ciba-Geigy in Europe and was initially developed by Novartis Pharmaceuticals, but had modest effects in treating medically resistant partial-onset seizures in adults and children. Eisai Pharmaceuticals subsequently obtained development rights and in 2008 obtained regulatory approval in Europe and the United States for using rufinamide to treat seizures in patients with Lennox–Gastaut syndrome. The drug is marketed in the United States with FDA approval as an orphan drug "Banzel" and in Europe as "Inovelon." Rufinamide has an orphan drug indication for treating tonic–atonic seizures in Lennox–Gastaut syndrome and has been used to treat other epileptic encephalopathies.

CHEMISTRY

Rufinamide (1-[2,6-difluorobenzyl]-1H-1,2,3-triazole-4-carboxamide) is a triazole ($C_2H_3N_3$) ring structure, which is structurally dissimilar to other AEDs (lamotrigine has a "triazine" two-ring structure) (Fig. 62.1).

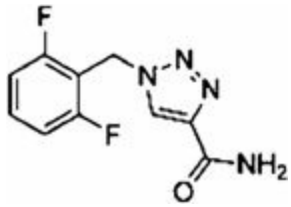


Figure 62.1. Rufinamide. MW 238.2, ($C_{10}H_8F_2N_4O$).

Rufinamide is nearly insoluble in water and slightly soluble in methanol and ethanol. This would make it difficult to prepare an intravenous formulation. Solubility in water and gastric fluid is approximately 40 to 70 mg/L at 37°C. Dissolution is the rate-limiting step for absorption. Rufinamide forms a white crystalline powder and is compacted into scored film tabs of 100-, 200-, and 400-mg tablets.

MECHANISMS OF ACTION

Rufinamide modulates voltage-dependent neuronal sodium channels; however, it also inhibits seizures triggered by γ-aminobutyric acid (GABA) antagonists, and its anticonvulsant mechanisms in humans are unknown. The drug interacts with sodium channels in cultured rodent cortical neurons, prolongs inactivation of voltage-dependent sodium channels in spinal cord neurons, and acts to reduce repetitive firing of sodium-channel dependent neurons (1). The drug does not interact,

however, with several subtypes of rodent and human voltage-gated sodium channels: rat $Na_v1.2a$, rat $Na_v1.8$, and human $Na_v1.5$ (2). Interactions with sodium channel isoforms, such as human $Na_v1.2$, involved in familial epilepsy syndromes have not been evaluated.

Rufinamide's effects in prolonging inactivation of voltage-dependent sodium channels are consistent with its potent inhibition of maximal electroshock–triggered seizures in rodents (oral ED50 = 4 to 24 mg/kg) (3). Rufinamide's inhibition of maximal electroshock seizures (MES) was additive with other AEDs, but it did not potentiate or reduce the effects of other AEDs (4). Rufinamide also prevents clonic seizures induced by injected (s.c. and i.p.) pentylenetetrazole (PTZ) in mice, but did not prevent seizures caused by oral PTZ treatment. Rufinamide caused behavioral toxicity on the rotarod test only at extremely high doses; consequently, rufinamide's protective indexes for MES and PTZ tests are much higher than traditional AEDs (e.g., phenytoin in MES model, valproic acid in PTZ model) (3).

Rufinamide inhibits seizures induced by the GABA-A antagonists bicuculline and picrotoxin, with less effect on strychnine-induced seizures. Rufinamide does not inhibit seizures in the WAG/Rij rat, however, which is a genetic model of absence epilepsy with GABA-A receptor abnormalities (5). Rufinamide also does not interact directly with GABA receptors or modulators. This suggests rufinamide's influences on cortical inhibition are indirect, possibly mediated by modulation of voltage-dependent sodium channels in cortical interneurons.

Rufinamide has mixed effects on chronic seizure models: it delayed the development of electrically kindled afterdischarges in the cat, but not in the rat. It markedly reduced recurring motor seizures induced by aluminum hydroxide placed on monkey cortex (6). Overall, these studies suggest that rufinamide modulation of voltage-dependent sodium channels may indirectly influence seizures via effects on cortical inhibition. However, associations between these mechanisms and effects on seizures associated with Lennox–Gastaut syndrome are unknown.

ABSORPTION, METABOLISM, AND DRUG INTERACTIONS

The pharmacologic profile for rufinamide is summarized in Table 62.1.

Table 62.1 Pharmacokinetic Properties of Rufinamide

Half-life	Mean 9.5 h (range 8–12 h)
T_{max}	Fed 6 h; fasted 8 h
Bioavailability	Fed 70%, fasted 49%
Protein binding	34%
Mean C_{max}	3.03 μg/mL (400 mg dose in healthy adult male volunteers)
V_d	Range: 50–80 L

Rufinamide is well absorbed orally in the fed state (≥85% absorption in healthy volunteers) with a slow rate of absorption; absorption decreases slightly at high doses (7). The relative extent of absorption of rufinamide was lower at a dose of 1600 mg/day compared to 200 to 800 mg/day in a large pharmacokinetic study (8). Bioavailability of single doses of rufinamide is increased by food; however, food effects were not seen with chronic dosing (9). Patients received rufinamide only with

food in clinical trials, and it is approved to be dosed with food. Peak rufinamide concentrations (T_{max}) occur approximately 6 hours after dosing when taken with food and approximately 8 hours when dosed while fasting (10). Rufinamide has relatively low (34%) protein binding—mostly to albumin—and is distributed in the bloodstream equally between erythrocytes and plasma (7). Rufinamide's apparent volume of distribution (V_d) is approximately 50 L at a 3200 mg/day dose and increases slightly with very high doses and high body surface area (11).

Rufinamide is eliminated via hydrolysis into an inactive carboxylic acid metabolite (CGP 47292), which is renally excreted. Less than 2% of rufinamide is recovered in the urine (4). A small fraction of metabolite is glucuronidated and subsequently excreted. Rufinamide is hydrolyzed by a carboxylesterase, which is concentrated in the liver, but is present in brain and other tissues (7). Rufinamide does not induce carboxylesterase and its metabolism is not dependent on cytochromes; thus, major drug–drug interactions are unlikely (7). With the exception of a valproic acid interaction in children, the overall pharmacokinetics for rufinamide are similar in children and in adults, including the elderly, with clearance proportionate to dose and body surface area (12). However, in one study in children, apparent clearance of rufinamide was higher in younger children than older children even when concomitant valproic acid was taken into account. Similar to that of other studies, concomitant enzyme inducing medications increased clearance in all age groups, particularly so in younger children (13). Moreover, human carboxylesterase 1, which is mainly involved in metabolism of rufinamide, has been shown to be inhibited by valproate or its metabolite valproyl-CoA in vitro, and thus, patients on concomitant valproate may need lower doses of rufinamide (14).

While no studies formally examined the relationship between serum concentrations and clinical response/efficacy of rufinamide, in one pediatric study of patients with epileptic encephalopathies, rufinamide plasma concentrations were extremely variable and no correlation between serum concentration and clinical response could be demonstrated (15). One study reported that plasma concentrations above 15 mg/mL are "useful" although the study found no validated therapeutic range (16).

In clinical studies, rufinamide had only small effects on concentrations of several other AEDs (17): Phenytoin clearance was decreased slightly, with plasma levels increasing 7% to 21%; carbamazepine, lamotrigine and phenobarbital concentrations decreased 7% to 13%; and topiramate and valproate concentrations were unchanged. Patients taking valproic acid, especially children, had increases in rufinamide concentrations (18). Valproic acid caused average increase in rufinamide concentrations of 40% in children and 11% in adults (12). Small children (<30 kg) with very high valproic acid concentrations (e.g., 100 mg/L) had increases in rufinamide concentrations of up to 70%; however, this varied widely across patients (18). Rufinamide doses were not adjusted in clinical trials for patients receiving valproic acid; however, reduced dose reductions of 50% to 60% have been recommended for small children (<30 kg) taking valproic acid (14). European regulators have requested an additional pediatric monitoring study to evaluate this interaction further. Adolescents and adults receiving valproic acid had much smaller increases in rufinamide concentrations compared to children: ≤26% increases in adolescents and <16% increases in adults (18). Other AEDs were associated with variable small-to-moderate decreases in rufinamide concentrations: carbamazepine (19% to 26%), phenobarbital (25% to 46%), phenytoin (25% to 46%), and primidone (25% to 46%). Lamotrigine and topiramate did not alter rufinamide concentrations (6). One pediatric study did not show any significant effect of rufinamide on the kinetics of concomitant AEDs (13). Among adolescents and adults however, one study showed that only valproic acid had any significant effect on rufinamide clearance (decrease) with no other

concomitant medication showing any effect (19).

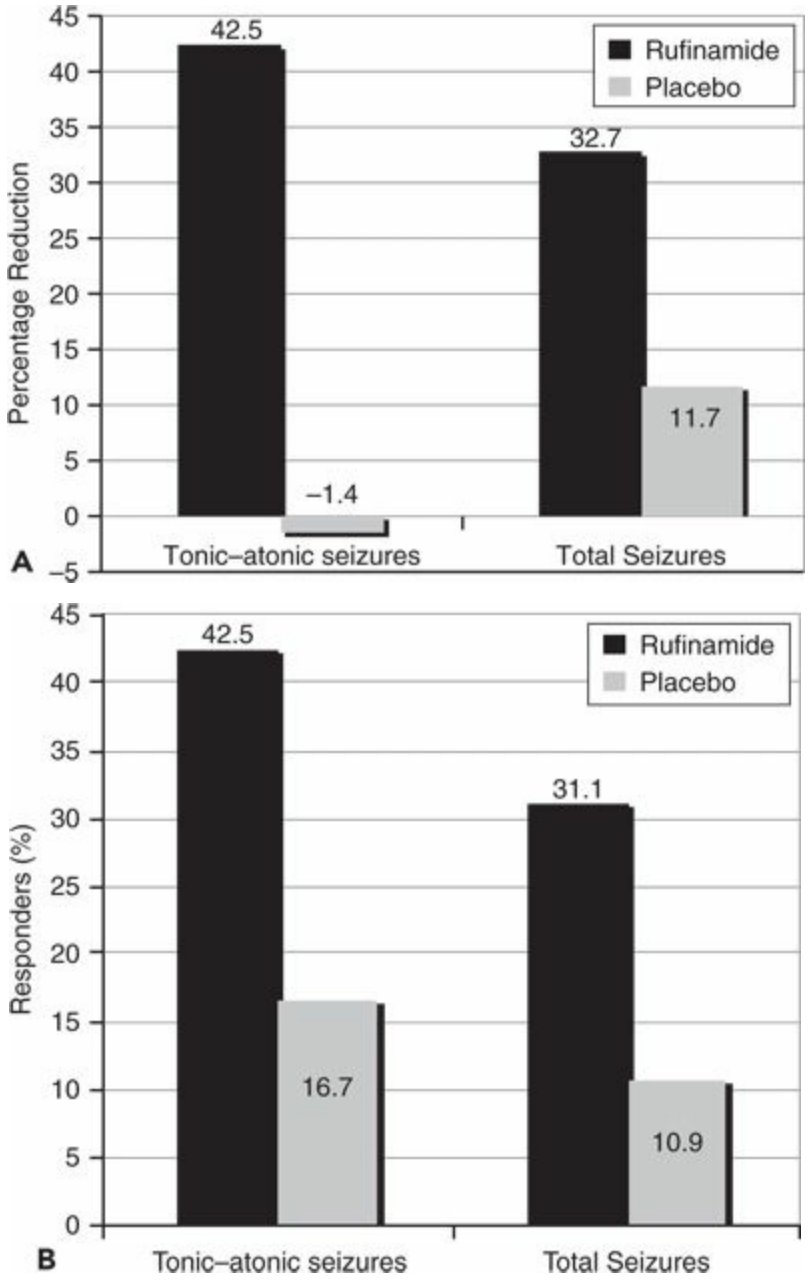
Rufinamide had a modest interaction with oral contraceptives: Repeated administration of 1600 mg/day of rufinamide decreased ethinyl estradiol concentrations by 22% and norethindrone by 14%. It is unclear whether higher doses of rufinamide might produce greater hormonal reductions and contraceptive failure (19). Triazolam clearance increased slightly with rufinamide treatment (4). Increased clearance is most likely caused by modest induction of CYP3A4 and is not believed to be clinically relevant (20).

Due to extensive metabolism, rufinamide elimination is not influenced by renal dysfunction, and no specific dosage changes are required for patients with renal impairments (11). No marked difference in rufinamide concentrations was found in patients experiencing severe renal impairment as compared to healthy individuals after a single 400-mg dose (18). During dialysis, area under the curve (AUC) was decreased by approximately 30%. Simulations over 1 week, however, estimate three 3-hour dialysis sessions would decrease total rufinamide exposure (AUC) by approximately 12%. This suggests that no specific dose adjustment of rufinamide is likely to be required for patients with renal failure undergoing hemodialysis (18).

CLINICAL STUDIES

Lennox–Gastaut Syndrome

Rufinamide is approved with an orphan drug indication for adjunctive treatment of Lennox–Gastaut syndrome in the United States and Europe. Patients with Lennox–Gastaut syndrome typically have multiple seizure types along with encephalopathies. Their most characteristic (and serious) seizure types are tonic and tonic–atonic "drop attacks," which cause sudden falls and injuries. Patients also have varying patterns of atypical absence, myoclonic, atonic, tonic–clonic, and complex motor seizures. Most patients have slow spike-and-wave discharges and generalized slowing on EEG. Effects of rufinamide in treating seizures in patients with Lennox–Gastaut syndrome were evaluated in a randomized, parallel-design, placebo-controlled study of children and adults >4 years (N = 138) (21). Seizures associated with falls (predominantly tonic and tonic–atonic seizures) and total seizures were assessed. Patients were treated with rufinamide 45 mg/kg, up to a maximum of 3200 mg/day, divided twice a day. Patients receiving rufinamide had a 42.5% median reduction in tonic–atonic seizures compared to a 1.4% increase in seizures for patients receiving placebo treatment (Fig. 62.2A). The patients' total seizure frequency was reduced 32.7% during rufinamide treatment compared to a median of 11.7% for placebo treatment. Seizure responder rates (proportions of patients with >50% seizure reduction) were also significantly higher for patients treated with rufinamide (42.5%) compared to placebo (16.7%) (Fig. 62.2B).


Percentage Reduction
45
40
35
30
25
20
15
10
5
0
−5
42.5
−1.4
32.7
11.7
Rufinamide
Placebo
Tonic–atonic seizures
Total Seizures
A
Responders (%)
45
40
35
30
25
20
15
10
5
0
42.5
16.7
31.1
10.9
Rufinamide
Placebo
Tonic–atonic seizures
Total Seizures
B

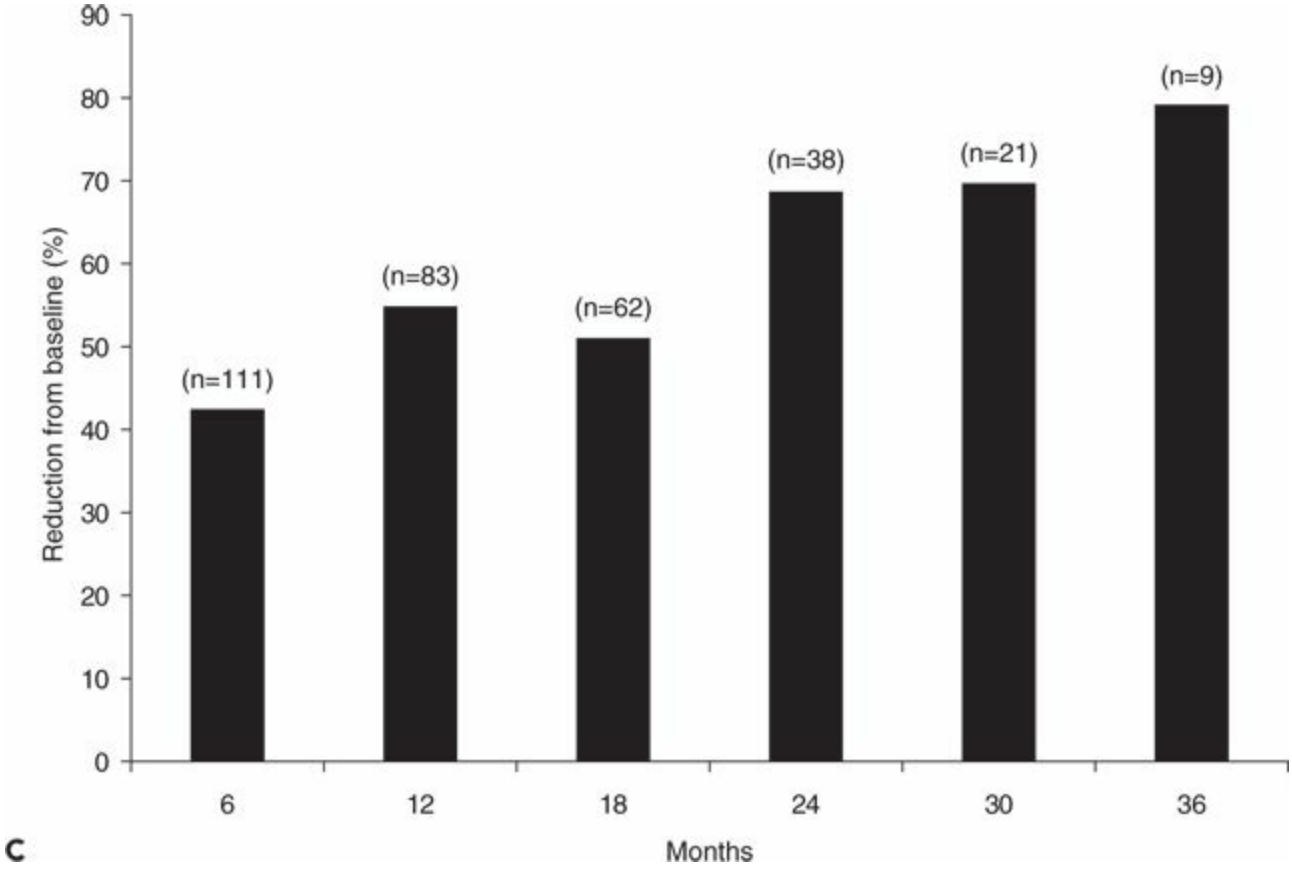


Figure 62.2. A: Median percentage reduction in total seizure frequency and tonic–atonic seizure frequency. **B:**Percentage of patients (responders) who experienced at least 50% reduction in tonic–atonic seizure frequency. **C:**Efficacy of adjunctive rufinamide therapy during long-term extension study treatment of patients with Lennox–Gastaut syndrome. (C, Data from Glauser T, Kluger G, Sachdeo R, et al. Open-label extension study of the efficacy and safety of rufinamide adjunctive therapy in patients with Lennox-Gastaut syndrome. Epilepsia. 2005;46(suppl 6):406.)

Efficacy was sustained during open-label extension treatment, with decreases in seizure frequency of 43% to 79% during 6 to 36 months of treatment; patients converting from placebo to rufinamide also had substantial reductions in seizures (Fig. 62.2C) (22). Responder rates for patients, during their most recent 6 months of therapy, were 45.1% for total seizures and 47.9% for tonic–atonic seizures. A total of 9.4% of patients were free of tonic–atonic seizures during their last 6 months of open-label treatment (23).

Most patients with Lennox–Gastaut syndrome tolerated rufinamide well, especially considering that treatment was combined with one to three concomitant AEDs (21) and titrated very rapidly. The most common adverse events (≥10%) seen in rufinamide-treated patients as compared to those receiving placebo were as follows: somnolence (24.3% vs. 12.5%), vomiting (21.6% vs. 6.3%), pyrexia (13.5% vs. 17.2%), and diarrhea (5.4% vs. 10.9%), respectively. Vomiting and somnolence were the only adverse events occurring at an incidence of 5% greater than placebo treatment. Of the 124 patients entering open-label extension treatment (median dose 1800 mg/day), 12 subsequently discontinued treatment due to adverse events (18). The most commonly reported adverse events during the uncontrolled extension treatment phase were vomiting (30.6%), pyrexia (25.8%), upper respiratory tract infection (21.8%), and somnolence (21.0%). Some of these symptoms appeared to be due to childhood viral illnesses rather than due to rufinamide treatment.

Rufinamide's effectiveness for treating seizures in Lennox–Gastaut syndrome was demonstrated in a single placebo-controlled study, but has generally been confirmed by the long-term extension treatment results and by several open treatment series: 41% of patients were >50% responders in a long-term open-label extension study (24). A multicenter prospective open treatment Italian series

reported 51% of children and adults with Lennox–Gastaut syndrome had ≥50% responses to rufinamide; 9.3% were seizure free over a mean follow-up of 12 months of treatment (25). During 12 weeks of maintenance treatment with rufinamide 20 to 40 mg/kg/day in a Korean study, 36% of patients were >50% responders and responders included patients with drop seizures, myoclonic seizures, and "epileptic spasms" (26). Similarly, in a single center Korean study of children and young adults, 35% of patients at 6 months were >50% responders (27).

Small retrospective series have reported some patients with other epileptic encephalopathies may respond to rufinamide treatment (28,29). In 38 patients (ages 17 months to 23 years) with "epileptic spasms," 53% of patients were >50% responders in one series (30). Other small retrospective series reported benefit in some children with Doose syndrome (myoclonic–astatic epilepsy), malignant migrating partial epilepsy of infancy, and epilepsy with myoclonic absences, with only a small proportion with Dravet syndrome responding to treatment (31).

In a small observational study from Europe, 8 patients with Doose syndrome were treated with rufinamide for 6 to 18 months: 6 out of 8 patients had a >75% reduction in their major seizure type (myoclonic–astatic seizures) immediately after initiation of adjunctive rufinamide; however, this efficacy was not sustained during long-term therapy (32). Another series noted greater rufinamide responses in patients with Lennox–Gastaut syndrome and epileptic spasms (with up to 40% of patients being 50% responders) compared to patients with Dravet syndrome and myoclonic seizures (29).

Partial-Onset Seizure Trials

Rufinamide consistently reduced the frequency of partial-onset seizures in adults in three large randomized, placebo-controlled, multicenter trials. Effect sizes were modest, though, and the drug was not submitted for regulatory approval for this indication. In a large (N = 357) placebo-controlled randomized trial of adults and adolescents (≥16 years) with difficult-to-control partial-onset seizures, rufinamide 3200 mg/day reduced median seizure frequency by 23.2% compared to a 9.8% decrease with placebo treatment (19). In another placebo-controlled randomized trial, rufinamide 3200 mg/day reduced median seizure frequency by 20.4% compared to a 1.6% increase during placebo treatment. Patients not receiving carbamazepine during rufinamide treatment in this study had a slightly higher median seizure reduction of 29% (33). A third large (N = 647) study in adults and adolescent (ages 15 to 65 years) with partial-onset seizures explored treatment with four doses of rufinamide 200, 400, 800, or 1600 mg/day (divided twice a day) and placebo. Patients had a significant linear trend in dose response across the four rufinamide doses (P = 0.003): 50% responder rates ranged from 9% with placebo to 4.7% with rufinamide 200 mg/day, 16% for 400 mg/day (P = 0.027), 12% for 800 mg/day dose (P = 0.012), and 14% with a 1600 mg/day dose (P = 0.016) (Fig. 62.3) (34).

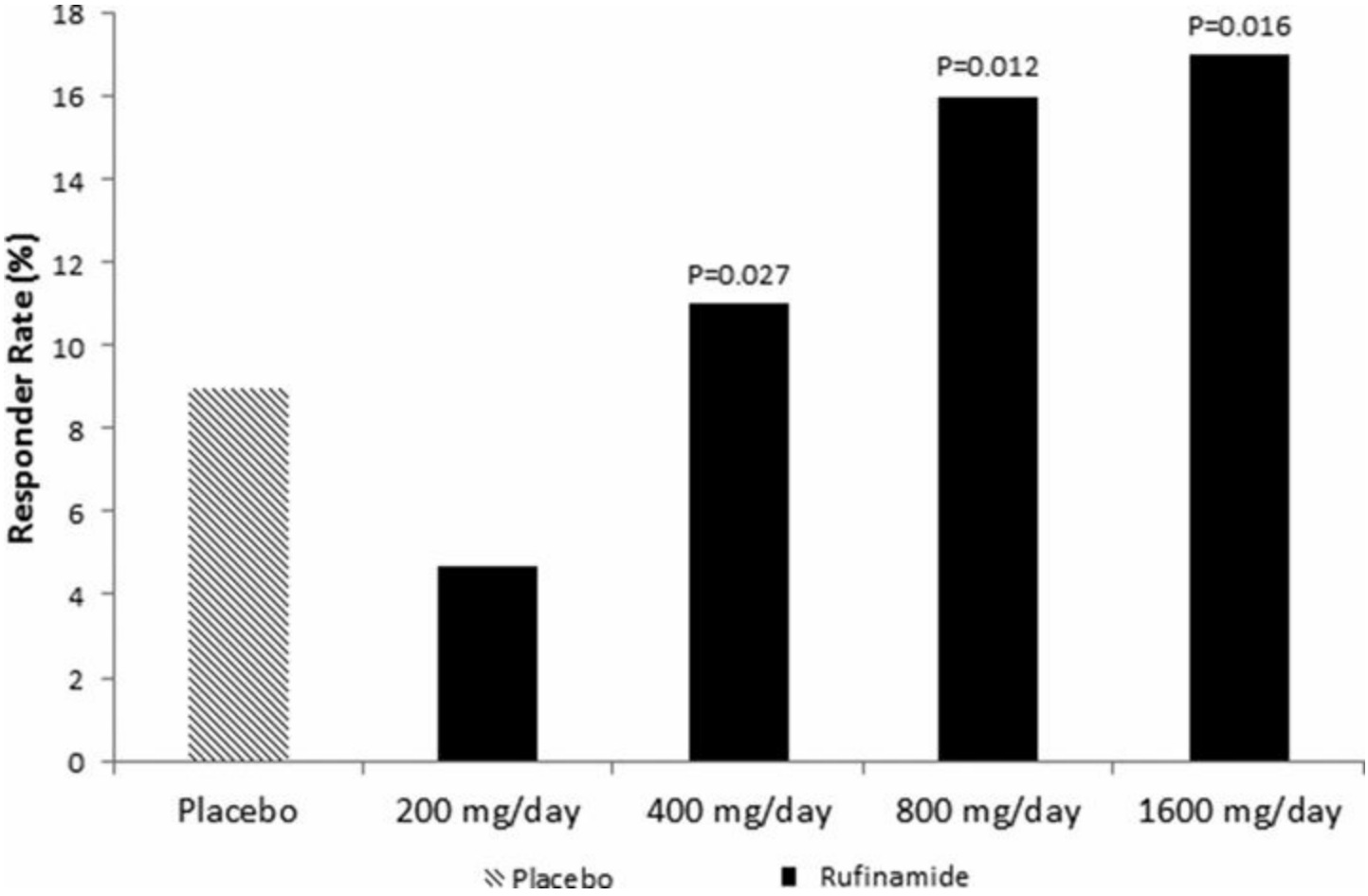


Figure 62.3. Greater than or equal to 50% responder rates for four doses of adjunctive rufinamide therapy compared to placebo treatment among adults and adolescents with partial-onset seizures. (Data from Elger CE, Stefan H, Mann A, et al. A 24-week multicenter, randomized, double-blind, parallel-group, dose-ranging study of rufinamide in adults and adolescents with inadequately controlled partial seizures. Epilepsy Res. 2010;88(2–3):255–263.)

Monotherapy Treatment for Partial Onset

Two clinical trials did not demonstrate the efficacy of rufinamide monotherapy treatment in adult and adolescent patients (>12 years of age) with medically resistant partial-onset seizures. One study (35) included patients (N = 104) with uncontrolled partial seizures completing an evaluation for epilepsy surgery. Patients were randomized to rufinamide 3200 mg (divided twice a day) or placebo with efficacy determined by time required for patients to reach an end point of four seizures. Although rufinamide treatment significantly increased patients' time to having one, two, or three seizures compared to placebo ($P < 0.04$), their times to reaching the primary end point of a fourth seizure was only slightly longer for patients treated with rufinamide ($P = 0.051$). The median times for patients to have second and third seizures, however, were more than twice as long for patients randomized to rufinamide monotherapy than for placebo-treated patients.

An additional outpatient high-versus-low-dose monotherapy study compared seizure recurrence in patients receiving rufinamide 3200 mg/day versus 300 mg/day (36). Efficacy end points were defined as proportions of patients reaching several exit criteria of recurring seizures. The number of patients meeting the exit criterion was not significantly different for the high-dose treatment (66.7%) and low-dose (72.5%) groups ($P = 0.44$). The median time to reach the exit criterion slightly favored high-dose rufinamide therapy (56 days) versus low-dose therapy (32 days) ($P = 0.097$).

Partial-Onset Pediatric Trials

A randomized, double-blind, placebo-controlled, adjunctive trial enrolled 269 pediatric patients between the ages of 4 to 15 years of age (37). Seizure frequencies for children treated with rufinamide (45 mg/kg/day) decreased by an average of only 7% compared to a 12.8% reduction with placebo treatment (P = 0.62). A number of children with very high seizure frequencies appeared to influence the assessment of seizure frequencies in this study. Children treated with rufinamide had slightly higher responder rates (>50% reduction in seizures) (27.2%) compared to those treated with placebo (18.3%), though this difference was not significant (P = 0.082).

Open treatment series have reported possible responses in some children treated with rufinamide. In an Italian observational study, children and adolescents (age range from 3 to 21 years old) received rufinamide 1000 to 3200 mg a day: 5.7% of patients became seizure free and 37.4% had >50% seizure reduction after 6 months of treatment with stable responses in patients continuing treatment for 12 months (38). In a recent open-label pediatric study of patients with refractory cryptogenic or symptomatic focal seizures, adjunctive rufinamide at doses of 1000 to 3200 mg a day (based on body weight), 30.9% of patients were ≥50% responders, while none became seizure free. Compared to other seizure types, frontal lobe seizures and secondarily generalized tonic–clonic seizures were most reduced with rufinamide. Patients taking one rather than multiple concomitant AEDs responded best to rufinamide treatment (39).

Generalized Epilepsy

The safety and efficacy of treating adult and adolescent patients (N = 153) with inadequately controlled, primary, generalized tonic–clonic seizures was evaluated in a multicenter, double-blind, placebo-controlled study using a relatively low 800 mg/day dose of rufinamide (40). Patients receiving rufinamide had only a modest, nonsignificant reduction in median frequency of generalized tonic–clonic seizures (36.4%) compared to placebo (25.6%) (P = 0.63); responses to higher doses have not been explored.

SAFETY AND TOLERABILITY

Rufinamide safety and tolerability were assessed in 11 double-blind, randomized, placebo-controlled studies; long-term safety was evaluated in 14 controlled and open-label extension studies. These included all patients receiving ≥1 dose of rufinamide. Overall, 98.2% of all patients with epilepsy received at least one concomitant AED, the most common medications being carbamazepine (52.9%), valproate (31.6%), phenytoin (22.9%), and clonazepam (19.7%).

Short-Term Therapy

Safety and tolerability were evaluated in patients receiving rufinamide treatment (N = 1317, with a mean age of 31.7 years) in controlled studies compared to those receiving placebo (N = 635, with a mean age of 28.6 years). The mean dose of rufinamide was 1373 mg/day with a median daily dose of 1000 mg/day. The most commonly reported adverse events associated with rufinamide treatment (compared to placebo) were headache, dizziness, fatigue, somnolence, and nausea (19,33,34) (Table 62.2). Other significant adverse events included rash (children 4%, adults <2%), AED hypersensitivity syndrome (three children), cognitive symptoms (mostly somnolence), psychiatric

symptoms, status epilepticus, and convulsions. The percentage of rufinamide-treated patients experiencing serious adverse events was slightly greater than for placebo-treated patients, especially at higher doses.

Table 62.2 Most Common Adverse Events Reported by Patients in Adjunctive Trials for Partial-Onset Epilepsy

	Rufinamide-treated patients	Placebo-treated patients
Short-term therapy (N = 1875)		
Headache	22.9%	18.9%
Dizziness	15.5%	9.4%
Fatigue	13.6%	9.0%
Somnolence	11.8%	9.1%
Nausea	11.4%	7.6%
Serious AEs	6.3%	3.9%
Long-term therapy (N = 1978)		
Headache	29.5%	
Dizziness	22.5%	
Fatigue	17.7%	
Serious AEs	13.2%	

Long-Term Therapy

Safety and tolerability during long-term rufinamide therapy were evaluated in 1978 patients (mean age of 31.3 years) in controlled and open studies lasting from <1 months to >4 years of exposure (41). The mean daily dose of rufinamide was 1700 mg/day with a median daily dose of 1600 mg/day. The most frequently reported adverse events were headache, dizziness, and fatigue. The majority of common adverse events appeared during the first 2 weeks of therapy, with few patients developing new adverse events during chronic therapy. Although most symptoms were mild to moderate in severity, at least one severe adverse event occurred in 20.8% of patients: 261 patients reported serious adverse events during treatment, most commonly convulsions, status epilepticus, and pneumonia. Additional single cases with hypersensitivity reactions (SJS and DRESS) and weight loss have been reported recently (42–44).

In extensive cardiac testing, rufinamide shortened QT intervals in ECG up to 20 ms in a large proportion (46%) of patients treated with recommended doses (2400 to 3200 mg/day) (11). Treatment, however, did not shorten QT intervals to a clinically significant range of <300 ms, which is associated with ventricular arrhythmias. There were no increased risks for sudden cardiac death or other cardiac abnormalities identified in clinical trials.

Pregnancy risks for women treated with rufinamide are unknown. Only 13 women (out of >2000 patients treated) in clinical trials had pregnancies: 6 had healthy babies, 3 had planned terminations, 1 had a spontaneous abortion, and 3 did not have pregnancy outcomes determined. A pregnancy registry has been established in Europe to monitor risks for pregnancy with rufinamide treatment; a U.S. AED registry monitors outcomes for patients treated with all AEDs. Due to a lack of outcome data, women of childbearing age receiving rufinamide are recommended to avoid pregnancies with careful contraceptive use. Patients becoming pregnant will require individual assessments of their risk–benefits for continuing rufinamide therapy.

Adverse Events Causing Discontinuation of Treatment

A larger proportion of patients discontinued rufinamide due to adverse events (N = 100; 8.1%) during double-blind studies than those receiving placebo (N = 27; 4.3%). The most common symptoms associated with patients discontinuing treatment were dizziness, fatigue, headache, nausea, and diplopia. The percentage of patients discontinuing treatment due to serious adverse events was also slightly increased for patients treated with rufinamide (6.3%) compared to placebo (3.9%)—"convulsions" were most commonly reported. During long-term extension treatment, 259 (13.1%) patients discontinued treatment due to adverse events; the most common symptoms were fatigue, headache, dizziness, and nausea. Emesis and drowsiness were most common adverse events among all pediatric studies.

CLINICAL USE

Rufinamide is approved in the United States and Europe with an orphan drug indication for adjunctive treatment of seizures in children (>4 years) and adults with Lennox–Gastaut syndrome. An extremely rapid 1-week titration schedule was used to initiate rufinamide treatment in the Lennox–Gastaut trial. This rapid schedule was approved for clinical use: in children, an initial rufinamide dose of approximately 10 mg/kg/day (divided twice a day), followed by an increase of 10 mg/kg every 2 days to a target dose of 45 mg/kg (or a maximum of 3200 mg/day), divided twice a day. These doses can be achieved using scored 200 and 400 mg tablets; an additional 100 mg tablet is available in Europe. The approved schedule for adults is similar: an initial dose of 400 to 800 mg/day (divided twice a day) followed by a 400 to 800 mg/day increase every 2 days to a maximum dose of 3200 mg/day, divided twice a day. Experience in regular clinical use, however, suggests that more gradual 2- to 3-week titration schedule may be better tolerated than rapid 1-week titration. Small children (<30 kg) adding rufinamide to valproic acid treatment may begin treatment at one-half these doses; this is particularly important when rufinamide is added to high doses of valproic acid in small children.

Therapeutic ranges for rufinamide blood concentrations are not established. Although, rufinamide blood concentrations are dose dependent, central nervous system (CNS)-related side effects and efficacy have not correlated well with blood concentrations during adjunctive treatment. Patients in the Lennox–Gastaut trial (target range of 45 mg/kg/day; maximum 3200 mg/day) had plasma concentration ranging from 5 to 48 mg/L. Infants treated with rufinamide (median dose 30 mg/kg/day) had higher mean steady-state concentrations (39 ± 24 mg/L) than children in the Lennox–Gastaut trial; however, side effects and efficacy also did not correlate well with plasma concentrations (45).

SUMMARY

Rufinamide is a unique AED, which prolongs inactivation of voltage-dependent sodium channels in neurons and has a very high protective index in animal seizure models, but also blocks seizures triggered by GABA-A receptor antagonists. Rufinamide was generally well tolerated in clinical trials with CNS-related side effects most common (headache, dizziness, fatigue, etc.). The drug was effective in a well-controlled clinical trial of Lennox–Gastaut syndrome and continues to be evaluated as adjunctive treatment of other forms of symptomatic epilepsy.

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CHAPTER 63 TOPIRAMATE

WILLIAM E. ROSENFELD

HISTORICAL BACKGROUND

Topiramate (TPM) is a highly oxygenated sulfamate-substituted monosaccharide that is structurally distinct from other anticonvulsant medications. Available in the United States as Topamax (Ortho-McNeil Pharmaceutical), or as a generic formulation, it is a broad-spectrum agent that has been extensively studied in double-blind, randomized, controlled trials in adults and children. It was initially approved for use as adjunctive therapy in adults with partial-onset seizures. Subsequently, TPM was approved as adjunctive therapy in children and adults with partial-onset seizures, primary generalized tonic–clonic seizures, and multiple seizure types associated with Lennox–Gastaut syndrome from 2 years of age and older.

TPM is also approved in the United States for monotherapy in adults and children 2 years of age and older with partial- onset or primary generalized tonic–clonic seizures. TPM is indicated for adults for the prophylaxis of migraine headaches as well. The drug was originally discovered in a screening protocol using the standard maximal electroshock seizure (MES) test. Anticonvulsant effects were similar to phenytoin and carbamazepine (1). Most of the known benefits and side effects were noted for this medication from the first couple of 1000 patients (except narrow-angle glaucoma that is a much rarer phenomena). Efficacy was seen early (in blinded studies, family and friends often noted so much improvement they were often referring other friends). Side effects were also noted early due to not yet knowing the most effective dosages without side effects. Too high and too rapid titration often occurred, and the most common side effects noted were word-finding and mathematical difficulties, paresthesias, weight loss, and kidney stones. A 1.5% incidence of kidney stones was seen early and remained the same even despite millions of patients being on such (not necessarily dose or titration related).

CHEMISTRY

TPM (2,3:4,5-di-O-isopropylidene-β-D-fructopyranose sulfamate; Fig. 63.1) is a white crystalline powder that is freely soluble in acetone, chloroform, dimethyl sulfoxide, and ethanol. TPM is supplied as 25-, 50-, 100-, and 200-mg tablets and as 15- and 25-mg sprinkle capsules that can be opened and sprinkled onto soft food for children and for patients who may have difficulty swallowing tablets.

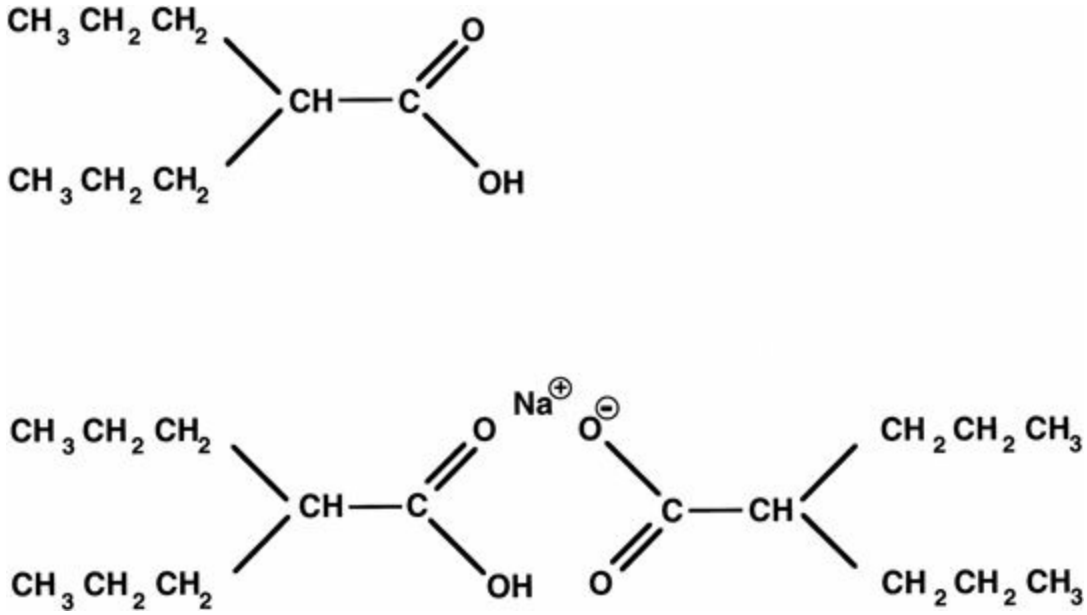

Figure 63.1. Topiramate (2,3:4,5-di-O-isopropylidene-β-D- fructopyranose sulfamate).

MECHANISMS OF ACTION

TPM has a unique combination of activities at various receptor sites and ion channels, which may account for its broad-spectrum profile in epilepsy and other neurologic disorders. It blocks the kainate/AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) subtype of the glutamate receptor (2–5), with no direct effect on NMDA (N-methyl- D-aspartate) receptor activity; blocks voltage-activated sodium channels to limit sustained repetitive firing (6–10); enhances α-aminobutyric acid (GABA)–mediated chloride flux at $GABA_A$ receptors (11,12); reduces the amplitude of high-voltage–activated calcium currents (13,14); and activates potassium conductance (15,16). It has been hypothesized that effects of TPM on voltage-activated sodium channels, high-voltage–activated calcium channels, $GABA_A$ receptors, and AMPA/kainate receptors reflect a common modulator involving protein phosphorylation (17). TPM is also a weak inhibitor of carbonic anhydrase isoenzymes (CA II and CA IV), which may modulate pH-dependent activation of voltage- and receptor-gated ion channels (18); its inhibitory effect is less than acetazolamide.

ANIMAL MODELS

The anticonvulsant properties of TPM have been demonstrated in several animal models of epilepsy. TPM exhibited potent and long-lasting anticonvulsant activity when evaluated using the MES test in rodents with a median effective dose of 47.6 mg/kg in the mouse and 15.8 mg/kg in the rat (19). TPM inhibited chronic motor seizures and absence-like seizures when administered intraperitoneally (17). TPM blocked sound-induced clonic and tonic–clonic seizures (20). TPM effectively inhibited tonic, clonic, and wild running seizures in a postischemia model of epilepsy in rats, and its potency was similar to that of phenytoin for all three seizure types (21). TPM also produced a dose-related inhibition of amygdala-kindled seizures in rats (22). Experimental studies have shown that TPM reduced seizure-induced hippocampal neuronal injury (23) and prevented spontaneous seizures following status epilepticus (24). In an experimental model of neonatal hypoxia/ischemia, TPM suppressed acute seizures and reduced subsequent susceptibility to neuronal injury and seizures

induced by a second insult (kainate) (25).

PHARMACOKINETICS

Renal elimination, low protein binding, and a long half-life make TPM relatively easy to manage from a pharmacokinetic perspective (Table 63.1) (26,27).

Table 63.1 Pharmacokinetic Characteristics of TPM

Characteristic	Value
Elimination half-life (h)	19–23
Peak plasma concentration (mg/L)	1.7 (100-mg single dose) 7.7 (400-mg single dose) 28.7 (1200-mg single dose)
Time to maximum concentration (h)	1.8–4.3
Fraction of systemically available drug excreted unchanged into the urine (%)	70–97
Apparent oral clearance (mL/min)	22–36
Apparent volume of distribution (L/kg)	0.6–0.8

Absorption

TPM is rapidly absorbed with peak plasma concentrations occurring in 1 to 4 hours with TPM doses of 100 to 400 mg. Absorption is nearly complete with <80% of a 100-mg dose recovered in urine. Coadministration with food slightly delays absorption but does not decrease bioavailability (28). TPM exhibits linear kinetics; plasma concentrations increase in proportion to dose increases (29).

Distribution and Protein Binding

The apparent volume of distribution for TPM is 38.5 to 58 L (0.6 to 0.8 L/kg, weight normalized), consistent with distribution to total body water. Binding to plasma proteins is minimal (13% to 17%) and is not considered to be a major factor in dosing and drug interactions (29).

Metabolism and Excretion

In the absence of hepatic enzyme induction, approximately 20% of a TPM dose is metabolized. When TPM is coadministered with enzyme-inducing antiepileptic drugs (AEDs), up to 50% of the TPM dose may be metabolized. Hepatic metabolism appears to involve hydroxylation, hydrolysis, and glucuronidation; none of the metabolites constitutes >5% of an administered dose, and they are quickly cleared (29).

Elimination of TPM is primarily via renal excretion, with 50% to 80% being eliminated in the urine unchanged. The half-life of TPM in adults is 20 to 30 hours in the absence of enzyme induction, allowing steady-state plasma concentrations to be reached in 4 to 8 days. In the presence of enzyme induction, the TPM half-life in adults is 12 to 15 hours (29). In children 4 to 17 years of age, clearance is approximately 50% higher than in adults (30). Steady-state concentrations for the same mg/kg dose were correspondingly lower in children than in adults. Consistent with the higher clearance, the calculated half-life of TPM in children is approximately 15 hours without enzyme

induction and 7.5 hours with enzyme induction. In young children (younger than 4 years old), clearance rates were the same or slightly higher than in older children (31). In elderly patients (65 to 85 years of age), clearance decreases only to the extent that renal function itself is reduced by age; age alone does not alter clearance in adults (32).

TPM clearance is reduced by 40% to 50% in patients with moderate (creatinine clearance 30 to 69 mL/min) or severe (creatinine clearance, <30 mL/min) renal impairment compared to subjects with normal renal function (creatinine clearance, >70 mL/min) (29). One-half of the usual TPM dose is recommended in patients with moderate or severe renal impairment. TPM plasma concentrations fell by an average of 50.1% during hemodialysis. The mean hemodialysis plasma clearance of TPM has been reported to be approximately nine times higher than that found in subjects not receiving hemodialysis (33). Modest decreases in TPM clearance have been reported when comparing age- and sex-matched healthy controls to individuals with moderate to severe hepatic impairment; mean clearance was decreased to 26% (31.8 vs. 23.5 mL/minute) and half-life increased to 36% (25 vs. 34 hours), with parallel increases in plasma concentrations (29).

THERAPEUTIC DRUG MONITORING

Drug monitoring is of relatively little importance in initial titration of TPM. It is most important for compliance and also if utilizing higher-dose therapy. Steady-state plasma concentrations of TPM are generally linear, with dose- proportional increases in plasma concentration (29). Mean plasma concentrations achieved during maintenance in randomized, controlled trials of TPM monotherapy were as follows: 50 mg/day, 1.6 and 1.9 μg/mL; 97 mg/day, 3.8 μg/mL; 189 mg/day, 6.4 μg/mL; 313 mg/day, 11.7 μg/mL; and 367 mg/day, 12.4 μg/mL (34). Studies of TPM as monotherapy have provided the opportunity to examine the relationship between TPM plasma levels and clinical response. In a study comparing 50 and 500 mg/day TPM as monotherapy, plasma concentrations >9.91 μg/mL were associated with better seizure control compared with plasma concentrations of 1.77 to 9.91 μg/mL and ≤1.76 μg/mL (35). However, because of the intraindividual variations in blood levels associated with seizure control and side effects, a traditional "therapeutic range" cannot be identified. As expected, plasma concentrations are higher when TPM is administered as monotherapy (6.4 to 12.4 μg/mL with approximately 200 to 400 mg/day) versus its use as add-on to enzyme-inducing AEDs (1.4 to 5.3 μg/mL with approximately 200 to 400 mg/day). Despite the substantially higher plasma concentration with monotherapy, the incidence of central nervous system (CNS)-related adverse events, particularly cognitive effects, was substantially lower with TPM monotherapy than with adjunctive therapy. This finding underscores the contribution of pharmacodynamic interactions to the occurrence of adverse events during TPM polytherapy and the limited benefit of therapeutic drug monitoring in TPM-treated patients.

The relationship between TPM dose and plasma level was examined in children in whom TPM was titrated to clinical response or side effects (36). Among 21 children aged 6 to 12 years, TPM plasma levels were predictably related to dose (1:1 ratio). With monotherapy, a mean dose of 9.7 mg/kg/day (range, 5.5 to 16.5 mg/kg/day) resulted in a mean plasma level of 9.8 μg/mL (range, 3.4 to 16.6 μg/mL). For 20 younger children (younger than 6 years of age), however, higher monotherapy doses were needed (mean, 22.5 mg/kg/day; range, 11 to 35 mg/kg/day) to achieve seizure control; mean plasma level was 14.8 μg/mL (range, 6.1 to 23.7 μg/mL). When TPM was administered with an enzyme-inducing drug, the TPM dosage in younger children (mean, 14.2 mg/kg/day) was double than that in older children (7.0 mg/kg/day) (36).

Patients with levels close to 25 μg/mL or more rarely obtained additional benefit at higher dosages and side effects increased. Therapeutic ranges are often quoted in the 2 to 25 μg/mL range. It is this author's opinion that there are two ranges. Monotherapy patients who are relatively easy to control can often be controlled in the 2 to 6 μg/mL range, and those who are more intractable may need higher doses.

DRUG INTERACTIONS

Interaction studies were performed with the three leading AEDs (at time of initial release of TPM)—carbamazepine, phenytoin, and valproic acid and also later with lamotrigine. Similar study designs were utilized.

Topiramate and Carbamazepine

The steady-state pharmacokinetics of carbamazepine and TPM as adjunctive therapy and monotherapy were determined in 12 adults whose epilepsy was stabilized with carbamazepine 300 to 800 mg t.i.d. (37). No significant differences were observed in the pharmacokinetics of total or unbound carbamazepine or carbamazepine epoxide in the absence of TPM or with TPM 100 to 400 mg b.i.d. TPM AUC, C_{max}, average concentration, and minimum concentration levels were approximately 40% lower in the presence of carbamazepine than with TPM monotherapy (27).

Topiramate and Phenytoin

The steady-state pharmacokinetics of phenytoin and TPM were determined in 12 adults with partial epilepsy who were stabilized on phenytoin (38). During concomitant phenytoin therapy, TPM pharmacokinetics were proportional for dosages ranging from 100 to 400 mg. During TPM adjunctive therapy with phenytoin, TPM concentrations were reduced by approximately 50%. The investigators hypothesized that the increase in TPM clearance during concomitant phenytoin therapy was due to enzyme induction by phenytoin. In half the patients, TPM had no measurable effect on the pharmacokinetics of phenytoin; in the other patients, however, particularly those taking phenytoin twice a day, phenytoin concentrations were approximately 25% higher. No patients required adjustment of phenytoin or discontinued the trial. In clinical practice, patients receiving dosages in the higher therapeutic ranges of phenytoin should be observed carefully, because they may be more likely to require a downward adjustment of phenytoin dosage (27).

Topiramate and Valproic Acid

The steady-state pharmacokinetics of valproic acid and TPM were determined in 12 patients whose partial epilepsy was treated with valproic acid (39). TPM plasma concentrations were approximately 14% lower during adjunctive therapy with valproic acid. Valproic acid concentrations decrease by 11% when TPM 400 mg b.i.d. was added. The clinical significance of these changes is probably minimal (27).

Topiramate and Lamotrigine

An open-label, sequential, single-group, dose-escalating, PK study was performed in 13 patients with

epilepsy. No PK interactions were noted between TPM and lamotrigine at observed doses of 100 to 400 mg/day TPM (40).

Topiramate and Oral Contraceptives

Interaction studies evaluating the effect of TPM on combination oral contraceptives showed that TPM has no effect on the progestin (norethindrone 1.0 mg) component (41,42). At doses of ≤200 mg/day, TPM has no significant effect on estrogen (ethinyl estradiol 35 μg) concentrations (41,42). Initial studies showed the mean serum estradiol to be reduced by 18% at 200 mg/day, but repeat testing at the same 200 mg dosage showed only an 11% decrease. At higher doses (400 and 800 mg/day), TPM was associated with 21% and 30% reductions, respectively, in ethinyl estradiol concentrations, suggesting a modest induction of estrogen clearance (42). The level of induction is substantially less than that associated with potent enzyme-inducing agents such as carbamazepine (42% reduction in estrogen concentration) (41). The dose- related effect of TPM on estrogen clearance is consistent with the concentration-dependent induction of cytochrome P450 (CYP450) CYP3A4 activity measured in vitro (43). TPM induced CYP3A4 enzymes only at concentrations >50 μM, a concentration that is unlikely to be achieved with dosages up to 400 mg/day; enzyme induction was still less than that associated with known inducers (phenobarbital and rifampicin) used in this study.

Predominantly, renal elimination and low protein binding minimize the potential for drug interactions. Pharmacokinetic interactions between TPM and other AEDs are limited primarily to the effects of enzyme-inducing drugs on TPM. TPM plasma levels are approximately 50% lower when TPM is given with an enzyme-inducing AED (37–45) compared to TPM use alone or in combination with non–enzyme- inducing drugs (37–39,39–45). The addition of TPM does not significantly affect plasma concentrations of carbamazepine (37), valproate (39), phenobarbital/primidone (44), or lamotrigine (40). However, phenytoin plasma levels may be increased as much as 25% in some patients, particularly those in whom phenytoin metabolism may be at or near saturation (45). Studies of TPM in models designed to predict drug interactions related to the CYP450 enzyme system have shown inhibition of only the CYP2C19 isozyme, which may account for the potential interaction with phenytoin (46). Although pharmacokinetic interactions between TPM and other AEDs are limited, the lower incidence of adverse effects with TPM monotherapy (35,47,48) suggests that pharmacodynamic interactions may affect tolerability when TPM is added to existing therapy.

A slight decrease in digoxin clearance has been observed with the addition of TPM (49) but generally does not require dosage adjustments. Changes in metformin pharmacokinetics suggest that diabetic control should be monitored when TPM is added or withdrawn (50).

EFFICACY

Adjunctive Therapy

Partial-Onset Seizures

The effectiveness of TPM as adjunctive therapy across a wide range of doses (200 to 1000 mg/day) in adults with refractory partial-onset seizures has been well documented in randomized, double-blind, placebo-controlled trials (51–59). Similarity of trial design and patient populations allowed

pooled analysis of data from six of these trials (51–56). Among 743 adults (median baseline frequency, 12 seizures per month), median seizure reduction was 44% with TPM treatment versus 2% with placebo ($P \leq 0.001$); 43% of TPM-related patients (placebo, 12%; $P \leq 0.001$) achieved at least 50% seizure reduction (60). During 11 to 19 weeks of double-blind treatment, 5% of patients in the TPM group were seizure free, while no patients in the placebo group were seizure free ($P \leq 0.001$) (60). Initially, it was felt that dosages of 200 mg/day would be placebo-like, and therefore, 79% of the original patients were at dosages of 400 to 1000 mg/day. On initial review of the data, it appeared that there was a flattening of the efficacy curve at higher dosages. However, one must remember that this was intent to treat data. If a patient due to side effects did not make it to his assigned upper dosage (even if seizure free or significantly reduced in seizure frequency), the patient was considered as not succeeding at that dosage. Therefore, from an efficacy point of view, there was a dose–response curve. Although dosages as high as 1000 mg/day were evaluated, the most clinically useful adjunctive therapy dosages appear to be 200 to 400 mg/day. In a 12-week, double-blind trial to further evaluate the lower end of the presumed dosing range (59), 200 mg/day TPM was added to carbamazepine. Median seizure reduction in TPM-treated patients ($N = 168$) was 44% (vs. 20% with placebo, $N = 91$; $P < 0.001$); 45% of TPM-treated patients (placebo, 24%; $P = 0.001$) achieved at least 50% seizure reduction. After 2 weeks, median seizure reduction in patients receiving TPM 100 mg/day ($N = 84$) was 60% (placebo, 17%; $P < 0.001$), which suggests that 100 mg/day may be a target dose at which seizure control should be initially evaluated.

The initial overestimation of TPM dosage needs is evident from prospective, in-practice studies in which adults with refractory partial-onset seizures achieved good seizure control with 264 mg/day (48% of patients had 50% or more seizure reduction rate; 9% were seizure free) (61) and 323 mg/day (68% of patients had a 50% or more seizure reduction rate) (62). When titrating to response, patients with fewer baseline seizures (>4 per month) required lower TPM dosages (303 mg/day) than those with higher baseline seizure frequency (341 mg/day in patients with four or more seizures per month) (62). In a prospective study, 17% of refractory patients had at least 50% seizure reduction and 8% were seizure free with TPM dosages of 100 or less mg/day (63).

In treatment-resistant epilepsy patients treated at a tertiary epilepsy center, estimated long-term retention rates among 393 TPM-treated patients were 52% after 1 year, 42% at 2 years, 30% at 3 years, and 28% at 5 years (64,65). Although these rates were higher than those with another new-generation agent (lamotrigine), the low retention rate at 5 years reflects the limitations of medical therapy in patients with refractory epilepsy.

TPM was evaluated as adjunctive therapy in 86 children (2 to 16 years of age) with refractory partial-onset seizures (66). With a mean daily dose of 6 mg/kg (target dose, 5 to 9 mg/kg/day), median seizure reduction was 33% (placebo, 11%; $P = 0.03$). More TPM-treated children had at least 50% reduction in seizures (39% vs. 20% with placebo; $P = 0.08$); 5% of children receiving TPM had no seizures, while no placebo-treated children were seizure free.

All 83 children completing the double-blind phase entered the long-term, open-label extension in which the dosages of TPM and concomitant AEDs could be adjusted according to clinical response (67). Mean treatment duration was 15 months, with some children being treated as long as 2.5 years; the mean TPM dosage was 9 mg/kg/day (range, 4 to 22 mg/kg/day). Among children treated for at least 6 months, 64% had at least a 50% reduction in seizures; 14% were seizure free for a minimum of 6 months. During open-label in-practice studies in children with refractory partial-onset seizures (68–71), 4% to 20% of TPM-treated children were seizure free during treatment periods as long as 33 months.

Lennox–Gastaut Syndrome

TPM was evaluated as adjunctive therapy in 98 patients with Lennox–Gastaut syndrome confirmed by an electroencephalographic (EEG) pattern of slow spike-and-wave, multiple seizure types, including drop attacks, and a history of atypical absence episodes (72). At a maximum dose of 6 mg/kg/day, median reduction for drop attacks was 15% compared with a 5% increase with placebo; 28% of TPM-treated patients were responders (placebo 14%). A combined measure of drop attacks and tonic–clonic seizures showed a 26% reduction with TPM and a 5% increase with placebo ($P = 0.015$); respective responder rates were 33% and 8% ($P = 0.002$). These outcomes compared favorably with those reported for lamotrigine in this population (73). The placebo-adjusted responder rate for drop attacks was 14% for TPM and 15% for lamotrigine; respective rates for major motor seizures were 25% and 17% (72,73).

During the long-term, open-label extension in which the dosages of TPM and concomitant AEDs could be adjusted according to clinical response (74), 55% of the 82 children treated with TPM for more than 6 months had at least a 50% reduction in drop attacks during the last 6 months of treatment; 15% experienced no drop attacks. Two patients were free of all seizures. The mean duration of TPM treatment was 18 months, with treatment periods as long as 3.4 years. The mean TPM dosage was 10 mg/kg/day (range, 1 to 29 mg/kg/day). Among patients treated as long as 8 years, 21% to 40% of patients had at least 50% seizure reduction, with major motor seizures being the most responsive (75,76).

Generalized Tonic–Clonic Seizures of Nonfocal Origin

Two double-blind, placebo-controlled trials (77,78) evaluated TPM in the treatment of generalized, nonfocal tonic–clonic seizures (i.e., primary generalized tonic–clonic seizures). Inclusion criteria specified tonic–clonic seizures with or without other generalized seizure types and EEG or CCTV/EEG patterns consistent with generalized epilepsy (generalized, symmetric, synchronous spike–wave discharges, and normal background activity); patients with Lennox–Gastaut syndrome or partial-onset seizures were excluded. In the two trials, more than 70% of patients had primary generalized tonic–clonic seizures plus at least one other type of generalized seizure (i.e., absence, myoclonic, or tonic).

TPM was initiated as adjunctive therapy in adults and children (at least 4 years of age) with refractory generalized tonic–clonic seizures despite treatment with one or two AEDs. The target dose was 5 to 9 mg/kg/day, and the maximum daily dose was 400 mg. In one trial (77), baseline seizure frequency in the TPM-treated group ($N = 39$) was five generalized tonic–clonic seizures per month (placebo 4.5 generalized tonic–clonic seizures per month; $N = 41$). Median seizure reduction was 57% (placebo 9%; $P < 0.02$) for tonic–clonic seizures and 42% (placebo, 1%; $P = 0.003$) for all generalized seizures. Among TPM-treated patients, generalized tonic–clonic seizures and all generalized seizures were reduced at least 50% in 56% and 46%, respectively (respective placebo values: 20%, $P = 0.001$; 17%, $P = 0.003$). No generalized tonic–clonic seizures occurred during the 20-week study in 13% of TPM-treated patients (placebo 5%); 5% had no generalized seizures of any type (placebo 0% of patients).

Because the two trials were identically designed, data were pooled and analyzed. As had been observed in the single trial, TPM reduced the frequency of generalized tonic–clonic and all generalized seizures, with significantly more patients achieving 50% or greater reduction in generalized tonic–clonic (55% vs. 28% with placebo; $P \leq 0.001$) and all generalized seizures (43%

vs. 19% with placebo; P = 0.001). Although small sample sizes limited analysis, TPM was also more effective than placebo in reducing the frequency of tonic and myoclonic seizures and did not exacerbate absence seizures.

All 131 patients who completed the double-blind phase entered an open-label extension phase (79). During the last 6 months of treatment, 16% had no generalized tonic–clonic seizures and 7% were seizure free for at least 6 months. TPM was also effective against other generalized seizure types; during the last 6 months of treatment, 10% of patients with absence seizures, 33% of patients with myoclonic seizures, and 21% of patients with tonic seizures were seizure free for at least 6 months.

In a study evaluating EEG changes and seizure control in TPM-treated patients with primary generalized epilepsies (80), more than half of the patients showed reductions in epileptiform spike-wave activity, although TPM was less likely to suppress activity in patients with very high discharge frequencies at baseline. As with other broad-spectrum AEDs, seizure reduction (36% seizure free) did not correlate with EEG response, and no correlation was observed between clinical or EEG response and TPM blood levels.

Juvenile Myoclonic Epilepsy

In a pilot study, 15 patients who had previously failed valproic acid (one wanted off strictly due to weight gain and 5 wished to get off due to weight issues) were switched from valproic acid to TPM. Myoclonic seizures stopped in 60% of patients, 49% of generalized tonic–clonic seizure patients became seizure free of that type of seizure, and 25% of absence seizure patients stopped having this type of seizure (81).

A small subset of patients with juvenile myoclonic epilepsy (JME) was included in the controlled trials evaluating TPM in primary generalized tonic–clonic seizures (77,78). Among 11 patients with JME receiving TPM, primary generalized tonic–clonic seizures were reduced at least 50% in 73% (vs. 18% of patients receiving placebo, N = 11; P = 0.03) (82). In addition, the frequency of myoclonic seizures was reduced, and the number of weeks without absence seizures was increased in TPM-treated patients. In a randomized, open-label study in patients with JME (83), TPM and valproate were similarly effective (seizure-free rates following 12 weeks' treatment: 47% and 33%, respectively). The treatment groups were similar in neurotoxicity scores; however, TPM was associated with less systemic toxicity than valproate.

West Syndrome

Eleven children with refractory West syndrome participated in a pilot study of TPM (84). At a maximum daily dose of 24 mg/kg, the frequency of infantile spasms was reduced by at least 50% in nine children, including five (45%) who were completely controlled. Ancillary seizures responded in four of six children. After 18 months of TPM (mean dosage, 29 mg/kg/day), eight children (73%) continued on medication, four (50%) children were free of spasms, and seven (88%) children had spasms reduced by at least one-half (85).

Childhood Absence Epilepsy

Five children 4 to 11 years of age with EEG-documented absence seizures and childhood absence epilepsy were treated with open-label TPM (maximum dose, 12 mg/kg/day) (86). Three children

experienced a minimum reduction of 50% at daily dosages of 5 to 6 mg/kg; two children were seizure free. Frequency was unchanged in the remaining two children, even at the maximum dosage.

Severe Myoclonic Epilepsy in Infancy

During a prospective, multicenter, open-label study in 18 patients with severe myoclonic epilepsy in infancy and refractory seizures of different types, three patients became seizure free, six patients had >75% seizure reduction, and four patients had >50% seizure reduction with TPM treatment (87). Seizure frequency was unchanged in five patients; no patients experienced seizure worsening. Mean treatment duration was 12 months (range, 2 to 24 months); mean TPM dose was 5.4 mg/kg/day (range, 2.8 to 10 mg/kg/day).

Patients with Mental Retardation, Learning Disabilities, and/or Developmental Disabilities

Among 64 patients (16 to 65 years of age) with refractory epilepsy and learning disability treated with TPM in an open- label study, 16 patients became seizure free and 29 patients had at least a 50% seizure reduction (88). Many patients, including 63% of those who were seizure free and 66% of treatment responders, were receiving TPM dosages of ≤200 mg/day. In a study evaluating the effect of TPM in 20 adults (21 to 57 years of age) with intractable mixed seizures, mental retardation, and development disabilities, two patients became seizure free and 11 patients had at least a 50% seizure reduction with TPM treatment (89). In addition, the duration and/or severity of seizures were reduced in 44% of patients. The mean duration of treatment was 42 weeks (range, 20 to 54 weeks); the mean TPM dose was 189 mg/day (range, 50 to 350 mg/day).

Refractory Status Epilepticus

In six cases of refractory status epilepticus unresponsive to sequential trials of multiple agents, including one patient who had been in a prolonged pentobarbital coma, TPM (300 to 1600 mg/day) administered via nasogastric tube successfully terminated refractory status epilepticus (90). TPM was effective against both generalized convulsive and nonconvulsive status epilepticus. All patients were subsequently discharged from the hospital.

Monotherapy

The 1990s ushered in a new era—at least in the United States—for clinical studies in newly diagnosed, previously untreated epilepsy. The use of traditional AEDs (carbamazepine, phenytoin, valproate) as first-line monotherapy is largely based on landmark Veterans' Administration Cooperative trials (91,92) and similar open-label trials in the United Kingdom (93,94). However, the U.S. Food and Drug Administration (FDA) began requiring randomized, double-blind trials demonstrating a statistically significant difference between treatments as evidence of efficacy, generating considerable debate as to how to safely and ethically accomplish this goal. One such approach is an active-control conversion-to-monotherapy design in which patients are randomized to study drug or a minimally effective active-control, and preexisting AED therapy is gradually withdrawn (95). Such a design parallels the technique clinicians use to switch patients to a second trial of AED monotherapy when the first agent has failed because of ineffective seizure control or

intolerable side effects. Such a design was used as a proof-of-principle trial for TPM monotherapy (96).

Monotherapy trial design becomes particularly complex when evaluating new AEDs in patients with newly or recently diagnosed epilepsy. The use of a placebo control in untreated epilepsy patients remains controversial, and only one such trial has been conducted (97). Unlike their European counterparts, regulatory authorities in the United States are unwilling to accept monotherapy equivalence trials for AEDs already approved as adjunctive therapy (95). The argument is that a trial showing equivalence of two treatments could be interpreted as meaning that both treatments were equally ineffective or that the trial simply failed to detect existing differences (95,98). Given the responsiveness of patients with newly diagnosed epilepsy, some have doubted the possibility of demonstrating a treatment effect with active-control or dose-control trials. These trial types are also controversial in relation to ethical equipoise (99).

TPM has been evaluated as first-line monotherapy in adults and children with newly or recently diagnosed epilepsy in three multicenter, randomized, double-blind trials. Two trials were dose-controlled trials (35,48), and one trial used a novel trial design to simultaneously compare TPM with two standard AEDs (i.e., carbamazepine and valproate) (47).

In the first dose-controlled trial (35), 252 adults and children who had been diagnosed with epilepsy within 3 years of study entry and who had one to six partial-onset seizures during a 3-month retrospective baseline were randomized to 50 or 500 mg/day TPM (patients weighing ≤50 kg were randomized to 25 or 200 mg/day). Patients were untreated or had been treated for more than 1 month with one AED. The primary efficacy outcome was time to exit, which was time to second seizure in 96% of patients. Time to exit was longer in patients receiving TPM 200/500 mg/day (median 422 days vs. 293 days in patients receiving 25/50 mg/day), although the difference was not significant. When time to exit was analyzed using time to first seizure as a covariate, the difference between treatment groups was significant ($P = 0.01$). This finding reflected the higher seizure-free rate in patients receiving TPM 200/500 mg/day (54% vs. 39% with 25/50 mg/day; $P = 0.02$) as well as the longer interval before the first seizure (median 317 days vs. 108 days with 25/50 mg/day; $P = 0.06$). In this study, seizure-free rates with 50 mg/day (39%) and TPM 400 mg/day (54%) were at the lower and upper ends for the range of seizure-free rates (36% to 43%) reported with therapeutic dosages of other AEDs in double-blind studies (100,101). The mean dosage among patients randomized to TPM 500 mg/day was 366 mg/day. A significant difference between treatment groups was observed for patients with one or two seizures in the 3-month baseline, but not for patients with three or more seizures in the 3-month baseline. This finding suggested that higher seizure frequency may serve as an indicator of more treatment-resistant seizures in patients with untreated epilepsy and is consistent with other reports linking higher seizure frequency before initial treatment with refractory epilepsy (102).

Results from the first dose-controlled study (35) suggested that TPM 50 mg/day was an effective dose in some patients responsive to anticonvulsant therapy and could serve as an active control to treatment with TPM 400 mg/day. Moreover, patients with one or two seizures in a 3-month baseline may represent the population of patients with newly diagnosed epilepsy who are most likely to benefit from monotherapy and not require polytherapy because of drug-resistant epilepsy. In the second dose-controlled study (48), 470 adults and children (weighing at least 25 kg) were eligible if they had untreated epilepsy diagnosed within 3 months of study entry, or if epilepsy had relapsed while they were not receiving anticonvulsant therapy. Patients could have only one or two partial-onset or generalized tonic–clonic seizures during the 3-month retrospective baseline. The primary

efficacy end point was time to first seizure; seizure-free rates at 6 months and 1 year were secondary efficacy measures. Kaplan–Meier survival analyses for time to first seizure showed a significantly greater treatment effect with the 400 mg/day group versus the 50 mg/day group (P = 0.0002). The probability of being seizure free was 83% with the 400 mg/day group and 71% with the 50 mg/day group (P = 0.005) after 6 months treatment and 76% and 59% (P = 0.001) after 12 months. A difference between dose groups emerged within the first week after randomization when patients were receiving 25 or 50 mg/day; the between-group difference was significant after 2 weeks when patients were receiving 25 or 100 mg/day. The mean dosage achieved for each of these groups was 46 mg/day (in the so-called 50 mg/day group) and 275 mg/day (in the so-called 400 mg group). The reason that the numbers were <50 and 400 mg/day was that for example for the higher dosage patients, they had to be increased to at least 150 mg/day but not necessarily to 400 mg/day. Approximately half of the patients were not fully titrated to 400 mg/day and approximately half were titrated up to 400 mg/day (investigator discretion). Similarly, one could stop at 25 mg/day for the low-dosage group and did not have to increase to 50 mg/day.

The effectiveness of TPM 100 mg/day as initial monotherapy in patients with newly diagnosed epilepsy was established further with a randomized, double-blind trial comparing TPM, carbamazepine, and valproate in adults and children (N = 613) with newly diagnosed epilepsy (47). No seizure types/epilepsy syndromes were excluded. During this trial, investigators selected carbamazepine (600 mg/day) or valproate (1250 mg/day) as the preferred therapy according to each patient's clinical presentation. Patients were then assigned to the carbamazepine or valproate treatment branch. Within each branch, patients were randomized to double-blind treatment with the investigator's choice of traditional AED (carbamazepine or valproate), TPM 100 mg/day or TPM 200 mg/day. Patients continued double-blind treatment until exiting the study or until 6 months after the last patient was randomized.

The initial efficacy analysis compared time to first seizure for the two TPM dosages (100 and 200 mg/day). If TPM 200 mg/day was significantly more effective than TPM 100 mg/day, then 200 mg/day was to be compared with carbamazepine and valproate. If 200 mg/day was not significantly more effective, the protocol required TPM dosage groups to be pooled within each branch and compared with traditional therapy. For the comparison between TPM and traditional therapy, the primary efficacy measure was time to exit; secondary efficacy end points were time to first seizure and proportion of patients seizure free during the last 6 months of double-blind treatment.

No difference was observed for the initial efficacy analysis comparing the two TPM dosages groups. Therefore, the combined TPM groups were compared with carbamazepine and valproate treatment. In both the carbamazepine and valproate branches, time to exit did not differ between the combined TPM treatment groups and traditional therapy. Because the branches were homogeneous, pooled data across branches were used to calculate 95% confidence intervals (CIs) for treatment differences. Although retention rates were higher among patients receiving TPM compared with those receiving carbamazepine or valproate, 95% CIs included zero, which indicated that between-group differences were not statistically significant. Similar results were observed for time to first seizure. The proportion of patients with no seizures during the last 6 months of double-blind treatment was 49% among patients receiving TPM 100 mg/day and 44% in each of the other three treatment groups (i.e., TPM 200 mg/day, carbamazepine, and valproate). The 95% CIs were narrow and included zero, indicating no difference among the four treatment groups.

Results from two trials showing that TPM 100 mg/day is effective in adults and children with newly diagnosed epilepsy support clinical findings suggesting that only low to moderate dosages of

AEDs are required in patients with new-onset epilepsy that is responsive to treatment (103). Pharmacokinetic–pharmacodynamic (PK-PD) modeling and simulation bridging showed no difference in PK-PD of TPM between adult and pediatric patients. Monotherapy regimens were identified in children 2 < 10 years of age (104).

Intravenous Use

There is no intravenous formulation approved to date. The safety and pharmacokinetics following a single dose in patients with epilepsy or migraines taking oral TPM was however performed. A 25 mg single dose caused minimal infusion site or systemic adverse effects (105).

Other Clinical Uses

TPM is now indicated for adults for the prophylaxis for migraine headaches. Two randomized, double-blind, placebo- controlled trials evaluated the efficacy of TPM treatment (50, 100, and 200 mg/day) in 970 patients with migraine (106,107). The primary efficacy measure was change in mean monthly migraine frequency from baseline during double-blind treatment. Compared with placebo, significant reductions in monthly migraine frequency were reported with TPM dosages of 100 and 200 mg/day; migraine frequency was also reduced with 50 mg/day, although the difference from placebo was not statistically significant. The proportion of treatment responders with a 50% or more reduction in monthly migraine frequency was significantly greater in TPM-treated patients (36% to 54% vs. 23% with placebo) (104,105). TPM may also have favorable effects in patients with cluster headache; in a case series, cluster remission occurred in nine of 10 patients (108).

TPM may have a potential role in movement disorder treatment. In a double-blind, placebo-controlled, crossover trial in 62 patients with essential tremor, TPM was associated with significant improvements in tremor severity, motor task performance, and functional disability (109), findings that were consistent with those in an earlier pilot study (110). In a retrospective chart review, TPM seemed to be effective in reducing tics in children and adolescents with Tourette syndrome (111); 59% (19/32) of patients had at least 50% reduction in tic severity scores.

Several studies suggest that TPM may be effective in various impulse control disorders. In a randomized, double-blind, placebo-controlled trial in 150 patients with alcohol dependence, TPM-treated patients had significantly fewer drinks per day, drinks per drinking per day, and heavy drinking days and significantly more abstinent days compared with placebo (112). Plasma α-glutamyl transferase, an objective index of alcohol consumption, was also significantly lower in TPM-treated patients. Among 61 obese patients with binge-eating disorder who were participating in a randomized, double-blind, placebo-controlled trial, TPM treatment was associated with significantly greater reductions in binge frequency, binge per day frequency, body mass index (BMI), body weight, and obsessive–compulsive scores (113). Open-label treatment with TPM has been reported to improve behavior, mood, weight control, compulsive eating problems, and self-mutilating behavior (notably skin picking) associated with Prader–Willi syndrome (114,115).

The observation that TPM is associated with weight loss and expected improvement in metabolic parameters (e.g., lipids, blood pressure, glucose levels) (116) led to studies of TPM (64 to 384 mg/day) in obese patients (117). After 6 months, mean percent decrease in baseline body weight was significantly greater among TPM-treated patients (range, 4.8% to 6.3% depending on TPM dose; 2.6% with placebo). A similar pattern of weight loss was observed in patients with diabetes who

participated in three double-blind, placebo-controlled trials evaluating the efficacy of TPM in painful diabetic neuropathy (118). Moreover, in these trials, diabetic control, measured as HbA1c levels, improved significantly compared with placebo, with reductions in HbA1c occurring independent of weight loss. These findings are supported by data from an animal model of diabetes, in which TPM demonstrated dose- dependent decreases in blood glucose and plasma triglycerides without significant body weight changes (119).

In view of the role of glutamate and AMPA in the pathobiology of neuronal injury, attention has been focused on TPM because of its activity as an AMPA antagonist. Potential neuroprotective and disease-modifying effects of TPM have been observed in models of seizure-related neuronal injury (23), focal cerebral ischemia (120), and glutamate excitotoxicity (121). Preliminary data in patients with diabetic neuropathy suggest that TPM may improve or restore nerve function through preservation/regeneration of C-fibers, with associated improvement in functional parameters (122). Studies using a cerebral microdialysis technique in patients with traumatic brain injury showed that TPM reduced glutamate levels compared with historical controls (123). In a double-blind, placebo-controlled trial, high-dose TPM (800 mg/day) did not provide beneficial effects in patients with amyotrophic lateral sclerosis and may have accelerated the loss of arm muscle strength. In this study, TPM treatment was associated with an increased risk of side effects (124). These findings are useful for advancing our understanding of potential therapeutic targets.

A recent translational medicine research report using a computational approach to discover new drug therapies for inflammatory bowel disease (IBD) suggested the possibility that TPM might be helpful. They utilized a trinitrobenzenesulfonic acid–induced rodent model of IBD (125).

Use in Pregnancy

“In 2011, TPM was reclassified from a Pregnancy Category C to a Pregnancy Category D drug.” Data in humans suggested a link between the drug’s use in the first trimester of pregnancy and oral cleft formation in newborns. “Pregnancy Category D drugs are those with positive evidence of human fetal risk based on human data but still may be used in pregnant women in certain situations when its benefits are thought to outweigh potential risks. Previously, data suggesting fetal harm with TPM were available only with animal studies” (126). In animal studies, fetal abnormalities were similar to those observed with other carbonic anhydrase inhibitors such as acetazolamide, whose use has not been linked to teratogenic effects in humans. “The recent FDA action stemmed from inspection of data provided by the North American Antiepileptic Drug (NAAED) Pregnancy Registry. Upon review of these data, the agency found that newborns exposed to TPM monotherapy during the first trimester of pregnancy were more likely to develop an oral cleft compared to those who were not (RR = 21.3; 95% CI, 7.9–57.1). Similar conclusions were drawn from a review of the United Kingdom Epilepsy and Pregnancy Register (incidence of oral cleft: 3.2% vs. 0.2%, RR increase of approximately 16-fold). In their published safety communication, FDA agency officials stressed, ‘The benefits and the risks of TPM should be carefully weighed when prescribing this drug for women of childbearing age, particularly when TPM is considered for a condition not usually associated with permanent injury or death.” They continued, “Appropriate alternative treatment should be considered.” (126). One company sponsored study with 75 pregnancies with 29 monotherapy exposures revealed two malformations. The other 46 pregnancies in that study were exposed to at least one other AED; 7 infants had a malformation (127). Preliminary experience from the UK Epilepsy and Pregnancy Registry that is a prospective observational registry and follow-up study revealed 203 pregnancies

with 173 live births. There were 16 major congenital malformations (MCM) (9%). Of these 16 patients, 3 cases were on monotherapy (out of 70 monotherapy cases) (4.8%) and 13 were on polypharmacy (11.2%). Four MCMs were oral clefts (2.2%). There were four cases of hypospadias among 78 live male births. Two of these cases were classified as major malformations (128). Caution is advised due to sample size and wide CIs. Of additional note, approximately half of these patients were migraine patients and not all were epilepsy patients. In addition, much of the data were in polypharmacy. These are the first data we have had on TPM in pregnancy and while these findings are of potential concern, until we have more research from other pregnancy registries, they cannot be interpreted as definitive (129). Pregnancy registries in the United States and Europe are collecting information about the use of TPM and other AEDs during pregnancy. A progress report in 2009 from the North American Antiepileptic Drug Registry showed 8 total malformations out of 197 enrolled monotherapy pregnancies with TPM (prevalence 4.1%) (95% CIs 1.9 to 7.6%) (130). Identified malformations were eight separate, common birth defects and did not show an increase for any specific abnormality. (Data preliminary since predictions would be much more certain with a larger sample size—preferably >600 pregnancies.)

TPM is extensively excreted in human breast milk, and nursing infants are exposed to TPM (plasma concentrations in infants are 10% to 20% of maternal concentrations); the significance of this exposure is unknown (131).

EXTENDED-RELEASE FORMULATIONS

Two extended release formulations were recently released or are about to be released. Trokendi XR, the first once per day extended release formulation using Microtrol technology, was released in the third quarter 2013 by Supernus Pharmaceuticals and Qudexy XR, a proprietary formulation of coated bead technology to deliver consistent release of TPM over a 24-hour dosing interval by UpsherSmith Pharmaceuticals, is in the late stages of development. TrokendiXR was approved in 2014 for initial monotherapy for patients >10 years old with either partial onset or primary generalized tonic–clonic seizures, and as adjunct treatment in patients >2 years old with partial onset seizures, primary generalized tonic–clonic seizures, or seizures associated with Lennox–Gastaut syndrome. TrokendiXR was approved strictly based on bioequivalence with $AUC_{0–24}$ 97%, C_{max} 88%, and C_{min} 100% (132). The USL255 probable release will be based on an adjunctive therapy study in patients from 18 to 75 years of age. Pharmacokinetics have shown $AUC_{0–24}$ (90% CI: 98%–104%), C_{max} (90% CI: 86%–95%), and C_{min} (90% CI: 99%–104%) (133).

ADVERSE EFFECTS

Central Nervous System

As expected with anticonvulsants, CNS effects were the most commonly reported side effects in randomized, controlled trials with TPM. Their relatively high incidence in early double- blind, placebo-controlled trials was attributable in part to high starting doses, rapid dose escalation, and high drug load when supratherapeutic dosages of TPM were added to maximum tolerated dosages of one or more AEDs (60). Various studies showed that the incidence and severity of CNS effects, as well as premature discontinuations because of side effects, could be reduced with more gradual dose

escalation, lower target doses, and reductions in the dosages of concomitant AEDs as TPM was titrated to effect (62,134,135).

Although many of the CNS effects were nonspecific complaints seen with all AEDs (e.g., somnolence, fatigue, dizziness, ataxia, confusion), the early studies were characterized by a relatively high incidence of adverse events coded to the term "abnormal thinking" per WHOART (World Health Organization Adverse Reporting Terminology) (51,52). Subsequently, neurobehavioral adverse events were coded with an expanded adverse event term list that included psychomotor slowing, memory difficulty, concentration/attention difficulty, speech problems, language problems, and mood problems, among others. A double-blind study comparing TPM with carbamazepine and valproate as monotherapy in newly diagnosed epilepsy was the first in which the adverse events occurring with other AEDs were coded with the dictionary that is unique to TPM trials (47). The incidence of neurobehavioral side effects was low with all three medications. TPM 100 mg/day and carbamazepine 600 mg/day were indistinguishable in terms of most neurobehavioral side effects (concentration and attention difficulty, 4% in each group; psychomotor slowing, 4%; confusion, 3%; speech disorders, 2%), which occurred less frequently in patients receiving valproate 1250 mg/day (concentration and attention difficulty, 1%; psychomotor slowing, 1%; no reports of confusion or speech problems). Cognitive problems not otherwise specified, as well as memory difficulty, were slightly more common with TPM than with the other agents (cognitive problems not otherwise specified: TPM, 3%; carbamazepine and valproate, 1%; memory difficulty: TPM, 8%; valproate, 6%; carbamazepine, 5%), while language problems were somewhat more common with carbamazepine (carbamazepine, 6%; valproate, 4%; TPM, 3%).

Although TPM and carbamazepine have not been compared in terms of their effects on objective measures of cognitive function, two studies have compared TPM and valproate added to carbamazepine in patients with uncontrolled partial- onset seizures (136,137). In a double-blind study in which patients were followed for 20 weeks, 1 of 17 neuropsychometric variables (short-term verbal memory) showed a statistically significant difference between treatments (worsening of scores with TPM and improvement with valproate). Although the study did not include measures of language function, it used the titration schedule most commonly used in clinical practice when adding TPM to other AEDs (i.e., 25 mg/day starting dose increased weekly in 25-mg increments to a target dose of 200 to 400 mg/day). In a double-blind study using a more rapid escalation schedule (50 mg/day starting dose increased weekly in 50-mg increments to a target dose of 400 mg/day) to add TPM to carbamazepine, cognitive performance was significantly worse from baseline in seven of 24 variables at the end of the 8-week titration period but in only 2 of 24 variables (controlled oral word association and symbol digit modalities) after an additional 3 months of treatment (137). Compared with valproate added to carbamazepine, TPM scores during neuropsychometric testing were slightly worse overall. In this study, it appeared that a subset of patients was more sensitive to TPM and accounted for much of the worsening in cognitive function scores. Because pharmacodynamic interactions are a major factor in the neurobehavioral adverse events that have been reported with TPM polytherapy, neuropsychometric testing during TPM monotherapy would be a better indicator of the effects of TPM on cognitive function. However, no such study in patients with epilepsy has been published. A short-term study in healthy volunteers showed that a high starting dose (100 mg/day) and escalation to 400 mg/day in 4 weeks was associated with significant decreases from baseline on measures of attention and word fluency (138). However, the results of this study have little clinical relevance since the 400 mg/day dosage was four times higher than the recommended target dose of 100 mg/day in newly diagnosed epilepsy.

Although the comparative study of TPM, carbamazepine, and valproate as monotherapy showed that language and speech disorders were actually no more common with TPM, at least as monotherapy, than with carbamazepine, the occurrence of word-finding difficulty during TPM therapy has generated considerable interest, as evidenced by the studies using comprehensive neuropsychometric test batteries. In addition, investigators have sought potential risk factors for adverse cognitive effects with TPM. In a prospective study from a tertiary epilepsy center, left temporal lobe epilepsy and simple partial seizures were most strongly associated with the occurrence of word-finding difficulty in the 31 of 431 patients (7%) who developed word-finding difficulty during TPM therapy (139). As in the double-blind cognitive function study (132), it appeared that the word-finding difficulty in a small subset of patients reflected a biologic vulnerability.

The original double-masked placebo-controlled studies were all forced titration studies that increased each patient's dosage to a target dose, usually at weekly increments of 100 to 200 mg/day. The recommended titration rate (weekly increments of 50 mg/day or less) is slower and has clearly been associated with improved tolerability (27). TPM may be increased at 25 to 50 mg/week increments, and it is this author's opinion that 2-week intervals may be best. If TPM is titrated too quickly, patients may complain of agitation, anxiety, or nervousness as well as word-finding difficulties. This can often be ameliorated by slowing the rate of titration. Keeping TPM total dosage per day at no >200 mg by 6 to 8 weeks is often best. Reduction in the dose of concomitant AEDs can further decrease side effects. Particularly in patients with high valproic acid levels, reduction of the dose of valproate can improve cognitive side effects. Patients with thrombocytopenia while taking valproate may have a further reduction in platelet count with the addition of TPM (39). Platelet counts increase when the valproate dose is reduced. In most cases, side effects are manageable and do not require discontinuation of the drug (27).

Adverse Effects in the Elderly

Most studies of TPM involved mostly young adults with only a few exclusively involving the elderly. Studies have found deficits in working memory and verbal fluency (140–144). Gross effects of TPM on daily life have been evaluated by examining motor vehicle performance and decrease in driving ability (144,145). In the case of the elderly patient, it has been suggested that the patients avoid other sedative AEDs with TPM, and preferable choices according to these authors might include CBZ, GBP, LTG, and levetiracetam (146,147) (Starting at a lower dose, perhaps at 25 mg/day and no more rapidly than 25 mg/week, has been suggested (148).

Psychiatric

In 2008, the FDA posted an advisory in regard to suicidality in regards to epileptic drugs "stating that as a class, there is a possible risk between 11 such drugs, including TPM and suicidal ideation within 1 week of beginning treatment. This seems to occur to the same extent in both epilepsy and psychiatric patients. The FDA states that the risk is roughly twice that of placebo-treated patients (0.43% vs. 0.22%)" (148,149). "TPM-treated patients have a prevalence of suicidal ideation, attempts, and completed suicide of 0.5%, compared with 0.15% of placebo recipients, in randomized, double-blind clinical trials" (150).

Carbonic Anhydrase Inhibition

Side effects that can be linked to TPM inhibition of carbonic anhydrase isozymes (CA II and CA IV) are paresthesia, renal stones, and decreased serum bicarbonate. Paresthesias are often transient, resolve with continuing treatment, and rarely lead to drug discontinuation. Paresthesias are more common with TPM monotherapy (35,47,48) than as add-on treatment (60), which is likely caused by higher TPM plasma levels in the absence of hepatic enzyme–inducing AEDs.

As in the general population, renal stone formation in TPM clinical trials was more common in men. Other risk factors for renal stone formation include personal or family history of renal stones, chronic metabolic acidosis, and coadministration of other carbonic anhydrase inhibitors or the ketogenic diet. Although chronic metabolic acidosis may increase the risk of renal stone formation, serum bicarbonate levels are not reliable predictors of renal stone formation. Patients should maintain adequate hydration to increase urinary output and lower the concentration of stone-forming substances.

In some patients, carbonic anhydrase inhibition is associated with laboratory findings of reduced serum bicarbonate levels. In clinical trials, the mean serum bicarbonate reduction was 4 mEq/L. Although reductions in serum bicarbonate levels are usually asymptomatic, nonspecific symptoms may include fatigue, anorexia, nausea, and vomiting; no correlation between these symptoms and serum bicarbonate levels was observed in TPM-treated patients. Cases of metabolic acidosis marked by hyperventilation and acute changes in mental status have been reported in patients receiving TPM, primarily children (151–153), although most cases have been asymptomatic (154–156). Reductions in serum bicarbonate levels generally occur early in treatment and tend to stabilize without progression during continued treatment (nevertheless, more pronounced at higher doses). Conditions that increase bicarbonate loss (e.g., renal disease, diarrhea, other carbonic anhydrase inhibitors), interfere with carbon dioxide regulation via the lungs (e.g., severe respiratory disorders, surgery, status epilepticus), or alter acid–base balance (ketogenic diet) may have additive effects. It is prudent to monitor serum bicarbonate in patients with any of these potentially exacerbating conditions.

Due to the potential for untreated hyperchloremic normal anion gap, metabolic acidosis the potential for osteomalacia (rickets) with reduced growth rates in children has been raised as a hypothetical concern. The effect of these metabolic abnormalities on adult bone remain speculative.

Adverse Effects in Children

During controlled clinical trials with TPM adjunctive therapy, the incidence of CNS effects in children, including cognitive effects, was generally lower than that in adults, perhaps reflecting a more gradual dose-escalation schedule (60,66,72,77,78). The most common CNS effects in children were somnolence and decreased appetite. TPM did not negatively affect measures of mental status as evaluated by parents and guardians during double-blind treatment (66), although a formal study with neuropsychological testing has not been performed in children. Temporary slowing of weight gain or minor weight loss occurred with TPM treatment; however, weight gain resumed in most children with continued therapy (157). TPM does not adversely affect growth, measured as height, in children (158).

Pooled data from three randomized, double-blind trials (35,47,48) in which 245 children/adolescents as young as 3 years of age with newly or recently diagnosed epilepsy received 50 to 500 mg/day TPM as first-line monotherapy showed that the incidence of CNS effects, including neurobehavioral effects, was lower than with adjunctive therapy, even though the treatment periods were longer (median 8 months; treatment periods as long as 2.2 years) (159). The most common CNS

effects were headache, decreased appetite, and somnolence. In most children, body weight increased or did not change; among 13 patients who lost 10% or more of baseline body weight, 12 were adolescents (12 to 15 years old). No child/adolescent discontinued TPM monotherapy because of weight loss. As noted above, metabolic acidosis may be more likely to be symptomatic in children receiving TPM compared with adults.

Idiosyncratic Toxicity

No clinically significant abnormalities in hematologic or hepatic function were reported during clinical trials (60), and laboratory test values remained generally unchanged other than expected reductions in serum bicarbonate levels and increased chloride levels.

TPM has been associated with a rare ocular syndrome consisting of acute myopia with increased intraocular pressure (160). The syndrome occurs bilaterally and at any age, in contrast to primary narrow-angle closure, which is rarely bilateral and rare in individuals younger than 40 years of age. Symptoms occur early in TPM therapy (within the first month) and include acute (usually quite apparent) onset of blurred vision and/or ocular pain and/or red eyes. Ophthalmologic findings were bilateral and could include severe myopia, conjunctival hyperemia, shallowing of the anterior chambers, and increased intraocular pressure. Mydriasis was an inconsistent finding. Symptoms resolve upon prompt discontinuation of TPM treatment.

Decreased sweating (oligohidrosis) and an elevation in body temperature have been reported in association with TPM use; the majority of reports were in children. Most cases occurred after exposure to hot weather (161).

Weight Loss

Weight loss of 1.6 to 6.5 kg was reported in patients during the clinical trials. Patients who weighed most (>100 kg) before TPM therapy experienced the greatest weight loss (mean weight loss, 9.6 kg) compared with those who weighed least (<60 kg) before TPM treatment (mean weight loss, 1.3 kg). For patients receiving long-term TPM therapy, body weight reductions were most commonly noted during the first 3 months of treatment and peaked at 12 to 18 months. This was partially reversed in some patients who gained weight starting with the second year of therapy (27).

Pooled data from double-blind, placebo-controlled trials and open-label studies showed that 85% of 1319 adults with epilepsy receiving TPM as monotherapy or as adjunctive therapy lost weight; mean body weight change was 3.8 kg loss (4.6% of baseline body weight) (162). Weight loss was a function of baseline body weight, with greater losses occurring in patients with higher pretreatment weight. Weight loss was gradual, typically began during the initial 3 months of therapy, and peaked at 12 to 18 months. Weight loss was accompanied by positive changes in lipid profile, glycemic control, and blood pressure. In a prospective study evaluating weight changes associated with TPM treatment (116), more than 80% of adults lost weight without changes in diet or exercise; obese patients (BMI $\geq$ 30 kg/m^2) had the greatest degree of weight loss. Reduction of body fat mass represented 60% to 70% of the absolute weight loss. In these patients, weight loss was associated with improvements in glucose, insulin, and total cholesterol levels.

Weight loss has been observed in patients receiving TPM for conditions other than epilepsy. During two double-blind, placebo-controlled trials in patients with migraine (106,107), dose-related decreases in body weight were observed; the mean percent change in body weight compared with

placebo was significantly greater in patients receiving TPM. During three double-blind, placebo-controlled trials in patients with diabetic neuropathy, 18% to 40% had clinically significant weight loss (5% or more of baseline body weight) with TPM treatment (116). The observed improvement in diabetic control, measured as reduction in HbA1c levels, did not seem to correlate with TPM-induced weight loss.

CLINICAL USE

The initial randomized, controlled trials with TPM as adjunctive therapy identified TPM 200 to 400 mg/day as an appropriate target dose in adults with refractory epilepsy; subsequent studies have shown that many patients respond to TPM dosages of ≤200 mg/day. While gradual introduction improves tolerability, TPM can be added rapidly, if needed. Reducing the dose of concomitant AEDs as TPM is added also improves tolerability. In children receiving TPM as adjunctive therapy, the recommended daily dose is 5 to 9 mg/kg; the starting dose of 1 to 3 mg/kg/day can be increased in 1- to 3-mg/kg increments every 1 to 2 weeks.

As first-line monotherapy in adults with newly or recently diagnosed epilepsy, 100 mg/day is an appropriate target dose to initially assess patient response. It appears the optimal starting dose in adults is 25 to 50 mg/day, with weekly or biweekly increases of 25 to 50 mg/day. As initial monotherapy in children, the recommended dose is 3 to 6 mg/kg/day, using a starting dose of 0.5 to 1 mg/kg/day and incremental increases of 0.5 to 1 mg/kg at 1- or 2-week intervals.

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CHAPTER 64 VALPROATE

ANGELA K. BIRNBAUM AND SUSAN E. MARINO

HISTORICAL BACKGROUND

For more than 40 years (1), valproic acid or valproate (VPA) has been used in the treatment of epilepsy. Prior to 1990, it was regarded as one of the major antiepilepsy drugs (AEDs), distinguished from previous agents by its broad spectrum of activity against many seizure types in both children and adults (2,3) as well as by its relatively low sedative effect. In addition to being the first agent to be highly effective against several primarily generalized seizure types, such as absence, myoclonic, and tonic–clonic seizures, VPA was found to be effective in the treatment of partial seizures, Lennox–Gastaut syndrome, infantile spasms, neonatal seizures, and febrile seizures (4,5). Although VPA is also used for the treatment of conditions other than seizures, these indications will not be included in the present discussion. For the purpose of this chapter, epilepsy seizure nomenclature will be used according to the study cited and may not reflect the newer naming nomenclature.

CHEMISTRY AND MECHANISM OF ACTION

Valproic acid (MW 144.21; Fig. 64.1), a short-chain, branched fatty acid, is a colorless liquid with low solubility in water. Other forms include (i) sodium valproate (MW 166.19), a highly water-soluble, hygroscopic white, crystalline powder, and (ii) divalproex sodium, a complex composed of equal parts of VPA and sodium valproate (Fig. 64.1). The antiepileptic activity of VPA, demonstrated in several animal models (6,7), includes protection against maximal electroshock-induced seizures; seizures induced chemically by pentylenetetrazol, bicuculline, glutamic acid, kainic acid, strychnine, ouabain, nicotine, and intramuscular penicillin; and seizures induced by kindling (8). This broad spectrum of efficacy of VPA in animal models suggests that the agent is effective in both preventing the spread and raising the threshold of seizures. Although several effects of VPA have been demonstrated at the cellular level, the precise mechanism underlying its antiepilepsy effect has not been fully elucidated. Identified mechanisms include potentiation of γ-aminobutyric acid (GABA)ergic function, inhibition of γ-hydroxybutyric acid formation (9), inhibition of voltage-sensitive sodium channels (10), antagonism of NMDA receptor–mediated neural excitation (5,11), and inhibition of histone deacetylase (HDAC) (12) that may act to induce the GABA synthetic enzyme, glutamate decarboxylase (13,14). It is not known to what extent any of these actions contribute to clinical seizure protection by VPA.

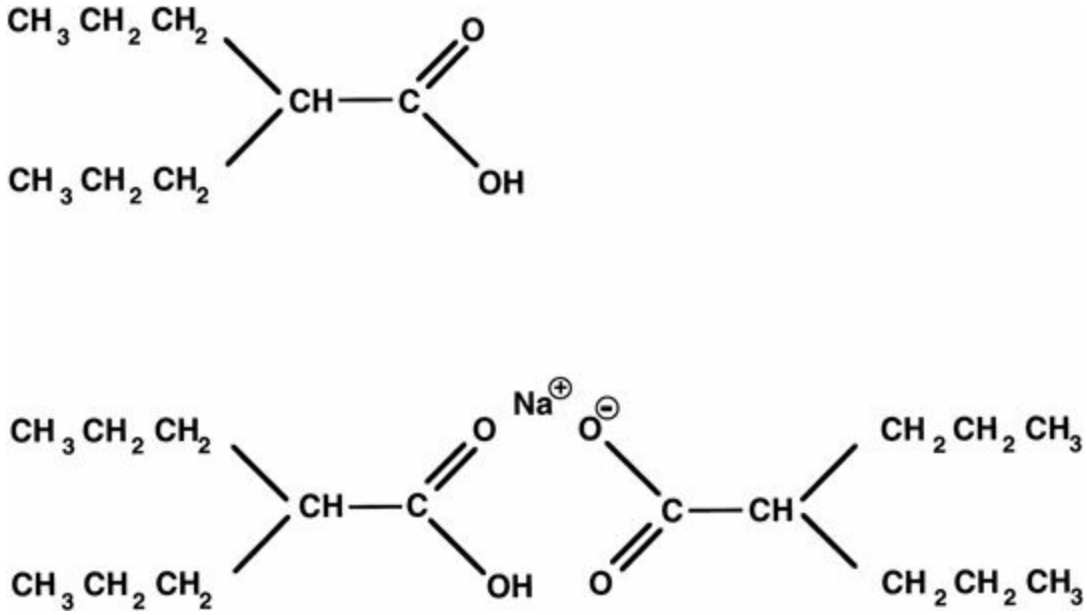

Figure 64.1. Structural formulas for valproic acid (N-dipropylacetic acid) and sodium hydrogen divalproate (divalproex sodium).

ABSORPTION, DISTRIBUTION, AND METABOLISM

The main pharmacokinetic parameters of VPA are summarized in Chapter 44, Table 44.1. Different preparations of VPA are available, although not all are available in any given country. Oral preparations of VPA include VPA capsules, tablets, and syrup (immediate-release); enteric-coated tablets of sodium valproate or sodium hydrogen divalproate (divalproex sodium); divalproex sodium enteric-coated sprinkles; slow-release oral preparations; and valpromide (the amide of VPA). A parenteral formulation of sodium valproate for intravenous (IV) use is also available.

The bioavailability of oral preparations of VPA is virtually complete compared with that of the IV route (15). The purpose of the enteric coating of tablets is to prevent gastric irritation associated with release of VPA in the stomach. The rate of absorption of VPA after oral administration is variable, depending on the formulation. Administration of syrup or uncoated regular tablets or capsules is followed by rapid absorption and peak levels within 2 hours. Absorption from enteric-coated tablets is delayed but rapid. The onset of absorption varies as a function of the state of gastric emptying at the time of ingestion, and peak levels may be reached only 3 to 8 hours after oral ingestion of enteric-coated tablets (16–18) (Chapter 44, Figure 44.1). Therefore, in patients treated chronically with enteric-coated VPA, the trough level may occur later than after administration of non–enteric-coated formulations. The bioavailability of enteric-coated sprinkles of divalproex sodium was compared with that of VPA syrup in 12 children, with no difference noted between the two formulations (19). However, the average time to maximal VPA concentrations was longer for sprinkles (4.2 hours) than for syrup (0.9 hours). Diurnal variation in VPA concentrations of particular VPA formulations has been observed with the enteric-coated tablets resulting in nighttime drug concentrations of 30% to 40% of daytime values (20–26). The extended-release divalproex formulation does not seem to exhibit this variation after administration to healthy volunteers (27). Rectal preparations from the syrup and capsule formulations can be prepared and have been given to patients (28,29).

The volume of distribution of VPA is relatively small (0.13 to 0.19 L/kg in adults and 0.20 to

0.30 L/kg in children). VPA is highly bound to serum proteins; this binding appears to be saturable at therapeutic concentrations, with the free fraction of VPA increasing as the total concentration increases (30): 7% at 50 mg/L, 9% at 75 mg/L, 15% at 100 mg/L, 22% at 125 mg/L, and 30% at 150 mg/L. VPA unbound fraction decreases from 15% at maximum concentration to 9% at 45 mg/L when rapid infusion (infusions of VPA administered in <60 minutes) of IV VPA is given (31). Several factors including induction status, albumin concentration, and infusion rate can significantly affect VPA pharmacokinetics. Infusion of VPA at a rate up to 3 mg/kg/min produces predictable total VPA concentrations when hepatic induction status and albumin levels are considered. Unpredictable protein binding can also be seen in critically ill patients and after rapid administration of VPA. Four hospitalized children receiving doses of 8.3 to 15.4 mg/kg in <15 minutes had a fraction unbound of 45% (32). Monitoring of unbound drug concentration may be useful when protein-binding alterations are suspected.

The elimination half-life of VPA varies as a function of comedication. In the absence of inducing drugs, the half-life in adults is 13 to 16 hours (16,33), whereas in adults receiving polytherapy with inducing drugs, the average half-life is 9 hours (15). In children, the half-life is slightly shorter. Cloyd et al. (26) reported an average half-life of 11.6 hours in children receiving monotherapy and 7.0 hours in those receiving polytherapy. Newborns eliminate VPA slowly; the half-life in this population is longer than 20 hours (24). In vitro studies from human liver microsomes show no difference in the rates of valproate–glucuronide formation in microsomes from young versus elderly (>65 years of age) livers (34). Approximately 55% of elderly nursing home residents are maintained at total VPA concentrations below the adult therapeutic range for epilepsy of 50 to 100 mg/mL regardless of indication (35,36). The population clearance from a study of 146 (405 VPA concentrations) elderly nursing home residents (average age 78.5 years ±8.0 [SD]) was 0.843 L/hour (37). Apparent oral clearances in elderly nursing home residents are reported to be 27% lower in female residents, even after adjusting for weight, and 25% greater in residents using the nonsyrup formulation (37). Approximately 20% of elderly nursing home residents take VPA syrup (35). The lower clearances seen with the syrup formulation may be a function of the patient's pathophysiology rather than a difference in the bioavailability of the syrup formulation. There can be considerable variability in VPA concentrations within an elderly nursing home patient even when receiving the same dose; therefore, the interpretation of a single drug measurement needs to be used with caution (38).

Several enzymes (UDP-glucuronosyltransferases: UGTs, β-oxidation, and cytochrome P450: CYP) are predominantly involved in the metabolism of VPA. The most abundant metabolites of VPA are glucuronide and 3-oxo-VPA, which represent about 40% and 33%, respectively, of the urinary excretion of a VPA dose (23). Several UGTs—UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A9, and UGT1A10—have been identified in vitro to be involved in forming the acyl glucuronide conjugate (34,39–41). Two desaturated metabolites of VPA, 2-ene-VPA and 4-ene-VPA, have anticonvulsant activity that is similar in potency to that of VPA itself (22). Because there is delayed but significant accumulation of 2-ene-VPA in the brain and because it is cleared more slowly than VPA (21), the formation of 2-ene-VPA provides a possible explanation for the discrepancy between the time courses of VPA concentrations and antiepilepsy activity (20). It appears that 2-ene-VPA does not have the pronounced embryotoxicity (42) and hepatotoxicity (43) of 4-ene-VPA. Both are produced by the action of cytochrome P450 enzymes, which are induced by certain other AEDs (23,44). This may explain the increased risk for hepatotoxicity in patients receiving VPA concomitantly with these agents (45). However, elevation of 4-ene-VPA levels has not yet been found in patients with VPA hepatotoxicity, short-term adverse effects, or hyperammonemia (46).

Cytochrome CYP2C9*1 is the predominant catalyst in the formation of 4-ene-VPA, 4-OH-VPA, and 5-OH-VPA metabolites (75% to 80%) with CYP2A6 and CYP2B6 being responsible for the remainder of these reactions. CYP2A6 is involved in approximately 50% of the formation of 3-OH-VPA (47). Population pharmacokinetic studies indicate that knowledge of a patient's CYP2C9 and CYP2C19 genotype may aid in predicting a patient's response to VPA (48).

DRUG INTERACTIONS

Pharmacokinetic interactions with VPA fall into three categories, based on the following features: (i) the metabolism of VPA is sensitive to enzymatic induction; (ii) VPA itself can inhibit the metabolism of other agents; and (iii) VPA has a high affinity for serum proteins and can displace other agents or be displaced from proteins (49–51). Concomitant administration of enzyme-inducing drugs has been repeatedly shown to lower VPA levels relative to the dose (52). Carbamazepine (53–55) and phenytoin (55) lower VPA levels by one-third to one-half, or even more in children (56–58). When children receiving polytherapy discontinued treatment with other agents, VPA levels increased 122% after withdrawal of phenytoin, 67% after withdrawal of phenobarbital, and 50% after withdrawal of carbamazepine (59). In elderly nursing home residents, VPA clearance is increased to 41% in residents who are also taking phenytoin or carbamazepine (37). In contrast, levels of VPA are increased by coadministration of felbamate: 28% with felbamate 1200 mg/day and 54% with felbamate 2400 mg/day (60,61).

VPA affects the kinetics of other drugs either by enzymatic inhibition or by displacement from serum proteins. Phenobarbital levels have been found to increase from 57% (62) to 81% (63) after the addition of VPA. Levels of ethosuximide can also be raised by the addition of VPA, mostly in the presence of additional AEDs (64). Although VPA does not increase levels of carbamazepine itself, levels of the active metabolite carbamazepine-10,11-epoxide may double (65,66). Elimination of lamotrigine is markedly inhibited by VPA, resulting in a two- to threefold prolongation of the lamotrigine half-life (67). Although this is a competitive interaction that is likely to be rapidly reversible upon discontinuation of VPA, the inhibition seems to persist even at low VPA concentrations (68,69). A pharmacokinetic interaction occurs between VPA and phenytoin, partly because both agents have a high affinity for serum proteins. Displacement of one highly protein-bound drug by a second highly protein-bound drug can cause a reduction in total but not unbound drug concentrations and does not necessarily require a dose change (25). However, VPA also interferes with the metabolism of phenytoin resulting in a decrease in total and an increase in unbound phenytoin concentrations (i.e., VPA increases the free fraction of phenytoin) (70,71). Thus, in the presence of VPA, total phenytoin concentrations in the usual therapeutic range may be associated with clinical toxicity. In contrast to inducing AEDs, VPA is not associated with oral contraceptive failure (72); however, oral contraceptives may decrease VPA levels in women taking both compounds (73).

EFFICACY

VPA is a highly effective first-line agent for the treatment of generalized seizures, such as generalized absence, tonic–clonic, and myoclonic seizures (74). The indication for VPA when it was first released in North America in 1978 was for treatment of absence seizures. In patients with typical and atypical absence seizures, a reduction of spike-and-wave discharges was demonstrated (75–78). In two studies, comparison of VPA and ethosuximide for the treatment of absence seizures showed equal

efficacy for the two agents (79,80). It appears that absence seizures are more likely to be fully controlled when they occur alone than when they are mixed with another seizure type (59,81). Overall, VPA appears to be somewhat less effective against atypical or "complex" absence seizures than against simple absences (82,83). VPA can also be used effectively in patients with recurrent absence status (84).

VPA was found to be effective in the treatment of certain generalized convulsive seizures (85–88). Among 42 patients with intractable seizures, generalized tonic–clonic seizures were fully controlled in 14 patients by add-on VPA therapy (59). VPA was compared with phenytoin in 61 previously untreated patients with generalized tonic–clonic, clonic, or tonic seizures, and seizures were controlled in 82% of VPA-treated patients versus 76% of those treated with phenytoin (89). In another randomized comparison of VPA and phenytoin in patients with previously untreated tonic–clonic seizures, a 2-year remission was achieved in 27 of 37 patients receiving VPA and in 22 of 39 patients receiving phenytoin (88). Monotherapy with VPA was assessed in two studies of patients with primary (or idiopathic) generalized epilepsies (81). Among patients who had generalized tonic–clonic seizures only, complete seizure control was achieved in 51 of 70 patients (90) and in 39 of 44 patients (81), respectively. VPA monotherapy in children with generalized tonic–clonic seizures was also found to be highly effective (91).

VPA is often a first choice for most myoclonic seizures, particularly for those occurring in patients with primary or idiopathic generalized epilepsies (81,82,90). In a study of VPA monotherapy for primary generalized epilepsies, 22 patients had myoclonic seizures and 20 of the 22 had at least one other seizure type, either absence or tonic–clonic. The myoclonic seizures were controlled by VPA monotherapy in 18 of the 22 patients (81). Patients with juvenile myoclonic epilepsy have an excellent response to VPA (92), which remains an agent of first choice for this condition unless you are a woman of child-bearing potential. Benign myoclonic epilepsy of infancy also responds well to treatment with VPA (91). Some success has been achieved with VPA in patients with postanoxic intention myoclonus (92,93). A combination of VPA and clonazepam is often used to treat the myoclonic and tonic–clonic seizures associated with severe progressive myoclonus epilepsy (94).

Like all other AEDs, VPA is less effective in the treatment of generalized encephalopathic epilepsies of infancy and childhood, such as infantile spasms and Lennox–Gastaut syndrome. In a series of 38 patients with myoclonic astatic epilepsy, seven patients became and remained seizure free with VPA therapy and 50% to 80% improvement was achieved in one-third of patients (82).

Reports on the use of VPA for the treatment of infantile spasms include a small number of patients or patients receiving corticotropin and VPA simultaneously (95–97). Overall, there was a trend toward a better response with corticotropin, but the incidence and severity of side effects was lower with VPA. A retrospective study of VPA monotherapy in 30 patients with simple partial and complex partial seizures in whom previous drugs had failed showed a remarkable response (98). Seizure control was achieved in 12 patients, a >50% seizure reduction occurred in 10 patients, and only 9 patients showed no improvement. Comparison of VPA with carbamazepine or phenytoin showed little difference (99,100).

Mattson et al. (101) reported the most comprehensive controlled comparison of VPA and carbamazepine monotherapy for the treatment of partial and secondarily generalized seizures. Several seizure indicators, as well as neurotoxicity and systemic neurotoxicity, were assessed quantitatively. Four of five efficacy indicators for partial seizures were significantly in favor of carbamazepine, and a combined composite score for efficacy and toxicity was higher for carbamazepine than for VPA at 12 months, but not at 24 months. Outcomes for secondarily generalized seizures did not differ

between the two agents. Two studies—one comparing VPA and carbamazepine (102) and the other comparing VPA, carbamazepine, phenytoin, and phenobarbital (103)—were conducted in children. Equal efficacy against generalized and partial seizures was reported with all agents. Unacceptable side effects necessitating withdrawal occurred in patients receiving phenobarbital, which was prematurely eliminated from the study. VPA was also evaluated in 143 adult patients with poorly controlled partial epilepsy randomized to VPA monotherapy at low plasma levels (25 to 50 mg/L) or high plasma levels (80 to 150 mg/L) (104). The reduction in frequency of both complex partial and secondarily generalized tonic–clonic seizures was significantly higher among patients in the high-level group.

Several studies have demonstrated the efficacy of VPA in the prevention of febrile seizures (105–111). Based on risk–benefit ratio considerations, VPA cannot be recommended for this indication. A small group of newborns with seizures have also been treated with VPA administered rectally (112) or orally (24). Results were favorable overall. In newborns treated with VPA, a long elimination half-life (26.4 hours) and high levels of ammonia were reported (24).

ADVERSE EFFECTS

Neurologic Effects

A dose-related tremor is relatively common in patients treated with VPA. If it does not improve sufficiently with dosage reduction, propranolol may be tried (113). Drowsiness, lethargy, and confusional states are uncommon with VPA, but may occur in some patients, usually at levels >100 mg/L. There have also been case reports of reversible dementia and pseudoatrophy of the brain (114–116). Treatment with VPA has been associated with a somewhat specific and unique adverse effect, characterized by an acute mental change that can progress to stupor or coma (117,118). It is usually associated with generalized delta slowing in the electroencephalographic tracing. The mechanism is not known with certainty, but it is probably not caused by hyperammonemia or carnitine deficiency. This encephalopathic picture is more likely to occur when VPA is added to another AED, and it is usually reversible within 2 to 3 days upon discontinuation of VPA or the other AED. In addition, when compared with other AEDs, VPA can significantly lower, in a dose-related fashion, the IQ of children 3 years of age who have been exposed to VPA in utero (119). These findings have been extended to 6-year-old children who continued to demonstrate reduced cognitive abilities across a range of domains after exposure to VPA in utero (119). A population-based study of Danish children found that maternal use of VPA during pregnancy is also associated with increased risks of autism and autism spectrum disorder (120). Therefore, it is strongly recommended that VPA be avoided in women of child-bearing potential especially if they desire to become pregnant.

Gastrointestinal Effects

The most common gastrointestinal (GI) adverse effects associated with VPA use are nausea, vomiting, GI distress, and anorexia. These effects may be due, in part, to direct gastric irritation by VPA; the incidence is lower with enteric-coated tablets. Excessive weight gain is another common problem (121,122). This is not entirely attributable to increased appetite, and decreased β-oxidation of fatty acids has been postulated as a mechanism (123). Excessive weight gain seems to be less of a problem in children, and a recent report suggests that VPA is not associated with greater weight gain,

compared with carbamazepine, in children (83).

Fatal hepatotoxicity remains the most feared adverse effect of VPA (21,124–127). Two main risk factors have been clearly identified: young age and polytherapy (124). The risk for fatal hepatotoxicity in patients receiving VPA polytherapy is approximately 1:600 at younger than 3 years of age, 1:8000 from 3 to 10 years, 1:10000 from 11 to 20 years, 1:31000 from 21 to 40 years, and 1:107000 at older than 41 years of age. The risk is much lower in patients receiving monotherapy; it varies between 1:16000 (3 to 10 years of age) and 1:230000 (21 to 40 years of age) (124). No fatalities in patients receiving VPA monotherapy have been reported in certain age groups (0 to 2 years, 11 to 20 years, and older than 40 years of age) (124). Because a benign elevation of liver enzymes is common during VPA therapy and because severe hepatotoxicity is not preceded by a progressive elevation of liver enzymes, laboratory monitoring is of little value despite the fact that it is often performed routinely. The diagnosis of VPA-associated hepatotoxicity depends mostly on recognition of the clinical features, which include nausea, vomiting, anorexia, lethargy, and, at times, loss of seizure control, jaundice, or edema. One study indicates a possible protective effect of L-carnitine administration in cases of established VPA-induced hepatotoxicity (128). Among 92 patients with severe, symptomatic VPA-induced hepatotoxicity, 48% of the 42 patients treated with L-carnitine survived, as opposed to 10% of the 50 patients receiving similar supportive treatment without L-carnitine. The results suggested better survival with IV, rather than enteral, L-carnitine (128).

Another serious complication of VPA treatment is the development of acute hemorrhagic pancreatitis (129–133). Suspicion should be raised by the occurrence of vomiting and abdominal pain. Serum amylase and lipase are the most helpful diagnostic tests, and abdominal ultrasonography may also be considered.

Hematologic Effects

Hematologic alterations are relatively common with VPA therapy, but they seldom lead to discontinuation of treatment (134,135). Thrombocytopenia (134,136) can fluctuate and tends to improve with dosage reduction. In conjunction with altered platelet function (137,138) and other VPA-mediated disturbances of hemostasis (139,140), it may cause excessive bleeding. Therefore, the common practice of withdrawing VPA before elective surgery may be recommended despite the fact that several reports found no objective evidence of excessive operative bleeding in patients maintained on VPA therapy (141–143).

Hyperammonemia

Mild hyperammonemia is a very common finding in asymptomatic patients receiving chronic VPA therapy, particularly in those taking VPA along with an enzyme-inducing AED (144,145), and routine monitoring of ammonium levels is not warranted. Although hyperammonemia can be reduced with L-carnitine supplementation (146), there is no documentation that this is necessary or clinically beneficial (147). Chronic treatment with VPA, especially in polytherapy, tends to lower carnitine levels (148,149); however, a role for carnitine deficiency in the development of severe adverse effects of VPA has not been established. A beneficial effect of L-carnitine supplementation in acute VPA overdoses has been suggested (150,151), and a panel of pediatric neurologists has made recommendations for routine supplementation with L-carnitine in a subgroup of pediatric patients

being treated with VPA (152).

Reproductive Issues

In women, VPA has been reported to cause menstrual irregularities, hormonal changes such as hyperandrogenism and hyperinsulinism, polycystic ovaries, and pubertal arrest (153–157). An additional concern has been the possible association of VPA therapy, polycystic ovaries, and elevated testosterone levels (153–155,158). In a comparison of women treated with VPA, 21 with phenobarbital, 23 with carbamazepine, and 20 healthy untreated women, polycystic ovary prevalence, ovary volumes, and hirsutism scores did not differ among the groups (159). Epilepsy itself, other AEDs, and additional factors may be involved in the development of polycystic ovary syndrome (160,161). Treatment with VPA during the first trimester of pregnancy has been found to be associated with an estimated 1% to 2% risk of neural tube defect (159,162,163); a pharmacogenetic susceptibility has been suggested (164). Folate supplementation appears to reduce the risk (165), and a daily dose of at least 1 mg should be considered in all female patients of child-bearing age who are taking VPA. Further, a recent study from the European Surveillance of Congenital Anomalies reports that the use of VPA monotherapy during the first trimester was associated with significantly increased risks for six specific malformations: spina bifida, atrial septal defect, cleft palate, hypospadias, polydactyly, and craniosynostosis (166). Taken together with the finding that by age 3, children who have been exposed to VPA in utero are cognitively impaired compared to children who had fetal exposure to other AEDs supports the recommendation by Meador et al. that "VPA not be used as a first-choice drug in women of childbearing potential" (119).

Miscellaneous Effects

Excessive hair loss may be seen during treatment with VPA, and although the hair tends to grow back, it may become different in texture (167) or color (168). Facial and limb edema can occur in the absence of VPA-induced hepatic injury (169). Children may develop secondary nocturnal enuresis after initiation of VPA therapy (99,122,170–172). Hyponatremia (173) has been reported in one patient. The occurrence of rash with VPA therapy is very rare (174).

CLINICAL USE

An initial VPA dosage of approximately 15 mg/kg/d is recommended, with subsequent increases, as necessary and tolerated, of 5 to 10 mg/kg/d at weekly intervals. The optimal VPA dose or concentration may vary according to a patient's seizure type (175). Daily doses between 10 and 20 mg/kg are often sufficient for VPA monotherapy in patients with primary generalized epilepsies (59,81,89,90); children may require higher doses (63,82), whereas elderly nursing home residents may require lower doses (35). Dosages of 30 to 60 mg/kg/d (in children, >100 mg/kg/d) may be necessary to achieve adequate VPA levels in patients being treated concomitantly with enzyme-inducing agents. If therapeutic levels of VPA are to be achieved rapidly or if patients are unable to take VPA orally, the agent can be administered intravenously (176). This route has also been suggested for the treatment of patients with status epilepticus, with an initial dose of 15 mg/kg (at 20 mg/minute) followed by 1 mg/kg/h (177). A more rapid loading with an initial dose of 20 mg/kg has also been advocated, given at a rate of 33.3 to 555 mg/min (178) or ≤6 mg/kg/min. Rapid IV VPA

loading seems to be well tolerated (179).

Because of the short half-life of VPA, it is common to divide the total daily dose into two or three doses. However, the pharmacodynamic profile of VPA may explain why equally good results have been achieved with a single daily dose (82,180,181). In addition, the availability of an extended-release divalproex formulation makes once-a-day dosing even more appealing. The value of monitoring serum levels of VPA is limited. First, there is a considerable fluctuation in VPA levels because of the short half-life and variable absorption rate of the agent. Second, there seems to be a poor correlation between VPA serum levels and clinical effect, and the pharmacodynamic effect of VPA may lag behind its blood concentrations (81,182–185). Although the usual therapeutic range for VPA serum levels is 50 to 100 mg/L (350 to 700 μmol/L), levels up to 150 mg/L may be both necessary and well tolerated. In selected cases, and particularly during combination therapy with enzyme-inducing agents, VPA serum levels can be valuable, but a single measurement must be interpreted cautiously (186). Routine monitoring of liver enzymes and complete blood count with platelets is a common practice, but may be of little value. It may be more useful to perform these tests if unusual bruising or bleeding occurs or if there are any symptoms or signs of liver failure.

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CHAPTER 65 VIGABATRIN

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HISTORICAL BACKGROUND

Vigabatrin (VGB) was initially synthesized in 1977 by Jung et al. (1), designed as a specific inhibitor of gamma-aminobutyric acid (GABA)-transaminase (GABA-T), the enzyme responsible for metabolizing GABA at the synapse. It was hypothesized that inhibiting GABA-T would then increase whole-brain levels of GABA, making it more available to its receptor site, thus increasing GABAergic inhibition. For decades prior to this, the role of GABA in seizure activity had been proposed by the apparent proconvulsant properties of compounds either inhibiting GABA synthesis or blocking its postsynaptic action, by the ability of drugs enhancing GABA-mediated inhibition to act as anticonvulsants in many animal models, and by the identification of abnormalities in the GABA receptor in certain genetically determined epilepsy animal models. Although several compounds have been developed over the last 30 years that function to modulate GABA-A–mediated inhibition via various mechanisms, VGB is the only drug that does so by specifically inhibiting GABA-T.

VGB was initially approved and marketed in the United Kingdom in 1989. Although the initial NDA for VGB in the United States was submitted in 1994 for adult patients with complex partial seizures (CPS), the medication was only approved for use in 2009. Since initial approval in 1989, over 1.5 million have been treated with VGB. Multiple clinical studies conducted around the world, including the United States, have established the efficacy of VGB in the treatment of refractory CPS and infantile spasms (IS).

GENERAL CHARACTERISTICS

VGB (4-amino-5-hexenoic acid or gamma-vinyl-GABA) is a structural analogue of GABA that contains a vinyl appendage (Fig. 65.1). It was designed to specifically and irreversibly inhibit GABA-T and is the only currently available drug with this mechanism of action. It may also stimulate GABA release (2). VGB is highly water soluble, only slightly soluble in ethanol and methanol, and insoluble in hexane and toluene. VGB is a white to off-white crystalline solid, with a molecular mass of 129.16 and a melting point of 171°C to 117°C. It exists as a racemic mixture of R(−) and S(+) isomers, which occur in equal proportions, and has no optical activity. The pharmacologic activity is thought to be associated only with the S(+) enantiomer, and the R(−) enantiomer is thought to be entirely inactive (3,4). The major pharmacologic effects are determined by effects of VGB on GABA-T half-life and activity rather than the drug itself.

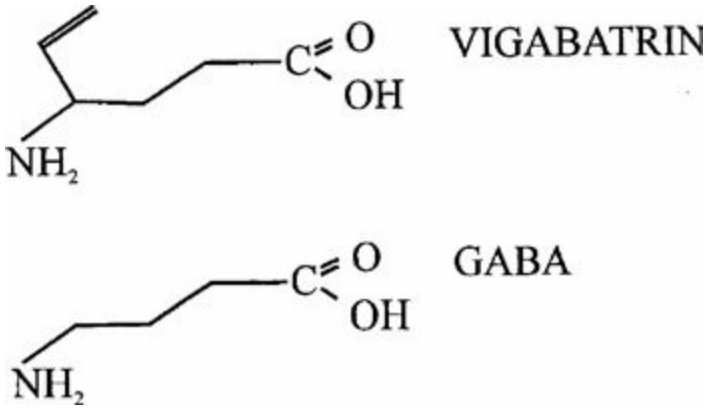

Figure 65.1. Chemical structure of vigabatrin.

PHARMACOKINETICS

Administration

Current formulations of VGB include 500-mg tablets and 500-mg powder packets or sachets. Following oral administration, VGB is almost completely absorbed, with peak VGB concentrations reached within 2 hours of administration of doses ranging from 0.5 to 3 g (3,5,6). VGB can be given at or between meals, as the presence or type of food does not have a significant effect on absorption and therefore should not influence clinical response.

Distribution

VGB is widely distributed throughout the body with a volume of distribution at steady state of 1.1 L/kg (7) and a half-life of distribution of 1 to 2 hours. Concentrations of VGB in the CSF are approximately 10% of blood levels (8). VGB has pharmacokinetics that is dose proportional and linear following single and repeated dosing (9,10). VGB does not bind to plasma proteins and does not cause hepatic induction of hepatic cytochrome P450–dependent enzymes (5,11). Passage of VGB across the human placenta occurs at a low level, comparable to other alpha-amino acids; the maximum amount of VGB that a nursing infant would be exposed to each day is approximately 3.6% of the R(−) and 1% of the S(+) enantiomer of the maternal VGB dose (12).

VGB has been shown to have minimal drug–drug interactions with other AEDs, ethanol, and oral contraceptive agents (13,14). VGB plasma levels are not affected by CBZ, clorazepate, primidone, or valproic acid. A modest reduction of about 20% in phenytoin plasma levels has been reported.

Metabolism

VGB is not metabolized, and is eliminated primarily as the parent drug by renal excretion. The half-life of VGB is approximately 5 to 8 hours, although it is thought that plasma levels do not correlate with clinical effect (7). Children have a lower AUC than do adults following VGB dosing, although renal clearance is similar. Therefore, children may require higher doses of VGB to achieve the same clinical effect as seen in adults.

SPECIAL POPULATIONS

Age

The renal clearance of VGB in healthy elderly patients (>65 years of age) was 36% less than that observed in healthy younger patients (10). The VGB half-life in elderly patients with reduced creatinine clearance is approximately twice that of normal healthy volunteers.

Gender

No gender-specific differences for the pharmacokinetics parameters of VGB have been observed.

Race

Limited data are available regarding race-specific variability in pharmacokinetics of VGB. A single report compared the pharmacokinetic parameters of Caucasian and Japanese patients; all parameters were similar except for mean renal clearance of VGB, which was slightly higher among the Caucasians.

Renal Impairment

As VGB is renally excreted, its pharmacokinetics is affected in the setting of renal impairment. Mean AUC values were found to increase 32% and 253% and $t_{1/2}$ increase 4.0 and 15.3 hours, respectively, in patients with mild to moderate (creatinine clearance of 40 to 79 mL/minute) and severe (creatinine clearance of 10 to 39 mL/minute) renal impairment (5).

EFFICACY

Now in clinical use for over 20 years, the efficacy of VGB in the treatment of partial-onset seizures and IS is well recognized.

Complex Partial Seizures

Numerous single-blind and double-blind studies have shown that VGB is effective in the treatment of intractable partial- onset seizures. A meta-analysis of the first 10 single-blind studies of VGB, which included a total of 352 patients, showed a 55.8% responder rate (patients with a >50% seizure reduction) (8,15–19).

Several European-conducted, double-blind, placebo- controlled, crossover studies also found VGB to be effective in the treatment of refractory partial-onset seizures. With doses ranging from 2 to 3 g/day as add-on treatment, the studies reported responder rates between 33% and 64%, with between 0% and 7% of patients becoming seizure free. In addition, two U.S. studies showed VGB to be effective as adjunctive treatment for intractable or refractory CPS. Both U.S. studies were placebo controlled and enrolled patients between 18 and 60 years of age; over 50% of patients in both studies were on two or more concomitant anticonvulsant medications at time of enrollment and had on average an over 20-year history of epilepsy, the majority having been treated with over three anticonvulsant medications. The first U.S. study, which included 182 patients, showed a 43% responder rate (compared to 19% placebo responder rate), including 5.4% of VGB-treated patients

who became seizure free (20). The second U.S. study, which enrolled 174 patients, evaluated doses of 1, 3, or 6 g/day of VGB, with significant reductions in seizure frequency seen in the two higher doses with a 51% responder rate in the VGB 3 g/day group and 54% responder rate in the VGB 6 g/day group (21). During the last 8 weeks of the study, 9.3% and 12.2% of patients in the 3 and 6 g/day groups, respectively, were seizure free, compared with no patients in the placebo-controlled or the VGB 1 g/day groups. Efficacy was also seen relatively early in the study, with a significant reduction in seizures seen after 14 days of treatment.

Open-label trials of VGB in children with mixed seizure types have shown similar efficacy of VGB in CPS as the adult studies (22,23), myoclonic seizures appeared to be exacerbated.

Infantile Spasms

The efficacy of VGB in the treatment of IS has been appreciated for over 20 years. The initial report of an uncontrolled study of VGB in 70 patients with IS in 1991 showed a 68% responder rate in infants with refractory IS with 71% of those with IS due to tuberous sclerosis complex (TSC) becoming seizure free (24). The effectiveness of VGB as a monotherapy treatment for IS was established in three controlled studies, including one conducted in the United States and two outside the United States, one of which was restricted to the treatment of IS due to TSC (25–27). In all three studies, cessation of IS was observed, with onset of efficacy between 2 and 4 weeks. The U.S. study, which was the largest study with 221 infants completing the study, found VGB effective across etiologies of IS and found that doses of >100 mg/kg/d were more effective than lower doses (25). In addition, several uncontrolled studies have examined the efficacy of VGB in IS, finding between 38% and 76% of infants having cessation of spasms (28–31). The UK Infantile Spasm Study (UKISS) compared the efficacy of VGB to prednisolone and ACTH in IS due to etiologies other than TSC; at 2 weeks of treatment, 54% of those on VGB had experienced cessation of spasms compared to 73% receiving hormonal treatment (30). On follow-up analysis at 12 to 14 months, 75% of those treated with VGB continued to be spasm free compared to 76% receiving hormonal treatment (31). An American Academy of Neurology practice parameter published in 2012 found that VGB "may be useful for short-term treatment of IS" (32). A meta-analysis of 11 randomized controlled trials in IS found VGB to be as effective as other treatments, namely ACTH and steroids, in the treatment of IS (33).

SAFETY

Adverse Events

Overall, VGB is well tolerated but can be associated with adverse events (AEs). The most frequently noted AEs in clinical trials for CPS and in clinical use included fatigue and somnolence; dizziness, nystagmus, tremor, headache, weight increase, blurred vision, diarrhea, and irritability can also be seen. Serious AEs were also noted in the controlled trials and included visual field defects (VFDs) (discussed below), status epilepticus, and psychiatric complaints including most commonly depression, but also confusion, aggression, insomnia, irritability, suicidal ideation, and suicide attempt. In clinical trials for IS, most common AEs included upper respiratory tract infection, otitis media, pyrexia, viral infection, irritability, somnolence, sedation, vomiting, constipation, pneumonia, diarrhea, insomnia, and rash. Serious AEs also were seen in the IS studies, most commonly status

epilepticus and pneumonia.

Chronic Toxicity

Intramyelinic Edema

Studies in animals revealed that treatment with VGB could be associated with intramyelinic edema (IME), or edema occurring within the myelin sheath (34,35). This finding, observed in rats and dogs but not monkeys, is characterized histopathologically by microvacuolation of specific regions of the brain, predominantly within the white matter.

IME was found to develop within several weeks of VGB treatment, stabilize without further progression, and resolve within 12 to 16 weeks after drug discontinuation. No residual histopathology was observed following drug discontinuation in dogs; however, rats retained swollen axons as well as foci of microscopic mineralization in the cerebellum. Further characterization of VGB-related IME identified both evoked potentials as well as MRI as sensitive noninvasive techniques to diagnose IME in rats and dogs. These studies also were used to support the absence of IME in monkeys and humans. Monkeys were treated with VGB at doses up to 300 mg/kg/d, which provided maximal plasma concentrations of 38 μg/mL, for up to 6 years to characterize possible toxicities; evaluation after 16 months of treatment did not yield conclusive evidence of IME. This dosing and plasma levels were consistent with that of infants and young children at a dosing of 50 mg/kg/d (36).

Additional studies to further characterize VGB-related IME in rodents included a juvenile toxicity study to evaluate the effects of VGB treatment on the physical and behavioral development of rats compared to controls (37). Microscopic evaluation of animals revealed mild vacuolar changes within the neuropil in select brain regions following VGB treatment at 50 mg/kg/d. Most affected brain regions included gray matter in the midbrain tegmentum, substantia nigra, dorsal subiculum, deep cerebellar nuclei, posterior thalamus, basal forebrain, and medulla oblongata. Additional although significantly less abundant vacuoles were also seen in some white matter tracks, including the medial longitudinal fasciculus and the medial forebrain bundle. Although it was not possible to determine which cell type was vacuolated, it was felt that the neuronal cell bodies, blood vessel endothelium, and perivascular astrocytic end processes were not affected. The authors felt that although the morphologic appearance was consistent with IME seen in older rodents, the distribution of involvement was different in the younger animals as it was found predominantly in subcortical gray matter. The behavior and development of these animals were evaluated by a variety of observational and standardized testing; there was no evidence of significant adverse developmental effects of these pathologic findings. Reproductive and ocular development were also assessed and not found to be significantly affected by the pathologic changes; however, the VGB-treated animals receiving higher doses of VGB (15 and 50 mg/kg/d) were found to have significant reductions in food intake and growth.

Subsequently, ultrastructural characterizations of these changes were performed using electron microscopy that showed an evolution of vacuoles, which were found to begin as splits of myelin sheaths along the intraperiod line (38). These initial splits in the myelin sheaths then expanded and evolved into large, fluid-filled, membrane-rich vacuoles. Lesions in the cerebellum were found to appear prior to those in the reticular formation and more rostral brain regions. The distribution of changes appeared to vary with age, species, and possibly timing and duration of treatment, although

the process appeared limited to myelinated nerve fibers or axons. Changes in adult rats were characterized by vacuoles in large white matter regions of the brain; neonatal and juvenile rats instead had lesions in white matter fibers traversing in or near the gray matter.

Following these observations, significant efforts were made to see if VGB treatment–related IME occurred in humans. Studies involved review of data obtained during several VGB clinical trials over a 15-year period of time, including review of effects of VGB treatment on brain MRI and evoked potentials. In addition, surgical brain and autopsy samples of VGB-treated patients were evaluated histopathologically for evidence of IME. In an estimated 350,000 patients' years of VGB exposure (correlating to approximately 175,000 patients treated for 2 years at an average daily dose of 2 g), no definite evidence of VGB-related IME was identified (39).

However, Pearl et al. (40) reported the initial observation of MRI T2 signal abnormalities involving the deep gray nuclei in 3/15 young children treated with VGB. Subsequent reports describe similar findings occurring in 20% to 30% of infants treated with VGB for IS (41–43). The characteristic MRI T2 signal changes seen involve the basal ganglia, thalamus, dentate nucleus, brain stem, and cerebellum. On diffusion-weighted imaging, apparent diffusion coefficient maps also suggested restricted diffusion in these regions. These changes appeared to resolve following drug discontinuation, dosage reduction, and also with continuation of drug. Risk factors for developing these MRI signal changes during VGB therapy are thought to include age (since observed during treatment for IS but not seen in older children or adults) and VGB dose (since changes are more frequently seen in infants on VGB doses of 150 mg/kg/d and higher). There are isolated case reports suggesting extrapyramidal symptoms in rare patients with these MRI findings (44), but further work is required to establish a clear association. It is unclear how these signal changes relate histopathologically to VGB-related IME well characterized in animal models, but they are thought to likely represent similar mechanisms.

Visual Field Defects

VGB treatment is associated with possible development of a VFD, typically characterized by a bilateral, concentric constriction of the peripheral visual fields. First reported in 1997 (45), this VGB-related VFD has now been well characterized by numerous studies providing understanding regarding the pathophysiology of the VFD as well as incidence, prevalence, and functional impact of the VFD as well as most effective methods to diagnose and monitor the VFD (46–49). The VGB-related VFD has been described as typically a slowly progressive bilateral concentric peripheral constriction of visual fields, which many studies have found to be more marked nasally than temporally. Central vision and color vision are spared.

Pathophysiology.

The retina has been identified as the site of injury in VGB-related VFD via nonclinical studies as well as electroretinography (ERG) studies in humans (50). Visual evoked potentials and brain imaging have demonstrated that the optic nerve and central visual pathways are not involved. ERG studies in humans have suggested that the postreceptor cone responses of the inner retina are most affected by VGB treatment, which has been supported by ophthalmoscopic identification of nerve fiber atrophy in some VGB-treated patients and abnormal nerve fiber layer thickness measurements by optical coherence tomography (OCT) (51,52). However, a single postmortem examination of human retina following VGB treatment showed cell loss in all retinal layers (53).

The pathophysiologic mechanisms of these changes and the related VFD are unknown, although several hypotheses have been proposed. One hypothesis suggested that since VGB is more effectively transported into the retina than the brain, the resulting levels of GABA could contribute to the retinal toxicity (54). Subsequent studies have suggested a possible role for aberrant protein kinase C-alpha activity (PKC-alpha) after identifying VGB dose–related changes in translocation of the enzyme in rod bipolar cells as well as a significant decrease in the number of PKC-alpha–labeled rod bipolar cells in VGB-treated animals (55). Most recently, the effects of VGB on taurine levels were investigated given the VFD similarities between VGB treatment and those characterized with taurine deficiency (56). The authors found significant reductions in taurine levels in VGB-treated animals compared to controls as well as in VGB-treated infants. Taurine supplementation led to diminished retinal toxicity in both rats and mice. Human clinical trials are currently underway to explore the possible role of taurine supplementation to reduce the risk for retinal toxicity.

Clinical Features.

The actual prevalence and incidence of VGB-related VFD are difficult to determine due to limited data sets and study design; however, they are thought to be influenced by age of the patient and extent of exposure to VGB (including dose and duration of treatment or cumulative VGB exposure). There is a likely 25% to 50% prevalence of VFD in adults, a 15% prevalence in children, and a range of 15% to 31% prevalence in infants (57). It is believed that the VGB-related VFD most likely occurs with more prolonged drug treatment, although there are limited prospective data. The earliest identification of a VFD in adults is after 9 months of treatment, with a mean time to onset of 4.8 years. The earliest identification of a VFD in children is after 11 months of treatment, with a mean time of onset of 5.5 years. In infants, the earliest onset of a presumed VGB-related retinal abnormal detected by ERG is 3.1 months. There are rare case reports of VGB-related VFD occurring in adults with <6 months of treatment. The literature also has varying estimates of the severity of the VGB-associated VFD, although most agree that it is usually mild and asymptomatic. However, severe visual peripheral field constrictions (defined as <30 degrees of retained temporal field or <60 degrees of binocular field) can occur (“tunnel vision”), and occur in 2% to 40% of patients. Although it is possible that the VFD can progress, it typically remains stable and may improve, although not normalize following drug discontinuation. Progression of the VFD following drug discontinuation cannot be ruled out, but available evidence suggests that it is unlikely for this to occur.

Clinical Assessment.

Standard methods for assessing visual fields in adults and older children include Goldmann kinetic perimetry and Humphrey’s static automated perimetry. Both are sensitive and specific enough to establish baseline visual field function and to monitor for possible treatment-related effects on peripheral function. Kinetic perimetry is less reliable in children <9 years of age and in the neurologically impaired population.

ERG is an electrophysiologic measurement of retinal function that can also be used to assess for possible VFD, especially in infants, young children, and others not able to cooperate with visual perimetry testing. Testing often requires sedation or anesthesia in infants, young children, and impaired individuals, which dramatically limits access. The 30-Hz flicker response component of the ERG is thought to be the most predictive of the presence and degree of severity of VGB-induced VFD (58,59). Other measures, namely b-cone amplitude, are also thought to be measures of VGB toxicity.

However, the exact relationship between these ERG findings in infants and subsequent visual field abnormalities has not firmly been established.

OCT is a recently developed technology that shows great promise for monitoring for possible VGB-induced VFD, although further studies are needed to better characterize its sensitivity and specificity.

Teratogenicity

Limited data are available on the teratogenic effects of VGB therapy in animals, except for a possible increased incidence of cleft palate in rabbits receiving a high dose, and possible mandibular and maxillary hypoplasia, arched palate, cleft palate, limb defects, and exophthalmia in the TO mouse after receiving high doses (300 to 450 mg/kg) (60). Similar to other AEDs, VGB has a class warning against use in pregnancy due to inadequate evidence of possible human teratogenic effects.

CLINICAL USE

Administration

The daily adult dose of VGB used in most clinical trials and reports is between 2 and 3 g/day, with 3 g accepted as an optimal adult dose. Higher doses can improve efficacy, such as the U.S. double-blind study that employed 6 g/day; however, higher doses have also been shown to be associated with increased side effects (21). If clinical response is not achieved at a dose of 3 g/day, consideration should be given to discontinuation of the medication, particularly given the risk of VGB-related VFD. In infants and children, dosing of VGB is similar to other medications, and calculated on a mg/kg/day basis. VGB is frequently titrated up to 100 to 150 mg/day in b.i.d. dosing as needed for seizure control. Although higher doses may be effective in some infants being treated for IS, caution should be used given the probable increased risk both of VGB-related VFD as well as VGB-related MRI T2 signal changes.

Titration

In order to minimize side effects, particularly psychiatric or behavioral difficulties, gradual titration of the medication is suggested for both adults and infants and children.

Discontinuation

Efficacy of VGB is usually seen within the first 3 months of treatment, earlier for IS. Should the medication not prove effective or tolerated, it should be discontinued. VGB should be tapered slowly to minimize possibility of rebound seizures, including status epilepticus, and of significant behavioral abnormalities. Discontinuing VGB over a period of 1 to 2 months is usually well tolerated.

The optimal duration of VGB treatment if effective is not clear, particularly given the possibility that VGB-related VFD increases with cumulative VGB exposure. Typically, infants being treated for IS have continued on the medication for 1 year; currently, the long-term efficacy of shorter duration treatment is being evaluated.

Laboratory Monitoring

Although assays to measure VGB levels in blood and CSF are available, they are not felt to be clinically useful as blood level has not been shown to correlate with clinical effectiveness. Routine blood monitoring of blood counts and hepatic enzyme levels are not recommended as VGB has not been shown to have a significant effect on these values. Due to limited drug–drug interactions with other AEDs, routine AED levels are also not recommended unless clinically indicated.

Clinical Monitoring

Due to the risk of VGB-related VFD, clinical monitoring of visual function is important. In adults, visual field perimetry should ideally be obtained at baseline and subsequently at regular intervals throughout the duration of treatment. Should abnormalities appear, consideration should be given to discontinue VGB treatment based on a risk–benefit assessment with the patient. In infants, young children, and those who are neurologically impaired and not able to cooperate with perimetry, visual fields should be assessed at baseline by confrontational testing. Repeat confrontational testing should be performed at 3-month intervals for the duration of treatment. Ideally, infants should also be followed by experienced pediatric ophthalmologists and by ERG, although access to these services is not always readily available, and should not delay treatment. Should abnormalities appear, consideration of discontinuation of VGB should also be considered, with careful risk–benefit assessment of continued treatment, especially in the context of VGB treatment for IS. In the United States, all patients are mandated to enter a patient registry as a requirement of FDA approval that established a Risk Evaluation and Mitigation Strategy to reduce the risk of vision problems and assess risk–benefit analysis for different populations. As part of this registry, ophthalmologic evaluation is required at 3-month intervals throughout the duration of VGB treatment in infants and adults due to the risks of retinal toxicity.

CONCLUSION

VGB has been shown to be an effective AED in a wide variety of seizure types affecting both adults and children, particularly refractory CPS and IS. It has a unique mechanism of action from other available AEDs and is generally well tolerated. However, VGB-related VFD is a possible and possibly significant side effect of the medication. Therefore, patients started on VGB should be closely monitored for visual field changes. VGB appears to be particularly effective in the treatment of IS, a catastrophic pediatric epilepsy syndrome with limited effective treatments available. In this setting, the use of VGB should be strongly considered, as the risks of the impact of uncontrolled IS on subsequent neurocognitive development may outweigh the risks of possible VGB-related VFD. The MRI T2 signal changes seen in infants treated with VGB are another possible risk of the medication. However, no significant clinical changes have been seen with these changes, and further studies are needed to understand any possible significance that could affect continuation of VGB treatment.

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CHAPTER 66 Zonisamide

TIMOTHY E. WELTY

Zonisamide was first synthesized in Japan. In the early 1980s, clinical trials of zonisamide were initiated in the United States. Due to reports of nephrolithiasis in patients receiving active drug, further development in the United States was halted. Development of zonisamide continued in Japan, and the drug was approved for marketing in Japan in 1989. Additional studies in Europe and the United States were initiated with approval for marketing granted in the United States in 2000. Zonisamide is an antiepileptic drug (AED) that appears to have broad activity in various seizure types and epilepsy syndromes.

CHEMISTRY

Zonisamide is classified as a sulfonamide AED that is a 1,2-benzisoxazole derivative and is the first compound from this group of chemicals to be developed as an AED. It is unrelated chemically to other AEDs (Fig. 66.1). It is moderately soluble in water (0.8 mg/mL) and has a pK_a of 10.2. Zonisamide is a white powder and has a molecular weight of 212.23.

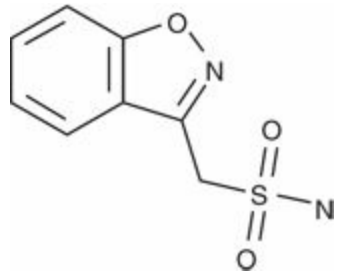

Figure 66.1. Zonisamide.

MECHANISM OF ACTION

There are several pharmacologic effects of zonisamide that may be responsible for its activity as an AED. Results from several studies demonstrate the most likely mechanism of action for zonisamide to be through blockade of T-type calcium channels, inhibition of slow sodium channels, and possibly inhibition of glutamate release (1–5). Zonisamide differs from ethosuximide in that zonisamide does not inhibit G protein–activated inwardly rectifying K^+ channels (6). Zonisamide does have activity as a carbonic anhydrase inhibitor, but this is not responsible for its antiepileptic activity (7). In animal models, zonisamide demonstrates broad spectrum as an AED (8–11). Beside its antiepileptic activity, zonisamide has some effect as a neuroprotective agent in ischemia (12,13). Additionally, other pharmacologic activities may make zonisamide useful in the treatment of Parkinson disease and essential tremor (14,15).

PHARMACOKINETICS

Absorption

Zonisamide is rapidly absorbed following oral administration with maximum concentrations achieved within 2 to 5 hours (16). The absolute bioavailability in humans is unknown, due to the lack of a parenteral product. Nagatomi et al. (17) measured the absolute bioavailability of orally administered zonisamide at 81% in rats. In the same study, the bioavailability of zonisamide in a rectal preparation was 96%. Zonisamide is metabolized by cytochrome P450 3A4 (CYP 3A4) (18). Intestinal CYP 3A4 may account for decreased bioavailability of the oral preparation.

Distribution and Protein Binding

Like many sulfonamide drugs, zonisamide has a dose-dependent decrease in volume of distribution (V_d/F) (19). The volume of distribution for a 200-mg dose is 1.8 L/kg and for an 800-mg dose is 1.2 L/kg. Saturable binding to erythrocytes, especially to intracellular carbonic anhydrase, is the most likely explanation for this phenomenon (20–22). Additionally, 40% to 60% of zonisamide is bound to plasma proteins, especially albumin (22,23).

Therefore, zonisamide is concentrated in the erythrocytes compared to plasma. With saturable binding to erythrocytes, the whole blood zonisamide concentration is nonlinear as the dosage increases. However, the plasma zonisamide concentration is linear with increased doses (16). Care must be taken in laboratory analysis and interpretation of zonisamide concentrations. Results should be identified as coming from whole blood or plasma.

Metabolism and Clearance

Following oral administration, the half-life ($t_{1/2}$) of zonisamide is estimated at 50 to 69 hours (16,24). Apparent oral clearance (Cl/F) following single and repeated oral doses is 0.6 to 0.71 L/hour (24). Less than 30% of zonisamide is eliminated unchanged in the urine, and most of the drug undergoes extensive hepatic metabolism (25). The relatively long $t_{1/2}$ and slow clearance allow for once-daily dosing of zonisamide.

Early studies of the pharmacokinetics of zonisamide suggested that concentrations increased in a nonlinear relationship to doses (19,26). Following an 800-mg dose, zonisamide clearance was 22% lower than clearance estimates following 200- and 400-mg doses. Clearance estimates at steady state with doses ranging from 400 to 1200 mg daily were 40% lower than those seen following a single 400-mg dose (16,27). One study showed steady-state zonisamide concentrations to be higher than predicted from single-dose data, but steady-state plasma concentrations did increase in a linear relationship to daily dose (28). These observations were considered to be related to the saturable, preferential binding of zonisamide to erythrocytes. However, an analysis of zonisamide doses and concentrations in children using a nonlinear mixed- effects model and population pharmacokinetic methodology demonstrated dose-dependent, Michaelis–Menten pharmacokinetics of zonisamide with a mean V_{max} of 27.6 mg/d/kg and K_m of 45.9 µg/mL (29). Because the V_{max} is well above the typical range of daily zonisamide doses, it is unlikely that the nonlinear nature of zonisamide clearance will profoundly impact clinical practice.

The major metabolite of zonisamide is 2-sulfamoylacetylphenol (SMAP), formed under anaerobic conditions by liver microsomal enzymes (18,30,31). The formation of SMAP appears to be primarily through cytochrome P450 3A4 (CYP 3A4) (18,30). In these studies, metabolism of zonisamide to SMAP was inhibited by cimetidine and ketoconazole, known CYP 3A4 inhibitors. Zonisamide is metabolized to a much lesser extent by CYP 2C19 and CYP 3A5 (32). Studies of the effect of genetic polymorphisms on zonisamide metabolism have shown a 16% to 30% reduction in clearance in individuals who were CYP 2C19 heterozygous extensive metabolizers or homozygous poor metabolizers compared to homozygous extensive metabolizers (33). The clinical implications of this observation are unclear.

Serum Concentrations and Doses

The manufacturer's recommended dose for adults is 300 to 400 mg daily, but doses of 600 mg daily have been used in clinical trials (34). Doses above 400 mg have not consistently been associated with increased efficacy. The recommended doses of zonisamide are typically associated with steady-state plasma concentrations of 10 to 38 µg/mL (24,29,35). However, a relationship between concentration and response has not been established. Other investigators have suggested that concentrations >30 µg/mL are associated with increased adverse effects (19,28). Therefore, it may be advisable to maintain zonisamide concentrations <30 to 40 µg/mL. The pharmacokinetics and dosing of zonisamide are summarized in Table 66.1.

Table 66.1 Summary of Zonisamide Pharmacokinetics and Dosing

Parameter	Value
Oral bioavailability	81%[a]
Volume of distribution (V_d/F)	1.2–1.8 L/kg[b]
Protein binding	40%–60%[c]
Half-life	50–69 h
Clearance (Cl/*F*)	0.6–0.71 L/h
Usual plasma concentrations	10–30 µg/mL[d]
Recommended dose	200–400 mg/d[e]

[a]Based upon animal data.

[b]Volume of distribution is inversely related to dose, due to saturable binding to erythrocytes.

[c]Additionally, zonisamide is highly and preferentially bound to erythrocytes.

[d]These are typical concentrations observed with usual doses. A relationship between concentrations and response has not been established.

[e]Higher doses have been used in clinical trials.

Special Populations

Pediatrics

No formal pharmacokinetic studies have been done in children. In a study of zonisamide for infantile spasms by Suzuki et al. (36), daily doses of 4 to 5 mg/kg yielded plasma concentrations of 5.2 to 16.3 µg/mL. Additional work by this group substantiated these findings with zonisamide doses of 4 to 12 mg/kg/d producing plasma concentrations of 5.2 to 30 µg/mL (37). Table 66.2 summarizes typical

mean plasma concentrations related to dose and age. A comparison of pharmacokinetic parameters derived from population data in children and adults shows a similar volume of distribution but more rapid clearance of zonisamide in children (29,39). Thus, children appear to require larger doses of zonisamide, based on body weight, to achieve plasma concentration similar to those seen in adults (40).

Table 66.2 Mean Zonisamide Plasma Concentrations Related to Age and Daily Dose (38)

Age (years)	Mean daily dose (mg/kg)	Mean plasma concentration (µg/mL)
>16	5.9	20.0
7–15	7.1	20.7
2–6	8.8	19.9
≤1	8.6	19.6

Three case reports have provided some documentation regarding transfer of zonisamide across the placenta and into breast milk. Kawada et al. (41) measured zonisamide concentrations in umbilical cord blood, infant blood, and maternal blood of two infants born to mothers taking zonisamide for epilepsy. In these infants, zonisamide concentrations were 92% of that in maternal blood. Kawada et al. also measured zonisamide concentrations in the breast milk of these mothers, showing these concentrations to be 41% to 57% of maternal plasma concentrations. In a separate case, evaluating zonisamide concentrations in breast milk to 30 days postpartum, Shimoyama et al. (42) observed breast milk concentrations to range from 81% to 100% of maternal plasma concentrations. It appears that zonisamide readily crosses the placenta. Zonisamide also appears in breast milk at concentrations similar to maternal plasma concentrations. No clinically important adverse effects related to zonisamide were documented in these case reports.

Pregnancy

A study of clearance of multiple AED, including zonisamide, in pregnant women demonstrated that changes in clearance are highly variable between women and between pregnancies. In general, doses increased during pregnancy. It is recommended that serum concentrations of zonisamide be closely monitored during pregnancy and appropriate dosage adjustments made (43).

Renal Failure

A single-dose study of zonisamide in individuals with moderate renal failure (creatinine clearance >0.6 L/hour) did not demonstrate any difference in pharmacokinetic parameters compared to normal individuals (44). Studies in severe renal dysfunction and multiple-dose studies in renal failure have not been reported.

DRUG INTERACTIONS

Because zonisamide is primarily metabolized through CYP 3A4 and to a lesser extent by CYP 2C19, it is potentially prone to drug–drug interactions involving these enzyme systems. Several interactions have been studied in animals and in humans (Table 66.3). However, the exact clinical implications of

these interactions are poorly documented.

Table 66.3 Drug Interactions with Zonisamide

Reduce zonisamide metabolism	Increase zonisamide metabolism	Variable effect on zonisamide metabolism
Cyclosporin A	Phenytoin	Carbamazepine
Ketoconazole	Phenobarbital	
Dihydroergotamine	Primidone	
Triazolam		
Diazepam		
Erythromycin		

Influence of Other Drugs on Zonisamide

Using in vitro studies of the CYP 3A system, Nakasa et al. (32) showed that cyclosporin A, ketoconazole, dihydroergotamine, and triazolam profoundly inhibit zonisamide metabolism. These drugs reduced zonisamide metabolism by 85% to 95% compared to control. Other known inhibitors of CYP 3A, diazepam, terfenadine, erythromycin, and lidocaine did not produce a marked reduction in metabolism. The percent reduction in metabolism with these agents ranged from 35% to 45%. Clinical correlates to these findings have not been documented, so recommendations for dosage adjustments in patient care are not available. However, patients receiving known inhibitors of CYP 3A may require lower doses of zonisamide to reduce the risk of adverse events.

Inducers of CYP 3A have been shown to increase the metabolism of zonisamide (32). Phenytoin and carbamazepine have been shown to induce zonisamide metabolism, with phenytoin possibly having a greater influence than did carbamazepine (45,46). In a study of 12 patients receiving phenytoin or carbamazepine concomitantly with zonisamide, the mean oral clearance (Cl/F) of zonisamide was 33.9 mL/h/kg with phenytoin and 20.6 mL/h/kg with carbamazepine (45). However, some researchers have observed inhibition of zonisamide metabolism by carbamazepine (32). Other known inducers of hepatic metabolism, especially phenobarbital and primidone, can also increase the metabolism of zonisamide (16). When zonisamide is used in combination with known CYP 3A inducers, doses of zonisamide may need to be increased to achieve seizure control. In the case of carbamazepine, care must be taken to determine if induction or inhibition is predominant in a given patient and zonisamide doses adjusted accordingly.

Zonisamide Influence on Other Drugs

Studies with zonisamide have shown that it does not induce or inhibit hepatic enzymes (47,48). A study of zonisamide's effects on ethinyl estradiol–norethindrone oral contraceptives demonstrated no alteration of hormonal effect or loss of contraceptive efficacy (49). A survey of interactions between zonisamide and cancer chemotherapy agents demonstrated no known interactions (50). It appears that zonisamide does not cause clinically significant alteration of the pharmacokinetic disposition of other drugs.

Drug–Food Interactions with Zonisamide

As a substrate for CYP 3A4, zonisamide is a candidate for drug–food interactions. Within the intestinal wall, are high concentrations of CYP 3A4 that can metabolize drugs before they are absorbed into systemic circulation. Several foods, especially grapefruit juice, lime juice, and Seville orange juice, contain substances that inhibit the activity of intestinal CYP 3A4. When these foods are eaten with drugs that are metabolized by CYP 3A4, there is increased absorption of the drug and a potential for adverse effects. Although this potential interaction with zonisamide has not been documented, it should be of concern. In a study of rectal administration (a route that bypasses intestinal CYP 3A4) of zonisamide, Nagatomi et al. (17) consistently demonstrated increased bioavailability and absorption of zonisamide.

CLINICAL TRIALS

Clinical studies of zonisamide have evaluated its use in several different types of epilepsy and epilepsy syndromes. Additionally, zonisamide has been used extensively in Japan and has gained increasing use in the remainder of the world. Despite this history, there have been no direct comparisons of zonisamide to other AEDs in specific seizure types. The best published comparison has been in two meta-analyses of clinical trials of other newer AEDs, including zonisamide (51,52).

Focal-Onset Epilepsies/Partial Seizures

Clinical studies of zonisamide have evaluated its use in several different types of epilepsy and epilepsy syndromes. The best published comparisons are in meta-analyses of clinical trials of other newer AEDs, including zonisamide (51–54). In the first study, Marson et al. (51) evaluated the odds ratio of zonisamide producing a ≥50% reduction in seizure frequency compared to placebo. Combining data from two clinical trials, zonisamide was shown to be significantly better than was placebo in controlling seizures. In a second meta-analysis, Marson et al. (52) identified the five most common adverse effects patients on zonisamide experienced. In a study designed to compare intention to treat to last observation carried forward methodology, zonisamide had a 3% seizure-free rate compared to 0.8%, 2.6%, 7.1%, and 1.4% for lamotrigine, oxcarbazepine, levetiracetam, and pregabalin, respectively (53). A Cochrane review of zonisamide for refractory partial epilepsy concluded that it is effective as adjunctive therapy in patients who have failed other pharmacotherapy (54).

Several clinical trials of zonisamide for partial seizures have been published (27,28,55–59). Each of these studies demonstrated that zonisamide was significantly more effective than was placebo in reducing seizures. For adults, a reduction in seizures occurs with doses ranging from 100 to 500 mg/day, and increasing doses in this range increases the number of patients who respond.

A summary of Japanese studies using zonisamide in pediatric patients with partial seizures estimated that 34% of children responded to zonisamide (39). Guerrini et al. (60) reported a randomized clinical trial of adjunctive zonisamide in 207 children, aged 6 to 17 years. Responder rates were 50% for zonisamide compared to 31% for placebo, a statistically significant difference. There was no difference in the incidence of adverse events between zonisamide and placebo treatments. Decreased appetite, weight loss, somnolence, vomiting, and diarrhea were more frequently associated with zonisamide. In a safety study of zonisamide in 107 patients, there was a significant reduction in all seizure types, with 7 patients discontinuing therapy due to serious adverse events (61).

Generalized Epilepsies

A small clinical trial suggested that zonisamide decreases cortical excitability in patients with idiopathic generalize epilepsies (62). Henry et al. (63) report two cases of progressive myoclonic epilepsy where zonisamide use was associated with reduced seizure frequency and improved functioning. A case series of patients with juvenile myoclonic epilepsy indicated that zonisamide was well tolerated and associated with reduced seizures compared to valproate (64). A similar retrospective study of juvenile myoclonic epilepsy indicated that zonisamide was easily titrated and had a rapid onset of action (65).

More extensive evaluation of zonisamide in primary generalized epilepsies has been done in children. In children with newly diagnosed infantile spasms, Suzuki et al. (36) used 3 to 10 mg/kg/d of zonisamide in an open-label trial. Of the children who started on zonisamide, four had complete seizure control and cessation of hypsarrhythmia with doses of 4 to 5 mg/kg/d. Kishi et al. (66) reported their experience with zonisamide in children with hypsarrhythmia. In three patients, zonisamide resulted in elimination of hypsarrhythmia and seizures. A larger study in 54 patients, newly diagnosed with West syndrome, was done (37). Zonisamide doses ranged from 4 to 14 mg/kg/d with a mean dose and serum concentration of 7.2 mg/kg/d and 15.3 μg/mL, respectively. Eleven infants had complete elimination of seizures and hypsarrhythmia, 7 children had >50% reduction in seizure frequency, and 14 with cryptogenic West syndrome responded. Of those who the authors categorized as not responding, 4 were seizure free transiently, 6 had a <50% reduction in seizure frequency, and 33 had no change in seizure frequency. The 11 individuals in this study who had elimination of seizures and hypsarrhythmia were entered into a long-term follow-up study, evaluating their response out to 79 months (mean duration of 53 months) (67). Seven of the infants who had an initial cessation of seizures continued to be seizure free. Presence of epileptiform activity on the EEG at the end of 3 weeks was predictive of recurrence of seizures. Yanagaki et al. (68) studied the use of zonisamide starting at 10 mg/kg/d, demonstrating this scheme was well tolerated in children with West syndrome.

Although case series reports and open-label studies suggest that zonisamide may be effective in patients with generalized epilepsies, it has not been well studied in this patient population. The most extensive information on zonisamide use in generalized epilepsies is in children with West syndrome and suggests that zonisamide may be an alternative treatment.

Monotherapy

Few clinical trials have evaluated the use of zonisamide in monotherapy for the treatment of epilepsy. The most extensive studies have been in children with West syndrome (36,67). Additionally, Kumagai et al. (69) studied zonisamide as a single agent in 44 children with epilepsy. In this open-label trial, 30 children with various seizure types became seizure free, and 6 children had to discontinue the drug due to adverse effects. A systematic review of adjunctive and monotherapy for partial seizures in children concluded that there was insufficient evidence to support zonisamide monotherapy (70).

The only published study of zonisamide monotherapy in adults was done by Wilensky et al. (28). Eight adults with partial seizures and receiving phenytoin were randomized to carbamazepine or zonisamide and then crossed over in an open-label design. Two subjects had improved seizure control with zonisamide compared to carbamazepine, and a third individual had a similar response but had to discontinue zonisamide due to the development of Stevens–Johnson syndrome.

The limited available data on zonisamide monotherapy treatment indicate that zonisamide may be effective as a single agent for epilepsy. However, larger, double-blind clinical trials must be done before zonisamide monotherapy can be recommended.

Nonepilepsy Indications

Preliminary clinical trials of zonisamide in disorders other than epilepsy indicate that it may be useful for other indications. One study of zonisamide in patients with mania and acute psychotic conditions indicated that 71% responded at least moderately to treatment (71). In an open-label trial of zonisamide in 35 patients with neuropathic pain, mean pain scores showed little or no improvement after 8 weeks of therapy (72). A trial in nine patients with Parkinson disease demonstrated that seven of the nine patients had improvement in their symptoms, especially wearing-off phenomenon, when zonisamide was added to their other medications (73). Preliminary data suggest that zonisamide is at least as effective as is propranolol in patients with head tremor or essential tremor (14,74).

ADVERSE EFFECTS

Common Adverse Effects

In the initial and major clinical trials of zonisamide as adjunctive therapy, several adverse effects were commonly reported (Table 66.4) (27,28,55–57). Schmidt et al. (55) reported the statistical evaluation of adverse events reported in their trial. Dizziness, somnolence, anorexia, abnormal thinking, ataxia, and confusion were more common with zonisamide compared to placebo. A meta-analysis showed that patients on zonisamide were more likely to experience anorexia, ataxia, dizziness, and fatigue compared to patients receiving placebo (52). These adverse events and their frequency are similar to those reported with other new AEDs.

Table 66.4 Most Frequently Reported Adverse Effects in Clinical Trials

Adverse event	Percent reporting range
Fatigue	3.3%–22.5%
Ataxia	3.3%–11.3%
Nausea/vomiting	4.2%–15%
Headache	5%–15.9%
Somnolence	5.2%–18.3%
Rhinitis	5.2%–14.4%
Confusion	5.6%–10.6%
Anorexia	6.7%–15%
Dizziness	6.9%–16.9%
Nervousness	8.8%–9.9%
Thinking abnormal	9.7%–11.3%

Adverse events in children appear to be similar to those in adults. The adverse events that are reported in >10% of children on zonisamide in combination with other AEDs are somnolence, anorexia, ataxia, fatigue, dizziness, cognitive impairment, irritability, and exanthema (39). Monotherapy of zonisamide in pediatrics has been more extensively studied than in adults. When zonisamide is used by itself in children, the only adverse effect that occurs in >10% of individuals is

somnolence (39). Thus, common adverse events, especially in children, may be limited by decreasing or eliminating other AEDs.

Zonisamide appears to produce a mild to moderate weight loss. A post hoc analysis of data from the major clinical trials demonstrated that significantly more patients on zonisamide (21.6%) lost >5 pounds compared to patients on placebo (57). A retrospective analysis of patients from European and American clinical trials (55–57) showed that 28.9% of individuals receiving zonisamide lost >5 pounds compared to 8.4% receiving placebo, a significant difference (75). The mean weight loss for all patients on zonisamide was 4.3 pounds. A double-blind, placebo-controlled study of 60 obese nonepileptic patients demonstrated a mean weight loss of 9.2 kg with zonisamide compared to a mean weight loss of 1.5 kg in those receiving placebo (76). A second study compared diet alone to diet and zonisamide in obese women (77). Women who took zonisamide had an additional 5 pounds weight loss compared to those only on a diet. Patients who are obese or have experienced weight gain associated with the use of other AEDs may benefit from the addition of zonisamide to their regimen.

Rare Adverse Effects

Early in the clinical trials of zonisamide, the formation of renal calculi was observed in some patients (56). Four patients of the 113 enrolled in this study had kidney stones form during the study. Kubota et al. (78) reported three cases of nephrolithiasis in patients receiving zonisamide, and Miyamoto et al. (79) reported the case of a 10-year-old girl with a kidney stone after starting zonisamide. Zonisamide is an extremely weak carbonic anhydrase inhibitor, but this does not fully explain the incidence of renal calculi (78). All published reports of renal calculi with zonisamide are in individuals who were taking other AEDs. Zonisamide is not contraindicated with patients with a history of kidney stones, but care should be taken when using zonisamide in these patients. Prudent management of patients on zonisamide should include adequate hydration to maintain good urine flow.

Allergic reactions to zonisamide are rare but did occur in the clinical trials. Rash was the predominant allergic type reaction reported, with at least four individuals (one with Stevens–Johnson syndrome) in these studies being discontinued due to dermatologic reactions. A mild, relative neutropenia was also observed in several individuals. A study by Hirsch et al. (80) demonstrates that there is no cross-reactivity with other AEDs. Because zonisamide is chemically related to sulfonamide drugs, caution should be taken when using zonisamide in patients who note a prior allergic reaction to these agents. The exact cross-reactivity in patients known to be allergic to sulfonamides has not been determined.

Oligohidrosis can occur with zonisamide and is marked by decreased sweating and hyperthermia. Postmarketing surveillance indicates that oligohidrosis occurs primarily in children, with all reported cases in individuals ≤18 years of age. The estimated rate of incidence is approximately 1 cases per 10,000 patient-years (81). When zonisamide is used in children, parents should be instructed to carefully monitor for decreased sweating and increased body temperature. Children on zonisamide should not be exposed for prolonged periods of time to extreme heat.

As with other AEDs that possess carbonic anhydrase inhibition activity, zonisamide can produce a metabolic acidosis. Individuals with impaired pulmonary or renal function are especially at risk for this side effect, and serum electrolytes should be monitored.

The cognitive effects of zonisamide were studied early in its development. Berent et al. (82) studied 11 patients who were on stable regimens of two to three other AEDs. When plasma concentrations of zonisamide exceeded 30 μg/mL, the acquisition and consolidation of new

information, especially verbal learning, were impaired. Miyamoto et al. (83) reviewed 74 reported cases of psychosis associated with zonisamide use, and only 14 of these cases exhibited symptoms of true psychosis. There were significantly more men than women with psychosis, and this group was younger than the general population of patients with epilepsy. Hirai et al. (84) reported on 27 children in a prospective clinical trial of zonisamide monotherapy, and 2 displayed behavioral disturbances. As with other AEDs, zonisamide may alter cognition and behavior in some individuals. It is difficult to truly assess the incidence of these effects, because none of the reports accounted for the number of individuals taking zonisamide. Additionally, most of the reports of cognitive or behavioral problems were in patients taking multiple AEDs.

Few data are available on the teratogenic effects of zonisamide. Kondo et al. (85) surveyed 381 hospitals in Japan during June 1989 regarding pregnancies in women using AEDs. Only two women exposed to zonisamide during pregnancy bore children with major malformations. In both of these cases, multiple AEDs were taken by the mothers. The authors conclude that zonisamide is associated with no greater risk of teratogenicity than are other AEDs.

SUMMARY

Clinical studies have proven the effectiveness of zonisamide as adjunctive therapy for partial seizures. Zonisamide has been used in a variety of age groups, seizure types, and as monotherapy. However, clinical study data outside of the primary indication are lacking. Current evidence suggests that zonisamide has broad utility as an AED in children and adults. The adverse effect and pharmacokinetic profile of zonisamide are favorable with few severe adverse effects reported and a long half-life that allows once-daily dosing.

Zonisamide should be considered an alternative adjunctive agent when typical AEDs have failed in treating partial seizures. It may also be useful in patients with other seizure types and in monotherapy. Individuals who are concerned about weight gain or desire to lose weight may benefit from zonisamide therapy. Care should be exercised when using zonisamide in patients with a history of renal calculi and true sulfa allergies. However, these items do not constitute absolute contraindications to zonisamide use. Zonisamide has been used safely and effectively in pediatrics, but children need to be monitored carefully for oligohidrosis.

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CHAPTER 67 ADRENOCORTICOTROPIN AND STEROIDS

CRISTINA GO AND O. CARTER SNEAD III

HISTORICAL BACKGROUND

In 1950, Klein and Livingston (1) reported on the efficacy of adrenocorticotropin (ACTH) therapy for childhood seizures after observing its benefits in various types of intractable generalized seizures. Eight years later, Sorel and Dusaucy-Bauloye (2) reported control of seizures and an improvement in electroencephalographic (EEG) findings for children with infantile spasms treated with the drug. The benefit of oral steroids in this condition was established soon after that of ACTH (3–7), and since then, both drugs have been used in a number of other epilepsy syndromes, including Ohtahara syndrome, Lennox–Gastaut syndrome, other myoclonic epilepsies, and Landau–Kleffner syndrome.

ACTH and steroid therapy appear to have a unique beneficial effect upon epilepsy syndromes that have an age-related onset during a critical period of brain development that can cause a characteristic regression or plateau of acquired developmental milestones at seizure onset and subsequent long-term cognitive impairment. For some of these patients, ACTH or steroids, or both, can improve the short-term developmental trajectory and the long-term prognosis for language and cognitive development, in addition to the beneficial effects on the convulsive state (8–13).

INFANTILE SPASMS

General Considerations

In 1841, Dr. William West (14) wrote a letter to Lancet in which he described an unusual condition affecting his 4-month-old son, James, as a peculiar form of infantile convulsions. He went on to describe a reduction in developmental trajectory in his child who was normal prior to the onset of the event. This letter, now over 160 years old, remains the most eloquent clinical description of what we now know as infantile spasms.

In 1952, Gibbs and Gibbs (15) described the classical interictal EEG pattern associated with this condition, called hypsarrhythmia, which is characterized by high-voltage chaotic slowing with multifocal spikes and marked asynchrony. The term West syndrome refers to an age-related triad of epileptic spasms, developmental regression, and hypsarrhythmia on EEG. Although this term has been used synonymously with infantile spasms, the latter should refer strictly to the massive myoclonus because infantile spasms may occur in the absence of either mental retardation or the hypsarrhythmia EEG pattern.

Published studies on the efficacy of ACTH and corticosteroids in infantile spasms display considerable variability in design, complicating the establishment of evidence-based recommendations for optimal treatment (16–18). There is general consensus on a few observations,

however. The cumulative spontaneous remission rate over the first 12 months of seizures is about 25% (19). Seizures are almost always intractable to treatment with traditional anticonvulsant drugs. ACTH or oral steroid therapy should significantly reduce seizures in 50% to 75% of patients, but ACTH protocols, particularly those employing high-dose, long-acting synthetic formulations, are associated with a significantly high rate of side effects (20,21). The best chance for a treatment response is probably between 4 and 12 months of age in children who are neurologically normal when spasms begin that have no demonstrable cause (11,12,20,22–24). The ultimate prognosis is dismal for most patients and depends heavily upon the cause of the spasms, preexisting neurologic and developmental status, the presence or absence of other seizures concomitant with the spasms, and the patient's age at seizure onset (8,12,20,25–28).

The controversies surrounding the management of infantile spasms continue to outnumber the areas of agreement. Which is the most effective therapy: ACTH or steroids; other medical treatment including the ketogenic diet; other anticonvulsants such as vigabatrin (VGB), valproic acid, benzodiazepines, topiramate, zonisamide, or levetiracetam; pyridoxine; or some or all of these in combination? What is the impact of treatment with ACTH compared with other forms of steroids, the ketogenic diet, or anticonvulsants on the long-term outcome in recurrence of spasms, evolution into other forms of intractable epilepsy, and cognitive or behavioral function? Does treatment change the outcome for a patient with preexisting impairment in cognition and a structurally abnormal brain? What is the optimal dosage of these drugs, and how long should the treatment last? Does the ultimate outcome depend on timing of treatment or dose of steroid employed? Does the efficacy of ACTH depend on the formulation (natural vs. synthetic, sustained release vs. short acting)? More than 160 years after this syndrome was described by Dr. West, most of these questions remain unanswered.

Mechanisms of Action

The pathogenesis of infantile spasms and therefore the mechanisms of action of ACTH and steroids in this condition are unknown, principally because of a paucity of valid animal models for this disorder (29–34). However, this void has begun to disappear with the recent description of several animal models that bear phenotypic similarity to one or more critical features of infantile spasms.

Infantile spasms are epileptic syndrome that begins in infancy within a narrow range of ages, with initial onset mostly between 3 and 7 months of life in more than 50% of cases. A number of abnormalities have been causally linked (symptomatic cases) to infantile spasms including an ever-increasing number of bewildering metabolic and genetic etiologies (35); however, infantile spasms may also occur without apparent cause (idiopathic and cryptogenic cases). The effect of ACTH and corticosteroids is frequently all or nothing, and the steroid-induced seizure-free state is often sustainable even after drug withdrawal. These observations support the theory that the developing brain experiences a significant stress response to various etiologies that results in this age-dependent epileptic encephalopathy. Within this very narrow developmental window, ACTH and steroids may be able to reset the deranged homeostatic mechanisms of the brain, thereby reducing the convulsive tendency and improving the developmental trajectory.

The Brain–Adrenal Axis

Evidence suggests that the effects of ACTH on infantile spasms may be independent of steroidogenesis (36,37). Efficacy studies have demonstrated the superiority of ACTH to

corticosteroids in treating infantile spasms and its efficacy in adrenal-suppressed patients (38–41). Substantial physiologic and pharmacologic data indicate that ACTH has direct effects on brain function: increasing dendrite outsprouting in immature animals (42); stimulating myelination (43); regulating the synthesis, release, uptake, and metabolism of dopamine, norepinephrine, acetylcholine, serotonin, and γ-aminobutyric acid; regulating the binding at glutamatergic, serotonergic, muscarinic type 1, opiate, and dopaminergic receptors (44,45); and altering neuronal membrane lipid fluidity, permeability, and signal transduction (42). These neurobiologic effects can influence synaptic function and neurotransmission and may reside in fragments of the peptide devoid of corticotropic activity.

Baram et al. (40,46,47) proposed the important role of corticotropin-releasing hormone (CRH) in the pathogenesis of infantile spasms as well as its response to ACTH. The hypothesis is that diverse etiologies resulting in infantile spasms cause activation of the brain's stress response, leading to excessive release of CRH. CRH is an excitatory neuromodulator, with potent age-specific convulsant effects demonstrated in animal models. In immature brains, CRH can cause neuronal hyperexcitability, seizures, and neuronal death in the amygdala and hippocampus (48,49). High brain CRH levels can decrease ACTH levels due to desensitization of CRH receptors after chronic activation, which then decreases ACTH release. Low ACTH levels have been found in the cerebrospinal fluid of children with infantile spasms (48,50).

ACTH has a down-regulatory effect on CRH by reducing CRH gene expression in specific brain regions, an effect demonstrated in the absence of adrenal steroids and achieved with the use of only the 4 to 10 fragment of ACTH, which does not release adrenal steroids (40). Melanocortin receptor antagonists blocked this effect, suggesting that these are the targets of ACTH action (40).

By suppressing CRH expression, possibly through the action of peptide fragments of ACTH on melanocortin receptors, neuronal hyperexcitability may be reduced, ameliorating infantile spasms (33,34). Indirect evidence to support this hypothesis was reported recently by Liu et al. (51), who found that genetic variants in the central melanocortin-4-receptor promoter are associated with the development of infantile spasms and influence treatment response to ACTH in children with infantile spasms. Clinical trials of ACTH fragments without activity on adrenals have yielded disappointing results (52,53), but these studies used the 4 to 9 rather than the 4 to 10 peptide fragment studied in animal models (40).

Efficacy and Dosage

Table 67.1 lists the different preparations of depot corticotrophin. The biologic activity, expressed in international units (IU), permits a comparison of potency but represents the relative ability of the peptide to stimulate the adrenals and may not reflect its ability to affect brain function. The biologic activity of natural ACTH in the brain may differ from that of synthetic ACTH (12) as a result of ACTH fragments and possibly other pituitary hormones with neurobiologic activity in the brain that are present in the pituitary extracts. These compounds could enhance the therapeutic efficacy of natural ACTH (54). Any differences in the biologic effects of sustained ACTH levels provided by the depot formulations, as opposed to those of the short-acting preparations, are unknown. Given in high doses, however, long-acting depot preparations are associated with an increased incidence of severe side effects, including death from overwhelming infection (21).

Table 67.1 Preparations of Depot Corticotropin

Preparation	Biologic activity (100 IU)[a] equivalent to	Duration of action (h)
Short-acting forms		
Corticotropin (ACTH 1–39)—porcine pituitary extract		
Acthar gel, 80 IU/mL	0.72 mg	24–48
ACTH-carboxymethylcellulose	Not available	~24
Cosyntropin/tetracosactin (ACTH 1–24)—synthetic		
Cortrosyn	1.0 mg	~24
Long-acting forms		
Cosyntropin/tetracosactin (ACTH 1–24)—synthetic		
Synacthen-zinc	2.5 mg	~72
Cortrosyn-Z	2.5 mg	~72

[a]Commercial preparations are described in IU, based on a potency assay in hypophysectomized rats in which depletion of adrenal ascorbic acid is measured after subcutaneous ACTH injection.

Although most efficacy studies of ACTH and steroids are retrospective, an expanding body of prospective data is available (12,18,27,55–65). Most published literature supports the hypothesis that the natural ACTH 1 to 39 peptide (p-ACTH) is superior to oral steroids. In randomized, controlled trials, spasms ceased in 42% to 87% of children treated with ACTH, compared with 29% to 33% of children treated with prednisone (49,50). In these studies, the relapse rates were 15% to 31% for ACTH and 29% to 33% for prednisone. The United Kingdom infantile spasms study (UKISS) compared a high-dose oral prednisolone protocol of 40 to 60 mg/day with IM synthetic ACTH, which showed spasms responder rates of 70% for prednisolone and 76% for ACTH with neither agents showing significant difference in EEG response rate at 14 days, $P = 0.61$ (18); however, further prospective studies are needed to confirm this finding.

Most institutions have their own treatment protocol for infantile spasms, with a wide variety of dose and duration (66–68). The most effective dose and duration of treatment with p-ACTH for remission of infantile spasms continues to be a controversial issue. Compared to prednisone, no major advantage was demonstrated by low doses of ACTH, whereas high doses were superior (58,59). High-dose p-ACTH at 60 IU/day or 150 IU/m^2/day has produced excellent short-term response rates of 87% to 93% in prospective studies (58,63). In the only randomized, prospective comparison of p-ACTH, however, Hrachovy et al. (60) found no difference between high-dose and low-dose therapy. A prospective study using synthetic ACTH (62) by Yanagaki et al. compared very-low-dose (0.2 IU/kg/day) and low-dose (1 IU/kg/day) ACTH and found equivalent efficacy, with response and relapse rates comparable to those in other studies. Describing a stepwise increase in dosage, Heiskala et al. (65) demonstrated that while some patients can be controlled on lower doses of carboxymethylcellulose ACTH (3 IU/kg/day), others required high doses (12 IU/kg/day). Spasms were controlled initially in 65% of patients, but the relapse rate was high.

While some evidence supports high-dose ACTH over low-dose ACTH or oral steroids in cognitive outcome (9,11), the data are contradictory and not class I. Glaze et al. (55) found no difference between low-dose p-ACTH (20 to 30 IU/day) and prednisone (2 mg/kg/day). In a comparison of high-dose p-ACTH (110 IU/m^2/day) and steroids, however, Lombroso (12) showed a higher rate of normal cognitive outcome in cryptogenic patients treated with ACTH than in those treated with prednisone alone (55% vs. 17%). In a retrospective comparison of different ACTH

dosage regimens (69), Ito et al. also noted a positive correlation between dose and developmental outcome.

Although some data support high-dose ACTH as being more effective than low-dose ACTH, the precise dosage and duration are undetermined. The optimal dose may lie between 20 and 200 IU/m^2/day. Doses of 400 IU/m^2/day or higher are contraindicated because of a high incidence of life-threatening side effects (20,21,60,69).

There are some data suggesting that a good response to ACTH appears to be associated with better long-term outcome (24,70) in children with cryptogenic infantile spasms.

Based on these and other data, the current American Academy of Neurology Evidence–based guideline for the medical treatment of infantile spasms has concluded that low-dose ACTH should be considered for treatment of infantile spasms. ACTH or VGB may be useful for short-term treatment of infantile spasms, with ACTH considered preferentially over VGB. Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to VGB in infants with cryptogenic infantile spasms, to possibly improve developmental outcome. A shorter lag time to treatment of infantile spasms with either hormonal therapy or VGB possibly improves long-term developmental outcomes (71).

Adverse Effects

ACTH and steroids, particularly at the high doses recommended for infantile spasms, can produce dangerous side effects. These are more frequent and more pronounced with ACTH. In prospective controlled trials, cushingoid features and extreme irritability were seen frequently; hypertension, while less common, was associated with higher doses (59–62). Vigilance is required for signs of sepsis, pneumonia, glucosuria, metabolic abnormalities involving the electrolytes calcium and phosphorus (72–74), and congestive heart failure (75,76). Of five deaths reported in prospective studies, at least two were directly attributable to ACTH (12,64).

Cerebral ventriculomegaly (59,77–81), which is not always reversible (55), can lead to subdural hematoma (82,83). The cause of the apparent cerebral atrophy is obscure, but its existence emphasizes the importance of diagnostic neuroimaging before initiation of ACTH.

Because hypothalamic–pituitary or adrenocortical dysfunction can result from ACTH therapy (84,85), morning levels of cortisol should be monitored during a taper and any medical stress treated with high-dose steroids (86). Treatment with ACTH or steroids can also be immunosuppressant and associated with infectious complications, perhaps as a result of impaired function of polymorphonuclear leukocytes (87). Both agents are therefore contraindicated in the face of serious bacterial or viral infection such as varicella or cytomegalovirus. Because of the high rate of fatal Pneumocystis pneumonia as an infectious complication of ACTH therapy (20,88–90), prophylaxis with trimethoprim–sulfamethoxazole, accompanied by folate supplementation and frequent blood counts, may be prudent in infants older than 2 months of age. In rare cases, ACTH also has been reported to exacerbate seizures (91,92).

Vigabatrin Versus Adrenocorticotropin

The 2004 American Academy of Neurology Practice Parameter for the medical treatment of infantile spasms has concluded that VGB is possibly an effective agent in the short-term treatment of infantile spasms (16). The 2012 American Academy of Neurology updated evidence-based guidelines for the

medical treatment of infantile spasms concluded that while either ACTH (level B) or VGB (level C) could be offered for short-term treatment of infantile spasms, the evidence suggests that ACTH may be offered over VGB (level C) (71). Based on data from randomized controlled trials, from 23% to 65% of children treated with VGB achieve short-term remission of infantile spasms, with relapse rates of 4% to 20% (18,61,70,93,94).

Although VGB is thought to be particularly effective against infantile spasms associated with tuberous sclerosis (61,95,96) and is frequently advocated as a first-line therapy for this disorder, the data supporting this are retrospective (16). The mammalian target of rapamycin (mTOR) pathway is a key signaling pathway that is dysregulated in TSC. Animal studies have shown that VGB partially inhibited mTOR pathway activity and glial proliferation in the knockout mice in vitro as well as reduced mTOR pathway activation in cultured astrocytes from both knockout and control mice. This may account for the unique efficacy of VGB in TSC (97).

Limiting its use is the characteristic concentric constriction of visual fields. This effect does occur in childhood, and the risk may be cumulative with longer duration of therapy (98–102). The incidence in very young children is not known, and perimetric testing is often impossible in this group. Electrophysiologic studies in infants, although not as sensitive as perimetry, have confirmed VGB-associated abnormalities (101–104). In 22% to 32% of infantile spasms patients treated with VGB, reversible abnormal MRI signal intensity or restricted diffusion-weighted imaging in the thalamus, basal ganglia, dentate nucleus, and the brainstem have been reported. Although the clinical significance of these MRI changes is unknown, there is concern that the changes reflect a medication-related neurotoxic effect (105,106). VGB may have a place as a short-term treatment, although its long-term safety remains uncertain.

Other Agents in Infantile Spasms

Valproate (107,108), nitrazepam (109), pyridoxine (110), felbamate (111), intravenous immunoglobulin (112), topiramate (113), zonisamide (114), ganaxolone (115), levetiracetam (116), and the ketogenic diet (117,118) have been studied in small uncontrolled trials. However, there is insufficient evidence of efficacy and safety to recommend any of these therapies at this time (16,71).

Recommended Protocols for Adrenocorticotropin

In our center, the standardized therapy for new-onset infantile spasms, regardless of the etiology or lack thereof is to use VGB as first-line therapy. The reason for the use of VGB is its ease of use and relative lack of side effects compared to ACTH. We require complete resolution of spasms and hypsarrhythmia on EEG to continue VGB alone for a full 6-month course. Failing that, ACTH is begun as described below. This protocol has been shown to achieve seizure freedom in 96% of children so treated (119).

The optimal dose of ACTH required to enhance short-term response and long-term cognitive outcome is unknown; however, relatively high doses given early in the disease, accompanied by a second course in the event of relapse, appear warranted. The following high-dose ACTH regimen that has been used successfully in more than 500 children (58,63,120) is recommended (Table 67.2). A suggested protocol using Synacthen (cosyntropin or tetracosactide) based on the study done by Snead et al. (63) with 0.25 mg of Synacthen equivalent to 25 units of corticotropin is also included. The initial dose of ACTH is 150 IU/m^2/day of ACTH gel, 80 IU/mL, intramuscularly in two divided doses

for 1 week. In the second week, 75 IU/m^2/day is given, followed by 75 IU/m^2 every other day in the third week. Over the next 6 weeks, the dose is gradually tapered. The lot number of the ACTH gel is carefully recorded. Usually, a response is seen within the first 7 days; if within 2 weeks no response is noted or a steroid effect is evident, the lot is changed.

Table 67.2 Protocol for ACTH Therapy for Infantile Spasms

Initial assessment before therapy begins

History and physical examination including Wood light
EEG with pyridoxine injection
Blood counts, routine blood chemical analysis, urinalysis including glucose, and thyroid and adrenal function tests
Electrocardiogram
Magnetic resonance imaging of the brain
Family counseling and education for administration and monitoring of side effects

Clinical monitoring during ACTH therapy

Blood pressure and urine dipstick for glucose: daily first week, then thrice weekly
Blood counts, routine blood chemical analysis weekly first month, then fortnightly
EEG once during and after therapy and as indicated
Provide the family with a letter describing treatment and prompting urgent assessment in case of fever or other signs of infection

High-dose schedule for natural ACTH

Week 1	150 IU/m²/d IM, two divided doses
Week 2	75 IU/m²/d IM, single daily dose
Reassess	If spasms stop and hypsarrhythmia resolves, continue with taper; if no clinical or EEG response, change ACTH lot or select alternative therapy and taper ACTH as appropriate
Week 3	75 IU/m²/d IM, alternate days
Week 4	60 IU/m²/d IM, alternate days
Week 5	50 IU/m²/d IM, alternate days
Week 6	40 IU/m²/d IM, alternate days
Week 7	30 IU/m²/d IM, alternate days
Week 8	20 IU/m²/d IM, alternate days
Week 9	10 IU/m²/d IM, alternate days
Week 10	5 IU/m²/d IM, alternate days, then stop ACTH

Lower-dose schedule for ACTH[a]

Weeks 1 and 2	20 IU/d

If response is complete: taper ACTH over 1-week period
If response is incomplete: increase 30 IU/d for 4 weeks then taper to zero over a 1-week period
If response remains incomplete: taper ACTH and try other medications

Suggested schedule for Synacthen (cosyntropin) in infantile spasms[b]

Week number	Date of injection	Dose given intramuscularly
Week 1	Day 1	1.9 mg/m²
	Day 3	1.9 mg/m²
	Day 5	1.9 mg/m²
	Day 7	1.9 mg/m²
Week 2	Day 9	0.94 mg/m²
	Day 11	0.94 mg/m²
	Day 13	0.94 mg/m²
Reassess after 2 weeks; responders will finish protocol on the following taper schedule		
If no clinical and EEG response, select alternative therapy and taper ACTH as appropriate		
Week 3	Day 15	0.75 mg/m²
	Day 17	0.75 mg/m²
	Day 19	0.75 mg/m²
	Day 21	0.63 mg/m²
Week 4	Day 23	0.63 mg/m²
	Day 25	0.5 mg/m²
	Day 27	0.5 mg/m²
Week 5	Day 29	0.38 mg/m²
	Day 31	0.38 mg/m²
	Day 33	0.25 mg/m²
	Day 35	0.25 mg/m²
Week 6	Day 37	0.13 mg/m²
	Day 39	0.13 mg/m²
	Day 41	0.06 mg/m²
		Then stop Synacthen depot

[a]Based on Hrachovy RA, Forst JD, Kellaway PR, et al. Double-blind study of ACTH vs. prednisone therapy in infantile spasms. J Pediatr. 1983;103:641–645 and Hrachovy RA, Frost JD, Glaze DG. High dose, long duration vs. low dose, short duration corticotropin therapy in infantile spasms. J Pediatr. 1994;124:803–806.

[b]This 6-week Synacthen protocol developed and used at the Hospital for Sick Children, Toronto, Ontario.

A low-dose ACTH protocol based on two studies by Hrachovy et al. (59,60) showed clinical and EEG response rates of >40% in children with infantile spasms and provided evidence suggesting that low-dose ACTH is probably as effective as high-dose ACTH for the short-term treatment of infantile spasms. Patients receive 20 U/day for 2 weeks. If response was documented, the dose of ACTH was tapered to zero over a 1-week period. If a response was not documented, ACTH was increased to 30 U/day for 4 weeks and then tapered to zero during a 1-week period.

Once the decision is made to embark upon a course of ACTH therapy, the child is admitted to a day care unit for initiation therapy. Parents are taught to administer the injection, measure urine glucose three times daily with Chemstix, and recognize spasms so as to keep an accurate seizure calendar. Any diagnostic workup indicated by clinical circumstances is also performed, including screening for occult infections. Before ACTH is started, an endocrine profile, complete blood count, urinalysis, electrolyte panel, baseline renal function tests, and calcium, phosphorus, and serum glucose levels are obtained. Blood pressure is measured and an electrocardiogram performed. The drug is not given if any of these studies show abnormal results. Diagnostic neuroimaging is indicated before initiation of ACTH or steroids because of the association with ventriculomegaly.

Blood pressure must be measured daily at home during the first week and three times weekly thereafter. Control of hypertension is attempted with salt restriction and amlodipine therapy rather than discontinuation of ACTH. The patient is monitored in the outpatient clinic weekly for the first month and then biweekly, with appropriate blood work at each visit. Waking and sleeping EEG patterns are obtained during and after the start of ACTH to assess treatment response. Because a response is usually noted within a week or two of initiating ACTH (57–59), positive results are suggested when properly trained parents report no seizures in a child whose waking and sleeping EEG patterns are normal.

If relapse occurs, the dose may be increased to the previously effective dose for 2 weeks and another tapering begun. If seizures continue, the dose may be increased to 150 IU/m^2/day and the regimen restarted.

Recommended Protocols for Prednisone and Prednisolone

If prednisone is chosen because of its oral formulation and lower incidence of serious side effects, the pretreatment laboratory evaluation described earlier is performed. The initial dose is 3 mg/kg/day in four divided doses for 2 weeks, followed by a 10-week taper (115). A multiple daily dose regimen of high-dose ACTH therapy is recommended to produce sustained elevations of plasma cortisol (57,63).

The UKISS by Lux et al. (18) used the following high-dose oral prednisolone regimen: initial dose is 10 mg four times a day for 2 weeks, increasing to 20 mg three times a day after 1 week if spasms continued, followed by taper of 10 mg every 5 days or, if on the higher-dose treatment, 40 mg daily, then 20 mg, then 10 mg for 5-day periods.

OTHER SEIZURE DISORDERS

Ohtahara and Lennox–Gastaut syndromes are believed to represent earlier and later manifestations, respectively, of a spectrum of infantile epileptic encephalopathies that include infantile spasms

(121–124). These conditions respond poorly to traditional anticonvulsant drug therapies but are sometimes improved by the antiepileptic drugs used in infantile spasms: ACTH, steroids, benzodiazepines, and valproic acid. ACTH of steroids also may be beneficial in Landau–Kleffner syndrome.

Ohtahara Syndrome

Also known as early infantile epileptic encephalopathy, Ohtahara syndrome is characterized by spasms beginning within the first 3 months of life associated with persistent burst suppression on the EEG in all stages of the sleep–wake cycle (121). Despite reports of improvement after ACTH (121,125), VGB (126), and zonisamide (121), the long-term prognosis usually is unchanged by any treatment (121,123) and involves high mortality and severely handicapped survivors. If used, ACTH should be administered as described for infantile spasms.

Lennox–Gastaut Syndrome and Other Myoclonic Disorders

ACTH and steroids have been found useful in younger children with various combinations of severe and intractable seizures, particularly atypical absence, myoclonic, tonic, and atonic seizures (1,38,120,127–132). This group includes patients with Lennox–Gastaut syndrome, a disorder characterized by mental retardation, generalized slow spike-and-wave discharges, intractable atypical absence, myoclonus, and frequent ictal falls. Several uncontrolled, retrospective studies suggest that ACTH is superior to oral steroids against these seizure types (121,127,129,130), and the regimen described in this chapter for ACTH or prednisone is recommended. Nevertheless, ACTH and steroids should be reserved for the most severe and intractable disease. Usually, the best result is temporary relief, because 70% to 90% of patients with multiple seizure types suffer a relapse during the ACTH taper (120).

In another age-dependent disorder first described by Doose (133), myoclonic astatic seizures begin between 7 months and 6 years of age in a previously normal child and are associated with generalized discharges on the EEG (134). This disorder is resistant to most conventional antiepileptic drugs; however, a retrospective study has reported response to the ketogenic diet, ACTH, and ethosuximide (134).

Landau–Kleffner Syndrome and Related Disorders

Described in 1957 (135), Landau–Kleffner syndrome, also known as acquired epileptic aphasia, is characterized by regression in receptive and expressive language associated with epileptic seizures. The usual presentation occurs between the ages of 2 and 8 years. Clinical seizures may precede, be coincident with, or develop after the onset of language deterioration, and up to 25% of patients with language loss and epileptiform EEG patterns never experience clinical seizures (136,137). Behavioral disturbances are frequent, ranging from hyperactivity and aggressiveness to autism and global cognitive deterioration. Some children display sustained agnosia and mutism; others show a waxing and waning course that parallels the EEG changes; still others demonstrate spontaneous resolution (137). The EEG typically shows 1- to 3-Hz high-amplitude spike and slow waves; these may be unilateral, bilateral, unifocal, or multifocal but often include the temporal region, with or without parietal and occipital involvement, and are activated in sleep (138).

Valproate and benzodiazepines may control the syndrome's clinical seizures but have only a

partial and transient effect on the EEG abnormalities (10,139). In 1974, McKinney and McGreal (140) described the beneficial effect of ACTH on the characteristic seizures, language regression, and behavioral change. Since then, although no controlled prospective trials of ACTH or steroids have been published, case reports and retrospective series have demonstrated improvements in seizure control and language in children treated with varying ACTH or corticosteroid regimens (10,137–139,141–143).

The use of ACTH or corticosteroids in patients with Landau–Kleffner syndrome appears justified; however, further study of dose and duration of therapy is warranted, as is exploration of new anticonvulsants. High-dose ACTH or prednisone, as described in this chapter for infantile spasms, may be useful, with a longer tapering schedule and concomitant use of valproic acid.

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CHAPTER 68 ANTIEPILEPTIC DRUGS IN CLINICAL DEVELOPMENT

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Despite advances in epilepsy treatment, there remains a continuing need for the development of new medications (1–4). Multiple new agents have been introduced in recent years, some of which are products of the Antiepileptic Drug Development Program sponsored by the U.S. National Institutes of Health (5). Many novel compounds with antiepileptic drug (AED) potential are currently in various stages of development (Tables 68.1 and 68.2) (6–10); however, not all of these compounds will complete the development cycle and be approved for use.

Table 68.1 Chemistry and Possible Mechanisms of Action of Some New AEDs

Drug	Chemistry	Possible mechanism of action
Eslicarbazepine acetate	*S-(–)-10-Acetoxy-10,11-dihydro-5H-dibenz/b,flazepine-5-carboxamide*; shares the dibenzazepine nucleus bearing the 5-carboxamide substitute with carbamazepine	Stabilizes the inactivated state of voltage-gated sodium channels
Brivaracetam	Pyrrolidone derivative in the same class as levetiracetam and piracetam	Binds to the SV2A like its parent compound levetiracetam, but with higher affinity; also inhibits sodium channel currents
PID	Chiral isomer of valpromide	(*R*)-Enantiomer is more potent; mechanism of action unknown
Carisbamate	*S-2-O-carbamoyl-1-o-chlorophenyl-ethanol*	Inhibits voltage-gated sodium channels; modest inhibition of high-voltage activated calcium channels
Ganaxolone	*3α-Hydroxy-3β-methyl-5α-pregnan-20-one*	Positive allosteric modulator of the $GABA_A$ receptor
Huperzine A	Sesquiterpene lycopodium alkaloid	*N*-Methyl-D-aspartate receptor and acetylcholinesterase inhibitor
JZP-4	3-(2,3,5-Trichloro-phenyl)-pyrazine-2,6-*diamine*; structurally related to lamotrigine	Sodium- and calcium-channel blocker
NAX 5055	Analog of the endogenous neuropeptide galanin	Agonist of galanin receptor subtypes GalR1 and GalR2; this is thought to decrease glutamate release
Retigabine	Carbamacic acid ethyl ester	*Opens inward rectifying K^+ channels; GABA potentiation*
Stiripentol	Aromatic allylic alcohol	Inhibits synaptosomal GABA uptake; enhances GABAergic transmission; inhibits hepatic cytochrome P450 enzymes
YKP3089	Unknown	Unknown

Table 68.2 Important Pharmacokinetic Parameters of New Antiepileptic Compounds in Humans

Drug	T_{max} (h)	Protein binding (%)	Half-life (h)	Excretion
Eslicarbazepine acetate	2–3	30	20–24	Renal
Brivaracetam	1–2	Weak	8	Renal
PID	Unknown	Unknown	Unknown	Unknown
Carisbamate	1–3	44	12	Renal
Ganaxolone	1.5–2	99	35–40	Hepatic
Huperzine A	Unknown	Unknown	Unknown	Unknown
JZP-4	Unknown	Unknown	10	Renal
NAX-5055	Unknown	Unknown	Unknown	Unknown
Retigabine	1–2	<80	8–10	Renal
Stiripentol	1.5	99	Nonlinear pharmacokinetics (Michaelis–Menten)	Unknown
YKP3089	1.5–3.5	Unknown	30–75	Unknown

In the fifth edition of this textbook, this chapter discussed 11 anticonvulsant drugs (11). Information on brivaracetam, carisbamate, ganaxolone, stiripentol, huperzine A, and YKP3089 has been updated. Nax 5055, JZP-4, and propylisopropyl acetate (PID) will not be discussed in this chapter as the interval development of these agents has stalled or ceased. Compounds newly developed as potential AEDs since the writing of the last edition have been added.

The chapter has also been reorganized; drugs whose chemical structures are related to preexisting parent compounds are discussed first under the derivative compound section, followed by neurosteroids (NS), anti-inflammatory agents, and other structurally novel compounds.

DERIVATIVE COMPOUNDS

Levetiracetam Derivatives: Brivaracetam

Brivaracetam (UCB 34714) is a pyrrolidone derivative in the same class as levetiracetam and piracetam. Like levetiracetam, it binds to the synaptic vesicle protein 2A (SV2A), but with higher affinity. In contrast to levetiracetam, brivaracetam also inhibits sodium channel currents as demonstrated in rat cortical neurons in vitro (12). It exhibits superior activity against secondarily generalized motor seizures in corneally kindled mice and prevents clonic convulsions in audiogenic-susceptible mice (13). Brivaracetam suppresses spike-and-wave discharges in Generalized Absence Epilepsy Rat from Strasbourg (GAERS) rats and also suppresses both motor seizure severity and after-discharge duration in amygdala-kindled rats (13). Brivaracetam was developed with the hope that it would (i) be more potent than levetiracetam due to its higher affinity binding, (ii) provide benefit to a larger percent of patients because of its additional impact on sodium channels, or (iii) have a more favorable behavioral side effect profile. None of these potential benefits have yet been proven.

Brivaracetam is rapidly absorbed following oral administration, displays linear pharmacokinetics, binds weakly to plasma proteins, and has an approximately 8-hour half-life (14,15). Inactive metabolites are primarily renally cleared (15). In contrast to levetiracetam, brivaracetam has been demonstrated in vitro to have some impact on metabolizing enzymes; it inhibits epoxide hydrolase and to a lesser extent CYP3A4 and 2C19 and is a weak inducer of CYP3A4 (16). Brivaracetam slightly reduces carbamazepine concentrations, while slightly increasing levels of carbamazepine-10,11-epoxide. Brivaracetam has equivocal effects on phenytoin, possibly lowering

serum concentrations, and has no effect on the concentrations of lamotrigine, levetiracetam, oxcarbazepine, topiramate, and valproic acid (6,17). High doses of brivaracetam have been shown to moderately reduce the estrogen and progesterone components of oral contraceptives, but this has not been shown to impact ovulation (6,16). However, a dose of 100 mg/day did not modify the pharmacokinetics of oral contraceptive steroid components (30 g ethinyl estradiol and 150 g levonorgestrel) (18). Enzyme-inducing AEDs increase brivaracetam clearance, leading to a 30% reduction of AUC (7). There is no change in exposure in elderly and renally impaired patients, indicating that no dose adjustments should be necessary (19). However, severe hepatic impairment will increase exposure by about 50% (7,18).

Tolerability is good overall; the majority of treatment- emergent adverse events (TEAEs) reported in Phase III trials were mild to moderate (8), the most common being headache, somnolence, dizziness, and fatigue (8,20). Cardiac repolarization in healthy subjects is not affected with doses of 75 and 400 mg BID (21).

Three Phase III clinical trials (Study N01252, N01253, and N01254) utilizing the primary efficacy end point of percent reduction in baseline-adjusted partial-onset seizure frequency have been conducted. Patients were randomized to a variety of drug doses (20, 50, and 100 mg/day in Study N01252; 5, 20, and 50 mg/day in Study N01253; and 20 mg/day with variable stepwise increases up to a maximum of 150 mg/day in Study N01254). In Study N01253, statistical significance was reached for the primary efficacy end point with the 50 mg/day dose versus placebo ($P = 0.02$) (22); this was not achieved for the 50 mg dose in Study N01252, but was at 100 mg/day dosing ($P = 0.05$) (22). In clinical trial N01254 (23), median percent reduction from baseline in partial-onset seizure frequency/week was 26.9% for brivaracetam versus 18.9% for placebo ($P = 0.070$), while 50% responder rates were 30.3% for brivaracetam versus 16.7% for placebo ($P = 0.006$) (23). Preliminary data also suggest possible efficacy of brivaracetam as an add-on agent in adults with generalized epilepsy (consisting of a combination of idiopathic, cryptogenic, symptomatic, and unknown, with 34/36 patients completing the treatment period) (23). The median generalized seizure days/week decreased to 0.63 on brivaracetam compared to placebo (1.26); median percentage reductions from baseline and ≥50% responder rates in generalized seizure days/week also favored brivaracetam treatment (42.6% and 44.4%, respectively) over placebo (20.7% and 15.4%, respectively) (23).

Multiple additional Phase III studies as well as multicenter open-label trials are ongoing at the time of writing of this chapter, including studies in children.

Vigabatrin Derivatives: CPP-115

Vigabatrin increases levels of γ-aminobutyric acid (GABA) in the brain by inhibiting its degradation through inactivation of the enzyme GABA-aminotransferase (GABA-AT) (24). Derivatives of vigabatrin have been created; strengthening the molecular structure of the drug has led to the development of a more potent analog with stronger binding capacity to the target enzyme GABA-AT (25). The molecule (1S,3S)-3-amino-4-difluoromethylenecyclopentanecarboxylic acid, a conformationally rigid vigabatrin analog, is a potent inactivator of GABA-AT and approximately 186 times more potent than is S-vigabatrin in vitro (25). However, the latter molecule possesses relatively low lipophilicity, which could limit permeability across the blood–brain barrier (25). The tetrazole analog (1S,3S)-3-amino-4-difluoromethylenyl-cyclopentanoic acid (CPP-115) is more highly lipophilic (25). In addition, CPP-115 is a time- and concentration-dependent inhibitor of

GABA-AT (25), less potent than is its parent compound, but more potent in vitro than is vigabatrin (25). CPP-115 was over 100 times more effective in the treatment of infantile spasms in a rat model, and efficacy against drug addiction in rat models was also demonstrated (26). And importantly, much less retinal damage has been observed at high doses of CPP-115 compared to effective doses of vigabatrin (26). CPP-115 has been licensed to Catalyst Pharmaceutical Partners, Inc., which has begun Phase I clinical trials at the time of writing of this chapter.

NEUROSTEROIDS

Étienne-Émile Baulieu (27) first defined NS as steroids synthesized de novo in the nervous system from cholesterol independent of the peripheral endocrine glands. This definition was expanded by Paul and Purdy (28) who further characterized "neuroactive steroids" as including "natural or synthetic steroids" that alter neuronal excitability. $GABA_A$ receptors are primary NS targets; at low concentrations, NS potentiate the action of GABA, and at higher concentrations, they directly activate the receptor at sites distinct from benzodiazepine and barbiturate modulatory sites (29), and anticonvulsant tolerance to NS has not been seen (30,31). NS exhibit broad-spectrum anticonvulsant effects in animal models, showing efficacy against Pentylene Tetrazole (PTZ), bicuculline, pilocarpine, and kindling-induced seizures (32). Similar to other GABA agents, however, NS may exacerbate generalized absence seizures (33,34). Ganaxolone is the only synthetic NS-based compound currently in development and is discussed below.

GANAXOLONE

Ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one) is the 3-β-methyl analog of the NS allopregnanolone (7). It is a positive allosteric modulator of the $GABA_A$ receptor and is similar to its natural analog allopregnanolone in potency and efficacy (35). Ganaxolone has protective antiepileptic activity in multiple seizure models (35–38). It is highly protein bound (>99%) (7), is rapidly absorbed, and is primarily hepatically metabolized via CYP3A4/3A5 enzymes (7). In vitro studies have failed to show significant interactions between ganaxolone and other AEDs (39). Ganaxolone is not a CYP3A4 inhibitor and has shown low or no potential to induce CYP3A4 metabolism, although concomitantly administered strong CYP3A4 inducers (carbamazepine and phenytoin) can increase ganaxolone's clearance (8). Ganaxolone has a 10-hour effective half-life and a terminal elimination half-life of 35 to 40 hours (7). Metabolites are eliminated in urine (25%) and feces (69%) (32). Plasma values are 5 to 15 times higher when taken with food, compared to fasting values; thus, several unique formulations have been created including two solid capsule forms, one immediate-release and the other pH-sensitive delayed-release. Ganaxolone possesses a favorable safety and toxicity profile in animals and is safe and well tolerated in humans (8). The most common TEAEs are headache, dizziness, fatigue, and somnolence (8,40). The 3β-methyl component of ganaxolone eliminates back conversion to the hormonally active intermediate dihydroprogesterone, potentially avoiding hormonal side effects (41).

In one Phase II clinical trial, 1500 mg/day of ganaxolone resulted in an 18% decrease of mean weekly seizure frequency, compared with a 2% increase in the placebo group over a 10-week treatment period ($P = 0.014$) (8). Twenty-six percent of subjects treated with ganaxolone versus 13% of those treated with placebo ($P = 0.057$) experienced >50% reduction in seizures during the maintenance phase (8). Sustained efficacy was demonstrated in a 104-week open-label extension of a

10-week double-blind randomized study, with no new safety concerns identified (8). Three Phase II open-label, adjunctive therapy studies have been performed in the pediatric population. The largest enrolled a total of 45 patients with partial or generalized refractory seizures, ages 2 to 15 years. A maximum dose of 12 mg/kg three times daily was administered for an 8-week maintenance period. Twenty-seven patients (60%) completed the entire study and 12 patients (27%) experienced a >50% reduction in seizure frequency (39). Ganaxolone is currently in Phase III development for epilepsy (8).

ANTI-INFLAMMATORY AGENTS

Targeting hyperexcitability and inflammation is another potential approach to seizure control (42). Evidence suggests that glia-mediated inflammation plays a role in the pathogenesis of seizures and epilepsy; one proposed mechanism is glial effects on the IL1β cascade, which ultimately leads to NMDA-mediated enhancement of Ca^{2+} influx, which in turn promotes excitability and excitotoxicity (43,44). Using therapies that target the inflammatory cascade particularly for those patients severely resistant to standard AED treatment may be helpful; results from animal studies are promising (45).

HE3286 (Triolex)

The orally active HE3286 is a synthetic derivative of the anti-inflammatory dehydroepiandrosterone (DHEA) metabolite, androstene-3β,7β,17β-triol (βAET) (46). While anti- inflammatory, HE3286 is not immunosuppressive (47); it is thought to have an anti-inflammatory mechanism of action distinct from corticosteroids and other agents (48). HE3286 has been used to treat collagen-induced arthritis, where it has been associated with various immune-related changes including the reduction of proinflammatory cytokines tumor necrosis factor-α, IL-6, IL-1β, and IL-23 (48).

Thus far, HE3286 demonstrates low potential for direct or indirect toxicity and possesses suitable pharmacokinetics for clinical development (47). It possesses a terminal half-life slightly longer in males than in females ($T_{1/2}$: 8.2 and 5.4 hours, respectively) (47). HE3286 readily permeates the blood–brain barrier in mice (47). It is extensively metabolized, and some of the various metabolites have been found to interact with CYP enzymes (47). Pharmacokinetic evaluations are ongoing. Toxicology studies in rats revealed no systemic or neurotoxicity at daily doses of up to 400 mg/kg in 4-week studies; doses of 200 mg/kg and 30 mg/kg in 13- and 26-week studies, respectively, also resulted in no toxicity (47). Dose-dependent, generally mild, estrogenic effects were observed in both sexes (47).

At the time of writing of this chapter, HE3286 was in preclinical development for use in refractory epilepsy using a chronic seizure mouse model at the Mario Negri Institute for Pharmacological Research, Milan, Italy.

VX-765

VX-765 ((S)-1-((S)-2-{(1-(4-amino-3-chloro-phenyl)-methanoyl)-amino}-3,3-dimethyl-butanoyl)-pyrrolidine-2-carboxylic acid ((2R,3S)-2-ethoxy-5-oxo-tetrahydro-furan-3-yl)-amide) is a selective and reversible inhibitor of interleukin converting enzyme, also known as caspase 1 (8,49). By this mechanism, it is able to reduce the production of IL-1β, which is thought to inhibit neuronal hyperexcitability.

Two small Phase IIA clinical trials have been completed. The first was a 6-week trial in which subjects were randomized 4:1 to VX-765 900 mg three times daily (TID) (n = 48), or placebo (n = 12). There was no long-term extension phase, but patients continued to count seizures for 6 weeks after drug was discontinued. The most common side effect was dizziness, and no serious side effects attributable to VX-765 emerged. 18.8% of subjects in the VX-765 group had a 50% reduction in seizures versus 8.3% in the placebo group (P = NS). However, in a post hoc analysis, seizure frequency appeared to diminish further in a "hybrid" period consisting of the last 2 weeks of treatment and the first 2 weeks of the posttreatment period, consistent with a delayed onset of treatment seen in animal studies (8,50). Subsequently, a 13-week dose-ranging study was initiated. Patients were randomized (1:1:1:1:1) before the first dose of study drug on day 1 to receive placebo or VX-765 300 mg, 600 mg, 900 mg, or 1200 mg TID. The study was initially designed to enroll 500 patients. It was stopped administratively due to a decision by the company not to pursue development, when only 55 patients had been randomized. At present, the fate of the molecule is uncertain (51).

OTHER STRUCTURALLY NOVEL COMPOUNDS

2-Deoxy-D-Glucose

2-Deoxy-D-glucose was discovered during studies exploring the possible molecular mechanisms underlying the anticonvulsant effect of the ketogenic diet (8). 2-Deoxy-D-glucose is a nonmetabolizable glucose analog that inhibits glycolysis and that has been shown to have beneficial acute and chronic antiepileptic effects in a number of in vitro and rat models of seizures (52). A recent report suggests that it may exert its anticonvulsant properties by up-regulation of the potassium receptor subunits Kir6.1 and Kir6.2 (53). There have been some concerns about its safety in animal models with report of cardiac muscle vacuolization and increased mortality in rats (54). The significance and reversibility of these findings are currently under investigation. An intriguing aspect of this compound is that it may be preferentially taken up at the site of active seizure focus and thus may have a specific role in the treatment of acute repetitive seizures and status epilepticus. Phase 11 studies in humans have been planned, including studies of use in status epilepticus.

Cannabinoids

There is a lot of current interest in the medical use of marijuana and its constituent compounds for the treatment of epilepsy. There are hundreds of unique compounds in marijuana (cannabis), and the ones that are unique to the plant are called cannabinoids. Two neuroactive compounds in marijuana (cannabis) are tetrahydrocannabinol (Δ^9-tetrahydro-cannabinol (Δ^9-THC), a psychoactive compound) and cannabidiol (non-psychoactive). Sativex, a derivative containing both constituents, has recently been approved in a number of countries for the treatment of pain and spasticity in multiple sclerosis (55). In the day-to-day practice of epileptology, some patients have reported that the use of marijuana has beneficial effects on seizure control, and indeed, the use of cannabis has a long history of use for the control of seizures in human epilepsy. Both THC and cannabidiol have been tested in animal models of epilepsy, but recently, there has been more focus on cannabidiol. Notably, while THC engages the endocannabinoid system, cannabidiol does not. However, cannabidiol does engage a number of other targets and is considered to be antioxidant. Its mechanism of action is currently unknown (56). It has been tested in animal models of epilepsy and is effective in the 6 Hz and

maximal electroshock model (57). CBD exerted anticonvulsant effects against PTZ-induced acute generalized seizures, pilocarpine-induced temporal lobe convulsions, and penicillin- induced partial seizures in Wistar-Kyoto rats (58,59).

Cannabidivarin, a propyl analog of cannabidiol, acting on the CB_2 cannabinoid receptor, has been shown to be anticonvulsant in mouse and rat models of seizures, including the maximum electroshock model, and the audiogenic seizure model in mice, and pentylenetetrazole model in rats (60). These effects were seen at doses that did not impair motor function.

Epidiolex is a natural plant-based form of cannabidiol delivered in an oil-based capsule that is in development for Dravet syndrome. Cannabidiol (Epidiolex) has been designated orphan drug status for the treatment of Dravet syndrome by the FDA. It is available in several expanded access programs. At the time of this writing, GBH Pharma is conducting an open-label dose-ranging trial in children with severe epilepsy. It is likely that cannabidivarin and other phytocannabinoids will be further investigated for specific use in human epilepsy.

Carisbamate

Carisbamate (S-2-O-carbamoyl-1-o-chlorophenyl-ethanol, formerly RWJ-333369) is a novel molecule in the carbamate class that has exhibited potent and broad activity in rodent seizure models including audiogenic seizure models and seizures induced by MES (Maximal Electroshock), PTZ, BIC (bicuculline), and picrotoxin, as well as in corneal-kindled rats (6). Carisbamate also suppressed the duration of spike-and-wave discharges in the GAERS model (61) and has shown efficacy in additional rat models. Approximately 44% of the drug is protein bound, and primary routes of metabolism include O-glucuronidation and carbamate ester hydrolysis followed by oxidation of the aliphatic side chain (62). Unlike felbamate, there is low likelihood of conversion to the reactive metabolite mercapturic acid or its conjugates (63). This is important as presence of mercapturic acid has been suggested as a potential cause of some of felbamate's serious idiosyncratic reactions. Carisbamate has a 12-hour half-life allowing for twice daily dosing and follows linear pharmacokinetics (64). Maximum concentrations (C_{max}) occur 1 to 3 hours after dosing. Oral (metabolic) clearance is low. It is primarily renally excreted. Carisbamate has minimal impact on CYP450 hepatic enzymes and only slightly increases valproic acid and lamotrigine clearance (63). While carisbamate has no effect on carbamazepine pharmacokinetics, the C_{max} of carisbamate is reduced by approximately 30% when administered with carbamazepine (65). Carisbamate plasma concentration is reduced to a lesser extent when administered with an oral contraceptive (63). A randomized, double-blind, placebo-controlled, dose-ranging Phase IIb study for adjunctive use in partial-onset seizures has recently been completed (66). At carisbamate doses of 300, 800, and 1600 mg/day, patients experienced a reduced seizure frequency of 24% ($P = 0.001$), 21% ($P = 0.006$), and 29% ($P < 0.001$), respectively, compared to a 6% reduction in the placebo group. The most common adverse events in patients were CNS related (headaches, dizziness, somnolence) and led to drug discontinuation in 6%, 12%, and 19% in each of the respective carisbamate-treated groups (vs. 8% in the placebo group). However, two other identical randomized placebo-controlled trials revealed that patients treated with carisbamate 400 mg/day had significant improvement ($P < 0.01$) in percent reduction of seizure frequency compared to placebo in one study, but not the other (67). Carisbamate 200 mg/day did not differ statistically from placebo in either study (67).

Johnson and Johnson filed a new drug application (NDA) to the FDA in 2008. After initial approval, the conflicting results from the completed studies led the FDA to not give marketing

approval in 2009, and development was suspended. This compound has recently been acquired by SK Life Science; it is presently unclear if it will continue in development for epilepsy. It may be useful to explore its use further in refractory idiopathic generalized epilepsy with photosensitivity.

Everolimus

Everolimus is an exciting new advance in the therapy of tuberous sclerosis complex and opens the way for more specific biologic therapies as advances in genetics and genomics uncover more specific molecular mechanisms underlying the epilepsies. Tuberous sclerosis complex is frequently associated with treatment resistant epilepsy and is the prototypic "mTORopathy" which also includes a proportion of other disorders associated with epilepsy including focal cortical dysplasia, ganglioglioma, and hemimegancephaly (68). The mTOR pathway is critical in the control of cell growth and proliferation in the development of the cerebral cortex. Aberrant control of the mTOR pathway due to pathogenic mutations in mTOR complex 1 (mTORC1) and other genes involved in the mTOR pathway may allow for abnormal cell growth and differentiation. Everolimus is a rapamycin analog (a "rapalog") with a superior pharmacokinetic profile to that of rapamycin. It has been shown to be effective and safe in the treatment of patients with tuberous sclerosis complex and associated subependymal giant cell astrocytomas (69). The recent EXIST-1 trial (70), involving 117 patients aged between 0 and 65 years, demonstrated a >50% reduction in the volume of subependymal giant cell astrocytomas in 35% of patients on active treatment, suggesting a clear disease-modifying effect of everolimus in tuberous sclerosis complex. Adverse effects include stomatitis and mouth ulceration and were mild and did not lead to treatment discontinuation in the EXIST-1 trial. Mean duration of active treatment was 41.9 weeks. Anecdotal reports have described the beneficial effects on seizure control in patients with refractory epilepsy associated with tuberous sclerosis complex (71); trials are now in progress or planned to test this exciting prospect more formally. If this is proven, then it may be that individuals with epilepsy associated with genetic defects involving the mTOR pathway more broadly may benefit from everolimus therapy.

Huperzine A

Huperzine A, an N-methyl-D-aspartate (NMDA) receptor and acetylcholinesterase inhibitor, is a sesquiterpene lycopodium alkaloid isolated from the Chinese club moss Huperzia serrata, traditionally used in China for swelling, fever and inflammation, blood disorders, and schizophrenia (7,72,73). Huperzine A is approved for use in China for Alzheimer disease and is considered a dietary supplement by the U.S. FDA, available in health food stores. A recent Cochrane Review of use of huperzine A in mild cognitive impairment failed to identify suitable randomized placebo-controlled trials (74). While huperzine A has not been shown to protect against seizures in the MES-induced seizure model, it has been found to be protective against subcutaneous PTZ-induced seizures in mice and NMDA-induced seizures and status epilepticus in rats (75). A maximum protection was observed at three doses of 1, 2, and 4 mg/kg in mice; however, rotarod test impairment was observed in a majority of mice at doses of 2 and 4 mg/kg (76). Given its mechanism of action, it has been speculated that huperzine A may be effective in the management of organophosphate poisoning, which is associated with acute symptomatic seizures (75). A trial is underway in patients with Alzheimer disease using doses of 200 and 400 g twice daily. A case report has described the apparent beneficial effect of huperzine A lasting over 6 months in a Bernese mountain dog with frequent complex partial

seizures (77). Further preclinical studies to better understand its mechanism of action and pharmacologic profile are underway with a view toward further clinical trials in epilepsy.

NAX 810-2 and Other Galanin Receptor-2-Based Therapies

Galanin is a neuropeptide with anticonvulsant properties, acting on galanin (Gal) receptor subtypes 1 and 2. Systemic administration of galanin leads to poor penetration across the blood–brain barrier and activation of peripheral GalR1, which leads to inhibition of insulin release and thus hyperglycemia. NAX 810-2 is the lead compound in a series of galanin analog with preferential binding to GalR2; it is safer and leads to less hyperglycemia. NAX 810-2 is active in a wide variety of animal models of epilepsy, including the mouse 6 Hz seizure model. It also appears to be effective in animal models of pain. Further preclinical studies are ongoing.

Propofol Hemi-Succinate

Propofol hemisuccinate (PHS), a water-soluble prodrug form of the anesthetic agent propofol, is delivered via nebulizer to the lung. The onset of action of PHS compared to propofol in proof-of-principle animal studies is delayed, which suggests conversion of PHS to propofol might occur (78). In mice, intraperitoneal PHS (60 to 80 mg/kg) elevated seizure thresholds in PTZ, bicuculline, picrotoxin, and kainic acid seizure models (78); however, intratracheal administration was more potent, elevating seizure threshold at lower doses (10 to 15 mg/kg). Onset of PHS activity in the PTZ mouse threshold model was at 5 minutes, maximal activity at 10 minutes, and loss of activity at 20 minutes (78). These findings suggest that intratracheal PHS administration provides potent seizure protection of rapid onset and brief duration (78). Intrapulmonary PHS is not known to cause pulmonary damage or inflammation. Human safety and efficacy studies of nebulized PHS are planned.

Stiripentol

Stiripentol (4,4 dimethyl-1-(3,4-methylenedioxyphenyl)- 1-penten-3-ol) is a structurally novel molecule belonging to the aromatic allylic alcohol family. It has been used in France and Canada for over 15 years, but only recently began development for use in the United States. Animal studies have shown that stiripentol both inhibits synaptosomal GABA uptake and also enhances GABAergic transmission in CA3 pyramidal neurons of immature rats (79,80). In addition, stiripentol inhibits the hepatic cytochrome P450 enzymes, which likely also contributes to the drug's antiepileptogenic properties when it is combined with other AEDs, as serum concentrations of many concomitant AEDs will rise (81). This feature of stiripentol has made it difficult to study clinically. Patients with refractory epilepsy are often on concomitant AEDs, making it difficult to attribute any observed therapeutic effects purely to stiripentol. Specifically, stiripentol inhibits CYP3A4, CYP2C19, and CYP1A2. The coadministration of stiripentol with carbamazepine significantly increases the ratio of carbamazepine to carbamazepine epoxide. Stiripentol also inhibits the hydroxylation of the active metabolite of clobazam, desmethylclobazam. These interactions underscore the need to reduce the dose of carbamazepine and clobazam when stiripentol is added as adjunctive therapy. Because of its broad inhibition of the CYP system, stiripentol has the propensity to cause many other drug–drug interactions, including the elevation of theophylline and caffeine through CYP1A2 inhibition. Stiripentol is 99% protein bound and demonstrates nonlinear pharmacokinetics, decreasing in clearance as drug dose increases (82).

Since 1995, studies in adults have been discontinued due to lack of efficacy; however, results in children have been more promising. The first trial was an open-label adjunctive therapy study, which included children with partial-onset epilepsy, as well as children with Dravet syndrome (severe myoclonic epilepsy in infants) (83). Two-thirds of the children with partial epilepsy treated with stiripentol were responders to drug, and 20% became seizure free. In addition, 10 out of 20 children with Dravet syndrome were responders, and three became seizure free. Given these findings, two additional small add-on trials were performed, one in France and one in Italy. Children 3 to 18 years of age with Dravet syndrome were enrolled. Stiripentol significantly reduced clonic and tonic–clonic seizure frequency and led to complete seizure freedom in 9/21 patients and 3/12 patients in the two respective trials (84). Whether these results are purely attributable to stiripentol alone, or to secondary increases in concomitant AEDs, remains to be determined. Adverse effects of stiripentol are fairly common, but can be minimized by adjusting doses of coadministered drugs. The most frequently observed adverse effects include drowsiness, slowing of mental function, ataxia, diplopia, loss of appetite causing weight loss, nausea, abdominal pain, and occasionally asymptomatic neutropenia (85). Currently, stiripentol is available from some hospitals in France and has been granted orphan drug status by the European Union for use in Dravet syndrome. In a recently published retrospective study in 82 children with Dravet syndrome in the United States, stiripentol use reduced seizure frequency, prolonged seizure occurrence, rescue medication use, and emergency room visits (86).

Tonabersat

Tonabersat is a novel benzoylamino benzopyran compound developed by SmithKline Beecham for the treatment of migraine and epilepsy (8). It binds to a site distinct from other CNS drugs and possesses a novel mechanism of action that possibly relates to uncoupling of neuronal gap junctions (8). Findings in rats suggest gap junctions play a role in the expression, duration, and propagation of seizures; in one study, blockade of gap junctions with carbenoxolone shortened seizure duration and decreased ictal discharge amplitude, while opening of gap junctions with trimethylamine increased ictal duration and amplitude and facilitated secondary epileptogenesis (87). Tonabersat has been tested in multiple animal models in preclinical studies; in vivo tonabersat demonstrated low toxicity with a TD50 > 250 mg/kg in mice and > 500 mg/kg in rats (8). Time- and dose-dependent inhibition of tonic extension seizures was observed in the rat MES model, and efficacy against audiogenic seizures has also been appreciated (8). Tonabersat was not effective against 6 Hz or picrotoxin-/bicuculline-induced clonic seizures (8). It also failed to inhibit seizures in either hippocampal or lamotrigine-resistant kindled rats (8). Tonabersat is currently undergoing Phase 1 clinical studies for epilepsy.

YKP3089

YKP3089 is a novel tetrazole-derived compound now in Phase 11 clinical development (8). It has been effective in a wide variety of epilepsy and seizure animal models, suggesting its potential use as a broad-spectrum AED (7). It also has efficacy in rodent models of anxiety. Its mechanism of action is currently unknown. Phase I clinical trials have documented linear pharmacokinetics over a single dose range of 5 to 750 mg and a half-life of 30 to 75 hours (7). Single dose studies have shown the drug to be well tolerated, with a low incidence of CNS-related adverse effects. The compound was

effective in a photosensitivity study. In this study, 12 patients were given a single dose of either placebo or 100, 250, or 400 mg of YKP 3089. The best response was seen at the highest dose of 400 mg. The 400 mg dose level of YKP3089 produced complete suppression of intermittent photic sensitivity in 1 out of 4 (25%) patients and partial suppression in 2 out of 4 (50%) patients in at least one eye condition (88).

A recently completed Phase II study demonstrated good efficacy. Patients with partial-onset seizures were randomized to placebo or to adjunctive 200 mg YKP3089 over a 6-week titration period followed by a 6-week maintenance period. There was a 50% responder rate of 50% in patients randomized to YKP versus 22% on placebo $P < 0.0001$. Twenty-eight percent of patients on active drug were seizure free during the maintenance phase versus 9% on placebo (88). A larger dose-ranging trial was ongoing at the time of this writing.

CONCLUSIONS AND FUTURE DIRECTIONS

The choice of clinically effective novel anticonvulsant compounds will likely expand and help more patients with epilepsy live with fewer seizures and side effects. However, with now over 20 AEDs available, the practicalities and logistics of performing the old type of trial designs in investigating new compounds is now a very significant challenge; new innovative trial designs are needed. As new drugs are released onto market, continued vigilance will be needed to detect rare idiosyncratic side effects, and this should include the use of postmarketing surveillance studies. Interest will grow in the elucidation of optimal combination therapies using the available and upcoming drugs. Improvements in drug delivery systems and an increased choice of parenteral formulations are other reasonable expectations. The identification of compounds with antiepileptogenic and neuroprotective properties remains a priority. Advances in our understanding of the genomic underpinnings of many of the epilepsies and continued pharmacogenomics research will help pave the way for tailored biologic therapies and more individualized drug prescribing.

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CHAPTER 69 LESS COMMONLY USED ANTIEPILEPTIC DRUGS

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The AEDs are generally divided broadly into the first-generation and second-generation agents, with the first generation consisting of those agents that became available prior to the mid-1980s and the second generation consisting of those agents that became available after 1992. Some go further and consider agents that emerged after 2000 as possibly making up a third generation of AEDs. The generations are largely differentiated from each other on the basis of tolerability differences rather than differences in efficacy, with newer agents generally considered less likely to be associated with toxic, dose-dependent side effects. There is little evidence of substantial and consistent superiority between different AEDs, although some may work better than others in an individual patient or in specific syndromes. While the newer agents have supplanted the older ones in many circumstances, older agents are still sometimes used when newer agents are not available or have failed to yield an adequate clinical response.

This chapter focuses on some of the older and less frequently encountered AEDs that are still in use in some parts of the world, albeit infrequently. Some of these agents are no longer available in the United States. They are presented in chronologic order of their development for the treatment of epilepsy: bromides, mephobarbital, acetazolamide, pyridoxine, ethotoin, and methsuximide.

BROMIDES

Historical Background

In 1857, at a time when seizures were linked to hysteria and masturbation, bromides were thought to have antiaphrodisiac properties and were introduced for the treatment of epilepsy (1). They remained the principal AED until phenobarbital became available in 1912 and are rarely used in the modern era.

Chemistry and Mechanism of Action

The anticonvulsant mechanism of bromides is thought to be related to hyperpolarization of postsynaptic membranes. Bromide has a smaller hydrated diameter than does chloride, crosses cell membranes faster, and tends to hyperpolarize postsynaptic membranes activated by inhibitory neurotransmitters (2).

Absorption, Distribution, and Metabolism

Bromide salts are rapidly absorbed from the GI tract and have nearly complete bioavailability, with a

volume of distribution similar to that of chloride ions (3). Tissues do not distinguish between these two anions, so their concentration in extracellular fluids depends on their relative intake and excretion. Bromides have a half-life of approximately 12 days after oral administration (3). Excretion by the kidneys occurs slowly and depends on concomitant chloride intake. A high chloride load increases the excretion of bromides and shortens the half-life. Conversely, a salt-deficient diet reduces bromide clearance and prolongs the half-life (3).

Efficacy and Clinical Use

Bromides are usually administered as triple bromide elixir (a combination of sodium, potassium, and ammonium bromide salts) containing 240 mg/mL of bromide salt. The usual dosage in children younger than 6 years of age ranges from 300 mg twice daily to 600 mg three times daily. For children older than 6 years of age, 300 to 1000 mg is administered three times daily (4). The therapeutic plasma concentration (3) ranges from 750 to 1250 μg/mL. The therapeutic window for bromides is narrow, with potential toxicity at plasma concentrations in the range of 1500 μg/mL. Careful monitoring is thus required, and a steady dietary salt intake should be maintained during treatment.

Interactions with Other Agents and Adverse Effects

Interactions between bromides and other agents have not been reported. Sedation is the most frequently encountered side effect, usually a result of chronic toxicity (bromism), which can also cause weakness, fatigue, headaches, irritability, confusion, restlessness, psychosis, and sometimes coma (5). Dermatologic manifestations include rash, nodular or pustular lesions, and ulcerations. Anorexia, constipation, and GI distress may also occur. Rare cases of acute intoxication with nephrotoxicity and ototoxicity have been reported. Bromism is treated by the administration of a large quantity of sodium chloride and a chloruretic agent. Hemodialysis or peritoneal dialysis can be used to lower bromide levels rapidly (6).

MEPHOBARBITAL

Historical Background

Hundreds of barbiturate compounds have been synthesized since barbituric acid was first produced in 1864, but only a few have been licensed by the U.S. Food and Drug Administration as hypnotics, anesthetics, or anticonvulsants (7). Three barbiturate agents have commonly been marketed as AEDs: phenobarbital, primidone, and mephobarbital (methylphenobarbital). Phenobarbital was introduced in 1912 and remains a major AED in use worldwide for a variety seizure types, most often for refractory status epilepticus in the United States. Primidone is a deoxybarbiturate that is metabolized to phenobarbital and phenylethylmalonamide. Phenobarbital and primidone are discussed in detail in other chapters. Mephobarbital is considered here.

Chemistry and Mechanism of Action

Mephobarbital is structurally similar to phenobarbital, with the addition of a methyl group at the 3 N position. All commercially available hypnotic barbiturates exhibit anticonvulsant activity at

anesthetic doses and inhibit epileptic seizures induced by electroshock, tetanus, strychnine, or pentylenetetrazol. This anticonvulsant activity is distinct from sedative or anesthetic effects and is not diminished by the concurrent administration of agents that counteract sedation (7). Barbiturates prolong and potentiate the action of GABA at $GABA_A$ receptors (8).

Absorption, Distribution, and Metabolism

Mephobarbital is highly soluble in lipids, is easily absorbed, and readily crosses biologic membranes. It is widely distributed in the body, with higher concentrations in adipose tissue and brain. It is metabolized to phenobarbital by demethylation in the liver, is affected by the cytochrome P450 system, and is partly excreted in human urine as a p-hydroxyphenyl glucuronide derivative of the parent drug (9). Phenobarbital is a hepatic enzyme inducer, possibly responsible for the gradual decrease in mephobarbital elimination half-life from approximately 50 hours initially to 12 to 24 hours during long-term therapy.

Efficacy and Clinical Use

Clinical use of mephobarbital began in 1932 (10). One might reasonably expect its efficacy and safety to be similar to that of its metabolite, phenobarbital, although well-controlled studies comparing it with other AEDs for the treatment of epilepsy have not been conducted. The therapeutic range of mephobarbital is expressed in terms of plasma phenobarbital concentrations because of the metabolite's slower metabolism. Usual therapeutic plasma levels of phenobarbital range from 10 to 40 μg/mL and steady-state plasma phenobarbital levels correlate closely with mephobarbital dose. Mephobarbital dosages of 3 to 4 mg/kg/day produce mean plasma phenobarbital levels of 15 μg/mL; a dosage of 5 mg/kg/day produces mean levels of 20 μg/mL (11). At higher mephobarbital doses, proportionately lower phenobarbital plasma levels are seen. This may suggest a rate-limited metabolism at high plasma mephobarbital concentrations (11).

Interactions with Other Agents and Adverse Effects

Any interaction that is known to occur with phenobarbital is also likely to happen with mephobarbital. The most common adverse effects with both agents include cognitive impairment, hypnotic effects, irritability, hyperactivity, and alterations in sleep patterns (7). Thus, when other, safer AEDs have failed and phenobarbital or mephobarbital must be used, patients should be treated with the lowest dose that effects adequate seizure control.

Another set of side effects of phenobarbital that are sometimes unintentionally minimized by both patients and physicians are impotence and decreased libido. In a Veterans Administration Cooperative study, Mattson and colleagues (12) found that 15% of patients complained of decreased potency, decreased libido, or both. Of 56 patients who took phenobarbital for 1 year, 14% reported a transient or continuous decrease in sexual function. The problem usually disappeared when phenytoin or carbamazepine was substituted for phenobarbital but not when phenobarbital was changed to another barbiturate.

ACETAZOLAMIDE

Historical Background

Carbonic anhydrase activity was first demonstrated in red blood cells in the early 1930s and has subsequently been found in many tissues, including the pancreas, gastric mucosa, renal cortex, eye, and the CNS. Inhibition of carbonic anhydrase activity was observed when sulfanilamide was introduced as a chemotherapeutic agent. A large number of sulfonamides have been synthesized and tested as carbonic anhydrase inhibitors and potential diuretics. Acetazolamide was first introduced in 1952 (13) and is still in limited use in the present day. It can be effective in several seizure types but has limited long-term utility because tolerance develops rapidly (14).

Chemistry and Mechanism of Action

Acetazolamide (N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl-)acetamide) is a weak acid that acts through inhibition of carbonic anhydrase, causing accumulation of carbon dioxide that is thought to be responsible for its anticonvulsant properties (15). Blocking carbonic anhydrase in other tissues, particularly red blood cells, causes even greater retention of carbon dioxide in the brain (15). Accumulation of carbon dioxide is thought to result in blockade of anion transport, disrupting seizure propagation as measured by prevention of maximal electroshock-induced seizures, which correlates with the degree of inhibition of brain carbonic anhydrase (16,17). The drug also alters choroid plexus function through its effect on carbonic anhydrase, decreasing production of CSF by limiting chloride and bicarbonate transport across the plexus, resulting in subsequent increased carbonic anhydrase synthesis in glial cells and glial proliferation, which may be a reason for the development of tolerance (14).

Absorption, Distribution, and Metabolism

Acetazolamide is rapidly absorbed from the GI tract, and peak plasma levels occur 2 to 4 hours after a single oral dose (14). In humans, the agent is 90% protein bound, so concentrations are lower in CSF than in plasma. The greatest concentration of acetazolamide is in red blood cells. After distribution to various tissues, it binds to carbonic anhydrase and remains in a relatively stable carbonic anhydrase–acetazolamide complex. The plasma half-life of acetazolamide is 2 to 4 days. It is eliminated in the urine unchanged. Increasing urinary pH increases excretion. Acetazolamide is also excreted in the bile and is resorbed from the intestinal tract.

Efficacy and Clinical Use

Acetazolamide is effective against multiple seizure types, but tolerance develops within weeks of continuous treatment (14). For this reason, it is primarily used on an intermittent basis to treat periodic seizure exacerbations. Perhaps the most common application of acetazolamide is in catamenial epilepsy (18). The drug can be started prior to the expected onset of menses in each cycle and continued through the period of increased seizure risk. Steady-state plasma levels occur 5 to 7 days after the initial dose, and adequate levels continue for 3 to 5 days after the agent is discontinued. The recommended daily dosage of acetazolamide is 10 mg/kg given in a single dose or in two or three divided doses. Usual effective therapeutic plasma levels range from 8 to 14 μg/mL. Acetazolamide is available in 125- and 250-mg scored tablets as well as delayed-release 500-mg tablets.

Interactions with Other Agents and Adverse Effects

Acetazolamide is a relatively benign agent, with only a few known adverse effects. Lethargy, paresthesias, rashes, abdominal distention, and cyanosis have been reported with its use. It can alter taste sensation in up to 90% of patients, giving a false flat taste to carbonated beverages (19). Renal calculi have been reported after long-term use. Patients who have been taking phenytoin, barbiturates, and/or acetazolamide for 5 years or more show decreased bone mineral density compared with healthy controls (20). Elimination of acetazolamide may decrease and its half-life may increase with the concomitant use of probenecid, which blocks renal tubular secretion of acids. The absorption of salicylate may be increased and that of amphetamine may be delayed when these drugs are taken with acetazolamide.

PYRIDOXINE

Historical Background

The role of pyridoxine (vitamin B_6) in neonatal seizures was first recognized in the mid-1950s. Two types of pyridoxine-related seizure syndromes occur in the newborn: that caused by pyridoxine deficiency (21) and that caused by pyridoxine dependency (22). These rare conditions carry a poor prognosis for mental development if prompt treatment is not rendered. Pyridoxine deficiency is a nutritional disorder in which vitamin B_6 levels are reduced, whereas they tend to be normal in pyridoxine dependency. Pyridoxine dependency is an autosomal recessive disorder that typically manifests in neonates, although onset has been reported up to the age of 19 months (23). Supplemental vitamin B_6 is the only effective treatment for both syndromes. In pyridoxine deficiency, a single dose is sufficient, whereas pyridoxine dependency requires continued vitamin B_6 administration.

Chemistry and Mechanism of Action

Pyridoxal phosphate, the active metabolite of vitamin B_6, is the coenzyme for glutamic acid decarboxylase and GABA transaminase, the enzymes necessary for the production and metabolism of CNS GABA. In pyridoxine-dependent and -deficient states, GABA levels in CSF are significantly reduced (24). Supplementation of vitamin B_6 reverses this deficit.

Efficacy and Clinical Use

Pyridoxine Dependency

The diagnosis is established by remission of seizures (generalized seizures or status epilepticus) with vitamin B_6 and relapse without treatment. Pyridoxine hydrochloride stops seizures within minutes when given parenterally at doses in the range of 50 to 100 mg (25). In pyridoxine dependency, lifelong supplementation with vitamin B_6 is needed. Withdrawal of pyridoxine even after several years of effective therapy causes seizures to recur within days or weeks (25). Untreated patients develop intractable epilepsy, and most die within days or months (26). Psychomotor retardation and

progressive neurologic deterioration result when therapy is delayed, so early diagnosis and treatment are important for stopping the seizures and preventing a chronic encephalopathy.

Pyridoxine-dependent seizures rarely may involve prolonged seizure-free periods with conventional AEDs before pyridoxine treatment (25). Bass and coworkers (27) reported other atypical features in a child whose seizures stopped only after repeated trials of pyridoxine. The investigators warned of the possibility of decreased levels of consciousness with intravenous pyridoxine and of the need to have resuscitative equipment available.

Recommended daily oral maintenance dosages range from 2 to 300 mg, corresponding to doses from 0.2 to 30 mg/kg/day (25,26), with most patients becoming seizure free with doses between 20 and 100 mg/day. To prevent psychomotor retardation in patients with this condition, adjustments in the vitamin B_6 dosage should be based on seizure control and on normalization of glutamate concentration in the CSF (28).

Pyridoxine-Responsive Epilepsy

The finding that CSF levels of GABA were lower in patients with infantile spasms than in controls led to efforts to treat this syndrome with vitamin B_6. In the first and largest trial, 13% of children became seizure free within 2 weeks of initiation of daily treatment with vitamin B_6 at doses of 30 to 400 mg (29). However, when vitamin B_6 was assessed in comparison to valproic acid in another study, no statistically significant difference was identified between patients treated with either in monotherapy, the two in combination appeared to be more effective than either alone, and corticotropin was more effective than was vitamin B_6 both as monotherapy and in combination with valproic acid, although seizures eventually recurred in many of those patients (30). Of note, Wang and Kuo (31) suggest using pyridoxal phosphate (PLP), the active form of vitamin B_6, instead of pyridoxine in pediatric epilepsy. They reason that PLP is as inexpensive as pyridoxine is and patients with one of the four inborn errors of vitamin B_6 metabolism, pyridoxine phosphate oxidase deficiency, respond to PLP and not to pyridoxine.

It has been reported that supplementation with vitamin B_6 may help to correct the behavioral disturbance seen in children who have levetiracetam-induced behavioral side effects (32). It is unclear whether this phenomenon is related to relative pyridoxine deficiency.

Adverse Effects

After IV vitamin B_6 administration, apnea, lethargy, pallor, decreased responsiveness, and hypotonia may occur immediately and persist for several hours (26,27). Perhaps the most well-recognized consequence of long-term pyridoxine use is the development of peripheral neuropathy (33).

ETHOTOIN

Historical Background

Phenobarbital was the agent of choice in the treatment of seizures in the United States until 1938, when phenytoin began to be marketed as an AED. Merritt and Putnam first reported on the

anticonvulsant properties of phenyl derivatives in animal studies and recommended clinical trials of phenytoin (5,5-diphenylhydantoin), demonstrating the superiority of the agent over phenobarbital due to its lack of significant hypnotic effects (34). Phenytoin soon became the world's most commonly used agent for the treatment of patients with generalized tonic–clonic and simple and complex partial seizures. Other hydantoins also were tested, but only ethotoin, which became available in 1956 (35), is still in use today—although it is no longer available in the United States.

Chemistry and Mechanism of Action

Ethotoin (3-ethyl-5-phenylhydantoin) is structurally similar to phenytoin, except for the deletion of one phenyl group from position 5 and the addition of an ethyl group in position 3 of the hydantoin ring. Ethotoin inhibits seizures induced by maximal electroshock and pentylenetetrazol. Hydantoins cause frequency-dependent suppression of the sodium-mediated action potential through enhanced inactivation of voltage- gated sodium channels (36).

Absorption, Distribution, and Metabolism

Ethotoin is slowly absorbed from the gastrointestinal tract. Absorption is dose dependent; the time to peak plasma concentration increases with increasing dose. This nonlinear profile may explain the poor correlation between daily dose and steady-state serum levels of ethotoin (37). Ethotoin is metabolized in the liver by hydroxylation and de-ethylation of the hydantoin ring.

Efficacy and Clinical Use

The clinical use of ethotoin has been primarily limited by its relatively short half-life of 6 to 9 hours (38), although lack of gingival hyperplasia and hirsutism, side effects commonly encountered with phenytoin, made ethotoin an attractive alternative. Because of its short half-life, ethotoin is given in four divided doses of 20 to 40 mg/kg/day. In a retrospective study of adults with medically refractory epilepsy, ethotoin as adjunctive therapy reduced overall seizure frequency, especially the frequency of tonic seizures (39). The efficacy of the agent, however, was reduced by one-half within 10 months, suggesting relatively rapid onset of tolerance. Ethotoin is ineffective in treating and may exacerbate absence seizures.

Interactions with Other Agents and Adverse Effects

No drug–drug interactions have been documented with ethotoin. Ethotoin can cause ataxia, diplopia, dizziness, insomnia, rash, GI distress, and rarely lymphadenopathy. Cleft lip, cleft palate, and other malformations have occurred in infants born to mothers taking ethotoin (40). Although ethotoin has been available for more than five decades, its efficacy and safety were not adequately established, and its use in the treatment of seizures and epilepsy has waned to the point that it is no longer available in the United States.

METHSUXIMIDE

Historical Background

Methsuximide belongs to the succinimide family, which also includes the more commonly used AED, ethosuximide. The latter is discussed separately. This group of agents emerged as effective for the treatment of absence seizures in the late 1950s and early 1960s. Methsuximide was introduced in 1957 for the treatment of refractory absence seizures but is also effective in the treatment of partial seizures (41). It is no longer used in the United States.

Chemistry and Mechanism of Action

Succinimides share a common heterocyclic ring. They can have either proconvulsant or anticonvulsant effects (42). This may be related to the substitution of different chemical groups in the succinimide ring (7). Methsuximide is a nonpolar chemical compound that is water soluble and slightly lipophilic. While its exact effects on excitable membranes are not known, its effectiveness against absence seizures suggests that it may block calcium currents similarly to ethosuximide (42).

Absorption, Distribution, and Metabolism

Methsuximide is quickly absorbed through the GI tract and is evenly distributed throughout the body, with peak plasma levels achieved within 2 to 4 hours. It has a mean half-life of 1.4 hours and is rapidly metabolized to N-desmethyl-methsuximide, which has a mean half-life of 38 hours and also has an anticonvulsant effect (43).

Efficacy and Clinical Use

Methsuximide is effective in a variety of seizure types, including absence seizures, myoclonic seizures, and focal-onset seizures (41,44). Tolerance to the anticonvulsant effect of methsuximide develops in approximately 50% of patients treated with maximal doses, and seizure frequency eventually returns to baseline. Rapid dose titration can be associated with toxicity that may lead to therapeutic failure, so dose should not be increased more often than every 2 weeks (45).

Interactions with Other Agents and Adverse Effects

Methsuximide interacts with other AEDs, necessitating close monitoring of serum levels and adjustment of concurrent AED dose, especially in the face of clinical toxicity (45). Methsuximide increases the mean serum concentration of phenobarbital by up to 37% and the mean serum concentration of phenytoin by up to 78% (46). Phenobarbital and phenytoin also increase serum levels of N-desmethyl-methsuximide compared with patients taking methsuximide alone (46). Methsuximide also decreased the mean serum concentrations of several other AEDs including carbamazepine (47), valproic acid (48), lamotrigine (49), and topiramate (50). Common side effects of methsuximide include GI disturbance, lethargy, somnolence, fatigue, headache, hiccups, irritability, ataxia, blurred vision, diplopia, inattention, and dysarthria (46).

CONCLUSION

Following the “Decade of the Brain” in the 1990s, there has been a dramatic increase in the number of therapeutic options available for the treatment of seizures in epilepsy, including new pharmacotherapies, neurostimulation, and other surgical innovations. We have come to accept that

mainstream, broad-spectrum AEDs—valproate, levetiracetam, lamotrigine, topiramate, zonisamide, and felbamate—can be effective in a variety of seizure types, whereas narrow-spectrum AEDs can exacerbate some primary generalized seizure types. We accept that the true role of some of the newest AEDs remains to be fully defined. However, within these broad generalizations, no AED has ever distinguished itself as being consistently superior in efficacy. Refractory epilepsy often remains refractory despite the advent of new therapies.

In striving to achieve seizure freedom without side effects in as many patients as possible, one is often required to keep an open mind to all therapeutic options, even older agents that have fallen out of broader use. While several of the agents discussed in this chapter are no longer available in the United States, they remain in use in some countries and remain appropriate therapeutic options in selected cases when more conventional therapies are unavailable. Finally, some innovations that first came to light decades ago still have practical significance today, such as the critical role of pyridoxine in some neonatal seizure syndromes and the potential role of acetazolamide in the treatment of periodic seizure exacerbations in catamenial epilepsy.

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CHAPTER 70 DIETARY THERAPIES FOR EPILEPSY

ERIC H.W. KOSSOFF

HISTORY

Approximately 100 years ago, there were few anticonvulsants other than phenobarbital and bromides available for the treatment of epilepsy. In July 1921, the ketogenic diet (KD) was first reported as beneficial by Dr. Wilder and colleagues at the Mayo Clinic in Rochester, Minnesota (1). This treatment restricted carbohydrates, protein, calories, and fluids while significantly increasing fat intake to comprise approximately 90% of calories. Early reports described that half of all patients were responders, which is strikingly similar to more recent reports. Within several years, it became one of the most popular treatments for adults as well as children with epilepsy.

However, as new anticonvulsants such as phenytoin and carbamazepine were rapidly introduced, the popularity of the KD diminished. For several decades, it was only used at select pediatric academic medical institutions, and nearly only as a last resort. Very little research or interest existed until the creation of the Charlie Foundation parent support group in 1994 by the father of a toddler with intractable generalized seizures (www.charliefoundation.org).

In the 20 years since the Charlie Foundation was founded, dietary therapies for epilepsy have undergone a radical transformation in popularity. Every year, at least 100 new articles devoted to dietary therapy are being published by both clinical as well as basic scientists. Large international symposia solely focusing on dietary therapies have been held in Phoenix in 2008, Edinburgh in 2010, Chicago in 2012, and a fourth in Liverpool in October 2014. Results from two prospective controlled trials demonstrating efficacy of the KD are available since 2008 and 2009, respectively. Additionally, an International Consensus Statement guiding ideal use was published in 2009 (2–4). There are now four different KDs available to choose from: the traditional "classic" KD, the medium-chain triglyceride (MCT) diet, the modified Atkins diet (MAD), and the low glycemic index treatment (LGIT) (5–7). Diets are being used for adults, all over the world (including developing countries), earlier (even initially) in the treatment of epilepsy, and for neurologic conditions other than epilepsy such as Alzheimer disease, brain tumors, and autism (8–11).

Despite this recent progress, the KD is still vastly underutilized. Many patients and parents self-refer to KD centers as local neurologists are not universally encouraging of the KD. Although in one series 72% of parents received information about the KD from their child neurologists, who were typically viewed as highly supportive, the average time from epilepsy to KD onset was 2.8 years (12). Adults and children living in many regions of Central America, Africa, and Southeast Asia are not routinely offered ketogenic therapy (9).

ADMINISTRATION

The composition of the traditional "classic" KD has not changed significantly in the past 100 years since its introduction. The diet "prescription" includes a ratio of grams of fat to carbohydrate and protein combined, and 4:1 is the most common starting ratio (13). Lower ratios, usually 3:1 or 2:1, are utilized for infants, adolescents, and patients in whom higher protein or carbohydrate amounts are required due to either tolerability or side effects (13). Calories and fluid amounts are typically not restricted but are measured and calculated for each child. Examples of foods eaten include butter, bacon, heavy whipping cream, mayonnaise, oils, eggs, and cheese. However, fruits, vegetables, meats, fish, and nuts are often included as well. Breads, pastries, rice, candy, cake, and juices are significantly restricted. Computer programs such as KetoCalculator and EKM have improved the flexibility and variety of food items and meals that children are able to eat on the diet.

The KD is most commonly started in the hospital as part of a several-day admission during which parents are educated how to weigh and measure foods using gram scales (13). Fasting for 24 hours is a traditional method to start the diet. While fasting is not required for long-term benefit (14), quicker onset of ketosis may lead to faster improvement in seizure frequency (15). Vomiting, hypoglycemia, and acidosis may occur during the KD initiation week, but seizures may also rapidly decrease.

Recent years have seen a modification in the way the KD is started, not only via eliminating the fasting period but some centers have also started the KD outside the hospital (16). The MAD and the LGIT are typically taught to parents and patients during brief training sessions in outpatient clinics. E-mail administration has also been reported as a feasible alternative diet initiation and management option for adults and children in remote settings or developing countries (17). Cultural, social, and religious issues need to be considered on an individual basis, and the KD can be adapted for each family.

Anticonvulsants are typically left unchanged during the admission, other than being switched to tablet forms to avoid excess carbohydrates in liquid (13). One study determined that zonisamide may be beneficial for seizure control when used at the onset of the KD; phenobarbital may be detrimental (18). Many families start the KD with a secondary goal of anticonvulsant reduction, but this is not universally achieved (12).

The KD should not be started at home by a family; a neurologist and dietitian team are required for its maintenance. A KD-trained dietitian often adjusts the diet during periodic follow-up clinic visits every 1 to 3 months in order to optimize growth, nutrition, and efficacy (13). Side effects are consistently monitored and prevented through the use of supplements (more details to follow). An international group of 26 neurologists and dietitians, experts in the KD, published a Consensus Statement regarding ideal implementation and management in 2009 (4).

MECHANISMS OF ACTION

Twenty years ago, the KD was believed to have an unknown mechanism of action. Now it is accepted that there are multiple likely reasons for its benefits (19). The KD utilizes a high-fat, adequate-protein (1 g/kg), low-carbohydrate diet that produces metabolic changes often associated with the starvation state. Changes in plasma ketones, insulin, glucose, glucagon, and free fatty acids can occur within hours of starting the KD. Fasting appears to have an independent effect on seizure control, however, even before actual KD food is provided. Preliminary results from animal studies suggest that the effect of intermittent fasting is mediated by a distinct mechanism from the KD (20). Similarly, added benefits of fasting can be seen in children treated with the KD (21).

The name of the KD derives from the theory that ketone bodies (acetoacetate, acetone, and beta-

hydroxybutyrate), created in the liver from long- and medium-chain fatty acids, are directly anticonvulsant when crossing the blood–brain barrier. Urine and occasionally serum ketone levels are generally checked in patients on the KD to ensure that the diet is being managed correctly, in a manner analogous to anticonvulsant levels. However, it is unclear if ketosis is truly a mechanism of action or solely a marker that the body has made the metabolic shift to burn fat.

Increased mitochondrial biogenesis, oxidative phosphorylation, enhanced gamma aminobutyric acid levels, reduced neuronal excitability and firing, and stabilized synaptic function have been shown to occur in patients on the KD (19). While these may be induced by ketosis, alternative mechanisms proposed include elevated plasma free fatty acids (including polyunsaturated fatty acids), reduced glucose fluctuations, increased activation of ATP-sensitive potassium channels and adenosine, caloric restriction, and elevated brain amino acids (19).

EFFICACY

The KD is an effective treatment for patients with epilepsy, regardless of age, gender, or seizure type. A 2006 meta-analysis of 19 observational studies (1084 patients) found that after 6 months, approximately 50% to 60% of children started on the KD had a >50% seizure reduction, with 30% having >90% seizure reduction (22). Approximately 10% will become seizure free after 6 months of use. This meta-analysis and others provided further evidence for the use of the KD, but also demonstrated that no randomized, controlled studies exist to provide Class I evidence in support of its use (22,23).

This changed in 2008, following a study examining the MCT and classic KD, with a 4-week waiting period for each arm serving as its own control (2). Each arm was also subsequently randomized to an additional 12-week control period of continued anticonvulsants. After 4 months, the seizure frequency was significantly lower in the 54 children on the KD (38% decrease in seizures), compared to the 49 controls (37% increase in seizures) ($p < 0.0001$) (2). Additionally, no difference was seen in efficacy between the classical and MCT diets, the latter being also a randomized arm of this trial. Although this control group did not include a new treatment (e.g., an adjunctive anticonvulsant), the results clearly demonstrate that the KD is an effective epilepsy treatment leading to longitudinal improvement over time.

A randomized, double-blind, placebo-controlled trial of 20 patients (60 g daily glucose vs. saccharin solution given sequentially as a crossover during an initial fasting period) was published by our group at the Johns Hopkins Hospital the following year (3). This double-blinded placebo-controlled study was successful with parents and investigators being unaware of which solution the child was given or their level of ketosis. Only a strong trend toward statistical significance was identified in favor of the saccharin (treatment) group over the glucose (placebo) group, $p = 0.07$. Likely reasons for the study not to reach statistical significance include insufficient glucose (and persistent ketosis in the placebo group), the effects of fasting on immediate seizures in both groups, and too short a period allowed for a return to a baseline level of seizure frequency during the crossover between the treatment arms. There was overall a mean decrease of 34 seizures per day over the 12-day study period ($p = 0.003$) (3). This study demonstrates that the KD can be studied in a blinded manner.

The most recent randomized and controlled study followed the Neal protocol but studied the MAD (24). In this randomized, controlled trial in 102 children aged 2 to 14 years, the MAD was more likely to reduce seizures by 50% after 3 months than were continued anticonvulsants (52% vs.

11.5%, p < 0.001). The likelihood of >90% seizure reduction was also more likely with the MAD (30% vs. 7.7%, p = 0.005).

"ALTERNATIVE" DIETS

Although the KD is helpful for approximately 50% of children who try it, there are some adolescents, adults, busy families with multiple children, and patients with very high baseline carbohydrate intake (or fat aversion) who are concerned about the difficulty in changing their lifestyle to begin the KD. For these patients, "alternative" diets may be new options to successfully allow them to try this nonpharmacologic approach. Three alternative diets have been described, including the MCT diet, LGIT, and MAD (Table 70.1).

Table 70.1 Comparison of the Four Major KETOGENIC DIETS in Clinical Use (1000 Kcal/day provided)

Diet	Fat (g), % calories	Protein (g), % calories	Carbohydrate (g), % calories
Classic long-chain triglyceride KD			
4:1	100 (90%)	17 (7%)	8 (3%)
3:1	9	18	14
2:1	92	20	26
1:1	77	37	40
Medium-chain triglyceride diet	78 (70%)	25 (10%)	50 (20%)
Low glycemic index treatment	67[a] (45%)	40–60[a] (28%)	40–60 (27%)
Modified Atkins diet	70[a] (70%)	60[a] (25%)	10–20 (5%)

[a]Values are approximate.

The MCT diet has been used since the 1970s. This diet provides large quantities of this highly ketogenic oil in order to free up more carbohydrates, and this in turn improves tolerability. The MCT diet was studied in a prospective, controlled, randomized manner by Dr. Neal and colleagues from London in 2008, and although the classic KD led to higher serum ketone levels, fatigue (at 3 months), and mineral deficiencies, there was no difference in growth, efficacy, and overall tolerability (5,25,26). There may be some benefit to dyslipidemia (27). The MCT diet is mostly used in the United Kingdom and Canada at this time.

The LGIT was first published by Dr. Thiele and colleagues from Boston in 2005, based on previously anecdotal reports of excessive carbohydrates (at times from cheating) leading to immediate seizure breakthroughs (28). This diet targets glucose by providing carbohydrates with glycemic indices <50 in order to maintain stable blood glucose levels (28). Although serum ketones do increase, changes are usually minimal. The LGIT is started as an outpatient without a fasting period. An update in 2009 from the same group includes 76 children, of which 50% of those remaining on the diet at 3 months had >50% seizure reduction (7). Nearly one-quarter found the LGIT restrictive and stopped this diet for that reason. Recent studies have described benefits for children with tuberous sclerosis complex and Angelman syndrome (29,30).

The fourth therapeutic diet, the MAD, was first published by our group in 2003 (31). The MAD is also started on an outpatient without a fast, but does not restrict calories, fluid, or protein (Table 70.2). Carbohydrates are restricted to 10 g/day (children) or 20 g/day (adults), and fats are strongly encouraged in order to maintain ketosis. When analyzed, the MAD mimics a 1:1 ketogenic ratio. To our knowledge, there are now 33 publications that detail the use of the MAD in children and adults,

with 207 (46%) of 452 total subjects having >50% seizure reduction after 6 months of which 108 (22%) had >90% improvement. These results are quite similar to findings in patients treated with the KD. One recent publication suggests that using one of the KD formulas (KetoCal) during the initial month may in fact boost the efficacy of the MAD by providing additional fat sources (6). Children can be switched from the MAD to the KD, with 30% of those switched having additional benefit, especially if their underlying condition was myoclonic astatic epilepsy (Doose syndrome) (32). Long-term outcomes on the MAD after 12 months appear similar to the short-term benefits as well (33). The MAD may also be especially useful for centers in developing countries with limited resources to implement the classic KD (34). At our center, the MAD has largely supplanted the KD for adolescents and adults nowadays.

Table 70.2 Modified Atkins Diet Protocol 2014

- Copy of a carbohydrate counting guide (paperback), recipes, and Web sites provided.
- Complete blood count, liver and kidney functions, anticonvulsant levels, and fasting lipid profile at baseline, 3, and 6 months.
- Carbohydrates restricted to 10 g/day for the first month for children, 15 g/day for adolescents, 20 g/day for adults. Carbohydrates can be increased after 2 months in many patients.
- Fats (e.g., 36% heavy whipping cream, oils, butter, mayonnaise) strongly encouraged. KetoCal shake daily during the first month advised.
- Clear, carbohydrate-free fluids ad lib.
- Daily low-carbohydrate multivitamin and calcium supplementation.
- Urine ketones checked weekly for the first 2 months and weight checked weekly throughout dietary therapy.
- Medications left unchanged for at least the initial month, but reformulated if necessary to tablet or sprinkle (nonliquid) preparations.
- Discontinue the diet if ineffective after 2 months.

INDICATIONS

For many years, as evidence for its efficacy grew, the KD was solely indicated for "children with intractable epilepsy" in chapters such as this and review articles. There were no particular indications mentioned with the exception of GLUT-1 (glucose transporter-1) deficiency and pyruvate dehydrogenase deficiency. As studies have demonstrated the benefits of the KD for specific conditions, this concept has changed. The 2009 Consensus Statement focused on indications and provided a list of "indications" for the KD is available (Table 70.3) (4). These included myoclonic astatic epilepsy, tuberous sclerosis complex, Rett syndrome, infantile spasms, Dravet syndrome, and children receiving only formula (4). Since 2009, the data justifying the strong benefit of the KD for Dravet syndrome, myoclonic astatic epilepsy (Doose syndrome), and mitochondrial disorders have continued to increase (35–37).

Table 70.3 Potential Indications and Contraindications for Dietary Therapy

Probable benefit (at least two publications)
Glucose transporter protein 1 (GLUT-1) deficiency
Pyruvate dehydrogenase deficiency
Infantile spasms
Myoclonic astatic epilepsy (Doose syndrome)
Tuberous sclerosis complex
Rett syndrome
Lennox–Gastaut syndrome
Severe myoclonic epilepsy of infancy (Dravet syndrome)
Mitochondrial disorders
Children receiving only formula (infants or enterally fed patients)
Refractory status epilepticus (especially FIRES)
Suggestion of benefit (one case report or series)
Landau–Kleffner syndrome
Lafora body disease
Juvenile myoclonic epilepsy
Absence epilepsy
Hypothalamic hamartoma
Angelman syndrome
Combined use with vagus nerve stimulation
Combined use with zonisamide at KD onset
Children with recently worsened seizures in the past month
*Contraindications (*relative)*
Pyruvate carboxylase deficiency
Porphyria
Fatty acid oxidation defects
Primary carnitine deficiency
Carnitine translocase deficiency
Pancreatitis
Cardiomyopathy
Inadequate ability to maintain nutrition, or comply with the KD restrictions
Combined use with phenobarbital at KD onset*
Children with a clear focal and potentially resectable lesion*
Severe gastroesophageal reflux*
Concurrent propofol use*

Pediatric patients with infantile spasms may be the fastest growing population to be started on the KD, perhaps due to the combination of its efficacy as well as ease of use with myriad ketogenic formulas widely available worldwide. Several studies have been published on the use of the KD for infantile spasms since 2001. The largest to date included 104 infants, of which 64% had at least a >50% decrease in their spasms within 6 months of treatment, including 38 (37%) who became spasm free for at least 6 months (38). As a result of this growing evidence for intractable infantile spasms, our center has used the KD in children for new- onset infantile spasms (if the family brings the child in within 2 weeks after seizure onset) (10). To date, 10 out of 24 (42%) infants became spasm free within 2 weeks of treatment. Additional information about the use of the KD for new-onset infantile spasms is available through the Carson Harris Foundation.

New indications continue to be studied. One exciting development has been the recent attention to the use of the KD for refractory status epilepticus (39). The epilepsy condition entitled FIRES (febrile infection–related epilepsy syndrome), often difficult to control with poor outcomes, appears to be very susceptible to the KD (40). Providing the KD as a formula through a nasogastric tube to a patient in an intensive care unit with status epilepticus is a very feasible option, with successful results typically described within 7 to 10 days (39). Prospective multicenter studies for refractory status epilepticus are under way. Other conditions recently reported as responding to dietary therapy

in recent years include absence epilepsy, juvenile myoclonic epilepsy, Sturge–Weber syndrome, and hypothalamic hamartoma.

Contraindications to the diet do exist and are primarily metabolic in nature. Children with malnourishment, primary carnitine deficiency, carnitine translocase deficiency, porphyria, pancreatitis, fatty acid oxidation defects, and cardiomyopathy should not be started on the KD (4). In addition, families with poor oral intake, vegan food preferences, dyslipidemia, parent noncompliance, and epilepsy surgery candidates [for whom surgery is more likely to lead to seizure freedom (41)] should receive detailed counseling on the KD prior to its implementation. One study suggested that those receiving phenobarbital at KD onset were less likely to respond as well (18).

ADULTS

Although described in the 1930s, KD treatment in adults with intractable epilepsy has more recently rarely been utilized and infrequently studied (8). Largely as a result of the emergence of the MAD as a less restrictive alternative, there has been a large amount of interest in this population and emergence of adult epilepsy diet centers (including in Baltimore and London) in the last few years. Evidence would suggest that when effective, the MAD will lead to seizure reduction within several weeks, thus the potential restrictiveness (if ineffective) need only be short-lived (15). Dietary therapy has been studied for adults with juvenile myoclonic epilepsy and refractory status epilepticus (39,42). The benefits of weight loss for obese patients with epilepsy may also be an additional valuable outcome. A prospective, randomized trial evaluating the MAD in combination with KetoCal [in a manner similar to a study in children (6)] is enrolling patients at our institution.

SIDE EFFECTS

Side effects do occur with dietary therapies as these treatments are neither alternative nor designed to be healthy (Table 70.4). They include constipation (improved with fiber supplements), acidosis (increased with illness), gastrointestinal upset and reflux, and lack of significant weight gain (occasionally weight loss) (13). Children who do not receive adequate vitamin and calcium supplementation will become deficient, and this must be avoided. At this time, the only mandatory supplements suggested in the Consensus Statement include an oral multivitamin, calcium, and vitamin D (4).

Table 70.4 Reported Side Effects of the KETOGENIC DIET

Common:
- Lack of significant weight gain
- Constipation
- Hypoglycemia (mostly with fasting)

Occasional:
- Gastrointestinal upset or gastroesophageal reflux
- Dehydration or acidosis (more frequent with illness)
- Dyslipidemia
- Growth slowing (especially in infants)
- Skeletal fractures (more common with long-term use)

Rare (case reports):
- Kidney stones (with use of oral citrates, otherwise occasional)
- Pancreatitis
- Cardiomyopathy
- Bruising
- Prolonged QT syndrome
- Basal ganglia changes
- Selenium and zinc deficiencies (if unsupplemented)
- Carnitine deficiency (symptomatic)

Less common, but potentially more serious side effects include dyslipidemia, kidney stones, bone fractures, and growth deficiency. Total and LDL cholesterol will often initially rise by 30% on the diet. However, lipid values stabilize after 6 months and return to normal values after several years on the KD (27,43). Kidney stones have been described historically in 6% of children placed on the KD but appear to be nearly completely prevented by empiric treatment with oral citrates (44). Decreased linear growth may occur, especially in young infants, and may be related to the level of ketosis rather than protein content of the KD (5,45). Less common side effects such as selenium and zinc deficiency, cardiomyopathy, pancreatitis, vitamin D deficiency, bone density decrease, and basal ganglia changes have also been reported. Years after the KD has been discontinued, there do not appear to be any obvious long-term adverse effects (46).

DISCONTINUATION

If ineffective, the KD can likely be discontinued within 3 to 6 months, as data suggest that benefits will occur in that time period. The optimal duration if beneficial is less clear, with several adults receiving the KD for several decades and being transitioned from pediatric KD centers (47,48). After 2 years, regardless of outcome, the risks of dietary therapy for general health and issues regarding compliance may outweigh benefits, and consideration of a gradual discontinuation should be discussed. Children with structural lesions, abnormal EEG findings, 50% to 90% seizure reduction, and those with tuberous sclerosis complex are at highest risk for worsening of seizures with diet discontinuation (49). There is no upper limit for KD duration, however, and each patient and family needs to be considered on an individual basis and involved in the decision-making process. We have found that many adults who are seizure free and driving will refuse to consider MAD discontinuation after 2 years when suggested.

Evidence indicates that once the decision has been made to wean the KD, the speed at which the diet is tapered and stopped is not relevant (50). Most children who are on the KD for long periods are weaned more slowly, in a manner similar to anticonvulsants. If ineffective, the KD can be stopped immediately without obvious ramifications (50). Our practice nowadays is to gradually reduce the ratio (or increase the daily carbohydrate limit for the MAD) every 2 weeks over a 2-month period. Abrupt discontinuations are more typically employed in monitored settings, such as a video–EEG

monitoring unit.

SUMMARY

The remarkable increase in interest of dietary therapy for epilepsy has led to expanded use for adults, new indications such as status epilepticus and infantile spasms, and worldwide availability. Careful questioning of methods of implementation has led to safer and less restrictive ways to start the classic KD in addition to the creation in the past decade of three "alternative" diets. Side effects are not only being clarified but also prevented with supplementation. As the mechanisms of action continue to be clarified, modifications to the KD will hopefully allow it to be more efficacious as well.

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CHAPTER 71 VAGUS NERVE STIMULATION THERAPY

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Epilepsy and seizures affect nearly 3 million individuals in the United States, with approximately 200,000 new cases diagnosed each year. Although antiepileptic drugs (AEDs) are the primary form of treatment, outcome surveys continue to reveal only mixed success even with the new AEDs, some with unique mechanisms of action, that have become available over the past 20 years (1,2). Approximately one-third of patients have seizures that are unresponsive to pharmacologic therapy (3–5). In addition, safety and tolerability issues associated with both the acute and chronic side effects and toxicity complications further diminish the effectiveness of AEDs (6–12). Nonadherence to AEDs, which is highly prevalent in the epilepsy population, also diminishes treatment effectiveness and further increases mortality as well as significantly increases health care utilization (13). Other treatment options are available for select subgroups of patients, including the ketogenic diet, which provides benefit to some children (14,15), and epilepsy surgery, which may manage or lessen poorly controlled seizures in 10% to 25% of patients (16). However, children and adults with uncontrolled seizures continue to carry a sad burden of higher mortality rates, higher rates of accidents and injuries, greater incidence of cognitive and psychiatric impairment, poor self-esteem, higher levels of anxiety and depression, and social stigmatization or isolation compared with the general population (17,18). The shortcomings of AEDs, dietary therapy, and epilepsy surgery in improving overall outcome highlight the need for other treatments, one of which is vagus nerve stimulation (VNS) therapy.

HISTORY

The effect of VNS on central nervous system (CNS) activity has been documented, with early attempts in the 1880s linking electrical vagus nerve and cervical sympathetic stimulation and carotid artery compression to the treatment of seizures (19). In the mid-1980s, Jacob Zabara, a biophysicist at Temple University, again suggested that electrical stimulation of the vagus nerve might prevent seizures. VNS therapy resulted from a hypothesis, formulated during his wife's Lamaze class, that the Lamaze method activated stretch receptors in the lungs, which in turn activated the vagus nerve (20). Vagus stimulation in the neck could quiet the abdominal muscle contractions that produce vomiting; Dr. Zabara likened these contractions to convulsions. Zabara believed that if VNS could alleviate vomiting and affect electroencephalographic (EEG) findings, it might ameliorate epilepsy. This theory was proved in his first canine studies (21), and a company—Cyberonics, Inc. (Houston, TX)—was founded in 1987 to develop VNS therapy, which would be delivered by a patented method using a generator device modeled after a cardiac pacemaker.

In 1988, the first patient to have a VNS therapy device implanted became seizure free (Table 71.1) (22). Five acute-phase clinical studies analyzing the safety and effectiveness of VNS therapy

followed (Table 71.2). The first two single-blind trials showed improved control in adults with intractable partial seizures who were not candidates for epilepsy surgery (22–24). The subsequent two randomized, blinded, active-control trials (E03, E05) led to approval of VNS therapy by the U.S. Food and Drug Administration (FDA) in July 1997 for the adjunctive treatment of refractory partial-onset seizures among patients 12 years of age or older. VNS therapy is also approved for the treatment of epilepsy without age or seizure type restrictions (in most countries) and treatment-resistant depression in more than 70 countries around the world, including member nations of the European Union, Japan, Canada, Australia, and China. As of October 2013, more than 70,000 patients have received VNS therapy worldwide.

Table 71.1 History of VNS Therapy

1985	First animal studies
1988	First human implant
1992	First randomized active-control study (E03) completed
1994	European community approval
1996	Second randomized active-control study (E05) completed
1997	U.S. Food and Drug Administration commercial approval
October 2013	70,000+ implants worldwide for both epilepsy and depression

Table 71.2 Efficacy of VNS Therapy in Clinical Studies

Study	Design	Seizure type	No. of patients	Age of patients (years)	First implant	No. of patients with >50% response (%)	Mean reduction in seizures/day (%)
E01	Pilot, longitudinal	Partial	11	20–58	1998	30	24[a]
E02	Pilot, longitudinal	Partial	5	18–42	1990	50	40
E04	Open, longitudinal	All types	124	3–63	1990	29	7[a]
E03	Randomized, parallel, high/low	Partial	115	13–57	1991	31/14	24[a]/6
E05	Randomized, parallel, high/low	Partial	198	13–60	1995	23/16	28[b]/15[b]

[a] $P \leq 0.05$, by Student t-test.

[b] $P < 0.0001$, by analysis of variance.

The VNS therapy system is made up of a pulse generator, a bipolar VNS lead, a programming wand with accompanying software for a handheld computer, a tunneling tool, and handheld magnets (Fig. 71.1) (24,25). The generator transmits electrical signals to the vagus nerve through the lead. The software allows placement of the programming wand over the generator for reading and altering stimulation parameters (Fig. 71.2; Table 71.3). Each stimulation period is preceded by 2 seconds of ramp-up time and followed by 2 seconds of ramp-down time.

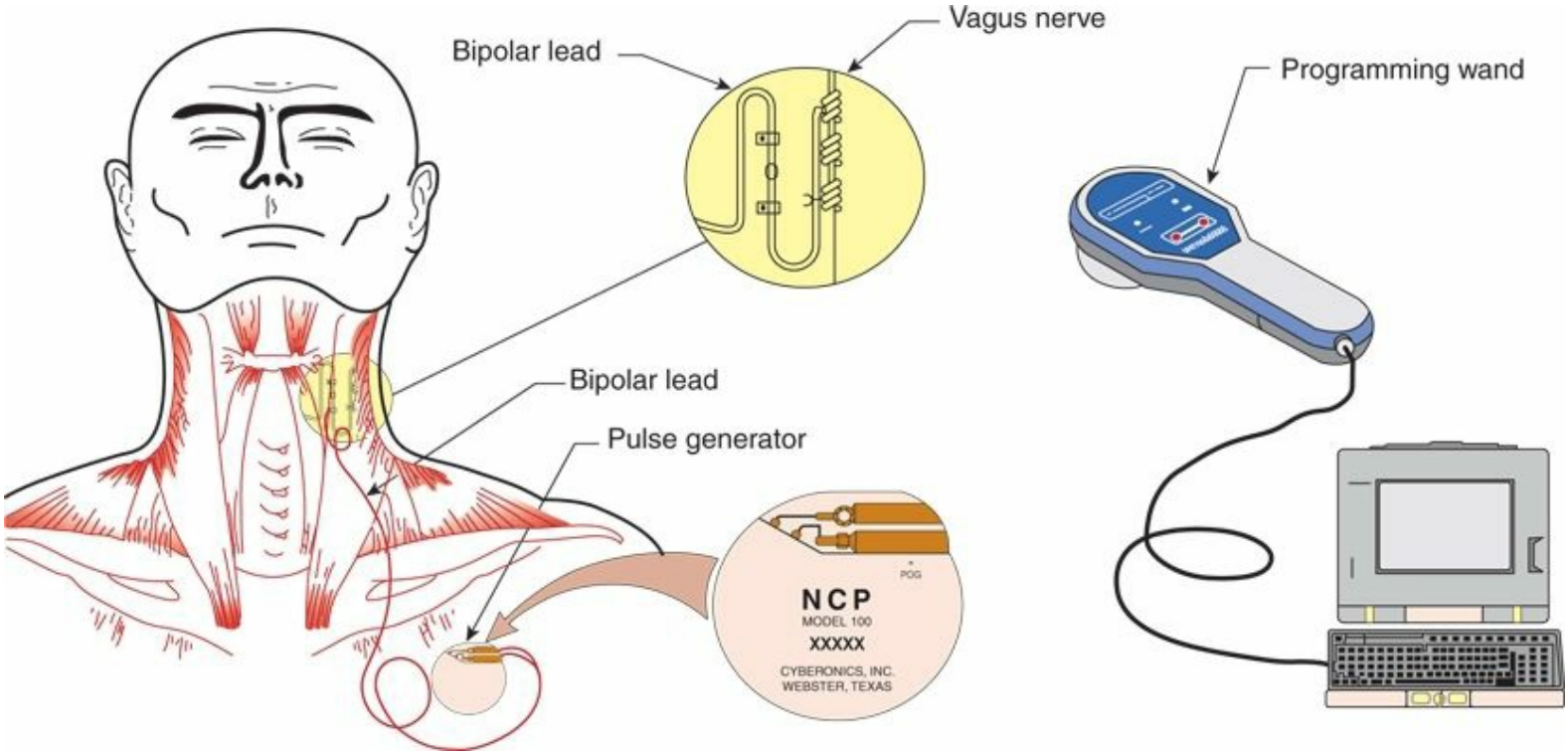

Figure 71.1. Implantable components of the VNS therapy system.

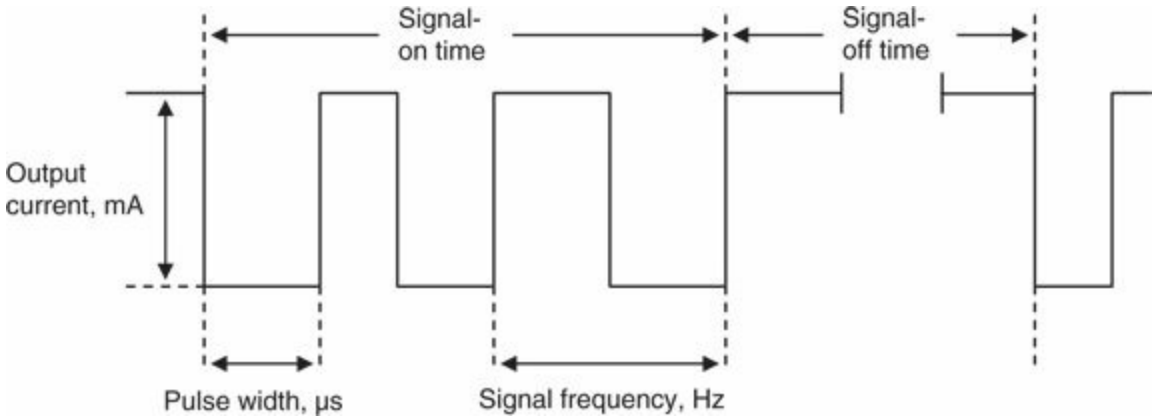

Figure 71.2. VNS therapy stimulation parameters.

Table 71.3 VNS Therapy Parameters

	High	Low	Rapid cycling[a]
VNS current (mA)	Up to 3.5	1.2 (0.25–2.75)	Up to 3.5
Frequency (Hz)	30 (20–50)	1 (to 2)	30
Pulse width (μs)	500	130	500
On time (s)	30 (to 90)	30	7
Off time (min)	5 (to 10)	180 (60–180)	0.2
Magnet current (mA)	Same as VNS	0	Same as VNS
On time (s)	30 (to 90)	30	30
Pulse width (μs)	500	130	500

Values in bold type are the most common settings from the E03 and E05 studies.
VNS, vagus nerve stimulation.

[a]From Refs. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures: The Vagus Nerve Stimulation Study Group. Neurology. 1995;45:224–230; Vonck K, Thadani V, Gilbert K, et al. Vagus nerve stimulation

for refractory epilepsy: a transatlantic experience. J Clin Neurophysiol. 2004;21:283–289; Koo B. EEG changes with vagus nerve stimulation. J Clin Neurophysiol. 2001;18:434–441.

Three models of the VNS therapy generators are currently available: the Pulse Model 102 (single pin) and Pulse Duo Model 102R (dual pin), the Demipulse Model 103 (single pin) and Demipulse Duo Model 104 (dual pin), and the newer AspireHC Model 105 (available in single pin only) (Fig. 71.3). The Demipulse generators, which are smaller and lighter than the Pulse generators, and the AspireHC generators have improved diagnostics and faster communication with the programming system. The Demipulse generators may have shorter battery life at higher duty cycles than the Pulse generators. Currently, two leads are available in the United States: the Perennia Model 303 and PerenniaFLEX Model 304. All current lead models are single pin and come in two sizes: 2.0 or 3.0 mm (inner diameters of the helical coil) to account for various sizes of the vagus nerve. Dual-pin leads are no longer available. Therefore, the dual-pin generators (Model 102R and Model 104) are for replacement procedures only in patients with the previous dual-pin lead models. The Demipulse and AspireHC generators and Perennia model leads are not yet available in all countries (see the Addendum for sources of information on the VNS therapy system).

Figure 71.3. The Pulse Model 102, Demipulse Model 103, and Aspire HC Model 105 VNS therapy generators.

EFFICACY

The two pivotal studies—E03 and E05—were designed to demonstrate that high (therapeutic) and low (nontherapeutic) stimulation of the vagus nerve had different effects on the frequency of partial seizures (26,27). The effects of VNS therapy during the 12-week randomized phases of the studies,

which began 2 weeks after implantation, were gauged against 12- to 16-week baseline periods. E03 acute-study patients (27) (N = 114 implanted) had epilepsy for an average of 22 years. Seizure frequency was reduced by at least half in 31% of patients in the high-stimulation group, compared with 14% in the low-stimulation group. No patients became seizure free during the acute phase, but some reported reduced seizure severity and improved postictal recovery periods. Patients in the high-stimulation group either aborted or decreased 59.8% of seizures with the magnet. No factors were identified that predicted response.

The similarly designed E05 study was the largest prospective, controlled trial of a device for epilepsy treatment ever conducted (26). Patients (N = 199) had a median of 0.51 to 0.58 seizures per day during baseline. One patient receiving high stimulation became seizure free, and 23.4% of patients had a 50% or more reduction in seizure frequency after 3 months of treatment. The presence or absence of aura did not predict efficacy. Of the implanted patients, 99% completed the study.

Long-Term Clinical Studies

All patients exiting study E03 were offered indefinite open-label treatment at high (effective) stimulation; 100 (88%) of the 114 patients completed an additional 12 months of VNS therapy at therapeutic stimulation levels (14 patients discontinued because of lack of efficacy but were included in the analysis as intent to treat) (28). A median 20% reduction in seizure frequency occurred in the first 3 months of the extension study and improved over the ensuing months. In two-thirds of patients, a minimum 50% reduction during the initial 3 months continued during months 10 through 12. Results among the 195 patients in the continuing long-term E05 study showed a 50% or more reduction in seizure frequency in 35% of patients and a 75% or more reduction in 20% of patients after an additional 12 months of VNS therapy at therapeutic stimulation levels (29). The median reduction in seizure frequency was 45%, with seizure frequency reductions sustained over time and only mild-to-moderate side effects reported.

Postapproval Long-Term Outcomes

In addition to the clinical trial data, postapproval outcome studies show that VNS therapy is an effective treatment with increasing or sustained response rates over time. Response rates from the literature for studies reporting on at least 100 patients with a minimum of 12 months to more than 5 years of follow-up range from 50% to 64% (30–34). A retrospective review of a prospectively created database of 436 consecutive patients, both adults and children, at a single center showed a significant reduction in mean seizure frequency (mean reduction of 55.8%; $P < 0.0001$) at a mean follow-up of 4.94 years (34). The overall response rate in this group was 64%. A subset of this group that had at least 10 years of follow-up (n = 65) showed continued improvement over time, with a mean reduction in seizure frequency of 75% at 10 years (last observation carried forward, 76%) (35). At each recorded interval at 6 months and at years 1, 2, 4, 6, 8, and 10, seizure frequency was significantly reduced from baseline ($P < 0.001$) (35). The overall responder rate at last follow-up was 91%, with 10 patients seizure free for at least 2 years before their last follow-up visit. Another retrospective study with at least 12 months of follow-up (mean of 44 months; range of 12 to 120 months) across multiple centers showed a 51% reduction in mean monthly seizure frequency (32). The overall responder rate was 59%, with an additional 13% of patients having a seizure frequency decrease between 30% and 50%. The seizure-free rate in this study was 9%. A prospective, open

evaluation of 64 patients reported results for up to 5 years of follow-up (36). No change in AED dosages occurred during the first 6 months of VNS therapy, which lasted for an average of 20 months. In this population with refractory seizures, 44% experienced a substantial reduction in severity and frequency over a long period. A report on long-term outcomes of 30 patients receiving VNS therapy (37) showed continued improvements over time, with 54% of patients at 1 year and 61% at 2 years exhibiting seizure frequency reductions of 50% or more compared with baseline. In a study of 269 patients on unchanged AEDs over 1 year, seizure frequency rates decreased over time from a median decrease of 45% at 3 months to a median of 58% at 12 months, indicating that response to VNS therapy over the long term is sustained and independent of AED changes (31). Small, prospective studies report similar results as well as additional benefits beyond seizure reduction such as reduced postictal periods and seizure duration (38,39). The mechanisms underlying the gradual improvements in response to VNS therapy seen over time in these long-term studies have yet to be elucidated. However, these findings continue to support the fact that VNS therapy has important long-term efficacy in the refractory epilepsy population.

Pediatric, Elderly, and Special Populations

Studies indicate that response to VNS therapy is independent of age, seizure type, or epilepsy syndrome. In a large consecutive series of 141 children 18 years of age and younger with treatment-resistant epilepsy and at least 1 year of follow-up, seizure frequency significantly improved with VNS therapy (mean reduction 58.9%, $P < 0.0001$) (40). The mean age at initiation of VNS therapy was 11.1 years (range, 1 to 18); 86 (61%) were under age 12 years when they received VNS therapy. The mean duration of VNS therapy was 5.2 years (range, 25 days to 11.4 years). The overall responder rate for this population was 65%, with 41% experiencing 75% or greater reduction in seizure frequency. Comparisons between those older than 12 years of age and those younger than 12 years of age showed no differences in efficacy or safety between the groups. Additional pediatric studies show similar findings in addition to showed increasing response rates over time similar to those seen in the real-world outcome data for adults with VNS (41–46). A retrospective study of 46 children implanted under the age of 18 (median age of 12.1 years) showed median seizure frequency reductions in the range of 60% over 3 years with VNS therapy, with response rates more favorable among patients <12 years of age (42). Particularly favorable results, including reduced seizure frequency and severity and improved quality of life (QoL), have been reported among patients in open-label studies of Lennox–Gastaut syndrome and other refractory childhood epilepsies, such as hypothalamic hamartomas, epileptic encephalopathies, Rett syndrome, Dravet syndrome, and tuberous sclerosis complex (41,47–66). Verbal performance, alertness, motor and cognitive functions, and general behavior improved, sometimes dramatically (49,51,60,67,68). A retrospective study (68) showed that improved QoL (particularly in the area of alertness) was associated with VNS therapy in patients with autism (N = 59) or Landau–Kleffner syndrome (LKS; N = 6), with more than half of the patients in each group also experiencing a 50% or more reduction in seizure frequency at follow-up (12 months of follow-up for autism and 6 months for LKS patients). Studies have also shown both seizure frequency reductions and improved QoL among both institutionalized and noninstitutionalized patients with mental impairment/developmental delay (69,70). VNS therapy also successfully stopped a case of refractory generalized convulsive status epilepticus in a patient 13 years of age (71). Another report among three children admitted to the intensive care unit (ICU) after developing status epilepticus showed that VNS therapy allowed early cessation of status and discharge from the ICU

(61). In a study of VNS therapy among geriatric patients, 50 years of age or more, 21 of 31 patients experienced a 50% or greater decrease in seizure frequency at 1 year, accompanied by significant improvements in QoL from baseline over time (72).

Open studies indicate that VNS is a favorable treatment option for a wide range of patients regardless of age or seizure type (40,73–79). A recent meta-analysis of VNS therapy efficacy showed that children and those patients with generalized epilepsy benefited significantly from VNS therapy (79). A study of stimulation parameters among patients of different ages (80) recommended age-related stimulation adjustments based on age-related changes seen in vagus nerve characteristics. Early studies indicated that children might respond more rapidly than adults, with reductions in the interval between stimulations resulting in improved control (Table 71.3) (51,62,67). Additional pediatric studies reported that higher output currents might be required, particularly when lower pulse durations are used (81–83). Optimal stimulus parameter settings for patients of various ages or with specific seizure types or syndromes, however, have not yet been defined.

MECHANISM OF ACTION

The mechanisms by which VNS reduces seizure activity in humans were not known at the time VNS therapy was approved by the FDA. However, considerable progress in mechanistic VNS research has been made over the last 15 years. Electrical stimulation of the peripheral vagus nerve requires polysynaptic transmission to mediate the antiseizure effect. The anatomical distribution of vagal projections underlies the therapeutic actions of VNS therapy. Vagal visceral afferents have a diffuse CNS projection, with activation of these pathways broadly affecting neuronal excitability (25,84,85). Another review (84) examined the vagus nerve projections and CNS connections, as well as the current animal and human imaging studies, which indicate that VNS exerts both acute and long-term antiepileptic effects.

EXPERIMENTAL STUDIES

The first studies of the anticonvulsant effects of VNS were conducted in 1937 (85). Subsequent experiments in cats showed that vagal stimulation produced EEG desynchronization (86) or synchronization, depending on the parameters used (87,88). Stimulation of the slow-conducting fibers most effectively resulted in EEG desynchronization. Hypersynchronized cortical and thalamocortical neuronal interactions characterize seizures; therefore, it was postulated that desynchronizing these activities would lead to anticonvulsant effects of VNS.

Initial work in cats and recent studies of strychnine-induced seizures in the dog, maximal electroshock and pentylenetetrazol-induced seizures in the rat, and the alumina-gel monkey model (21,86,89–92) showed that cervical vagal stimulation decreased interictal epileptiform discharges (IEDs) and shortened or aborted seizures; the antiepileptic effects outlasted the stimulus (21,89,92,93) and depended on its frequency and cumulative duration (89–91,93). These effects are now known to be mediated by activation of myelinated A and B fibers (94–96). Most central projections of the vagus nerve terminate in the nucleus of the solitary tract, with extensions to brainstem nuclei, thalamus, amygdala, and hypothalamus. Increased release of gamma-aminobutyric acid (GABA) and glycine by brainstem and subcortical nuclei was proposed as the antiepileptic mechanism of VNS therapy (90,91). Brainstem nuclei are known to influence seizure susceptibility (97–101); based on animal studies, the nucleus of the tractus solitarius is likely the key brainstem

structure involved in transmitting and modulating VNS antiseizure effects.

Also unknown are the processes that mediate the sustained anticonvulsant effect of VNS therapy, but this effect, which outlasts the stimulation, suggests long-term changes in neural activity. Expression of fos immunoreactivity was induced by VNS in regions of the rat brain important in epileptogenesis (102) ; fos immunolabeling in the locus caeruleus suggested VNS modulation of norepinephrine release. Increased norepinephrine release by the locus caeruleus is antiepileptogenic. In rats with chronic or acute locus caeruleus lesions, VNS-induced seizure suppression was attenuated, supporting a noradrenergic mechanism (97). This first evidence of a structure mediating the anticonvulsant action of VNS may have pharmacologic implications for clinical practice. Drugs that activate the locus caeruleus or potentiate norepinephrine effects may enhance the efficacy of VNS. Pending the results of further animal testing, it is likely that the antiepileptic action of VNS is mediated through neuronal networks that project from brainstem to forebrain structures. Vagal projections to noradrenergic and serotonergic neuromodulatory systems of the brain may also explain the positive effects of VNS in improving mood disorders.

In summary, animal studies have established three distinct temporal patterns for the anticonvulsant effects of VNS: (i) acute abortive effects, in which an ongoing seizure is attenuated by VNS; (ii) acute prophylactic effects, in which seizure-inducing agents are less effective in provoking seizures when applied at the end of VNS; and (iii) chronic progressive prophylactic effects, in which total seizure counts are reduced more following chronic VNS stimulation. In addition, animal studies have shown that VNS can antagonize the development of epilepsy in the kindling model of epileptogenesis (103). Based on these studies, the mechanism of action of VNS therapy appears to be largely distinct from that of AED therapies (84).

CLINICAL STUDIES

Initial scalp recording performed in a small number of adults did not demonstrate a significant effect of VNS on EEG total power, median frequency, power in any of the conventional frequency bands (104), interictal epileptiform activity, or the waking or sleep background rhythms (22,104–106). At seizure onset, however, VNS has terminated both the clinical and the EEG seizure activity (106). Studies that are more recent have suggested that some patients may have a change in IEDs with VNS. Fifteen adults with refractory partial-onset seizure disorders showed a significant reduction in IEDs during stimulation and the interstimulation period immediately following stimulation, compared with baseline, with the reduction in interical epileptiform discharges greater among patients whose seizures decreased by more than 50% on VNS. Additionally, the patients who had a significant decrease in interical epileptiform discharges experienced the positive effect of magnetic activation, resulting in extra stimulation, abolishing seizures (107). A single adult patient undergoing presurgical evaluation with intrahippocampal depth electrodes showed alteration of interical epileptiform discharges by VNS (increased spikes at 5 Hz, decreased at 30 Hz) (108). Chronic VNS in children was recently reported to reduce IEDs (109). However, this population was quite different from that in the earlier adult series. Included were patients with generalized and partial-onset seizures, greater frequency of interical epileptiform discharges, and younger age. During 12 months of VNS therapy, both generalized and focal spikes were diminished; however, this did not correlate well with seizure reduction. Pattern reversal visual evoked potentials, brainstem auditory evoked potentials, and cognitive (P300) potentials were all unaffected by VNS (110).

Release of anticonvulsant neurotransmitters at the projection sites of vagus nerve afferent fibers

was hypothesized as a mechanism of action (110,111). Cerebrospinal fluid samples assayed for amino acid and neurotransmitter metabolites in 16 patients before and after 3 months of VNS therapy showed a treatment-induced increase in GABA (an inhibitory amino acid), a decrease in aspartate (an excitatory amino acid), and an increase in ethanolamine (a membrane lipid precursor) (111).

Positron emission tomography (PET) $H_2{}^{15}O$ cerebral blood flow (CBF) imaging identifies the neuroanatomical structures recruited by VNS in humans. A pilot study of three adults showed activation of the right thalamus, right posterotemporal cortex, left putamen, and left inferior cerebellum (112). Localization to the thalamus may explain the therapeutic benefit of VNS and is consistent with the role of that structure as a generator and modulator of cerebral activity. Moreover, anatomic and physiologic evidence from both animal and human data further support the role of the thalamus in epilepsy (113), with stimulation of either the anterior thalamic nucleus or centromedian thalamic nucleus in animals being associated with anticonvulsant effects (114). In a study of high and low stimulation (115), PET demonstrated CBF alterations at sites that receive vagal afferents and projections, including dorsal medulla, right postcentral gyrus, thalamus, cerebellum bilaterally, and limbic structures (bilateral hippocampus and amygdala). The high-stimulation group had more activation and deactivation sites, although the anatomical patterns during VNS were similar in both groups. Finally, acute CBF alterations were correlated with long-term therapeutic response, in an attempt to exclude those regions that show changes in VNS-induced synaptic activity, but may not participate in VNS-related anticonvulsant actions (116). Decreased seizure frequency was associated with increased CBF only in the right and left thalami. Studies of chronic VNS therapy have shown the same anatomical distribution of CBF (112,117). Demonstration of these acute regional alterations does not clarify the mechanism of action of long-term, intermittent VNS, which may involve neurotransmitters or neurochemicals at those sites that outlast the stimulation.

Functional magnetic resonance imaging (fMRI) evaluating the time course of regional CBF alterations during VNS therapy can be performed safely in patients implanted with a vagal nerve stimulator (118). Preliminary fMRI studies have agreed with the PET studies, with the most robust activation observed in the thalami and insular cortices, with some activation also seen in ipsilateral basal ganglia, anterior parietal cortex, and other cortical areas (118,119).

SELECTION OF CANDIDATES

In the United States, VNS therapy is indicated as an adjunctive treatment for adults and adolescents 12 years of age or older with refractory partial-onset seizures (24). In the European Union, VNS therapy is indicated as an adjunctive treatment for patients with partial- or generalized-onset seizures without an age limitation. However, indications for VNS therapy were derived from the clinical trial experience, not from an understanding of its physiologic action. Age, sex, seizure type or syndrome, etiology, frequency of seizures, or IEDs do not predict response to VNS therapy. The type or number of coadministered AEDs also does not predict response (73,120). However, many studies show favorable outcomes in many of these populations, although complete seizure freedom is rarely achieved (79). A recent study also indicates that VNS therapy should be considered in patients with posttraumatic epilepsy, which is often resistant to AED therapy and not often amenable to epilepsy surgery (121).

In October 2013, the American Academy of Neurology updated the evidence-based VNS therapy guidelines for the treatment of epilepsy (122). The updated guidelines provide an update on data regarding the efficacy and safety of VNS therapy for epilepsy since publication of the original

guidelines in 1999. Previous guidelines did not provide guidance on many of the epilepsy patient populations in which VNS therapy is actively being used. The literature review found 1274 manuscripts for VNS therapy since the last review. Of these, 216 articles were reviewed to answer 8 clinical questions, summarized in Table 71.4. The clinical evidence supports the use of VNS therapy across a range of refractory epilepsy populations, and the impact of the reviewed studies (with specific focus on the intensity and magnitude of the responses) continues to be quite supportive.

Table 71.4 Summary of AAN Updated Evidence-Based Guidelines for VNS Therapy

Clinical question	Recommendation/clinical context
Is VNS therapy beneficial in children with epilepsy?	VNS therapy may be considered as adjunctive treatment for children with partial or generalized epilepsy (C)
Is VNS therapy beneficial in patients with LGS?	VNS therapy may be considered in patients with LGS (C)
Is VNS therapy associated with mood improvement in patients with epilepsy?	In adult patients receiving VNS therapy for epilepsy, improvement in mood may be an additional benefit (C)
Is VNS therapy associated with reduced seizure frequency over time?	VNS therapy may be considered progressively effective in patients over multiple years of exposure (C)
Does rapid cycling[a] improve seizure frequency more often than do standard stimulation settings?	Optimal VNS therapy settings are still unknown. The evidence is insufficient to support a recommendation for the use of standard stimulation vs. rapid stimulation.
Does using additional magnet-activated stimulation trains for auras or at seizure onset interrupt seizures?	VNS therapy magnet activation may be associated with seizure abortion when used at the time of seizure auras (C). Seizure abortion with the magnet use may be associated with overall response to VNS treatment (C)
Have new safety concerns emerged since the last VNS therapy assessment?	No new safety concerns were identified The rates of Sudden Unexpected Death in Epilepsy (SUDEP) dropped in the first 2 years of VNS therapy
Do adverse effects differ among children and adults?	Children may have greater risk for wound infection than adults due to behaviors more common in children. Extra vigilance in monitoring for occurrence of site infection in children should be undertaken.

[a]Rapid cycling is shorter On times and Off times, typically 7 s On and 30 s Off compared with standard settings, typically 30 s On and 5 min Off.

C, based on data from class III studies; U, unproven, data inadequate or conflicting.

Although optimal use parameters continue to be defined, candidates should meet the following criteria: (i) medically refractory seizures, (ii) adequate trials of at least two AEDs, (iii) exclusion of nonepileptic events, and (iv) ineligibility for epilepsy surgery (Fig. 71.4). Focal resective surgery (temporal lobectomy or lesional neocortical epilepsy) is preferred in appropriate patients because of its superior seizure-freedom rate (123–125). Recent open studies suggest that VNS therapy may be used among patients considered for corpus callosotomy, producing lower rates of morbidity (116–129), and among those who have previously undergone epilepsy surgery (41,130–132). A study of 376 patients (110 who had at least 1 failed craniotomy before VNS and 266 with no history of intracranial epilepsy surgery [IES] before VNS) showed no significant difference in the mean percentage seizure reduction between patients with and without a history of IES (59% vs. 57%; P = 0.42) (132). Earlier use (within 2 years of seizure onset or after failure of two or three AEDs) of VNS therapy may also produce a higher response rate and reduce the negative side effects associated with long-term epilepsy and AED therapy, which hinder development (30,40,133,134). Patients with a history of nonadherence to their AED regimens, particularly those on polypharmacy, may also be good candidates for VNS therapy because of the assured compliance and lack of further drug–drug interactions with VNS therapy (135,136).

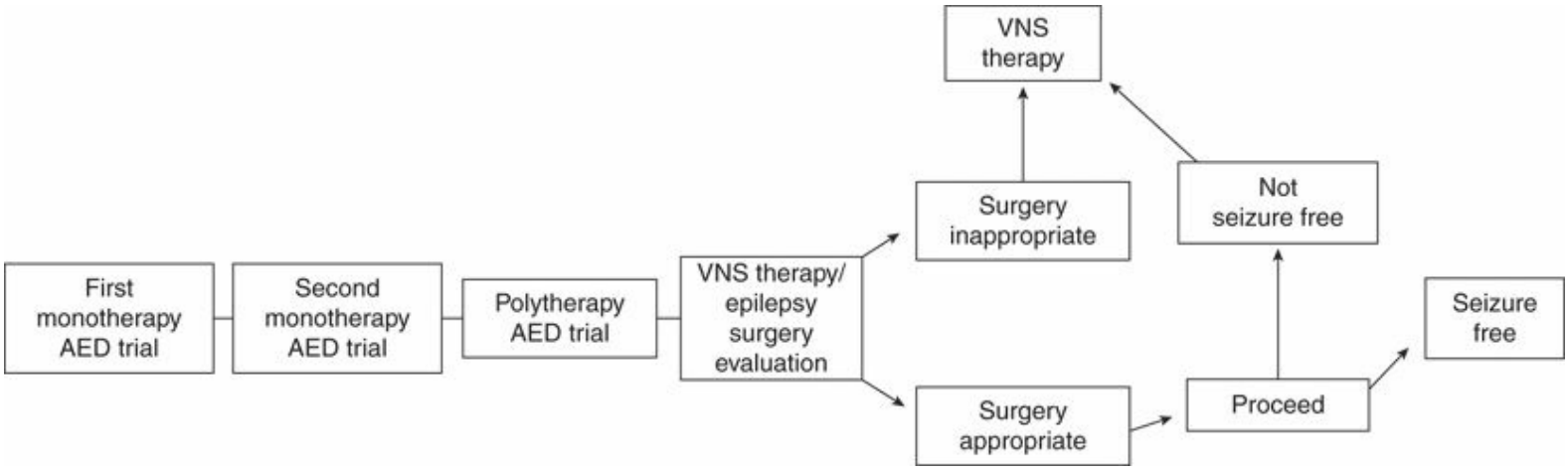

Figure 71.4. Treatment selection flow chart. AED, antiepileptic drug; VNS, vagus nerve stimulation therapy.

Use of VNS therapy is contraindicated in patients with prior bilateral or left cervical vagotomy, and safety and efficacy have not been established for stimulation of the right vagus nerve. Patients with existing pulmonary or cardiac disease should be evaluated carefully before implantation; chronic obstructive pulmonary disease may increase the risk for dyspnea. Patients with cardiac conduction disorders were not studied in the controlled trials. A cardiologist's evaluation should precede implantation, with postprocedural Holter monitoring performed if clinically indicated. Patients with a history of obstructive sleep apnea should be treated with care, as an increase in apneic events during stimulation is possible (137,138). Lowering stimulation frequency (i.e., pulse width and signal frequency to 250 μs and 20 Hz, respectively) may prevent exacerbation of this condition (137). However, most studies showing a decrease in airflow during sleep with VNS therapy reported this condition to be clinically insignificant (138). Moreover, beneficial effects on sleep and increases in slow-wave sleep also have been reported with VNS therapy, which may play a role in the antiepileptic mechanisms of VNS (139,140).

INITIATION AND MAINTENANCE

Hospitalization for implantation of the device is preceded by evaluations by a neurologist and by a surgeon with experience in the carotid sheath. With the patient typically under general anesthesia (although local or regional anesthesia has been used successfully as well) (141), the lead wires are placed on the left cervical vagus nerve and the generator is placed in a subcutaneous pocket in the left upper chest (142,143). Intraoperative electrical impedance testing ensures integrity of the system. Rare cases of bradycardia, asystole, or both mandate initial lead testing in the operating room (24,144,145); the anesthesiologist should be notified immediately before this test. Stimulation following intraoperative bradycardia has been shown to be safe, with no change in cardiac rhythm upon initiation of postoperative VNS, which was started under ECG monitoring (146). Reimplantation of a second VNS therapy generator upon battery depletion in two patients also showed no occurrence of bradycardia (146). Correct placement of the lead electrodes around the vagus nerve is critical. If there is concern about the lead placement, two methods have been utilized to help confirm correct placement of the electrodes intraoperatively (147), depending on the type of anesthesia used for the procedure. For patients receiving general anesthesia, the larynx and vocal cords can be monitored by fiberoptic endoscopy for contraction of the left lateral larynx wall and vocal cord tightening. For patients being implanted under local and regional anesthesia, stimulation

intensities can be increased until a voice alteration is noticed. The procedure neither is harmful to the patient nor greatly extends the length of the surgery.

Prophylactic antibiotics may be administered both in the operating room and postoperatively. The patient can be discharged after the procedure, which usually lasts for <1 hour, or can be observed overnight. Discharge education should include care of the incisions and use of the magnet. In clinical studies, the generator's output current was kept at 0 mA for the first 2 weeks; however, programmed stimulation is now being initiated at 0.25 mA in many operating rooms (41). Dosages of AEDs are generally kept stable for the first 3 to 6 months of stimulation unless an early response is noted.

A few weeks after implantation, the patient is examined to confirm wound healing and proper generator operation either to begin or to continue programming. Output current is increased in 0.25 mA increments as long as stimulation is comfortable (Table 71.1). The subsequent stimulation schedule is determined by patient response. Standard parameter settings range from 20 to 30 Hz at a pulse width of 250 to 500 μs for 30 seconds "on" time and 5 minutes "off" time (83). For an adult, to generate an action potential in the nerve (a therapeutic effect), research shows that optimal output current settings may range from 0.75 to 1.75 mA (148). At each visit, the generator and the battery are assessed for end of service; the battery's life expectancy of 7 to 10 years depends on the programmed stimulation parameters. If VNS therapy is to be continued, the generator can be replaced at the appropriate time in <20 minutes.

VNS may be continued indefinitely and without damage to the vagus nerve as long as the stimulation is <50 Hz and the on time remains less than the off time (24,149,150). Two safety features that protect patients from continuous stimulation or uncomfortable side effects are the magnet and the watchdog timer. The magnet can act as an "off" switch when held or taped over the generator. The watchdog timer is an internal monitor that limits the number of pulses to be delivered without an "off" time to prevent excess stimulation.

COMPLICATIONS AND ADVERSE EFFECTS

Surgical complications and difficulties are rare. Fracture of the electrode, related to fatigue at the junction between contact and the lead wire, was a common problem with early devices (23,151–154). Substitution of a quadrifilar wire and, later, a trifilar lead body coil improved electrode tolerance that had been compromised by repetitive neck motion. The two newest lead models (Perennia Model 303 and PerenniaFLEX Model 304) are designed to be even more resistant to fractures than previous models. The PerenniaFLEX is similar in design to the Model 302 but has a lead body designed with three high fatigue silicone tubes; the bifurcation is still caudal to the anchor tether but designed with a smoother transition to facilitate strain relief bend. The Perennia is constructed with a trifilar lead body coil and a continuous bilumen lead body silicone tube with the bifurcation cephalad to the anchor tether; this design makes the handling characteristics of the Perennia lead feel stiffer during the implantation procedure compared with the Model 302 and 304 leads. The Perennia model leads are approved by the FDA but are not currently available in all countries.

Incisional infections are unusual and generally respond to antibiotic therapy. Fluid accumulation at the generator site with or without infection occurs in 1% to 2% of implantations and resolves with aspiration and antibiotics; the rare cases of refractory infection require removal of the generator. However, one case of deep wound infection associated with implantation of the generator was reported to be managed successfully with open wound treatment without removal of the device, an

alternative option if removal of the device appears hazardous (155). Unilateral vocal cord paralysis, which accompanies approximately 1% of implants, may be caused by excess manipulation of the vagus nerve, and subsequent damage to the vagal artery and its reinforcing arterioles (156); in most cases, it remits completely over several weeks.

Common side effects, which occur primarily when the stimulator is actually delivering a pulse (Table 71.5), are dose dependent and usually mild or absent when VNS parameters are appropriately programmed (26,27,157); many patients become accustomed to them with time. Most patients experience hoarseness or a change in vocal quality and tingling over the left cervical region on delivery of the electrical pulse. Subjective dyspnea or a sensation of muscle tightening in the neck may occur, without changes on pulmonary function testing (26). Cough or throat pain during stimulus delivery sometimes necessitates a reduction in current or pulse width (158).

Table 71.5 Adverse Events with Vagus Nerve Stimulation[a]

	No. of patients (%)	
Adverse event	E03 and E05 patients (N = 314; 591 device years) > 3 months' follow-up	E03 and E05 patients with high stimulation (N = 152) > 3 months' follow-up
Voice alteration	156 (50)	91 (60)
Increased coughing	129 (41)	57 (38)
Paresthesia	87 (28)	32 (21)
Dyspnea	55 (18)	32 (21)
Dyspepsia	36 (12)	22 (15)
Laryngismus	10 (3.2)	9 (5.9)

[a]Number of patients reporting the adverse event at least once in the E03 and E05 randomized studies.

Despite the widespread visceral efferent projections of the vagus nerve, systemic effects are rare. Pulmonary function does not change significantly in patients without concomitant lung disease (26,159) but may deteriorate in the face of intense stimulation and obstructive lung disease (159). Inhalation of ipratropium bromide or lowering of the stimulus frequency or current is recommended. No substantial effects on cardiac function were reported during clinical studies (24,26,27,157,160). An analysis of total mortality and sudden death in epileptic patients (to August 1996) revealed the expected rate in individuals with severe, intractable epilepsy (161,162). The clinical studies demonstrated no clinically relevant effects on the gastrointestinal system, serum chemistries, AED concentrations, vital signs, or weight.

Rare reported side effects associated with VNS therapy include diarrhea (163), sternocleidomastoid muscle spasm (164), phrenic nerve stimulation (165), tonsillar pain (166), emergent psychiatric disorders (167,168), and prominent drooling and vomiting (169). Of seven patients treated with VNS therapy who developed a major psychiatric disorder (167), all had a history of a dysphoric disorder and most had daily seizures before treatment with VNS. The severe dysphoric or psychotic conditions emerged once seizure frequency was reduced by 75% or more but remitted or improved satisfactorily with psychotropic medication, with two patients also requiring a decrease or interruption of VNS therapy. Children with a history of dysphagia may experience swallowing difficulties during VNS therapy (169–171); adjusting the device settings or using a magnet to turn off the stimulator during mealtime may help. The majority of side effects, including many of the rare incidents reported, are amenable to stimulus modifications, which could include

changes in output current and/or pulse width.

ADVANTAGES AND DISADVANTAGES

Many patients maintained on VNS therapy can decrease their total AED burden, which typically results in a more alert patient who, while still receiving polytherapy, is without the cognitive or systemic side effects typically associated with multiple therapies. Therefore, use of AED monotherapy with VNS therapy may produce a better risk to benefit ratio than treatment with two AEDs. Even when AEDs cannot be substantially decreased or withdrawn, however, VNS therapy may allow amelioration of seizures with no risk of toxic organ reactions, drug interactions or failures, allergies, rashes, and other systemic adverse effects or cognitive side effects (172,173); in some patients, memory, alertness, mood, and communication have been shown to improve (105,174–178). Improvements in QoL independent of treatment effect on seizure frequency, as well as increased daytime vigilance, have also been reported (179–181). In addition, because the beneficial results are maintained without active patient participation, VNS therapy may be an ideal treatment for the partially compliant (135,136). Teratogenesis is not expected with VNS therapy. Although no controlled studies of VNS therapy in pregnancy have been conducted, an animal study showed no harm to fertility or to the fetus (182). Cases also have been reported in the literature of patients who became pregnant while on VNS therapy and gave birth to healthy babies (36,183). Finally, VNS therapy can both prevent and abort seizures. The ability to trigger the device externally (with the magnet) and to interrupt the seizure or improve the postictal phase empowers the patient and provides a sense of control over epilepsy.

On the other hand, VNS is an empiric therapy, with no way to predict response except by trial. The initial cost (often between $15,000 and $25,000) can be prohibitive without coverage by a third-party payer. Over the life of the system, however, this cost approximates that of many of the new AEDs (184). Moreover, although weeks to months may elapse before seizure frequency decreases, cost-effectiveness studies indicate that VNS therapy provides a substantial cost-savings benefit to hospitals over the long-term course of treatment (185,186). These cost benefits are sustained over time and are sufficient to cover or exceed the cost of the device. Further savings can be seen in significant reductions in health care utilization and time spent on epilepsy-related matters with VNS therapy over time. One study looked at health care utilization of 138 patients with refractory epilepsy comparing 1 year of baseline data followed by 4 years of quarterly follow-up data with VNS therapy and showed significant reductions in the numbers of emergency department visits (99% decrease), hospitalizations (70% decrease), and hospital lengths of stay (67% decrease) beginning with the first quarter after VNS implantation and therapy ($P < 0.05$ for all postimplantation quarters) (187). A 91% decrease was also seen in outpatient visits post-VNS therapy, and significant decreases were seen for average number of days on which patients could not work because of health-related concerns ($P = 0.002$) and average time spent caring for health problems ($P < 0.001$), which further reflect positive changes in the QoL of both patients and their caregivers as a result of VNS therapy in addition to health care utilization savings. In a US study evaluating the long-term medical and economic benefits of VNS therapy using Medicaid data from 5 states ($n = 1655$), VNS therapy was associated with lower average health care costs and epilepsy-related clinical events (135). Hospitalizations, emergency room visits, and outpatient visits all were significantly reduced during the post-VNS period compared with the pre-VNS period ($P < 0.0001$). Serious events such as grand mal status, fractures, and traumatic head injuries also were reduced in the post-VNS period. Despite the initial

expense of VNS therapy, the reductions in health care utilization and epilepsy events resulted in a net cost savings for VNS therapy after 1.5 years of treatment.

According to the manufacturer of the device, a transmit-and-receive head coil MRI should be used for head and extremity scans rather than a full-body MRI, with the generator programmed to 0 mA for the procedure and returned to the original settings thereafter (24). MRI scans following these procedures are safe in 1.5 and 3 T scanners (24). However, successful head coil MRIs have been performed among patients both with and without the device turned off (188). If the device does remain on during the MRI, the device should be interrogated postprocedure to ensure that the magnetic field did not deactivate the device or change the pre-MRI settings. Although not recommended by the manufacturer, successful body coil MRIs with the use of an ice pack over the area of the device leads have been reported among three patients (189). Diathermy, which could heat the system above safe levels and thereby cause either temporary or permanent tissue or nerve damage, should be avoided in patients receiving VNS therapy.

FUTURE DEVELOPMENTS

VNS therapy has raised interest in the role of neurostimulation as a treatment for refractory epilepsy. Since the first device implantation more than 20 years ago, the number of AEDs has increased; yet, uncontrolled seizures continue. The codification of refractory epilepsy by the ILAE in 2010 (190) increased visibility around the need for nonpharmacologic treatment options earlier in the course of the disease rather than waiting until multiple medications have failed and surgery is not an option. Other research questions, if answered, have the potential to dramatically improve the overall treatment of all patients with epilepsy. Are there unique stimulation parameters for certain seizure types (e.g., partial vs. generalized), syndromes (e.g., Lennox–Gastaut), or age groups? What are the psychosocial effects of VNS therapy on the families of individuals with epilepsy? Answers to such questions and improvements in technology will expand the role of VNS therapy for uncontrolled epilepsy.

Additional options for nerve stimulation in the treatment of refractory epilepsy currently under investigation include trigeminal nerve stimulation (TNS), transcutaneous vagus nerve stimulation, and transcutaneous auricular vagus nerve stimulation. TNS is proposed to activate similar pathways as VNS but less invasively and with the ability to provide bilateral stimulation (191). Although subjects in the treatment group of the initial randomized controlled trial for TNS in epilepsy were more likely to respond than patients in the control group, the study did not demonstrate efficacy of TNS in refractory epilepsy (192). Pilot studies of transcutaneous VNS in small groups of patients with refractory epilepsy are underway. Studies to determine whether any of these noninvasive options could potentially be used as a screening tool for VNS therapy may be warranted.

ADDENDUM

Videotapes and information on the VNS therapy system are available free to patients, nurses, and physicians from Cyberonics, Inc. (www.cyberonics.com).

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PART V EPILEPSY SURGERY

SECTION A IDENTIFYING SURGICAL CANDIDATES, DEFINING THE EPILEPTOGENIC ZONE, AND MAPPING ELOQUENT CORTEX

ASSOCIATE EDITOR: TOBIAS LODDENKEMPER

CHAPTER 72 ISSUES OF MEDICAL INTRACTABILITY FOR SURGICAL CANDIDACY

SAMUEL WIEBE AND NATHALIE JETTÉ

INTRODUCTION

Patients with drug-resistant epilepsy have a very low likelihood of achieving sustained seizure freedom with further trials of antiepileptic drugs (AEDs), and the treating clinician should consider early on whether these patients might be candidates for epilepsy surgery. Yet, the diagnosis of medically intractable epilepsy can be sobering. It communicates the chronicity of the condition and the futility of further AED trials. Therefore, arriving at this diagnosis requires careful and comprehensive consideration of the individual patient's diagnosis and management, which is best done in a systematic manner. Clinicians should first review the diagnosis of epilepsy, the type of epilepsy and seizures, and their frequency. They should then assess the treatments prescribed, how they have been administered, and whether extraneous factors may contribute to the lack of seizure control. Finally, they should establish which AEDs have failed and why. If reasons other than drug resistance or intolerance exist, they should be addressed before arriving at the diagnosis of medical intractability. This systematic approach is particularly important when surgery is being considered as the next therapeutic option, but also should be undertaken every time seizures recur or fail to respond to AEDs.

THE MISDIAGNOSIS OF EPILEPSY?

The misdiagnosis of epilepsy is a common cause of pseudoresistance, defined as ongoing seizures (or spells) due to misdiagnosis or inappropriate treatment (1). Epilepsy misdiagnosis has been reported to occur in 5% to 30% of cases in a variety of settings (2,3). These estimates include not only missing an epilepsy diagnosis but also undertreatment or incorrect treatment of epilepsy. Unfortunately, diagnosing epilepsy can be challenging due to the lack of standardized criteria or laboratory tests to guide clinicians.

There are a wide variety of symptoms and conditions that can mimic seizures and epilepsy, respectively (3). These include cardiovascular disorders (e.g., syncope, transient ischemic attaches, transient global amnesia, arrhythmia), movement disorders (e.g., tics, paroxysmal dystonia), sleep disorders (e.g., night terrors in children in particular, narcolepsy and cataplexy), and mental health conditions (e.g., psychogenic nonepileptic seizures). Syncope and psychogenic nonepileptic seizures represent the two most common causes of epilepsy misdiagnosis (3).

Impact of Misdiagnosis

Misdiagnosing epilepsy can have serious consequences. For example, a patient may be inappropriately exposed to AEDs and their side effects including neurotoxic effects and hypersensitivity reactions. A woman of childbearing potential misdiagnosed as having epilepsy and started on AEDs could potentially expose her fetus to the potential teratogenic and neurodevelopmental effects of this AED (4). A patient may also experience, as a result of being misdiagnosed with epilepsy, unnecessary negative psychosocial outcomes such as the loss of driving privileges and/or employment and stigmatization (3,5,6). Patients with psychogenic nonepileptic seizures are vulnerable and may end up in a critical care unit due to AED toxicity and sedation (7) as a result of overtreatment due to "pseudoresistance." We advocate early prompt diagnosis of psychogenic nonepileptic seizures, which has been associated with better outcomes (8). Finally, misdiagnosis could even result in death if the symptoms are due to a cardiac cause such as a life-threatening arrhythmia that is not treated promptly.

COMMON ERRORS IN THE DIAGNOSIS OF EPILEPSY AND SEIZURES

Epilepsy drug resistance may also occur due to incorrect classification of the epilepsy syndrome or seizure types. A detailed history (including a witness history) and diagnostic investigations will increase the likelihood of accurately diagnosing a patient with the correct type of seizures and epilepsy syndrome (9).

Accurate epilepsy and seizure classification is necessary for many reasons but most importantly to guide treatment. For example, some AEDs can worsen certain types of seizures and result in pseudoresistance, while others are suboptimal for specific seizure types. Once it has been determined that a patient has epileptic seizures, the following questions should be explored to ensure that the correct therapy is used (2,10):

1. What type of seizure(s) is the patient having?
2. Does the patient have focal or generalized epilepsy?
3. If the epilepsy is focal, is it temporal or extratemporal?
4. What is the cause of the epilepsy, that is, structural, metabolic, of presumed genetic origin, or of unknown etiology?

Three common errors in the diagnosis of seizures and epilepsy may result in incorrect treatment and AED pseudoresistance, that is, incorrect distinction between focal and generalized epilepsy, confusion between myoclonic or tonic seizures and focal motor seizures, and inability to distinguish between absence and focal dyscognitive seizures.

Generalized Versus Focal Seizures

Failure to recognize generalized epilepsy is of particular concern because AEDs such as carbamazepine and phenytoin can control bilateral convulsive seizures (formerly known as generalized tonic–clonic seizures) but have been shown to worsen absence and myoclonic seizures (7). The distinction may be challenging because seemingly focal symptomatology may accompany

generalized seizures. In one study (11), focal EEG abnormalities were identified in 45% of patients with various types of generalized epilepsies of presumed genetic origin. Another study examined clinical features of 58 patients with EEG-confirmed generalized epilepsy of presumed genetic origin (12). Many of these patients had focal EEG or clinical features (e.g., head turning to one side). Most importantly, 71% of these patients were on inappropriate treatment, of which 55% were pseudoresistant to AEDs. Optimizing treatment with AEDs indicated for the relevant syndromes resulted in 78% of the pseudoresistant patients becoming drug responsive (12). Misdiagnosing generalized epilepsy can occur in part because of the incorrect assumption that generalized epilepsy or presumed genetic origin is rare beyond childhood. It is important to recognize that a sizeable proportion of generalized epilepsies of presumed genetic origin begin after ages 18 (35%) and 20 (28%) (13).

Myoclonic or Tonic Versus Focal Motor Seizures

The myoclonic seizures of juvenile myoclonic epilepsy (JME) are frequently misdiagnosed as focal seizures with motor features, and as such may be inappropriately treated with agents indicated for focal epilepsies (5). This can result in an exacerbation of myoclonic seizures. Tonic seizures (often noted in those with generalized epilepsies of structural or metabolic causes) are often similarly misdiagnosed as focal seizures of supplementary motor area origin and as a result can be inadequately treated (14).

Absence Versus Focal Dyscognitive Seizures

Absence seizures, particularly if they are atypical, can be misdiagnosed as focal dyscognitive seizures (i.e., complex partial seizures). Both are longer in duration than typical absence seizures and can be associated with automatisms and postictal confusion. The EEG provides important diagnostic information, but the correct diagnosis requires a comprehensive and detailed history, physical examination, and investigations (especially EEG and brain MRI). Misdiagnosing atypical absence seizures as focal dyscognitive could be detrimental to patients because each seizure type requires different AEDs. Using AEDs indicated for focal epilepsies can be associated with worsening atypical absence seizures, and treating focal seizures with a drug such as ethosuximide will not be beneficial.

CAUSES OF POOR SEIZURE CONTROL

Establishing the diagnosis of epilepsy, and determining the type of epilepsy and seizures, provides an important roadmap for choosing the correct AED for an individual patient. However, even with a correctly chosen AED, other factors can contribute to poor seizure control and AED pseudoresistance. These include using a wrong dose, interactions with other medications, poor adherence to a correctly chosen AED, and lifestyle issues.

Incorrect Treatment

Incorrect medical treatment of patients with epilepsy has been long recognized as an important contributor to pseudoresistance (2). It occurs more often in general practice than in specialists' clinics and is seen both in adults (15) and children (16). In one study, incorrect or suboptimal AED

therapy in patients with uncontrolled seizures occurred in 56% of those with newly diagnosed epilepsy and 41% of those with chronic epilepsy (17). In this study, seizures remained uncontrolled due to a treatment trial of only a single AED (39%), inadequate use of AEDs (44%), and development of side effects at low AED doses (29%). These are all important aspects that should be explored in patients with uncontrolled seizures, before deeming them medically intractable.

Incorrect AED

Studies of patients with chronic, uncontrolled seizures show that about 60% of these cases are due to drug resistance (17–19), whereas 40% have pseudoresistant epilepsy. Most commonly, pseudoresistance in these patients is due to receiving the wrong medication for their epilepsy syndrome, which in some studies is reported in 30% of adults (19) and 37% of children (20). Common among these errors is the use of carbamazepine for absence seizures, ethosuximide for complex partial seizures, phenytoin for epileptic spasms, or vigabatrin for myoclonic seizures. Patients with primary generalized epilepsy are particularly vulnerable to receiving incorrect AEDs. In one study, failure to obtain or interpret a history of myoclonic jerks resulted in incorrect diagnosis and inappropriate treatment of two-thirds of patients with JME (21).

Incorrect Dosage

Incorrect AED dosage is important as a cause of pseudoresistance. The AED dosage at which most patients achieve seizure control is usually modest to moderate, for example, 600 mg of carbamazepine, 1000 mg of valproate, and 200 mg of lamotrigine, and correspond to about two-thirds of the WHO defined daily dose (DDD) for these medications (http://www.whocc.no/atc_ddd_index/) (22). Only 15% to 20% of patients require higher dosages to achieve seizure freedom (23). Patients who fail a first AED at low dosages (presumably because of side effects) are significantly more likely to be controlled with additional trials of AEDs (24). For example, those who fail the first AED at doses lower than 50% of the DDD are 60% more likely to achieve sustained seizure freedom with further AED trials. This has two implications for planning referrals for presurgical evaluation. First, failure of a dose equivalent to 50% to 75% of the DDD might be considered as drug failure and count toward the definition of drug resistance, without having to escalate to the full DDD. Second, in patients who fail an AED at a higher dosage (>75% of the DDD), clinicians should be ready to discuss referral for presurgical evaluation early on, because these patients have a lower likelihood of future seizure control.

Drug Interactions

The pharmacokinetics of many of the older-generation AEDs (i.e., phenytoin, phenobarbital, carbamazepine, primidone, valproate) and to a lesser degree some of the newer AEDs (e.g., lamotrigine, topiramate, zonisamide, felbamate) involve hepatic metabolism through pathways such as the cytochrome P450 isoenzyme system and uridine glucoronyl transferases, which can be activated by a number of drugs, resulting in lower steady-state serum concentration of AEDs and ultimately loss of seizure control. Of particular importance are interactions among various AEDs, which may be overlooked in busy clinical practice. For example, the plasma concentration of valproic acid can be reduced by 49% to 76% in patients who are also treated with phenobarbital, phenytoin, and carbamazepine (25). Notable examples of interactions resulting in decreased steady

state of various AEDs are listed in Table 72.1 (25,26). Poor seizure control should prompt a thorough assessment and correction of coadministered medications before establishing the diagnosis of pharmacoresistant epilepsy.

Table 72.1 Drug Interactions That may Cause Lower AED Concentrations and Poor Seizure Control

Drug added	AED effect decreased
Oral contraceptives	Lamotrigine
Rifampicin	Older-generation AEDs
Carbapenem	Valproic acid
Antivirals nevirapine and efavirenz	Older-generation AEDs
Carmustine, vinblastine, methotrexate, and bleomycin	Phenytoin (decreased absorption)
Cisplatin	Carbamazepine, valproic acid
Methotrexate	Valproic acid
Antacids	Phenytoin, phenobarbital, carbamazepine, gabapentin
St. John's wort, alcohol	Older-generation AEDs
Enzyme-inducing AEDs (phenytoin, carbamazepine, phenobarbital, primidone)	Benzodiazepines, lamotrigine, zonisamide, felbamate, tiagabine, topiramate, older-generation AEDs

Older-generation AEDs = phenobarbital, primidone, phenytoin, carbamazepine, valproate.

Nonadherence

Nonadherence, generally defined as medication-taking behavior that does not coincide with medical advice or instruction, is common in epilepsy and can result in loss of seizures control. Nonadherence in epilepsy has been assessed using a variety of methods, has a prevalence 30% to 70%, and results in increased costs, hospitalizations, emergency room visits, seizures, and mortality (27–31). In patients with apparent pharmacoresistance, clinicians should explore the possibility of poor adherence to AEDs through careful elicitation of AED usage, serum levels, pill counts, or even hospital admissions to assess adherence and serum levels serially. Common factors associated with AED nonadherence include unacceptable side effects, poor communication or understanding regarding AED use, unaffordability, inconvenient dosing, and lower socioeconomic status (27–31).

Lifestyle and Psychosocial Factors

Common and imminently correctable lifestyle factors associated with an increase of breakthrough seizures and pseudoresistance to AEDs include poor sleep habits, alcohol and substance abuse, and exposure to specific triggers. The relation between sleep and epilepsy has been known since antiquity, and the admonition to maintain good sleep hygiene to prevent seizures can be traced to hippocratic writings (32). Laboratory and human observations support the epileptogenic effect of

sleep deprivation, particularly for generalized seizures and epilepsies (32). The role of alcohol and substance abuse in triggering seizures is well recognized; can be due to direct toxicity, withdrawal, enzyme induction, or drug interactions; and should be explored as a cause of uncontrolled seizures (33). Finally, among psychosocial factors, stressful life events (34), depression, and anxiety are often identified as causes of seizure exacerbation or loss of seizure control, and patients associate emotional well-being with better seizure control (35). The association of depression and seizures is bidirectional and mediated through a number of direct (e.g., neurotransmitters) and indirect (e.g., nonadherence) mechanisms (36).

DRUG-RESISTANT EPILEPSY

Definition

Once pseudoresistance to AEDs has been ruled out, clinicians face management of drug-resistant epilepsy. Based on broad consensus and using a pragmatic approach aimed at creating an operational definition that could be applied in clinical practice, in 2010, the International League Against Epilepsy established the current definition of drug-resistant epilepsy as "failure to achieve sustained seizure freedom with adequate trials of at least two appropriately chosen and used AED regimens (whether administered as monotherapies or in combination)" (37). Although simple at first glance, its implementation requires several key elements clinicians need to consider (38). First, inappropriately or inadequately used AEDs do not count toward establishing drug resistance, and if the former cannot be assessed, the outcome of that particular AED is considered as "undetermined" for the individual patient. Second, AED side effects are of crucial importance in clinical practice but were not included as a defining factor of drug resistance because the focus was on lack of response, rather than poor tolerability (38). Third, seizure freedom refers to seizure freedom from all seizure types, big and small, as recognized by patients, caregivers, and the clinical team. Finally, sustained seizure freedom has to last at least 1 year or three times the previous longest seizure-free period, whichever is longer. This time period has a practical rationale (e.g., employment, driving, decision to start or change AED) and was derived from the statistical "rule of 3," in which the 95% probability of seizures not occurring is roughly equivalent to three times the longest seizure-free period previously experienced by the patient (38). This definition has clear implications for considering surgical evaluation and candidacy earlier, rather than later.

Predictors and Trajectories of Drug Resistance

Several factors can help predict AED resistance in epilepsy, thereby helping identify early in the process patients who may benefit from presurgical evaluation (3). The epilepsy syndrome is among the most consistent predictors of drug resistance. Patients with presumed genetic epilepsies and frequently self-limited epilepsy syndromes (e.g., childhood absence epilepsy or benign rolandic epilepsy with centrotemporal spikes) are more likely to achieve remission than those with epilepsies of structural or metabolic causes (3). Other factors that can foreshadow drug resistance include age of onset (<1 year or >12 years), neonatal seizures, focal seizures or multiple seizure types, high initial seizure frequency, MRI showing hippocampal atrophy (<10% achieve remission), cortical dysplasia (<25% achieve remission) or dual pathology, neurologic deficits (3), and failing the first two AEDs at moderate or high doses (24). Attentive clinicians who identify these factors early on can advise

patients promptly regarding the possibility of surgery.

Once patients fail two initial AEDs, they have a very low chance of future sustained seizure freedom (3). About two-thirds of patients achieve remission with the initial AED, and the probability of achieving remission decreases by 50% with the failure of each subsequent two AEDs (18,39,40). However, drug resistance is a dynamic process, patients move in and out of drug resistance over time in a complex but increasingly understood pattern of relapses and remissions. Four main outcome patterns have been identified in cohort studies of medically treated patients with epilepsy: (a) 40% of patients enter permanent early remission, usually with the first or second AED; (b) 20% enter a delayed but permanent remission with additional AED trials; (c) 15% exhibit a relapsing–remitting disease course; and (d) 25% to 30% never achieve remission despite AED treatment (3,41). Importantly, patients may enter a period of seizure remission after being deemed drug resistant. However, studies consistently show that the majority of these patients relapse (3,42), further emphasizing the importance of timely referral for presurgical evaluation rather than waiting for eventual, unsustained periods of seizure control.

The Role of Surgery

There is extensive evidence about the highly favorable risk–benefit and cost-effectiveness ratio of epilepsy surgery in carefully selected patients, as well as of its durability and favorable impact on psychosocial aspects, quality of life, and prevention of early death (3). Yet, surgery remains underutilized. Wait times for surgical referral seem unchanged over the last two decades and therefore impervious to the evidence (43). Efforts to improve appropriate referral of patients for presurgical evaluation include creation of user-friendly, rigorously developed tools that can assist front-line clinicians (and patients) assess whether presurgical evaluation may be appropriate (44). However, clinicians and educators need to understand the factors underpinning referral. The message about the benefits and safety of epilepsy surgery has been issued repeatedly but perhaps not effectively. Clinicians and patients need to be aware that the likelihood of achieving sustained seizure remission is very low after meeting the definition of drug resistance and that other therapeutic avenues, including surgery, should be explored earlier than later.

CONCLUSIONS

Pseudoresistance to AEDs is highly prevalent and should be systematically addressed in patients with poor response to AEDs. In patients meeting the definition of drug-resistant epilepsy, clinicians need to formulate a rational treatment plan based on the likelihood of achieving seizure remission with further AEDs. This includes consideration of evaluation for epilepsy surgery. Although the diagnosis of medical intractability is certainly an indication for considering epilepsy surgery, patients may not have to be intractable before being evaluated for possible epilepsy surgery. Consider, for example, a patient who has entered a second remission of seizures after having relapsed and whose MRI shows a well-defined epileptogenic lesion known to have a low probability of sustained seizure remission, such as hippocampal sclerosis or focal cortical dysplasia. In these patients, evaluation for epilepsy surgery should be entertained early on in the course of the disease, with appropriate consideration of risks and benefits.

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CHAPTER 73 MAGNETIC RESONANCE IMAGING IN EVALUATION FOR EPILEPSY SURGERY

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Prior to the advent of modern neuroimaging, candidates for epilepsy surgery were selected based on seizure semiology, neurologic examination, and EEG features. Direct cortical EEG, intraoperatively or with implanted electrodes, was often critical to identify the epileptogenic zone. The epileptogenic lesions per se were identified only after histopathologic analysis of resected brain tissue. CT and later MRI provided powerful tools for the identification of the epileptogenic lesions preoperatively, thereby changing the approach of presurgical evaluation in patients with lesions. Invasive neurophysiologic techniques became unnecessary in many cases, and the pool of surgical candidates widened with improved postsurgical outcome (1–3).

Brain MRI is currently the best available tool for identification of epileptogenic lesions. It provides two critical details of a lesion—the presumptive pathology and the precise anatomic location. The strong soft tissue contrast of MRI makes it particularly well suited to identify even the most subtle structural abnormalities such as cortical dysplasias that are often associated with refractory epilepsy. The multiplanar capabilities of MRI allow study of the precise anatomic location of these lesions in relation to eloquent cortices, which is a critical point for surgical planning. Newer MRI techniques, including 3-T magnets, functional MRI (fMRI), and diffusion tensor imaging (DTI), have further improved the detection of subtle abnormalities and provided information about brain function and network connectivity.

The intent of this chapter is to provide the reader with a working knowledge of major anatomical landmarks on brain MRI relevant to the eloquent cortex location, a general understanding of various MRI pulse sequences, and how these images are applied in the evaluation of patients with epilepsy. A mini-atlas of common epileptogenic lesions is displayed at the end of the chapter. Other related topics including fMRI, voxel-based morphometry, and DTI are addressed in Chapters 77, 78, and 79, respectively.

MAJOR ANATOMICAL LANDMARKS OF THE BRAIN ON MRI

Epileptogenic lesions resulting in medically refractory epilepsy commonly include mesial temporal sclerosis (MTS), malformations of cortical development (MCD), encephalomalacia, slow-growing benign tumors, hamartomas, and vascular malformations. In most cases, the anatomic location and extent of these otherwise benign lesions are more critical than the pathology itself. Anatomic location of the lesion is the chief determinant of the type of epilepsy syndrome. The extent of the lesion and its

spatial relationship to eloquent areas of the brain has major implications for the surgical strategy. Hence, a three-dimensional working knowledge of MRI neuroanatomy is critical for optimal interpretation of the lesions. Extensive review of neuroanatomy is beyond the scope of this chapter. The main focus of this section is to review the anatomy relevant for the location of the eloquent cortex and temporal lobe anatomy, as temporal lobe epilepsy remains the most common surgically remediable epilepsy syndrome in most epilepsy centers.

Eloquent cortex refers to areas of cerebral cortex that are indispensable for defined cortical function and whose damage leads to predictable pattern of neurologic deficits. The key eloquent areas relevant to epilepsy surgery are the primary motor cortex, Broca area, Wernicke area, and visual cortex. Although routine MRI provides information about the expected location of these regions, fMRI provides additional functional information, particularly important when the lesions occur in early life or the anatomy is distorted by lesions.

Broca and Wernicke Areas

In most right-handed subjects and a significant number of left-handed subjects, the language areas reside in the left hemisphere. Broca area refers to the expressive language area, and Wernicke area refers to the receptive language comprehension center. The location of Broca area in the dominant inferior frontal gyrus is relatively consistent. On the contrary, the location of Wernicke area is variable. Identification of the presumptive location of Broca and Wernicke areas begins with the knowledge of anatomy of the sylvian fissure.

The sylvian fissure has three major components: an anterior ascending and anterior horizontal rami, a central stem with its minor rami, and a posterior terminal ascending ramus. Broca area is located in relation to the anterior end of sylvian fissure, and the Wernicke area is located in relation to the posterior end of the sylvian fissure in the dominant hemisphere. The central stem of the sylvian fissure is in relation to the inferior regions of the motor and sensory cortex.

Sagittal sections of MRI provide excellent view of the sylvian fissure and the various gyri in relation to it (Fig. 73.1A and B). In far lateral sagittal sections, the V- or Y-shaped anterior horizontal (anterior arm of V or Y) and anterior ascending rami (posterior arm of V or Y) of the sylvian fissure can be identified (see Fig. 73.1A and B). The sulcus that is superior and perpendicular to these anterior rami is the inferior frontal sulcus, and the sulcus posterior and parallel to the anterior ascending rami of the sylvian fissure denotes the inferior precentral sulcus. The “M”-shaped region around the banks of the V- or Y-shaped anterior rami of sylvian fissure forms the inferior frontal gyrus, which is limited superiorly by the inferior frontal sulcus (4,5). The inferior frontal gyrus consists of three regions, namely, pars opercularis, pars triangularis, and pars orbitalis (Fig. 73.1B). In most normal subjects, pars opercularis, which lies between anterior ascending rami and the inferior precentral sulcus, and/or the region around the anterior ascending rami in pars triangularis, harbor the Broca area in the dominant hemisphere (4). On coronal sections, precise identification of location of Broca area is difficult but may be accomplished by tracing the inferior frontal sulcus posteriorly.

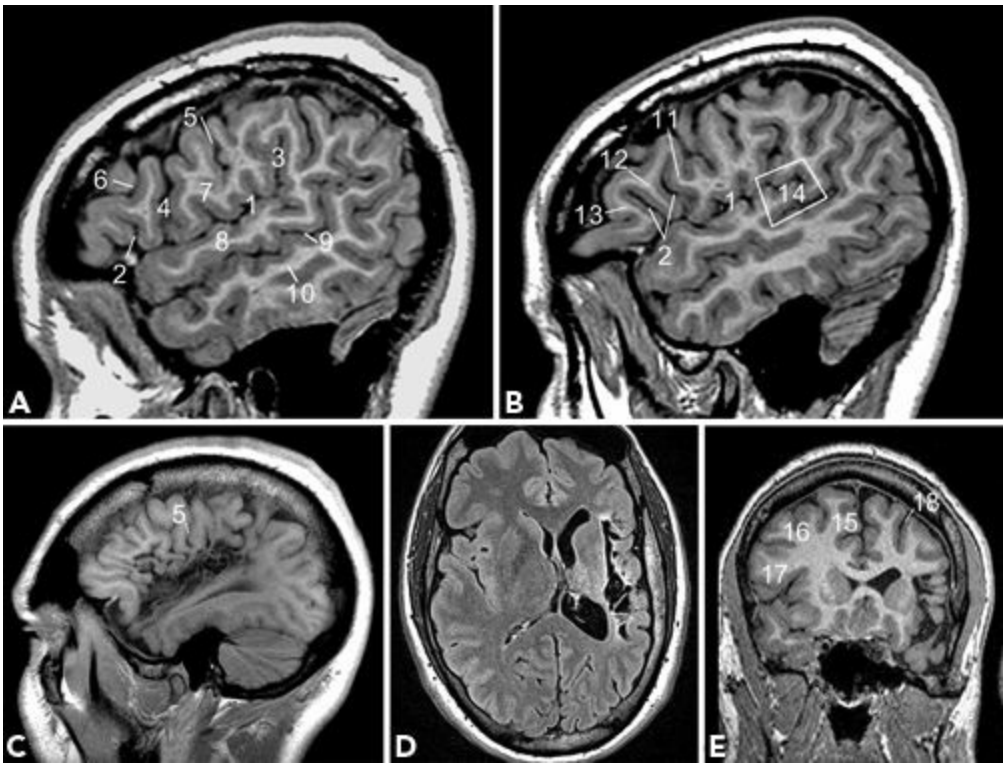

Figure 73.1. Broca and Wernicke area: **A, B:** Major landmarks on sagittal images to identify Broca and Wernicke area. **C–E:** Left perisylvian encephalomalacia due to perinatally acquired ischemic injury displayed in sagittal, axial, and coronal planes. The lesion involves the region of potential Broca and Wernicke areas (fMRI in this subject confirmed language representation in the right hemisphere, likely a result of plasticity due to early brain injury). (1, sylvian fissure; 2, "V"-shaped anterior rami of sylvian fissure; 3, posterior ramus of sylvian fissure; 4, precentral sulcus—inferior part; 5, central sulcus; 6, inferior frontal sulcus; 7, precentral gyrus—inferior part; 8, superior temporal gyrus; 9, superior temporal sulcus; 10, middle temporal gyrus; 11, pars opercularis; 12, pars triangularis; 13, pars orbitalis; 14, usual location of Wernicke area over the dominant hemisphere; 15, superior frontal gyrus; 16, middle frontal gyrus; 17, inferior frontal gyrus; 18, superior frontal sulcus.)

Wernicke area is located in relation to the posterior end of sylvian fissure, which terminates in the temporoparietal region as the ascending posterior rami. Wernicke area lies in the posterior part of the superior temporal gyrus (4.5 cm posterior to the tip of the temporal pole) extending around the banks of the posterior terminal ascending ramus of the sylvian fissure or around the superior temporal sulcus in the language-dominant hemisphere (Fig. 73.1B). In a minority, the middle or inferior temporal gyrus harbors Wernicke area. Rarely, Wernicke area may lie within the anterior part of the superior temporal gyrus (6–8). On coronal sections, tracing the sylvian fissure and superior temporal sulcus posteriorly may assist in the identification of Wernicke area. Atypical locations of language area tend to occur when congenital or early-acquired brain lesions are located in the vicinity of the presumptive language areas (Fig. 73.1C–E). These lesions may result in shift of the language areas to the perilesional regions or, in extreme cases, to the contralateral homologous region of the brain. This can be confirmed by a Wada test or fMRI studies.

Primary Motor Area: The Precentral Gyrus

Surgery for epileptogenic lesions around the central sulcus poses special challenges due to the risk of motor deficits. A thorough knowledge of the anatomy of the central sulcus and precentral gyrus—the primary motor area—is crucial to localize the lesions around this region. The central sulcus and the precentral gyrus are best identified on the axial and sagittal images (Figs. 73.2 and 73.3). The precentral gyrus is outlined anteriorly by the precentral sulcus and posteriorly by the central sulcus.

On axial MR images (Fig. 73.2A and B), five features help to localize the central sulcus and precentral gyrus (9–11):

1. The central sulcus begins near the interhemispheric fissure and descends in a slight forward angle toward the sylvian fissure. The central sulcus is longer than other adjacent sulci and is least intersected by other sulci. The precentral sulcus is frequently discontinuous and intersected by superior and inferior frontal sulci on its course toward the sylvian fissure.
2. The sagittally oriented superior frontal sulcus at its posterior end meets the coronally oriented precentral sulcus; the adjacent gyrus posterior to the precentral sulcus is the precentral gyrus.
3. The right and left marginal sulci (the ascending terminal portion of the cingulate sulcus on the medial surface of hemisphere) on either side of the interhemispheric fissure produce an easily recognizable mustache-like image (Fig. 73.2A). The central sulcus is usually the first sulcus anterior to this marginal sulcus in most individuals.
4. The precentral gyrus is often 1.5- to 2-fold bigger (sagittal thickness) than the adjacent postcentral gyrus.
5. The hand motor area on the precentral gyrus has an easily recognizable morphologic pattern in most individuals and can further aid in identification of the precentral gyrus. The most common morphologic pattern described on axial image is the “inverted omega” or “knob”- or “knuckle”- like appearance, with its rounded knob abutting the central sulcus. Other morphologic patterns such as “horizontal epsilon” and “asymmetric horizontal epsilons” have been recognized (10,11).

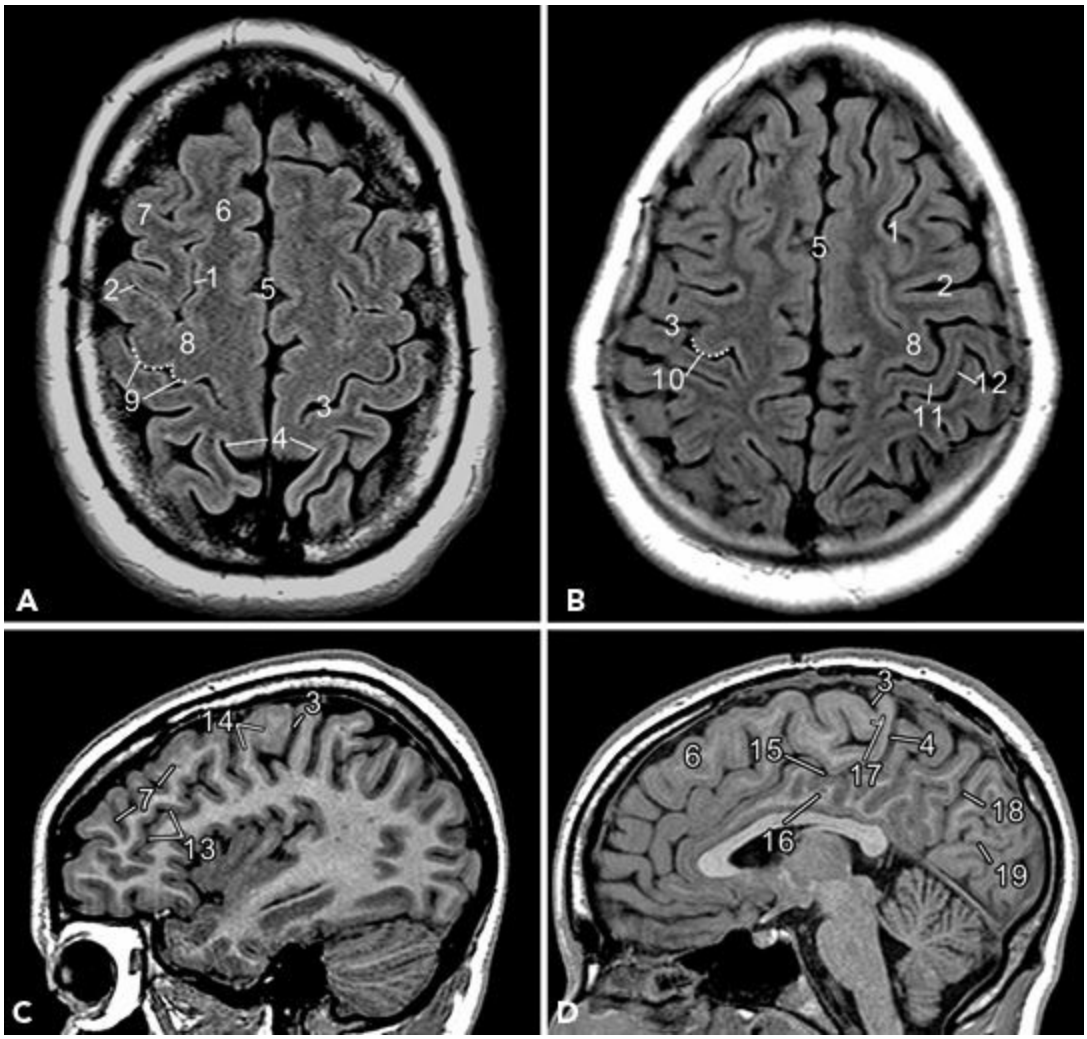

Figure 73.2. Primary motor area: Major landmarks on axial **(A** and **B)** and sagittal images **(C** and **D)** to identify the central sulcus and primary motor area (precentral gyrus). (1, superior frontal sulcus; 2, precentral sulcus; 3, central sulcus; 4, marginal sulcus (note mustache-like appearance); 5, interhemispheric fissure; 6, superior frontal gyrus; 7, middle frontal gyrus (note "zigzag appearance" in sagittal image); 8, precentral gyrus; 9, "horizontal epsilon"–shaped hand motor area; 10, "knob"-shaped hand motor area in a different subject; 11, postcentral gyrus; 12, postcentral sulcus; 13, inferior frontal sulcus; 14, posteriorly directed "hook"-shaped hand motor area on sagittal plane; 15, cingulate sulcus; 16, cingulate gyrus; 17, paracentral lobule; 18, parietooccipital sulcus; 19, calcarine fissure.)

On sagittal MR images, the central sulcus and precentral gyrus can be identified at three different levels—the far lateral surface, along the hand motor region, and over the medial surface (Figs. 73.1A and 73.2C and D).

1. As described in the earlier section of Broca area, in far lateral sagittal images, at the anterior end of sylvian fissure, the anterior ascending rami of sylvian fissure can be identified (Fig. 73.1A). The sulcus posterior and parallel to the anterior ascending rami denotes the inferior precentral sulcus, which descends inferiorly and often meets the sylvian fissure. The central sulcus lies posterior and parallel to the precentral sulcus, and it usually does not unite with the sylvian fissure unlike the precentral sulcus. Thus, the opercular (lower) part ends of the precentral gyrus and postcentral gyrus (primary sensory cortex) together form the subcentral gyrus (4,5).
2. Further medially, in the mid parasagittal sections (Fig. 73.2C), the hand motor area may be recognized as a posteriorly directed "hook"-shaped appearance (the sagittal view of the "knob" described on axial plane) and usually better visualized if thin sagittal sections are obtained.
3. Further medially (Fig. 73.2D), in the medial surface of the cerebral hemisphere,

identification of the cingulate sulcus and its ascending segment—the marginal sulcus—assist in delineation of the central sulcus. The central sulcus makes a small dip in the medial surface and is often the first sulcus anterior to marginal sulcus. The region on either side of the central sulcus on the medial side forms the paracentral lobule, which carries motor and sensory representation for contralateral lower extremity.

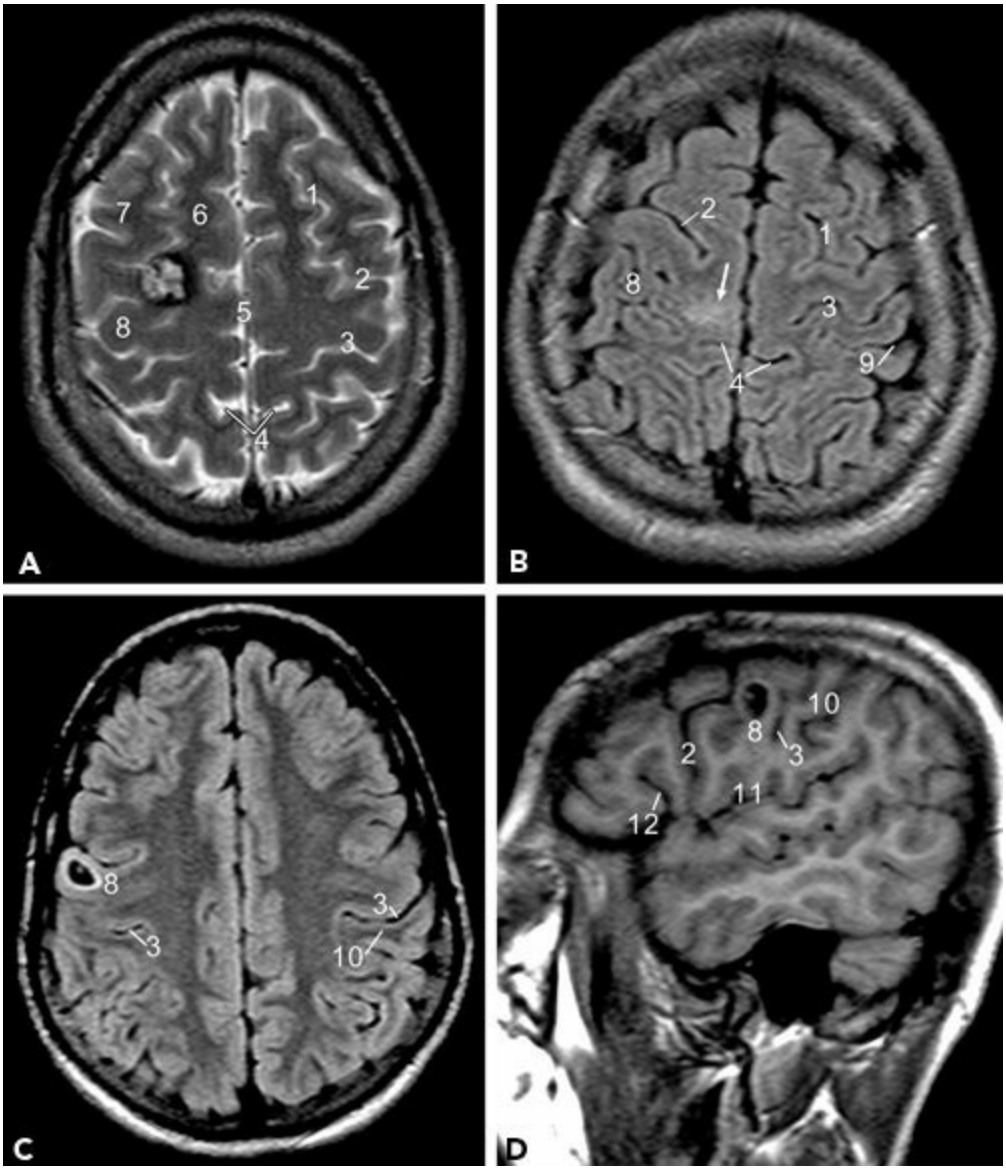

Figure 73.3. Lesions around the region of the central sulcus and precentral gyrus. **A:** T2-weighted image shows a cavernoma at the junction of the right superior frontal gyrus and precentral gyrus. **B:** FLAIR image shows an area of hyperintensity over the paramedian precentral and postcentral gyrus. **C, D:** A cystic lesion in the precentral gyrus over the lateral convexity displayed in axial and sagittal planes. (1, Superior frontal sulcus; 2, precentral sulcus; 3, central sulcus; 4, marginal sulcus; 5, interhemispheric fissure; 6, superior frontal gyrus; 7, middle frontal gyrus; 8, precentral gyrus; 9, postcentral sulcus; 10, postcentral gyrus; 11, sylvian fissure; 12, anterior rami of sylvian fissure.)

On coronal MR images, precise identification of the central sulcus and precentral gyrus is difficult using the coronal slices alone. On volume acquisition images, the inferior precentral gyrus may be identified by tracing the inferior frontal sulcus posteriorly.

Visual Area: The Calcarine Cortex

Calcarine cortex, the primary visual area, is located in the inferior and superior lips of the calcarine

fissure in the occipital lobes. Calcarine fissure can be readily identified on the sagittal and coronal images (Figs. 73.4 and 73.5) (12). On sagittal images close to midline (Fig. 73.4A), in the medial surface of the occipital lobe, calcarine fissure extends from a point below the splenium of corpus callosum to the occipital pole. The parietooccipital sulcus extends from the anterior part of calcarine fissure and extends upward in an oblique direction toward the dorsal surface of the brain. Between the parietooccipital sulcus and the calcarine fissure lie the cuneus—a wedge-shaped region in the medial occipital lobe. Precuneus lies anterior to this, between the parietooccipital sulcus and the marginal sulcus. On axial images, the parietooccipital sulcus is more readily visualized on multiple slices because of the oblique orientation of the parietooccipital sulcus (Fig. 73.4B).

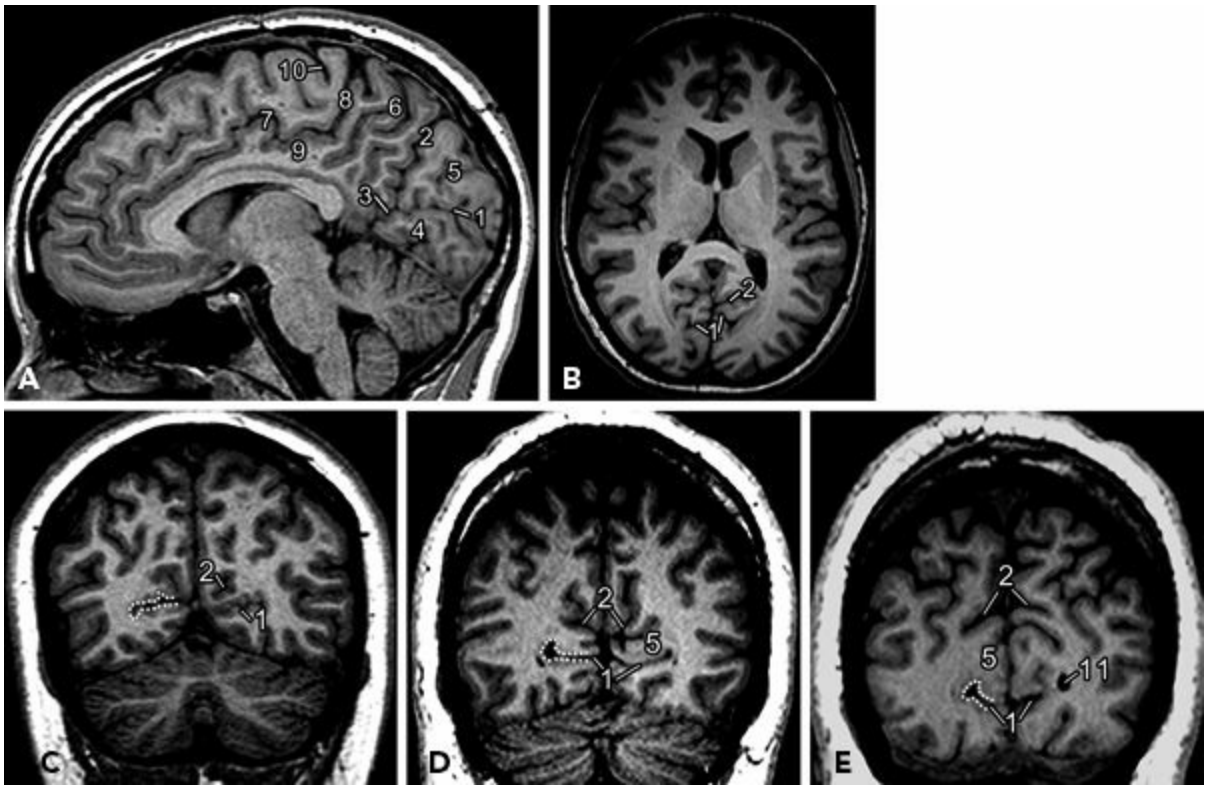

Figure 73.4. Visual cortex: Major landmarks on sagittal **(A)**, axial **(B)**, and coronal **(C–E)** planes to display calcarine fissure and parietooccipital sulcus. (1, calcarine fissure; 2, parietooccipital sulcus; 3, anterior calcarine sulcus; 4, lingual gyrus; 5, cuneus; 6, precuneus; 7, cingulate sulcus; 8, marginal sulcus; 9, cingulate gyrus; 10, central sulcus; 11, occipital horn of lateral ventricle.) Dotted lines on coronal images indicate region of visual cortex on the right side.

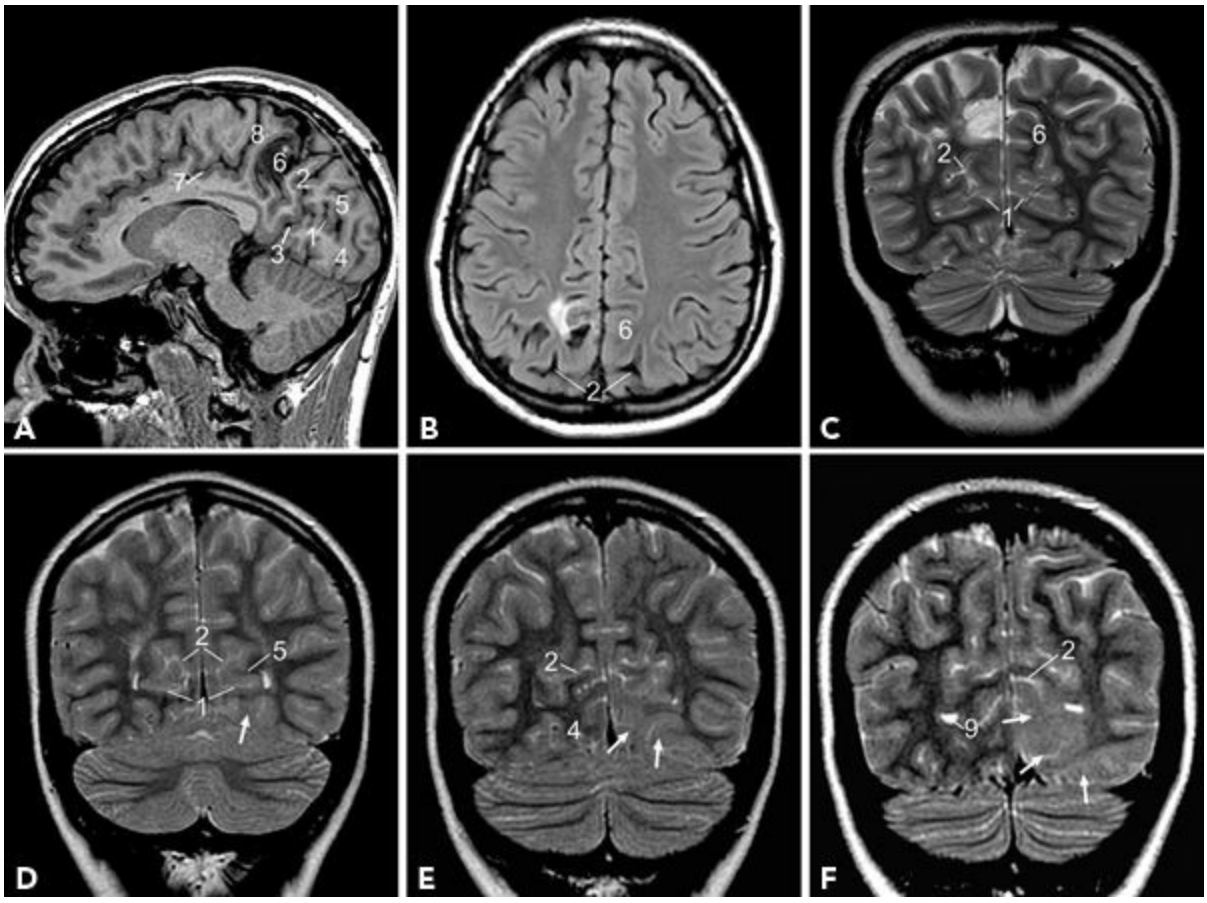

Figure 73.5. Lesions around the calcarine fissure and parietooccipital sulcus. **A–C:** Residual tumor with postoperative changes noted in the right precuneus region displayed in sagittal, axial, and coronal planes. Note that the lesion is anterior to the parietooccipital sulcus and posterior to the marginal sulcus. **D–F:** T2-weighted image shows hyperintensity (arrows) of the cortex and subcortical white matter in the left occipital lobe; lesion is inferior to calcarine fissure in anterior images **(D)** but involves calcarine fissure, cuneus, and lateral occipital gyrus in posterior sections **(F)**. (1, calcarine fissure; 2, parietooccipital sulcus; 3, anterior calcarine sulcus; 4, lingual gyrus; 5, cuneus; 6, precuneus; 7, cingulate sulcus; 8, marginal sulcus; 9, occipital horn of lateral ventricle.)

On coronal MR images, both calcarine fissure and the parietooccipital sulcus are readily identified as the two major fissures in medial occipital lobes that diverge as they course posteriorly (Fig. 73.4C–E). Calcarine fissure becomes shallow as it courses posteriorly and does not quite extend to the occipital pole. The parietooccipital sulcus is generally deeper and reaches dorsal surface and can normally be somewhat asymmetric in depth and configuration (12).

Temporal Lobe

Broadly, temporal lobe epilepsy is categorized as mesial temporal epilepsy and lateral temporal epilepsy syndromes based on presumed anatomic origin of epileptogenicity. Temporal lobe on its outer surface is limited superiorly from the frontal lobe by sylvian fissure. The posterior limits of temporal lobe are poorly defined by an imaginary line from the preoccipital notch of the basal aspect of temporal lobe to the superior aspect of the parietooccipital sulcus. Lateral temporal region consists of three major gyri, namely, the superior, middle, and inferior temporal gyri divided by the superior and inferior temporal sulci. There are two gyri on the basal aspect—the laterally located fusiform or occipitotemporal gyrus and the medially located parahippocampal gyrus (PHG). The fusiform gyrus is limited laterally from the inferior temporal gyrus by the lateral occipitotemporal sulcus and separated medially from the PHG by the collateral sulcus. Temporal structures medial to the collateral sulcus are referred to as mesial temporal structures (13–17).

Mesial temporal structures are best visualized on volumetric high-resolution coronal MR images (Fig. 73.6). Hippocampal formation, amygdala, and PHG are usually considered together as part of the mesial temporal epilepsy network. The term hippocampal formation is often used to denote the hippocampus proper along with the dentate gyrus. Hippocampus derives its name from its morphologic resemblance to a "sea horse," best appreciated on sagittal images (Fig. 73.6A). It has three parts, namely, head, body, and tail of hippocampus, from anterior to posterior. The head and body of hippocampus extend posteriorly along the inferomedial border of temporal horns of lateral ventricles (Fig. 73.6A and B). Head of hippocampus is the most voluminous part and occupies the anterior end of hippocampus (Fig. 73.6D). Head of the hippocampus is further recognized by its typical undulating superior margin produced by the digitations on the ventricular surface of the structure, better visualized on coronal T2-weighted or inversion recovery images. Many landmarks have been used to identify body and tail of hippocampus, but the most useful would be internal landmarks such as fimbriae and crus fornix—the output tracts of hippocampus. On the coronal MR images, posterior to the head of hippocampus, the appearance of fimbriae signals the junction of head and body of hippocampus (Fig. 73.6E). Further posteriorly, the clear appearance of crus fornix signals the beginning of the tail of hippocampus (Fig. 73.6F). The tail of the hippocampus and fornix course superiorly and medially along the medial margins of atria of lateral ventricles. The dentate gyrus is often indistinguishable from the hippocampus proper and forms a single unit on MR images. The dentate gyrus runs parallel to the hippocampus with its cuplike superior surface covering the CA4 region, forming the hilus of hippocampus. The dentate gyrus continues anteriorly as the band of Giacomini, also referred as tail of dentate gyrus, and posteriorly curves around the callosum as indusium griseum. The amygdala, located on the roof of the temporal horn of the lateral ventricle, is anterior and superior to the head of hippocampus (Fig. 73.6C). The amygdala fuses with the globus pallidus superiorly (13–18).

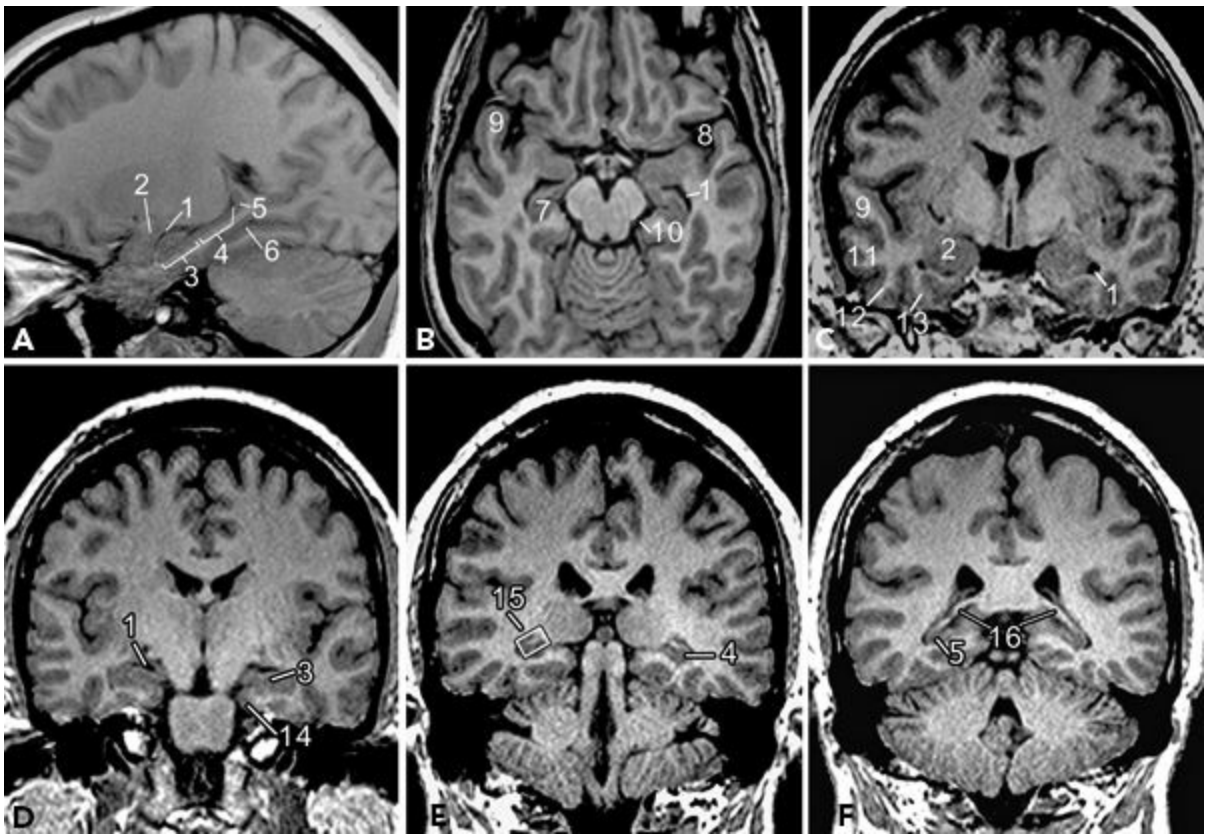

Figure 73.6. Temporal lobe structures displayed in sagittal **(A)**, axial **(B)**, and coronal **(C–F)** planes. (1, temporal horn of lateral

ventricle; 2, amygdala; 3, head of hippocampus; 4, body of hippocampus; 5, tail of hippocampus; 6, collateral sulcus; 7, hippocampus; 8, sylvian fissure; 9, superior temporal gyrus; 10, ambient cistern; 11, middle temporal gyrus; 12, inferior temporal gyrus; 13, occipitotemporal (fusiform) gyrus; 14, parahippocampal gyrus; 15, fimbriae—hyperintense structure within the box; 16, crus of fornix.)

The PHG is located inferolateral to the hippocampal formation and extends posteriorly along the margin of the tentorium cerebelli in contact with the ambient cistern medially. The hippocampal sulcus separates the PHG from hippocampal formation superiorly, and collateral sulcus separates it from the fusiform gyrus laterally on the basal aspect (Fig. 73.6C and D). Anterior end of the PHG is hooked backward and medially, to form the uncus. The PHG has two components, namely, the subiculum and the entorhinal area. Subiculum, the superomedial part of PHG, is continuous with the CA1 of hippocampus and forms the bed of hippocampal formation. Entorhinal area is a poorly demarcated area located in the uncus and the anterior extension of PHG. In the posterior part, the anterior end of calcarine fissure divides the PHG into a superior and an inferior part. The superior part called isthmus curves up and continues with the cingulate gyrus, and the inferior part continues posteriorly with the lingual gyrus of occipital lobe (13–16).

MRI: TECHNICAL CONSIDERATIONS

Most centers use a 1.5 T MRI for routine imaging to evaluate for medically refractory partial epilepsy. 3 T MRI scanners are now widely available and increasingly used for epilepsy protocol imaging. 3 T MRI is likely to replace the 1.5 T MRI for imaging of potential epilepsy surgical candidates. Most MRI studies for evaluation of epilepsy incorporate a sagittal T1-weighted spin-echo acquisition as a scout image to position the slices of the subsequent pulse sequences. The other sequences and the imaging planes are tailored according to the referral information about presumptive epileptogenic zone. Broadly, two kinds of protocols are used in epilepsy imaging—temporal lobe protocol and extratemporal protocol. Different centers use different sets of sequences in these protocols. In general, high soft tissue contrast, thin sections, and imaging in all three planes are critical to epilepsy protocols. A cost- and time-effective protocol, frequently employed at Cleveland Clinic, is shown in Table 73.1.

Table 73.1 Epilepsy Protocol MRI Commonly Used at Cleveland Clinic

Mandatory sequences[a]	Supplemental imaging that may be helpful
Temporal	
Sagittal T1 (4-mm slices)	Axial TSE T2
Coronal three-dimensional gradient-echo (1-m slices) sequence (e.g., SPGR, MP-RAGE)	Axial TSE IR (4-mm slices)
Coronal TSE T2 (4-mm slices)	T2* gradient-echo—axial and coronal[b]
Coronal TSE FLAIR (4-mm slices)[c]	Contrast study as needed[d]
	DWI[e]
Extratemporal	
Sagittal T1 (4-mm slices)	Coronal TSE T2 (4-mm slices)[f]
Coronal three-dimensional gradient-echo sequence (e.g., SPGR, MP-RAGE) (1-mm slices)	Coronal TSE IR (4-mm slices)[f]
Axial TSE T2 (4-mm-thick slices)	T2* gradient-echo—axial and coronal
Axial TSE FLAIR (4-mm slices)	Contrast study as needed[d]
	DWI[e]

[a]3 T MRI is preferred.
[b]Gradient-echo sequences or SWI—in cavernomas, arteriovenous malformations, remote hemorrhages, posttraumatic epilepsy, Sturge–Weber syndrome.
[c]FLAIR is unhelpful and sometimes misleading in children below 18–24 months of age.
[d]Contrast study—for tumor-like lesions, vascular malformations, suspected Sturge–Weber syndrome, acute symptomatic seizures.
[e]DWI—acute symptomatic seizures, suspected strokes, cystic lesions (epidermoid cyst), tumors.
[f]Should ensure study of entire brain including frontal and occipital poles.
TSE, turbo-spin echo; SPGR, spoiled gradient-recalled echo; MP-RAGE, magnetization-prepared rapid acquisition gradient echo; IR, inversion recovery; FLAIR, fluid attenuated inversion recovery; SWI, susceptibility-weighted imaging; DWI, diffusion-weighted imaging.

In general, T1-weighted (short repetition time [TR], short echo time [TE]) images serve largely to define the anatomy, and T2-weighted (long TR and long TE) images are well suited for detecting most brain pathology. Fast spin-echo (FSE) or hybrid rapid acquisition relaxation enhancement sequences have replaced the earlier double-echo T2-weighted imaging because of inherent advantages in signal-to-noise ratio, acquisition time, and reduction in motion artifacts (19,20). The heavily T2-weighted images provide strong contrast between CSF and brain parenchyma and tissues with long T2 relaxation times. On the other hand, strong contrast produced by very long TRs and long echo trains can be detrimental and may obscure some parenchymal lesions and gray–white junction (19). The series of 180-degree pulses used in FSE T2 images reduces artifacts in plane with CSF motion as well as susceptibility artifacts at bone–CSF interfaces or adjacent to metallic foreign

bodies. However, the same effect makes the visualization of some blood products less evident than on conventional spin-echo imaging. The absence of 180-degree rephasing pulse in the gradient-echo sequences accentuates the local susceptibility artifact related to blood by-products and compensates for this shortcoming of FSE sequences. Consequently, a gradient-echo sequence should be used in any patients in whom vascular malformations or prior trauma is the apparent etiology (Fig. 73.7).

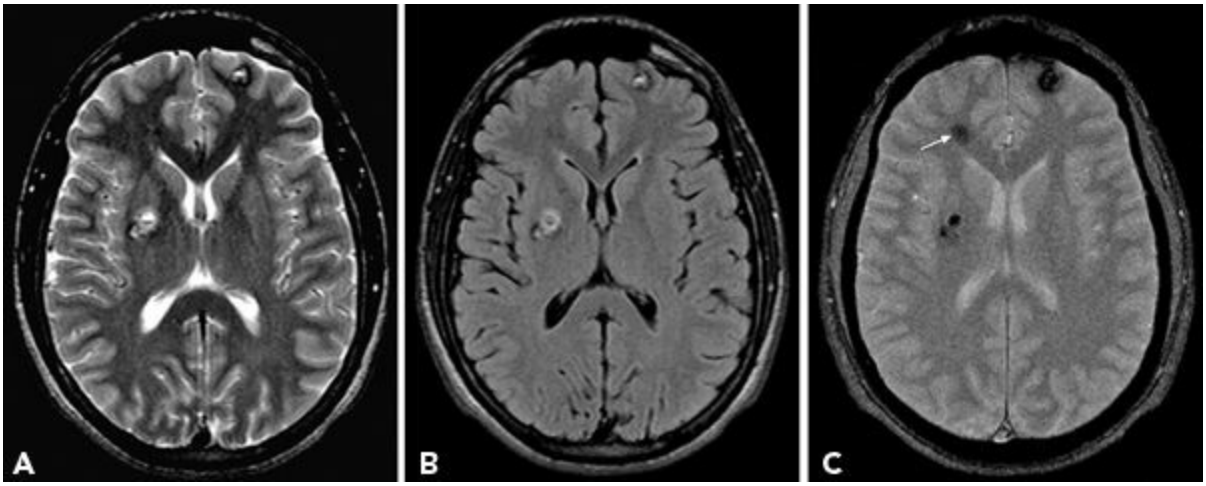

Figure 73.7. Axial T2-weighted **(A)**, FLAIR **(B)**, and gradient-echo images **(C)** show multiple cavernomas. Gradient-echo sequence reveals additional lesion in right frontal region (arrow) that is inconspicuous on T2 and FLAIR images.

FLAIR images improve the detection of lesions by suppressing the CSF signal and accentuating the signal of lesions with relatively short T1 and long T2 relaxation times (21). Fast FLAIR incorporates a preparatory 180-degree pulse and inversion time before the long TR/long TE FSE sequence to nullify the signal intensity of CSF. Hence, it has a specific advantage over T2 for lesions in the brain–CSF interface, namely, periventricular and subpial cortex location, as the CSF signal appears dark. In MTS, the hyperintense signals in the hippocampus may be obscured by the hyperintense CSF in the temporal horns on T2 sequences (21–23). FLAIR, by suppressing the CSF signal, accentuates the abnormality in the hippocampal region. Although FLAIR is often thought to be as "a heavily T2-weighted image with dark CSF," the nature of FLAIR sequence causes anything with relatively short T1 and long T2 relaxation times to be hyperintense on the FLAIR images. Some of these lesions may be overlooked on the T2-weighted study alone (Fig. 73.8). Direct comparison of T2 and FLAIR makes it clear that the lesions that are evident on both sets of images are often more obvious on the fast FLAIR. Lesions that are better visualized by fast FLAIR include subtle hyperintensity blurring the gray–white junction of MCD, subcortical foci of gliotic hyperintensity in areas of encephalomalacia, and the extent of infiltration of low-grade neoplasms.

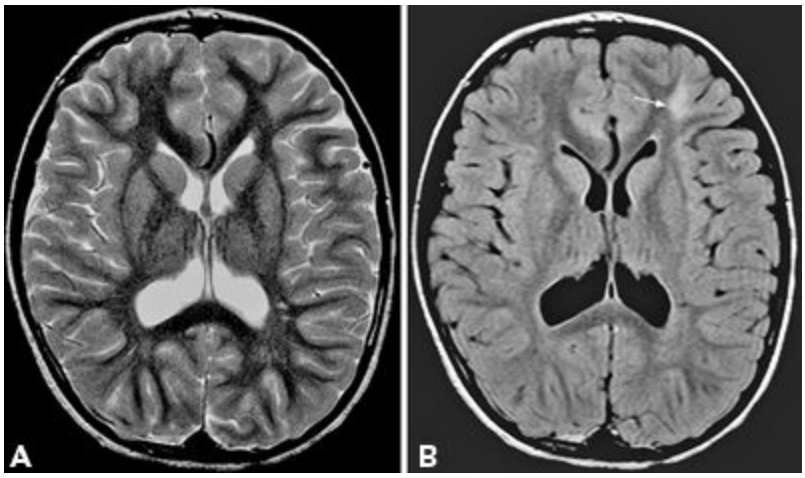

Figure 73.8. MR images to demonstrate superior visualization of subcortical hyperintensity associated with focal cortical dysplasia on FLAIR sequence. The dysplastic region in the left frontal region, nearly invisible on the T2-weighted image **(A)**, is conspicuous (arrow) on the FLAIR image **(B)**.

FLAIR has its own limitations. (i) Motion artifacts due to CSF pulsations, often more striking in the basilar cisterns, can blur the medial temporal regions. Fast T2 sequences are less susceptible to this, and hence, correlation with T2 makes this a relatively minor issue. (ii) Suppression of contrast between gray and white matter may obscure visualization of small foci of heterotopic gray matter without correlative pulse sequences. (iii) Detection of prior hemorrhages is limited with both fast FLAIR and fast T2 images because of the common sequence structure. (iv) Lastly, the contrast on fast FLAIR seems to be most limiting in young children (<2 years) with immature white matter. Normal children in this age group demonstrate patchy foci of hyperintensity in the subcortical and sometimes periventricular white matter that may be misinterpreted as abnormal. Conventional spin density images tend to be more helpful in this age group.

Volumetric High-Resolution Imaging

Conventional spin-echo imaging is generally sufficient to characterize a lesion when it is relatively large. In the case of smaller lesions, it may be difficult to interpret the nature of lesion or even identify the abnormality at all without high-resolution volumetric imaging. The best example of this would be the case of focal area of the dysplastic cortex, which constitutes the major substrate in many patients with refractory extratemporal epilepsy. Diagnosis of these subtle malformations requires critical evaluation of the thickness and morphology of cortical mantle, delineation of the interface between gray and white matter, and detection of minor signal intensity changes in the subcortical white matter. The 4- to 5-mm-thick slice of the routine T2 and FLAIR images frequently fails to detect such subtle abnormalities. Consequently, three-dimensional high-resolution volumetric imaging with T1-weighted gradient- echo protocols has become an integral and critical part of imaging for epileptogenic lesions.

Sequences such as fast spoiled gradient-recalled echo (SPGR), magnetization-prepared rapid acquisition gradient echo (MP-RAGE), and fast spoiled gradient-recalled acquisition in a steady state (GRASS) can be performed rapidly with very short TRs and TEs that provide strong T1-like contrast between gray and white matter (24,25). The hypointensity of the gray matter is quite comparable to the adjacent CSF, and hence, signal abnormalities in the gray matter are generally quite subtle. Conversely, many lesions in the white matter are obvious, but the signal intensity characteristics are frequently nonspecific. Lesions such as gliosis, heterotopia, and neoplasm may have the same degree

of hypointensity and may be indistinguishable based on volumetric sequence alone. Lesion morphology, correlation with other pulse sequences, and the clinical setting are necessary to distinguish the lesions. Images acquired through the volumetric study protocols do not have the true T1 contrast as they are gradient-echo sequences and not spin-echo sequences as in conventional T1 image. Hence, lesions that are typically hyperintense on T1 images such as blood products, dystrophic calcification, and proteinaceous fluids may not be apparent on this high-resolution volumetric imaging using gradient-echo sequences.

These three-dimensional sequences are designed to cover the entire head with very thin 1-mm contiguous slices. These thin slices are especially sensitive to detection of subtle dysmorphism of the cortical mantle and can also highlight minimal mass effect by depicting effacement of the adjacent sulcus in case of small tumors. Detection of subtle variations in configuration and volume of hippocampus is greatly improved by high-resolution volumetric imaging and has markedly reduced the need for invasive monitoring in patients with suspected MTS (26). Similarly, detection of concomitant malformation of cortical development in patients with MTS is critical in presurgical evaluation. Routine 4- to 5-mm FLAIR and T2 images are susceptible to volume averaging artifacts and thus misleading when one tries to assess the morphology of hippocampus. Even minimal tilt of the head in the scanner may accentuate this problem. The thin, contiguous three-dimensional slices minimize the volume averaging errors and improve detection of selective atrophy, developmental dysplasia, and subtle masses such as gliomas in the hippocampal formation by visual inspections alone. Volume averaging errors are further minimized if the slices are taken perpendicular to the long axis of the hippocampal formation. Quantitative volumetric analysis of the hippocampal formation and T2 relaxometry—a technique to quantify the signal intensity—may potentially improve recognition of subtle variations in volume and signal abnormality, respectively, as compared to visual inspection alone. However, these techniques are time consuming with minimal additional advantage if any and are not routinely used in clinical practice (27,28).

Other MRI Techniques and Their Utility in Epilepsy

In the last decade, newer MR imaging techniques have tremendously improved our understanding of the disorders of the brain. Careful selection of these sequences may provide useful information in selected causes of epilepsy such as cavernomas, posttraumatic epilepsy, epidermoid cyst, tuberous sclerosis, and acute symptomatic seizures. Some of the newer techniques provide information about the function and connections of the brain further assisting in surgical strategy.

Diffusion-weighted imaging (DWI) has revolutionized the neuroimaging of acute stroke but has limited role in epilepsy. In DWI, diffusion weighting is achieved by two strong diffusion-sensitizing gradients applied symmetrically around the 180-degree radiofrequency pulse of a spin-echo sequence. This leads to dephasing followed by rephasing of protons. Protons that have moved during and after the dephasing gradient move randomly, which leads to incomplete rephasing and signal attenuation. Areas with restricted diffusion of water molecules retain the signal and appear bright on DWI. The degree of diffusion restriction can be quantified by apparent diffusion coefficient (ADC) value. Areas with restricted diffusion appear bright on DWI with low signal intensity (correspondingly low ADC values) on ADC maps (29,30). In focal epilepsies, peri-ictal changes with foci of hyperintensity on DWI with decreased ADC values presumably due to cytotoxic edema have been reported (31,32). Isolated low ADC values without overt hyperintensity on DWI are more common in the peri-ictal studies (33). Conversely, interictal DWI has revealed increased ADC

values, which may reflect neuronal loss and increased extracellular space. Other disorders related to epilepsy that may show DWI abnormalities include the following: cortical and subcortical abnormalities in status epilepticus, tumors such as epidermoid cyst (Fig. 73.9), and transient lesions of splenium of corpus callosum related to seizures and antiepileptic drugs (34–36). A significant increase in ADC has been reported in epileptogenic tuber compared to other tubers in patients with tuberous sclerosis and may be helpful in surgical decisions (37).

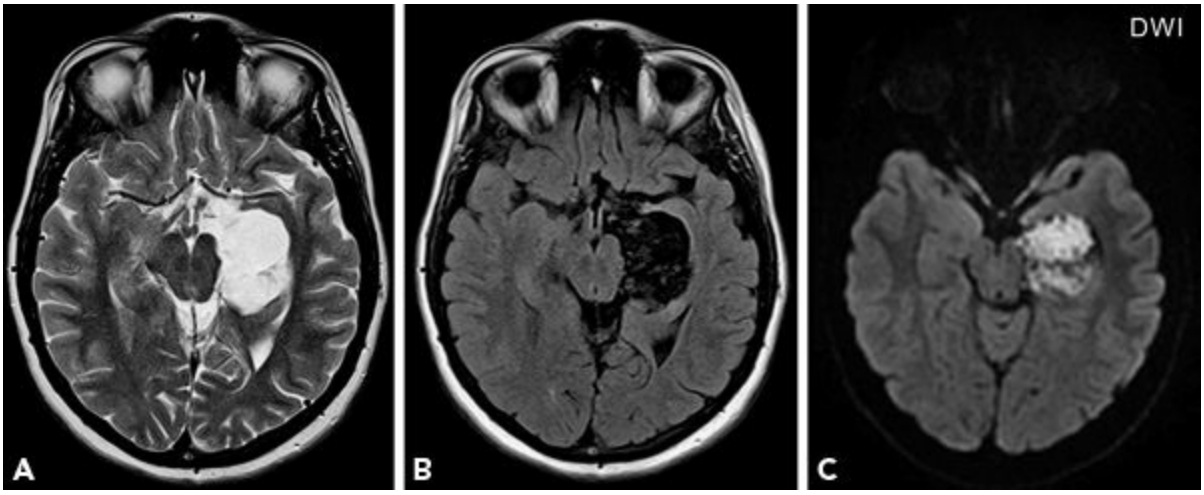

Figure 73.9. A cystic lesion in the left medial temporal region, with signal characteristics similar to CSF, hyperintense on T2-weighted image **(A)** and hypointense on FLAIR **(B)**, shows diffusion restriction on DWI **(C)** consistent with epidermoid cyst. Histopathology confirmed the diagnosis.

DTI demonstrates the connections of different regions of the brain. Unlike conventional DWI, the diffusion-sensitizing gradients are applied in six different directions in DTI. As a result, the directionality of water diffusion is studied in addition to magnitude of diffusion. In general, the diffusivity is greater parallel (i.e., along the long axis of the tracts) to than perpendicular to the fiber tracts, and this can be quantified by DTI (38,39). DTI and its role in epilepsy evaluation are presented in greater detail in Chapter 78.

Susceptibility-weighted imaging (SWI) techniques that exploit differences in magnetic susceptibility of tissue components may provide additional information in epileptogenic lesions containing blood products such as cavernomas, certain posttraumatic epilepsies, and Sturge–Weber syndrome. T2* gradient echo (GRE) is the most commonly used sequence for detecting remote blood products. However, SWI—now widely available commercially—is superior to T2* GRE in detection of remote hemorrhages. SWI is a high-resolution three-dimensional gradient-echo technique, which exploits the small differences in magnetic susceptibility among different components of the tissue such as deoxygenated blood, iron, and calcium compared to the surrounding brain tissue. This also illustrates the smallest of veins (because veins contain higher deoxygenated blood) in the submillimeter caliber in great detail. Lesions such as cavernomas tend to be multiple, and some lesions not apparent on T2* GREs may be recognized with SWI (40). In Sturge–Weber syndrome, SWI improves detection of transmedullary and periventricular veins and cortical gyral abnormalities compared to contrast-enhanced T1 images (Fig. 73.10). The cortical gyral abnormalities on SWI seem to represent venous stasis–related hypoxia and correspond to the hypometabolic areas detected on FDG-PET. Thus, SWI has the potential to show functional information in addition to anatomical details in Sturge–Weber syndrome (41,42).

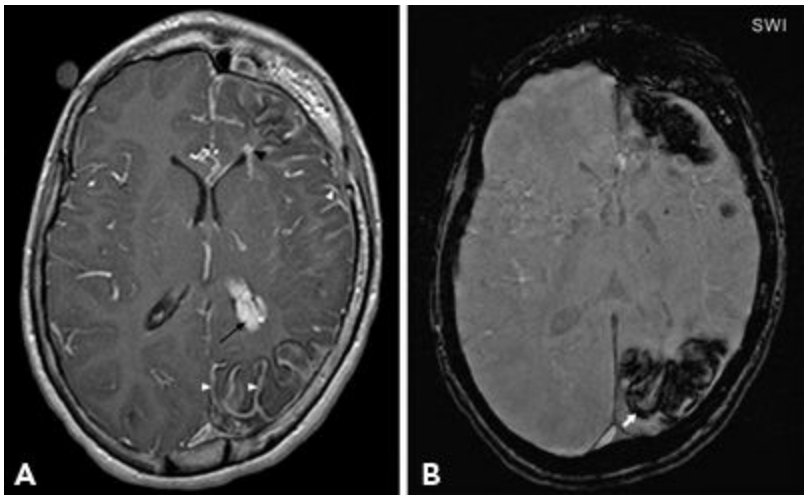

Figure 73.10. Contrast-enhanced T1-weighted image **(A)**, and susceptibility-weighted image (SWI) **(B)** in a child with Sturge–Weber syndrome. Contrast study shows enlarged periventricular veins (black arrowhead), abnormal leptomeningeal (white arrowheads), and choroid plexus enhancement (black arrow). SWI is superior to visualize the extent of cortical abnormality (arrow). Also, note diffuse left hemispheric atrophy and thickening of ipsilateral calvarium. (Courtesy of Dr. Ingrid Tuxhorn, Cleveland, OH.)

STRATEGIES TO IMPROVE LESION DETECTION

Conventional epilepsy protocol imaging as outlined, using a 1.5 T MRI, is sufficient for most cases of chronic epilepsy. However, the scenario of a patient with medically refractory epilepsy with no lesions detected on MRI is fairly common in epilepsy centers. Failure to diagnose a structural abnormality reduces the likelihood of consideration for epilepsy surgery. Invasive monitoring with subdural grids and depth electrodes may be required in some of these patients. The success rates for epilepsy surgeries done in such patients with "unremarkable MRI" are substantially lower (43–45). The single most common epileptogenic substrate that evades detection in such situation is MCD. Appropriate utilization of newer techniques in MRI may improve the detection of MCD and other subtle lesions missed by the routine epilepsy protocol. Reviewing the initial MRI with a more experienced reader familiar with characteristics of the subtle MCD is probably the first step to improve the detection. Localization data acquired from seizure semiology, EEG, MEG, and other imaging modalities such as PET and SPECT may also help localize the area of interest, and a more focused review of the images can be helpful in some cases. Some of the imaging strategies that may be employed to improve lesion detection are discussed in the following section.

3 T MRI AND 7 T MRI

Increase in the magnetic field strength in 3 T MRI improves the signal-to-noise ratio and contrast-to-noise ratio, thereby improving the detection of subtle lesions (46). The gray–white contrast is superior on the volumetric high-resolution imaging with 3 T MRI, despite the difference in T1 relaxation times of brain tissue at 3 T (Fig. 73.11). Subtle blurring at the gray–white junction without hyperintensity on T2 or FLAIR, a common and sometimes the only MRI finding of MCD, is better visualized on these images. 3 T MRI is not without its disadvantages. One potential disadvantage with 3 T MRI is decreased gray–white contrast with T1 spin-echo imaging compared to 1.5 T MRI. Inversion recovery sequences can alleviate this effect but cannot be used when one attempts to compare these images with a contrast-enhanced T1 image, as inversion recovery pulse interferes with visualization of contrast. Reducing the excitation flip angle improves gray–white contrast despite

reduction in signal-to-noise ratio. Higher magnetic field strength also accentuates the susceptibility effects, and this can cause artifacts. Conversely, studies that exploit the susceptibility effects, namely, SWI and fMRI techniques such as BOLD (blood oxygenation level dependent), are benefited by 3 T MRI. Other minor limitations of 3 T study include increased acoustic noise and increased device incompatibility (46–48).

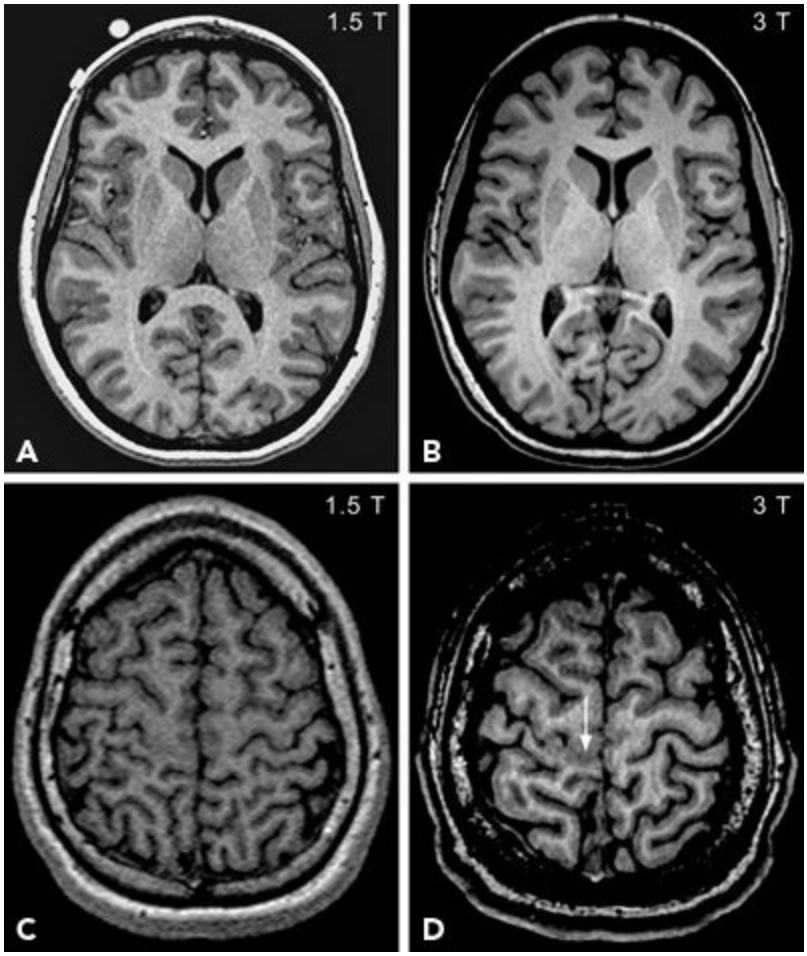

Figure 73.11. Comparison between 1.5 T and 3 T MRI (same patient). **A, B:** Axial MP-RAGE images with 1.5 T **(A)** and 3 T **(B)** MRIs show improved signal-to-noise ratio resulting in better gray–white contrast, on 3 T MRI. **C, D:** Subtle blurring of gray–white region on the banks of central sulcus (arrow), barely visible on the 1.5 T MRI **(C)**, is better visualized on 3 T MRI **(D).**

Clinical experience with 3 T MRI in epilepsy suggests improved detection of lesions compared to 1.5 T imaging. A 20% to 48% increase in detection of new or additional information by 3 T study compared to 1 to 1.5 T MRI (46,49–51) has been reported in some studies. Two of these three studies also used phased array coils, and it is unclear whether the improved lesion detection rate was solely due to higher magnetic field strength. Higher detection rate of MCD is the main reason for improved yield of 3 T MRI in these studies. Anecdotal experience suggests that these lesions are often visible on 1.5 T studies but are diagnosed with more certainty by 3 T study. 7 T MRI is currently available for use in few centers. In a group of patients with mesial temporal lobe epilepsy, 7 T MRI showed differences in patterns of atrophy in mesial structures (52). The clinical impact of these findings in management of patients remains to be studied.

Surface Coils and the Multichannel Phased Array Coils

Surface coils instead of the routine head coils have been used in an attempt to improve imaging of

selected regions of the brain and help to confirm or exclude suspicious abnormalities over the presumed epileptogenic zone. Surface coils improve the signal-to-noise ratio thereby improving the spatial resolution of the structures close to the surface coils (Fig. 73.12). The structures away from the "view" of the surface coils are poorly visualized. As a result, poor imaging quality for deeper structures makes surface coils less desirable for evaluation of mesial temporal structures. In the past, limited coverage of brain by surface coils required careful planning with preimaging working hypothesis about the possible epileptogenic zone to guide the placement of surface coils. Localizing information from seizure semiology, EEG, video-EEG, prior MRI (in case of subtle questionable abnormalities), and other studies such as SPECT and PET should guide the placement of the coils (53). Limited coverage of cortex (and the resultant "tunnel vision"), overall increase in scan time, need for preimaging hypothesis, and decreased signal-to-noise ratio for the deeper structures were major limitations precluding routine use of surface coils.

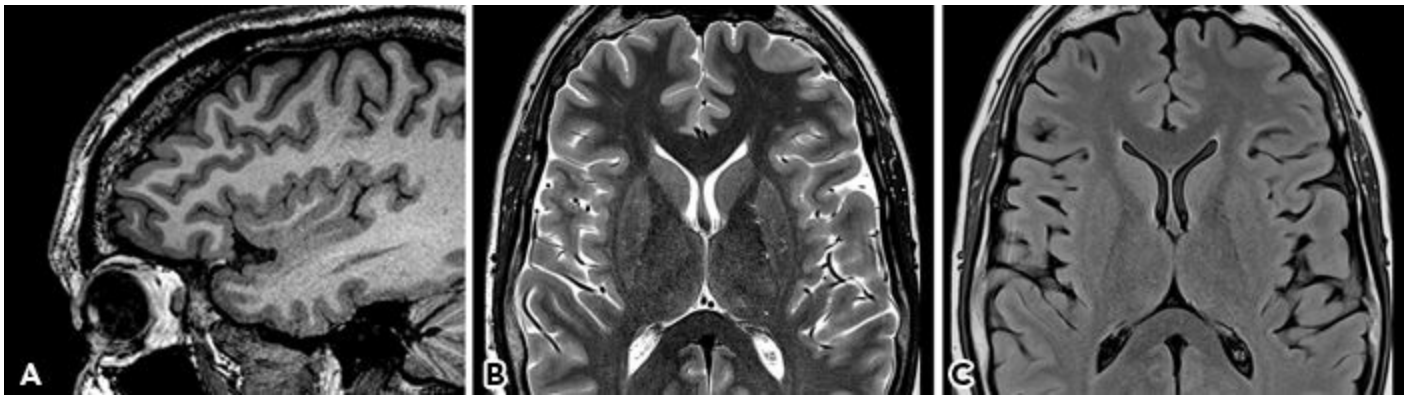

Figure 73.12. MRI with surface coils placed over the frontal regions yield high-resolution images of the frontal lobe. Deeper structures farther from the coil (temporal structures on sagittal image and basal ganglia on axial images) are poorly visualized due to decreased signal-to-noise ratio.

Increased anatomical coverage by increase in the number of elements in the phased array coils has minimized the limitations of traditional surface coils. Using 3 T MRI with eight-channel flexible phased array coils in 40 patients with focal epilepsy, a 65% increase in yield was reported in a subgroup of patients with previous unremarkable 1.5 T MRI (50). Though the differences appear robust, this study did not distinguish the effect of the higher field strength from the effect of surface coils. In another recent study of 25 patients with extratemporal epilepsy, 3 T MRI with two flexible surface coils was compared with 1 to 1.5 T MRI. Though additional abnormalities were seen in 20% of cases on 3 T MRI, authors concluded that there was no added benefit with the use of surface coils (49).

Three-Dimensional Reconstructions

Each of the pixels that constitute a two-dimensional MR image actually has a third dimension in anatomic imaging—the dimension of the thickness. As three-dimensional MRI produces slices without an interslice gap, it avoids the problem of lost data found with conventional two-dimensional imaging. If the imaging voxels in the three-dimensional acquisitions are designed to achieve an equivalent length in all three imaging planes (isotropic data), the images can be reconstructed in any alternate plane without compromising the spatial resolution or fidelity when compared to the original images. On the other hand, if the voxels were too anisotropic, the reconstructed images will be

noticeably degraded compared with the original data. In practice, data can only be "nearly" isotropic as patients will not routinely tolerate the length of time required to acquire truly isotropic data.

With standard imaging planes, the complex interposition of gyrus and sulcus of the normal brain's convolutional pattern potentially leads to errors in interpretation of thickness in gray matter. Slices that cut through the in-plane cortex (along the gray matter) lead to apparent thickened cortex and potential misdiagnosis as malformed cortex. Conversely, cautious avoidance of such "overcalls" can potentially lead to underdiagnosis of truly thickened areas of malformed cortex as well. Subtle MCDs may be suspected on the original images but are difficult to confirm in the original plane, until after the images are reconstructed in other planes. Alternatively, the lesion may be clearly apparent on the original acquisition; yet, there may be difficulty in delineating the spatial relationships of the lesion relative to the adjacent eloquent cortex. Volumetric high-resolution images obtained in epilepsy protocols can be reconstructed in various planes. Reformatting the images in multiple planes may enable to view the images in a plane perpendicular to the gyri thereby reducing the spurious thickening of the cortex seen in images in plane with the gyri.

Image reconstruction in a curvilinear plane—a plane parallel to the cortical surface and perpendicular in relation to the gyri—is being performed at some centers. The resultant images show progressively deeper surfaces of the brain like "peeling an onion." In this technique, a surface is obtained initially by manually outlining the cortical surface in the coronal plane at selected intervals. This surface serves as a matrix to generate progressively deeper slices using a software. These curved slices will result in more uniform distribution of gray matter on both hemispheres assisting in comparison of homologous regions of the cortex (54–56). Apart from improving the detection of subtle MCDs, such surface reconstructions have the potential to assess the location of subdural grids and depth electrodes more precisely. However, the clinical utility of these techniques in large patient population has not been studied.

Several centers now use other postprocessing techniques in multiple ways. Voxel-based morphometry is a promising automated technique to detect subtle dysplastic lesions by accentuating the abnormalities in the gray–white junction (57). Voxel-based morphometry and its role in epilepsy evaluation are presented in Chapter 77.

Serial MRI in Infants and Young Children

Signal characteristics of immature myelin in infants and young children can pose significant challenges in interpretation of studies obtained in infancy. Lesions such as MCDs and cortical tubers have varying signal characteristics based on the developmental stage of the myelin of the lesions and the surrounding brain. For example, in infants, the dysplastic cortex and adjacent subcortical regions may appear hypointense on T2-weighted images and hyperintense on T1 sequences, contrary to the reverse pattern seen in older children and adults (58–60). The lesion characteristics change to the more typical adult pattern over time with progressive myelination. In some patients, with progressive myelination, these lesions tend to become less obvious or rarely "vanish" on follow-up imaging (61). Reviewing only the most recent images may fail to detect the lesions. Conversely, a "new lesion" of MCD may be detected on follow-up imaging in a child with previously "normal MRI" in early infancy. The poor visualization of the lesions on earlier MRI may be explained by the poor background contrast of the bright immature myelin on the T2 images (62). Follow-up MRI during 2nd year of life or later allowing normal myelination to take place may unmask areas of MCD with decreased or absent subcortical myelin. Similarly, cortical tubers of tuberous sclerosis may be more

evident on follow-up imaging (Fig. 73.13). Apart from changes in myelination, increased growth of tubers and dystrophic calcification may contribute to their better visibility on follow-up imaging. Serial MRIs are also helpful in other epileptic disorders such as Rasmussen encephalitis and Sturge–Weber syndrome to demonstrate progressive regional or hemispheric cortical atrophy.

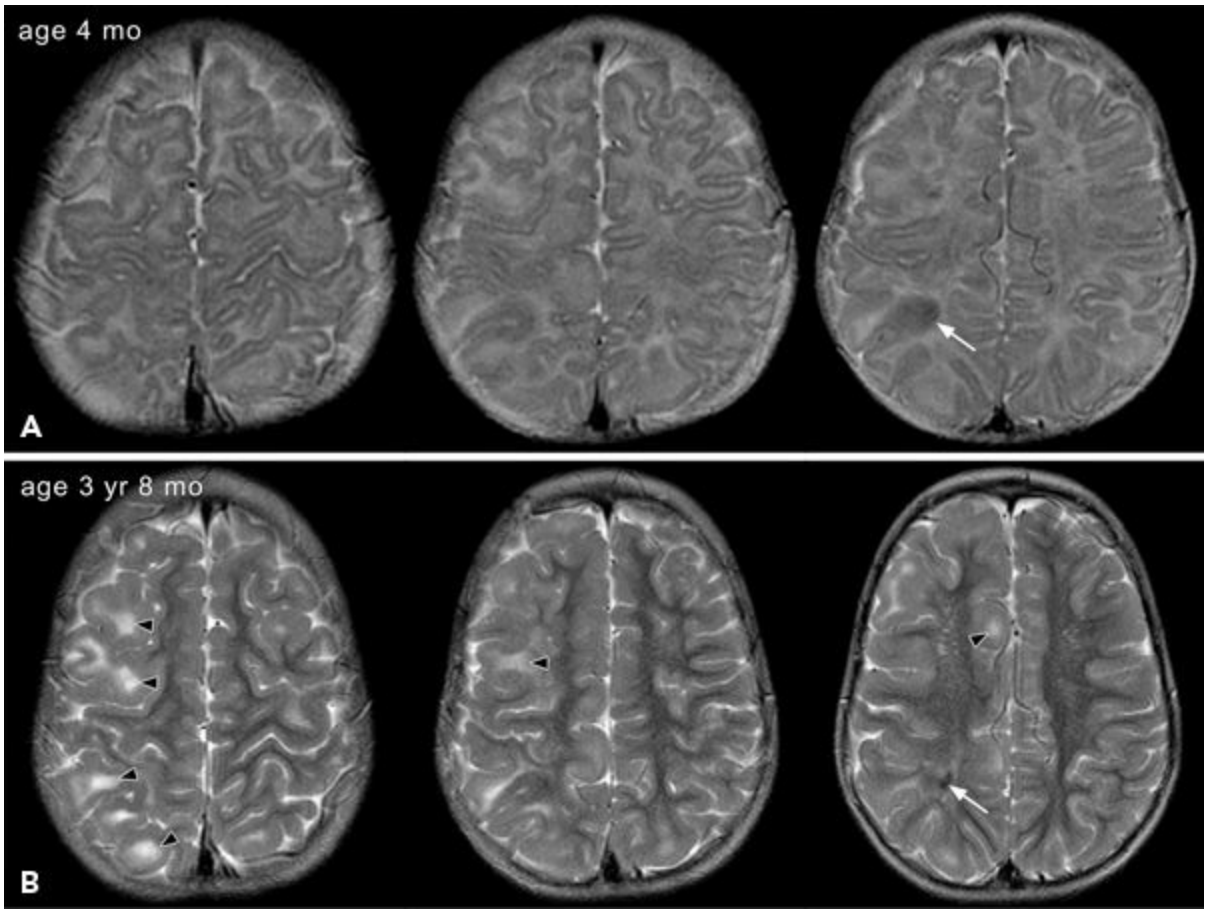

Figure 73.13. MRI in a child with tuberous sclerosis performed at 4 months of age **(A)** and at 3 years and 8 months of age **(B)**. Cortical and subcortical tubers (arrowheads) were more evident on follow-up imaging because of myelination of white matter, improving the "background contrast." Increase in size of lesions with brain growth, calcification (arrow), and abnormal myelination around the lesions may also contribute to better visibility on follow-up MRI. (Courtesy of Dr. Ajay Gupta, Cleveland, OH.)

MINI-ATLAS OF SOME TYPICAL EPILEPTOGENIC LESIONS

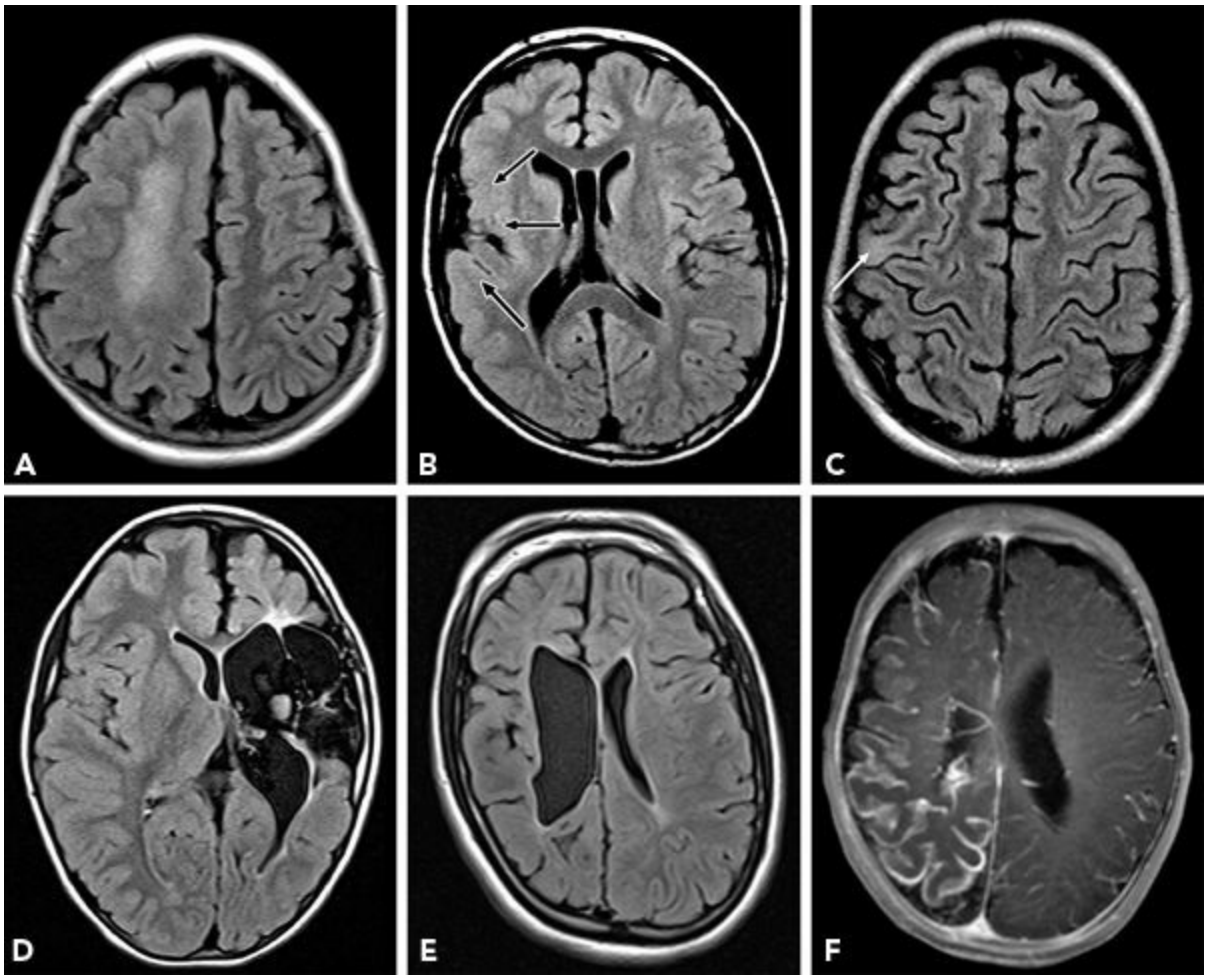

Figure 73.14. Hemispheric epileptogenic lesions. **A:** Right hemimegalencephaly. **B:** Right multilobar dysplasia with relative sparing of medial occipital region (black arrows). **C:** A case of Rasmussen encephalitis with atrophy of right hemisphere and hyperintensity in the precentral gyrus (white arrow). **D:** Cystic encephalomalacia and gliosis on the left hemisphere due to remote ischemic stroke. **E:** Perinatal brain injury with right hemispheric atrophy—both cortical and subcortical. Note minimal involvement of the left hemisphere as well. **F:** A case of Sturge–Weber syndrome with right hemispheric atrophy with leptomeningeal enhancement and enlarged periventricular veins.

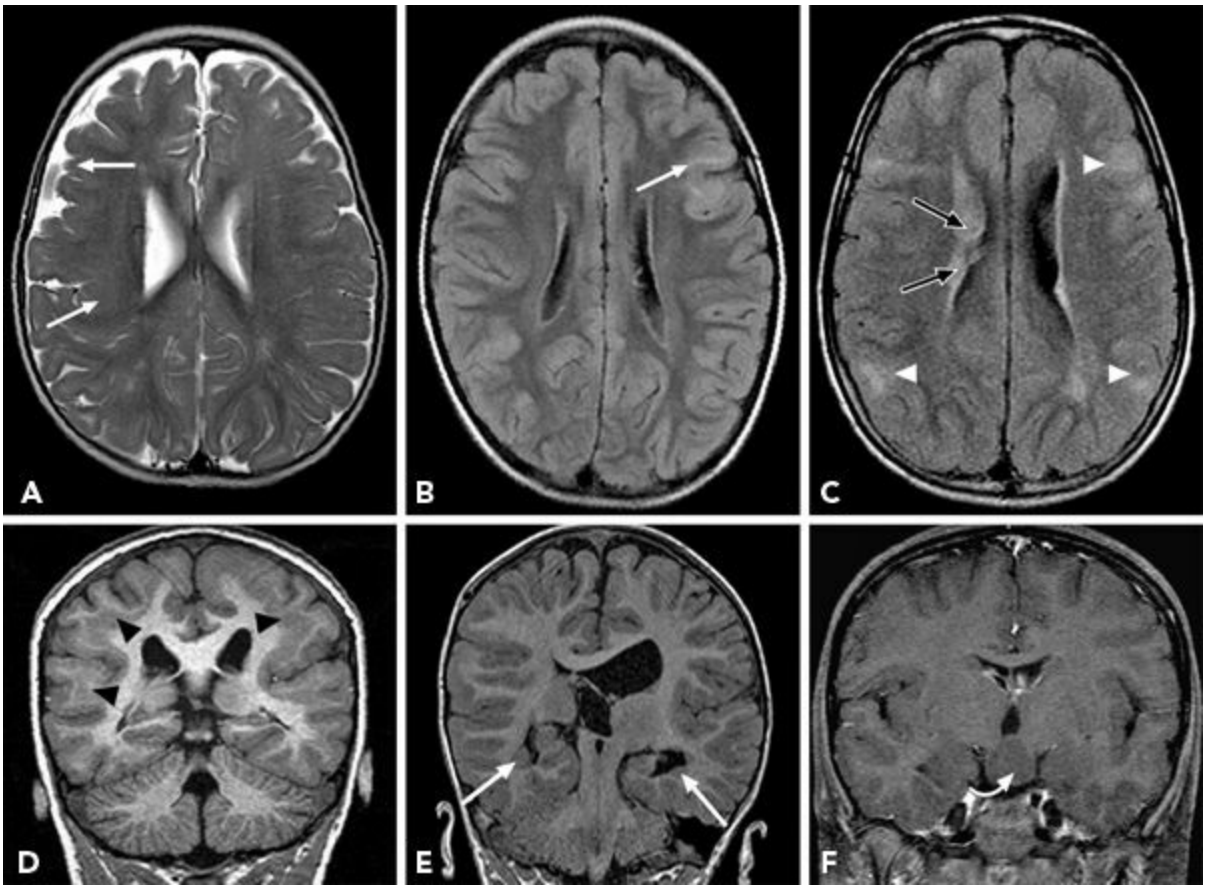

Figure 73.15. Focal MCD and related disorders. **A:** Right frontal malformation with abnormal sulcal pattern and thickened cortex (arrows). **B:** Left frontal dysplasia with subcortical hyperintensity (white arrow). **C:** Cortical tubers (white arrowheads) and subependymal nodules (arrows) in tuberous sclerosis. **D:** Diffuse subcortical band heterotopia—"the double cortex." (black arrowheads) **E:** Multiple malformations including periventricular nodular heterotopia around temporal horns (arrows) and maloriented right hippocampus. **F:** Hypothalamic hamartoma—note signal intensity of the lesion similar to the gray matter (curved white arrow).

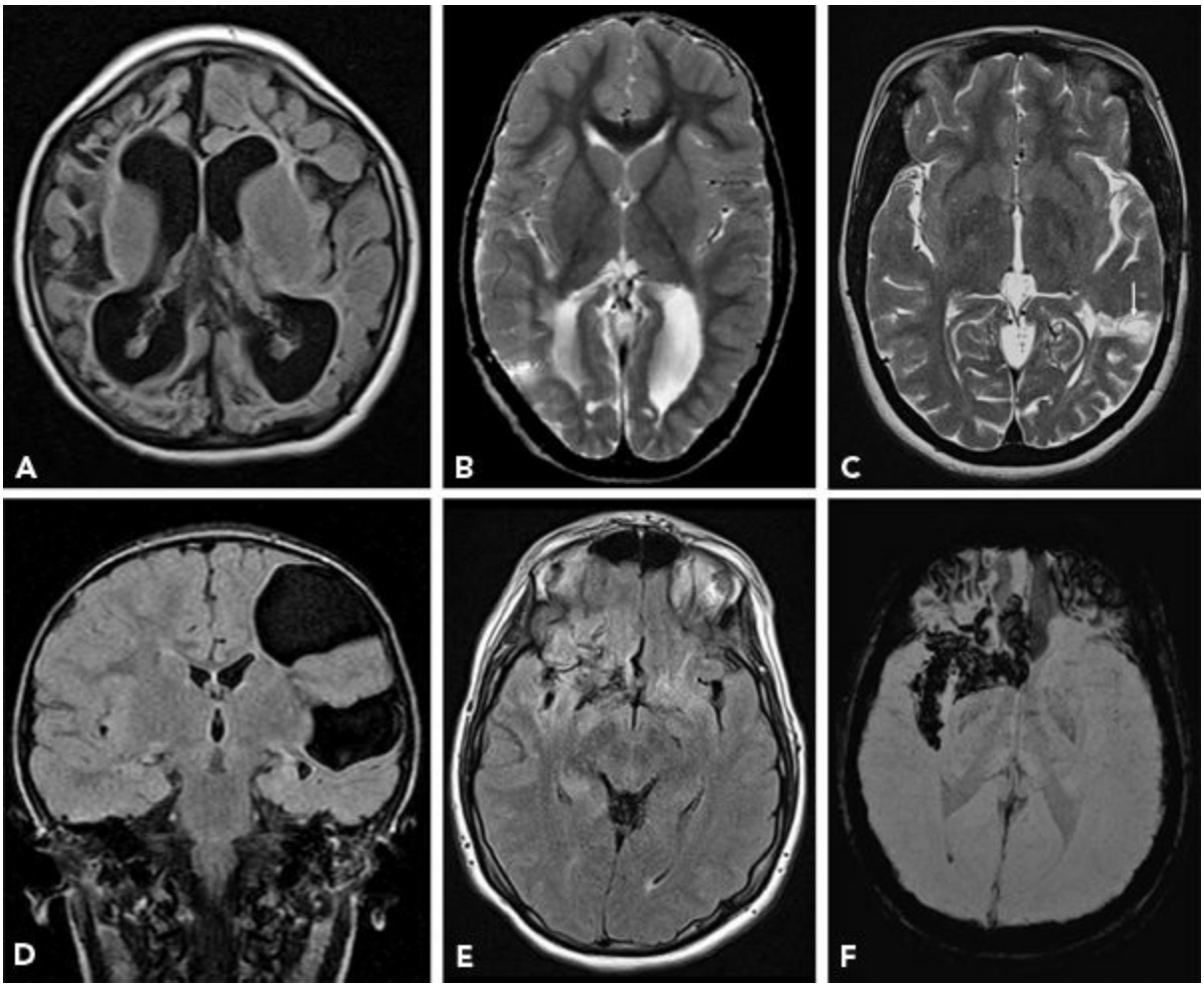

Figure 73.16. Porencephaly and encephalomalacia of various etiologies. **A:** Diffuse multicystic encephalomalacia and gliosis secondary to global hypoxic ischemic injury. **B:** Periventricular leukomalacia due to perinatal brain injury. **C:** Left posterior temporal encephalomalacia due to prior ischemic stroke in a patient with sickle cell anemia. **D:** Porencephalic cysts in left frontal and temporal lobes related to multiple hemorrhages in the neonatal period. Also, note left MTS. **E, F:** Encephalomalacia due to remote herpes encephalitis on FLAIR images **(E)**. Susceptibility-weighted images **(F)** show marked hypointensity in the regions of prior petechial hemorrhages.

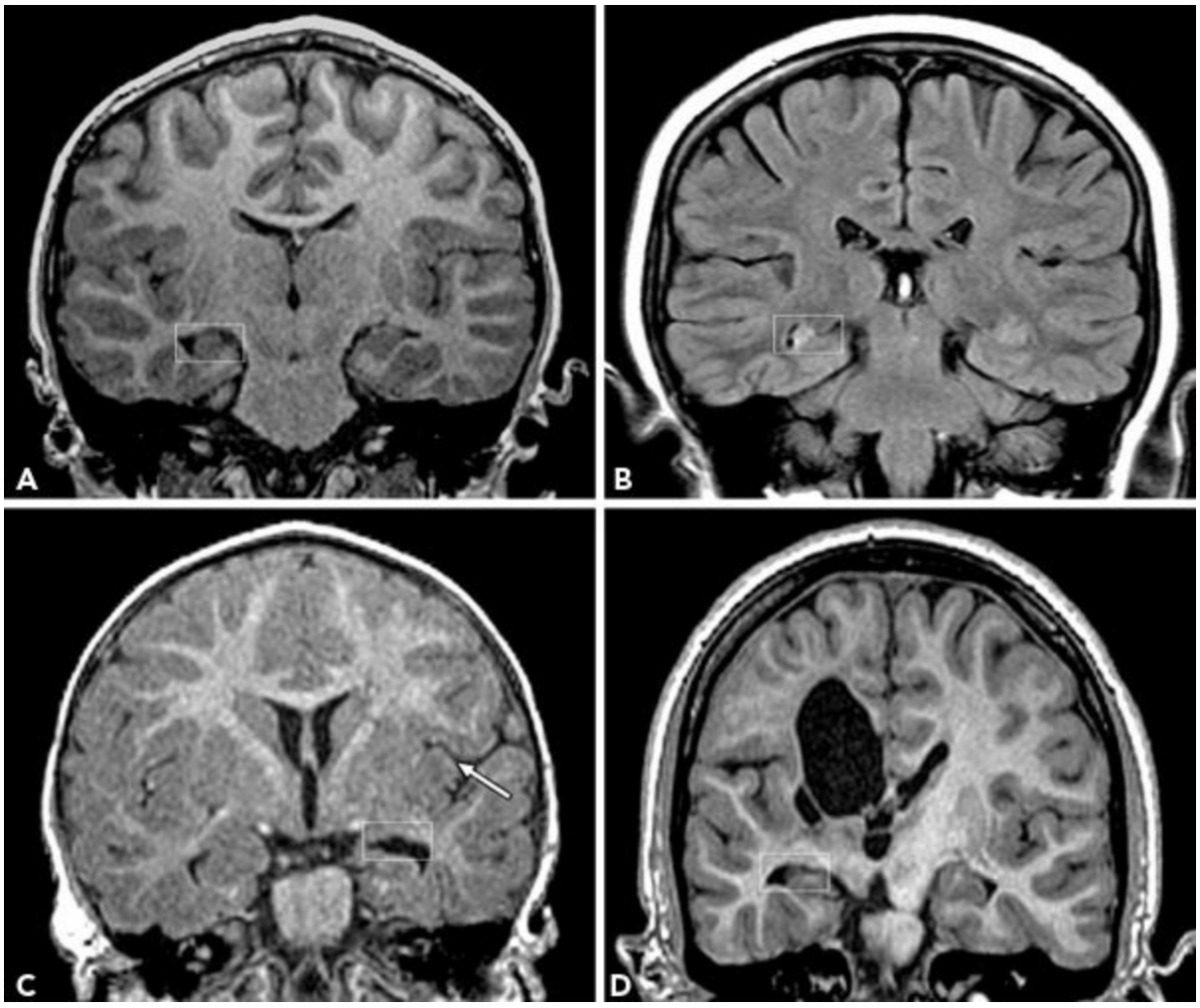

Figure 73.17. MTS and dual pathology. **A, B:** Right MTS with prominent volume loss and hyperintense signal of hippocampus. **C:** Left hippocampal atrophy (in the rectangular box) with atrophy of the ipsilateral frontotemporal cortex as evident from prominent left sylvian fissure (arrow). **D:** Right hippocampal atrophy (in the rectangular box) associated with porencephaly right frontal subcortical region and basal ganglia.

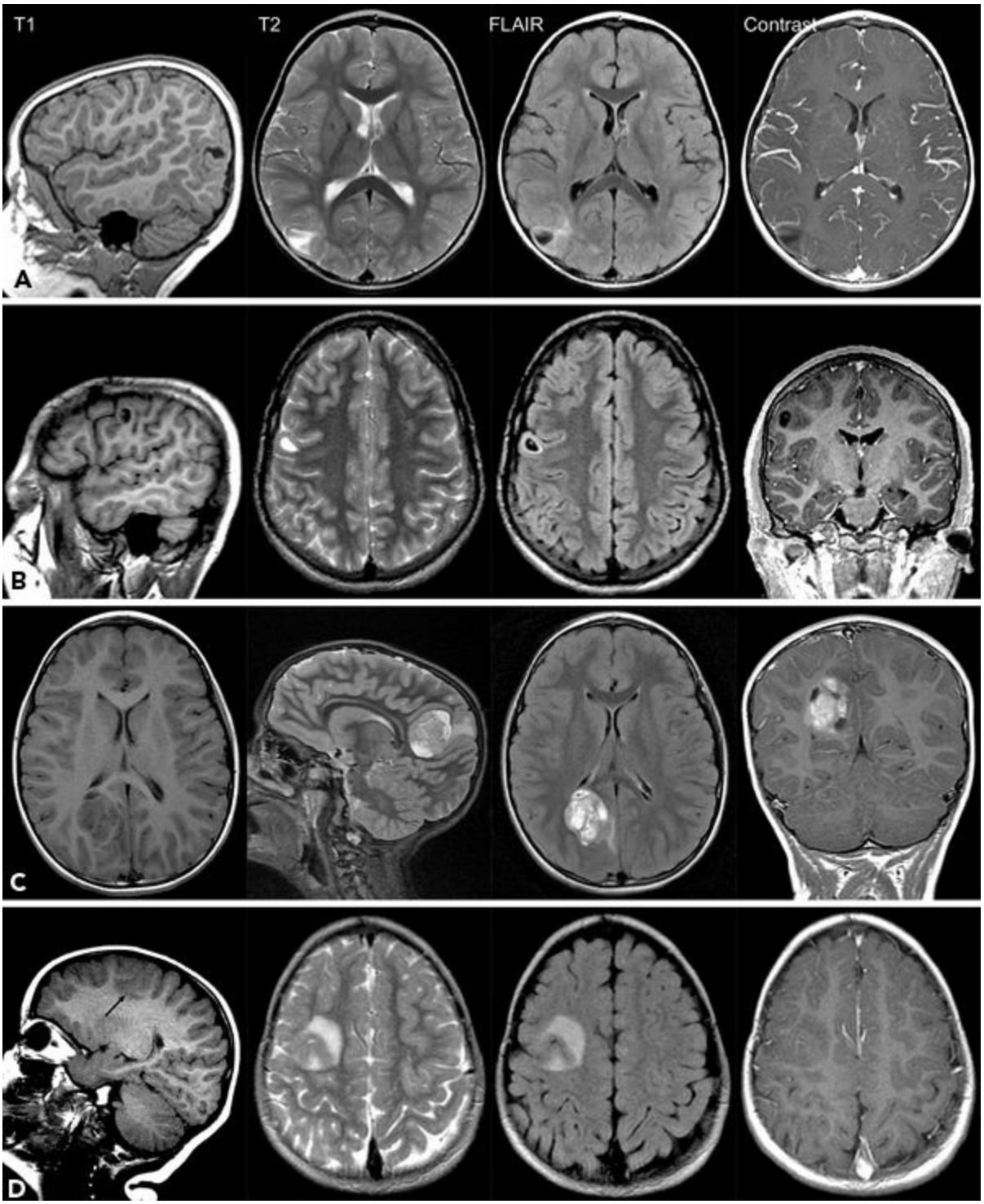

Figure 73.18. Tumors and hamartomas. **A:** A nonenhancing lesion with cystic and solid components in the right parietooccipital junction without mass effect. Histopathology showed features of ganglioglioma. **B:** A predominantly cystic lesion in the right precentral gyrus without contrast enhancement or mass effect, similar to lesion on (**A)**. Histopathology confirmed dysembryoplastic neuroepithelial tumor. **C:** A predominantly solid tumor in the right precuneus and posterior cingulate region, with prominent heterogeneous contrast enhancement and mild mass effect. Histopathology showed evidence for pleomorphic xanthoastrocytoma. **D:** A nonenhancing lesion in the right posterior frontal region with evidence of vasogenic edema. A low-grade glioma was suspected. Histopathology showed features of meningioangiomatosis, a hamartomatous lesion.

MAGNETIC RESONANCE SPECTROSCOPY

Magnetic resonance spectroscopy (MRS) offers the potential to noninvasively analyze the biochemical composition of a specific brain area. Certain patterns of focal alterations in the biochemical structure may reflect altered neuronal or glial function providing localizing information.

MRS can be acquired in any conventional high-field MRI system with appropriate software (63). Proton spectroscopy is the most widely accepted MRS technique in clinical settings, as it demands no additional hardware and has superior spatial resolution than alternative nuclei such as phosphorus. MRS generates a proton spectrum for a voxel or group of voxels that can be as small as 1 cm^3. Only limited areas of the brain can be studied in a time fashion that is acceptable for clinical practice. It is therefore necessary to have a preimaging hypothesis about the location of epileptogenic focus to decide on the placement of spectroscopy voxels. The position of the voxel is chosen based on localizing information available from conventional MRI or other localizing information when MRI is normal. Restricted anatomic coverage with single-voxel techniques is a major limiting factor when the lesions are large or indistinct or absent on the MRI. Multivoxel technique provides the capability of greater anatomic coverage and is particularly appealing if the location of epileptogenic focus is uncertain.

The primary choice in parameters with conventional MRS is between short and long TEs. Long TE acquisition produces spectra that include N-acetylaspartate (NAA), choline, creatine/phosphocreatine, and possibly lactate. Short TE acquisitions include the same metabolites as well as myo-inositol, glutamate and glutamine, gamma-aminobutyric acid (GABA), alanine, glucose, scyllo-inositol/taurine, and protein/lipids (64–66). Changes in relative quantities of these metabolites, in comparison with corresponding tissue on the presumably normal contralateral hemisphere or controls, are used to characterize the tissue metabolically. NAA signal is the best studied and most sought after signal on MRS; NAA signal though signifies neuronal loss or dysfunction, a linear correlation between the two has not been found. Mitochondrial dysfunction without actual neuronal loss has also been postulated as the mechanism for low NAA signal. Decreased regional NAA concentration in the epileptogenic zone is the most characteristic interictal abnormality described in intractable partial epilepsy. Abnormal lactate peaks in the epileptogenic zone may be identified when MRS study is performed within 6 hours of seizures.

Use of MRS in localization of epilepsy has been studied in both temporal and extratemporal epilepsies. In patients with bilateral mesial temporal abnormalities, the epilepsy may arise predominantly from one side. In such cases, studies using single-voxel technique comparing the two temporal lobes have provided additional concordant lateralizing information enabling surgical decisions (63,67,68). In a meta-analysis of MRS in temporal lobe epilepsy, presence of ipsilateral MRS abnormality and absence of bilateral abnormalities were associated with seizure good outcome. However, bilateral MRS abnormalities may be seen in as many as 35% of temporal lobe epilepsy patients with good outcome (69). In a study of nonlesional extratemporal epilepsy, widespread spectroscopic abnormality—greatest in the presumed epileptogenic zone—has been reported (70,71). The true impact of MRS on surgical decision making for complex patients with poor localization information is unclear and has not been studied critically to provide meaningful integration of MRS in the presurgical epilepsy workup.

Ability to study tissue levels of glutamine and GABA by MRS offers lot of scope to study various epileptic disorders, as elevation of the excitatory glutamate and reduction of inhibitory GABA can result in seizures. Elevation of “glutamine plus glutamate” in frontal lobes has been reported in idiopathic generalized epilepsies as well (72,73). Despite the attractive concept of noninvasive biochemical sampling of the brain, MRS has not impacted epilepsy practice to earn a definitive role in routine presurgical workup. With the advent and wide availability of other tools such as PET and SPECT, the role of MRS has further diminished.

CONCLUSION

Anatomic visualization of substrates of epilepsy by MRI has tremendously advanced the field of epilepsy surgery. Various MRI techniques providing information on function and connections of the various areas of the brain have further helped the surgical strategy. Still, a significant number of patients with refractory partial epilepsy do not have an identifiable lesion on MRI. Epilepsy surgery in such cases, when performed, often requires invasive intracranial monitoring with subdural grids and depth electrodes, despite which the outcome remains poor. Malformation of cortical development is the most common lesion that evades detection in these cases. Further improvements in MRI techniques and its integration with other modalities such as SPECT, PET, and MEG may help to improve the detection of these lesions and minimize the need for invasive monitoring. Development of newer MR techniques in the future may also have the potential to improve the understanding of the cytoarchitectural and molecular abnormalities of the brain with a greater impact in the field of epilepsy.

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CHAPTER 74 VIDEO–EEG MONITORING IN THE PRESURGICAL EVALUATION

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Surgery remains an important option in the treatment of intractable partial epilepsy. Thirty to forty percent of patients with epilepsy will not respond to first- or second-line medications (1). Such patients remain subject to the consequences and risks associated with intractable seizures. Surgery has been shown to be effective and safe for select patients with medically intractable focal epilepsy (2). Successful surgery requires the identification of patients in which the epileptogenic zone is localizable. Video–electroencephalogram (EEG) monitoring plays a crucial role in epileptogenic zone estimation and in the selection of surgical candidates. Localization requires the integration of clinical, imaging, and video–EEG monitoring data before final plans are determined. Video–EEG monitoring may provide the only localizing information in some patients, particularly in those without an underlying neuroimaging abnormality. It also helps in confirming the epileptogenic significance of structural lesions that may be encountered in the evaluation of intractable epilepsy patients and may help clarify the most relevant lesion in patients with more than one lesion. In addition, video–EEG monitoring may also help verify whether a single or more than one seizure focus is present in a potential surgical patient. Finally, the video recordings obtained can be shown to witnesses of the patient's habitual seizures in order to confirm that the patient's typical seizure type was recorded in the evaluation process prior to making final surgical decisions.

This chapter discusses the clinical personnel, equipment, and safety issues to consider in establishing an epilepsy monitoring unit. The importance of ictal semiology and specific localizing signs are reviewed. Finally, the principles and limitations of ictal EEG are addressed, highlighting the findings most likely to be encountered in patients with surgically remediable focal epilepsy.

EQUIPMENT AND PERSONNEL

Guidelines for the technical and clinical aspects of video–EEG monitoring have been published (3) (see also http://www.acns.org/pdf/guidelines/Guideline-12.pdf). Important considerations regarding video–EEG monitoring safety are discussed below and summarized in Table 74.1.

Table 74.1 Summary of Important Quality and Safety Attributes of a Video–EEG Monitoring Facility

Video–EEG monitoring: equipment, safety, facilities, and personnel

Video–EEG acquisition equipment
- Digital video–EEG acquisition systems with remote viewing capability, 20 channels minimum
- Redundant data storage in case of server and local hard drive failure
- Amplifiers with temporary local data storage capability
- Cameras (ceiling mounted) with remote control, autofocus, low-light capabilities

Safety monitoring and intervention preparedness
- Continuous observation of patient by nurse or EEG technician
- Continuous monitoring of EEG by technologist preferred
- EKG monitoring
- Pulse oximetry
- IV access and maintenance
- Supplemental oxygen and airway availability
- Hand-off process for night coverage
- Standardized protocol and orders for acute seizure emergencies
- Standardized dismissal process

Facilities
- Inpatient preferred
- Safe bathroom features
- Unobstructed path to patient
- Close proximity of EEG technicians and nursing staff to patient

Personnel
- EEG technician—24-h coverage optimal
- Nursing—24-h availability necessary
- Physician (primary and on-call)—24-h availability necessary
- Rapid response team and intensive care availability

Video–EEG Equipment

Most epilepsy centers use digital video–EEG acquisition systems for video–EEG monitoring. Digital video allows viewing of recorded events remote from the video–EEG monitoring area, provided the hardware and network infrastructure available is adequate to meet the high-volume data stream demands. The video camera selected should have low-light recording capabilities in order to allow the capture of nocturnal events. Cameras selected should also have autofocus functionality and remote control capabilities for camera angle and zoom so as to enable technical staff to acquire optimum video during an event.

The advantages of digital EEG data over analog are significant. Digital EEG data lends itself to postacquisition processing, which is not possible with analog EEG. Spike and seizure detection algorithms can also be run during digital EEG acquisition, which may help in the detection of abnormalities. Selection of amplifiers that allow local data storage with flash memory during disconnections from the primary network offers additional advantages, particularly in active patients such as young children, and those few patients who may require transport away from the central EEG

recording area during evaluation.

Personnel

The presence of appropriately trained and experienced EEG technologists is crucial in order to ensure quality recordings. Twenty-four–hour technician coverage is optimal, as equipment issues can arise at any time potentially affecting several hours of data if not promptly addressed. Continuous observation is also critical in patient safety. Nursing staff familiar with seizure identification and management is also important. Patients undergoing epilepsy monitoring are at risk for falls, seizure-related injuries, aspiration, and cardiorespiratory complications, all of which can be mitigated by prompt nursing intervention (4). Nursing and EEG technology personnel are also crucial to provide clinical testing during seizures for semiologic analysis purposes. Physician coverage must be available to manage prolonged seizure activity or seizure-related cardiorespiratory complications. Twenty-four–hour EEG interpretation should also be available in the event questions arise regarding the EEG or clinical status during off hours. Remote access to ongoing video–EEG monitoring data is very helpful for this purpose.

SEIZURE PROVOCATION, PATIENT MANAGEMENT, AND SAFETY CONSIDERATIONS

The goal of presurgical video–EEG monitoring is to record a complete sample of a patient's seizures in order to clarify the region or regions of seizure onset. Sleep deprivation, photic stimulation, hyperventilation, exercise, and supervised medication withdrawal are commonly used to increase the yield of recorded seizures. Drug withdrawal should only be performed in a setting in which real-time seizure detection and medical intervention are available.

Supervised Medication Withdrawal

Medication withdrawal should be individualized for each patient, balancing the need to record a sufficient number of seizures and the risks based on the patient's individual seizure history. Starting medication withdrawal prior to admission is not generally advisable given the risks. A common approach is to reduce the dose of one medication by 33% to 50% on the first monitoring day and then to continue reducing the dosages of one or more drugs at a similar rate on successive days until a sufficient number of seizures have been recorded. Individual patient attributes should be kept in mind when strategizing medication withdrawal for epilepsy monitoring purposes. For example, withdrawal may not be necessary at all in patients with a high seizure frequency on full medication therapy. Conversely, some patients with long seizure-free intervals may require a more abrupt withdrawal schedule in order to achieve the monitoring goals. Also, psychiatric difficulties may arise when withdrawing certain antiepileptic drugs with mood stabilizing properties such as valproate, topiramate, carbamazepine, and lamotrigine. Once a tapering plan is decided, it is important to clearly communicate the schedule and goals to the team so that medications are resumed as soon as the objectives have been met, even if this occurs after hours.

Patient Care, Monitoring, and Planning

A standardized rescue plan should be established in the monitoring unit in order to minimize treatment delay in acute seizure emergencies. This rescue plan should include objective criteria for treatment initiation, such as a number of seizures over a defined time period, or for seizures lasting beyond a defined maximal seizure duration. Other criteria for intervention may include the occurrence of a generalized seizure in a patient without a prior history or the emergence of agitation in a patient. While protocols are useful, customization to meet the unique needs of individual patients are often necessary. Creation of an admission order set for the epilepsy monitoring unit containing the standard protocol is advised to ensure that rescue plan orders are put in place at admission. All health care team members need to be educated as to the unit's standard rescue plan. Immediate access to the patient's records is required, and regular updates as to the goals of admission need to be documented clearly and communicated to the team and handed off to cross-covering personnel so that once the goals of monitoring have been achieved, antiepileptic medication can be resumed.

Rescue plans typically entail use of intravenous (IV) medications as a component. It is important that IV access be secured in all patients undergoing medication withdrawal upon admission and that processes be in place to monitor IV viability so that it can be relied on in the event of an emergency. It is critical to inquire specifically about drug allergies and significant nonallergic idiosyncratic reactions to potential rescue medications at admission so that needs for deviation from the standard rescue plan can be identified early. IV lorazepam or diazepam at subanesthetic levels are typically used in epilepsy monitoring rescue plans. IV fosphenytoin can also be considered, but requires EKG and blood pressure monitoring and should only be used in a setting where cardiac arrhythmia and hypotension can be acutely managed if detected.

Given the risk of cardiac arrhythmia during seizures (5), continuous EKG monitoring should be performed during video–EEG monitoring. Continuous pulse oximetry should also be used as apnea can complicate seizures. Twenty-four–hour physician availability is necessary to handle any acute situations that may arise during hospitalization. ICU and supportive services such as a rapid response team should be available in the event of the need for acute airway management and resuscitation.

Uniform policies for ambulation and activity should be established and made clear to patients upon admission due to the risk of seizure-related falls and injury. Sharp corners in the seizure-monitoring environment should be minimized. An unobstructed path to the patient bed needs to be ensured so that staff can attend to the patient in a timely manner. Bathroom fixtures pose safety risks, and accommodations need to be considered to minimize the potential for injury in the event a seizure occurs there. Side rails with pads are reasonable to help prevent patients from falling out of bed during a seizure; however, they can pose an unintended risk in some cases, particularly those with hypermotor semiology.

Risks of Video–EEG Monitoring

Medication withdrawal can result in first-time generalized tonic–clonic seizures and other new-onset seizure types in patients without a history of similar seizures, and this can be traumatic for the patient and family. Tongue bite wounds are not infrequent but rarely require treatment beyond conservative measures. Other injuries that can occur in association with video–EEG monitoring include vertebral compression fractures and shoulder dislocations. Caution is required when reducing antiepileptic medications in patients with a previous history of shoulder dislocation and in patients with an established diagnosis of osteopenia. Seizure-related falls can lead to subdural hematoma and skull fractures. Exercise modalities that do not require an upright posture should also be considered. If

treadmills and exercise bicycles are used, a nurse or aide need to be present to help prevent seizure-related falls.

Postictal psychosis can arise in the EEG monitoring setting (6). Patients with a prior history of postictal psychosis are at higher risk, but psychosis can occur for the first time in the EEG monitoring setting. Clinical presentation may include aggressiveness and combative behavior, posing a risk to the staff. An action plan needs to be anticipated in patients deemed at risk based on prior history and availability, and close collaboration with psychiatric services is crucial in these cases.

Dismissal from the Video–EEG Monitoring Unit

Patient stability needs to be assured prior to dismissal. Patients undergoing EEG monitoring often have been subjected to significant changes in antiepileptic medication therapy over a short period of time, which may predispose them to further seizures following discharge. Typically, the patient's usual medication regimen should be resumed 24 hours prior to dismissal. In some cases, it may be prudent to reload patients with parenteral or oral loading doses of their maintenance therapy in anticipation of dismissal. In particularly unstable patients, one should consider obtaining serum levels in order to ensure achievement of therapeutic drug concentrations prior to discharge. It is also advisable to ensure appropriate supervision for the next 1 to 2 days following dismissal by family or other appropriate caretakers.

VIDEO–EEG AND LOCALIZATION OF THE EPILEPTOGENIC ZONE

Clinical Localization: Ictal Semiology

Analysis of ictal semiology can provide valuable localizing information complementary to the ictal EEG (7). Concordance between the ictal semiology and other localizing data helps strengthen hypotheses regarding localization, while discordance should raise concerns. Similarly, the presence of multiple semiologies suggests the possibility of multiple seizure foci, which may influence the prospects for surgical success. Lateralizing and lobar localizing signs are not present in all seizures in all patients, but are specific when present. In one study, lateralizing signs were present in 46% of recorded seizures and 78% of patients (8). Lateralization by ictal semiology was correct in 78% of a population with excellent surgery outcome in two studies (8,9). In terms of lobar localization, temporal versus frontal lobar localization could be correctly determined in 76% of patients by semiologic analysis of a cohort of patients with Engel class I outcome (10). Lateralizing and localizing signs of significance in epilepsy surgery patients are summarized in Tables 74.2 and Table 74.3 and discussed further below.

Table 74.2 Ictal Semiology: Contralateral and Ipsilateral Lateralizing Signs

Contralateral signs
Unilateral dystonic hand posturing
Unilateral forced head turning at secondary generalization
Unilateral clonus
Eye deviation at secondary generalization
Ictal hemiparesis
Postictal (Todd) paresis or visual field deficit
Figure of 4, fencing, or M2E upper extremity limb posturing
Ipsilateral signs
Unilateral manual automatisms
Unilateral postictal nose wiping
Unforced early head turning
Unilateral eye blinking
Unilateral piloerection
Dominant hemisphere
Postictal aphasia
Nondominant hemisphere
Ictal speech preservation
Ictal vomiting (in temporal lobe seizures)
Ictal spitting

Table 74.3 Ictal Semiology: Lobar Localizing Signs

Temporal lobe localization
- Aura characteristics
  - Epigastric rising; olfactory, dysgeusic, auditory hallucinations
  - Experiential—déjà/jamais-vu; dissociative symptoms
- Oral and/or manual automatisms
- Dystonic hand posturing
- Ictal spitting, postictal nose wiping
- Postictal confusion lasting several minutes
- Postictal aphasia present (if dominant hemisphere involved)

Frontal lobe localization
- Explosive onset
- Hypermotor activity
- Lower extremity automatisms (bicycling, kicking)
- Nocturnal seizure clustering of several per night
- Brief or absent postictal confusion
- Postictal aphasia infrequent unless primary language cortex involved

Occipital lobe localization
- Unilateral simple visual hallucinations (shapes and colors)
- Eye deviation
- Nausea/vomiting, migraine in children

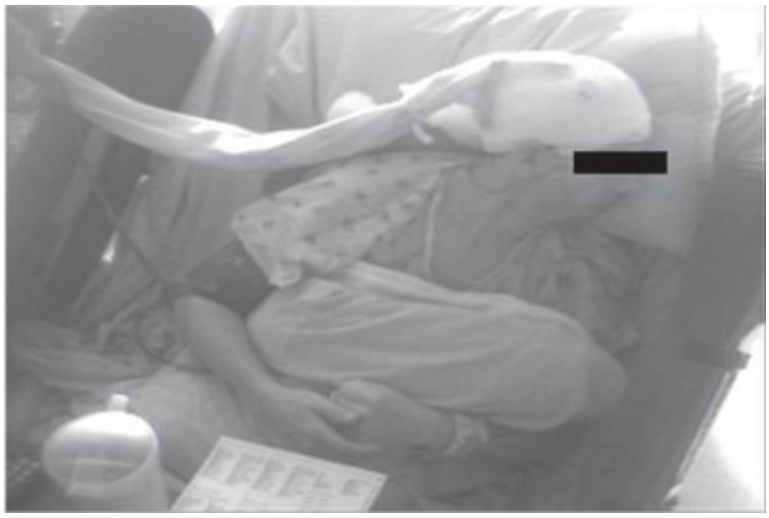
Peri-Rolandic localization
- Unilateral clonic activity as earliest seizure manifestation
- Unilateral sensory disturbance as earliest seizure manifestation
- Todd paralysis

A number of principles need to be kept in mind when analyzing ictal semiology. First, clinical seizure manifestations are influenced by the propagation of seizure activity from one cortical region to another, which can lead to false localization. For example, aphasia may occur in patients with seizures of nondominant temporal origin following spread to the dominant hemisphere. Second, while the specificity of some of the semiologic signs approach 90%, the sensitivity is lower, and localizing clinical signs may be absent in some patients (8,10). Third, seizures arising in functionally silent regions may not show clinical manifestations until spread to eloquent cortex has occurred, which might falsely suggest seizure origin in the region of propagation. Finally, some regions of the brain lead primarily to subjective perceptual changes that are not appreciable on review of video data due to the absence of a motor or behavioral correlate.

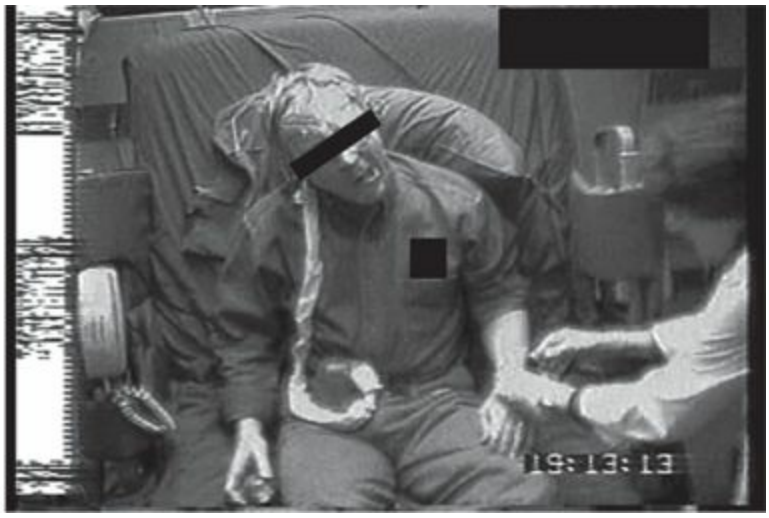
Lateralizing Signs

Some clinical signs are primarily of lateralizing value. These are summarized in Table 74.2 and are discussed in more detail in the following section. Select lateralizing signs are illustrated in Figures 74.1 through 74.3.

A



B



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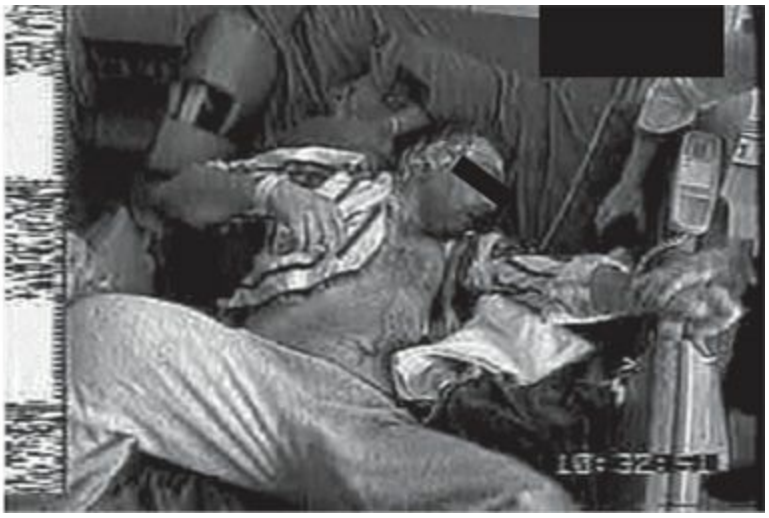

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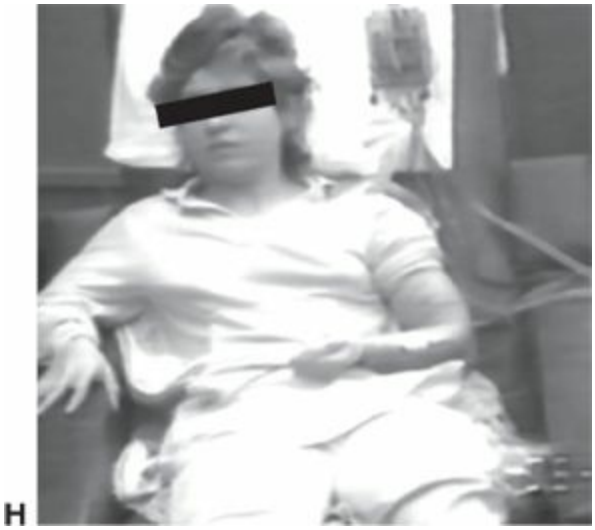
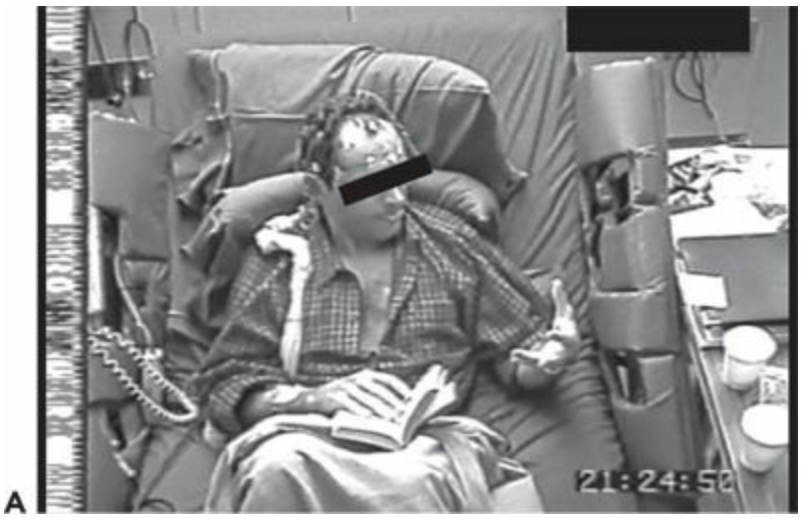


Figure 74.1. Lateralizing signs in patients with partial seizures. **A:** Unilateral dystonic hand posturing on the left and unforced head turn to the right during a right temporal seizure in a patient with right mesial temporal sclerosis. **B:** Forced head turning to the left during progression to a secondary generalized seizure in a seizure of right temporal origin secondary to mesial temporal sclerosis. **C:** Left facial contracture and clonus during a seizure of right frontocentral onset in a patient with a right peri-Rolandic cortical dysplasia. **D:** Unilateral postictal nose wiping involving the ipsilateral hand in a patient with right temporal seizures. **E:** "M2E" posturing in a patient with right temporal seizures of unknown etiology. **F:** "Fencing" posture in a patient with a secondary generalized seizure of right temporal neocortical onset. **G:** "Figure of 4" posturing with left upper extremity extended during a secondary generalized seizure of right temporal origin. **H:** Ictal paresis involving the left upper extremity during a right parietal seizure of unknown etiology.



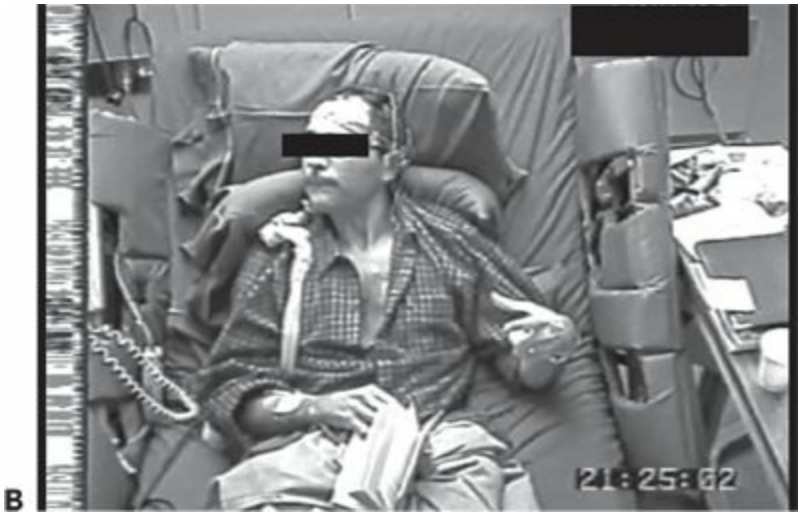


Figure 74.2. Semiologic signs of lobar localizing significance in partial epilepsy. **A:** Oral automatisms and "regarding the hand" (left hand in this case) in a patient with temporal lobe epilepsy. **B:** Dystonic left hand posturing, continued oral automatisms, and nonforced right head turn during a right temporal lobe seizure.

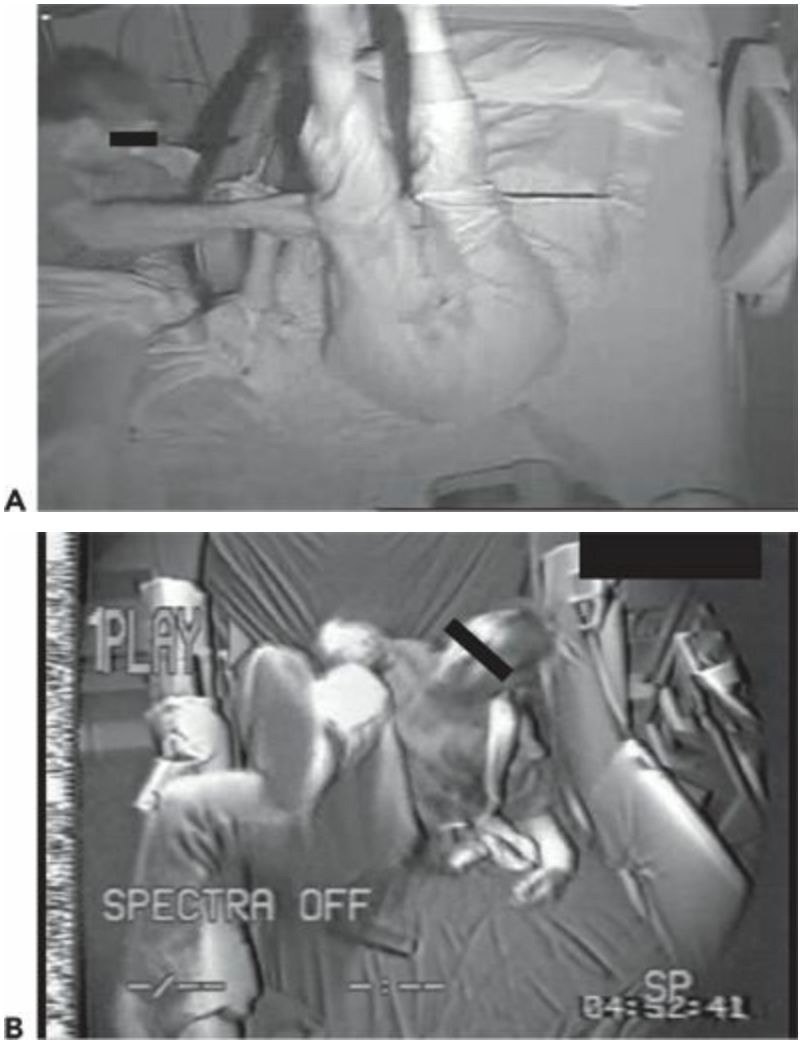


Figure 74.3. A and B: Complex lower extremity automatisms in two patients with frontal lobe epilepsy.

Ictal Speech Preservation and Aphasia.

Ictal speech preservation is highly suggestive of nondominant lateralization in temporal lobe seizures, while ictal aphasia suggests involvement of the dominant hemisphere, frequently of the dominant temporal lobe (11). Ictal aphasia may also occur in nondominant temporal lobe seizures following

contralateral propagation. Measuring the time to speech recovery can help in such cases. In one prospective study, recovery of speech within 1 minute of seizure onset was associated with nondominant lateralization (12). Ictal aphasia is less common in dominant hemisphere extratemporal seizures, except for those seizures arising in close proximity to the operculum. When assessing speech during seizure activity, it is important to make sure that any detected speech alteration is not primarily due to orolingual motor impairment, for example, secondary to tonic, clonic, or atonic involvement of the tongue or larynx, as the localizing implications are different.

Unilateral Dystonic Hand Posturing.

Unilateral dystonic hand posturing is associated with contralateral seizure onset (13). This sign is common in temporal lobe seizures and thought to be due to seizure propagation to neighboring basal ganglia. Figure 74.1A shows a patient with unilateral dystonic hand posturing.

Ipsilateral Unilateral Manual Automatisms.

Unilateral manual automatisms are of lateralizing significance primarily when seen in association with unilateral dystonic posturing affecting the contralateral hand (13). When present, unilateral automatisms usually involve the ipsilateral hand. Unilateral automatisms can be mistaken for unilateral upper extremity clonic activity. Distinguishing unilateral automatisms from clonus is important as the lateralizing implications are opposite.

Unilateral Forced Head Turning (Version) at Secondary Generalization.

Forced head turning during transformation from a partial to a secondary generalized seizure typically occurs in the direction contralateral to the hemisphere of seizure onset (14). Head-turning movements are considered versive if they are unquestionably forced and involuntary, resulting in sustained or unnatural posturing (15). Figure 74.1B shows an example of forced head turning. Conversely, early nonforced head turning usually occurs ipsilateral to the seizure focus, but this is less reliable than late forced head turning. Figure 74.1A shows ipsilateral nonforced head turning in addition to contralateral dystonic hand posturing.

Unilateral Forced Head Turning (Version) at the End of Secondary Generalization.

Forced head turning at the end of a secondary generalized tonic–clonic seizure is frequently ipsilateral to the side of seizure onset. Spread of the seizure to the contralateral hemisphere during the course of the seizure is responsible for late ipsiversion (16). Therefore, late version, unlike initial version, is frequently ipsilateral and cannot be assumed to indicate seizure onset in the contralateral hemisphere.

Unilateral Facial or Limb Clonic Seizures.

Unilateral clonus lateralizes to the contralateral hemisphere. Unilateral facial clonic seizures can sometimes present on the scalp EEG in the form of asymmetric rhythmic muscle artifact involving the derivations overlying the affected facial and scalp muscles. Figure 74.1C shows unilateral left facial contraction contralateral to a right frontocentral seizure focus secondary to a right precentral focal cortical dysplasia.

Ictal Vomiting.

Ictal vomiting is an uncommon seizure manifestation that correlates with nondominant lateralization when present in temporal lobe seizures (17), although exceptions with dominant onset exist (18). Ictal vomiting may also present in occipital seizures, in which case it is of less lateralizing significance.

Postictal Nose Wiping.

Nose wiping with one hand following temporal lobe seizures typically involves the ipsilateral hand (19). Postictal nose wiping is more characteristic of temporal as opposed to extratemporal seizures (20). Unilateral nose wiping is illustrated in a patient following a right temporal lobe seizure in Figure 74.1D.

Ictal Spitting.

Ictal spitting is usually associated with nondominant temporal lobe seizures (21). It is thought to be due to hypersalivation secondary to stimulation of the central autonomic network.

Unilateral Piloerection.

This typically occurs ipsilateral to the seizure focus and is usually seen in temporal lobe seizures (22).

M2E, Fencing, and Figure of 4 Posturing.

"M2E" posturing refers to a posture consisting of contralateral shoulder abduction, elbow flexion, and head deviation toward the elevated arm. This is depicted in Figure 74.1E in a patient with right frontal seizures. The "fencing" posture refers to a position assumed during secondary generalization where the contralateral upper extremity is extended, the ipsilateral arm flexed and abducted at the shoulder, and head rotated contralateral to the seizure focus. The hips may be abducted as well. An example is shown in Figure 74.1F. "Figure of 4" posturing refers to a position where the contralateral upper extremity is extended and the ipsilateral upper extremity flexed at the elbow so that it crosses the extended arm giving rise to the shape of the number "4" (23). An example is shown in Figure 74.1G.

Todd's Paresis and Ictal Paresis.

While relatively uncommon, unilateral postictal Todd paralysis correlates with seizure lateralization to the contralateral hemisphere. Todd paralysis is more common in seizures arising from the peri-Rolandic region, but can be seen in the context of temporal lobe epilepsy. "Ictal paresis" is a rare semiologic manifestation typically occurring contralateral to the seizure focus in patients with extratemporal seizures (24). Ictal paresis can be mistaken for transient ischemic attacks. An example is shown in Figure 74.1H.

Lobar Localization

Semiology can help with lobar localization, particularly in differentiating temporal and extratemporal seizures.

Temporal Localization.

An aura of experiential phenomena such as an out-of-body experience, epigastric rising sensation, and olfactory and dysgeusic hallucinosis suggests temporal localization. Manual and oral automatisms present frequently during temporal lobe seizures, and verbal and nonverbal vocalizations may be present. Cessation of activity at seizure onset is common. Dystonic hand posturing may occur. Figure 74.2A and B show unilateral dystonic hand posturing and oral automatisms in a patient during a right temporal lobe seizure. Temporal lobe seizures typically last 1 to 3 minutes in duration. A postictal confusional period lasting a few to several minutes followed by a desire to sleep is also typical in temporal lobe seizures. However nondominant temporal lobe seizures and those with limited bitemporal involvement may not be associated with a significant postictal period.

Frontal Lobe Seizures.

The clinical presentations of extratemporal frontal lobe seizures are protean. A number of semiologic differences have been identified (10). In contrast to temporal lobe seizures, frontal lobe seizure auras, if present, are usually less descript, at times consisting of vague light-headedness. Frontal seizures are often brief, lasting 1 minute or less, and are sometimes characterized by an explosive onset, with prominent hypermotor activity and complex lower extremity automatisms such as bicycling movements and kicking (Fig. 74.3A and B). Vocalizations, such as the utterance of profanities and screaming, may also occur. In some patients, extratemporal seizures, in particular frontal lobe seizures, occur more frequently out of sleep (25). While nocturnal predominance may be seen in temporal lobe seizures as well, a seizure pattern of multiple brief clusters of seizures occurring exclusively during sleep is more characteristic of frontal lobe seizures. Nongeneralized seizures of frontal origin are often followed by a brief postictal period relative to that of temporal lobe seizures. However, not all frontal lobe seizures behave in the same manner. Some frontal lobe seizures may evolve over prolonged periods of time, and postictal confusion may sometimes be seen. Semiology is particularly important in the process of diagnosing frontal lobe seizures, as the ictal EEG is often nondiagnostic in these patients, particularly in those with seizures of supplementary motor or orbital frontal onset (26).

EEG Localization in Video–EEG Monitoring

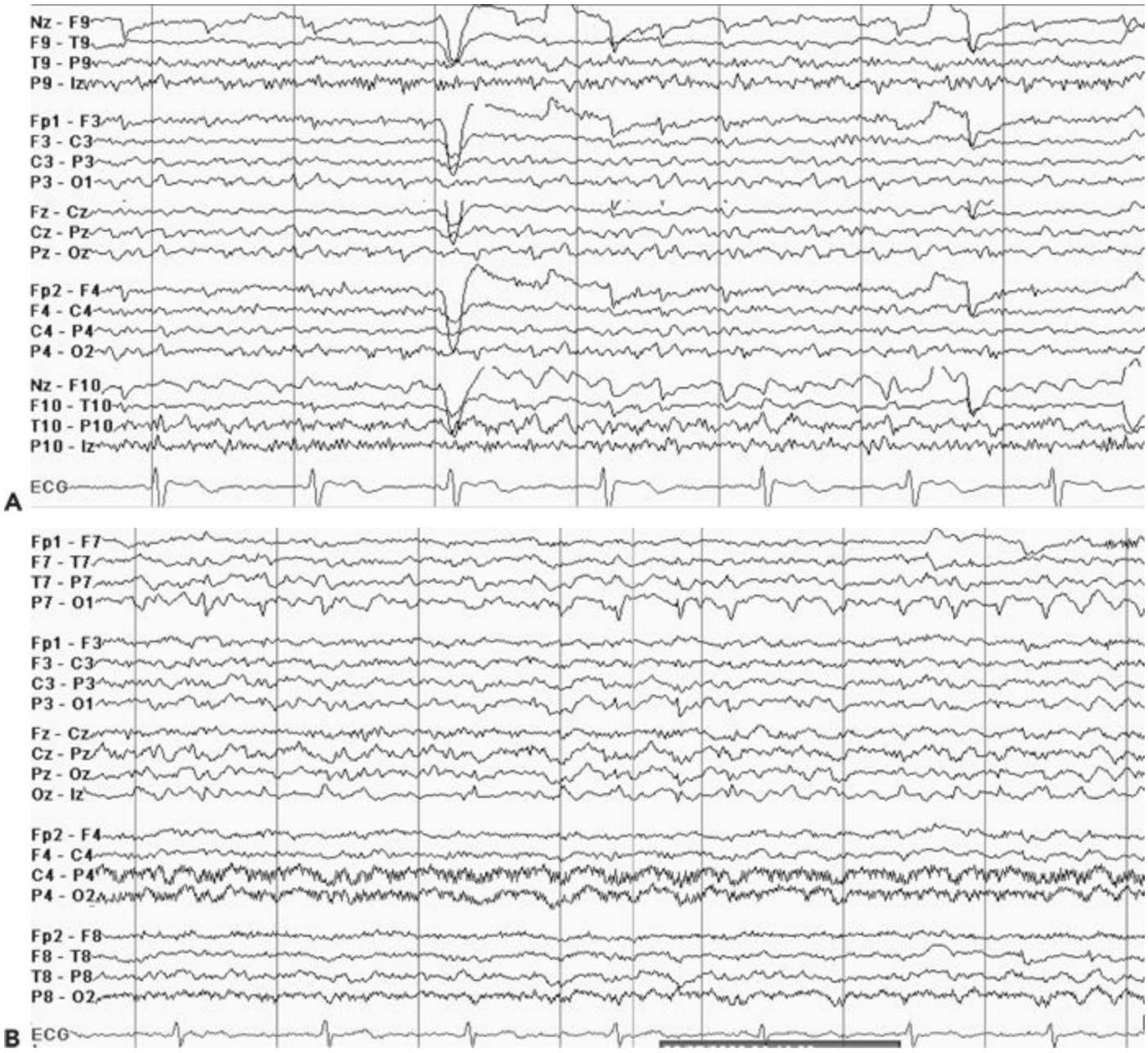
Interictal and ictal EEG analysis are essential in the presurgical evaluation. An understanding of the localizing patterns seen in partial epilepsy and limitations of ictal EEG localization are essential.

A minimum of 20 scalp EEG channels should be used when performing prolonged video–EEG monitoring. Midline, right, and left parasagittal and right and left temporal head electrodes should be utilized. Additional inferior temporal electrodes should be considered in patients where a temporal lobe focus is suspected. Nasopharyngeal, foramen ovale, and transsphenoidal electrodes have been advocated by some to improve the sensitivity and specificity of ictal EEG localization, particularly in patients with mesial temporal seizures.

Interictal Epileptiform Abnormalities

Although the ictal EEG receives the most scrutiny in video–EEG monitoring, the interictal recording is also of localizing value. The interictal background may contain focal slowing or suppression over the epileptogenic region, which can help localize areas of brain dysfunction relevant to the patient's

seizures. Also, the presence of interictal epileptiform abnormalities beyond the boundaries of the epileptogenic zone or contralateral to the suspected focus may influence surgical prognostication (27). Generalized interictal epileptiform activity may be seen in addition to focal abnormalities in some patients with focal epilepsy, suggesting a mixed seizure disorder. Finally, in some cases, the interictal EEG may be of greater localizing value than the ictal EEG, particularly in extratemporal focal epilepsy. Figure 74.4A–D shows focal interictal epileptiform abnormalities in four patients undergoing epilepsy surgery evaluation. In the extratemporal cases shown (see Fig. 74.4B–D), the interictal activity had clearer localizing attributes than the ictal EEG.



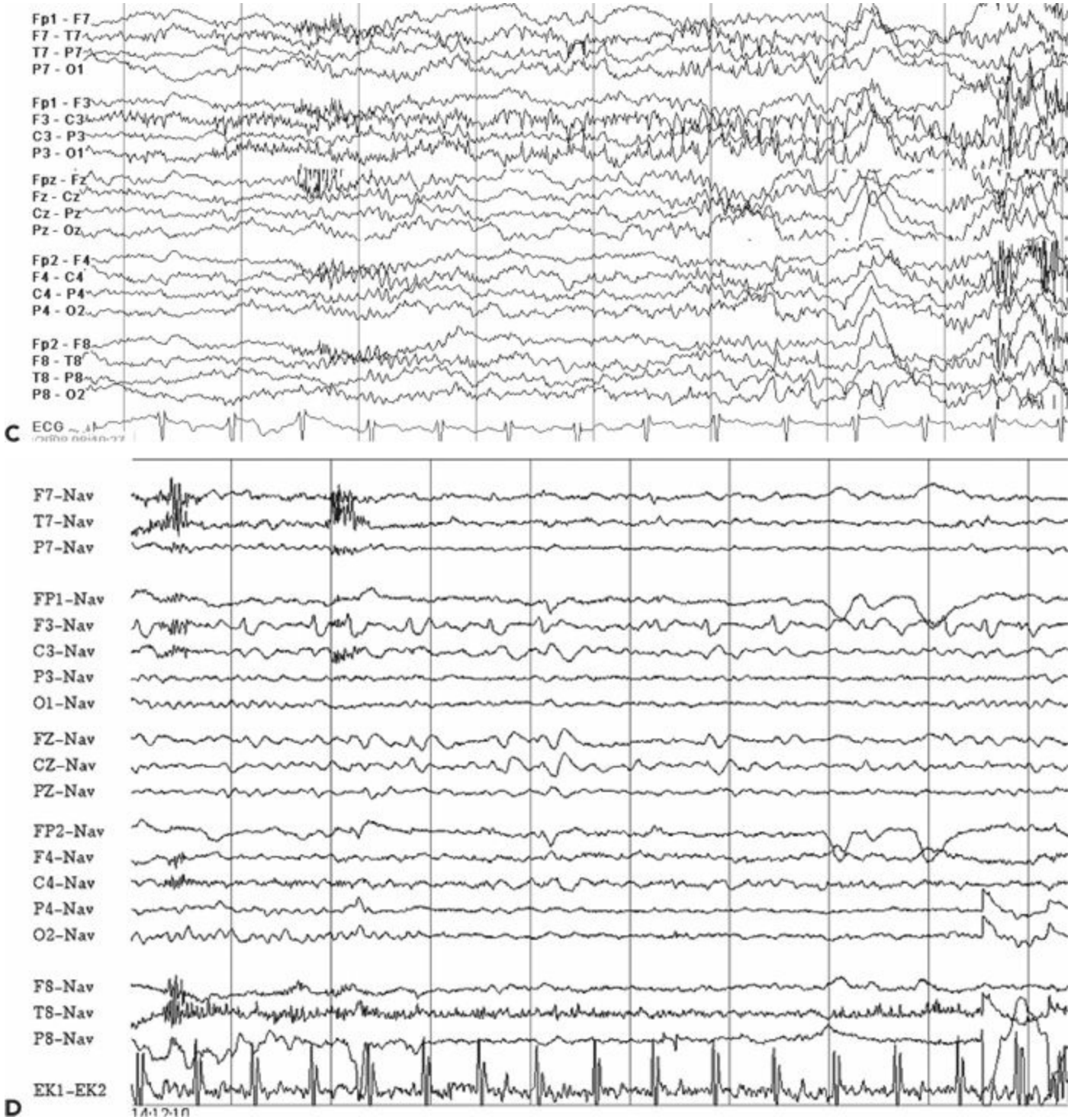


Figure 74.4. Localizing interictal abnormalities in epilepsy surgery patients with partial epilepsy. **A:** Right temporal sharp waves and temporal intermittent rhythmic delta activity (TIRDA) in a patient with right temporal lobe epilepsy secondary to mesial temporal sclerosis. **B:** Left occipitoposterior temporal spikes in a patient with a left medial occipital cortical dysplasia. **C:** Left centroparietotemporal spikes in a patient with a cortical dysplasia localized to the left inferolateral postcentral gyrus region. **D:** Repetitive left frontal spikes in a patient with nonlesional frontal lobe epilepsy localized with intracranial monitoring to the left dorsolateral frontal region.

The interictal EEG may be of prognostic value in epilepsy surgery patients. Anatomic concordance of interictal abnormalities and other localizing data in a given patient confers a favorable prognosis in temporal lobe epilepsy surgery (27). In addition, the quantity of interictal activity may be of prognostic value in certain epilepsy syndromes. In one temporal lobe epilepsy surgical series, 29% with frequent spikes (>60 spikes per hour) experienced an excellent surgical outcome compared to 81% with infrequent spikes (<60 spikes per hour) (28). One explanation proposed for this observation was that frequent interictal discharges may be an indicator of a

neocortical temporal seizure focus as opposed to mesial temporal.

The Ictal EEG

While analysis of the ictal EEG plays an essential role in epilepsy surgical planning, there are some limitations. In a retrospective study of patients with Engel class 1 surgical outcomes, ictal EEG localization was possible in 57% of recorded seizures and 72% of patients, and false localization occurred in 6% (29). In light of these and similar findings, it is clear that the ictal EEG cannot be relied on in isolation. Proper selection and counseling of patients for epilepsy surgery requires correlation of the ictal EEG, interictal EEG, neuroimaging, and semiology in addition to other localizing tests if needed.

Limitations of Ictal EEG.

Acquisition of an interpretable ictal scalp EEG often poses technical challenges. In frontal lobe seizures, artifact secondary to hypermotor behavior may obscure the EEG. Oral automatisms during temporal lobe seizures may give rise to myogenic artifact in the temporal derivations, which may obscure the ictal EEG.

Other factors are important to consider when evaluating the ictal EEG. High-frequency discharges >100 Hz are now recognized as important features of the epileptogenic zone on intracranial recordings (30). However, such activity may not be appreciable on scalp EEG given their low amplitude and frequency limits of most routine EEG amplifiers. Acquisition of the ictal EEG is also limited by the unfavorable location of many cortical regions with respect to scalp EEG electrode localization, and the topographical discrepancies between the complexities of the cortical surface versus scalp. Due to these factors, fewer than 10% of spikes involving a cortical surface area of <10 cm^2 on subdural recordings are usually detectable on the scalp EEG (31). As a result, certain regions of the brain, such as the insula, interhemispheric regions, and inferior cortical regions, do not lend themselves to scalp EEG analysis. Given this, there are significant limitations as to the resolution of ictal EEG localization. For example, it may be possible to determine that a seizure arises from the temporal region, but it may not be possible to determine whether it is of medial or neocortical temporal onset. Finally, seizures arising from some cortical regions may show their earliest expression on the ictal EEG in a brain region of propagation. For example, orbital frontal foci are often indistinguishable from temporal lobe foci based on EEG given the proximity of the orbital frontal cortex to the temporal head region. Occipital seizures are also known to propagate early to the temporal lobes, which may give rise to false-positive EEG localization.

Another limitation of EEG localization is encountered in infants, children, and adolescents with refractory epilepsy due to congenital or early-acquired focal or hemispheric epileptogenic lesions. Such patients may have hypsarrhythmia, generalized slow spike-and-wave complexes, or other generalized patterns on ictal and interictal EEG, with few or even no focal features. Selected children with early developmental lesions may be favorable candidates for epilepsy surgery, despite generalized manifestations on EEG (32). The mechanism for the diffuse EEG expression in such children is unknown, but a factor may be the earlier interaction between the focal lesion and the developing brain.

Features of Ictal EEG Recordings.

The seizure pattern recorded in an individual patient with a single epileptogenic zone typically remains consistent from seizure to seizure. Significant variability of the ictal EEG in a single patient should raise the possibility of a relatively large epileptogenic zone or multiple seizure foci. Conversely, seizures from the same brain region in different patients may show interindividual variability due to individual differences in anatomy and physiology.

A variety of ictal EEG discharge patterns have been described in association with focal seizures. These include (i) rhythmic theta, delta, or alpha activity; (ii) paroxysmal fast activity (rhythmic activity in the beta frequency range or higher); (iii) suppression (focal, asymmetric, or diffuse); (iv) repetitive epileptiform abnormalities; and (v) arrhythmic mixed frequency activity (33,34).

The distribution of the EEG discharge is important. While focal, regional, or lateralized discharges are more typical in the focal epilepsy population, the presence of bisynchronous or diffuse activity at onset does not necessarily exclude the possibility of a surgical focus. For example, bisynchronous and diffuse ictal EEG onset may be present in surgical candidates with supplementary motor area seizures. In such cases, intracranial monitoring is often necessary to resolve localization. Mesial temporal and lateral frontal seizure foci are most amenable to localization with ictal scalp EEG. Conversely, localization of mesial frontal, orbital frontal, parietal, and occipital seizure foci is difficult with ictal EEG.

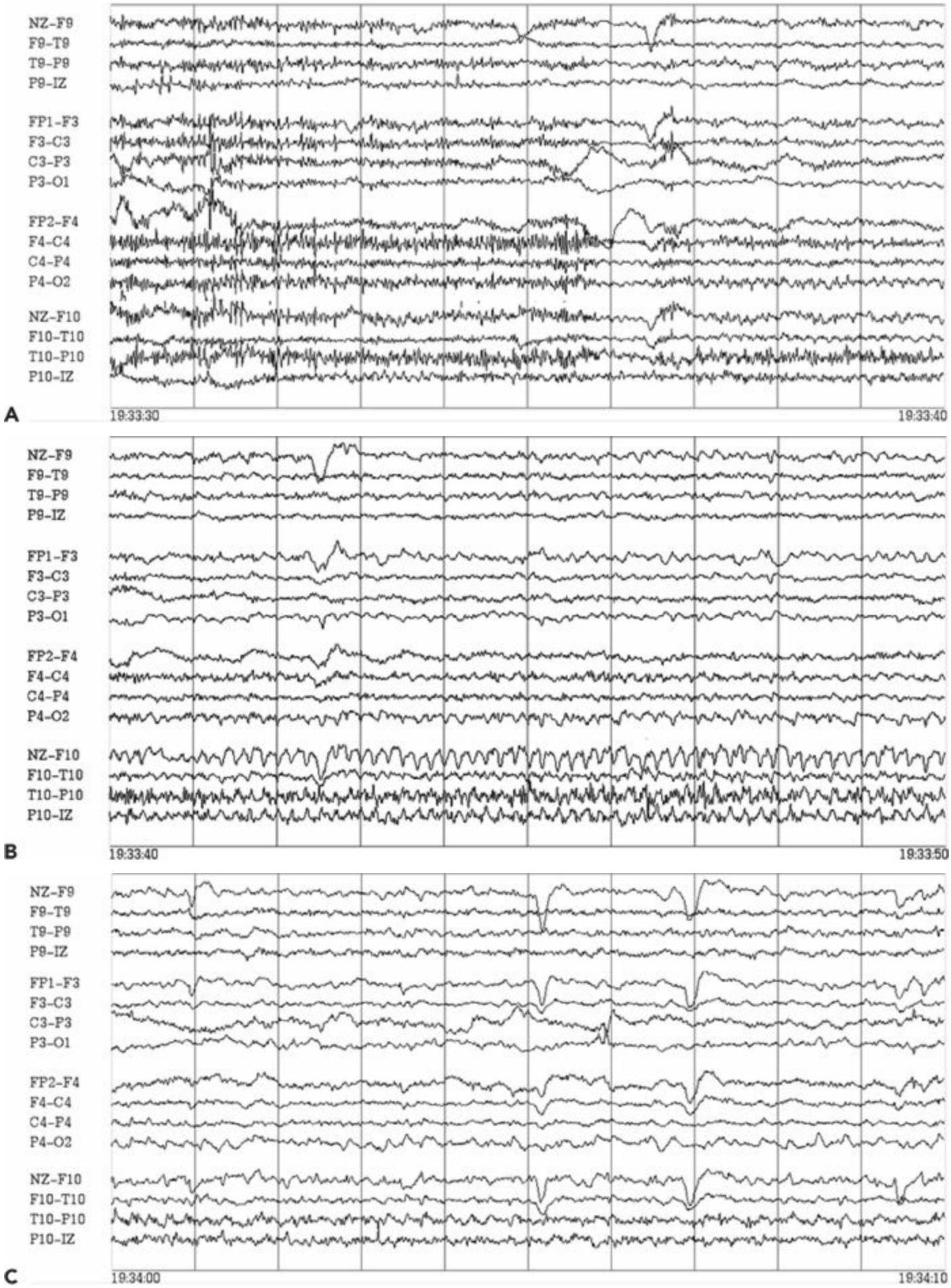
Determining the Ictal EEG Onset.

The video and EEG should be reviewed in concert in order to determine whether the timing of the ictal EEG onset correlates with clinical onset. In general, an EEG onset that precedes the clinical onset provides a better estimate of the epileptogenic zone, and the first 30 to 40 seconds of a seizure provide the most useful localizing information. Due to seizure propagation, later portions of the seizure discharge are of less value. The postictal record however can be useful, particularly in temporal lobe epilepsy where localized slowing can sometimes be seen in the ipsilateral temporal region.

Temporal Lobe Seizures: Mesial Versus Neocortical Temporal Onset.

Mesial temporal seizures typically manifest as an evolving rhythmic theta discharge arising over the ipsilateral temporal derivations. A typical right mesial temporal seizure is shown in Figure 74.5A–D. The discharge morphology is often sinusoidal at onset, the individual waveforms showing a rounded contour rather than sharp in the early portion of the seizure (see Fig. 74.5A). Sometimes a transient suppression of the EEG background may precede temporal lobe seizures. This may be lateralized or diffuse and is more apparent in seizures arising out of sleep (35). Temporal lobe seizures may also begin with semirhythmic repetitive epileptiform discharges at onset rather than a sinusoidal morphology. While temporal seizures are typically focal or lateralized at onset, they may be bilateral or diffuse, evolving into a more lateralized discharge over the ipsilateral temporal region after the first several seconds of the seizure. As the seizure continues, the waveforms often become sharper in appearance and the frequency increases slightly (see Fig. 74.5B). Rhythmic activity then begins to appear in the parasagittal and midline regions, presumably secondary to propagation to the cingulum or due to formation of a vertical dipole in the mesial temporal region with the positive component oriented superiorly (36). Contralateral temporal spread often develops in the middle to latter portions of the seizure. At seizure termination, the discharge frequency typically decreases to the delta

frequency range (see Fig. 74.5C), and ipsilateral semirhythmic 1- to 2-Hz delta activity may be present in the postictal period (see Fig. 74.5D).



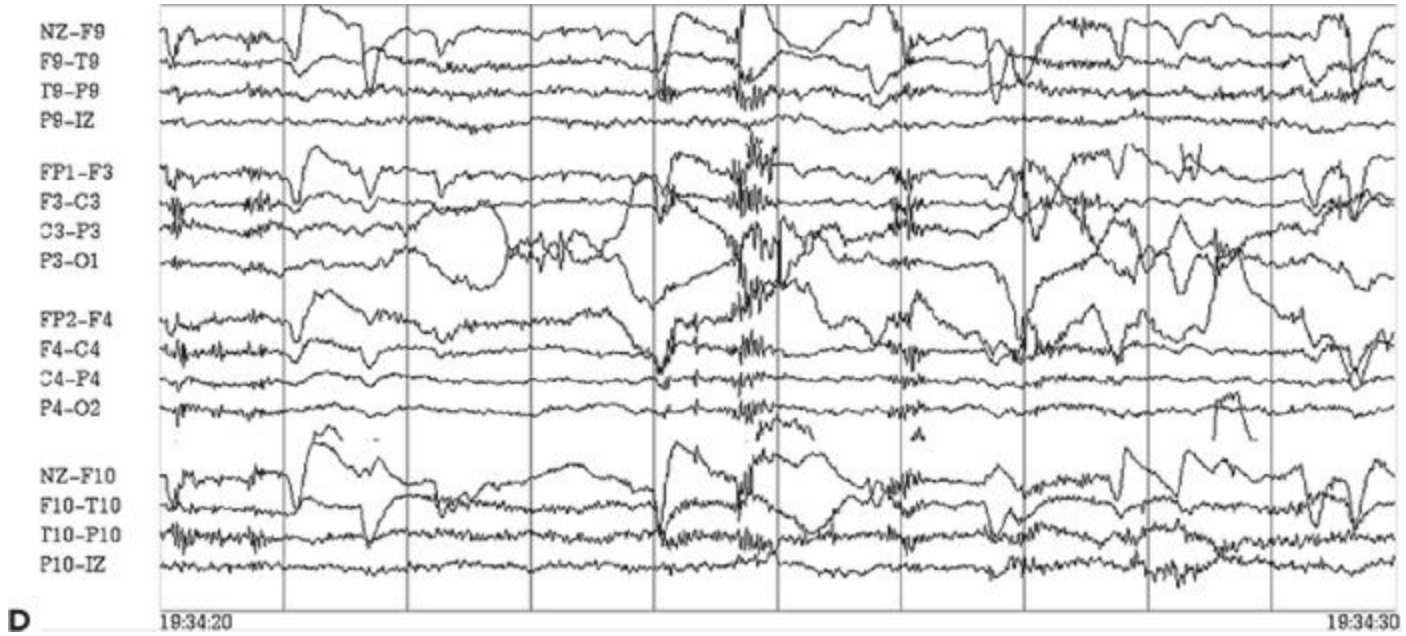
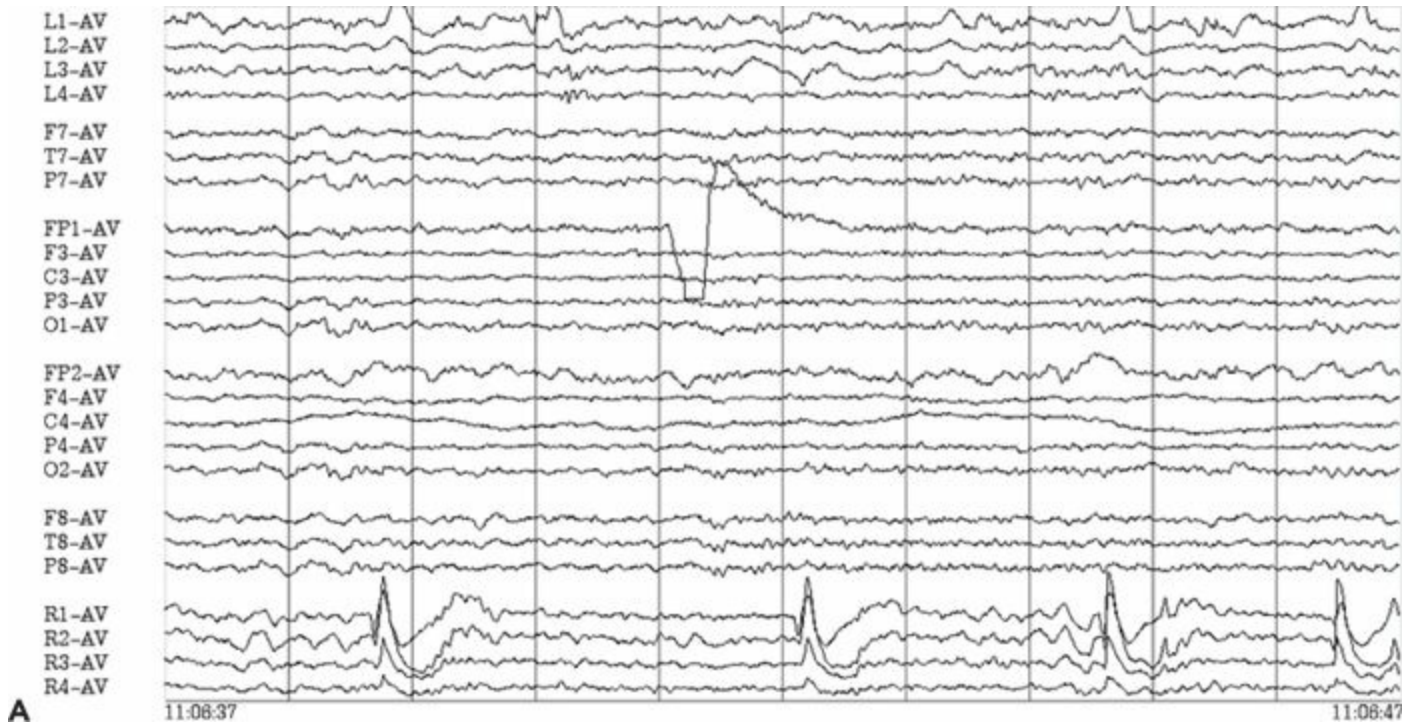


Figure 74.5. Ictal EEG evolution during a right temporal seizure in a patient with mesial temporal sclerosis. **A:** Ictal EEG onset consists of sinusoidal rhythmic theta over the right temporal derivations. **B:** The discharge evolves to form rhythmic sharply contoured theta activity with phase reversal over the right anterior temporal derivations. **C:** The right temporal discharge frequency decreases toward the end of the seizure to the delta frequency range. **D:** Subtle lateralized postictal delta slowing and attenuation of the background is present over the right hemispheric derivations following seizure termination.

False ictal EEG lateralization is uncommon in temporal lobe epilepsy but can occur, that is, in seizures that spread from one hippocampus to the other prior to propagation to the ipsilateral temporal neocortex. It can also occur when the seizure onset is such that the ictal EEG field is oriented parallel to the scalp electrode surfaces. Sometimes the EEG seizure onset presents with bitemporal discharges, and in this scenario, ictal EEG lateralization may not be possible. Mesial temporal depth electrode recordings may be necessary to resolve seizure lateralization in such cases. Figure 74.6A and B shows a recording in a patient undergoing simultaneous scalp and bitemporal depth electrode recordings demonstrating a relatively belated bitemporal scalp EEG discharge 48 seconds after right mesial temporal depth onset.



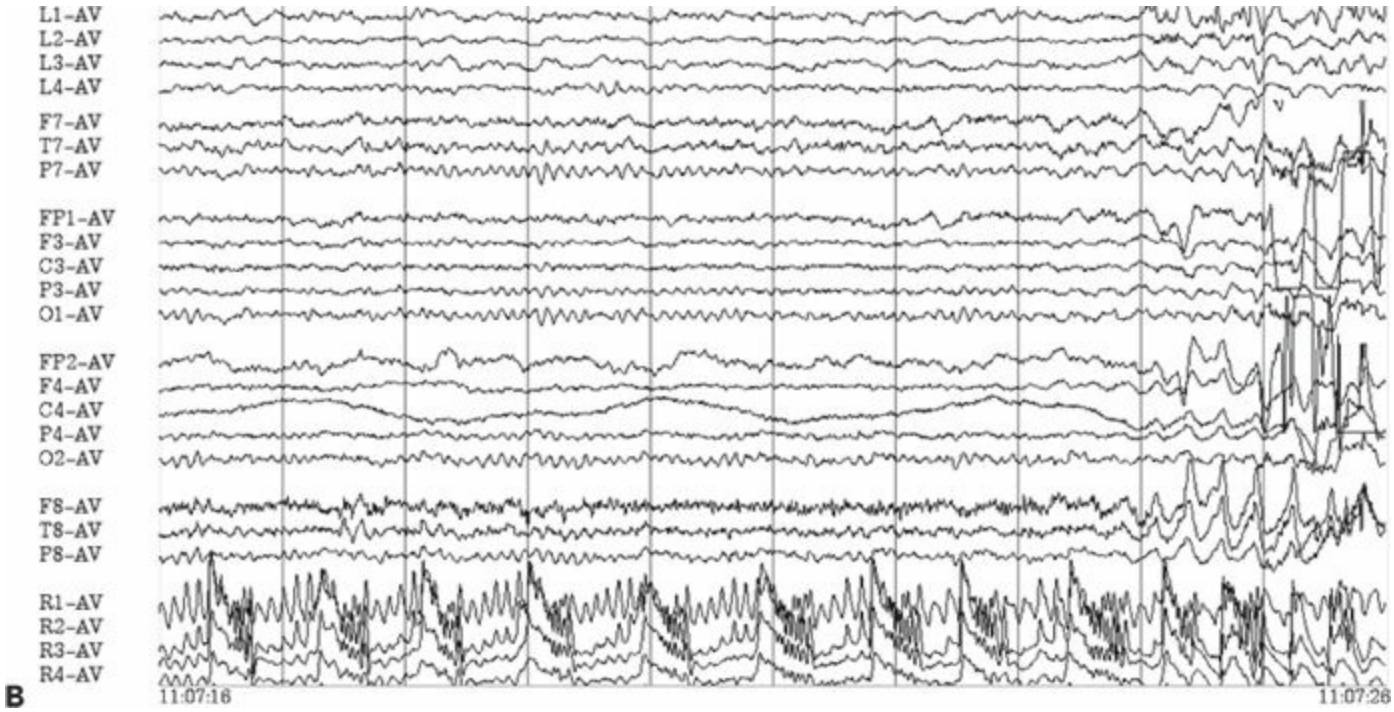


Figure 74.6. Simultaneous bitemporal depth and scalp EEG recording in a patient with temporal lobe epilepsy. **A:** Seizure onset in the right temporal depth (labeled R1-4-AV) without associated changes in the right temporal scalp derivations (labeled F8, T8, P8–AV). **B:** Right temporal scalp activation begins 48 seconds after right medial temporal depth onset, consisting of high-amplitude rhythmic sharp activity involving F8, T8, P8—AV in the last 2 seconds of the figure.

Neocortical temporal seizures cannot be reliably distinguished from medial temporal seizures on scalp EEG alone; however, some features suggest neocortical localization. In one study, the mean discharge frequency at seizure onset in neocortical temporal seizures was 1 Hz less than mesial temporal seizures (37). In another study, mesial temporal seizures presented with an initial regular 5- to 9-Hz inferotemporal rhythm and occasionally by a vertex/parasagittal positive rhythm of the same frequency and neocortical temporal seizures showed an irregular polymorphic 2- to 5-Hz discharge or repetitive semiperiodic sharp waves at onset (38). Seizures without a clear lateralized EEG discharge were most commonly neocortical in this study. In another series, mesial temporal seizures were more likely to show fast rhythmic sharp waves (>4 Hz) at seizure onset than neocortical temporal seizures (mean 81% vs. 60%, $P = 0.05$), neocortical seizures were more often bilateral at onset (mean 55% vs. 26%, $P < 0.05$), and bilateral propagation occurred more rapidly (mean 23 vs. 74 second, $P < 0.005$) in neocortical than mesial temporal seizures (39). Sphenoidal electrodes can help delineate mesial and neocortical temporal seizures; however, intracranial monitoring is usually necessary to resolve sublobar localization in surgical cases.

Seizures from cortical regions other than the temporal lobes may show the earliest EEG activity over the temporal derivations due to extensive corticocortical connections between the temporal and extratemporal cortical regions and hence lead to false EEG localization. In one study of 33 nonlesional patients with temporal lobe seizure activity on ictal scalp EEG, 11 had an extratemporal seizure focus on intracranial monitoring with propagation to the temporal region (40). There is no EEG feature that can reliably distinguish a propagated temporal discharge from a temporal origin rhythm. In addition to propagation from other cortical regions, certain deep structures connected to the limbic system such as the hypothalamus in the setting of hypothalamic hamartomas may show the earliest EEG discharge over the temporal regions potentially leading to false localization. The use of dense array EEG acquisition may help resolve sublobar and lobar localization challenges posed by nonlesional epilepsy cases. However, the complexity of the cortical surface anatomy and

discrepancies between the cortex and scalp surfaces pose barriers to the ability to resolve source localization with scalp ictal EEG.

Frontal Lobe Seizures.

The EEG is of less localizing value in frontal lobe seizures. There are several reasons for this including artifact secondary to hypermotor behavior that often accompanies frontal seizures and the complex anatomy of the frontal lobe, much of which is located at a distance with respect to scalp electrodes. While some ictal EEG features are relatively characteristic for frontal lobe seizures, ictal EEG localization was not found to be a significant prognostic factor in one series of successful frontal lobe epilepsy surgery cases (41).

The ictal EEG in mesial frontal seizures often does not show a scalp EEG discharge at clinical seizure onset due to the disadvantageous localization of the seizure-onset zone with respect to the recording electrode surface. As the seizure progresses in mesial frontal seizures, rhythmic theta or delta activity may appear late over the midline and bilateral parasagittal regions. The EEG often remains obscured by artifact throughout seizures of mesial frontal origin, particularly in those with hypermotor semiology. Several other ictal patterns have been described in association with mesial frontal seizures including generalized spike and wave, a diffuse electrodecremental pattern, and rhythmic vertex alpha activity. It is often difficult to lateralize mesial frontal seizures on EEG. In the absence of a structural or functional imaging abnormality in such cases, intracranial monitoring is usually necessary.

Focal ictal EEG abnormalities are more likely to be present in patients with dorsolateral frontal seizures due to the closer proximity of the area of seizure onset to the recording electrodes. The ictal onset in dorsolateral frontal seizures may manifest as a focal low-amplitude high-frequency discharge, an example of which is depicted in Figure 74.7. Such a discharge at onset may be prognostically favorable in epilepsy surgery candidates. Recording multiple seizures may help increase the yield of the ictal scalp EEG in these patients.

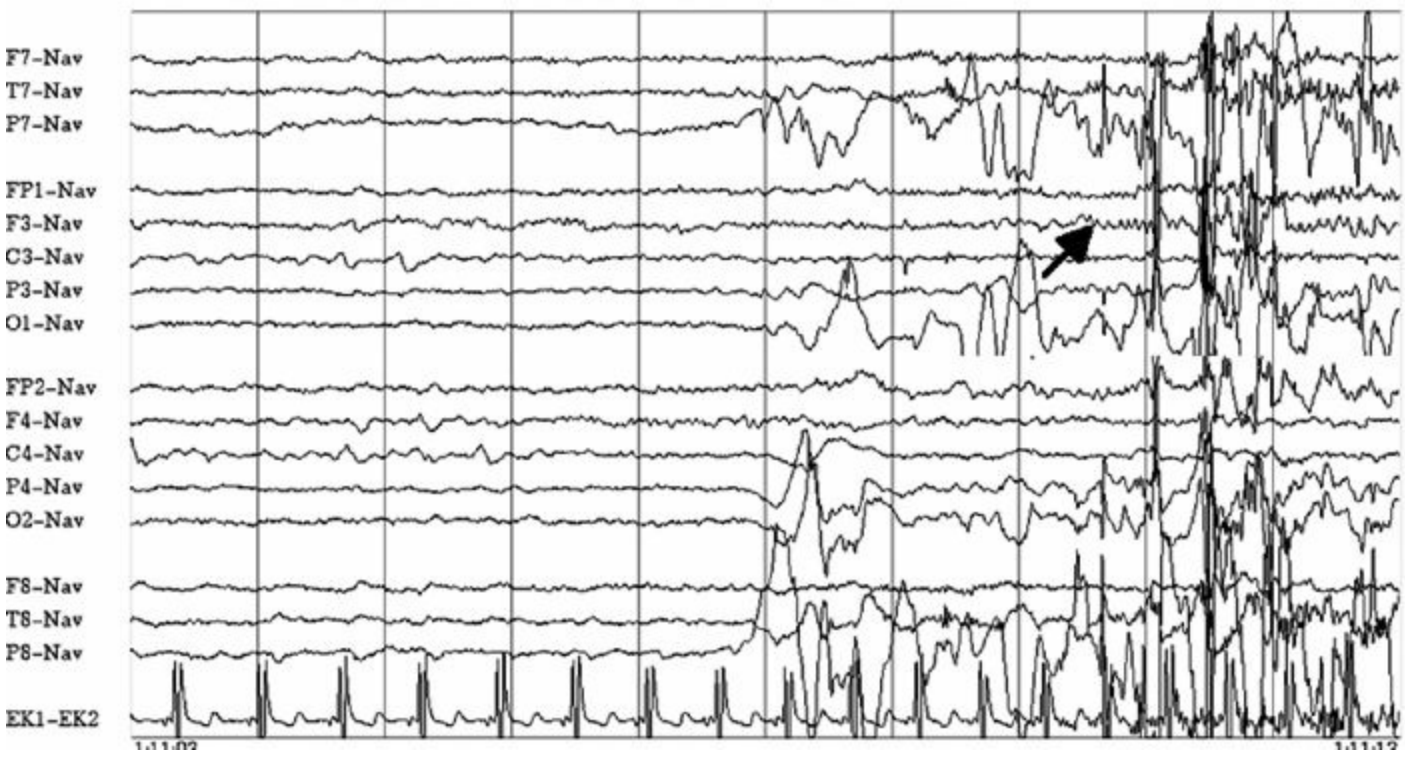


Figure 74.7. Ictal EEG during an extratemporal seizure of left lateral frontal onset. This patient's interictal EEG is shown in Figure 74.1D. At clinical onset, there is attenuation of the EEG background and a high-frequency discharge ("beta buzz") present over the left frontal region (arrow).

Orbital frontal seizures often propagate to the ipsilateral temporal region, which can cause erroneous localization to the temporal lobe. Orbital frontal seizures can also spread to other regions of the frontal lobe.

Occipital Lobe Seizures.

Occipital seizures are difficult to localize on ictal EEG even in lesional patients. Seizures arising from the calcarine cortex may give rise to bilateral or contralateral discharges due to the anatomic orientation of the medial occipital cortical surface relative to the scalp electrode recording surface. Confounding matters further from an EEG standpoint is the fact that occipital seizures often spread to the temporal and frontal regions, which can result in false localization to these areas if other localizing data are lacking.

Parietal Lobe Seizures.

The parietal lobe is the least common area of seizure onset in focal epilepsy, and the ictal EEG is often not localizing. Like seizures from other extratemporal sites, parietal seizures often propagate to neighboring regions, leading to challenges in clinical and ictal EEG localization in the absence of a structural lesion on magnetic resonance imaging (MRI). In one large surgical series, the sensitivity of ictal EEG in a seizure-free parietal lobe epilepsy cohort was 35.7%, compared to 64.3% for MRI, 50% for PET, and 45.5% for ictal SPECT (42).

CONCLUSION

Video–EEG monitoring is essential in the presurgical evaluation of patients with medically refractory focal epilepsy. There are some risks to video–EEG monitoring. Therefore, it is important to put in place appropriate policies and safety measures to minimize the potential for harm in these patients. Twenty-four–hour patient observation by nursing or technical staff is essential to ensure prompt identification of seizure activity and associated complications in monitored patients. All data acquired during video–EEG monitoring, including the ictal semiology, the interictal EEG, and the ictal EEG, should be analyzed in the process of seizure localization. Conclusions based on analysis of the video–EEG session then need to be correlated with neuroimaging and other localizing data prior to final surgical planning.

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CHAPTER 75 NUCLEAR IMAGING (PET, SPECT)

WILLIAM DAVIS GAILLARD

Functional imaging studies using radiotracers, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), are performed primarily to identify or confirm the ictal focus in preparation for surgery and to investigate the pathophysiology of partial and generalized seizure disorders. Less commonly, PET is performed to identify eloquent cortical regions to be spared during epilepsy surgery.

PRINCIPLES: PET AND SPECT

Radiotracer studies using PET or SPECT allow for the in vivo assessment of physiologic function in humans. Such studies include glucose consumption ([^{18}F]fluoro-2-deoxyglucose; [^{18}F]FDG), cerebral blood flow ([^{15}O]water), and neurotransmitter synthesis (dopamine and serotonin) or receptor–ligand binding (agonists or antagonists to benzodiazepine, opiate, serotonin, and N-methyl-D-aspartate [NMDA] receptors). A physiologic probe designed to assess a targeted function is labeled with a radioactive tag. The decay of the radioactive tag is associated with the emission of high-energy particles, or gamma rays, that are subsequently detected by the scanner, and their origin is then computed. PET has a practical resolution of 2 to 3 mm, which is superior to that of SPECT. Furthermore, unlike SPECT, PET studies can be quantitated. Use and application of PET ligands are determined by compound half-lives: ^{18}F-tagged compounds have a 110-minute half-life, ^{11}C a 20-minute half-life, and ^{15}O a 2-minute half-life. As a consequence of its longer half-life, [^{18}F]FDG cannot be used to assess short-lived physiologic phenomena such as ictal states, whereas the very short half-life of [^{15}O]water renders it suitable for capturing the brief activity of cognitive processes. Given the relatively short half-life of PET ligands, data acquisition must occur shortly or immediately after injection.

In contrast, SPECT ligands have a longer half-life. ^{99m}Tc-Hexamethyl-propyleneamine oxime (^{99m}Tc-HMPAO) or ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD) for cerebral perfusion has replaced ^{123}I-based ligands such as [^{123}I]iodoamphetamine and [^{123}I]trimethyl-hydroxymethyl-iodobenzylpropane diamine, so that data can be collected hours after injection. SPECT is less expensive and more readily available than PET, but the basic premises are similar. SPECT ligands used in epilepsy are primarily markers of perfusion, though some receptor ligands are also available, such as [^{123}I]iomazenil ([^{123}I]IMZ), for benzodiazepine receptor studies. The compounds that mark blood flow, HMPAO and ECD, have a distribution in the brain that is proportional to cerebral blood flow. Both ligands are lipophilic; they generally cross the blood–brain barrier on their first pass through brain tissue, become trapped, and exhibit little subsequent redistribution. A potential limitation is that neither ligand has linear uptake at high cerebral blood flow rates, and thus cerebral

blood flow is underestimated under certain circumstances (1). Although there are some individual differences in tracer distribution (1), the efficacy of HMPAO and ECD in epilepsy studies is comparable.

PET IN THE EVALUATION OF EPILEPSY

[^{18}F]FDG-PET and Temporal Lobe Epilepsy

The most clinical experience for evaluating patients with partial epilepsy is with [^{18}F]FDG-PET. Several studies demonstrate interictal regional decreases in glucose consumption that are invariably ipsilateral to the seizure focus—typically, but not always, most pronounced in the temporal lobe (Figs. 75.1 and 75.2) (2,3).

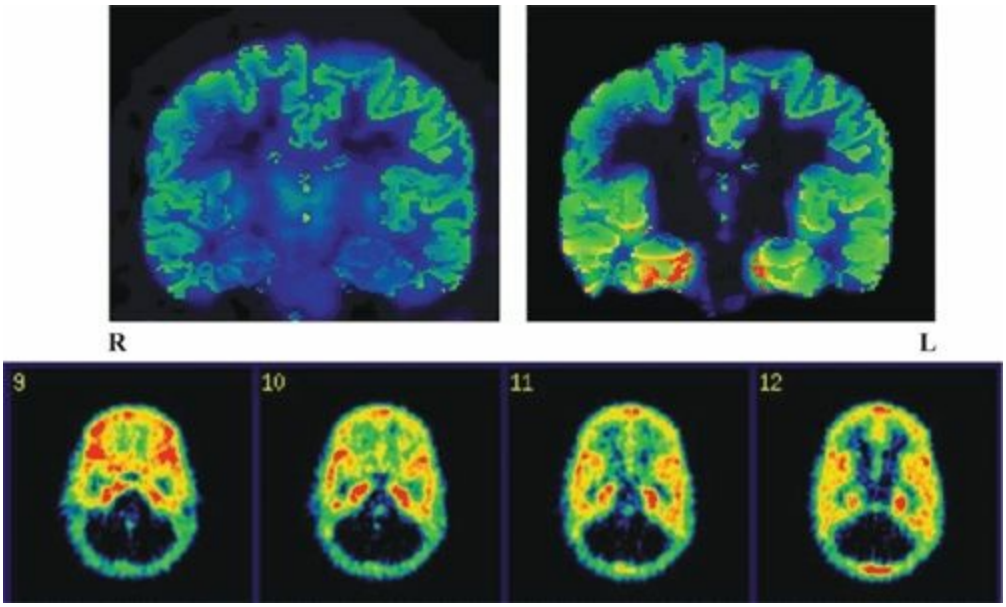
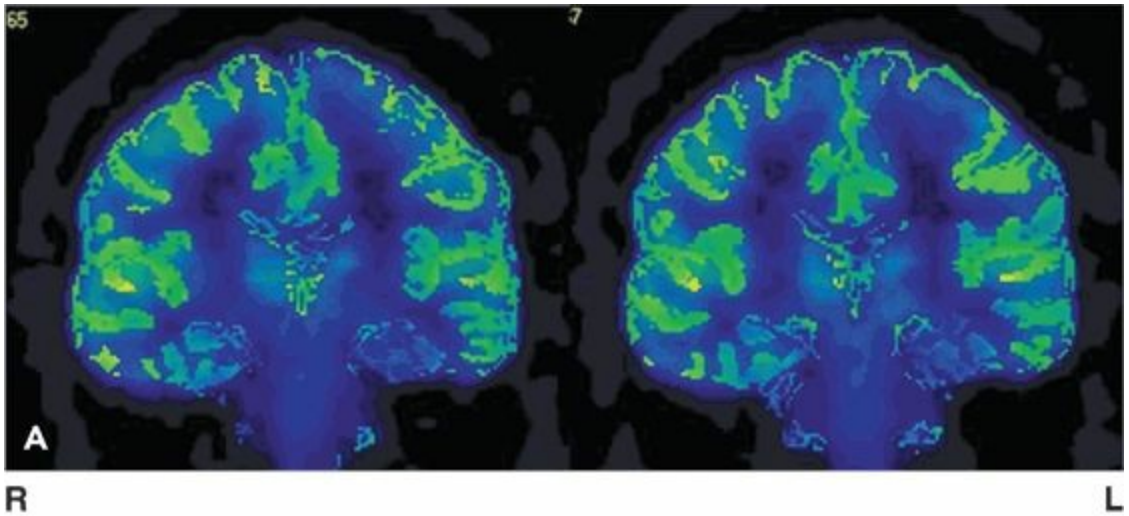


Figure 75.1. [^{18}F]FDG-PET (**upper row left**) showing normal glucose uptake. [^{18}F]FCWAY-PET (**top row right**) shows decreased binding in the left temporal lobe, most pronounced in the amygdala and hippocampus. Lower row are axial views of [^{18}F]FCWAY PET in a normal volunteer. There is no ligand binding in the cerebellum, reflecting absence of 5HT 1A receptors in cerebellar tissue. Raphe nucleus ligand binding can be seen. Left image is the right brain. (Courtesy of Dr. William H. Theodore. National Institutes of Health, Bethesda, Maryland.)



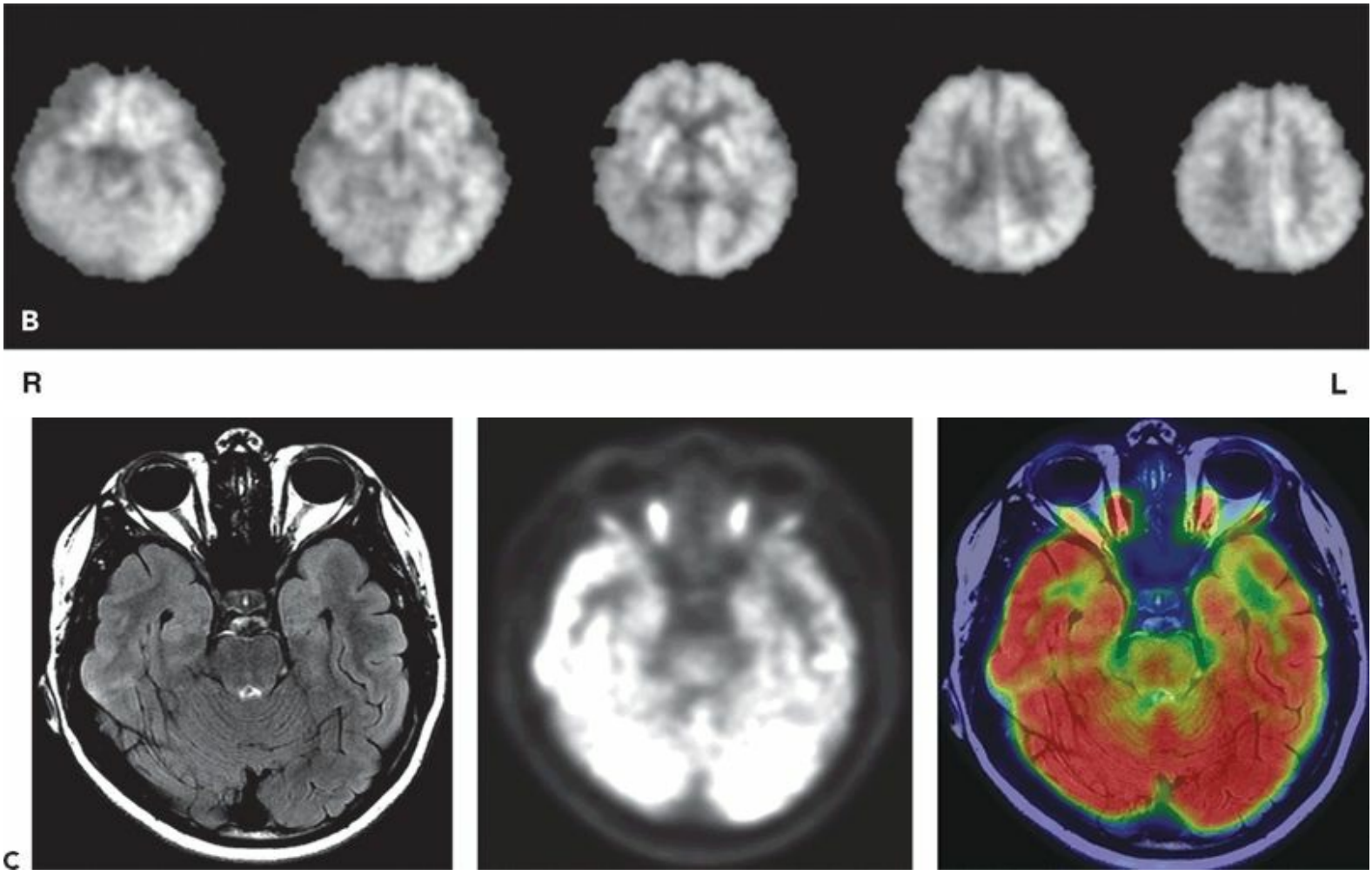


Figure 75.2. A: [^{18}F]FDG-PET in an adult with left TLE showing decreased glucose uptake in mesial temporal regions following partial volume correction. (Courtesy of Dr. William H. Theodore. National Institutes of Health, Bethesda, Maryland.) **B :** [^{18}F]FDG-PET scan in a 14-month-old child with focal seizures (right posterior quadrant focus), secondary generalization, and normal MRI. Figure shows right posterior quadrant hypometabolism. **C:** [^{18}F]FDG-PET scan of a 15-year-old female, with focal epilepsy with altered consciousness, who has subtle left anterior mesial tip temporal focal cortical dysplasia (MRI) and widespread decrease in hypometabolism (PET). MRI, PET, and coregistered PET/MRI are shown. Left image is the right brain. (National Institutes of Health, Bethesda, Maryland.)

Sixty-five percent to 90% of patients with temporal lobe epilepsy (TLE) demonstrate regional hypometabolism; this figure is closer to 90% on recent generation scanners and approximately 60% for patients with normal MRI (4–6). The area of decreased glucose utilization is often more extensive than the epileptogenic zone and may extend into the adjacent inferior frontal or parietal lobe neocortex (3) and occasionally into the ipsilateral thalamus (7) and contralateral cerebellum (3). The regional abnormalities are invariably unilateral to the ictal focus. However, lobar localization is somewhat less reliable, about 80% to 90%. False lateralization as demonstrated after surgery (2) occurred in few patients, specifically when interpretation relied upon nonquantitative analysis, or occurred during subclinical seizures (2,8). Focal interictal regional hypometabolism also predicts a good surgical outcome (5,9–11). Different investigators using different methods and regional analyses have found several different regional hypometabolism patterns predictive of good outcome: inferior lateral temporal, anterior lateral, and uncus (5,9,11). Additionally, extent of resection of PET abnormalities correlates with postoperative outcome (12). Bilateral temporal hypometabolism is associated with a less optimistic surgical outcome and in half of patients reflects bilateral foci (13). Patients with focal temporal abnormalities have a 93% likelihood of good surgical outcome, and those without, 63% likelihood of good outcome (10,11). The ability to confirm the focus and predict

surgical outcome is better when quantitative means are used, typically when asymmetry indexes [AI; e.g., AI = 2(left − right)/(left + right)] are greater than two standard deviations from normative data or about 10% to 15%. However, region of interest measures may be less useful for small, well-demarcated neocortical abnormalities that reflect limited focal cortical dysplasia. Lesser degrees of asymmetry, though visually apparent, may result in misleading information and erroneous conclusions (4,10,11). Voxel-based statistical methods performed in a standard anatomic atlas that allows comparison of individual patient images to normal control group data have been advocated as an alternative means of reliable analysis (14). Given that [^{18}F]FDG-PET is often performed to confirm the focus, focal abnormalities may reduce the need for, or extent of, invasive monitoring when laterality of the focus is in doubt (2,10,11). Issues of frontal versus temporal focus may not always reliably be resolved by interictal [^{18}F]FDG-PET studies, and invasive studies or other PET ligand studies may be needed. Conflicting localizing or lateralization data nearly always merit invasive monitoring.

Ictal [^{18}F]FDG-PET studies are uncommon because of technical constraints such as ligand availability and unpredictability of seizures. They may show profound focal increases in glucose consumption, but results may also be normal or show decreased consumption. The results depend on the delivery of ligand, time and duration of the seizure, and degree of offsetting postictal hypometabolism. Although of interest, they are of limited clinical use, except during focal status epilepticus (15).

The reasons for regional hypometabolism are incompletely understood. Glucose consumption occurs primarily at the synapse. Regional hypometabolism appears to reflect a decrease in glucose influx from reduced glucose transport across the blood–brain barrier, which correlates with subsequent reduced phosphorylation. Cell loss with ensuing synaptic loss and altered remote projections, or degree of hippocampal atrophy in mesial temporal sclerosis, may account for a portion, but not all, of regional hypometabolism in TLE (16,17). Hypometabolism does not correlate with lifetime generalized tonic–clonic seizure or complex partial seizure (CPS) frequency (18). Dysplastic tissue with aberrant synaptic connectivity can have either decreased or normal glucose consumption (19). The abnormalities in some circumstances appear to be functional, as some patients have profound decreases in glucose uptake and no discernible pathology; regional decreased glucose uptake may vary with relation to previous ictal events and clinical manifestations of the previous seizure. In patients with mesial temporal sclerosis, the predominant regions that may manifest decreased glucose consumption are the lateral neocortex and, to a lesser extent, the frontal cortex. This may reflect the distant projection of functional loss in mesial structures. Frontal hypometabolism and contralateral hypometabolism appear to be reversible with successful temporal lobectomy (20).

Studies differ in the extent to which patients with mesial temporal seizures show pronounced lateral hypometabolism: mesial greater than lateral, lateral greater than mesial, and equal mesial and lateral temporal reductions in glucose uptake have been reported (3,4,21). Patients with neocortical temporal epilepsy may have greater lateral than mesial metabolic abnormalities (21). Patterns of hypometabolism may reflect seizure characteristics and seizure propagation. However, there is sufficient variability among patients that individual predictions of seizure focus within the temporal lobe based on [^{18}F]FDG-PET cannot be made.

[^{18}F]FDG-PET will be abnormal when MRI shows significant abnormalities, for example, in mesial temporal sclerosis, tumor, vascular malformation, infarct, and most instances of cortical dysplasia. In this setting, [^{18}F]FDG-PET provides little additional information beyond MRI.

[^{18}F]FDG-PET may be more sensitive than MRI in TLE under some circumstances. Current PET techniques are helpful in 85% to 90% of patients, volumetric MRI in 60% to 70%, and magnetic resonance spectroscopy (MRS) in 55%. Higher-resolution scanning techniques, including high-resolution fast spin echo, fluid-attenuated inversion recovery, T2 relaxometry, magnetization transfer, and high-resolution thin-cut spoiled gradient recall anatomic sequences, and use of higher magnetic field strength (3T and now 7T) have reduced the utility of [^{18}F]FDG-PET (22). Comparison studies report varying efficacy results with different imaging modalities, which frequently reflect the particular research strengths of the investigators rather than the intrinsic advantages of the techniques studied.

Although glucose consumption in the temporal cortex is decreased, perfusion is often maintained, especially in the lateral neocortex (4,23). Interictal studies of cerebral blood flow using [^{15}O]water find a decrease in perfusion in only 50% of patients, but one-fifth of these provide falsely localizing information (4). This experience is similar to that in interictal SPECT studies and quantitative perfusion ascertained by arterial spin-labeled fMRI (5,24). These data suggest that vascular tone may be impaired in TLE and that the relationship between metabolism and perfusion is altered. For these reasons, interictal blood flow studies are unreliable markers of the epileptogenic zone and do not predict surgical outcome (4).

FDG-PET in Newly Diagnosed and Nonrefractory Localization–Related Epilepsy

Metabolic abnormalities are less common in patients with recent-onset, nonrefractory, or well-controlled partial epilepsy. Thirty percent of adults with nonlesional epilepsy within <3 years of seizure onset have focal [^{18}F]FDG-PET (25). Forty to 50 percent of adults without refractory seizures of limited duration (<5 years) have focal abnormalities (25,26). Presence of focal abnormalities does not predict 2-year outcome. Other studies report 20% of adults with well-controlled partial seizures had regional metabolic abnormalities. In these adult populations, localization of seizures is less certain than in patients with refractory epilepsy—an important consideration because patients with extratemporal lobe epilepsy are less likely to have abnormal [^{18}F]FDG-PET studies.

Chronic partial epilepsy typically begins during childhood. Twenty percent of children with new-onset focal epilepsy and normal MRI demonstrate regional hypometabolism. All (ipsilateral) abnormalities occurred among the children with a suspected temporal lobe focus. (27). Follow-up studies did not show any change in extent or magnitude of regional hypometabolism; a combination of MRI and PET findings predicted outcome—those with persistent abnormalities fared less well (28). In another study, regional hypometabolism changed in relation to seizure frequency in children with worsening seizures (29). Similar to adults, 70% of children with chronic partial epilepsy (duration 10 years) have focal metabolic abnormalities. There is evidence that adult patients with a greater duration of epilepsy are more likely to have focal [^{18}F]FDG-PET abnormalities (3,23,27). Partial seizures of greater duration are also associated with a greater dissociation between metabolism and blood flow (4,23). These [^{18}F]FDG and cerebral blood flow studies, along with cross-sectional studies using volumetric MRI, may be taken as evidence that TLE in some patients is associated with chronic and continued neuronal injury (23,30).

Other PET Ligands in Temporal Lobe Epilepsy

In addition to widespread reduction of glucose utilization in cortical projection areas, with relatively preserved perfusion, ligand-binding studies reveal additional functional abnormalities in patients with TLE (Table 75.1). These findings reflect hippocampal atrophy, loss of neuron populations, or a neuronal response to epilepsy.

Table 75.1 PET Ligands in Temporal and Neocortical (Nonlesional) Epilepsy

Ligand	Tracer	Action	Temporal lobe epilepsy	Neocortical
FDG	^{18}F	Glucose uptake and consumption	Decreased mesial, lateral	Decreased
FMZ	^{11}C	GABA-A receptor benzodiazepine site antagonist	Decreased HF, amygdala	Mixed
FCWAY	^{18}F	5HT1A receptor antagonist	Decreased HF, amygdala, insula	
MPPF	^{18}F	5HT1A receptor antagonist	Decreased mesial temporal lobe	
AMT	^{11}C	Precursor, 5HT/kynurenine synthesis	Increased in normal HF	Increased dysplasia; epileptogenic tubers
Carfentanil	^{11}C	Opiate mu receptor agonist	Increased TL neocortex, decreased amygdala	
Cyclofoxy	^{18}F	Opiate mu, kappa receptor antagonist	Increased ipsilateral TL	
Diprenorphine	^{11}C	Opiate mu, kappa, delta receptor agonist	No change	
Methyl ketamine	^{11}C	NMDA receptor antagonist	Decreased	
Fallypride	^{18}F	D2/D3-receptor	Decreased, ipsilateral temporal pole, lateral cortex	
SCH23390	^{11}C	D1 receptor		ADNFLE, reduced in striatum
Fluoro-L-DOPA	^{18}F	Dopamine precursor	Decreased, bilateral caudate, putamen, and substantia nigra	
Doxepin	^{11}C	H1 receptor agonist	Decreased	
Deprenyl	^{11}C	MAO B inhibitor (glial)	Increased	
PBR28	^{11}C	Translocator protein (activated microglia and astrocytes)	Increased (especially in MTS)	
GR205171	^{11}C	Neurokinin-1 receptor	Increased	

ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; AMT, alpha-^{11}C-methyl-L-tryptophan; FCWAY, ^{18}F-trans-4-fluoro-*N*-2-[4-(2-methoxyphenyl) piperazin-1-yl]ethyl-*N*-(2-pyridyl)cyclohexane carboxamide; FDG, ^{18}F-deoxy glucose; FMZ, ^{11}C-flumazenil; HF, hippocampal formation; MAO, monoaminooxidase; MPPF, 2′-methoxyphenyl-(*N*-2′-pyridinyl)-p-^{18}F-fluoro-benzamidoethylpiperazine; NMDA, *N*-methyl-D-aspartate; TL, temporal lobe; MTS, medial temporal sclerosis.

GABA-A Receptor Studies

Unlike [^{18}F]FDG-PET, which typically demonstrates hypometabolism that is more widespread than the epileptogenic zone, PET with [^{11}C]flumazenil ([^{11}C]FMZ), a benzodiazepine antagonist of the gamma-aminobutyric acid (GABA)-A receptor, shows focal abnormalities confined to the hippocampal formation (6,31). Autoradiography of pathologic tissue indicates that most decreased [^{11}C]FMZ binding is proportional to cell loss (6). In contrast, some [^{11}C]FMZ-binding studies performed in patients with mesial temporal sclerosis argue for an absence or downregulation of GABA receptors beyond that expected by atrophy alone. After accounting for partial volume effect, a 38% reduction in [^{11}C]FMZ binding is found in sclerotic hippocampus beyond reduction in hippocampal formation volume (31). In partial epilepsy, a greater degree and extent of decreased [^{11}C]FMZ binding are seen in patients with more frequent seizures, and decreased binding may extend to projection areas of the epileptogenic region (32). In mesial temporal sclerosis, there is decreased

[^{11}C]FMZ binding in one-third of patients in the contralateral hippocampal formation but to a lesser extent than in the epileptogenic hippocampus. This finding is similar to those in MRS studies. However, in patients with a temporal focus and normal MRI, [^{11}C]FMZ-PET is less useful (6). SPECT with [^{123}I]IMZ, a benzodiazepine ligand (33), shows results similar to those of the PET ligand and more useful than cerebral blood flow–based SPECT (34).

Serotonin Receptor and Synthesis Studies

Serotonin (5HT) IA receptor binding is reduced, to a greater degree than reduced glucose uptake, in epileptogenic mesial temporal lobe and adjacent insula as deduced by the selective antagonists including those with normal MRI [^{18}F]trans-4-fluoro-N-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide ([^{18}F]FCWAY) and [^{18}F]2′-methoxyphenyl-(N-2′-pyridinyl)-p-18F-fluoro-benzamidoethylpiperazine [^{18}F]MPPF (see Fig. 75.1) (35–37). Regional [^{18}F]FCWAY binding contributes to likelihood of achieving seizure freedom following temporal lobe resection (10). Alpha-[^{11}C]methyl-L-tryptophan ([^{11}C]AMT) is increased in the hippocampus ipsilateral to mesial TLE in patients with normal hippocampal formation volumes, but not MTS (38). [^{11}C]AMT, designed as a serotonin precursor, may also be a marker for quinolinic or kynurenic acid, compounds implicated in excitatory neurotransmission (38,39). Decreased receptor binding in mesial temporal structures is more pronounced than reductions in cerebral metabolism. Decreased binding also correlates with severity of depression in epilepsy patients (40) comparable to patients with primary depression.

Other Ligands

Table 75.1 lists findings from several studies of investigational ligands in limited populations using probes for opiate, histamine, and NMDA receptors as well as glial markers. Studies using [^{11}C] PBR28, a probe of the translocator protein that is increased in activated microglia and astrocytes, hence a marker of inflammation, find increased binding in the hippocampus, amygdala, and fusiform gyrus in the epileptogenic temporal lobe; the asymmetry was highest in patients with mesial temporal sclerosis (Fig. 75.3) (41).

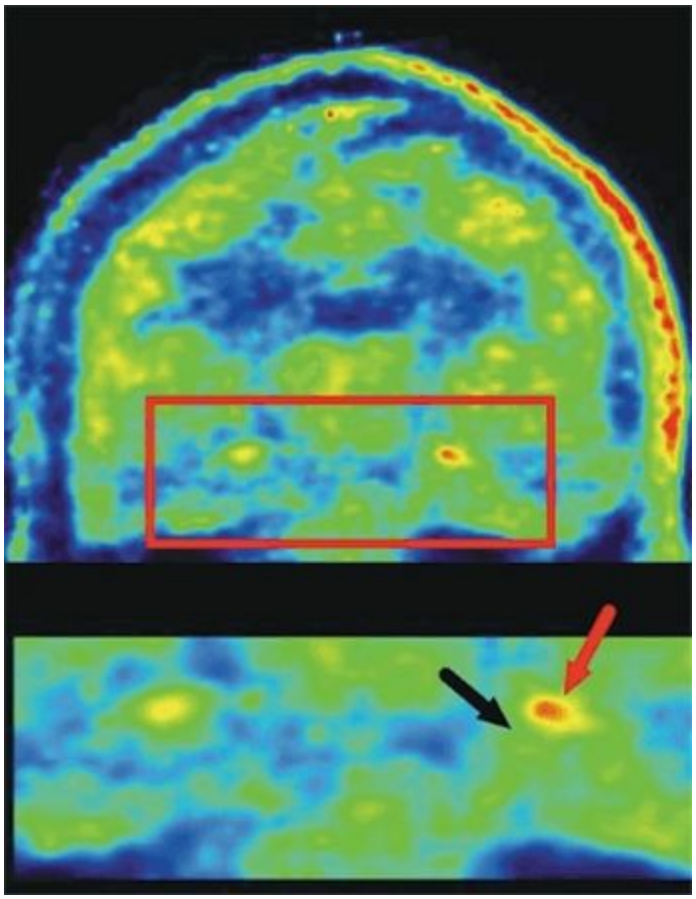


Figure 75.3. Coronal image from [11C] PBR28 PET in an adult patient with left-sided TLE demonstrating increased ligand uptake in the epileptogenic hippocampus (black arrow hippocampus; red arrow increase ligand binding in hippocampal formation): the hippocampal area is magnified in the bottom row. Left image is the right brain. (Courtesy of Dr. William H Theodore, National Institutes of Health, Bethesda, Maryland;. Hirvonen J, et al. Increased in vivo expression of an inflammatory marker in TLE. J Nucl Med. 2012;53(2):234–240.)

PET in Extratemporal Lobe and Neocortical Epilepsy

[^{18}F]FDG-PET is less efficacious in identifying the epileptogenic zone in extratemporal lobe epilepsy than in TLE (42). Most extratemporal lobe epilepsy series include patients with structural lesions that, not surprisingly, show concordant hypometabolism. When patients with abnormal MRI findings are excluded, 11% to 50% of the relatively small patient populations remaining show regional decreases in glucose consumption (6,43). Some investigators have found a good correlation between regional hypometabolism and the epileptogenic zone; others have found a reasonable correlation with side, but not site, of ictal origin. FDG-PET abnormalities remote from the lesion lessen prospects of surgical outcomes. Coregistration of FDG-PET and high-resolution MRI may increase yield of identifying malformations of cortical development, the most common presumed cause of "nonlesional" epilepsy in children and adults (see Fig. 75.2C) (44,45).

[^{11}C]FMZ-PET studies yield mixed and inconsistent results (6,46). [^{11}C]FMZ binding may be reduced and is more restricted in cortical extent than [^{18}F]FDG-PET abnormalities, when present. It appears to correlate with the site of ictal activity and, if resected, is associated with improved outcome (47). Patients with acquired lesions may have regional focal reductions in [^{11}C]FMZ binding concordant with the lesion, but most marked at the margins (46). In other studies, two-thirds of patients with neocortical epilepsy and normal MRI had [^{11}C]FMZ abnormalities, either increased or decreased, which were bilateral in half of the subjects (46,48). Techniques that correct for gray

matter volume averaging may be helpful in identifying abnormal [^{11}C]FMZ binding in cortical dysplasia (48). Given these mixed findings, the role of [^{11}C]FMZ in nonlesional epilepsy remains unclear. In patients with extratemporal lobe partial epilepsy, ictal SPECT may be a better identifier of the epileptogenic cortex, which is discussed below.

PET in Generalized Epilepsy

PET has been used to explore generalized epilepsies, predominantly of the absence type. Glucose consumption and perfusion are globally increased (49). [^{15}O]Water studies performed during electroencephalographic (EEG) bursts of spike and wave demonstrate not only an increase in global perfusion but also a preferential increase in the thalamic regions, supporting the notion of the thalamus as the facilitator of absence events (50). There are no differences in [^{11}C]FMZ or [^{11}C]diprenorphine binding in absence epilepsy. In juvenile myoclonic epilepsy, [(11)C]PE2I, a marker of dopamine transporter activity, is reduced in the midbrain and the high-affinity dopamine (D2/D3) receptor ligand [^{18}F]fallypride ([(18) F]FP) is reduced in the putamen (51).

PET in Children with Epilepsy

[^{18}F]FDG-PET studies of normal development show increased glucose utilization in all brain areas, peaking around 5 to 8 years of age, that parallels synaptic (52). Mature patterns of glucose uptake are established in the primary motor and sensory cortex before they are consolidated in the association cortex. [^{18}F]FDG-PET studies of children with partial epilepsy show regional abnormalities similar to those seen in adults with temporal or extratemporal lobe epilepsy and are discussed above (see Fig. 75.2). Although primary generalized epilepsies are typically viewed as pediatric disorders, imaging studies in these populations have only been performed in adults (see PET in Generalized Epilepsy). Pediatric epilepsy syndromes that have been studied include infantile spasms, Lennox–Gastaut syndrome, Landau–Kleffner syndrome, Rasmussen encephalitis, and several of the cortical dysplasias, including tuberous sclerosis.

Children with infantile spasms may show extensive hypometabolism, usually in posterior brain regions (19). These abnormalities often correspond to MRI abnormalities and may identify areas of dysgenesis not readily apparent with older MRI techniques. However, some children with a generalized EEG and normal MRI exhibit regional metabolic abnormalities (53). PET has been used in these cases to remove the epileptogenic zone in children with catastrophic epilepsy. In some children, however, the metabolic abnormalities seen at onset of infantile spasms may resolve with time and thus may represent a functional state that is potentially reversible with successful medical therapy (54). In children with Rasmussen encephalitis and hemimegalencephaly, widespread hemispheric hypometabolism is typically seen. PET has been advocated in some circumstances to assess the integrity of the good hemisphere before extensive cortical resection (19,55).

In tuberous sclerosis, tubers are often hypometabolic, whereas there is some evidence that the more epileptogenic tubers have increased serotonin or kynurenic acid synthesis, reflected by increased [^{11}C]AMT uptake (56). [^{11}C]AMT uptake is also increased in focal cortical dysplasia; MRI (especially in children <2 years) and [^{18}F]FDG-PET may be normal (Fig. 75.4) (39,56).

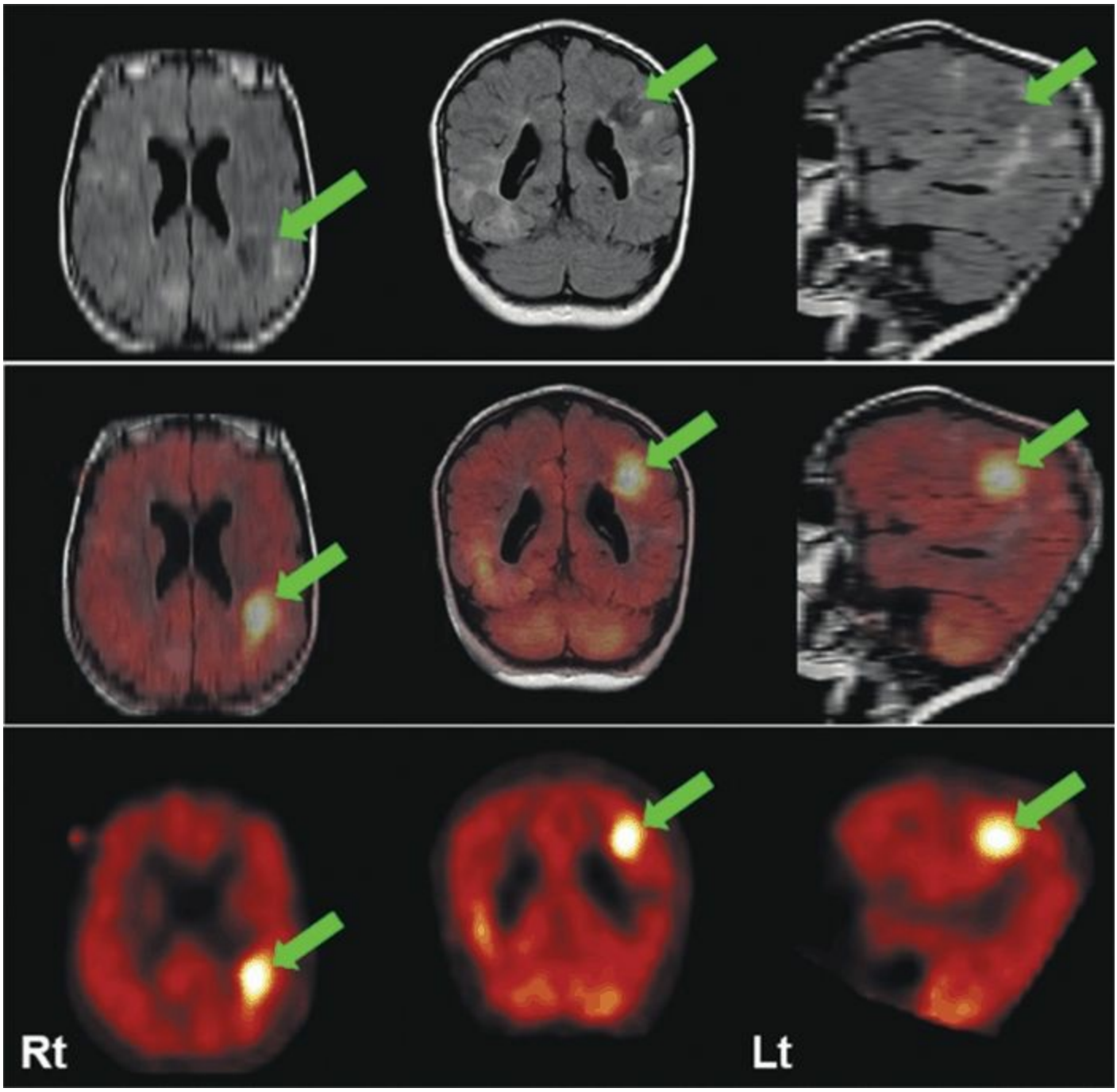


Figure 75.4. MRI (FLAIR) (**upper row**) and [^{11}C] AMT-PET (**bottom row**) and coregistered images (**middle row**) in a 2-year-old child with tuberous sclerosis. [^{11}C] AMT-PET shows markedly increased ligand uptake in epileptogenic parietal tuber (arrow) that is hypometabolic with [^{18}F]FDG-PET (not shown). (Courtesy of Dr. Harry Chugani, Detroit Children's Hospital.)

PET studies in Lennox–Gastaut and Landau–Kleffner syndrome have yielded mixed results. Children with Lennox–Gastaut syndrome may have focal or multifocal abnormalities, diffuse cortical hypometabolism, or normal studies (57,58). Children with generalized EEG, nonfocal examinations, longer- duration seizures, and normal MRI have normal or diffusely hypometabolic studies. A minority of children exhibit regional metabolic abnormalities, either hypometabolic or hypermetabolic, but many of these children have focal neurologic examinations or partial seizures (57,58). In Landau–Kleffner syndrome and electrical status epilepticus of sleep, inconsistent results have been seen with [^{18}F]FDG-PET, mostly involving temporal hypometabolism. However, other areas may be hypometabolic or hypermetabolic (59).

PET and Antiepileptic Drugs

Several studies have examined the effect of antiepileptic drugs on glucose consumption and to a lesser extent on cerebral perfusion. The GABA-ergic receptor agonists phenobarbital and benzodiazepine reduce glucose consumption by 20% to 30%. In contrast, vigabatrin, an inhibitor of GABA degradation that increases cerebrospinal fluid GABA, reduces glucose uptake by only 8.1% (60). The sodium channel blockers carbamazepine and phenytoin reduce glucose uptake by 9.5% and 11.5%, respectively. Valproate, when used in conjunction with carbamazepine in patients with epilepsy, results in a 22% reduction. However, with monotherapy in normal volunteers, the reduction is only 9.5% with a decrease in perfusion of 14.9%. Although the effects of antiepileptic drugs appear to be global, there is some evidence with valproate of greater decreases in cerebral blood flow in the thalamus, which may reflect an effect of valproate in controlling generalized epilepsies.

CEREBRAL BLOOD FLOW STUDIES USING SPECT

SPECT and Seizure Focus Identification

Interictal SPECT studies demonstrate regional hypoperfusion in 40% to 50% of patients with partial epilepsy of temporal lobe origin that is ipsilateral to a proven epileptogenic area. However, approximately 5% to 10% of studies are falsely lateralizing (4–6,61). These findings are similar to those of interictal perfusion studies performed with [^{15}O]water PET, discussed above. SPECT is more suitable for ictal studies than either [^{15}O]water or [^{18}F]FDG-PET and has provided both useful and reliable information. This is possible because both ^{99m}Tc-HMPAO and ^{99m}Tc-ECD have a rapid first-pass uptake but long half-life. The long half-life permits bedside injection at ictus as well as time to arrange for data acquisition scanning within 4 to 6 hours after injection. Ictal SPECT, when compared with an interictal study, demonstrates regional hyperperfusion in 67% to 90% of patients (Fig. 75.5). In a majority of patients, this correlates with the ictal focus and has been validated with simultaneous invasive video-EEG. These findings hold true for temporal as well as extratemporal lobe epilepsy in both children and adults (5,62–64). The usefulness of ictal studies approaches that of [^{18}F]FDG-PET in patients with TLE, and ictal studies are probably superior for extratemporal focus localization (65–67). Partial seizures often show more reliable results than secondarily generalized seizures (68). False localization is reported in 3% to 4% of studies, presumably because of seizure propagation, and is more likely to occur with later injection times (5). Subtraction techniques with MRI coregistration provide enhanced comparison and semiquantitation of perfusion changes between the interictal and ictal states compared with visual comparison alone (32% to 39% vs. 83% to 85%) (see Fig. 75.5) (69). Focal ictal SPECT also predicts whether surgical outcome will be good (67,70). Many SPECT studies have included patients with clear structural abnormalities such as tumor, mesial temporal sclerosis, and vascular malformations. As with [^{18}F]FDG-PET, in this setting, it is unclear whether SPECT contributes to the patient evaluation (71). It is most useful in evaluating patients with nonlesional partial epilepsy, especially extratemporal partial epilepsy. Ictal subtraction SPECT may also be useful in evaluating patients who have failed initial surgery.

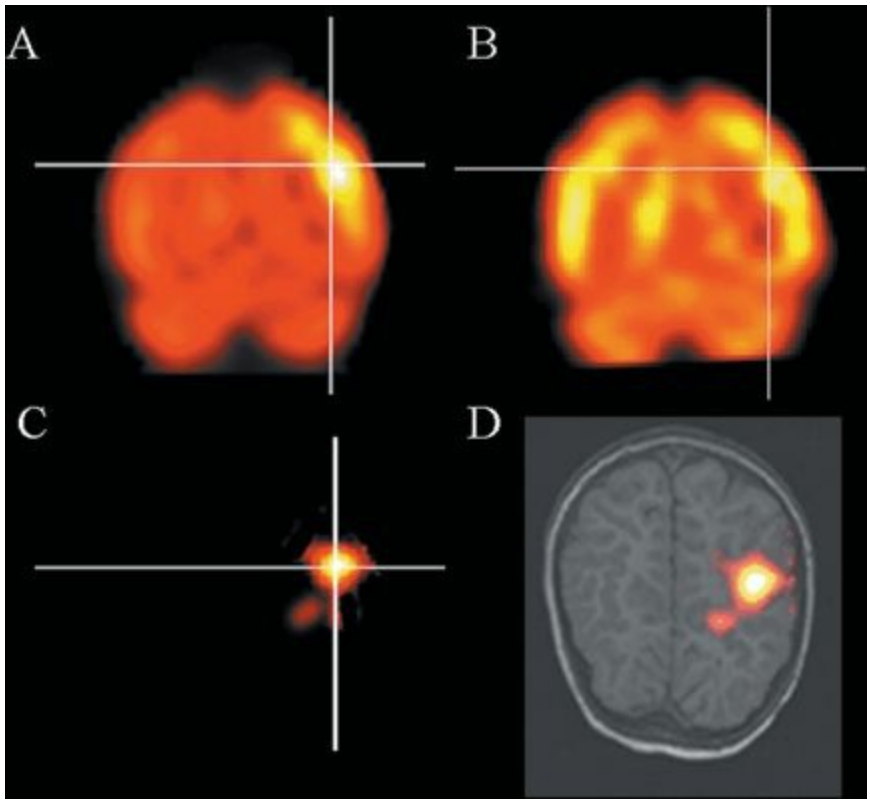


Figure 75.5. Ictal ^{99m}Tc-hexamethyl-propyleneamine oxime single photon emission computed tomography (SPECT) in a young adult with refractory partial seizures. **A:** Interictal SPECT. **B:** Ictal SPECT. **C:** Subtraction image of interictal from ictal SPECT. **D:** Subtraction SPECT coregistration with magnetic resonance image (SISCOM). Study demonstrates increased ictal perfusion in the parietal lobe. Here, the right side of the image is the left brain. Chronic invasive recording and surgery subsequently confirmed the ictal focus identified by subtraction SPECT techniques. (Courtesy of Dr. Gregory Cascino, Mayo Clinic, Rochester, Minnesota.)

Ictal SPECT findings are related to the timing of injection and the clinical manifestations of seizure propagation (72). For an ictal SPECT study to be useful, injection of the ligand must occur during the ictus and no later than 30 seconds after cessation of the seizure. The earlier the injection (<20 seconds from seizure onset), the more reliable are the study results, and the better the surgical outcome (73). During the ictus, there is focal increase in cerebral blood flow to the involved cortex, often with decreased perfusion in adjacent areas. After the seizure, there is postictal hypoperfusion, which may return to an interictal state rapidly (64). Postictal hypoperfusion abnormalities are more reliable than interictal hypoperfusion (60% to 70% vs. 40% to 50%, respectively). After ligand injection, lorazepam is sometimes administered to diminish the likelihood of subsequent seizures. The data from the scan can be acquired up to 6 hours after the injection. Furthermore, it is important to recall that if a patient has multiple seizure types, each type must be captured. Automated systems may be helpful to improve timing and reliability of ligand delivery; video-EEG monitoring is critical for interpretation of SPECT studies (74). Newer SPECT ligands (^{99m}Tc-HMPAO and ^{99m}Tc-ECD) have greater stability and offer a longer window of injectability (from 30 minutes to 4 hours after composition).

[^{15}O]WATER PET AND BRAIN MAPPING OF CORTICAL FUNCTION

Although interictal [^{15}O]water PET has not been useful in identifying the epileptogenic zone and the

short half-life of [^{15}O]water makes ictal studies impracticable, [^{15}O]water PET have proved useful in identifying eloquent cortex to be spared during surgery. fMRI has supplanted most brain mapping with [^{15}O]water PET (see Chapters 79 and 80 for more extensive discussion of brain mapping). The principles underlying brain evaluation with [^{15}O]water PET and fMRI are similar. Both techniques rely on the observation that increased neuronal activity, primarily at the synapse, is associated with regional increases in cerebral blood flow (75,76). Detecting the location of changes in blood flow that occur during cognitive tasks (e.g., involving language) allows the mapping of neural networks involved in these tasks. PET is a direct measure of cerebral blood flow, has the advantage of measuring capillary rather than venous blood flow, and is less sensitive to motion—thus allowing spoken and overt responses—and may be more suitable for patients who are less cooperative or who are cognitively impaired. PET can also be used to image patients with contraindications to MRI (e.g., implanted metallic devices).

Although [^{15}O]water PET studies of language and cognition are typically analyzed and presented as group rather than individual data sets, advances in PET technology allow for repeated injections of [^{15}O]water in individuals, resulting in less radiation exposure and making feasible reliable individual perfusion maps of cognitive processes (77). Such methods are reliable for lateralization and, unlike the intracarotid amobarbital procedure, localization of language function. Most of these studies rely on verbal fluency or naming tasks, similar to fMRI studies reviewed below, which readily identify anterior language areas.

Bookheimer et al. (78), using an auditory comprehension and naming task, compared individual activation patterns with PET and subdural grid stimulation and found excellent correlation between the disruption elicited by cortical stimulation and the cerebral blood flow activation elicited by task performance. Their study is the first to confirm the assumed reciprocal relationship between activation as defined by local increase in blood flow and the disruption of function elicited by cortical stimulation. Like other functional studies, these studies are valid only for specific aspects of language assessed by the experimental paradigm. Not all activated areas may be critical to language function. Furthermore, what is crucial may not exceed statistical threshold and may not be apparent. Other studies using PET to identify the motor sensory cortex find good correlation (<5 mm) with corticography (79).

CLINICAL RECOMMENDATIONS FOR USE OF METABOLIC AND FUNCTIONAL IMAGING IN EVALUATION OF PATIENTS WITH PARTIAL EPILEPSY

MRI, MRS, PET, and SPECT provide complementary information. When a structural lesion is present, for example, with a tumor or mesial temporal sclerosis, then further imaging, though of interest, usually does not provide information relevant to clinical care. MRS and PET may add information in patients with TLE when routine MRI is normal. [^{18}F]FDG-PET provides excellent lateralization of seizure focus but less reliable localization and a lower yield in patients with extratemporal epilepsy. Ictal SPECT is most useful in extratemporal lobe epilepsy, where other modalities are less helpful or unavailable; without EEG confirmation, invasive studies are usually

indicated in these settings. The contribution of new PET ligands is not well established, but [^{11}C]FMZ, [^{18}F]FCWAY, and [^{11}C]AMT may provide additional localizing information. [^{15}O]water PET is a reliable technique for lateralization and localization of language and location of motor function.

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CHAPTER 76
MAGNETOENCEPHALOGRAPHY

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The past two decades have seen an explosion of techniques for more refined functional assessment of brain status, in both health and disease, along with incredible progress in anatomic imaging that has brought us resolution undreamed of 15 or 20 years ago. Foremost among these in the clinical realm are fMRI and magnetoencephalography (MEG), techniques that complement each other by their differing resolution in time and space and by the very different nature of the signals that they record (1). The unique features and essential differences of the methods that can be used to assess functional coupling between different brain areas—or its disruption—can be exploited to great advantage in the evaluation of epilepsy patients when multiple complementary imaging modalities are combined.

The goal at epilepsy surgery centers during intensive presurgical evaluation of patients is to ascertain whether the patient has epilepsy, to identify the type of epilepsy, and—if focal—to find the location of the epileptogenic zone or network, with a view toward possible surgical resection. This goal is achieved by employing a variety of diagnostic and localization techniques in a slightly different fashion depending on the medical center. However, almost all centers rely on the most noninvasive methods first. For patients whose epileptogenic focus is undetermined after video-EEG (VEEG) monitoring, additional noninvasive testing is required. MEG is a technique that records the results of the identical phenomenon, that is, neural currents, but which is complementary to EEG.

MEG measures the minute magnetic fields that are generated within the brain and that can be recorded from outside the head, unimpeded by tissue boundaries, such as meninges, skull, and scalp. Synchronous activation of about 10^7 synapses produces a detectable field outside the head, and the skull and other extracerebral tissues are essentially transparent to the magnetic fields emanating from these neuronal networks. The magnetic fields generated by the brain and recorded by MEG are very small, approximately 50 to 250 fT or about a billion times smaller than the earth's magnetic field. MEG measurements are entirely noninvasive; patients are not exposed to any radiation, harmful agents, or strong magnetic fields.

While other modalities infer brain function indirectly by measuring changes in blood flow, metabolism, oxygenation, etc., MEG, as well as EEG, measures neuronal and synaptic function directly, and, like EEG, MEG enjoys submillisecond temporal resolution. The brain sources generate magnetic fields that can be recorded by external sensors. These magnetic signals are not distorted by anatomy, because magnetic susceptibility is the same for all tissues—including the skull. Hence, MEG allows for a more accurate measurement and localization of brain activities than does EEG. Because one of its primary strengths is the ability to precisely localize electromagnetic activity within brain areas, MEG results are always coregistered to the patient's MRI. When combined in this way with structural imaging, it has been called magnetic source imaging (MSI), but MEG is best understood as a clinical neurophysiologic diagnostic test.

A current dipole generated in the cerebral cortex produces not only electric potentials but also

magnetic fields (2–4). MEG is a noninvasive tool that provides precise localization of the epileptic activity generating these fields—both interictal and sometimes ictal (as shown in one of the patient examples below)—as well as mapping of functional cortex. Clinical whole-head systems currently have 200 to 300 magnetic sensors, thereby offering very high resolution. The measurement of magnetic fields provides information not only about the amplitude of the current but also its orientation (5).

The origin of the electrical currents in the brain must be inferred from the extracranial electric potentials (EEG) or magnetic field (MEG), based on a projection of extracranial field data onto the surface or into the volume of the brain. This task is easier and more accurately accomplished with MEG because, unlike EEG, the magnetic field is not distorted by the inhomogeneous and poorly defined conductivities of the layers that separate the currents in the brain from the electrode sensors on the surface of the scalp. Especially important in epilepsy, MEG also has a higher signal-to-noise ratio than EEG (6), and a higher detection sensitivity for interictal discharges. An area of discharging cortex of at least 6 to 10 cm^2 is required for an epileptic spike to be seen on EEG (7), and to be easily recognizable requires 20 to 30 cm^2 (8), whereas MEG needs only 4 to 6 cm^2 (9–11).

Dipole sources in sulci or fissures generate tangential currents and are the likely major contributors to the activity recorded by MEG, resulting in several favorable brain areas for MEG source localization. Theoretically, the roof of the temporal lobe, opercular area, mesial frontoparietal cortex, and deep sulci, such as the central sulcus, are optimal areas for MEG source generators because these regions include large volumes of cortical area that are perpendicular to the surface of the head, thereby generating mostly tangential currents. Epileptic sources in these regions not uncommonly produce discharges that are clearly visible on MEG, but not detectable on simultaneously recorded EEG (12). Another reason that regions outside the temporal lobe are most probably more accessible to MEG than temporal sources is because the magnetic field originating from the lowest part of the brain, for example, basal temporal cortex, may not always be adequately recorded (13), and therefore, MEG's recording and localization abilities are better in extratemporal lobe epilepsy (ETLE) than in TLE (11,14). A recently published small series comparing intracranial recordings to MEG found that MEG detected and localized 95% of the neocortical spikes, but only 25% to 60% of mesial spikes (15). Thirdly, the spherical head model, typically employed for calculation of epileptic spike location, is a better approximation in the extratemporal regions (16).

The two primary clinical indications for MEG are well established (and confirmed specifically by the applicable CPT codes issued in 2003)—namely, epilepsy localization and mapping prior to neurosurgical lesion resection. In the evaluation of patients with epilepsy, the role of MEG can be further defined:

- Identification of epileptogenic areas that are difficult or impossible to identify on scalp EEG
- Confirmation of the ictal-onset zone established by other tests
- Demonstration of widespread or multifocal discharges suggesting an unfavorable prognosis for epilepsy surgery
- Identification of eloquent areas of cortex and their proximity to planned areas of resection

The recent (2009) MEG policy by the American Academy of Neurology specifically highlights the value of MEG "when discordance or continuing questions arise from amongst other techniques designed to localize the focus." In nonlesional cases, or in patients where the EEG is nonlocalizing, MEG can be particularly helpful. Even when it picks up no new areas of epileptic activity, MEG

provides more precise localization than scalp EEG (17). A substantial minority of epilepsy patients, especially nonlesional cases, will still require invasive recording prior to resective surgery, and MEG has been shown to be of crucial assistance in determining the placement of the intracranial electrodes. In MRI-positive cases, MEG is especially helpful in pinpointing the source of epileptic activity when lesions are extensive or multiple.

BACKGROUND

The first human MEG recordings were made by Cohen in 1968 (18), but the field awaited the development of ultrasensitive magnetic field measurement sensors, superconducting quantum interference devices (SQUIDs), in order to achieve the adequate sensitivity needed clinically. The early single-channel, then 7-channel, then 37-channel devices evolved to become commercially produced whole-head systems in the mid-1990s (19,20). Present MEG systems contain hundreds of magnetic sensors surrounding the head, and are able to record in either a seated or supine position.

The advantages of MEG for recording brain signals have a strong theoretical basis and are well known in practice:

- No exposure to radiation, magnetic field, or other active device.
- Inherently higher source resolution.
- Reference free, that is, no contamination by signal from the reference.
- Easy to obtain multichannel, whole-head, high–spatial-density recordings.
- No direct connection to patient required.
- Signals not attenuated or distorted by bone and scalp, or other inhomogeneities that exist between brain and surface.
- Head modeling during source analysis is significantly simpler, less prone to error, and hence more accurate due to lack of signal distortion.

MEG has been found to be valuable in preoperative evaluation of patients being considered for epilepsy surgery (21,22), and MEG's use in these patients has been the subject of several other reviews (23,24). Nevertheless, few studies exist that compare MEG localization with direct intracranial electrode recording (ICEEG), and the patient numbers have been small (10,11,15,25).

One of a handful of studies that has demonstrated true clinical value for MEG in a prospective, blinded crossover-controlled, single treatment case series of 69 sequential patients was published by Sutherling in 2008 (26). Although the effect on outcome was not studied, they looked at the decisions made at patient management conference before and after presentation of MEG results. They found that MEG provided entirely new information in 33%, altered the ICEEG examination (phase 2) in 23%, and changed the surgical decision in 20%. All of the patients in this study were extratemporal, and the postoperative outcome results demonstrated clear benefit from MEG in 21% of the patients who went to resection (9% of the patients in the study).

In an important 2006 publication, Knowlton et al. (27) studied the effect of MEG on the subsequent placement of ICEEG electrodes in a prospective study of 115 patients, 43% of whom were ETLE. By the design of the study, MEG could only prompt the addition of supplemental electrodes after an initial decision was made without considering MEG. Forty-nine patients proceeded to intracranial evaluation, where this study investigated the concordance between ICEEG and MEG localization to the sublobar level, with a view toward the practicality of eventually

substituting MEG for ICEEG in some patients. MEG and ICEEG had about the same success in localizing the epileptic source, 65% and 69%, respectively. Agreement at a sublobar level between tests was good; 55% were localized and concordant for site. There were 7 cases (14%) who were localized by ICEEG but not by MEG and 3 cases (6%) localized by MEG but not by ICEEG. MEG's positive predictive value for seizure localization was 82% to 90%, depending on whether computed against ICEEG alone or in combination with surgical outcome. A notable conclusion from this study is that the absence of ictal recordings (usually the situation in MEG) did not affect the results.

In another 2006 paper, Knowlton (28) demonstrated in a blinded prospective study that, beyond the basic evaluations using scalp VEEG monitoring and MRI, MEG was more valuable than were the other noninvasive techniques, consistently demonstrating higher sensitivity and specificity values than FDG-PET and ictal SPECT in the evaluation of 72 patients subsequently evaluated with intracranial recordings. Furthermore, localization concordance with the ICEEG on a sublobar level was greatest with MEG.

In a study comparing a short-duration MEG with multiday scalp VEEG monitoring, Pataraia et al. (29) found MEG to be superior to long-term VEEG, with MEG localization in the resected area in 70%, but EEG concordant in only 40%. MEG evaluation has even been advocated as the screening tool of choice for frontal lobe epilepsy by a group in the Netherlands (30). Simultaneous MEG and EEG were recorded in 24 patients; in 18 patients, at least 6 spikes per hour were recorded. Not only were spikes much more frequent on MEG than EEG, but localization via MEG was successful in twice as many patients as EEG (14 vs. 7 patients).

MODELING OF THE SOURCE AND THE HEAD

The fundamental task of the MEG procedure and the accompanying analysis by the magnetoencephalographer is to solve the "inverse problem," that is, determination of the electrical source currents, which must have produced the magnetic field external to the head during the MEG recording. This is an "ill-posed" problem that depends on suitable models of the source and the head.

Both EEG and MEG measure exactly the same phenomena, namely, summated electrical currents produced by excitatory and inhibitory postsynaptic potentials (PSPs), primarily from the pyramidal cells in the upper layers of the cortex. Simplifying assumptions suggest that a single pyramidal cell can generate a 20 fA-m current (31); more recent computational models and experimental evidence suggest that a single cell may generate as much as 200 fA-m (32). As a rough approximation, 1 million PSPs are summed up; therefore, the modeling approach is to lump together these intracellular "impressed" currents flowing within the cell bodies and their corresponding potentials along their cellular walls into one overall "primary source" (33) called the "equivalent current dipole" (ECD). Thus, 1 million PSPs can theoretically generate a 20 nA-m to 200 nA-m ECD, or equivalently, 10 to 100 microamperes of current flowing along 2 mm of the cortical column.

This primary current model, comprising impressed currents within the cell bodies and their corresponding microcellular boundary potentials, is in contrast to the "macrocellular" model that emphasizes the location of the ECD in the brain with respect to the other "macro" boundaries, namely, the inner skull, outer skull, and scalp surfaces. The ECD creates a potential field pattern at all of these surfaces, which EEG records at the scalp. This same ECD and its corresponding potential pattern also create a current flow throughout the brain, in turn generating a magnetic field recorded as the MEG. The ECD is considered the "primary source," the potentials on the boundaries are the "secondary sources," and the currents generated by the ECD are the "secondary" or "volume"

currents. Thus, MEG measures the magnetic field due to the combined primary and secondary current flow, whereas EEG measures the potentials of the secondary sources at the scalp as generated by the ECD (31,33). Each modality therefore measures a different component of the same underlying neuronal activity, and the two combined are quite complementary.

As introduced, the ECD must be considered in relationship to the macro boundaries, where the conductivity changes markedly, which effectively creates secondary sources and alters the volume current pattern. This "head modeling" is a computational challenge in its own right, separable from issues of source modeling. The boundary with the greatest impact on source modeling is the skull, with a resistivity on order of 100 times greater than the scalp or CSF on either side. As reviewed elsewhere (34), many models and computational methods have been introduced on how to best model the impact of the skull on the EEG and MEG model. The oldest and simplest model considers the head to be a single perfect sphere, or a series of concentric spheres, that models the skull surfaces and scalp. Recent years, with the routine adoption of MRIs, have seen the use of more sophisticated models that tessellate these same surfaces with tiny triangular elements, yielding "boundary element modeling" (BEM).

Obtaining a correct solution for the EEG is difficult, involving substantial complexity of the head model. However, MEG is in fact mostly insensitive to any boundary other than the shape of the inner skull (34,35). Thus, MEG head modeling is generally far more robust than EEG to the inevitable head modeling approximations, and indeed, the sphere or series of overlapping spheres are often adequate for MEG head modeling (16). Clinical software packages generally offer either the sphere model or BEM solutions to the head modeling problem.

The ECD emphasizes a focal location on the cortex. By electromagnetic superposition, we can model more complex distributions of multiple or distributed sources by simply adding together the individual ECDs. A "multiple dipole model" assumes several distinct ECDs are (nearly) simultaneously active, whereas a "distributed" source model considers an extended contiguous region of cortex, such that a single ECD no longer suffices to explain the complexity of this broad region. The most widely used model in patients with epilepsy is the single equivalent current dipole (SECD) (21,36,37). This decision is partly based on extensive experience and validation, as well as the simplicity and speed of computation using this model. The other factor that makes the SECD so well suited in epilepsy is our clinical concept of curable focal epilepsy as arising from a small and restricted source, exactly the circumstance best modeled by the SECD.

If, as stated above, both MEG and the more familiar EEG record the same phenomenon, why is "source localization" so tightly associated with MEG? Because MEG modeling is more robust and the forward model so straightforward and computationally efficient, conventional MEG practice is to analyze the location of waveforms of interest using these computerized modeling techniques (e.g., the SECD). For assessment of the location of the electrical activity from EEG, computerized modeling methods are often problematic, and the electrical field distributions are easier to interpret visually without resorting to computational methods, as detailed in Chapter 7.

RECORDING TECHNIQUE

Whole-head MEG systems have a cylinder-shaped Dewar (container vessel) with a helmet-shaped concavity on one end, into which the subject's head is placed for measurement (5,31). Typically, 100 to 300 channels of magnetic sensors coupled to SQUIDs are arrayed over the inner surface of the concavity, immersed in the liquid helium within the Dewar, and maintained at a temperature of 4.2 K.

The equipment containing the Dewar with the MEG sensors (Fig. 76.1) is housed in a magnetically shielded room (MSR) in order to block magnetic interference coming from the environment. Active noise cancellation, that is, real-time feedback compensation, helps to counteract any residual interference, which penetrates into the MSR. Implanted devices such as vagal nerve stimulators, pacemakers, and responsive neural stimulators do not preclude MEG recording (38–40), but postprocessing to eliminate extracranial interference is required (e.g., spatiotemporal signal space separation [tSSS] (41).

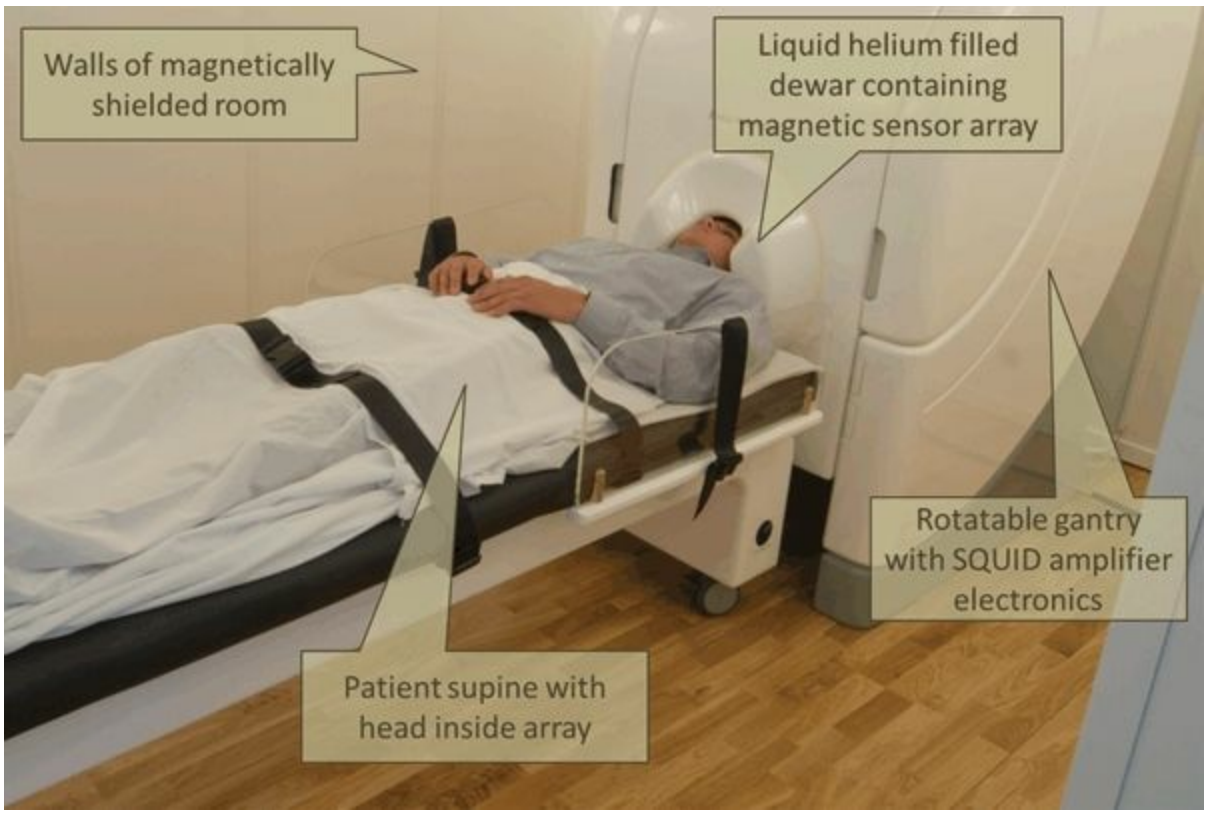

Figure 76.1. MEG can be recorded in either the supine or seated position. Patients are placed in a seated position when it is necessary to view a screen or to carry out a task requiring hand–eye coordination. In epilepsy patients, the supine position is used most often in order to promote sleep as an activation procedure for epileptiform activity. The MSR is large enough to accommodate a screen for presentation of visual stimuli or to allow a parent or caregiver to accompany an anxious patient during the MEG study.

In contrast to electroencephalography, where the electrodes are in fixed positions on the scalp, the MEG sensors bear only a vague relationship to brain regions. In addition, the location of the head within the Dewar varies from patient to patient, and it changes even during a recording session on an individual patient. The spatial relationships of the sensor locations to the brain are obtained indirectly based on three-dimensional digitization of several anatomical landmarks, for example, nasion and preauricular points, and by "head position–indicating" (HPI) coils that are affixed to the head with collodion. The locations of the HPI coils, as well as the locations of the anatomical fiducials, are carefully digitized so that their positions can be coregistered with the same landmarks ascertained from the patient's MRI.

Because the patient must remain relatively still during MEG recording, duration is limited and generally confined to the interictal state (24). Typical MEG monitoring times for epilepsy patients range from 40 minutes to a few hours. Continuous head-position monitoring and correction obviates the need for general anesthesia. Systems that can continuously monitor and correct for head movement have been developed (42,43) and clinically validated (44). Incorporation of these movement

compensation methods into commercial MEG systems has dramatically increased their practical clinical utility, especially in children who are unable to stay still. MEG is now extensively employed in children (45–51). While it is well known from EEG that epileptic spikes, which indicate the "irritative zone," are not always coincident with the ictal onset zone, localization by MEG is generally a robust indication of the epileptogenic zone (52,53).

ANALYSIS AND INTERPRETATION

It is important to review the raw MEG waveforms and to realize that these "brain waves" are analogous to the familiar EEG waveforms (Fig. 76.2). Experience as an electroencephalographer can be applied to MEG, and the fundamental concepts of field determination and source localization, previously established for EEG, are also similarly applied to MEG interpretation (54). Review of the recorded data, typically about 1 hour per patient, is accomplished by paging through 10-second pages in a process quite similar to the traditional electroencephalographic review of high-density EEG, employing several "montages" of MEG sensors. In contrast to EEG, MEG is inherently reference free (55).

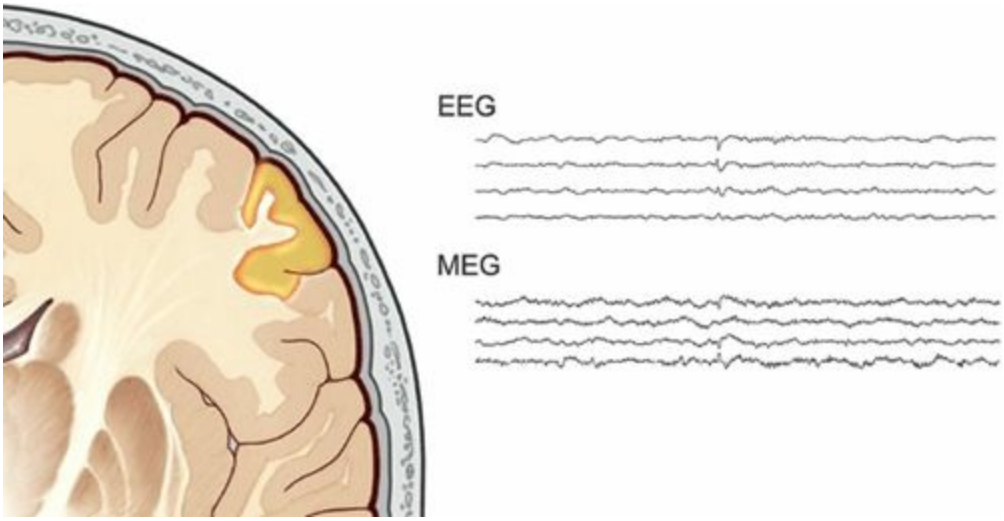

Figure 76.2. Epileptic activity is embodied as an electrical signal. The electrical current also generates a magnetic signal at the same time. Although the morphology and apparent polarity can be different, they record the same phenomenon. EEG is better at detecting radially oriented activity, while MEG sees tangential activity better. It is rare for MEG to be blind to a source, however, as some tangentially oriented cortex is almost always involved, as illustrated by the spike in this figure.

Although there are some differences between normal variants seen in MEG and EEG, identification of MEG spikes essentially follows traditional EEG criteria: Sharp contour, standing out from the surrounding background, following a physiologic distribution, and often presenting with an aftergoing slow wave. The EEG can be viewed separately (blindly if desired) or simultaneously (Fig. 76.3), but in the majority of patients, spikes and sharp waves are more copious on the MEG channels than on EEG (30,54). Since EEG and MEG record the same phenomenon, epileptic spiking for example, reports should include the results of MEG localization along with interpretation of the simultaneous EEG.

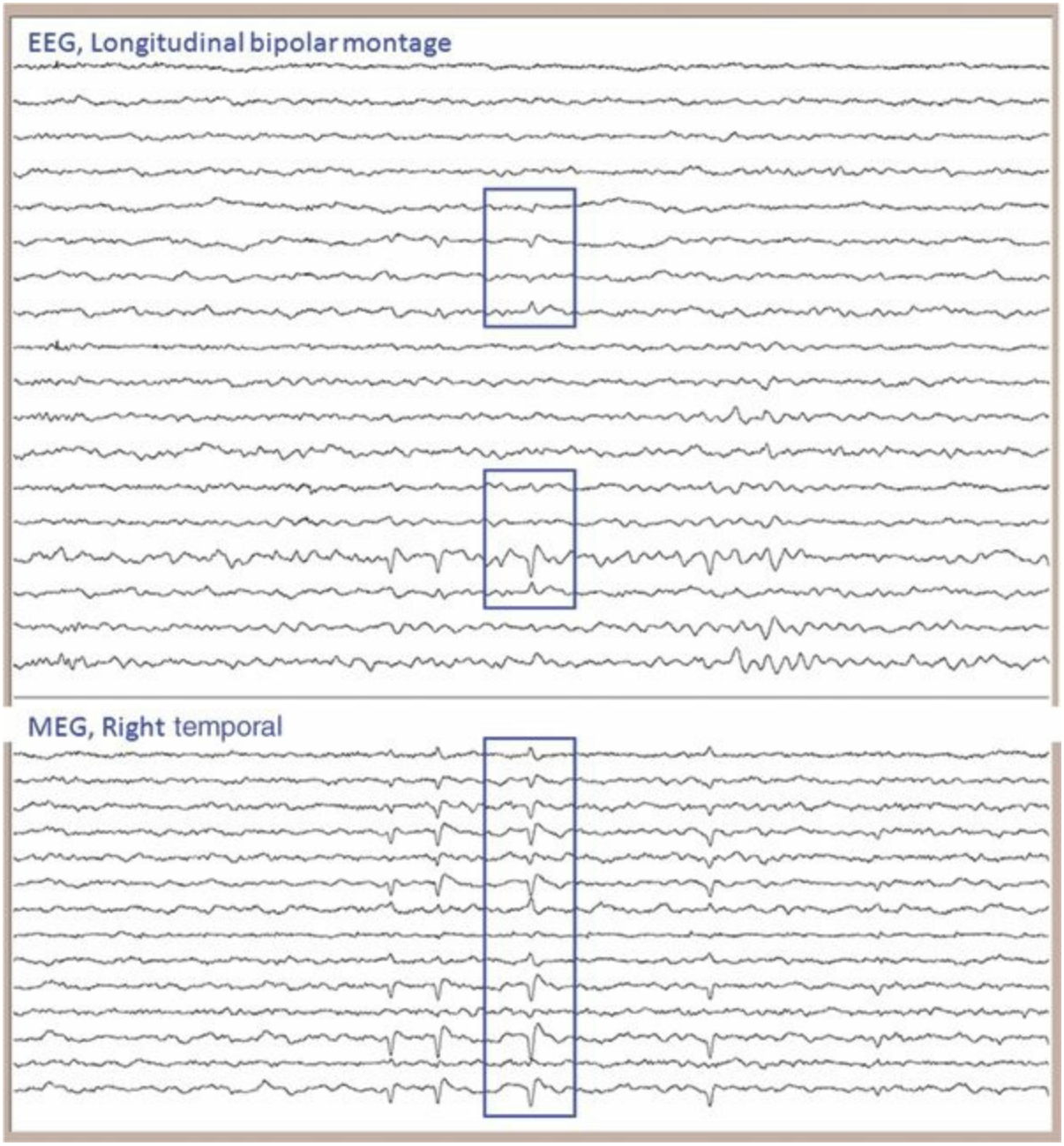

Figure 76.3. It is critical to review both the MEG channels and the simultaneously recorded EEG. They can be displayed and reviewed separately or, as shown here, together. The time window shown is 10 seconds (in this and all subsequent figures). It is important to ensure that the MEG can localize spikes habitually seen on the patient's previous EEG. Looking at only the MEG spikes which are coincident with EEG, however, would waste a wealth of information that the abnormalities seen only or more prominently on MEG provides.

After identifying and marking candidate spikes in the raw waveforms, the next step is to ascertain what part of the brain is generating these epileptiform discharges. Magnetic field distribution is usually displayed as an iso-field contour map with the aid of computerized calculation. The field distribution produced by a single current dipole is observed as a pair of influx and outflux field maxima distributed on each side of the dipole location (5). Assuming a single dipolar generator for a typical "dipolar" field distribution, an ECD is localized below the middle point of both influx and outflux field maxima. As introduced above in source modeling, this localization is carried out by synthesizing a putative dipole location in a plausible (typically spherical) head model, computing the theoretical field pattern associated with this location, comparing it to the actual measured field pattern, and then iteratively adjusting the location until theory and measurement achieve the "best fit."

The reason that the term "single equivalent current dipole" (or SECD) is encountered frequently

in MEG is often misunderstood. We look for a "dipolar field" distribution for reassurance that employment of the SECD model is appropriate. Modeling the source of cerebral currents as an SECD offers a convenient and rapid method for finding the location of that source. Dipole models are well established for known regional sources, such as somatosensory evoked responses. However, for sources of unknown origin like epileptic spikes, the interpreter must make sure that the SECD is reasonable, as the solution can be significantly biased by the interpreter's assumptions. Several automated approaches have been proposed to avoid such biases (56–58), but there has been scant utilization of such techniques in clinical work.

Computerized source estimation is more feasible in MEG than in EEG, because of the relatively simpler source and volume conductor models. Employing the vendor's (Elekta Neuromag, Helsinki, Finland) or third-party (such as CURRY [Compumedics, Charlotte, NC], BESA [MEGIS, Gräfelfing, Germany], etc.) software, epileptic spikes can be localized using an equivalent current source dipole model, on an interactive basis as each spike is encountered, in order to continuously build and test a hypothesis. Alternatively, spike identification can be carried out in a first pass, then source localization as a second pass. Our process is to carry out localization of individual spikes, and never to average spikes, because of the well-known pitfalls of spike averaging (59). Whether the localization of each spike is considered acceptable is based on:

- Presence of a dipolar appearing magnetic field pattern
- No simultaneously occurring artifact
- Stability of the localization with time (i.e., within a window of approximately 5 to 50 ms)
- Acceptable goodness of fit/confidence volume (usually a function of SNR)

Figure 76.4 illustrates the selection of a time point to localize, the magnetic field potential at the scalp surface, and SECD-modeled source of the sharp wave in the right parietal operculum.

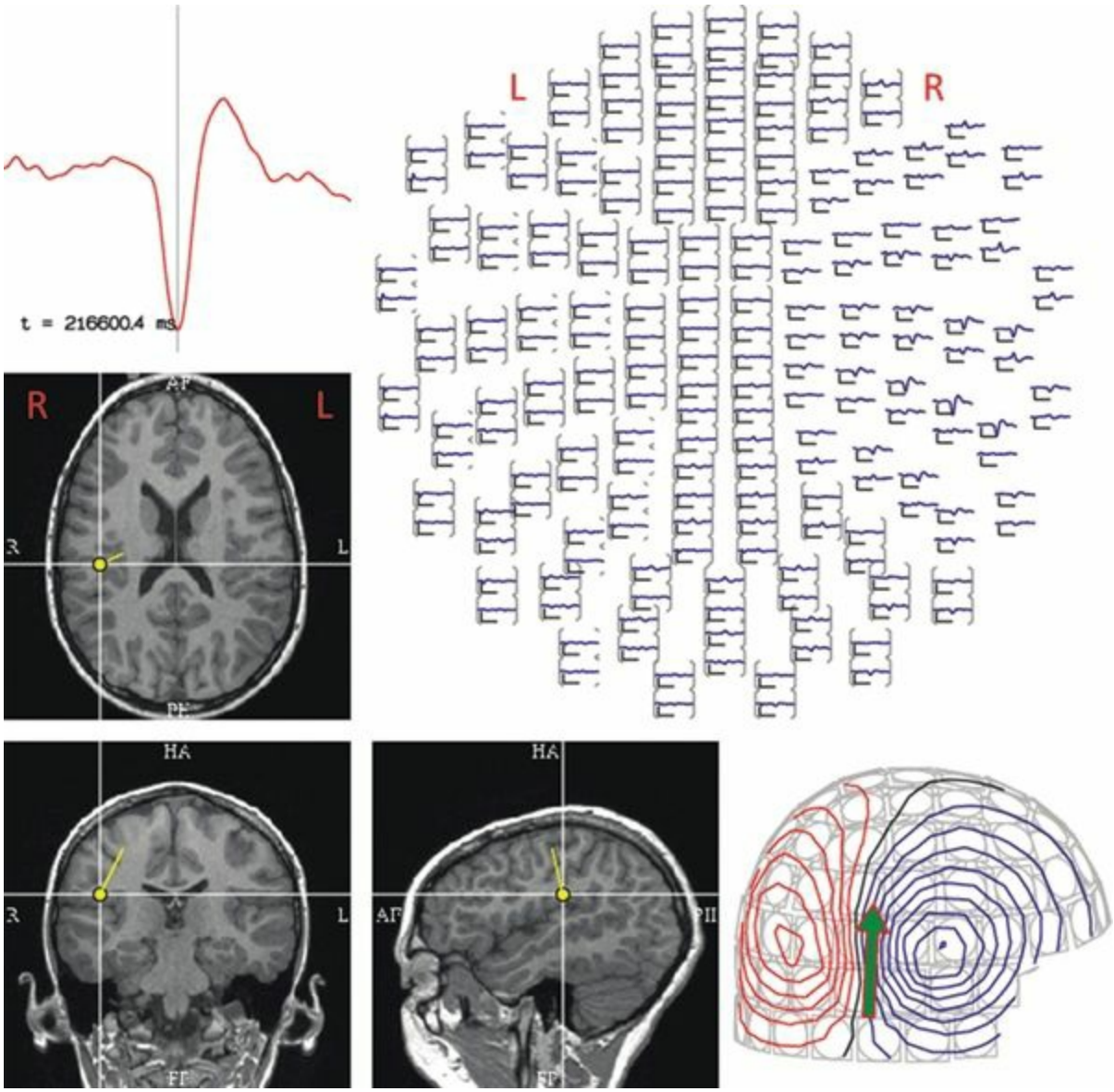

Figure 76.4. This figure depicts the analysis steps that are part of the SECD localization, for the sharp wave that is displayed in Figure 76.3. A representative signal from one of the MEG sensors is shown in the time-expanded graph in the upper left. In the top view of 204 (out of a possible 306) sensors (shown at the upper right), the magnetic activity of this same epoch can be seen maximally in the right temporal sensors. The magnetic field distribution over the head, shown in the lower right, with red indicating magnetic efflux (i.e., exiting the head) and blue showing influx (i.e., entering the head) illustrates a typical "dipolar field." The results of SECD analysis are instantly coregistered to the patient's MRI, implicating a source in the right parietal operculum. (R = right, L = left.)

Sources deemed to be acceptable are coregistered to the patient's own MRI, primarily based on three spatial fiducials, the nasion, and both preauricular points. Using these digitized landmarks and continuous monitoring of the position of the HPI coils during the recording, the location and orientation of the ECD solution can be coregistered with the anatomy and displayed graphically. Typically for epileptiform discharges, dipole locations of several representative spikes are shown (13,36,51,60–62). Some magnetoencephalographers try to superimpose as many as 100 dipoles on one image, in an effort to convey the extent or variability of spike distribution (63).

In electroencephalography, source localization has not yet been broadly accepted as a clinical tool (64). Visual, manual inference of the localization, aided by judicious montage selection (see Chapter 7), has served the electroencephalography community well. Part of the poor penetrance of source localization into the EEG community is due to the requirement for modeling the conductivity of all of the layers of the head and the inherent inaccuracy that this suboptimal modeling produces. In addition, the application of a large number of EEG sensors (sometimes called "high-density EEG") in

order to have sufficient data points for improved source localization has historically been a practical limitation. MEG suffers from neither of these limitations (65,66). Computerized source localization methods are always included as part of the analysis of MEG signals. Not only are the 300 or more time series difficult to analyze visually, but the underlying physics of MEG source modeling make it considerably simpler and more accurate than for EEG. Simple, single-layer, spherical head models have proven adequate for MEG source localization (16,67). In a study from Utrecht (68), spikes localized with MEG were closer to the presumed epileptogenic lesion (tubers) than those localized from EEG recorded at a separate time. In addition, agreement on identification of spikes was higher (as measured by kappa scores) on MEG (151 channels) than on EEG (mostly 85 channels).

Whether the localizations of all detected spikes are diagnostically significant is determined from:

- Number of acceptable dipoles
- Tightness of the dipole cluster
- Orientation of the dipoles
- Plausibility of the location

Studies of the localization accuracy of MEG have shown variable results, primarily dependent on the phenomenon under study (e.g., epileptic spikes vs. SEF), the location of the activity (e.g., dorsal, inferior, mesial), signal-to-noise ratio (which is dependent on room shielding, noise cancellation methods, etc.), localization technique (ECD vs. linear methods), and types of subjects (highly motivated volunteers vs. clinical patients). In studies employing phantoms, typical MEG accuracy for dipole localization is 2 to 4 mm, while EEG achieves only 7 to 8 mm (69,70). The higher spatial resolution is a function of not only the typically greater number of sensors used in MEG relative to EEG but, more importantly, an inherently more accurate forward model (70,71).

In either modality, however, it is important to distinguish the resolution of a single dipole versus a pair (or more) of dipoles, simultaneously fit to the same time slice. If the SECD is unsuitable due to high modeling error, one approach is to employ two synchronous dipoles. As theoretically examined previously (72), while the modeling error is naturally reduced (due to more modeling parameters), the stability of the location of two dipoles is dramatically diminished. The resolving ability of a pair of synchronous dipoles may be as poor as several cm (72). In practice, the vendor or commercial software may not provide automatic fitting procedures and error control of the multiple synchronous models, further complicating routine clinical application, in contrast to the single ECD. An alternative to multiple dipole modeling is to attempt modeling the non-SECD source as a “patch” constrained to cortex (73,74), but this approach also requires a much greater degree of sophistication in reliably and routinely extracting cortical surfaces from a patient’s MRI and then designing the parameters of the patch (e.g., the extent and pattern of assumed activation across the patch). Thus, for routine clinical modeling, the SECD remains the viable approach.

The temporal resolution of MEG is limited only by the sampling rate of the recording system, meaning that it is possible to record wide-band MEG signals all the way to the upper frequency limits of any brain process. This is particularly important in epilepsy where the high spatial and temporal resolution of MEG makes it possible to analyze propagation of epileptic activity and to evaluate the relationship of multiple areas of epileptogenicity, as the case in Figure 76.5 illustrates.

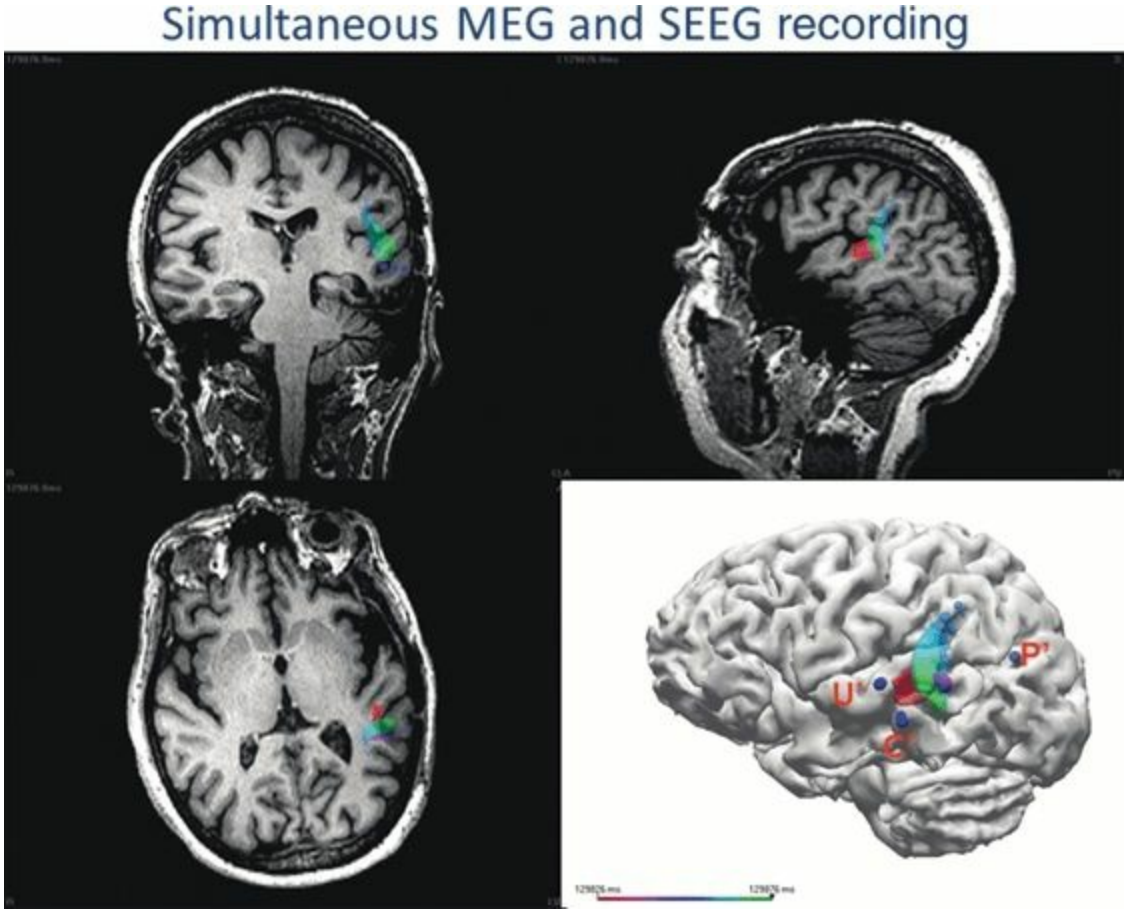

Figure 76.5. This 55-year-old patient had undergone a previous left temporal lobe resection, but automotor seizures with left temporoparietal seizure activity on scalp EEG activity recurred within 2 months. During her intracranial evaluation with SEEG electrodes, spike activity was seen at the C' and U' electrodes, but the main area of concern was at the P' electrode where the onset of seizures was noted. Because of the proximity of Wernicke area, the C' area was not a candidate for surgical removal, but U' could be removed. The patient was sent to the MEG laboratory for simultaneous MEG and SEEG recording with the following questions posed: Is C' entirely separate? Or is there some connection from P' to C' and U'? A sequential dipole fit was performed on spikes detected maximally at C' on the SEEG, evaluating the rising slope of the spike, and the trajectory of the entire 50 ms time course is shown by the multiple dipoles moving from red to green. The epileptic activity moves from the posterior bank of the resection to the posterotemporal gyrus (pink epoch), then back to the posterior bank of the resection, and onward to the posterior superior temporal gyrus (purple epoch), and finally, there is posterior propagation toward the occipital area (green epoch).

INDICATIONS AND BENEFITS IN EPILEPSY

MEG provides another localization data point in the workup of patients being considered for epilepsy surgery. Concordance or discordance of multiple-modality information helps to guide the therapeutic strategy, and it is helpful prognostically as well. In a study of 22 children with normal or minimal MRI findings, good outcome correlated with inclusion of MEG dipole clusters within the resected area, and none of the patients with scattered dipoles or with clusters not resected became seizure free (49). This study confirmed that the best outcomes following epilepsy surgery occur when VEEG and MEG localization results are concordant. Similarly for patients who underwent invasive recordings at our institution, 87.5% were seizure free when ICEEG and MEG were concordant and resected, but only 30% of discordant cases achieved seizure freedom (75).

In patients with tuberous sclerosis, MEG has been used to identify the “hot tuber,” that is, the most epileptogenic of the lesions, whose removal will likely result in the best surgical outcome, using either source analysis (76,77) or other techniques such as “synthetic aperture magnetometry” (78,79).

Especially in those patients with skull defects, as a result of either previous neurosurgery or

traumatic injury, EEG localization may be misleading. In these difficult patients, MEG's immunity to the effects of variations in conductivity offers reliable localization (50,80,81). MEG can also prompt a focused rereview of MRI, converting a nonlesional case into an MRI-positive case (82,83).

APPLICATION AND UTILITY IN COMPLICATED EPILEPSY PATIENTS

Because of the complexity of their evaluation and the difficulties encountered while trying to develop a treatment plan, the majority of the referrals to the MEG lab include patients with intractable epilepsy who are being considered for epilepsy surgery. The typical scenarios where MEG can be of particular benefit are when:

- Other noninvasive tests do not adequately localize the epileptogenic zone or produce conflicting results.
- The MRI is normal.
- More refined definition of the focus in relation to structural lesions is needed.
- Multiple or extensive lesions are present, and it is unclear which part of the lesion or adjacent cortex is epileptogenic.
- Preexisting cranial defects from previous neurosurgery or other alterations of the anatomy distort the localization provided by EEG.
- Contemplated surgical resection is adjacent to essential functional areas of the brain.
- Guidance for placement of intracranial electrodes is required.

The following three cases typify the challenges and results obtained in the evaluation of epilepsy patients with MEG.

Nonlocalizable on Scalp EEG

This 55-year-old, right-handed male, with the onset of seizures at age 25, has mostly nocturnal seizures consisting of asymmetrical tonic posturing. Previous EEGs were negative, MRI was negative, and the ictal SPECT showed bilateral frontal activation. During scalp VEEG monitoring, the findings included only extremely rare bifrontal spikes and nonlocalizable seizures. The sharp waves on MEG shown in Figure 76.6, however, were easily detected, and they were robustly localized in a tight cluster, which was subsequently confirmed by intracranial recording.

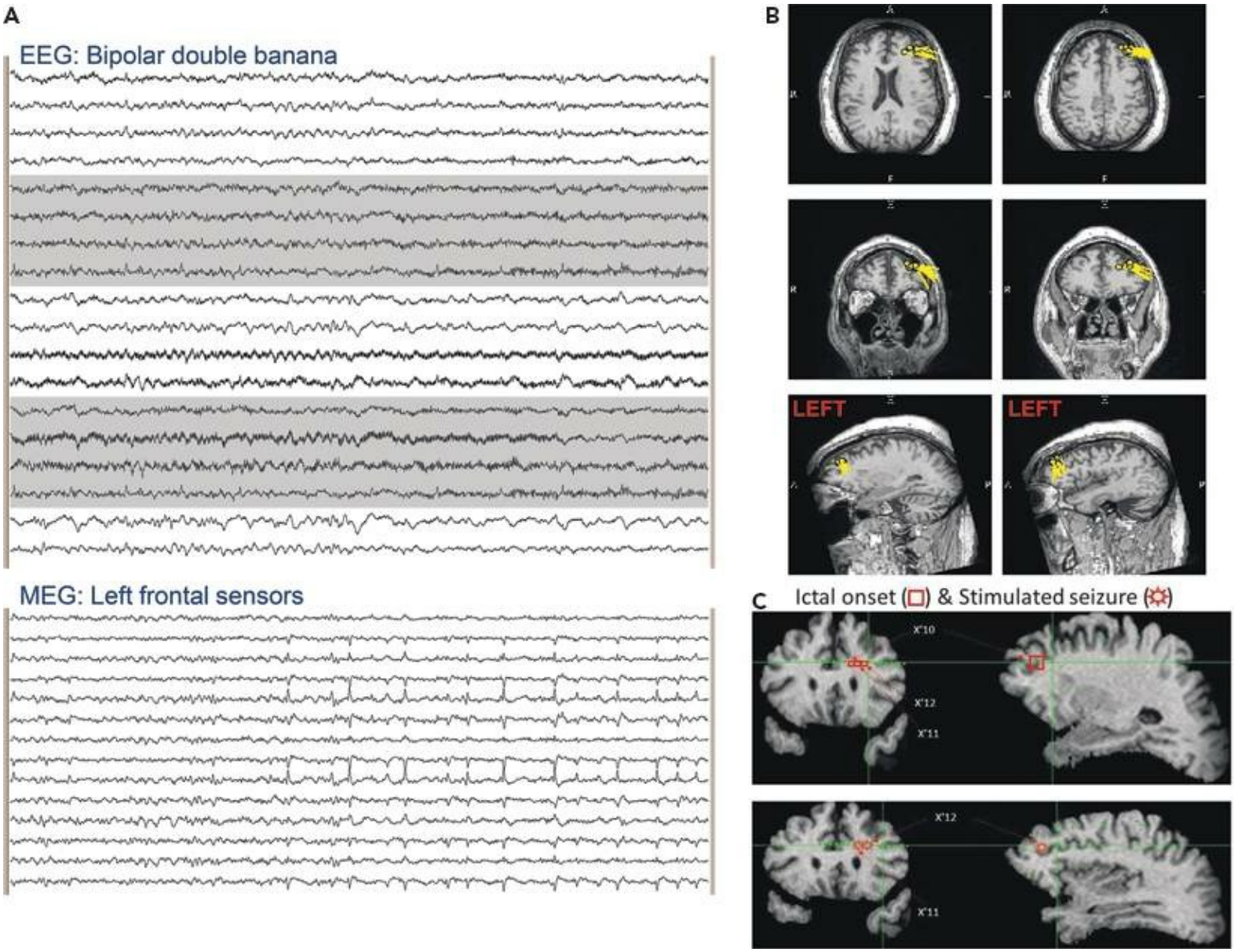

Figure 76.6. The EEG in (**A**) (standard longitudinal bipolar montage) shows no detectable epileptiform activity. The selected MEG channels from the same time epoch at the bottom of (**A**) show frequent sharp waves, which are localized to the left middle frontal gyrus and superior frontal sulcus in (**B**). The subsequent intracranial EEG investigation summarized in (**C**) demonstrates that the patient's seizures were coming from the same location. Eleven spontaneous seizures were captured with onset at SEEG electrode contacts X'10,11,12, and the seizures evoked by electrical stimulation were at the same location.

Multiple, Widespread Areas on EEG

In this 32-year-old patient, the EEGs displayed a multifocal picture that appeared to implicate several areas. The patient's seizure onset was at age 6, and his seizures consisted of abdominal aura, followed by dialeptic seizures, progressing to generalized tonic–clonic seizures. The MRI showed right hippocampal sclerosis, but the PET showed hypometabolism of the both medial temporal lobes, as well as the posterior aspect of the right temporal lobe. The results in Figure 76.7 illustrate how MEG was able to clarify the propagation of the epileptic activity, because of its high temporal and spatial resolution.

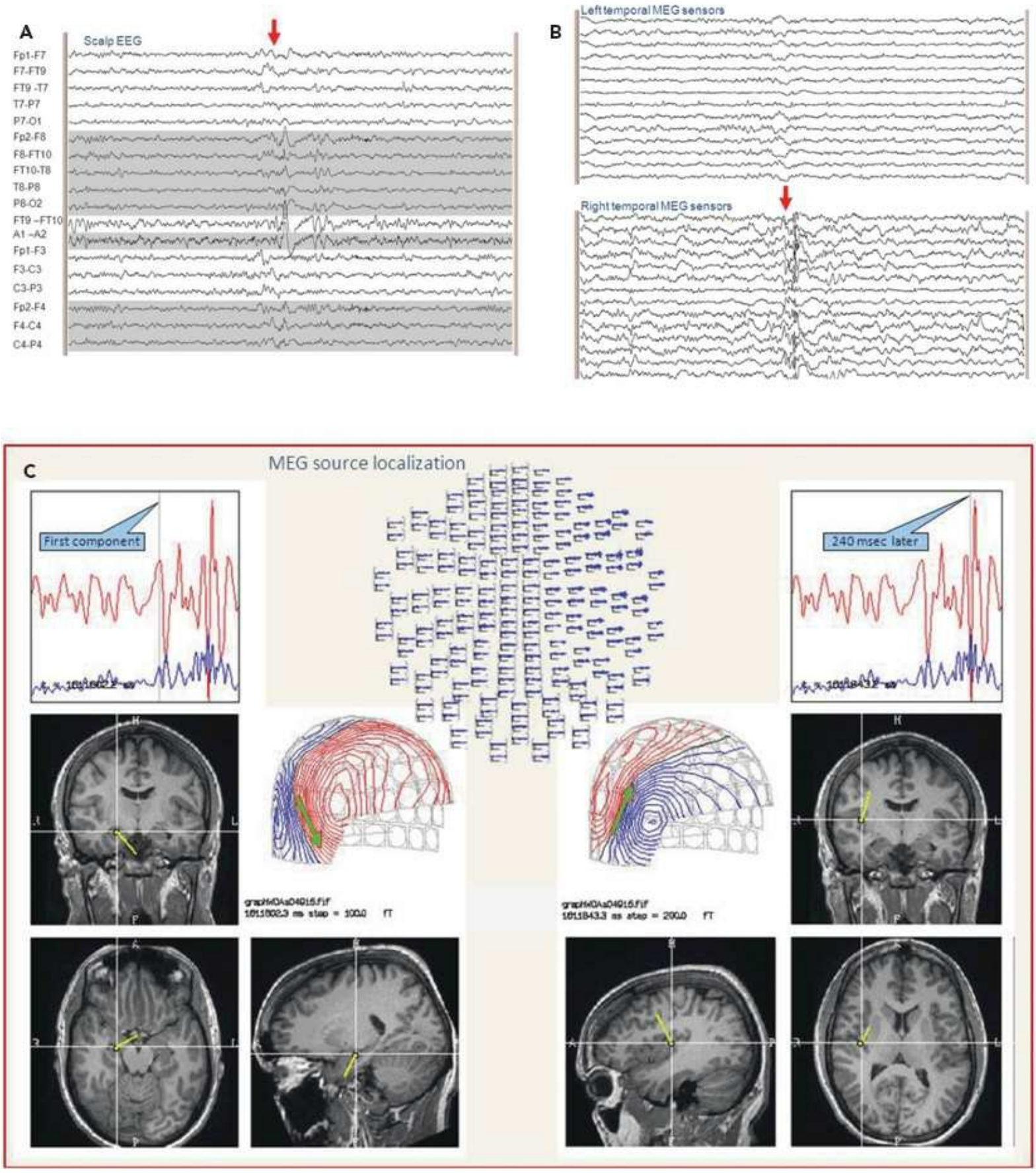

Figure 76.7. The EEG, in (**A**), shows polyspikes with a complicated distribution in the right frontotemporal region. The selected MEG sensors seen in (**B**) during the same time epoch show clear definition of the multiple components of the polyspikes. The localization of the sequence of these components shown in (**C**) clarifies the spread from the right hippocampus to the insula.

Ictal MEG Recording

Although seizures in the MEG are relatively uncommon, they can be serendipitously captured. At the Cleveland Clinic, this occurs in approximately 10% of the patients referred to the MEG laboratory, and when they occur, these recordings of ictal onset by MEG can yield precise localization of the epileptogenic zone. The patient illustrated in Figure 76.8 had six seizures during MEG recording, one of which was a clinical seizure, manifest as a left somatosensory aura, and the rest showed no clinical signs. The MEG demonstrated a clear difference, with the seizures accompanied by clinical manifestations propagating from the posterior middle frontal gyrus to the postcentral gyrus. This propagation pattern was confirmed when the patient underwent intracranial monitoring with subdural grid electrodes.

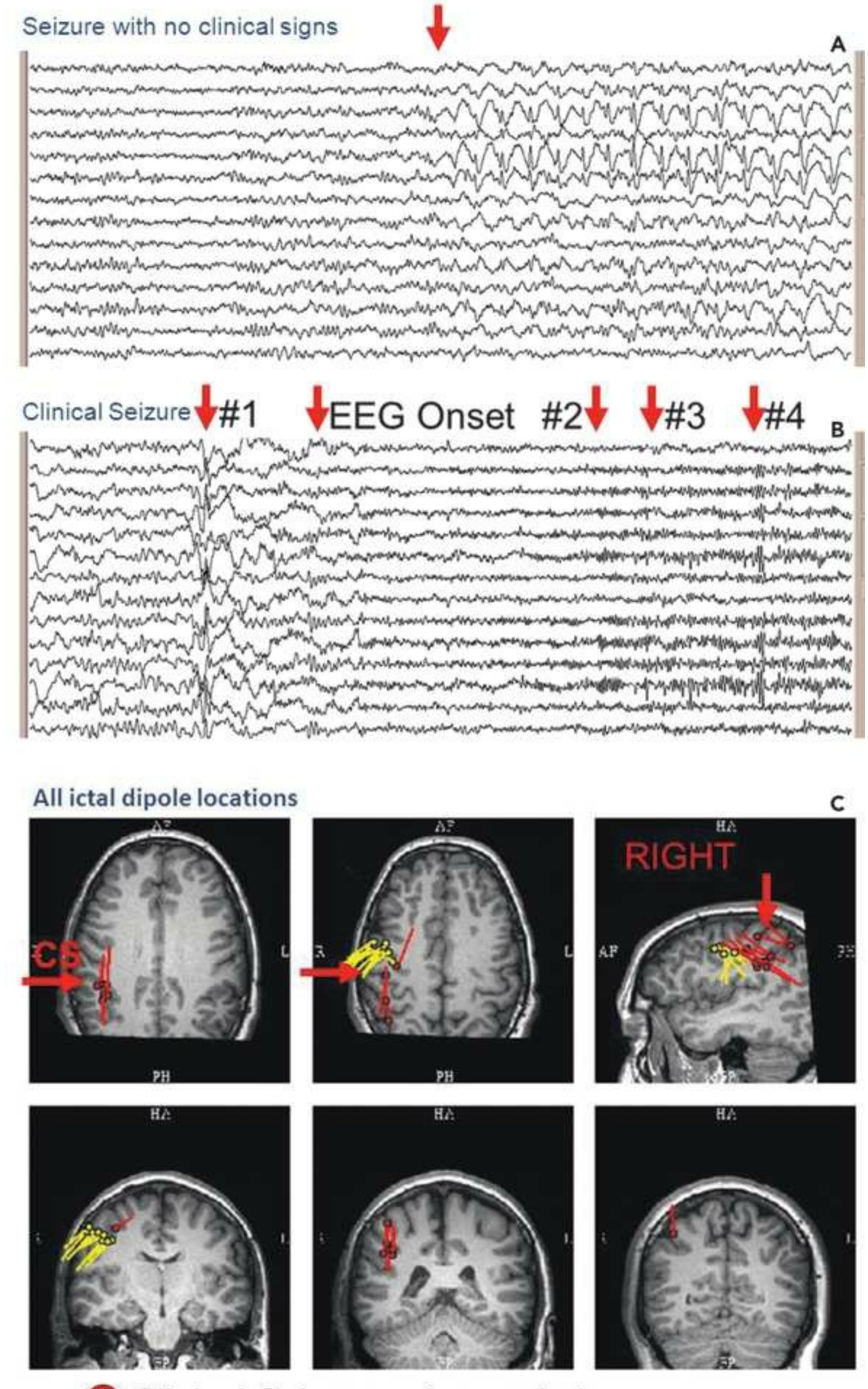
MEG waveforms in the right parietal sensors during two different seizures
Seizure with no clinical signs
A
Clinical Seizure
#1
EEG Onset
#2
#3
#4
B
All ictal dipole locations
C
RIGHT
Clinical Seizures, 1 recorded
NCS Seizures, 2 dipoles each from 5 recorded

Figure 76.8. An ictal MEG recording captured six seizures in this patient. Five, with no clinical signs, ranged in duration from 10 to 50 seconds, one of which is shown in (**A**). The seizure without clinical signs showed spike-and-wave complexes, maximally in the right parietal sensors. The clinical seizure on MEG, shown in (**B**), was marked by background attenuation, the development of an increasing beta discharge, followed by polyspikes in the right parietal sensors. Localization of the portions of the clinical seizure indicated by the arrows was performed and is illustrated by the red dipole locations in (**C**). From each of the seizures without clinical signs, two time points each were localized, indicated on the figure by the yellow dipoles. Location of the central sulcus is marked by "CS." The propagation, which is shown by the red dipoles, explains the reason for the clinical manifestations (**B**).

When the noninvasive data are not entirely concordant, or when the surgical strategy requires further localization, implantation of intracranial electrodes may be contemplated (see Chapter 81 in this volume). MEG's role in providing guidance for the implantation is extremely important in order to assure adequate sampling of the epileptogenic areas.

SENSITIVITY AND YIELD

MEG has a different spatial sensitivity than EEG and generally does show more spikes than scalp EEG (30,54,84). The sensitivity of MEG is higher for tangentially oriented current flow (55,85–88). However, Hillebrand and Barnes (89) found that <5% of the cortical surface is within 15 degrees of the radial orientation, and at that point, the strength is 25% of that of the tangential dipole. In a more recent study (90), potential sources were distributed over all possible cortical areas. A cortical patch was defined as radial if the orientation angle was within ±10 degrees from the scalp surface normal, and it was defined as tangential if the orientation angle was within ±10 degrees of a line parallel to the scalp surface. The ratio between the number of tangential and radial sources was approximately 3:1. Therefore, for realistic sources in heads, which are never exactly spherical, MEG is very rarely blind to a source due to orientation.

Comparison of the sensitivity of MEG versus EEG to epileptic spikes has been investigated by many authors (24,71,91–93), some concentrating on the temporal lobe (94), over an extended period of MEG's history. Recent studies looking blindly at EEG and MEG, which were recorded simultaneously, have consistently shown a higher sensitivity for MEG (54,95–97). An example of the oft-reported "MEG-unique" spikes is illustrated in Figure 76.6.

It is important to understand that not all epileptic discharges produced in the cortex are detectable externally by either EEG or MEG. Certainly, there are prominent spikes, which are recorded easily by intracranial electrodes, but which are invisible on MEG. The combination of signal amplitude, volume of discharging tissue, and distance to the sensors determines the degree to which the MEG sensors can see neural activity (10) as illustrated in Figure 76.9 (98). The strength of the magnetic field decreases in proportion to the square of the distance from the current dipole, according to the Biot–Savart law. Therefore, the sensitivity of MEG to deep sources is similar to scalp EEG (87). In addition, there are some unusual situations where almost none of the sources are tangentially oriented, such as in polymicrogyria, where MEG's sensitivity will be poor (88).

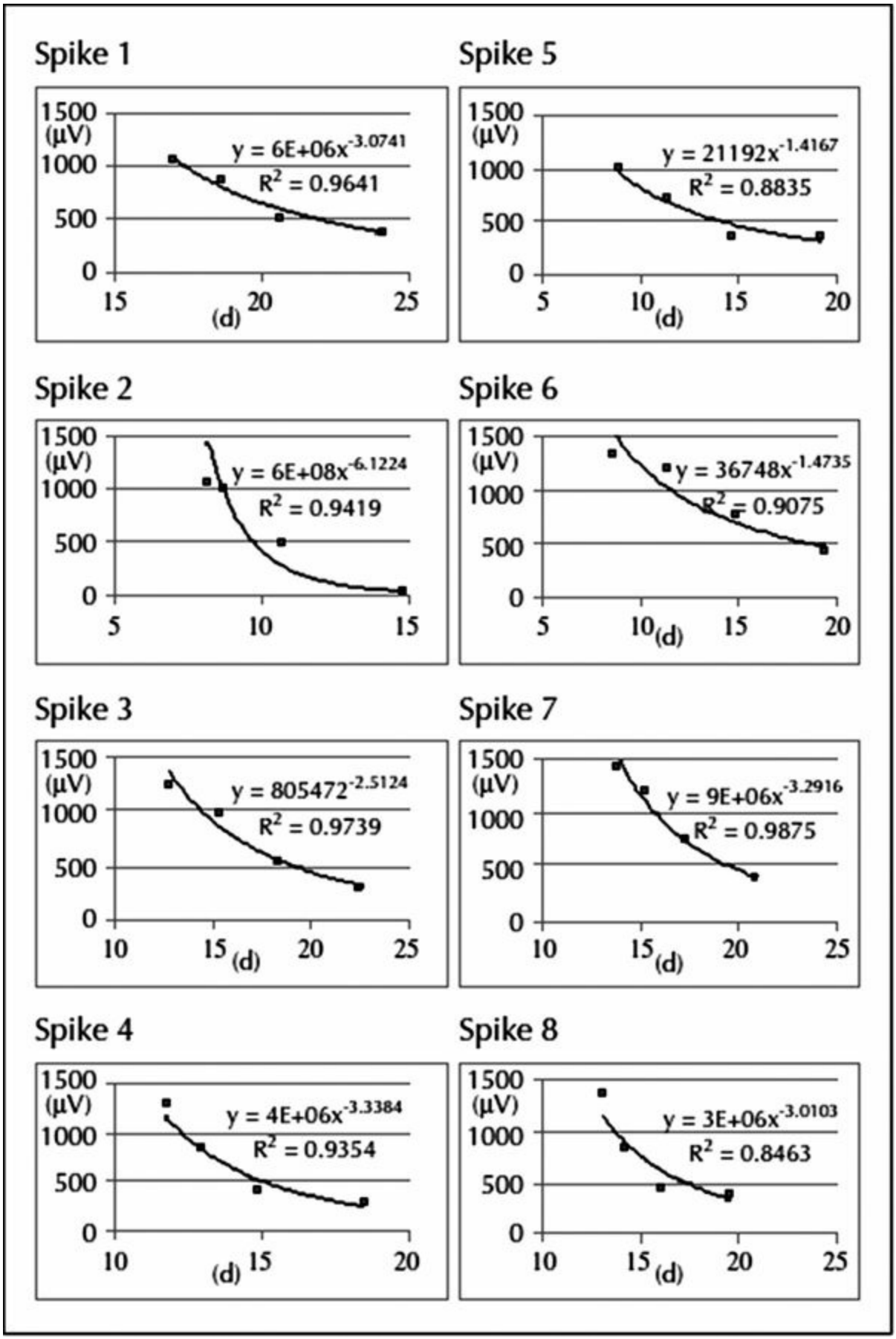

Figure 76.9. Results of the analysis of eight spikes from different locations recorded simultaneously with MEG and SEEG, showing the relationship between the electrical amplitude (μV; y-axis) on each SEEG contact and the distance (d; mm; x-axis) from each spike dipole to the SEEG contacts. The falloff as a function of distance was well approximated by a quadratic function with a high R^2 value (>0.80) for all of the simultaneously recorded spikes. The MEG dipole locations reflect the center of the discharge, and the SEEG contacts detect this activity via volume conduction. (130)

Although generally the focus of magnetoencephalography in epilepsy is on localizing interictal spikes, other forms of analysis can be very helpful. Pathologic slow waves can be localized, especially in patients with structural lesions, as an indication of the epileptic substrate (99–101). Techniques based on an assumption of abnormal connectivity can localize epileptogenic areas even in the absence of any frank spikes (102,103).

MAPPING OF ELOQUENT CORTEX

Since another very important task during preoperative evaluation of epilepsy patients is the identification of eloquent cortical areas nearby the proposed surgical resection, MEG fulfills this second purpose through its functional mapping capability. Functional MRI localization of eloquent areas based on hemodynamic activation (see Chapter 73) has high resolution, but may be difficult in children where the MRI can produce claustrophobia, and parents cannot easily accompany and comfort the child (104,105). Because sensory and motor functions are close to the central sulcus, because the orientation of the current flow is in the tangential direction that MEG is best at recording, and because the areas activated by typical evoked field paradigms are small regions easily modeled by SECD, MEG is especially good at localization of somatosensory and motor cortex.

Evoked magnetic fields (MEFs) are generated using stimuli very similar to those used in the familiar evoked electrical potentials. Magnetoencephalography shares with EEG high temporal resolution, but its chief advantage for mapping is in its high spatial resolution. MEFs are therefore done for localization; unlike electrical EPs, MEF latencies and latency asymmetries are not typically employed to screen for abnormalities. The precision and validity of MEFs in the primary modalities of somatosensory evoked fields (106–108), auditory evoked fields (109,110), and visual evoked fields (111–113) have been well established. The potential evoked by voluntary movement of a single finger, widely used in MEG to map the motor cortex (114,115), produces a complex neuromagnetic response: first, a decrease of beta and a simultaneous movement-related increase in gamma are seen followed by a rebound in beta above baseline, amenable to coherence analysis (116). Higher cortical functions such as language are also amenable to MEG source localization (117–123).

FUTURE OPPORTUNITIES FOR MAGNETOENCEPHALOGRAPHY

MEG is primarily an advanced tool, with availability limited to multidisciplinary epilepsy centers, used in selected patients as described above. The number of centers with MEG capability is increasing, however, and greater reliance on MEG as a screening method has been advocated (30). Furthermore, more compact MEG systems are in preparation making more widespread use of MEG more feasible in the future. Recently, MEG has been heavily utilized as a tool for investigating connectivity (124). In epilepsy, the hypothesis, which drives this approach, is that epileptogenic regions are hyperconnected. Investigation may employ simple measures of coupling of power in various frequencies (125) or coherence (102,126). Research utilizing more advanced methods such as imaginary coherence (127,128) or phase coupling (129) is also being evaluated for their clinical utility.

Although MEG has not yet been prospectively demonstrated to replace invasive recording, MEG

has the potential to change the way that we interpret depth/SEEG recordings in the multidisciplinary environment. In a study examining several cases of simultaneous depth and MEG recordings, Kakisaka et al. (130) showed that intracranial electrical source activity falls off in a logarithmic manner, and MEG can help to clarify confusing ICEEG results (Fig. 76.10) and may help to prevent inaccurate ICEEG interpretations that lead to surgical failure.

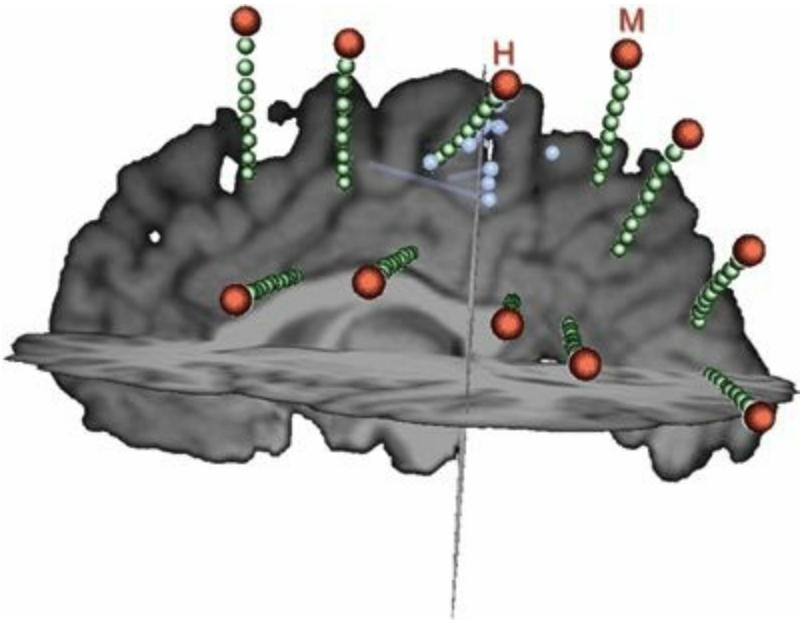

Figure 76.10. During intracranial EEG evaluation in this patient, interictal and ictal discharges were seen over a wide area of SEEG contacts (green), most prominently on several contacts of the H and M electrodes. As demonstrated quantitatively in Figure 76.9, the activity recorded by SEEG drops off rapidly with distance from the source. As seen in this figure, the spacing between SEEG electrodes is substantial. MEG can help to "fill in the gaps" produced by the sparse intracranial electrode coverage. In this case, the MEG localization (dipoles shown as blue spheres and their orientation indicated by blue rods) suggests that the abnormal activity is coming from between the H and M electrodes.

CONCLUSION

MEG is particularly valuable during the evaluation of epilepsy patients when other noninvasive measures (intensive inpatient VEEG monitoring, MRI, and PET) are not concordant or have not yielded a consistent hypothesis. MEG has distinct advantages over EEG for the purposes of precise localization (17), especially in patients with skull defects or when a focal abnormality is suspected, but the EEG appears to show bilateral synchrony. MEG has a higher sensitivity for the detection of epileptic spikes (30,38,44,62,98,130–133), and MEG's ability to precisely localize the epileptogenic zone is superior to scalp EEG (17,30). In some studies (60,61,134,135), MEG has been shown to reduce the need for invasive monitoring. Although MEG cannot completely replace invasive EEG recordings, its use may guide the placement and tailor the design of intracranial investigations, and in some patients obviate unnecessary invasive evaluations.

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CHAPTER 77 MRI POSTPROCESSING TECHNIQUES AND CLINICAL APPLICATIONS

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INTRODUCTION

In the presurgical evaluation of drug-refractory epilepsies, the importance of accurately detecting and delineating an MRI lesion cannot be overstated. Discovering a previously undetected lesion can drastically change the presurgical planning and surgical outcome. The lack of a lesion on MRI has consistently been shown as a predictor for surgical failure (1,2). In contrast, MRI-positive surgical candidates are two times more likely to become seizure free after epilepsy surgery than MRI-negative patients (3).

Although visual inspection of high-resolution MRI can detect a fair number of epileptogenic lesions, such as hippocampal sclerosis (HS) and focal cortical dysplasia (FCD), conventional visual analysis can be quite limited in its ability to recognize the existence and extent of subtle lesions. However, with the advent of advanced MRI acquisition and postprocessing techniques, novel quantitative image analyses can increase the yield of visualized structural lesions relevant to the underlying epilepsies in a sensitive, replicable, and rater-independent fashion, and thus significantly complement conventional MRI visual analysis. In this chapter, we aim to summarize the state-of-the-art image postprocessing methodologies in the context of presurgical evaluation and epilepsy research.

OVERVIEW OF IMAGE PROCESSING

A typical MRI epilepsy protocol usually includes a 3D T1-weighted volumetric acquisition, coronal thin-section T2-weighted and fluid-attenuation inversion recovery (FLAIR) acquisitions, in addition to other sequences. Of these, the volumetric sequences provide exquisite anatomical detail from contiguous thin slices that can be reformatted to any plane; as such, these sequences are usually the most useful for postprocessing. A first step for most image processing methods is correction of MR field inhomogeneity, which causes undesired variation in signal intensity across the image. The next step is alignment of a given image volume to a 3D stereotactic space, which enables comparison of brain structures among different individuals. Large population control averages are generally used as the common reference (4). Importantly, references for adults should not be used to study pediatric cohorts. Subsequently, each voxel is differentiated and classified into tissue classes, primarily gray matter (GM), white matter (WM), and cerebrospinal fluid. Tissue classification and segmentation provide the basis for further analyses such as voxel-based morphometry (VBM), shape analysis, and texture analysis.

VBM has been one of the most popular postprocessing algorithms to date. This fully automated technique extracts GM and WM maps from individuals to make statistical comparisons with respect to a normal database (5). Contrary to methods restricted to a selected brain area at a time, VBM detects structural differences throughout the brain without a priori assumptions (6). An important step in VBM analysis is smoothing of the segmented GM and WM maps with an isotropic Gaussian kernel. Image smoothing reduces variability of individual anatomy and inaccuracies from spatial normalization, therefore increasing the signal-to-noise ratio. In the smoothed images, each voxel represents a weighted average of the neighboring voxels (i.e., GM and WM "concentration"). Importantly, the size of the Gaussian kernel should correspond to the mean size of the abnormality to be detected. Statistical inference is performed using the general linear model allowing for testing of GM/WM changes related to a specific variable. VBM was originally developed to perform group analysis, but it can be optimized to assess structural abnormalities on an individual level.

MRI POSTPROCESSING IN TEMPORAL LOBE EPILEPSIES

HS is the most frequent cause of refractory temporal lobe epilepsies (TLE) and the most frequent pathologic substrate in patients with TLE (7). The primary features of HS on the MRI are loss of volume, loss of internal architecture, and signal hyperintensity on FLAIR and T2-weighted sequences (8–10). Experienced raters generally identify visually obvious HS; however, quantitative postprocessing analysis can reliably detect subtle and bilateral hippocampal abnormalities, as well as cortical abnormalities accompanying HS.

Volumetry

Before calculating hippocampal volume, segmentation of the hippocampus needs to be performed. Manual segmentation of the hippocampus is accurate, reproducible, and able to detect volume loss with a high degree of sensitivity (11,12), which typically involves the hippocampal head and body, as well as the entorhinal cortex in patients with TLE (11). Manual segmentation is, however, time consuming and rater dependent. An increased demand to study large cohorts of healthy and pathologic brains has motivated the development of automated segmentation procedures. Most methods employ deformable (13,14), appearance-based (15), or atlas-based approaches (16). Although automated segmentation algorithms in healthy controls have generally performed satisfactorily, in TLE patients, the agreement between manual labeling and automated segmentation has been relatively low. The reduced accuracy may result from the observation that about 40% of TLE patients show hippocampal "malrotations" (17), that is, atypical shape and positioning of the hippocampus that are mainly characterized by a rounder appearance and atypical orientation of the hippocampus, and an abnormally deep and verticalized collateral sulcus (18–20). A recently developed surface-based multitemplate automated algorithm (21), however, achieved a level of accuracy in TLE patients virtually identical to healthy controls, with submillimeter precision.

Shape Analysis

Visualization of hippocampal shape may extend evaluation to details not evident by measurements of the hippocampal volume. Using a large-deformation high-dimensional mapping method (HDM-LD),

Hogan et al. studied 30 TLE patients with histopathologically confirmed HS and their age-matched controls. The asymmetry in the shape of the hippocampus was studied by forming an asymmetry vector field based on flipping the right-side hippocampal surface to the left side in each patient. The HDM-LD technique showed significant inward deviation in the Sommer sector of the sclerotic hippocampi. Another established method to quantify fine-scale local position and curvature in the hippocampus is through a medial axis model (22,23). This methodology was applied to 88 patients with TLE, 78 patients with malformation of cortical development, and 46 age- and sex-matched healthy controls (24). The analysis of curvature revealed medial bending of the posterior hippocampus in patients with TLE, compared with a superomedial shift of the hippocampal body observed in patients with malformation of cortical development (24).

An extension of shape analysis to adjacent convexities often shows a pathologic relationship. For example, hippocampal malrotation in TLE is associated with increased complexity of the temporolimbic cortices, encompassing parahippocampal, temporopolar, insular, and frontoopercular regions, implying that neurodevelopmental factors may play a role in the epileptogenic process of TLE (20).

Voxel-Based Analyses

VBM has consistently revealed GM reduction extending beyond the atrophic hippocampus, not only the adjacent parahippocampal and anterior temporal regions but also the frontal lobe, suggesting a disruption of frontolimbic pathways. The widespread abnormalities have been shown to be associated with seizure frequency (25), epilepsy duration (26,27), precipitating factors (28), and cognitive dysfunction (29–32). Patients with persistent seizures after removal of the hippocampus may present a more widespread neocortical GM volume loss (33,34).

The sensitivity of voxel-based analysis can also be increased by directly mapping T2 relaxation times, that is, analyzing absolute T2 value rather than the T2-weighted signal. In the vast majority of TLE patients with hippocampal atrophy, T2 relaxation times within the hippocampal GM ipsilateral to the focus have increased by at least 10 ms when compared to controls (35–37). Using a dual-echo sequence (38,39), Bernasconi et al. studied the hippocampal T2 relaxation times of 11 patients with unilateral TLE and no evidence of atrophy on the volumetric MRI (40). More than 80% of these patients exhibited abnormally high T2 relaxation times in the hippocampus ipsilateral to the epileptic focus, suggesting that T2 mapping can provide additional lateralizing information in TLE patients with normal MRI (40).

Pell et al. proposed a voxel-based relaxometry approach that provides an unbiased general search of the whole brain volume and does not require manually drawn regions of interest at the hippocampus. Their approach was tested in 19 TLE patients with unilateral HS and in 38 healthy controls and showed comparable performance to conventional region-of-interest analysis (41).

Cortical Thickness

Bernhardt et al. assessed the reproducibility of neocortical thinning and its clinical significance with respect to surgical outcome in TLE (42). They evaluated 58 TLE patients with hippocampal atrophy on volumetry and 47 TLE patients who had normal hippocampal volumes. In both groups, similar topology and rates of neocortical thinning were found predominantly in frontocentral, temporal, and cingulate regions, demonstrating that static and dynamic effects of epilepsy similarly impact the

neocortex of patients with or without hippocampal atrophy (42). This study also examined temporal changes in cortical thickness in TLE patients with multiple scans, showing progressive cortical thinning in the frontal lobes. The cortical thinning was found to be significantly larger in patients with ongoing seizures than in patients with controlled seizures, providing compelling evidence that TLE is a progressive disorder (42).

MRI POSTPROCESSING IN EXTRATEMPORAL LOBE EPILEPSY

In extratemporal lobe epilepsy (ETLE), FCD is the most common pathologic substrate underlying patients undergoing epilepsy surgical evaluation (43). FCD is also the most common underlying pathology in epilepsies with apparently normal MRI (44). Typical MRI findings of FCD include indistinction of gray–white junction, T2/FLAIR cortical signal abnormality, T1 cortical signal abnormality, abnormally thickened cortex, and subcortical T2/FLAIR abnormality. FCD lesions are generally much more difficult to detect compared with other types of lesions, as they can be quite subtle with small sizes, appearing buried in the complex convexities of the neocortex. Given the practical constraints of time, MRI readers may miss lesions that are only discerned with increased scrutiny. This is especially problematic when noninvasive clinical data, such as scalp EEG and semiology, do not point to a specific area. Thus, MRI readers lack a testable anatomic hypothesis, and subsequently the study may be read as negative. Under these circumstances, a whole-brain MRI postprocessing technique directing the reader's attention to potentially dysplastic abnormalities may prove to be essential. Another advantage of MRI postprocessing for the neocortex is that it operates in 3D. This allows the simultaneous consideration of information from consecutive slices, whereas conventional visual analysis examines the brain volume one slice at a time, and therefore requires a high level of expertise to synthesize information from consecutive slices.

Voxel-Based Analyses

Several studies have applied VBM on T1-weighted volumetric MRI to detect FCD in individual patients. In patients with MRI-visible FCD, increase in GM concentration colocalized with the lesion in 63% to 86% of cases (45–50). Increased sensitivity tends to be associated with an increase in false-positive results. Practically, balance between sensitivity and specificity may be achieved on a case-by-case basis. When there is an a priori hypothesis based on clinical and EEG data to confine the analysis to a certain brain region, one may opt for maximal sensitivity; whereas when EEG or other functional imaging data do not point to a region of interest, it is essential to eliminate false positives and opt for maximal specificity. In addition to colocalizing the lesions, VBM studies consistently reported GM abnormalities extending beyond the visible FCD, sometimes distant from the epileptogenic area (47–49,51,52). In the absence of false positives in normal controls, these changes could be due to occult dysplastic regions undetectable by visual analysis or represent an abnormal gyration (48). It is also conceivable that these changes may potentially become active at a later stage and cause seizure recurrence after surgery (53). It would be thus advisable to interpret the significance of structural abnormalities beyond the primary structural lesion in relation to electroclinical data and functional imaging modalities.

Quantitative MRI contrasts such as T2 relaxometry, double inversion recovery, and magnetization transfer ratio imaging have yielded 87% to 100% sensitivity in patients with MRI-visible FCD;

however in patients with a negative MRI, the sensitivity was reported to be <30% (51,54–56). Consistent with the VBM studies, signal changes outside the putative epileptogenic zone were found in 6% to 42% of patients (51).

Computational Models of FCD

Computer-based models, first introduced by Bernasconi et al. (57), can be generated to search for the distinctive morphologic characteristics of FCD on MRI. Enhancement of the GW junction blurring has been used to detect subtle cortical malformations (58–60) and can provide helpful information in patients with MRI interpreted as negative using conventional visual analysis (58,61,62), as illustrated in Figure 77.1.

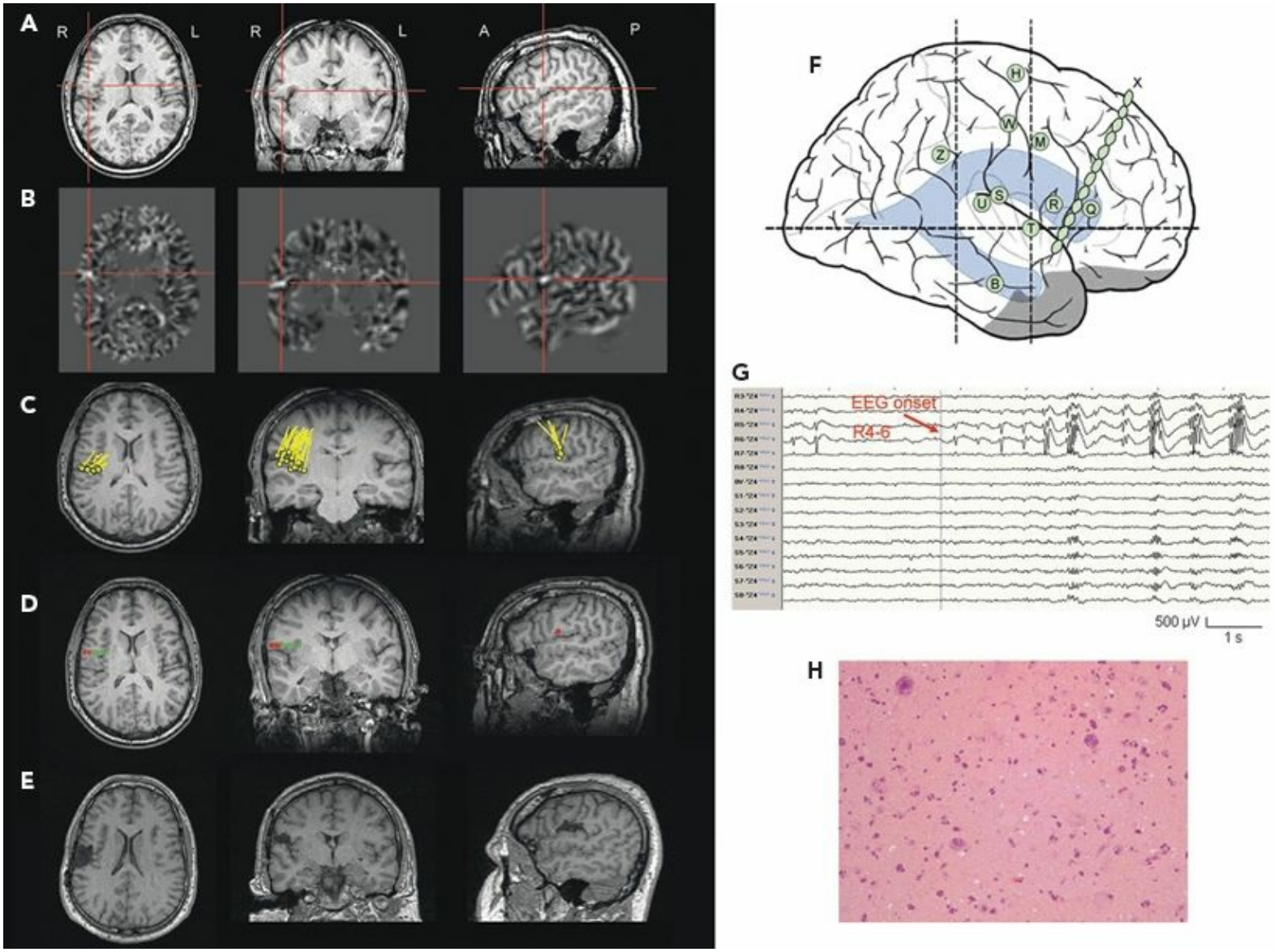

Figure 77.1. A 30-year-old male presented with pharmacoresistant seizures preceded by an aura of a tingling sensation deep in his throat, spreading to his left face, and then followed by left face clonus with occasional left arm posturing. Scalp EEG monitoring did not reveal any ictal anomaly. Previous high-resolution 3-tesla MRI was reported as normal. An FDG-PET study showed subtle hypometabolism involving the right frontal and temporal operculum. Ictal SPECT was nonlocalizing. MRI postprocessing of the GW junction was performed on 3D T1-weighted volumetric sequence. Review of the GW junction feature map led to the identification of a structural abnormality at the right frontal operculum ($z > 4$), as shown in **(B)**, coregistered with the patient's MRI in **(A)**. This abnormality is concordant with magnetic source imaging interictal dipole localization **(C)** and seizure onset on stereo-EEG **(D)**. Limited resection (**E**) included the abnormality and rendered the patient seizure free. **F:** Stereo-EEG (SEEG) implantation schema. **G:** Ictal onset on SEEG. R4-6 corresponds to red contacts in **(D)**. Stimulation of R4-6 induced the habitual seizure of the patient, with the same

ictal EEG pattern as shown in **(G)**. **H:** Histopathology showing features of FCD ILAE type IIb with balloon cells (HE; original magnification = 200×). To date, the patient has been seizure free for more than 4 years.

Quantifying cortical thickening and signal hyperintensity, in addition to evaluating gray–white matter transition, provides a more comprehensive analysis of the complex and variable morphologic anomalies related to the various forms of FCD (63). Bernasconi et al. proposed morphologic and first-order texture models creating 3D maps of cortical thickness, gradient (transition between GM and WM), and a relative intensity operator designed to emphasize T1 signal hyperintensity. The first-order texture models were then combined into a single composite map to optimize visibility. In a group of 16 patients with histologically proven FCD, visual analysis of the composite map increased sensitivity by 30% when compared to conventional MRI visual analysis, while maintaining a high specificity (57). Figure 77.2 illustrates the application of first-order texture models to a patient with frontal lobe epilepsy.

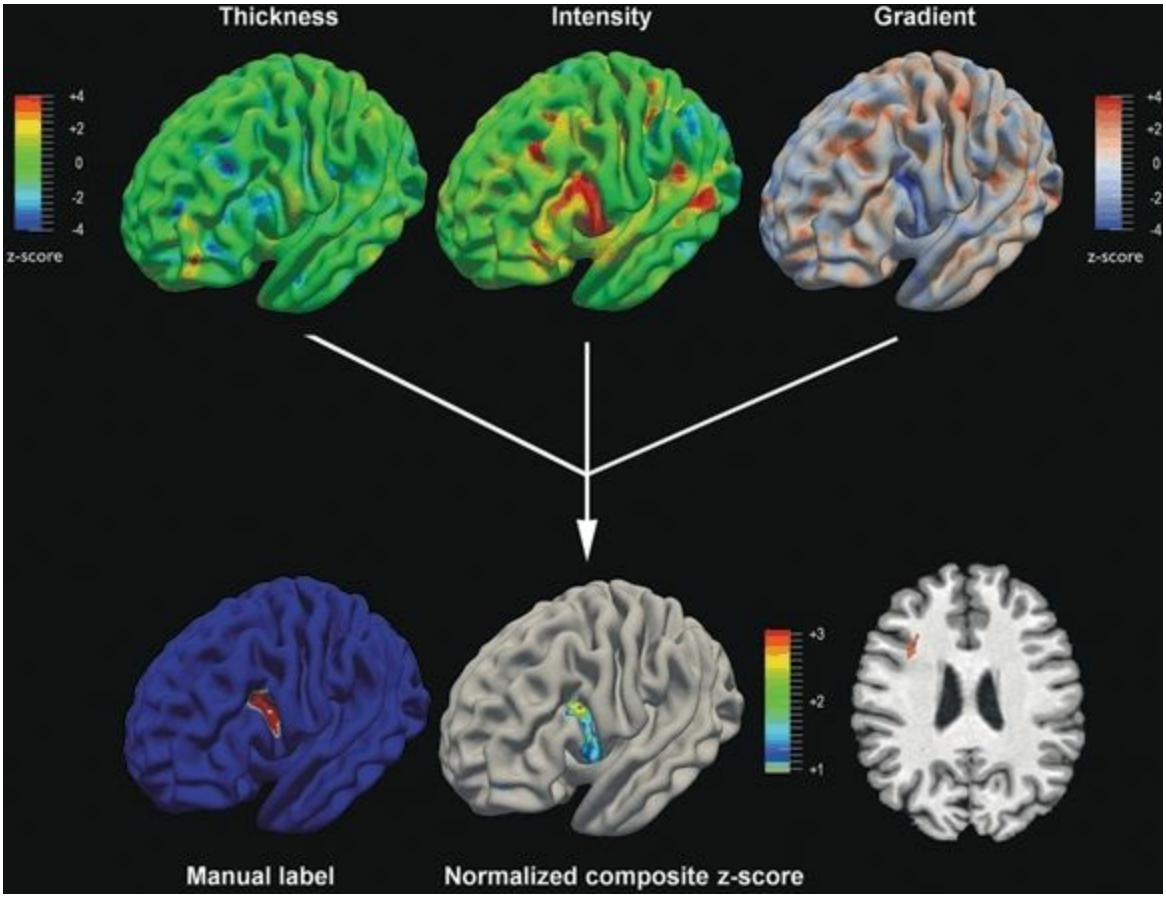

Figure 77.2. In this patient with frontal lobe epilepsy, high-resolution 3-tesla MRI was reported as normal, likely because of the subtle nature of the dysplasia, as demonstrated by the coronal T1-weighted MRI section (**right lower corner**, red arrow). The upper panels display the T1-weighted derived computational models normalized with respect to controls (z-score maps). The cortical thickness map is unremarkable. Conversely, the gray matter intensity map and the gradient map (modeling gray–white matter blurring) show significant anomalies. The normalized composite map identifies the lesional area as the only anomaly compared to controls and shows almost identical overlap with the lesion label obtained trough manual segmentation. Histopathology of the surgical specimen confirmed the diagnosis of FCD ILAE type IIb.

In a subsequent study of 23 patients with histologically proven FCD by Colliot et al., FCD lesions were characterized by simultaneous GM thickening, hyperintense signal, and blurring of the GM–WM transition in 78% of the patients. In all patients, the FCD lesion had at least two of these three characteristics. These MRI postprocessing features occurred regardless of the lesion volume, and they characterized not only large FCD lesions but also subtle ones that had been overlooked by visual

inspection (64).

Antel et al. reported further development of this approach consisting of second-order texture analysis to quantify tissue organization through quantification of spatial relationships of gray-level intensity pairs that is less apparent to the human eye (65). Second-order features, including angular second momentum, contrast, and difference entropy, were used to develop automated pattern recognition using a novel two-stage Bayesian classifier to perform FCD lesion detection. This fully automated technique was applied to a group of 18 patients with histologically confirmed FCD, and correctly detected the FCD in 83% of them. In contrast, conventional visual MRI analysis was able to detect the FCD in only 61% of patients (65).

Notably, consistent with findings from voxel-based methods, computer-based models have revealed structural abnormalities that did not colocalize with any EEG abnormalities (62,65,66). Inspection of the feature maps revealed that these abnormalities exhibited patterns similar to FCD; however, visual analysis of these regions on the original structural MRI did not show any FCD. Given the absence of false-positive findings in normal controls, combined with report of diffuse or nonfocal cortical involvement in FCD (66–69), these clusters may indicate dysplastic abnormalities much more widespread across the hemispheres than the changes visible on the MRI and may explain, at least in part, why in some cases complete resection of MRI lesion does not always lead to seizure freedom.

MRI-visible FCD is sometimes considered the "tip of the iceberg" as the extent of the underlying structural pathology often goes beyond it. The exact delineation of the spatial extent of an FCD lesion carries significant clinical relevance as it can guide surgical resection. Colliot et al. proposed an automated method to segment FCD lesions on T1-weighted MRI using a combination of deformable models (70). In this approach, a feature-based level set driven by known MRI characteristics of FCD first separates lesions from nonlesional tissue. A second deformable model, designed to expand the previous result toward the cortical boundaries while preventing lateral intracortical motion into healthy tissues, finalizes the lesion segmentation. The quantitative evaluation in 18 FCD patients demonstrated strong agreement with expert manual labels (70).

Sulcal Morphometry

Sulcal and gyral abnormalities in ETLE patients are characterized by a spectrum of changes ranging from clefts of various depth to broad gyri (71), shallow or deep sulci, or gyral simplification (72,73). In the absence of visually discernible cortical thickening and GM blurring, these sulcal morphologic signs may be the only marker for cortical dysgenesis (71). Besson et al. reported that 85% of small FCD lesions that elude visual inspection were found at the bottom of an abnormally deep sulcus (74). Local weakness within the developing cortical mantle, co-occurrence of incomplete maturation, decreased neuronal density, and disrupted connectivity in the areas surrounding the FCD may play a role in the mechanism underlying this presentation (43,75). Regis et al. utilized a sulcal root/meridian parallel model for automated extraction, identification, and statistical analysis of cortical sulci (76). This approach was tested in a small series of MRI-negative patients with frontal lobe epilepsy, in whom subtle abnormal gyration patterns were found in the epileptogenic zone. Interestingly, small FCD not detected with MRI was found on histopathology, particularly in the depth of the posterior superior and intermediate frontal sulci (76).

CHALLENGES AND FUTURE DIRECTIONS

The detection of cortical abnormalities in patients with nonlesional epilepsy represents a considerable challenge for the future. The sensitivity to detect lesions that are undetectable by conventional MRI has been shown to increase proportionally to the number of techniques employed, suggesting that each contrast interrogates specific aspects of tissue structure. As subtle FCD lesions may only differ slightly from the normal cortex, a multivariate framework may be necessary to assess the combined sensitivity of various contrasts (43).

In the context of presurgical evaluation, results of MRI postprocessing will need to be confirmed with modalities that can characterize the pathophysiologic features of suspicious imaging findings, such as EEG, magnetic source imaging, PET, or SPECT. This is particularly important in the presence of multiple abnormalities detected by postprocessing, as illustrated in Figure 77.3. Understanding of postprocessing-positive structural changes outside the putative epileptogenic zone will require further correlative studies with electrophysiology, pathology, and long-term surgical follow-up.

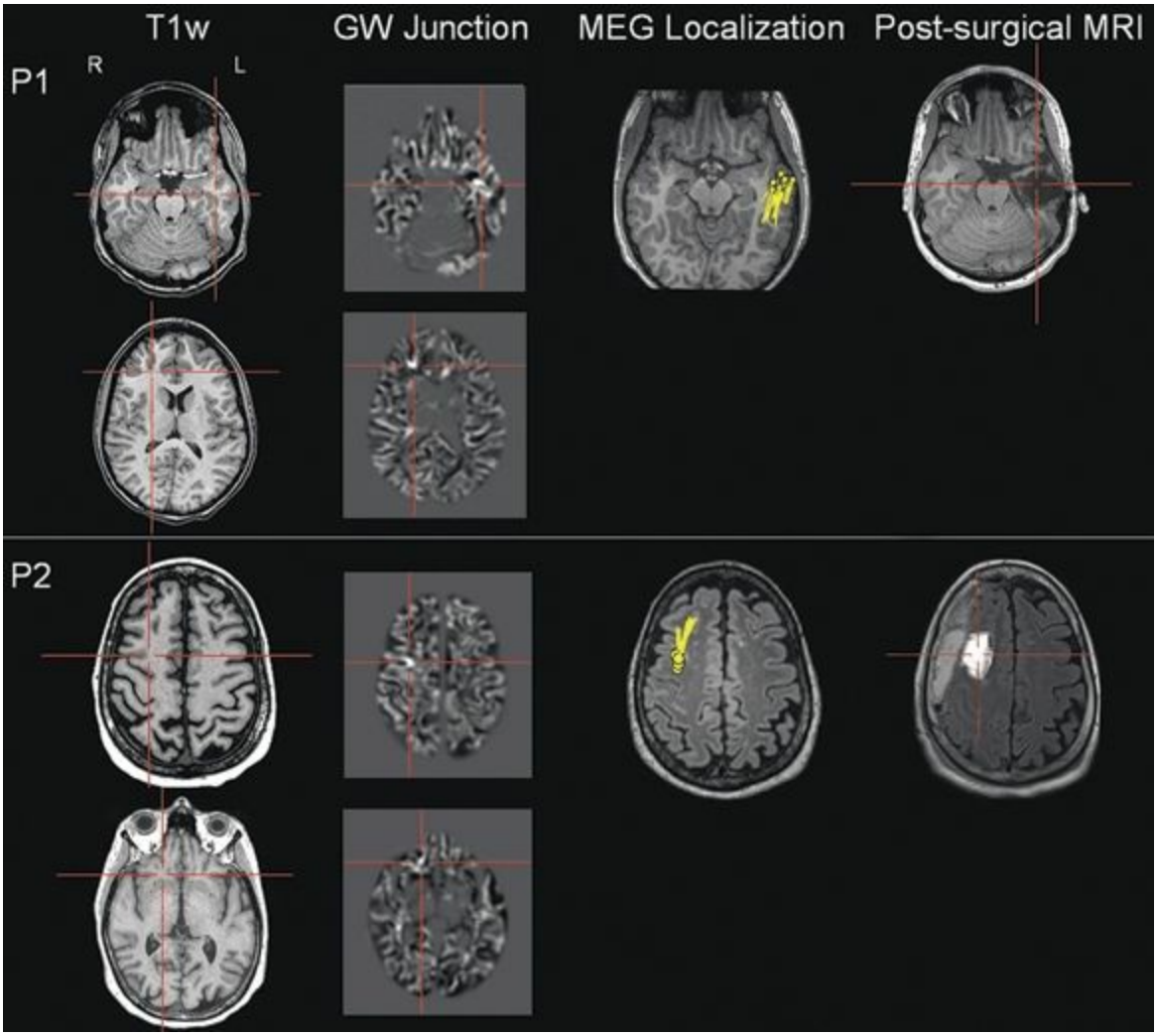

Figure 77.3. These two patients (P1 and P2) illustrate the importance of correlating MRI postprocessing findings with an electrophysiologic measure. For both patients, high-resolution 3-tesla MRI was reported as normal. In P1, scalp EEG evaluation showed left temporal interictal spikes, and ictal onset was in the left temporal and right centroparietal regions. In P2, scalp EEG evaluation showed right frontocentral interictal spikes, and ictal onset was in the right frontocentral and right temporoparietal regions. Within each panel, the conventional T1-weighted images are in the first column; the MRI postprocessing results of the GW junction are in the second column; the magnetic source imaging (MSI) localization is shown in the third column; the postsurgical MRI is shown in the last column. Each patient had two $z > 4$ abnormalities indicated by the GW junction feature map from postprocessing, but only one

MSI focus. The abnormality concordant with the MSI focus was resected and led to seizure freedom in both patients (follow-up >12 months).

Improved spatial resolution and tissue contrast provided by ultra–high-field (7T) MRI is going to continue to expand the power of image processing. This will allow refining further the in vivo patterns of brain pathology within anatomically and functionally distinct areas and may provide the basis for more accurate histopathologic correlative studies (77). Future studies are needed to evaluate whether 7T MRI can provide additional diagnostic information in patients with a subtle, overlooked dysplastic lesion at lower field strengths.

CONCLUSION

Improving noninvasive localization is paramount in the surgical treatment of refractory epilepsies. As a noninvasive and cost-effective approach, MRI postprocessing is promising because unlike visual assessment, it provides quantitative, reliable, and reproducible data. For patients with lesions too subtle to be detected by conventional MRI visual analysis, MRI postprocessing techniques, integrated by a multimodality approach with other functional measures, allow for more accurate identification of epileptogenic abnormalities. Thus, MRI postprocessing techniques have the potential to increase the diagnostic yield of MRI in any epilepsy center utilizing a standardized epilepsy protocol on a 1.5-T or 3-T scanner. Moreover, these techniques have the potential to reveal the extent of cortical abnormalities invisible to the eye, which could further improve surgical outcomes. It is our hope that MRI postprocessing techniques will be used as an important complement to the test battery of existing presurgical evaluation in an increasing number of epilepsy centers.

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CHAPTER 78 DIFFUSION TENSOR IMAGING (DTI) AND EEG-CORRELATED FMRI

BEATE DIEHL AND LOUIS LEMIEUX

Magnetic resonance imaging (MRI) techniques have greatly improved our ability to investigate the structure and function of the epileptic brain (1). Detecting possible underlying structural abnormalities or causes of epilepsy is one important aspect of such advances, and currently pathologic lesions are identified in about 80% of all refractory focal epilepsies (2). In addition, novel imaging results are being explored to inform about cortical function or dysfunction in patients with epilepsy, as well as correlates of the ictal-onset zone and irritative zone (3).

The objective of epilepsy surgery in pharmacoresistant focal epilepsies is the complete resection or at least disconnection of the epileptogenic zone while preserving eloquent cortex (2,4). This chapter focuses on the contribution of two novel imaging technologies to optimize surgical results. Diffusion tensor imaging (DTI) is a novel MRI technology that allows measurement of water diffusion in the brain tissue, providing information of microstructural changes. In addition, white matter architecture and tract morphology can be interrogated allowing for the first time to reconstruct major tracts in vivo.

The simultaneous recording of electroencephalographic (EEG) and functional MRI (fMRI) was first demonstrated in patients with epilepsy in the early 1990s and has since become an important research tool in epilepsy and beyond (5). Simultaneous EEG–fMRI (or simply "EEG–fMRI") is uniquely capable of providing data to address the question: What patterns of hemodynamic change take place throughout the brain (5) in relation to epileptiform discharges seen on scalp EEG? For interictal pathologic activity, simultaneous EEG is indispensable while ictal hemodynamic changes can be studied meaningfully without reference to concurrent EEG in some patients. Although EEG–fMRI has been primarily used as a localization technique, it can be combined with ever more advanced modeling methodologies to study the dynamics of networks. Together, both technologies may allow for novel insights in understanding the ictal-onset zone, irritative zone, and functional deficit zone.

DIFFUSION MR IMAGING

Principles of Diffusion Imaging

The MRI signal results from the radio frequency excitation of water protons in tissue. In a medium without any boundaries, the random translational motion or brownian motion of water molecules results from the thermal energy carried by these molecules. In the brain, however, such diffusion is

restricted by intra- and extracellular boundaries. Various animal models have been used to assess the most important boundaries affecting diffusion in the brain, revealing that myelin is the main barrier to water diffusion (6–9).

The principles of diffusion MRI were first developed in vivo in the mid-1980s (10,11). In diffusion-weighted imaging (DWI), images are sensitized to diffusion by using pulsed magnetic field gradients incorporated into a standard spin echo sequence (10,12). Taking measurements in at least three directions allows for characterization of the mean diffusion properties within a voxel in the image.

By applying diffusion gradients in six or more directions, the diffusion tensor, a mathematical construct, can be calculated. This allows assessing not only the amplitude of diffusional motion but also the directionality (13–15). The fact that diffusion is not the same in the three main spatial directions, but is asymmetric in the brain and restricted in certain directions, gave rise to the concept of "anisotropy" (13,16). DTI has been developed to explore this directional information and to gain greater insights in the structural changes, possibly on a microscopic level. Fractional anisotropy (FA) is a scalar (unitless) index most commonly used to assess the overall degree of directionality; it ranges from 0 (full isotropy) to 1 (complete anisotropic diffusion). Diffusion in different directions, such as parallel (main direction of diffusion) and perpendicular to the main fiber tract orientation, can be studied. Together, these quantitative measures help to characterize the integrity of the underlying white matter and may allow the understanding of the pathophysiologic mechanisms consistent with such diffusion abnormalities.

Exploring white matter changes in epilepsy, how they relate to epileptogenicity, and whether they may be a surrogate marker for cognitive difficulties is a matter of ongoing research. Furthermore, DTI in combination with tractography has become a powerful opportunity to subdivide compartments of white matter representing different tracts and study their diffusion properties selectively.

Experimental Insights into Tissue Structure Using DTI

Several animal models of tissue injury and degeneration have been used to measure serially diffusion changes and correlate them carefully with histology. Using an in vitro model of wallerian degeneration in frog sciatic nerve, axonal and myelin degeneration causes a decrease in diffusion anisotropy due to reduced parallel and increased perpendicular diffusivity (9). Myelin has been shown to modulate perpendicular diffusivity (7,8), although it is not the only factor involved (17). In humans, reductions in the principal direction and increases in radial diffusivities have been shown in chronically degenerated white matter tracts (18). Serial DTI measurements in three patients who underwent corpus callosotomy to treat medically refractory seizures and drop attacks revealed interesting insights into the diffusion changes in the corpus callosum after the surgery (19). An initial decrease in parallel diffusivities evidencing the breakdown of the axons (19,20) is followed in the chronic stage (2 to 4 months later) by an increase of the radial diffusivities as myelin sheath degeneration is noted. Water molecules become more mobile perpendicular to the axons, resulting in an increase in radial diffusivities.

Tractography

Lastly, anisotropy information forms the basis of reconstructing tracts. Anisotropy in white matter results from the organization of tissue as bundles of axons and myelin sheaths run in parallel, and the

diffusion of water is freer and quicker in the long axis of the fibers than in the perpendicular direction (17). By assuming that the largest principal axis of the diffusion tensor aligns with the predominant fiber orientation in an MRI voxel, we can obtain vector fields that represent the fiber orientation at each voxel. The three-dimensional reconstruction of tract trajectories, or tractography, is an extension of such vector fields (21). However, tractography only came into use in the late 1990s, due to the complexities to develop reliable computer algorithms to reconstruct the tracts. Some of the limitations and technical difficulties of tractography include the spatial resolution of DTI, which is in the order of several millimeters, as well as noise. Various acquisitions and postprocessing analysis techniques have been proposed (21), and methods continue to evolve. Voxel sizes are much larger than the resolution needed to image single axons. Hence, in vivo DTI studies can, at present, only display an approximation of the main tract direction and do not have a resolution even close to a cellular level. White matter tractography is generally done in two different ways, either with a method known as "deterministic" tractography or with a "probabilistic" method. Using deterministic methods, seed points are placed, and the tract grows in both directions along the dominant diffusion direction. This requires a preset threshold for angles and FA, and track is terminated when it reaches a voxel with subthreshold FA, or when the turning angle exceeds this threshold. As the main direction of water diffusion is used for tract reconstruction, crossing fibers will not be represented, and only the main tracts and its main direction will be displayed. The probabilistic methods probe fiber orientation distributions at each voxel and are computationally more intensive, but can more reliably reconstruct crossing fibers.

To date, atlases have been published of anatomical correlation of the DTI-based FA maps and tractography results (22–24), which are largely based on comparison to anatomical drawings and dissection maps.

There is no doubt that validation is of central importance for the development of tractography; how to validate and against what gold standard is a matter of debate.

Peri-Ictal DWI and DTI Changes in Humans

DWI has initially been introduced in clinical practice for the early detection of stroke. It has proven to be very sensitive to areas affected by ischemia (10). Subsequently, peri-ictal and postictal changes in diffusivity have been observed in animal models of status epilepticus and in patients both after status epilepticus and after single short seizures. Systematic investigations of diffusion changes in rats following bicuculline-, kainic acid–, and pilocarpine-induced status epilepticus have highlighted changes closely correlated with the presumed area of seizure onset and with the resulting histopathologic changes. Furthermore, such changes are dynamic, leading initially to restricted diffusion due to cytotoxic edema and, after several days, to normalization or facilitated diffusion (25–28). Diffusion imaging may, therefore, provide an opportunity to directly image the areas involved in seizure generation and possibly spread.

The first report of diffusion changes in a patient with focal status epilepticus was published in 1997 (29). Status consisted of clonic jerking of the right leg, which continued for 22 days and was followed by transient paresis. DWI during status showed decreased diffusion in the motor cortex of the right leg (Fig. 78.1) and an area of facilitated diffusion in the underlying white matter. This was explained by a shift of water into cortical neurons at the site of the seizure focus, that is, cytotoxic edema that is associated with restricted diffusion and vasogenic edema with a shift of water in the extracellular space in the underlying white matter (30).

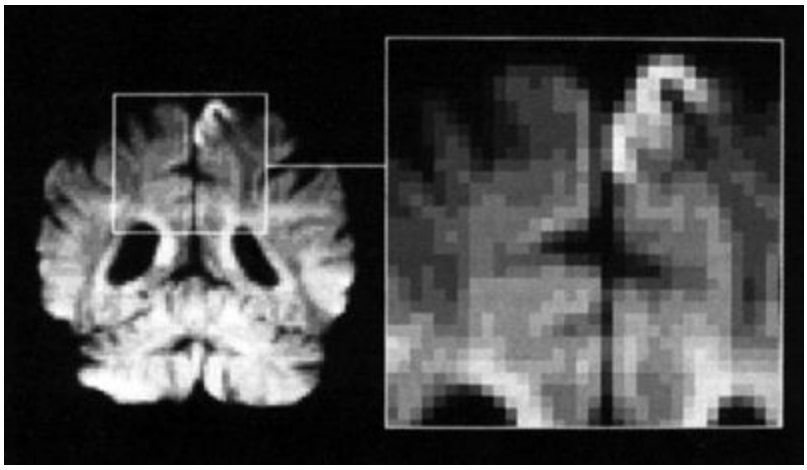

Figure 78.1. Area of restricted diffusion in the left superior frontal gyrus shown in a patient with right leg clonic status epilepticus. (From Wieshmann UC, Symms MR, Shorvon SD. Diffusion changes in status epilepticus. Lancet. 1997;350(9076):493–494, with permission.)

Following this case report, multiple systematic investigations have explored peri-ictal DWI in an attempt to assess the usefulness of this novel technology to delineate the ictal-onset zone. Overall, the presence of dynamic diffusion changes has been documented in the majority of cases, but the correlation between the presumed epileptogenic zone and the diffusion changes is quite variable (31–35). Correlations seem closer in patients with longer seizures (or status) and short duration between seizure end and scan (31,33). A single case report in man confirms that restricted diffusion is a marker of the ictal-onset zone: An area of restricted diffusion adjacent to the lesion in the right frontal lobe in a patient with repetitive prolonged focal motor seizures corresponded to the region of focal electrocorticographic seizures that was mapped intraoperatively (36).

Studies using DTI to study peri-ictal changes allowed for comparison of the sensitivity of diffusivity changes versus anisotropy changes and to assess whether DTI provides higher sensitivity to seizure-induced changes. The results remain rather disappointing, and it has become apparent that dynamic changes affected the diffusivity to a much higher degree than the directionality (32). Peri-ictal mean diffusivity reductions are seen in about half of the patients investigated, but only a relatively small proportion (20%) colocalized with the presumed ictal-onset zone, even when patients were scanned within 45 minutes after the seizure (35). In addition, whole-brain analysis using statistical parametric mapping (SPM) revealed distant areas of diffusivity change, possibly highlighting the network involved in ictal spread.

In order to minimize delays between seizure and scanning, flumazenil was used to induce seizures in patients assessed for epilepsy surgery (37). Despite almost immediate MRI scanning, diffusivity decreases were seen in the hippocampus on the seizure-onset side and in both parahippocampal gyri.

Therefore, it seems possible that diffusion changes after single seizures appear more transient and require immediate access to scanning. If in the future such an environment can be provided, in combination with higher-resolution scanning and possibly also higher field strengths of MR scanners, postictal studies may be of higher yield.

Interictal DTI and DWI Changes

Temporal Lobe Epilepsy

Patients with mesial temporal lobe epilepsy (TLE) due to hippocampal sclerosis reveal increased diffusivity in the ipsilateral hippocampus, indicative of structural disorganization and expansion of extracellular space, reflecting neuronal loss and other microstructural changes (38–43). These changes parallel the abnormalities noted on conventional MRI scans with atrophy and T2 signal increase. When assessing DWI compared to conventional MRI using volumetric T1 acquisitions and FLAIR, it was not more sensitive in detecting hippocampal sclerosis (40). In addition, in patients without lateralizing differences between the hippocampal formations, both hippocampi often showed increased apparent diffusion coefficient compared to a control population, indicating bilaterality of the disease. Such bilateral abnormalities are present throughout the limbic system, including fornix and cingulum in both adults (44,45) and children (46).

When patients with TLE were evaluated using a region-of-interest approach, diffusion abnormalities extend into the ipsilateral hemisphere and even into the contralateral hemisphere (44,45,47–50), as has recently been summarized in a meta-analysis of 13 studies comparing white matter tracts ipsilateral and contralateral to the epileptogenic temporal lobe to controls (51). Such more widespread changes have been confirmed using voxel-based approaches, which compare one individual to a group of normal controls and thus do not have selection bias to a particular region of interest (50). These changes are not reversible after successful temporal lobectomy, which may suggest structural abnormalities as opposed to functional changes due to seizures (52).

DTI can also identify abnormal areas in temporal and extratemporal focal epilepsy with normal conventional MRI. Out of 30 patients, increases in diffusivity were found in 8 patients (26%), and 6 of the 8 diffusivity alterations were in the presumed epileptogenic zone (53). In addition, group analysis of nonlesional left TLE patients revealed increased diffusivity and reduced anisotropy within the ipsilateral temporal lobe; the right TLE group displayed a trend in the same direction (53). Although such a group effect is not helpful in an individual patient, it suggests that given greater sensitivity and increased signal-to-noise ratios, an effect in individual patients may be demonstrated. Overall, such occult lesions are most likely caused by disruption of white matter architecture due to dysgenesis or by seizure- related damage leading to atrophy, gliosis, and expansion of the extracellular space, resulting in increased diffusivity and potentially also decreased anisotropy.

Extratemporal Lobe Epilepsy

Case numbers of extratemporal epilepsies in the presurgical epilepsy workup are rising, and these cases are often challenging as precise localization of the epileptogenic zone in relation to cortical function is mandatory. Diffusion changes are seen in a variety of lesions associated with focal epilepsy and often localize outside the temporal lobe, such as cortical dysplasia.

Reductions in anisotropy and increase in diffusivity within the MRI visible lesion and also outside of it have been reported in a variety of cortical dysplasias (54,55). Reductions in FA in most patients in normal-appearing white matter surrounding dysplastic lesions are likely due to gliosis, axonal loss, poor myelination, or increased cell bodies (e.g., ectopic or abnormal neurons, balloon cells). In addition, distant anisotropic changes can also be observed, possibly due to wallerian degeneration of tracts or gliosis resulting from chronic seizures. Investigations on the impact of cortical dysplasia on connectivity and adjacent tracts showed decreased tract size and displacement of tracts in larger dysplasias, as well as rarefaction of subcortical connections surrounding cortical dysplasia (56). Figure 78.2 shows altered connectivity in a patient with right temporooccipital epilepsy, with polymicrogyria and heterotopic gray matter in the same region.

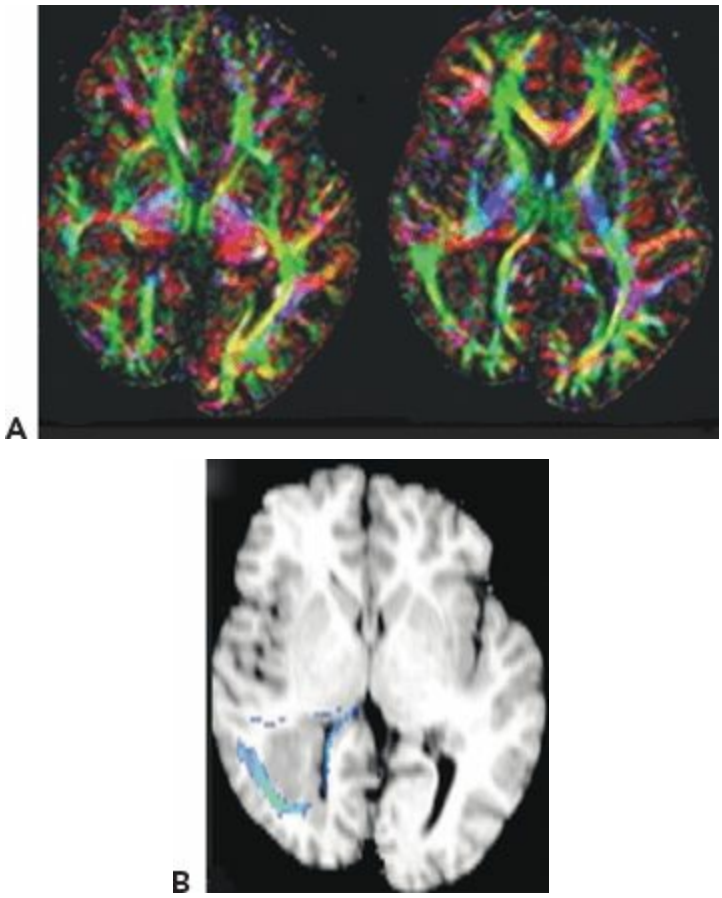

Figure 78.2. Malformations of cortical development and alterations of connectivity. Twenty-six-year-old with intractable focal epilepsy arising from the right temporooccipital region. MRI showed right > left posterior quadrant polymicrogyria and heterotopic gray matter in the right posterior quadrant. **A:** Axial colorized fiber orientation maps showing displacement of the right superior frontooccipital fasciculus and superior longitudinal fasciculus. **B:** Two-dimensional illustration of the tractography results overlaid onto the T1 image demonstrates the spatial relationship between the heterotopic gray matter and the white matter tracts.

Probing Diffusion Changes: What Can It Tell Us in Human Epilepsy

Analyzing the pattern of diffusion changes with respect to diffusivities parallel and perpendicular (radial) to the main axonal direction provides in vivo insights into the underlying cause of diffusivity increase and decreased FA. Several studies revealed that the most commonly seen pattern of DTI changes associated with focal epilepsy was unchanged parallel diffusivity and increased perpendicular diffusivity (45,47,48,57,58). As detailed above, such a pattern of FA changes seen in most studies evaluating DTI in TLE is most consistent with chronic wallerian degeneration, possibly due to cell loss in the temporal lobe secondary to seizure-induced cell death.

In order to evaluate potential mechanisms for such more widespread diffusion changes in TLE, it was investigated if different underlying pathologies as determined by preoperative MRI cause differential diffusion changes (45). Patients with TLE and hippocampal sclerosis were compared to nonlesional TLE: While some white matter bundles are affected equally in both forms of TLE, abnormalities of the bundles directly related to the mesial temporal structures (i.e., the fornix and cingulum) appear to be unique to TLE with hippocampal sclerosis.

It has been demonstrated that DTI can be used to delineate the neurocognitive correlates of localized white matter damage in TLE, such as working memory (59), visual and verbal memory, and language dysfunction (57,60), and research into such structure function relationships is ongoing.

Interictal DTI and DWI Changes: Conclusion

Interictal DTI highlights areas of abnormal diffusion measures in temporal and extratemporal lobe epilepsies, both lesional and nonlesional. Specifically, mean diffusivity appears more sensitive to changes seen in patients with chronic refractory epilepsy compared to FA. The only exception may be cortical dysplasias. DTI abnormalities are seen in all areas, indicating pathology on conventional MRI. In addition, DTI changes may often be found outside the lesions, both contiguous and less frequently also noncontiguous to the lesion. Abnormalities mostly with increased diffusivity and reduced FA have also been found in patients with cryptogenic focal epilepsy. Analysis of water diffusivity changes reveals a pattern of increase in perpendicular diffusivity and not of parallel diffusivity. This may indicate wallerian degeneration as one of the main mechanisms accounting for the structural changes underlying the DTI abnormalities remote from focus and lesion.

Such abnormal areas in patients with intractable epilepsy, therefore, probably represent structural disruption, possibly reflecting either an underlying pathology or gliosis due to secondary damage. This requires further study with MRI–histology correlation in more patients.

Interictal DTI and Irritative and Ictal-Onset Zone

Close correlations between the interictal abnormalities highlighted using DTI, pathology, and epileptogenicity are rare. Intracranial recordings in a patient with cryptogenic focal epilepsy showed seizure onset in the right orbitofrontal region, colocalizing with an area of abnormal diffusivity (61), and postresection pathology revealed gliosis. Of note, however, is that this patient is not completely seizure free.

Few papers have evaluated in detail the concordance between diffusion abnormalities and irritative zone and ictal-onset zone as evaluated using invasive recordings. Two studies have used voxel-based statistical approaches to highlight areas of abnormal diffusion in a small number of patients undergoing stereo-EEG evaluations (62,63). In one study (63), 13 of the 16 patients were found to have DTI abnormalities. DTI abnormalities consisted mainly of increases in mean diffusivity and were concordant with the epileptogenic zone in seven. FA abnormalities added little in localization. The specificity of DTI abnormalities was better in extratemporal lobe epilepsy: 20% of TLE had congruent findings, whereas four of five extratemporal epilepsies concurred.

Another study investigated 14 patients with frontal lobe epilepsy (9 nonlesional), and almost all patients showed areas of increased diffusivity (62). In this study, the sensitivity of diffusion imaging in defining regions that were the site of electrical abnormalities was about 57% for the area of seizure onset and 65% for the irritative zone, and the specificity was low. It is of note, however, that areas of diffusion abnormalities may not have been sampled, as coverage is necessarily limited with stereo-EEG. An interesting aspect in this study is that lesional epilepsies had very high sensitivity, as the lesion led to diffusion abnormalities, but very low specificity. In nonlesional epilepsies, cases in which epileptologists may particularly turn to novel imaging for additional support of a hypothesis for invasive recordings, three out of the nine patients had diffusion changes in the seizure-onset zone.

Overall, the limited data available suggest that diffusion changes correlate better with areas of interictal spiking than the ictal onset. Furthermore, the presence of DTI abnormalities certainly does not mean that the seizures are arising in the vicinity. However, DTI changes may provide some additional information to guide placement of invasive electrodes. Interestingly, a recent study using a surface-based laminar analysis of gray and white matter showed differential findings regarding diffusivity in the seizure-onset zone (64), compared to healthy controls. In 18 children with nonlesion extratemporal lobe epilepsy, such analysis revealed increased diffusivity in the cortical gray matter,

most pronounced in the outer fraction of the gray matter, also involving the white matter underlying the epileptic cortex. The electrographically normal cortex, in contrast, showed decreased diffusivity in inner and middle cortical fractions compared to controls. The authors speculated whether this may be indicative of surround inhibition.

In conclusion, data remain sparse and correlating electroclinical abnormalities using invasive recordings with diffusion changes may allow for better insights in the future.

Tractography and Epilepsy Surgery

DTI is the first imaging modality that allows direct noninvasive visualization of white matter tracts. Several investigations have focused on retrospectively correlating DTI-based tractography with postoperative deficits, to assess if this technology could provide predictive information for a deficit and could maybe even aid in preservation of function if such information were integrated in neuronavigation systems. Anterior temporal lobectomies can cause a contralateral superior quadrantanopsia in up to 10% of patients by disrupting Meyer loop. The anterior extent of Meyer loop has large interindividual variability and cannot be visualized using conventional imaging (65). Tractography has been used to demonstrate the optic radiation in normal subjects (66), and its use was subsequently explored for temporal lobectomies (67,68) and the anteroposterior extent of the damage to Meyer loop as determined postoperatively correlated well with the degree of visual field loss (68). Pre- and intraoperative DTI-based fiber tracking (69) showed significant correlation between the fiber tracking estimation and the outcome of visual field deficits after surgery.

These data provide evidence that tractography has the potential to inform about risks of epilepsy surgery procedures. Once successfully implemented into neuronavigation systems, this information may also be used intraoperatively to tailor resections (70). Aside from the technical issues of performing tractography in health and disease, the intraoperative brain shift after craniotomy is another significant impediment. The availability of intraoperative MRI may represent one method to correct for this movement and may improve the accuracy of the data to aid surgical planning.

Extratemporal surgeries will also benefit from visualizing crucial connections and tracts such as the pyramidal tract. Implementation of DTI-based tractography has already been shown to benefit patients undergoing brain tumor surgeries and resections of vascular malformations (70–74) and will certainly be increasingly used in epilepsy surgery.

EEG–fMRI

Up to now, the localization of the generators of interictal epileptiform discharges (IEDs) has been mainly addressed through EEG and magnetoencephalography (MEG), techniques with exquisite temporal resolution. fMRI offers good spatial resolution and localization of events that are accompanied by a blood oxygen level–dependent (BOLD) response (5). A question that must be addressed first when considering fMRI as an epilepsy localization tool is whether epileptiform paroxysmal events (interictal and ictal) are associated with detectable BOLD signal changes. In this regard, evidence from multiple sources including visual observation of the cortex during surgery, PET, SPECT, and near-infrared spectroscopy (NIRS) is conclusive: Seizures are commonly accompanied by regional hemodynamic changes. In the case of interictal discharges, the above techniques are unsuitable, some due to their fundamentally limited temporal resolution (PET, SPECT) and others due to limited spatial sensitivity profiles, such as NIRS. fMRI with its temporal resolution

of the order of a few seconds and excellent whole-brain mapping capability may offer a way to map out hemodynamic changes throughout the brain linked to short events from individual IEDs, to runs of spikes, and sharp waves to seizures. Importantly, fMRI's localization capability is independent of the extent or complexity of the involved brain region or regions, in contrast to EEG/MEG source analysis, and therefore may be more capable of revealing their full extent. The EEG is used as an indicator of events of interest, such as spikes or ictal discharges, from which a model of the fMRI signal is derived a posteriori and used for analysis of the fMRI time series data. The adjunct of simultaneous video can provide important information for the fMRI modeling (75).

fMRI of Spontaneous Brain Activity: Data Acquisition, Analysis, and Interpretation

In the following paragraph, we discuss some of the main technical aspects, applications, and findings of fMRI used to map spontaneous hemodynamic changes in patients with epilepsy. In most studies, the patient is asked to lie in the scanner with eyes closed and whole-brain scanning is performed in the expectation of capturing events of interest, usually interictal discharges, although drugs have been used in a small number of studies to modulate epileptiform activity specifically for the purpose of fMRI (76,77). Because of the random nature and temporal characteristics of epileptic activity, the fMRI data thus acquired are commonly analyzed within the framework of event-related designs, in contrast to the more conventional block designs used in many cognitive studies. This is done using the EEG (and video, when available) as a basis for modeling the variations in the BOLD signal related to epileptic activity. For this purpose, short epileptiform discharges such as single spikes have been likened to, and represented mathematically as, brief stimuli. As described in Chapter 79, the BOLD response to brief stimuli develops and resolves over a period of roughly 25 seconds, generally peaking between 5 and 7 seconds, and then undershoots the baseline slightly, roughly 15 seconds poststimulus, before returning to baseline, and is therefore essentially biphasic (i.e., it has positive and negative phases); this is the hemodynamic response function (HRF) (78). We note that a substantial amount of intersubject and interregional variability of the HRF in healthy subjects has been documented (79). The possibility of deviation of the shape of the HRF in patients with epilepsy due to the effects of pathology or other factors has implications for the technique's sensitivity and potential clinical usefulness. Furthermore, the choice of an accurate representation of the HRF is greater for the detection of regions of BOLD change in event-related designs than for block designs. Importantly, event-related designs are generally less efficient than block designs for the detection of BOLD changes.

Before embarking on a review of the application of EEG–fMRI in focal epilepsy, we discuss a small number of fMRI studies of seizures for which concurrent EEG was not used.

fMRI of Seizures (Without Concurrent EEG)

fMRI data acquired in the resting state have been used to map BOLD signal changes linked to ictal or peri-ictal events. The lack of concurrent EEG means that the analysis and interpretation of the fMRI is heavily reliant on clinical changes observed during the events and the use of this information for the labeling of scans as being ictal or interictal. Apparent BOLD changes were revealed by subtraction of scans acquired at baseline from scans acquired during motor seizures in a child (80). In one study (81), the authors identified patterns of signal change in the absence of any overt ictal activity, and

these changes were consistent with invasive localization. In another case report, ictal signs identified in relation to scan acquisition times were used to plot T2* signal changes relative to a baseline value voxel by voxel, revealing regions of signal increase and decrease preceding and during the motor seizure (82). Federico et al. (83) studied preictal fMRI changes based on visual observation without concurrent EEG in two cases. Regions of signal change were identified by comparing blocks of scans immediately preceding the seizures to blocks acquired 3 to 5 minutes before ictal onset. Inspection of the signal time course in those regions and "control" regions revealed patterns suggestive of specific preictal BOLD increases and decreases to a lesser extent taking place around 10 minutes before seizure onset in one case, similar to a case in which EEG was recorded during fMRI. Although interesting, this type of analysis of fMRI data is suboptimal in many respects such as potential subjectivity of the identification of the event onset (and the resulting model of the BOLD signal) and possible bias associated with physiologic and scanner-related artifacts (5).

EEG-Correlated fMRI: The Technique

While the clinical manifestations may be used as event markers for seizures, this is not the case for subclinical events such as IEDs. Therefore, the study of the hemodynamic changes associated with IED necessitates the recording of EEG during fMRI. Concurrent EEG, and video, may help in the interpretation of ictal events for the purpose of fMRI modeling. The technique that consists in the simultaneous acquisition of EEG and fMRI data is commonly referred to as EEG-correlated fMRI, or EEG–fMRI. Due to the various interactions between the two technologies, data quality and patient safety are serious concerns and have been the subject of a large amount of work since the first ever EEG recording took place inside an MR scanner (84). The main problems are pulse-related and image acquisition artifacts on EEG, image artifacts due to passive components (EEG leads and electrodes) and active components (EEG amplifier/digitizer) (85).

While many developments have led to the commercialization of EEG recording systems capable of providing the investigator with basic tools capable of producing good quality data for some applications, such as EEG–fMRI of visually identifiable IED, EEG and image data quality continue to preoccupy many users partly because some problems may never be completely solved (e.g., pulse-related artifact on EEG) and partly because the application boundaries continue to be pushed (increasing scanner field strength, study of ever more subtle EEG features, etc.). Therefore, EEG–fMRI data acquisition continues to be a field of development and investigators undertaking EEG–fMRI investigations in epilepsy are advised to obtain continuous technical support.

EEG–fMRI of Seizures

Although potentially most relevant for presurgical localization, the study of the hemodynamic changes during ictal patterns is problematic due to safety concerns, and the rarity and unpredictability of seizures in most patients mean that ictal EEG–fMRI studies are generally fortuitous. Once such data have been acquired, their analysis is made difficult due to the effects of head motion, the long duration of the events (same time scale as some fMRI artifacts), and the uncertain relationship between clinical and EEG manifestations on one hand and the pathologic neurophysiologic activity on the other. Nonetheless, based on simple fMRI modeling assumptions, ictal EEG–fMRI has shown BOLD increases often of larger amplitude and extent than interictal patterns and associated higher yield* than interictal EEG–fMRI. For example, using a flexible modeling strategy adapted to long

events, a large, electroclinically concordant BOLD increase was revealed in relation to a single subclinical seizure (86). In a patient with multiple seizures, a similarly concordant pattern of BOLD increase was revealed with large contralateral areas of simultaneous BOLD decreases (87). In a series of eight selected cases with malformations of cortical development (MCD) in whom seizures were studied using EEG–fMRI, the relationship between ictal and interictal BOLD patterns and MR-visible lesions seemed to reflect the specific pathology; for example, in cases with nodular heterotopia, there was a tendency for the ictal BOLD changes to involve the overlying cortex (88). In a recent series of patients recruited specifically for the purpose of studying preictal and ictal hemodynamics, typical seizures were captured in 20/55 cases (89). Across the group, there was a tendency for widespread preictal fMRI changes, followed by more localized, often in the vicinity of the confirmed or presumed seizure-onset zone, hemodynamic changes at onset and subsequent spread during seizure evolution.

*…Yield: proportion of cases in which significant event-related BOLD changes are revealed.

†…The actual delay may have varied due to the manual nature of the process, but an uncertainty of the order of ±1 second would be of little consequence given the time scale of BOLD changes.

EEG–fMRI of Interictal Epileptiform Discharges

The overwhelming majority of cases studied using EEG–fMRI have focused on revealing BOLD changes linked to IED. The primary aim of early studies in patients with focal epilepsy has been the demonstration of IED-related changes to localize the generators of the discharges, with the focus gradually shifting to the study of the details of the BOLD map localization in relation to other tests (MRI, EEG, etc.) and other aspects of these patterns such as the sign of BOLD change.

Two variants of the technique have been used for this purpose: IED-triggered fMRI and the more flexible and now widely used continuous EEG–fMRI. In IED-triggered fMRI, the MR acquisition, usually of a single image volume, was started following the identification of a spike or sharp wave; a fixed delay of a few seconds between spike and scan was employed, calculated based on the assumption that IED-related BOLD change will follow the course of the normal HRF.† A set of images acquired following IED were compared to images acquired following periods of background EEG. Such studies revealed significant BOLD increases in a large proportion of cases mostly concordant with the presumed or suspected generator localization (76,77,90–94). We note that these studies largely ignored the possibility of IED-related BOLD decreases. The finding of BOLD increases in expected locations in the majority of cases in which IED were captured confers a degree of validity to the assumption that IED-related changes are roughly in line with the HRF derived from physiologic stimuli in healthy subjects, peaking at around 6 seconds postspike.

Due to the appeal of having access to the entire EEG record during scanning, IED-triggered fMRI has now been superseded by continuous EEG–fMRI that was made possible by EEG scanning-related artifact correction algorithms (95,96). In continuous EEG–fMRI, scans are acquired without interruption resulting in a continuous time series of scan data. Importantly, the analysis of continuous EEG–fMRI data to reveal regions of increase or decrease BOLD signal related to events of interest (e.g., pathologic EEG discharges) is based on building models (general linear model [GLM]) of the BOLD signal over the entire scanning session, which can be challenging due to spontaneous changes in brain state at rest (97,98).

The analysis of EEG–fMRI is commonly based on conventional, visual EEG interpretation by expert observers and therefore suffers from the same limitations, although the impact of this

subjectivity has not been thoroughly investigated (see (5) for a review of the technique's principles and limitations; see (99) for a rare study on the impact of EEG interpretation on the fMRI results). Using this approach in selected case series in focal epilepsy, and assuming that the IED-related HRF does not deviate substantially from the norm, regions of statistically significant BOLD signal changes were revealed in around 70% of the cases in whom IEDs were captured during scanning sessions with durations of the order of 40 to 60 minutes (90,100). Overall, the pattern of BOLD increases and decreases is often complex, although the localization of the BOLD increases tends to match the presumed or confirmed IED generator localization. BOLD decreases tend to be more remote and less representative of the IED field distribution (100,101). In TLE, a similar mix of BOLD increases and decreases involving the ipsilateral and contralateral (homologous) cortex was observed (100–102), with a consistent pattern of BOLD decrease in the precuneus (103), reminiscent of the so-called default-mode network (Fig. 78.3) (104).

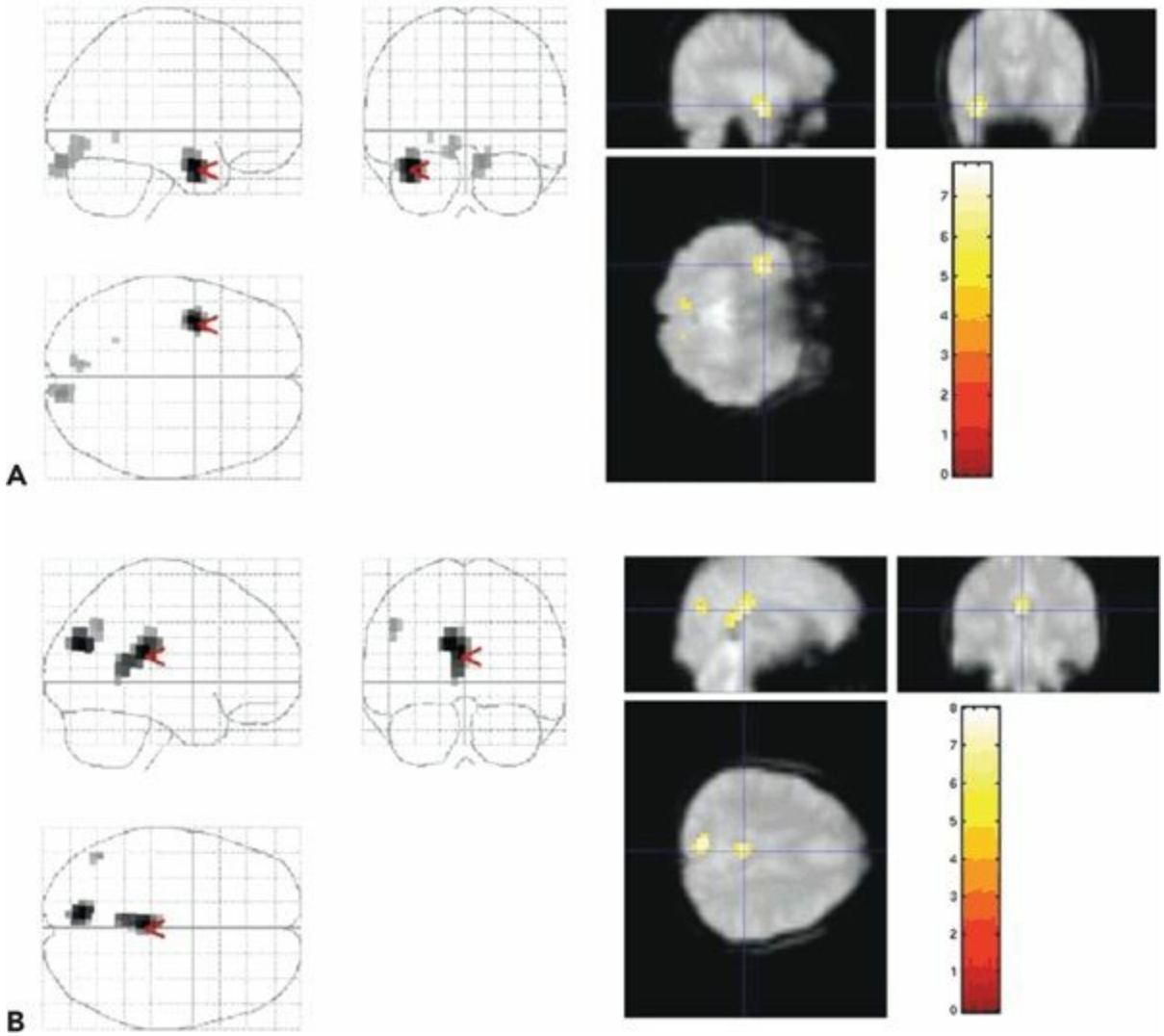

Figure 78.3. IED-related BOLD changes. Patient with left hippocampal sclerosis and left temporal IEDs who underwent EEG–fMRI. **A:** BOLD increase in the left temporal lobe with smaller clusters in the occipital region. The red arrow and cross hair represent the location of the most significant BOLD change. The left of the figure shows all statistically significant BOLD changes superimposed onto the SPM "glass brain." The right of the figure shows parasagittal, coronal, and axial sections through the EPI data at the location of the statistical maximum. **B:** Retrosplenial BOLD decrease associated with the same IED. This effect, which is thought not to represent activity of the source of the spike seen on EEG, is commonly observed in relation to interictal activity in the temporal lobe. (From Salek-Haddadi A, Diehl B, Hamandi K, et al. Hemodynamic correlates of epileptiform discharges: an EEG-fMRI study of 63 patients with focal epilepsy. Brain Res. 2006;1088(1):148–166, with permission.)

One of the advantages of continuous EEG–fMRI over spike-triggered fMRI is that it allows one to estimate the shape of the IED-related HRF, which is important if deviations from the norm are suspected with potential impact for analysis sensitivity. This can be done by using different sets of functions instead of the canonical HRF such as Fourier expansions or series of gamma functions (105–107). The results of this type of study are somewhat conflicting and differences of opinion persist on the best approach for modeling IED-related BOLD changes in terms of sensitivity. For example, a study has revealed BOLD signal changes seemingly preceding IEDs mostly generalized in nature; these have been labeled "noncausal" (107). However, the specificity of such deviations is uncertain. On the other hand, it has been shown that rare statistically significant deviations from the normal HRF, such as time course with a peak earlier than the normal 6 seconds postevent, are mostly remote from the presumed generators and suggestive of data-fitting artifacts (108) and, perhaps most importantly, that no notable increase in yield results from the inclusion of causal noncanonical HRF in the GLM (100). Deviations from the causal relationship: EEG abnormality → time-locked BOLD change may be particularly relevant in studies of seizures (83) where it is known that scalp EEG often does not reflect the earliest electrophysiologic changes. No such evidence, from simultaneous scalp and intracerebral measurements, for example, exists for interictal discharges to our knowledge.

Comparisons of the localization of IED-related BOLD changes with spike source analysis based on high-density EEG have been performed as a form of cross-validation. Comparisons of fitted point dipoles or more sophisticated distributed source model with IED-related BOLD clusters from spike-triggered fMRI data showed a relatively coherent pattern of spatial concordance and the complementary and valuable nature of the information derived from the two techniques, although the agreement criteria and fMRI modeling and source imaging procedures vary greatly between studies (109–113). When considered, the sign of IED-related BOLD change‡ did not significantly affect the degree of concordance with the presumed or confirmed generators (111,113).

‡…Taken in this context to be the sign of the first or dominant peak (or through) of the average IED-related BOLD time course relative to baseline.

Comparisons of IED-correlated fMRI maps and intracranial EEG findings have also been performed in the spirit of cross-validation. An early study in a small group of patients showed that in cases where one electrode was located near BOLD clusters, at least one of the electrode contacts showed epileptiform activity (109). In a series of 25 patients with drug-resistant epilepsy from 3 epilepsy centers, the localization of interictal scalp EEG–fMRI was compared to intracranial EEG (13 cases) and/or localization of resected tissue and surgical outcome (21 cases) (114). Using a novel technique designed to tackle the problem posed by the relatively frequent occurrence of the absence of IEDs on the EEG recorded during fMRI (usually limited to around 30 minutes), the authors proposed to map the hemodynamic correlates of EEG patterns derived from IEDs recorded outside the scanner. Using EEG topographic maps derived from clinical long-term EEG recordings, and by calculating their spatial correlation with topographic maps calculated from the intra-MRI EEG as a function of scan time, Gouiller et al. showed a quasi-doubling of sensitivity and good anatomical concordance with the "gold standard" localization particularly for lateral temporal and extratemporal epilepsy.

EEG–fMRI has been used to study the characteristics of the IED-related BOLD changes in specific pathologies (115–117). In relation to gray matter heterotopia and MCD, variability in the BOLD patterns was in line with previous findings, with a tendency for BOLD increases within the pathologically abnormal regions and decreases generally but not exclusively more remote from the abnormality (116,117). The neurobiology of the observed patterns remains to be fully elucidated, but

IED-related BOLD decreases in MCD have been attributed to either a loss of neuronal inhibition in the presence of normal neurovascular coupling in the regions surrounding the abnormality or abnormality of neurovascular coupling. Similar patterns of IED-related BOLD signal changes were revealed, involving the lesion and remote regions in patients with cavernomas (118) and tuberous sclerosis (in children) (119).

While the promising results of studies comparing localization based on EEG–fMRI to other forms of localization, the technique's role in presurgical evaluation remains unknown. To our knowledge, no prospective randomized, controlled trial has been performed to assess the efficacy of imaging techniques for the purpose of presurgical evaluation to date, and this also applies to EEG–fMRI (120). In a group of 29 patients in whom surgery could not be offered based on the results of routine investigations, clusters of significant IED-correlated BOLD signal change concordant with presumed seizure focus were revealed in eight cases (121). In four patients, the BOLD maps consisted of multiple clusters, in line with the results of other tests. In the other four cases, the BOLD maps consisted of a single cluster, two of which were concordant with intracranial EEG, allowing surgery to be considered. Based on this evaluation as a second-line technique, the authors suggested that EEG–fMRI can play a significant role in presurgical evaluation.

In a series of 23 patients with FCD, sensitivity was 95% of the 12 cases in whom IEDs were recorded during fMRI (122). The authors found that widespread, discordant regions of IED-related hemodynamic change reflected widespread seizure-onset zone and were associated with poor surgical outcome. Further evaluation of the role of EEG–fMRI as part of the panoply of presurgical localization tests is required.

CONCLUSION

DTI and EEG–fMRI offer novel and complementary information to localize the epileptogenic zone. EEG–fMRI's unique characteristics among functional imaging techniques make it likely to make a strong contribution to the definition of the irritative zone and of the ictal-onset zone in a smaller proportion of cases. However, its role in focus localization and contribution to the presurgical evaluation remains to be determined.

DTI may increase the sensitivity of MRI to lesions and improve our understanding of the local and remote impacts of the epileptogenic lesion on pathways and networks. In addition, it may help us better understand the often progressive cognitive changes seen in uncontrolled focal epilepsy and the functional deficit zone. Whether this information will be useful in predicting deficits following epilepsy surgery is unknown. MRI tractography will be increasingly used for neuronavigation during epilepsy surgery and may help limit surgical morbidity. Lastly, combining tractography and EEG–fMRI may provide novel insights in propagation of epileptic activity and for identifying effective and functional connectivity between cerebral areas involved in the epileptic network and the structural basis of this. With its greater ability to capture widespread, multifocal epileptic generators than EEG/MEG, EEG–fMRI may have a specific role as a predictor of more complex surgical cases. However, continued active research is required to translate these impressive advances in neuroimaging to improved outcomes.

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CHAPTER 79 LANGUAGE AND MEMORY MAPPING

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INTRODUCTION

The effectiveness of surgery for the treatment of drug-resistant epilepsy is well established, and side effects of surgery are usually minor. The most common cognitive side effects are relative loss of naming ability and relative decline in verbal episodic memory ability, each of which occurs in roughly 50% of patients who undergo left temporal lobe resection. Because not all patients show these declines, and most epilepsy surgeries are elective, it is appropriate to offer patients an individual assessment of risk whenever possible. Risk of naming and memory deficits is inversely correlated with the severity of temporal lobe pathology, which is related in turn to such factors as age at onset and duration of epilepsy, baseline preoperative naming and memory performance, and structural imaging (MRI, PET, SPECT) biomarkers. In addition, the risk of naming and verbal memory decline is correlated with hemispheric lateralization of these functions; thus, functional mapping of language and memory has an important role to play in the preoperative assessment of risk. Language mapping may also have a role to play in guiding the placement of resection boundaries to spare critical functional zones.

Over the past two decades, functional magnetic resonance imaging (fMRI) has become widely used for both lateralization and localization of language, largely supplanting the intracarotid anesthesia (Wada) test. Compared to the Wada, fMRI is noninvasive and therefore safer, provides more precise localization, and is considerably less expensive. The bulk of this chapter will review current evidence supporting the validity of using fMRI for preoperative risk assessment. There may remain, however, important indications for the Wada test in selected cases, and an algorithm is proposed for identifying such cases. The chapter concludes with an overview of other techniques used for language mapping, including magnetoencephalography (MEG), cortical stimulation mapping (CSM), and electrocorticography (ECoG).

FMRI LANGUAGE MAPPING

fMRI is based on neurovascular coupling, wherein focal increases in neural activity produce focal increases in cerebral blood flow. Increased blood flow results in a net decrease of deoxygenated hemoglobin in the affected capillary and venous beds, which causes the ambient magnetic field in these regions to become more homogeneous (deoxyhemoglobin is paramagnetic; i.e., it produces a microscopic perturbation of the magnetic field). This local “smoothing” of the magnetic field leads to a focal increase in the MRI signal measured with acquisition sequences that are sensitive to field inhomogeneity, or T2*. This link between neural activity and MRI signal, called the blood oxygen level–dependent (BOLD) effect, is the basis for nearly all fMRI. Because it depends on changes in

blood flow that develop over several seconds, BOLD fMRI is a hemodynamic imaging method and lacks the temporal resolution of EEG or MEG.

An important fact to emphasize is that fMRI measures relative changes in BOLD signal; thus, fMRI activation maps represent a difference between conditions, not absolute levels of activity in a single condition. An fMRI result can only be defined by specifying at least two conditions (often referred to as the activation condition and the baseline) under which the BOLD signal was measured. A frequent error is to mistake the quiet, "resting" state as a true baseline with little or no neural activity. In reality, the conscious resting state involves a large amount of neural activity, much of it reflecting internal use of language and conceptual knowledge (1). For example, people often plan or imagine future or past activities when they are at "rest," and these planning and imagining processes require retrieval of concepts (and words) for things, people, and events. Consequently, fMRI protocols that try to identify language zones by comparing a speaking or speech listening task with a resting baseline are likely to identify mainly motor and auditory cortices rather than language zones (2).

Another important point to stress is that fMRI language protocols vary substantially; there is no single standard task contrast for mapping language areas with fMRI. This reality reflects, in part, the fact that language is not a single process, but rather a set of distinct processes supported by somewhat separable (though highly interacting) brain networks. Some of these processes and their neural substrates are discussed briefly below.

Phoneme Perception

Speech is composed of complex and rapidly changing auditory signals that are perceived as consonant and vowel sounds, known as phonemes. The identification of phonemes is a distinct stage in speech comprehension separate from word identification, as illustrated by the fact that nonsense phoneme strings like "brillig" can be uttered by a speaker and perceived by a listener without conveying any meaning. The rare syndrome called pure word deafness is an isolated deficit of phoneme perception, in which patients cannot distinguish between heard phonemes but show perfectly normal written word comprehension and speech production, indicating intact word and concept knowledge.

Functional imaging studies have conclusively localized phoneme perception to the superior temporal gyrus (STG) and superior temporal sulcus (STS) in both hemispheres (3,4). These regions are activated whenever subjects listen to speech sounds (whether words or meaningless pseudowords) compared to less complex sounds such as noise or tones. These observations are consistent with localization data from patients with pure word deafness, who typically have bilateral lesions restricted to the STG and STS (5). This modern conceptualization of the STG as a region supporting phoneme perception is notably different from the traditional conceptualization of this region as "Wernicke area." As typically defined, Wernicke area is responsible for word comprehension, whereas the imaging and lesion data clearly implicate the STG in a prelexical auditory perceptual process.

The clinical importance of this distinction cannot be overstated. It is an unfortunate fact that many clinical fMRI language mapping protocols use passive listening to spoken words, contrasted with scanner noise or another nonspeech sound, to ostensibly identify language comprehension networks. The resulting activation, invariably involving the STG bilaterally, is usually labeled "Wernicke area" and taken to represent areas critical for word comprehension. There are, however, several

misconceptions in this approach. The activation represents an auditory perceptual process, not a word comprehension process (3); thus, damage to these regions will not cause a word comprehension deficit. Because the process is bilaterally represented, a unilateral lesion is unlikely to produce even a deficit of phoneme perception (6). Finally, because words and concepts are constantly being activated when subjects are "resting" in the scanner (even when passively listening to noise), the contrast between words and noise fails to evoke any change in neural activity in the brain regions that support word and concept processing.

Phonologic Access

Language production requires mental retrieval of words, a process referred to as phonologic access. Phonologic access occurs after a concept has been retrieved and can be thought of as retrieving a label or name for the concept (7). Inability to access phonologic representations results in anomia and phonemic paraphasia during speech production tasks. The brain regions implicated in phonologic access are in the left posterior perisylvian area, particularly the posterior STG, posterior STS, and supramarginal gyrus (SMG). Contrasts between visual stimuli that can and cannot be named (e.g., pictures vs. nonsense shapes; pronounceable vs. unpronounceable letter strings) reliably produce activation in these regions (8,9) as do silent word generation tasks (10,11). These regions overlap partly with those implicated in speech perception, though the phonologic access system is more posteriorly located. These systems cannot be entirely overlapping, since lesions in the posterior perisylvian cortex produce phonemic paraphasia but not speech perception deficits (i.e., conduction aphasia). As noted above, the speech perception system is also bilaterally represented, which may explain why it is more resistant to left STG damage than is the phonologic access system, which is more strongly left lateralized.

Semantic Memory

Semantic memory refers to knowledge about concepts, objects, people, actions, events, properties, relationships, etc. Much of this knowledge is represented symbolically in language and underlies our understanding of word meanings. Aspects of this knowledge are retrieved whenever we speak spontaneously, name objects, or comprehend language.

The neural basis of semantic processing has been addressed in a large number of functional neuroimaging studies, and the results of these studies are remarkably consistent, showing a broadly distributed network of brain regions underlying semantic memory storage and retrieval. Five major brain regions are implicated: (i) the ventral temporal lobes, including middle and inferior temporal, fusiform, and anterior parahippocampal gyri; (ii) the angular gyrus; (iii) anterior parts (pars orbitalis and pars triangularis) of the inferior frontal gyrus (IFG); (iv) dorsomedial prefrontal cortex, including the superior frontal and portions of the middle frontal gyrus; and (v) the posterior cingulate gyrus (12). These are multimodal and supramodal regions, distant from primary sensory and motor areas, and likely involved in integrating highly abstract information. Activation in these regions tends to be left lateralized, though most studies show at least some activation in homologous regions of the right hemisphere. As noted above, people continuously activate these semantic networks when they are spontaneous thinking, planning, or imagining; therefore, language mapping protocols that seek to identify these regions require an active baseline task that prevents spontaneous thinking and does not engage concept retrieval, such as an attentionally demanding perceptual task (2).

The functional imaging results are consistent with pathologic data from patients with semantic disorders. For example, lesion localization studies in patients with transcortical sensory aphasia, a syndrome characterized by multimodal semantic impairment with intact phonologic processing, implicate widely distributed regions of the left ventral temporal lobe and angular gyrus (13). Semantic dementia, a degenerative disorder characterized by gradual loss of semantic knowledge, is associated with progressive neuronal loss in the anterior and ventral temporal lobes bilaterally (14). Whereas these temporal and parietal lesions damage the semantic memory store itself, dorsal left prefrontal lesions impair the ability to retrieve information from the semantic store. These latter lesions produce transcortical motor aphasia, a syndrome characterized by inability to initiate spontaneous speech (13).

Retrieval, Selection, and Maintenance

Using language depends on a variety of executive "control" processes, including the ability to voluntarily activate phonologic or semantic information as needed for a given task, the ability to select the correct name or concept when a number of competing alternatives are activated, and the ability to maintain the selected item(s) in short-term memory while the task is completed. For example, if the task is to answer a question, such as "What farm animal gives milk?", it is necessary to use the content words in the question (i.e., farm, animal, give, milk) to activate a field of associated concepts, select from among several activated alternatives (e.g., cow, goat, sheep), use the selected concept to retrieve an associated name, and maintain the concept and name in an activated state during production of the response. These control processes depend mainly on the left prefrontal cortex (15,16).

This modern view of the left prefrontal cortex contrasts with the traditional concept of "Broca area" as a region involved only in speech production. In fact, the same retrieval, selection, and maintenance operations are required for many tasks in which no speech production occurs, such as silently naming a picture, or comprehending a sentence. Damage to the prefrontal cortex produces obvious impairments on a range of language production tasks, but usually not because speech articulation or motor sequencing is impaired. Rather, frontal lesions impair the ability to voluntarily retrieve concepts and verbal labels and to maintain these in short-term memory. The contribution of these regions increases as the need for these control processes increases, for example, as sentences become more complex or ambiguous, or items to be retrieved become less familiar.

Summary

Our understanding of human brain language networks has improved dramatically as a result of functional imaging research. The classical aphasia model linking "comprehension" with the posterior STG and "production" with the IFG is a vast oversimplification and incorrect in many important respects. A clear understanding of component language processes and their relationship to specific activation and baseline tasks is critical for the design and interpretation of clinically useful language mapping procedures. The selection of language activation tasks for fMRI is reviewed in more detail elsewhere (17).

FMRI LANGUAGE MAPPING IN EPILEPSY

SURGERY

Language lateralization by fMRI has been compared to Wada language testing in numerous studies (18), usually by assigning patients to categories such as "left dominant," "right dominant," or "mixed" on each test and calculating rates of concordance between the tests. The proportion of concordant cases depends on how these arbitrary categories are defined, as well as other factors such as the fMRI tasks and the numerical methods for calculating asymmetry. A sample size–weighted average across 23 such studies showed an overall concordance rate of 85%, a value that agrees closely with the rate observed in the largest study, which showed concordance of 86% in a sample of 229 patients (19). Thus, concordance between fMRI and Wada language lateralization tests is good but not perfect.

The longstanding use of language dominance categories (i.e., left, right, and mixed) is gradually giving way to the realization that language lateralization is a continuously graded rather than an all-or-none phenomenon, with relative degrees of dominance rather than distinct categories (20–22). Thus, while most patients who undergo left hemisphere surgery for epilepsy are left dominant for language, there is variation within this group in terms of the degree of left dominance. This variability raises the question whether graded degrees of language dominance are reflected in graded levels of risk.

A standard approach for expressing lateralization in fMRI studies is to calculate a laterality index (LI) expressing the asymmetry of activation in numerical form. The first such LI was based on a simple count of the voxels that survived statistical thresholding in each hemisphere (20). The formula (L - R)/(L + R), where L and R refer to the voxel counts in each hemisphere, yields a number that varies from +1 when all activated voxels are on the left side to −1 when all activated voxels are on the right. LI values obtained with this method vary somewhat as a function of the threshold used for defining activated voxels; thus, several authors have explored alternative asymmetry measures that do not require thresholding (21–24). No consensus regarding the optimal method for calculating activation asymmetry has yet emerged from these studies.

Predicting Naming Outcome

The primary cause of discordance between fMRI and Wada language testing is that fMRI tends to detect more right hemisphere involvement in language processes than the Wada (19). Many authors have assumed that this indicates a degree of inaccuracy on the part of fMRI (25), but the real "gold standard" in this case is not the Wada test but rather prediction of language outcomes. Which test is more accurate in predicting risk? To answer this question, one study (26) analyzed language fMRI in 24 left temporal lobe epilepsy (TLE) patients. The fMRI paradigm used a contrast between an auditory word comprehension task ("semantic decision") and a nonlinguistic tone discrimination task ("tone decision"). An analysis of this contrast is shown in Table 79.1, illustrating the use of controls for nonlinguistic aspects of the word comprehension task and the selective activation of phoneme perception and semantic processes (27). Asymmetry of activation for this task contrast is correlated with language lateralization on the Wada test (20). All patients also underwent Wada testing preoperatively and assessment of object naming using the Boston Naming Test (BNT) before and 6 months after anterior temporal lobe (ATL) surgery.

Table 79.1 Component Process Analysis of an fMRI Language-Control Task Contrast

	Semantic decision	Tone decision
Attention	+	+
Working memory	+	+
Motor response	+	+
Low-level auditory	+	+
Phoneme perception	+	
Semantic memory	+	
Concept retrieval, selection	+	

Thirteen patients (54%) showed variable degrees of decline relative to a control group of 32 right ATL patients. The fMRI LI was the strongest predictor of naming outcome ($R = -0.64$, $P < 0.001$), indicating that stronger language lateralization toward the left (surgical) hemisphere was associated with poorer naming outcome. This fMRI measure showed 100% sensitivity, 73% specificity, and a positive predictive value (PPV) of 81% in predicting significant decline. By comparison, a Wada language lateralization index showed a somewhat weaker correlation with outcome ($R = -0.50$, $P < 0.05$), 92% sensitivity, 43% specificity, and a PPV of 67%. The authors also created multivariate models to determine the contribution of fMRI relative to other noninvasive predictors. Both age at epilepsy onset and preoperative performance showed strong trends toward a correlation with outcome, and together, these variables predicted approximately 27% of the variance in outcome. Adding the fMRI LI to this model accounted for an additional 23% of the variance ($P < 0.01$). Addition of the Wada language asymmetry score did not further improve the model (R^2 change = 0.01).

Another study on this topic examined naming outcome in 10 left ATL patients who had discordant fMRI and Wada language results preoperatively (28). Such patients are relatively rare because the baseline rate of discordance is only approximately 15%, less than half of these discordant cases are likely to have left ATL surgery, and not all surgery patients are available for postoperative testing. Using optimized multivariate prediction models derived from 55 left ATL patients with concordant fMRI and Wada language lateralization, predicted change scores were computed using either the fMRI LI or the Wada language asymmetry index. Of the 10 cases, naming outcomes were more accurately predicted by the fMRI model in 7, more accurately by the Wada model in 2, and equally well by both tests in the remaining case.

Though based on relatively small samples, these results show how preoperative fMRI language lateralization can be used to predict risk for language decline in the setting of left ATL resection, allowing patients and physicians to more accurately weigh the risks and benefits of the surgery. It is crucial to note, however, that these results hold true only for the particular methods used in these studies (both of which were conducted at the same center) and may not be generalizable to other fMRI protocols, analysis methods, patient populations, or surgical procedures. Future studies should confirm these results using larger patient samples and test whether other fMRI protocols in current widespread use have similar predictive capability.

Tailoring Resections

Although many centers use fMRI language activation maps to plan resection boundaries, the evidence

supporting this approach is largely anecdotal, and several known limitations of fMRI suggest caution in using this approach. The largest obstacle is variability in the sensitivity of fMRI. As mentioned above, task contrasts used for fMRI language mapping vary considerably and produce markedly different activation patterns (2). Poor detection of semantic memory networks in the anterior and ventral temporal lobe is a particular problem (29). Regions declared inactive using one task contrast often show activation using a different contrast. Individual factors such as degree of head movement and variation in attention can markedly alter the magnitude of noise relative to the task-related signal of interest, resulting in large individual variation in sensitivity even for the same task contrast.

A second source of uncertainty in language fMRI is the potential for activation to be "nonessential." Language tasks typically engage attention and other nonspecific cognitive processes. These processes can produce activation on fMRI language maps, and resection of these nonspecific activation zones would not necessarily produce language deficits. More generally, language and other complex cognitive functions are supported by broad networks with a wide distribution across the brain. The effects of damaging a small region within such a large network are largely unknown. The clinical consequences of these problems with sensitivity and specificity are substantial. A brain region believed to be "safe" to resect because it fails to show activation may in fact provide an essential process that is not detected because of an insensitive task contrast or subject-specific noise. On the other hand, a brain region believed to be essential simply because it is activated may in fact be performing a nonessential function.

Although several published reports describe good outcomes using fMRI language maps to tailor resections (e.g., (30)), none of these studies incorporated quantitative measures of language ability, nor did they include control patients who did not undergo tailored resections. As discussed below, CSM remains the clinical standard for detecting essential language zones. Unlike fMRI and other activation methods, CSM produces a temporary functional lesion and therefore more directly indicates the potential effects of resection. Correlation between fMRI and CSM language maps has been highly variable across studies, likely reflecting variation in the tasks used and other methodologic factors, but appears to be moderate at best (31). Some centers use fMRI maps to identify brain regions to be examined with CSM, thereby increasing the efficiency of CSM and the number of stimulation trials that can be conducted at each electrode (32). This application assumes a high degree of sensitivity for fMRI, which, as noted above, is currently a problematic assumption.

LATERALIZATION OF EPISODIC MEMORY FUNCTIONS: FMRI AND WADA

Functional imaging of memory systems can assist with two clinical tasks: (i) lateralization of seizure foci in TLE, and (ii) assessment of risk to memory function from ATL surgery. For seizure focus lateralization, the memory portion of the Wada test may detect asymmetric dysfunction of the mesial temporal lobe (MTL), which can be used as an adjunct test for seizure focus lateralization (33,34). When functional asymmetry consistent with the side of seizure focus is demonstrated on Wada testing, seizure control is better than when no asymmetry or reversed asymmetry is observed (35–37). Although several studies suggest that MTL activation asymmetry on fMRI may also be correlated with side of seizure focus and seizure outcome in TLE (38–41), sample sizes in these studies have been small, and no studies have yet examined whether fMRI contributes additional predictive value beyond ictal EEG, ictal semiology, PET, structural MRI, and other markers of seizure focus lateralization.

The other goal of memory lateralization is to assess risk to memory function from ATL surgery. Verbal episodic memory decline after left ATL resection is observed in 30% to 60% of such patients (42–52). One main focus of the preoperative evaluation in ATL surgery candidates is, therefore, to estimate risk of verbal memory decline in patients undergoing left ATL resection. Nonverbal memory decline after right ATL resection is much less consistently observed in both groups and individuals (47,48,51,52).

The Wada memory test was originally developed for the purpose of predicting global amnesia after ATL resection (53), though its reliability for this purpose has often been questioned (54,55). Studies of its ability to predict relative verbal memory decline have been inconsistent, with several suggesting good predictive value (43,46,56) and others showing little or none, particularly when used in combination with noninvasive tests (48,51,52,57–59). Noninvasive tests that are modestly predictive of memory outcome include structural MRI of the hippocampus, interictal PET, preoperative memory function, and age at onset of epilepsy (42,44,48–52,60–63).

An often neglected key point in the discussion of memory lateralization is that the goals of seizure focus lateralization and memory outcome prediction call for fundamentally different methodologic approaches. In the case of seizure focus lateralization, the ideal functional test activates the MTL symmetrically in healthy people, thus allowing optimal detection of deviation from normal symmetry in either direction. In contrast, prediction of verbal memory outcome requires a procedure that specifically identifies verbal memory processes, which typically show strong lateralization. Pictures and objects are encoded into memory in both verbal and nonverbal forms, producing bilateral MTL activation in healthy people (64), and thus are ideal for detecting seizure focus lateralization. In contrast, bilateral activation responses to pictures may predict little or nothing regarding verbal memory outcome, because they represent a mix of verbal and nonverbal processes.

Predicting Verbal Memory Outcome with fMRI

Several studies examined the use of preoperative fMRI to predict verbal memory change from ATL surgery (for a detailed review, see (65)). Several studies (40,41,66) used pictorial scene-encoding tasks that activate the MTL bilaterally on fMRI, a pattern that suggests activation of both verbal and nonverbal memory systems. Prediction of verbal memory outcome using these paradigms was weak at best. In contrast, Bonelli et al. (67) examined activation during a word-encoding task and observed a strong relationship between hippocampal activation asymmetry and verbal memory change in 29 patients undergoing left ATL surgery. The method used an “asymmetry image” created in each individual by contrasting activation levels in mirror-symmetric voxels in the left and right temporal lobe. A small sphere around the hippocampal voxel with the highest asymmetry value was used as a region of interest (ROI) in each patient. The authors observed a strong correlation ($R^2 = 0.23$, $P = 0.008$) between activation asymmetry in this ROI during word encoding and change in verbal memory scores after left ATL surgery, indicating that greater asymmetry toward the left was associated with greater decline in verbal memory. This fMRI measure showed 100% sensitivity, 41% specificity, and 35% PPV for predicting a significant verbal memory decline.

An alternative approach uses language lateralization to predict verbal memory change (52), based on the assumption that material specificity of episodic memory encoding reflects the type of information the MTL receives from the ipsilateral neocortex. If so, then language lateralization should be a reliable indicator of verbal memory lateralization. Binder et al. studied 60 left ATL patients preoperatively with the semantic decision–tone decision fMRI contrast discussed above (Table

79.1), as well as a battery of verbal and nonverbal memory measures before and 6 months after surgery. All patients also underwent preoperative Wada language and memory testing. The strongest predictor of verbal memory change was preoperative memory performance ($R^2 = 0.44$, $P < 0.0001$). The next strongest predictor was fMRI language LI ($R^2 = 0.19$, $P < 0.001$). Wada memory asymmetry was only marginally predictive ($R^2 = 0.11$, $P < 0.05$) and in fact was a weaker predictor than Wada language asymmetry ($R^2 = 0.16$, $P < 0.01$). Age at epilepsy onset was also modestly predictive ($R^2 = 0.12$, $P < 0.01$). The noninvasive measures (preoperative performance, age at onset, fMRI LI) were combined in a multivariate model that explained 59% of the variance in verbal memory change. This model showed 90% sensitivity, 80% specificity, and 69% PPV for predicting significant decline. Addition of the Wada language and memory data did not significantly improve the model.

It is noteworthy that language lateralization, whether measured by fMRI or the Wada test, turns out to be a better predictor of verbal memory outcome than Wada memory asymmetry. The explanation for this apparent paradox rests on two hypotheses. First, verbal memory encoding processes tend to colateralize with language processes. Second, visual stimuli such as pictures and objects can be dually encoded as both names and visual objects. Wada memory procedures that use such stimuli (including the Wada test used by Binder et al.) therefore do not provide a measure of verbal memory lateralization, but rather a measure of overall memory lateralization that includes both verbal and nonverbal encoding processes. Thus, verbal memory lateralization is more tightly linked with language lateralization than with Wada memory asymmetry. Of greatest concern are patients who show marked declines in verbal memory postoperatively despite preoperative Wada results indicating lateralization of memory to the right side (52). In such cases, overall memory as measured by the Wada was lateralized to the right, but verbal memory remained on the left, a situation that cannot be determined using dually- encoded visual stimuli.

Summary

fMRI can be used to help predict the risk of verbal memory decline from left ATL surgery, using either asymmetry of hippocampal activation during a verbal encoding task or overall language lateralization. Prediction models can be further improved by combining fMRI data with indices of preoperative memory ability and age at seizure onset. In one large study, Wada testing did not improve prediction accuracy compared to a model combining fMRI and other noninvasive measures (52).

These results call into question the routine use of the Wada test for predicting material-specific verbal memory outcome, particularly if a validated fMRI test is available. Some centers use the Wada to assess risk for global amnesia, which can occur after bilateral MTL damage (53,68,69). According to this theory, anesthetization of the targeted MTL is necessary to discover whether the contralateral hemisphere is healthy enough to support memory on its own. Empirical observations, however, provide little support for such an approach. Global amnesia following unilateral temporal lobe resection appears to be rare in the extreme (70–72) and was usually associated with preoperative structural deficits of the contralateral hippocampus. Evidence suggests that contralateral hemisphere "memory failure" on the Wada test suffers from poor test–retest reliability and does not reliably predict amnesia (54,55,71,73–78). Wada testing is the only option for patients with contraindications to MRI or inability to comply with activation tasks. For other patients, we propose that use of the Wada test be reserved only for those at greatest risk for global amnesia, that is, patients undergoing unilateral ATL resection who have structural or functional evidence of damage to the

contralateral MTL. Figure 79.1 illustrates this decision algorithm.

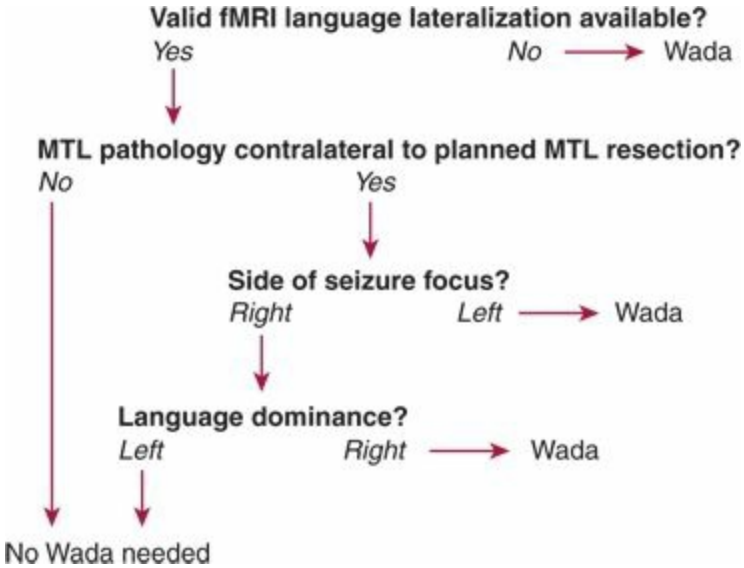

Figure 79.1. A suggested algorithm for use of the Wada test in patients undergoing surgery on the medial temporal lobe (MTL). Wada language and memory testing is generally recommended when a validated fMRI language lateralization protocol is unavailable or cannot be performed. Wada testing may also be helpful in patients with clear evidence of MTL pathology contralateral to the planned side of surgery, as these patients may be at risk for global amnesia. This risk is negligible, however, when surgery is conducted in the non–language-dominant hemisphere. Thus, if surgery is planned in the right hemisphere and the left hemisphere is language dominant by fMRI, Wada memory testing is likely of little predictive value.

MAGNETOENCEPHALOGRAPHY LANGUAGE MAPPING

MEG measures the magnetic fields that result from intracellular currents generated by excitatory and inhibitory postsynaptic potentials. In contrast to fMRI, this is a direct measurement of neural activity. In contrast to EEG, the sensors used in MEG are primarily sensitive to tangential sources (i.e., sources in the sulci oriented parallel to the surface of the head). Typical MEG systems provide hundreds of sensors spread across both hemispheres. The large number of channels and the more limited propagation of the magnetic fields allow for improved spatial resolution compared to typical scalp EEG recordings while retaining the excellent temporal resolution of EEG.

Activity measured with MEG must be modeled mathematically to deduce the source(s) responsible for the observed sensor signals, a process referred to as solving the inverse problem. Numerous methods have been used, ranging from modeling with a single equivalent current dipole (73–75) to modeling with thousands of potential sources distributed throughout the cortex (76–79). These models allow images to be generated depicting localized activity on the subject's MRI, referred to as magnetic source imaging. As with EEG, the signals can be characterized either by averaging phase-locked responses (evoked response) or by averaging changes in power within a specific frequency band (induced response).

As with fMRI, the choice of testing paradigm plays a significant role in the activations observed with MEG, and many different language paradigms have been used. Direct comparisons between these studies are complicated by differences in source localization method and other factors. Relatively few have compared MEG results with Wada language testing. In the most extensively studied protocol (73–75), patients performed an auditory word recognition memory task using

previously studied target words intermixed with distractor words. Evoked responses, averaged over target and distractor words relative to a resting baseline, were modeled using single equivalent current dipoles at 4-ms intervals, and LIs were computed by counting the number of late (>200 ms) dipole solutions in the superior temporal region of each hemisphere. In the largest of these studies (74), the MEG LIs agreed with Wada language testing in 74/85 patients (87%). A study performed at a different center using the same MEG protocol, however, showed complete agreement between MEG and Wada language testing in only 24/35 patients (69%) (75). Using more lenient criteria, the authors reported "complete or partial agreement" in 86% of the patients.

Bowyer et al. (76) used a silent verb generation task (think of an action associated with a presented noun; e.g., airplane—fly) and a silent picture naming task for MEG language lateralization and compared the results with Wada testing in 27 patients. A current density model called MR-FOCUSS was used for localization of the averaged evoked response relative to a resting baseline. LIs were computed for three different latency intervals: 150 to 550 ms, 208 to 270 ms (called "receptive language processing" by the authors), and 396 to 476 ms ("expressive language processing"). For the verb generation task, concordance with the Wada was 81% for the longest interval, 56% for the "receptive" interval, and 63% for the "expressive" interval. For the picture naming task, concordance was 78% for the longest interval, 48% for the "receptive" interval, and 89% for the "expressive" interval.

Hirata et al. (78) used a MEG paradigm in which patients silently read Japanese words. Sources of induced beta/ low-gamma (13 to 50 Hz) desynchronization were localized using a distributed model called synthetic aperture magnetometry (80). A language LI, calculated using the difference between left and right peak responses in a frontal ROI, was concordant with Wada language testing in 51/60 patients (85%). A similar smaller study examined induced beta desynchronization using a verb generation task. Lateralization by MEG was concordant with Wada language lateralization in 13/14 patients (93%) (79).

MEG shows promise as a noninvasive method for language lateralization, with a few studies showing concordance rates of roughly 80% to 85% with Wada language testing. These results should be validated in larger samples. Methods used in these studies have varied widely, and an optimal approach is not yet clear. No studies have tested the ability of MEG to predict language or verbal memory outcomes after surgery.

CORTICAL STIMULATION MAPPING

Direct electrical stimulation of the brain was initially used to identify the motor and sensory cortex (81). Stimulation of these areas typically yields positive phenomena, such as a movement or focal body sensation. In contrast, stimulation of language zones typically disrupts function; thus, language mapping requires the use of active tasks. Both the choice of task and the nature of the error with stimulation are important for understanding the potential impact of resection at or near the stimulation site (82). Three regions are typically targeted during CSM language mapping: the lateral frontal lobe, lateral temporal and inferior parietal lobes, and the basal temporal lobe.

Frontal regions associated with language processing include the inferior frontal and middle frontal gyri, and stimulation of this region has been associated with both language production deficits (e.g., writing or speech arrest) and comprehension deficits (83–85). Lateral temporal and parietal regions associated with language processes include the superior and middle temporal gyri, the angular gyrus, and the SMG. As with frontal lobe CSM, deficits in both language production and

comprehension have been reported with CSM in these posterior regions (84,86). Basal temporal language sites, typically located in the fusiform gyrus, have also been associated with both language production and comprehension deficits during stimulation (87).

It is important to recognize that disruption of language tasks during CSM may occur from a variety of distinct causes. Stimulation of the language cortex typically results in speech arrest, paraphasic errors, or comprehension errors; however, stimulation of other regions may produce similar responses, and differentiating between these findings is critical to avoid false localization. Stimulation over primary motor and premotor areas controlling the lips and tongue may result in difficulty speaking or even overt speech arrest. Stimulation over motor planning regions, such as the supplementary motor area, can produce negative motor deficits that disrupt speech. Careful attention to lip and tongue movements along with the use of repeated simple phonemes (e.g., "ba-ba-ba") can help identify motor phenomena that are interfering with testing. Stimulating at a lower intensity may also help clarify the nature of the deficit in cases of speech arrest, as the lower intensity will often produce a less complete impairment, allowing observation of dysarthric or apraxic deficits or changes in speech volume or pitch associated with these motor areas. Experiential phenomena elicited by stimulation (e.g., hallucinations and déjà vu) may distract patients enough to cause arrest of speech or failure to attend to the task. Reminding the patient to report any such sensations, and regular questioning to assess what the patient felt with any observed response, will help identify potential distracting phenomena. Another type of response that can limit testing is the presence of ipsilateral facial or head pain resulting from dural spread of the current. Focal seizures can also be triggered by stimulation, leading to disruption of speech as an ictal phenomenon. Simultaneous EEG monitoring during stimulation will alert the clinical team to afterdischarges or seizures that may be interfering with participation.

Given the differences in language deficits that can occur following injuries to these anatomically distinct regions (88), a targeted approach to mapping the different regions with different task paradigms appears reasonable. However, studies have demonstrated a broader range of stimulation-induced deficits than would be predicted based on lesion localization data. One such study involved 45 patients with subdural grid electrodes implanted over the left hemisphere (84). Language tasks included assessment of automatic speech production (recitation of the alphabet, counting), spontaneous speech production (repeating single words or short phrases, reciting their zip code), auditory comprehension (following one-, two-, or three-step commands and answering simple questions), and written comprehension (reading silently a question or command and answering/following). The lateral frontal lobe was examined in 43 patients. Language production deficits were identified in 25 (58%), and language comprehension deficits were identified in 11 (26%); 30 (70%) had at least one detected language site. Among 43 patients with lateral temporal electrode coverage, 38 (88%) had at least one detected language site. Deficits in language production occurred in 29 patients (67%), and deficits in language comprehension were observed in 26 (60%). The basal temporal lobe was examined in 29 patients, and 13 (45%) had at least one language site identified; detailed analyses of the elicited dysfunction were not obtained in all patients. There was no difference in the frequency of comprehension disruptions between the anterior and posterior language regions, whereas language production was more likely to be disrupted in the anterior language area.

In an attempt to improve correlation with functional imaging studies, Ojemann et al. (89) used a verb generation task (generate a verb associated with a visually presented noun) during CSM. These results were also compared with an object naming task. A total of 14 patients were studied, 10 of

these during an awake craniotomy. Verb generation sites were identified in 13 patients, with 5 demonstrating frontal disruption sites and 11 showing lateral temporal lobe sites; three patients had both frontal and temporal sites. Spatial overlap between verb generation and object naming sites was incomplete. Ten patients had sites where stimulation disrupted verb generation but not object naming, and seven patients had sites where stimulation disrupted object naming but not verb generation. These data further highlight the limitations of a strictly anatomically driven approach to stimulation paradigms. Of note, the resections in this series did not involve the verb generation language areas, so their clinical importance for resection planning could not be assessed.

These data underscore the importance of a comprehensive approach to language assessment during CSM in any potential language regions. Task paradigms used for mapping at a given center are often specific to the center, often with strong influences from the primary training sites of the physicians at that center.

Despite the widespread use of CSM as a "gold standard" for localization of language in the operative setting, data supporting its usefulness for preserving language function are limited. The 14 patients described by Ojemann and Dodrill (90) underwent CSM during picture naming, sentence reading, and a short-term verbal memory task. Postoperative language deficits were more likely when the resection fell within 2 cm of a site showing stimulation-evoked naming impairment. Similar results were seen for sites with stimulation-evoked short-term verbal memory impairment, but this was less reliable than picture naming.

These data together with the previous picture naming work of Penfield and Roberts (91) led to the establishment of picture naming as one of the standard tasks for CSM language mapping, and the resection of visual naming sites was avoided. While CSM was most often applied to areas on the lateral convexity, stimulation in the basal temporal regions was also found to disrupt language functions (92). This finding is of clinical significance, because, unlike posterior lateral temporal regions where positive naming sites are often observed, the basal temporal cortex is often within the ictal-onset zone and thus the planned area of resection. In a series of patients mapped with multiple language tasks (92), 13 whose resections included basal temporal language-positive sites showed a 9% mean decrease on the BNT postoperatively, compared with a 4% decrease in 12 patients with no language-positive sites resected ($P = 0.03$).

The validity of CSM for preventing postoperative naming deficits was investigated in a multicenter retrospective study capitalizing on variation in the utilization of CSM and surgical approaches between centers (93). A total of 217 patients who underwent left ATL surgery were categorized into four groups: those who underwent tailored temporal resection with CSM either intraoperatively ($n = 23$) or extraoperatively ($n = 27$) and those who underwent temporal lobectomies without CSM either with a standard temporal lobectomy ($n = 118$) or with a modified temporal lobectomy sparing the STG ($n = 49$). All four groups had a statistically significant decline in mean postoperative naming (BNT) performance. There was no difference in BNT change score between the two groups who had cortical mapping and the two groups who did not ($P > 0.35$). Among those who had mapping, there was no difference in outcome between those undergoing intraoperative versus extraoperative mapping ($P > 0.4$). Among those who did not have mapping, there was no difference between standard and modified temporal resection ($P > 0.43$).

As this study and others illustrate, some patients experience postoperative naming decline despite CSM with picture naming, raising doubts about the sensitivity of this task. Hamberger et al. (94) studied an alternative task in which subjects produce a name in response to an auditory verbal description (e.g., "What does a king wear on his head?"). CSM using this task detected more language

sites in the ATL than did a picture naming task. In a subsequent study (95), 19 patients underwent tailored resections designed to stay at least one centimeter away from picture naming sites, without regard to the description naming results. Declines in postoperative naming function were seen in 3/12 patients (25%) with preservation of both visual and auditory naming sites and in 6/7 patients (86%) in whom visual naming sites were preserved but at least one description naming site was resected (P = 0.02). Interestingly, resections in both groups mainly caused declines in picture naming. This dissociation between the modality tested versus the modality impacted postoperatively challenges the assumption that cortical stimulation necessarily mimics the postoperative state.

Although distinct anatomic regions responsible for language and associated with language responses during CSM have been identified, a broad assessment of language functions including both language production and comprehension is recommended. Despite this recommendation and the continued use of CSM as a clinical gold standard, the evidence that tailoring resections based on CSM (regardless of the language paradigm utilized or the region being resected) actually leads to sparing of language functions is relatively limited. Optimization and validation of CSM remains a work in progress.

ELECTROCORTICOGRAPHY

Direct cortical stimulation not only requires an invasive procedure to gain access to the cortex for stimulation, it also delivers small amounts of current that may produce afterdischarges or seizures, which may limit or even preclude reliable testing at one or more sites. Testing is done on one site at a time, which can result in a lengthy procedure. The use of implanted intracranial electrodes for stimulus-induced mapping (electrocorticography, or ECoG) allows simultaneous testing of all the recording electrodes without the application of current. This offers the possibility of a shorter procedure that can map a broader area of cortex without the risk of induced seizures.

Evidence concerning the validity of ECoG for language mapping is currently limited to a few small studies comparing ECoG with CSM language mapping. The majority of these focused on induced changes in the gamma or high gamma frequency bands, though desynchronizations in lower (alpha and beta) frequency bands have also been explored. In one of the larger examples, involving 13 patients, the sensitivity of ECoG for identifying naming or mouth-related motor function areas was 43% and the specificity was 84% (96). Another study with 13 patients reported a sensitivity of 91% and specificity of 62% using an auditory description naming task (97). A similar study with 12 patients reported a sensitivity of 63% and specificity of 57% (98). In all of these studies, ECoG tended to show more language sites than CSM. No studies have yet examined the effects of resecting or sparing ECoG activation sites on language outcome.

PRAGMATIC ISSUES

Not all functional mapping techniques are available at all centers, and not all patients are candidates for all types of studies. Expertise with fMRI varies considerably from center to center, and regrettably some centers still conduct language and memory mapping studies without input from cognitive scientists, often resulting in data of dubious value. MEG and ECoG are not universally available at all surgical centers, and expertise and methodologic approaches with these techniques also vary substantially. Patients may be unsuitable for fMRI because of claustrophobia, implanted devices, or inability to perform activation tasks. Restrictions on MRI in patients with implanted

devices have lessened in recent years, and even many patients with vagal nerve stimulators and cardiac pacemakers can be scanned under certain conditions (99–101). Correlation between fMRI and Wada language testing has so far been demonstrated only using active tasks that induce changes in the level of language or memory encoding in which a patient is engaged. As discussed above, the use of "passive" tasks is unlikely to accomplish this modulation of higher cognitive activity reliably. Although language lateralization measures obtained using active tasks are robust to variation in the level of task performance (19,102), patients should at a minimum perform above chance levels to ensure that there is some degree of engagement in the tasks. When a validated fMRI protocol is unavailable, or a patient cannot undergo fMRI, Wada testing for language and episodic memory lateralization is the current preferred alternative.

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CHAPTER 80 MAPPING MOTOR FUNCTION

MARTIN STAUDT, JUAN CARLOS BULACIO, AND DILEEP R. NAIR

INTRODUCTION

The motor region of the brain occupies the caudal aspects of the frontal lobe. Brodmann divided this region into two main areas: area 4 (or BA4) called the primary motor (or M1) region and area 6 (or BA6) called the premotor region. This correlates with the functional cognitive–motor gradient of the frontal lobe distributed along a rostrocaudal axis. The cognitive aspects of motoric function are more rostrally distributed within the premotor region, whereas the caudal aspects involved in the execution of movement are within the primary motor cortex (1).

Investigations of patients with focal epilepsy arising in the frontal lobe require some comprehension of the spatial relationship to these motor regions in making sense of seizure semiology as well as in planning epilepsy surgery. The evaluation for epilepsy surgery attempts to identify epileptic regions of the brain and its relationship to any adjacent eloquent cortex (2). The identification of cortical and subcortical structures harboring sensorimotor functions is a crucial step in the planning and execution of surgical procedures, which potentially involve or neighbor these structures. Of the many primary and nonprimary sensorimotor areas in the human brain, the identification of primary motor cortex (M1) and of primary somatosensory cortex (S1) is most critical, since lesions in these areas always bear the risk of permanent deficit. Nonprimary motor areas (like the supplementary motor area [SMA], premotor regions, or the secondary somatosensory cortex [SII]) are less critical in this respect. Resection of the SMA region could lead to temporary contralateral weakness and even mutism, but these deficits usually resolve over a period of one to several weeks (3). This chapter therefore focuses on the mapping of M1 and S1, and its relevance for epilepsy surgery.

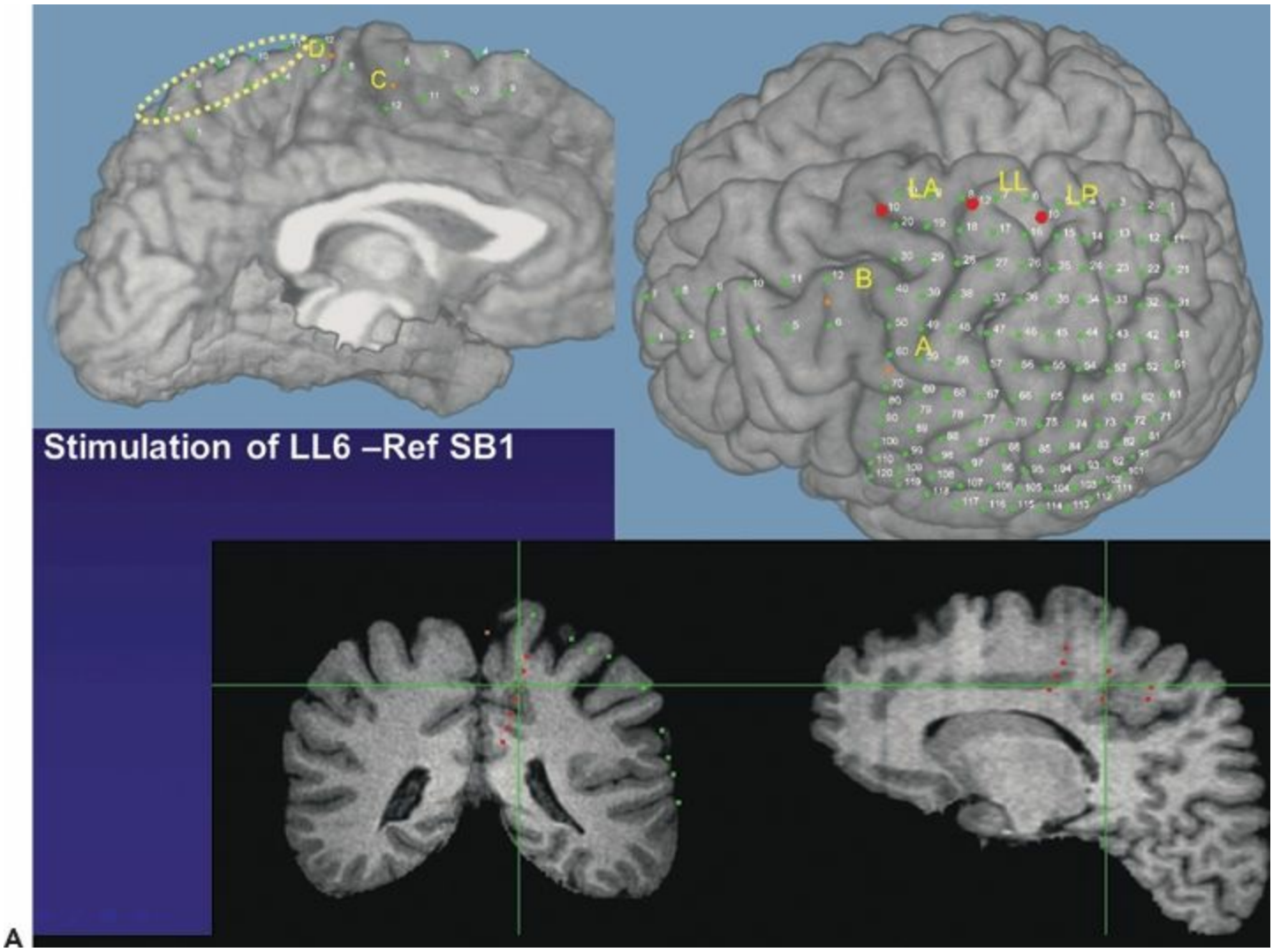
INVASIVE MAPPING

Extraoperative Direct Electrical Cortical Stimulation

Direct electrical stimulation of the cerebral cortex has been used for over 50 years in the localization of eloquent cortex (4). This method of mapping can be performed during surgery or with the use of chronically implanted subdural or depth electrodes. This section mostly discusses eloquent function mapping with cortical stimulation in extraoperative setting using subdural electrodes. Identification of eloquent cortex located in or near the epileptogenic zone is often one of the primary indications for using invasive recordings (5).

Cortical stimulation via subdural electrodes may produce two observable effects in the motor cortex: (a) a positive phenomenon, that is, activation of some function, such as clonic or tonic

movements, or (b) a negative phenomenon, that is, interference with a function, such as cessation of motor activity or loss of muscle tone. Cortical stimulation also has the potential to induce seizures, and therefore, continuous electrocorticographic monitoring is essential to monitor for afterdischarges. Afterdischarges are epileptiform discharges that may be elicited by electrical stimulation. Monitoring for afterdischarges can inform adjustment of stimulation parameters to prevent clinical seizures. It is also important not to ascribe function to a region of cortex that was associated with afterdischarges as the resultant clinical manifestation may have occurred based on the propagation to a site distant from the region that was stimulated (Fig. 80.1).



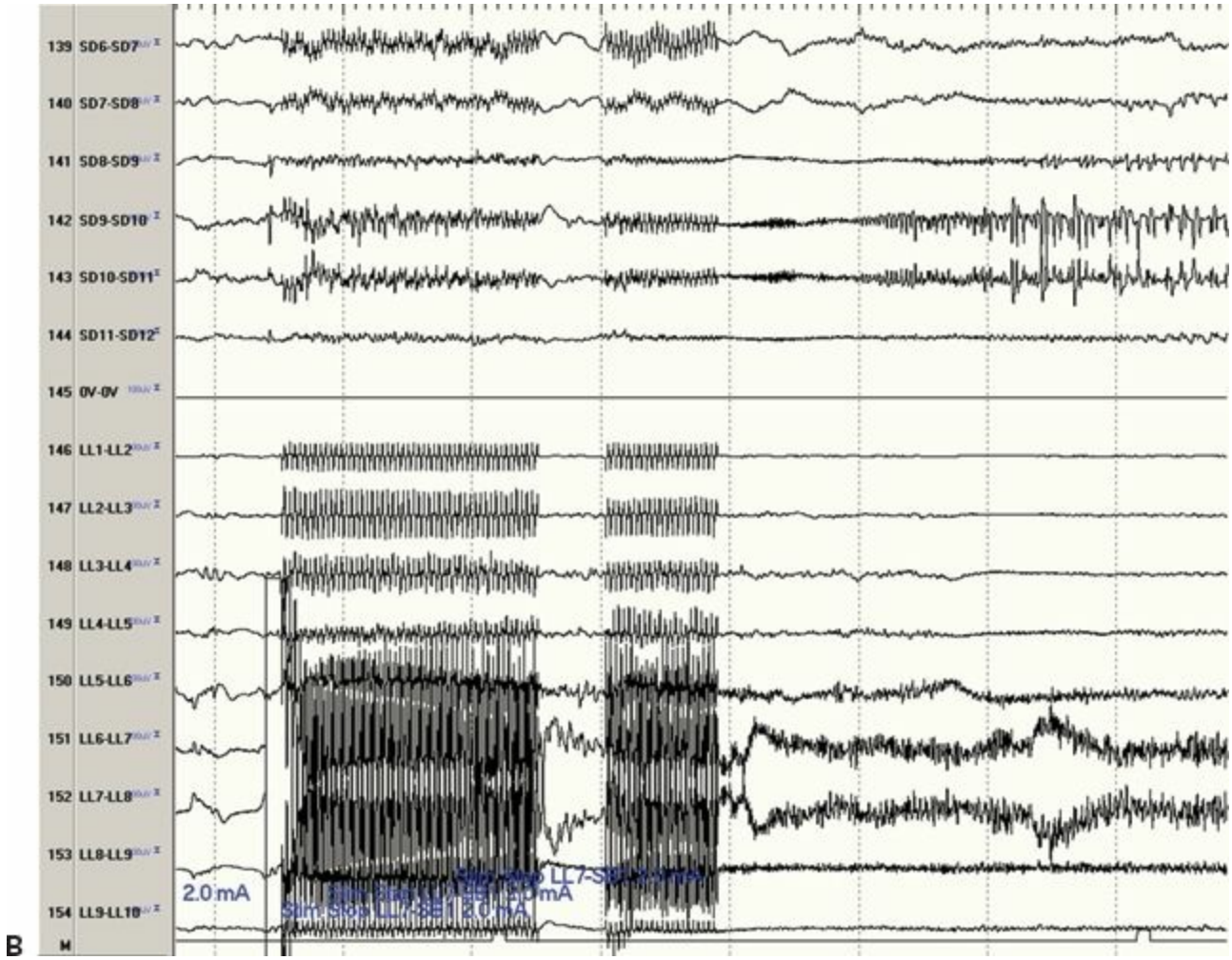


Figure 80.1. Figure A is an MRI coregistration of four subdural arrays (plates) and three depth electrodes. The subdural arrays include a high-density 10 × 12-electrode array (labeled "A" plate) and three 2 × 6-electrode subdural arrays (labeled "B" plate covering the left dorsolateral frontal cortex, "C" plate covering the mesial left frontal cortex, and "D" plate covering the mesial parietal cortex). The three depth electrodes each have eight electrode contacts and are placed in the caudal portion of the superior frontal gyrus (LA depth), in the precentral sulcus (LL depth), and close to the central sulcus (LP depth). Figure B shows the electrocorticography during electrical stimulation of the LL depth electrode. The channels are displayed in a bipolar recording of the "D" plate and LL depth. Stimulation of depth electrode LL6 referenced to subdural electrode B1 elicited an afterdischarge noted most prominently at subdural electrode D10 greater than at subdural electrodes D7, D8, D9, and D11.

Although patients are often weaned from their anticonvulsants during their stay in the epilepsy monitoring unit in order to better assure that seizures are captured, they are often restarted on anticonvulsants prior to the beginning of stimulation testing, typically by acutely loading them the day before. Reinstitution of anticonvulsant medication acutely without titration, however, may complicate cortical stimulation testing, as patients may become fatigued or toxic, making interpretation of clinical symptoms related to cortical stimulation more difficult. Stimulation mapping may be less reliable in the setting of general anesthesia. Some functions, such as language, can only be tested in the awake state. Mapping language in cooperative patients can be performed either during an awake craniotomy or in the invasive EEG–video monitoring unit (2).

Stimulation and Testing Procedure

Cortical stimulation is carried out in a systematic fashion in order to adequately map the accessible functions. Completion can sometimes take several days. The stimulation parameters used at the Cleveland Clinic are as follows: 25 Hz, biphasic, constant current stimuli, of duration 0.3 ms, with intensity ranging from 1 to 15 mA. The stimulus is applied to an "active" electrode, while a distant

"reference electrode" in a noneloquent region serves as a nonactive current sink. The active electrode is varied electrode by electrode throughout the entire grid, thereby testing the function of the cortical region underlying each electrode in turn. When the stimulus is applied to two adjacent electrodes, the typical close bipolar configuration, ascertaining which of the two electrodes elicited the given functional effect can be difficult. Therefore, many neurophysiologists initially stimulate all involved electrodes covering adjacent electrodes of the area of interest and subsequently confirming electrodes with suspected function during stimulation against a "silent," usually more distant, electrode. The stimulus intensity is increased in steps of 1 to 2 mA while carefully watching for functional changes as well as for the occurrence of afterdischarges.

When stimulation testing has been completed, a map outlining the various eloquent functions can be compared with the maps of ictal and interictal activity to help guide surgery resection margins. In the ideal situation, areas found to be responsible for eloquent functions are separated from the epileptogenic zone.

In general, surgical resection of eloquent cortical areas identified by cortical stimulation will lead to neurologic deficits. There are exceptions, however, and surgical removal of some "eloquent" cortical areas (such as primary motor face area) leads only to temporary neurologic deficits, with complete or almost complete neurologic recovery.

Neurophysiologic Effects of Cortical Stimulation

There are three general types of neuronal structures that can be affected by electrical stimulation: local neurons, afferent inputs, and fibers of passage. The current density, membrane depolarization, or hyperpolarization can affect the voltage distribution seen in the tissue medium generated by stimulation (6). The stimulation-induced membrane polarization in turn affects voltage-gated ion channels to induce action potentials, which in turn results in the clinically observed behavioral response (2). However, a neuron can either be activated or suppressed in response to extracellular stimulation depending on its position in relation to the electrode and the stimulation parameters being used. The sum of the effect from stimulation to neuronal output is made up of the direct effect on local neurons and the indirect effect of induced transsynaptic excitation and/or inhibition (2). Electrical stimulation of the human cortex is one experimental model that could reproduce the effect of activation of the cortex by an epileptiform discharge (7). Depolarization and hyperpolarization of cell membranes produces action potentials, which results as positive or negative clinical effect. Positive or negative clinical effects are dependent on stimulus intensity and stimulated area (8–10).

Mapping Primary Motor and Primary Sensory Areas

Direct cortical stimulation of the premotor and motor areas has been widely used to localize human motor function. The main objective is to identify the primary motor cortex so that surgical damage can hopefully be avoided in cases where the anatomical landmarks may have been distorted due to the presence of a lesion or in nonlesional cases where the resection needs to be maximized (11). Penfield's and Jasper's description of the somatotopic distribution of human motor function in the primary motor cortex has stood the test of time with only a few variables patterns observed in individual patients (4). Using gradual increments in the square wave biphasic stimuli, the patient is observed for motor responses involving contralateral muscle contraction. For the most part, the central sulcus is a reliable demarcation separating motor and somatosensory cortex, and there is a

consistent relationship among tongue, face, thumb, and finger in the dorsoventral axis (Fig. 80.2). Somatosensory function can be elicited from the human brain by electrical stimulation, from three areas—the primary sensory cortex (SI) in the postcentral gyrus, the SII in the frontal and parietal operculum, and the supplementary sensorimotor area in the mesial surface of the frontal and parietal cortex. The SI can be defined as the postcentral or anterior parietal region. The clear somatotopy of SI corresponds to that of the motor strip with the exception of the representation of the genitals that is found only in the postcentral cortex (12).

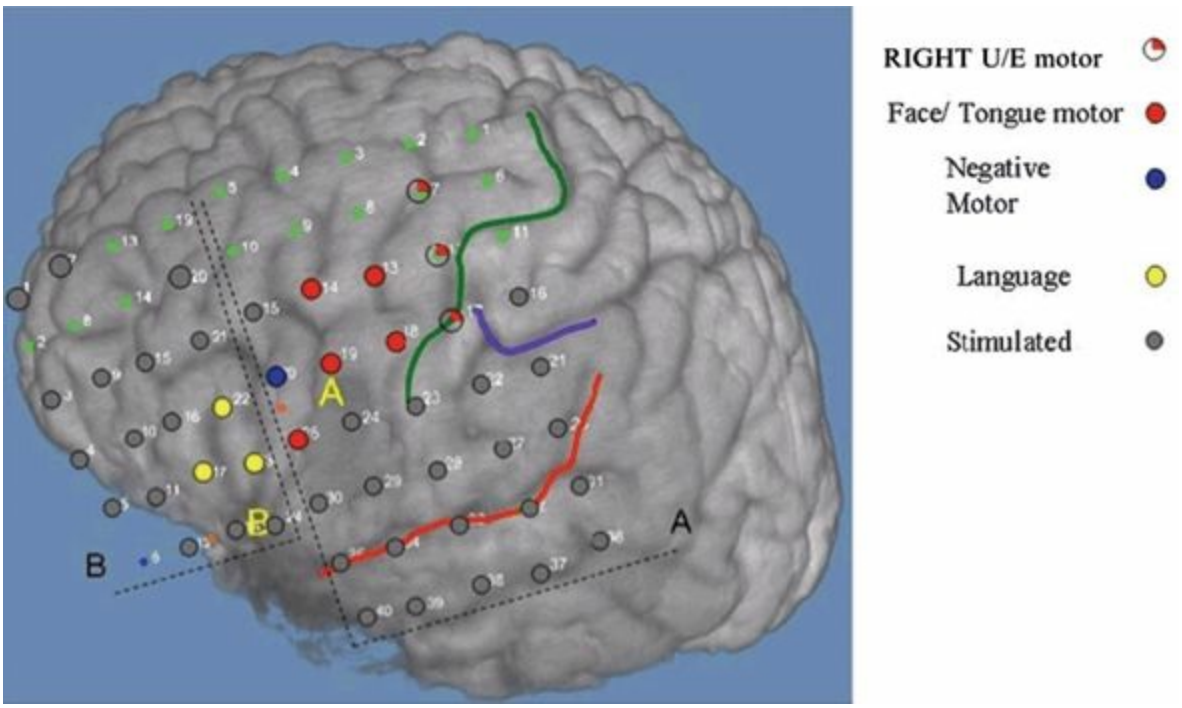


Figure 80.2. An 18-year-old girl with severe pharmacoresistant epilepsy and encephalomalacia in the left inferior frontal gyrus posterior to pars triangularis and pars opercularis. Grid A (5×8). Grid B (4×6). Positive motor function (red), negative motor function (blue), motor speech (yellow), electrodes stimulated without clinical manifestations (gray), central sulcus (green line), sylvian fissure (red line). (U/E, upper extremities).

Special Considerations in Children

Cortical mapping in children poses additional unique challenges. The changes inherent to a developing nervous system and absence of firm guidelines for electrical safety necessitate that the energy and charge requirements be kept to a minimum. In addition, the cooperation from pediatric patients is commensurate with the age and level of development and as such may be limited. This makes it challenging to obtain a reproducible objective study of cortical stimulation in selected patients with mental handicaps and in the very young (13).

The stimulation paradigm in infants and young children could be different from used in adults. The longer chronaxies characteristic of immature cortex and poorly myelinated nervous system require increments of both stimulus intensity and pulse duration in order to approach the chronaxie while minimizing the energy required eliciting a response. Stimulation is begun at a low intensity (1.0 mA) and gradually increased in increments of 0.5 to 1.0 mA, keeping an eye on afterdischarges and/or clinical response. Pulse durations are increased from a starting level of 0.3 ms up to a maximum of 1.0 ms. Jayakar et al. (14) were also able to demonstrate that most clinical responses in children were obtained at or above the afterdischarge threshold. This was felt to be a result of maturational factors giving rise to variations in the coupling of functional responses to afterdischarges. Faced with

an absence of clinical response in the presence of afterdischarge therefore does not exclude the presence of eloquent cortex under that electrode. Motor tasks administered must be tailored to the patient's age and neurocognitive status.

Response Characteristics

Motor responses can be obtained at all age groups with some ontogenic trends. In children younger than 2 years of age, tongue movements are difficult to elicit, and they may demonstrate bilateral rather than unilateral responses from the lower face when the lower rolandic region is stimulated. Individual finger movements are usually first manifest at or after 3 years of age. Clonic finger movements appear after tonic finger movements. These observations are likely to be a result of the maturing systems in Brodmann area 4.

Cortical Somatosensory Evoked Potentials

The mapping of the evoked cortical response to peripheral nerve stimulation can give clues to the localization of central sulcus as well as somatotopic organization of the sensorimotor cortex of hand, face, and leg regions. The responses are cortically generated contralateral to the side of peripheral nerve stimulation over the primary somatosensory cortex. In this regard, the responses from cortical evoked potential mapping can be used to cross-check the functional mapping of other modalities such as cortical stimulation. This may be particularly important in children in whom it may be difficult to reliably interpret responses from cortical stimulation (15), or in patients with malformations around the sensorimotor cortex (16).

The standard methodology for somatosensory evoked potentials applies when performing cortical somatosensory evoked potentials (SEP) mapping. An electrical transcutaneous monophasic stimulation (current durations of 100 to 300 μsec) is applied over a peripheral nerve. Median nerve at the wrist, posterior tibial nerve at the ankle, and mandibular branch of the trigeminal nerve are common sites of stimulation for cortical SEP mapping of the hand, foot, and face regions, respectively. Due to the stimulation artifact encountered while performing trigeminal nerve stimulation, the polarity of the stimulation is alternated in order to diminish the stimulus artifact. The intensity of the stimulation is set either at motor threshold or slightly above motor threshold. Stimulus rates of 1 to 10 per second are commonly used, and averaging of 500 sweeps usually results in good signal-to-noise recordings from scalp somatosensory evoked potentials (17). Cortical SEPs usually can be recorded with less number of sweeps as the signal-to-noise ratio is five to eight times higher than with scalp recordings. Band pass should be set from 3 Hz to 2000 Hz.

Cortical SEP mapping is obtained using subdural electrodes placed over the mesial and lateral convexity of the frontoparietal cortex. These responses can be recorded acutely during surgery or in the extraoperative setting. Cortical SEP responses to median nerve stimulation show initial peak latencies around 20 ms in adults. Responses consist of an initial negativity in the hand postcentral gyrus area (called N1 or N20) and a smaller positive polarity in the precentral region (called P1 or P20) (18,19). These two opposite polarity potentials make a phase reversal between the post- and precentral gyrus across the central sulcus in a referential derivation (Fig. 80.3.) (20). Following these initial N1/P1 responses, a second prominent positive peak (P2 or P25) response can be seen that appears over the postcentral gyrus. These occurrences of these waveforms can be explained by a two-dipole model over the postcentral gyrus (18,19). The generator of the initial N1/N20 response is

thought to be in the posterior wall of the central sulcus (Brodmann area 3b). The horizontal dipole in area 3b thus produces a widely distributed polarity inversion across the central sulcus. The source of the P2 or P25 response is thought to be due to a radially oriented generator at the crown of the postcentral gyrus (Brodmann areas 1 and 2), which is more narrowly distributed with no polarity inversion.

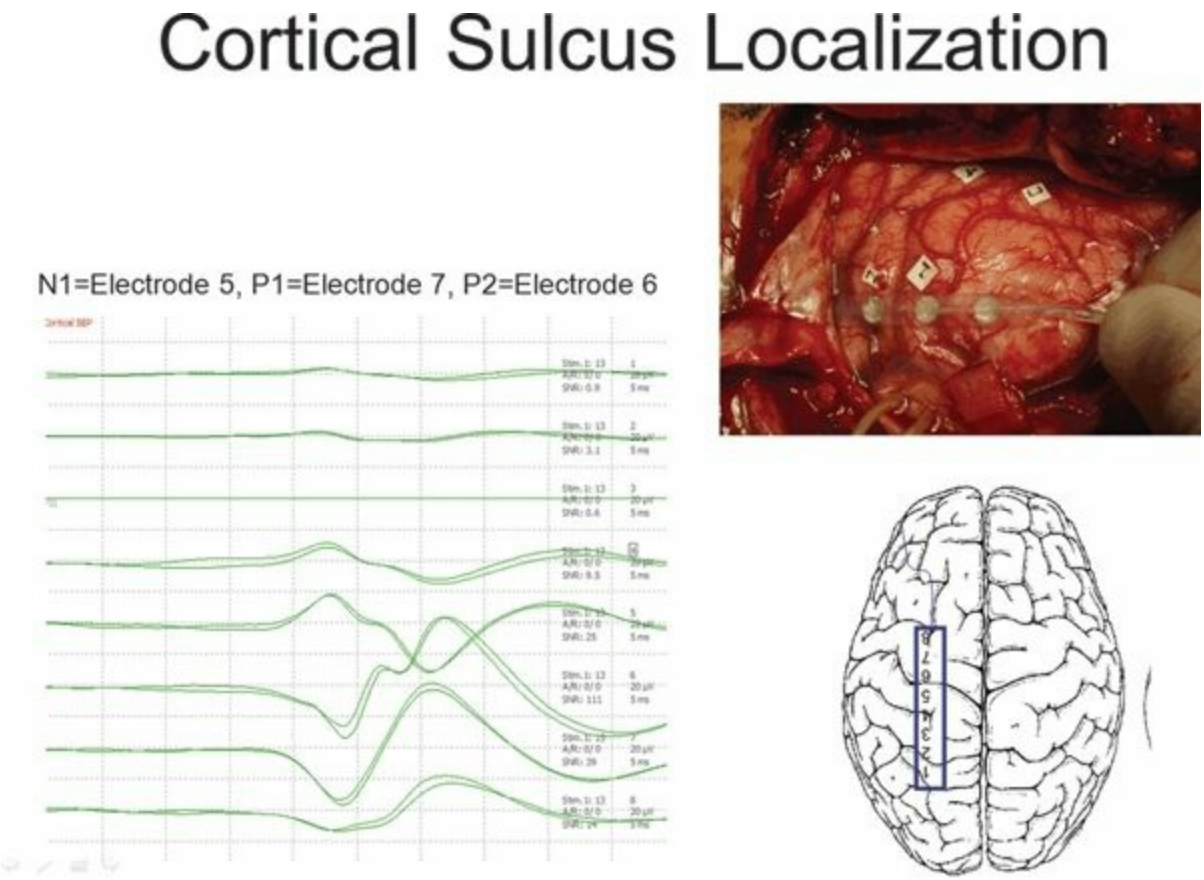


Figure 80.3. Cortical somatosensory evoked potentials (SEP) mapping performed intraoperatively on a 1×8 subdural strip placed over the left frontoparietal lateral convexity. The recordings are referenced to a needle electrode placed in the surgical scalp incision. The N1 or N20 response is seen maximally at electrode 5, the P1 or P20 response is seen at electrode 7, and the P2 or P25 response is seen at electrode 6.

Trigeminal nerve stimulation produces a cortical SEP response around 15 ms, with similar polarity inversion across the central sulcus with a N15 response over the face postcentral gyrus and P15 over the face precentral gyrus. The P15 response is not always seen even when a N15 is obtained (21). Posterior tibial cortical SEP response shows an initial positive peak around 37 ms (called the P37) seen over the medial surface of the mesial parietal lobe in the region of the leg postcentral gyrus. This component has a quite steep fall off and usually makes no polarity inversion (22).

NONINVASIVE MAPPING

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive procedure that can be used to search for cortical areas sending out corticospinal motor projections. During a TMS examination, short but strong magnetic pulses are applied via handheld coils to the surface of the head, which induce an

electric current in the underlying brain tissue. When the coil is positioned over the primary motor cortex, this electric current is transmitted transsynaptically to pyramidal cells. In these cells, a volley of action potentials is generated that travels down the corticospinal tract, depolarizes the alpha motor neurons in the anterior horn of the spinal gray matter, and thus produces a short muscular contraction. This muscular contraction can be recorded via surface electromyography electrodes, the so-called motor evoked potential (MEP). With the use of focal "figure-of-eight" coils, the stimulation is highly specific, so that rather detailed somatotopic information can be obtained for the stimulated motor cortex. TMS is easy to perform, inexpensive, and not painful nor harmful; the method has, however, several disadvantages:

- Contraindications have to be taken into account (similar to MRI).
- There might be a—very low—risk to induce a seizure in epileptic patients.
- Infants, toddlers, and preschool children often have high stimulation thresholds, which makes it sometimes impossible to obtain useful results in this age group.
- Many antiepileptic drugs further increase the stimulation threshold.
- A basic level of patient compliance is required.

Although being quite specific, the spatial information that can be obtained from "standard" TMS is rather crude, since only stimulation points on the scalp can be determined for certain target muscles. This disadvantage can be overcome with the additional use of neuronavigation together with TMS, which allows a 3-D co-registration of the stimulation points with a 3-D MRI data set, so that the stimulated cortical structures can be identified. Nowadays, several manufacturers offer such "neuronavigated TMS systems," which are increasingly used as a noninvasive alternative or in preparation of more invasive mapping procedures prior to epilepsy surgery.

Due to its noninvasiveness, TMS also allows an investigation of brain structures remote from the site of the operation. Most importantly, it allows the investigation of the contralesional hemisphere, searching for the phenomenon of "interhemispheric reorganization of primary motor representations"—which can be of utmost importance in the planning of resections including the central (rolandic) region of one hemisphere, for example, for hemispherectomies.

When cortical malformations or early brain lesions involve the primary motor cortex or the corticospinal tract of one hemisphere, the contralesional hemisphere can maintain its (normally transient) ipsilateral corticospinal projections (23,24). Thus, the contralesional hemisphere can "take over" motor control of the (paretic) extremities. This phenomenon can easily be studied using simple focal TMS: In these patients, TMS of the contralesional hemisphere will elicit MEPs in target muscles of both the contralateral (nonparetic) side and of the ipsilateral (paretic) side of the body, with a similar latency (difference typically not more than 1 ms) (25). There is growing evidence that this finding (short-latency MEPs in the paretic hand after TMS of the contralesional, but not of the lesioned hemisphere) predicts preserved hand function after resections of the rolandic areas or hemispherectomies of the lesioned hemisphere (26).

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a second noninvasive procedure that permits mapping of the sensorimotor system. In contrast to TMS, fMRI is not specific for the primary motor cortex, but typically shows several components of the sensorimotor system, including M1S1, but also

areas like the SMA, premotor cortex, or the cerebellum.

fMRI also allows for an investigation of somatotopy. In the clinical setting, most centers have a set of task for the visualization of upper and lower extremity as well as for the face. At the pediatric epilepsy center in Vogtareuth, we use active or passive fist clenching, active or passive flexion/extension of the toes, and "kissing movements" of the lips. In sufficiently cooperative subjects, this method allows reliable identification of the somatotopic aspects of the pre- and postcentral gyrus (M1S1). This can be helpful when lesions or malformations have distorted the anatomical landmarks that are normally used for the identification of M1S1 or when growing tumors have shifted these representations. In the absence of interhemispheric motor reorganization (see above), active and passive movement will produce similar results, so that in less cooperative subjects, one can rely on passive movements alone.

In patients with interhemispheric reorganization of M1, however, the interpretation of active and passive hand movements becomes rather complex:

Interhemispheric reorganization (as described above for corticospinal motor projections) is apparently not available for primary somatosensory projections. For these projections, however, a different mechanism of "developmental plasticity" is available: Due to the late maturation of thalamocortical projections, they can "bypass" even large white matter lesions and still reach the postcentral gyrus to form the primary somatosensory cortex (27). Therefore, many patients with ipsilateral corticospinal motor projections show a "hemispheric dissociation" between an (ipsilaterally reorganized) M1 representation of the paretic hand, while its S1 representation is still organized contralaterally, that is, in the lesioned hemisphere (28). And since fMRI of active movements with the paretic hand activates both M1 and S1, these patients show activation of both rolandic areas—ipsilateral (contralesional) M1 and contralateral (ipsilesional) S1. In contrast, passive hand movements will, in this situation, only activate the contralateral (ipsilesional) S1. But even when this typical constellation is identified, TMS must still be recommended to test both rolandic activations for the presence or absence of corticospinal motor projections (Fig. 80.4).

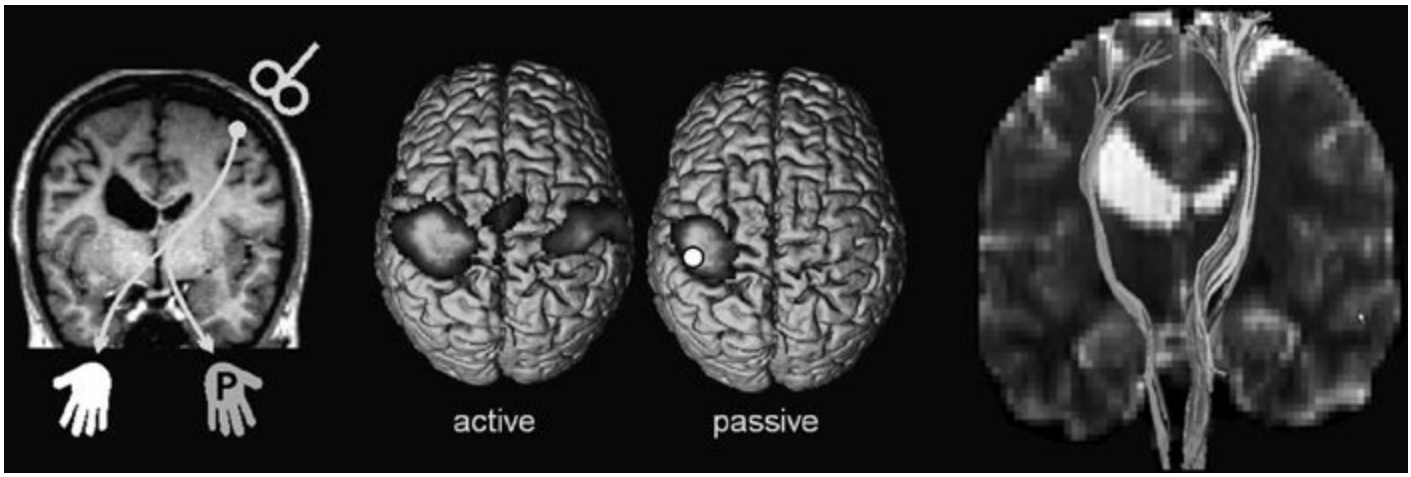


Figure 80.4. An example of a patient with a large unilateral periventricular brain lesion and ipsilateral corticospinal projections from the contralesional hemisphere to the paretic hand (left). fMRI during active movements of the paretic hand (P) reveals bilateral activation of the rolandic (pericentral) cortices; during passive movement of the paretic hand, only the contralateral rolandic area in the affected hemisphere is activated, indicating a contralaterally preserved primary somatosensory (S1) representation of the paretic hand in the affected hemisphere. Accordingly, the white dot represents the topography of the magnetoencephalographically determined S1 representation of the paretic hand. Finally, diffusion tensor tractography (right) visualized trajectories of somatosensory afferent fibers that bypass the lesion on their way to the rolandic cortex of the affected hemisphere. (From Staudt M, Braun C, Gerloff C, et al. Developing somatosensory projections bypass periventricular brain lesions. Neurology. 2006;67:522–525.)

The phenomenon of M1–S1 dissociation is not confined to patients with early white matter lesions, but can also occur in patients with early cortico-subcortical infarcts and in patients with unilateral brain malformations, for example, hemispheric polymicrogyrias. The importance of these investigations again is provided by first observations that hemispherectomies in such patients with presumed M1–S1 dissociation did not abolish an active grasping ability of the paretic hand—although these operations probably disconnected the paretic hand from its S1 representation (26). In this context, it is important to note, however, that not all patients with rolandic or hemispheric polymicrogyrias show this phenomenon of M1–S1 dissociation: In some of these patients, the M1 representation of the paretic hand is still located within the polymicrogyric cortex (Fig. 80.5) (29,30).

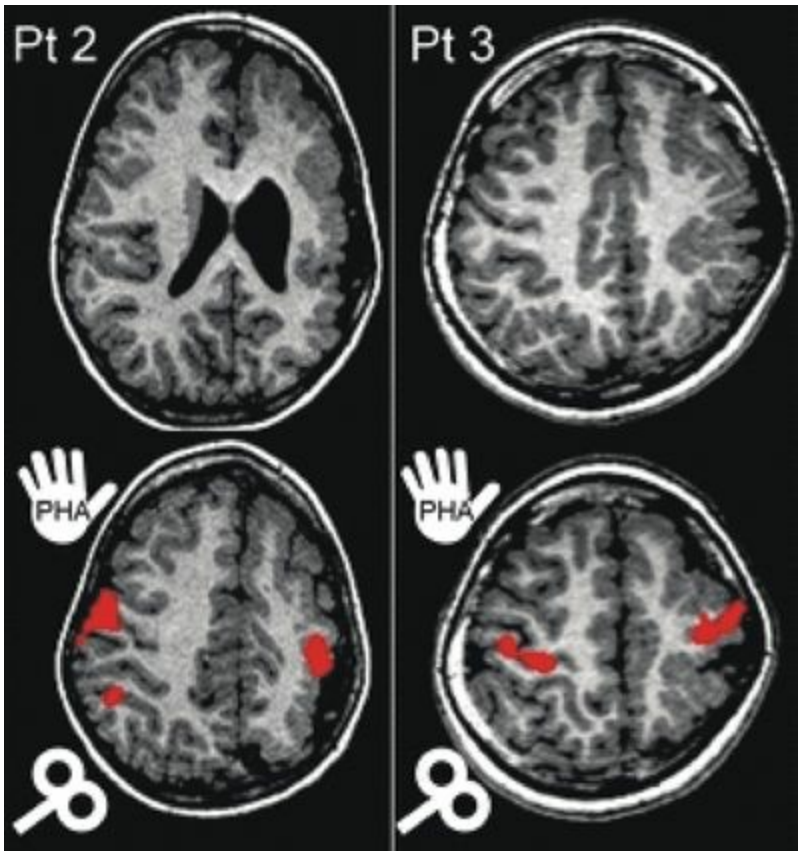


Figure 80.5. Two patients with hemispheric polymicrogyrias and congenital hemiparesis. TMS (indicated by the white figure-of-eight coil) elicited MEPs in the paretic hand (PHA) only by stimulation of the contralesional hemisphere, while TMS of the polymicrogyric hemisphere did not elicit any responses. fMRI during active movements with the paretic hand, however, elicited activation both in the rolandic region of the ipsilateral (contralesional) hemisphere and in the polymicrogyric hemisphere. This combination is highly suggestive for the phenomenon of a hemispheric M1–S1 dissociation. Both patients were still able to grasp actively with their paretic hands after hemispherectomy. (From Zsoter A, Pieper T, Kudernatsch M, Staudt M. Predicting hand function after hemispherotomy: TMS versus fMRI in hemispheric polymicrogyria. Epilepsia. 2012;53: e98–e101.)

CONCLUSIONS

The main goal of cortical stimulation is to ensure precise mapping results allowing maximal resection of epileptogenic tissue in areas adjacent to functionally significant cortex. Long-term results following subdural electrode implantation are much better when implantations are for functional mapping than for localization of the epileptogenic zone (31). Noninvasive mapping techniques like fMRI or TMS can provide information that has a major impact on surgical decisions. This is particularly important in the detection of reorganizational processes in patients with early brain lesions.

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CHAPTER 81 STRATEGIES AND INDICATIONS FOR EVALUATION WITH INVASIVE ELECTRODES

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INTRODUCTION

The main goal of epilepsy surgery is the complete resection (or disconnection) of the cortical areas or networks responsible for the generation of seizures (epileptogenic zone, EZ), with the main clinical purpose of complete seizure control in patients who have otherwise failed multiple antiepileptic medications. The EZ may at times overlap with functional (eloquent) cortex. For these reasons, accurate and comprehensive mapping of the anatomoelectroclinical (AEC) network defining the epileptic condition is most important during the presurgical evaluation. Equally important is mapping of the extent of the EZ and its possible overlap with clinically testable functional regions. In order to presurgically define the anatomical location of the EZ and its proximity to possible cortical and subcortical eloquent areas, an array of noninvasive tools are available: recorded seizure semiology, scalp electroencephalographic (EEG) recordings (ictal and interictal epileptic patterns), magnetic resonance imaging (MRI), positron emission tomography (PET), ictal single photon emission computed tomography (SPECT), neuropsychological testing, and/or magnetoencephalography (MEG) (1–3).

In this chapter, we discuss the main goals of presurgical evaluation of patients with medically intractable epilepsy and the indications and the surgical strategies for the placement of subdural or stereoelectroencephalography (SEEG) depth electrodes. The rationale behind the choice of each one of the two intracranial EEG recording techniques is also discussed.

GOALS AND TECHNIQUES OF PRESURGICAL EVALUATION

Following the establishment of the diagnosis of pharmacoresistant epilepsy (usually defined as a failure to respond to two or more adequately chosen and used antiepileptic medications) (4), a presurgical evaluation is indicated with two main goals: (i) mapping of the AEC network leading to the identification of the EZ and its extent and (ii) assessment of the functional status of the epileptic region(s). Achievement of both goals will lead to optimization of postresective seizure and functional outcomes following epilepsy surgery.

Multiple techniques may be used in order to achieve the above-stated goals: scalp EEG and video–EEG monitoring is needed to confirm the diagnosis of epilepsy (interictal and ictal EEG

recordings) and to identify the network structures that may be involved in seizure generation and progression (through analysis of the recorded seizure semiology) leading to the formulation of a clear AEC hypothesis. Further validation of the anatomic hypothesis is achieved through imaging (the identification of lesion on MRI), with or without metabolic imaging (including FDG-PET hypometabolism that may point to focal regions of cortical dysfunction). Other studies that may include ictal (and interictal) SPECT, MEG, EEG-fMRI, among others, further point to areas of dysfunction within a network or identify the three-dimensional localization of interictal epileptic regions, respectively.

These noninvasive studies identify the epileptogenic area and its possible anatomical cause usually in more than half of patients undergoing presurgical workup (around 70% of the patients who are operated on at Cleveland Clinic in 2012) (Unpublished data). But a formulation of a clear AEC hypothesis may not be possible in some patients, or an AEC is generated, but the exact location of the epileptogenic area within the network, its extent, and/or its overlap with functional (eloquent) cortex remain unclear. These patients may be candidates for an invasive evaluation using either subdural grids (SDGs) or SEEG depth electrodes.

RATIONALE FOR THE USE OF INVASIVE EVALUATION TECHNIQUES IN EPILEPSY SURGERY

Three major presurgical resection details are needed in the process of defining the EZ: (i) accurate localization, (ii) mapping of EZ extent, and (iii) assessment of functional status of the EZ.

As an electroclinical concept, the localization of the EZ is done in the majority of cases through scalp EEG recordings. It is usually complemented by functional semiologic details of the ictal events (seizures). Additional anatomic, metabolic, and/or functional techniques help to anatomically identify and localize the possible epilepsy-producing lesion. The gold standard techniques for the localization of the epileptogenic zone (scalp EEG and video recordings of the seizure semiology) are sufficient to approximate the location of the epileptogenic zone (3,5–7) and to generate an AEC network hypothesis. Nevertheless, scalp EEG does only approximate the boundaries of the epileptic region. This is mainly due to the fact that scalp EEG detects only epileptiform activity that results from EEG synchronization of relatively large areas of cortex, estimated in some studies to be between 6 and 10 cm^2, and EEG recordings are affected by the smearing effect of bone and other high-resistance structures (e.g., meninges and scalp) between the cortical generators and the recording electrodes (1,8,9).

A thorough analysis of the seizure semiology and the sequence of ictal clinical manifestations adds functional and clinical depth to the EEG data and therefore contributes to the generation of the AEC hypothesis. An AEC hypothesis is pursued in cases with focal lesions on the MRI that are overlapping with the electroclinical network. Additional information may be provided by PET, MEG, and other anatomic/functional/metabolic techniques.

The localization of functional areas in the brain and mapping of their extent and their potential spatial overlap with the EZ are an essential part in the process of developing an adequate and individualized resective surgical strategy (1,6,10). As focal cortical dysplasias (FCDs) are the most common pathologic substrates for focal epilepsies and are differentially located in the frontal lobe

(therefore in potentially eloquent cortex), an understanding of the functional status of the involved region(s) and its anatomical and pathologic correlations are essential (1,6,11,12). Some FCD lesions are characterized by significant FLAIR signal increase on MRI and located in anatomically functional areas (e.g., primary motor, Broca area). The center of these lesions (in particular type IIB lesions) may not be functional (upon direct electrical stimulation) and may show no evidence of intrinsic epileptogenicity as assessed through direct mapping of the ictal onset zones (12). On the other hand, FCD lesions with mild or no FLAIR signal increase may be functional and intrinsically epileptogenic (13,14). Similar electrocorticography (ECoG) patterns were reported in patients with low-grade glial tumors (e.g., dysembryoplastic neuroepithelial tumor and ganglioglioma), whereas pathologically dysplastic and intrinsically epileptic areas are found immediately surrounding these lesions (15). Functional cortex may be displaced within the same hemisphere, and therefore, the exact location of function may have direct implications on the options for epilepsy surgery.

Therefore, the precise anatomical localization and mapping of eloquent cortex and its relationships with a well-defined epileptic area are the two most important components of any presurgical evaluation. Delineation of these aspects will facilitate the surgical planning and optimize the chances for a safe resection of the epileptic region (thus maximizing the chances for seizure freedom and minimizing the risks of neurologic deficits). For these reasons, there is a need for direct cortical recording and electrical stimulation mapping of selected areas of the brain based on clear hypothesis generated by a detailed presurgical evaluation.

INDICATIONS OF INVASIVE EVALUATION IN EPILEPSY SURGERY

The main indications for an invasive evaluation in focal pharmacoresistant epilepsy (with the main purpose of direct cortical recording) are to address the main challenges and limitations of various noninvasive techniques. Based on the limitations outlined above of the various noninvasive techniques, an invasive evaluation should be considered in any one of the following cases whereas:

1 . MRI-negative cases: The MRI does not show a cortical lesion in a location that is concordant with the electroclinical/functional hypothesis generated by the video–EEG recordings.
2. Electroclinical and MRI data discordance: The anatomical location of the MRI-identified lesion (and at times the location of a clearly hypometabolic focal area on PET) is not concordant with the electroclinical hypothesis. These include cases of deeply seated brain lesions such periventricular nodular heterotopia or deep sulcal lesions. In addition, scalp EEG recordings in 85% to 100% of patients with FCD show interictal spikes that range in their distribution from lobar to lateralized and from difficult to localize to diffuse (including generalized spike-and-wave patterns in some cases of subependymal heterotopia) (16,17). The spatial distribution of interictal spikes is usually more extensive than is the structural abnormality as assessed by intraoperative inspection or MRI visual analysis (16,18).
3 . Multiple, in part discordant lesions: There are two or more anatomical lesions with the location of at least one of them being discordant with the electroclinical hypothesis, or both lesions are located within the same functional network, and it is unclear if one (or

both) of them is (are) epileptic.

4 . Overlap with eloquent cortex: The generated AEC hypothesis (MRI-negative or MRI-identifiable lesion) involves potentially highly eloquent cortex. The identification of the EZ, mapping of its extent, and its relationship with potentially eloquent cortex are not typically resolved in these cases. These include patients with suspected focal cortical dysplasia as the possible pathologic substrate for epilepsy (13,19–21).

In these instances, an invasive evaluation usually leads to the formulation of a clear resective surgical strategy. The recommendation for invasive monitoring and its type is made during a multidisciplinary patient management meeting that includes neurologists, neurosurgeons, neuroradiologists, and neuropsychologists. Areas and networks of coverage/sampling are determined based on a well-formulated AEC hypothesis including results of the noninvasive studies. We use two extraoperative invasive methods to accomplish these goals: SDG electrodes and stereotactic placement of depth electrodes (stereoelectroencephalography, SEEG).

THE SUBDURAL GRID METHOD

Prolonged intracranial recordings were initially reported in 1939 when Penfield et al. used epidural single contact electrodes in a patient with an old left temporoparietal fracture and whose pneumoencephalography disclosed diffuse cerebral atrophy (22). Decades later (1980s), the use of SDG arrays became more popular in North America following multiple publications that demonstrated their safety and efficacy (1,23,24). Prior to that, most invasive techniques used in North America involved extraoperative recordings from epidural electrodes or intraoperatively placed neocortical surface electrode recordings.

SUBDURAL GRID IMPLANTATION TECHNIQUE

Subdural electrodes consist of discs (stainless steel or platinum) that are embedded in strips or sheets of polyurethane or other synthetic materials. These are implanted over the cortical surface corresponding to the AEC hypothesis. Variability in shape and size of the electrodes permits some flexibility in tailoring the extent and shape of the coverage area. Custom-designed arrays of subdural electrodes have been configured for placement in specific anatomical locations. For example, to record from interhemispheric brain regions, rows of electrodes arranged in curvilinear fashion are designed to follow the curvature of the corpus callosum. SDGs are inserted through either open craniotomy incisions or burr holes and registered stereotactically for extraoperative mapping. The cortical coverage may extend beyond the visualized cortical area(s), as grids may be slid over the edges of the craniotomy to cover adjacent areas for better ECoG recordings or functional sampling. Besides the ECoG recordings and direct electrical stimulation studies, grids can be used to record somatosensory evoked potentials after stimulation of the trigeminal (lip) or median nerves. Somato-sensory evoked potentials (SSEP) with cortical recordings provides a highly accurate neurophysiologic mean for central sulcus localization.

Incision and craniotomy should allow for placement of electrodes in addition to the anticipated area of resection. Positioning of the patient should allow for stereotactic guidance in the event that depth electrodes are to be placed during the same operation. As part of the Cleveland Clinic Epilepsy Center surgical protocol, perioperative antibiotics, dexamethasone, and mannitol (0.25 g/kg) are

given. The incision should be large enough to allow for a sizable craniotomy. Usually a T-shaped or large question mark incision is used. If basal temporal coverage is needed, the incision should extend down to the zygoma. Orbitofrontal coverage can be easily achieved as long as the incision allows for visualizing the key hole and turning a flap just above this level. Interhemispheric coverage necessitates an incision that extends to the midline. In order to facilitate placement of electrodes, the basal and mesial surfaces should be carefully inspected for cortical draining veins that might impede grid placement. Using bayoneted forceps, and under a constant stream of irrigation, the grid electrodes can be slid into place. Any resistance would likely indicate the presence of a draining vein, and therefore, the trajectory of the grid should be adjusted.

If indicated, depth electrodes may be inserted using semistereotactic guidance prior to inserting lateral cortical coverage. The entry point should be in the middle of a gyrus, avoiding sulci, with a trajectory that is as perpendicular to the cortical surface as possible. The parenchyma serves to anchor the electrode in place. Using the wand to find the trajectory from the entry point, the pial surface is incised and the electrode is inserted. Once the depth electrodes are in place, the grids for lateral coverage can be placed. Again using bayoneted forceps, the larger grid electrodes are laid over the cortical surface, tucking the edges under the borders of the dural flap. Once in place, each electrode wire is secured to the nearest dural edge with a stitch. The remaining closure is performed using standard neurosurgical technique (Fig. 81.1).

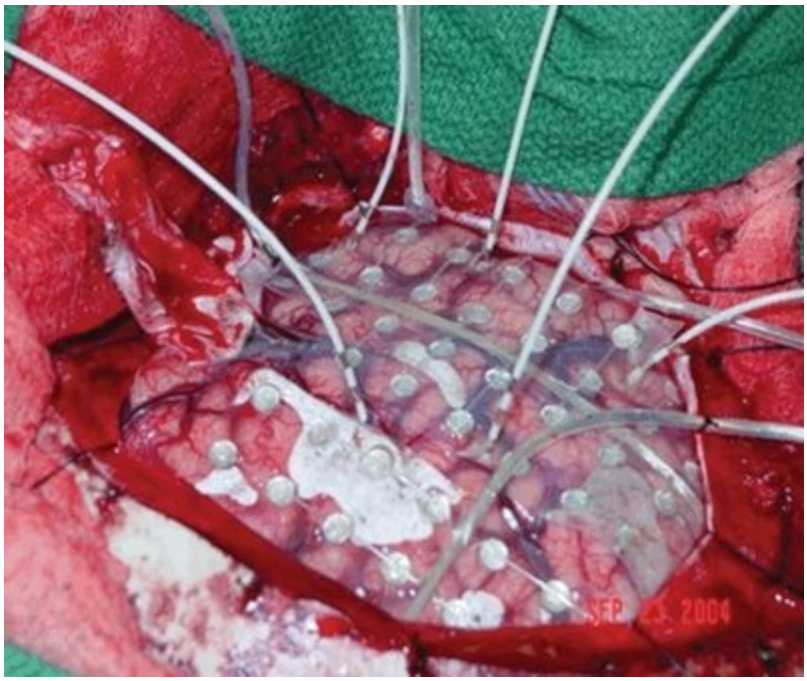


Figure 81.1. Intraoperative aspect of SDG/depth electrode implantation in a patient with extratemporal epilepsy and nonlesional MRI. The picture shows a large right-sided temporofrontal craniotomy with placement of SDGs at the dorsolateral convexity of the temporal area. Depth electrodes were implanted in the mesial structures of the temporal lobe (amygdala and hippocampus) and frontal opercular areas.

PRINCIPLES AND INDICATIONS OF SUBDURAL ELECTRODE PLACEMENT

Extraoperative mapping with the subdural method (which includes SDGs and strips) has the main advantage of allowing optimal coverage of the subdural space adjacent cortex with adequate and

continuous superficial functional mapping capabilities (13,25–27). A major strength of subdural electrodes consists in the comprehensive anatomical coverage of cortical surfaces, therefore allowing accurate anatomical–electrical and functional mapping of the areas of coverage. Limitations of SDG electrodes include the inadequate/partial/incomplete intrasulcal, deep brain, and interhemispheric coverage and the relative difficulty in multilobar, three-dimensional, and large functional network sampling (28). These characteristics are highlighted in the published results on the successes and failures following SDG implantation (29). The best resective surgical outcomes following SDG implantation are achieved in patients with clear cortical lesions (in particular tumors) and those patients in whom the SDG implantations were placed with the main purpose of functional mapping (12,29). On the other hand, the worst outcomes were seen in patients with no clear lesions on the MRI, nonspecific histopathology, and those who underwent either a sublobar resection or multilobar resections.

These characteristics suggest that the best candidates for extraoperative invasive evaluation with SDG are those patients with clear cortical surface lesion(s) (excluding the interhemispheric, cingulate gyrus, deep sulcal, and mesial frontal/temporal regions), specifically patients undergoing invasive evaluation for electrofunctional/eloquent cortex mapping in the setting of a superficial cortical lesion. Intraoperative ECoG, as compared to chronically implanted SDGs, is a limited option because it usually only provides information restricted to interictal activity. When used in patients under general anesthesia, anesthetic agents may influence EEG activity by altering the thresholds of afterdischarges and motor responses creating a misleading EEG picture (19). Additionally, intraoperative functional mapping often requires a cooperative patient that can tolerate being awake during surgery under local anesthesia. This is particularly difficult in the pediatric population.

LIMITATIONS AND COMPLICATIONS OF SUBDURAL GRID IMPLANTATIONS

The main limitations of SDG include surgical morbidity risks and the spatial/cortical sampling limitations as detailed above. SDG electrodes are foreign bodies that are surgically inserted in the cranial vault, and risks of the procedure include wound infection, flap osteomyelitis, acute meningitis, cerebral edema, and hemorrhage (30–32). Concerns about increased intracranial pressure may reduce the maximal number of electrodes that can be inserted and therefore may lead to incomplete or limited spatial coverage. Other limitations may include the technical challenges that are associated with SDG implantations following a first resective surgery failure (so called “re-do” surgeries). Technical challenges mainly occur due to cortical adhesions in this setting. As stated above, one of the main weaknesses of the subdural methodology is the inability to record from deep cortical areas, as in the depth of sulci, interhemispheric regions (in particular the cingulate gyrus), mesial temporal or frontal structures, and insula/opercular regions (28). Depth electrodes implanted using a non- or semistereotactic technique can partially compensate for the rather incomplete deep/mesial structure coverage with SDG, but as these electrodes are not fully stereotactically implanted, their placement may not be very accurate (29).

THE STEREOELECTROENCEPHALOGRAPHY METHOD

The SEEG method was developed in France by Jean Talairach and Jean Bancaud during the 1950s and has been mostly used in France and Italy as the method of choice for invasive mapping in refractory focal epilepsy (17,33,34). The principle of SEEG is based on AEC correlations with the main aim to conceptualize the 3-dimensional spatiotemporal organization of the epileptic discharge within the brain based mainly on seizure semiology. The implantation strategy is individualized, with electrode placement based on a preimplantation hypothesis that takes into consideration the primary organization of the epileptiform activity and the hypothetical functional epileptic network that may be involved in the propagation of seizures. For these reasons, the preimplantation AEC hypothesis is the most important element in the process of planning for SEEG electrodes placement. If the preimplantation hypothesis is incorrect, the placement of the depth electrodes will be inadequate and the interpretation of the SEEG recordings misleading. The most important characteristic of SEEG methodology is that it enables precise recordings from deep cortical and subcortical structures, multiple noncontiguous lobes, as well as bilateral explorations while avoiding the need for large craniotomies (21,28,35–38).

The SEEG technique was originally described as a multiphase and complex method, using the Talairach stereotactic frame and the double grid system in association with teleangiography (6,39). Despite its long reported successful record, with almost 60 years of clinical use, the technical complexity regarding the placement of SEEG depth electrodes may have contributed to its limited use in centers outside Europe. Taking advantage of new imaging and computational innovations, more modern and less cumbersome methods of stereotactic implantation of depth electrodes can be applied on a routine basis.

PRINCIPLES AND TECHNIQUE OF SEEG IMPLANTATION

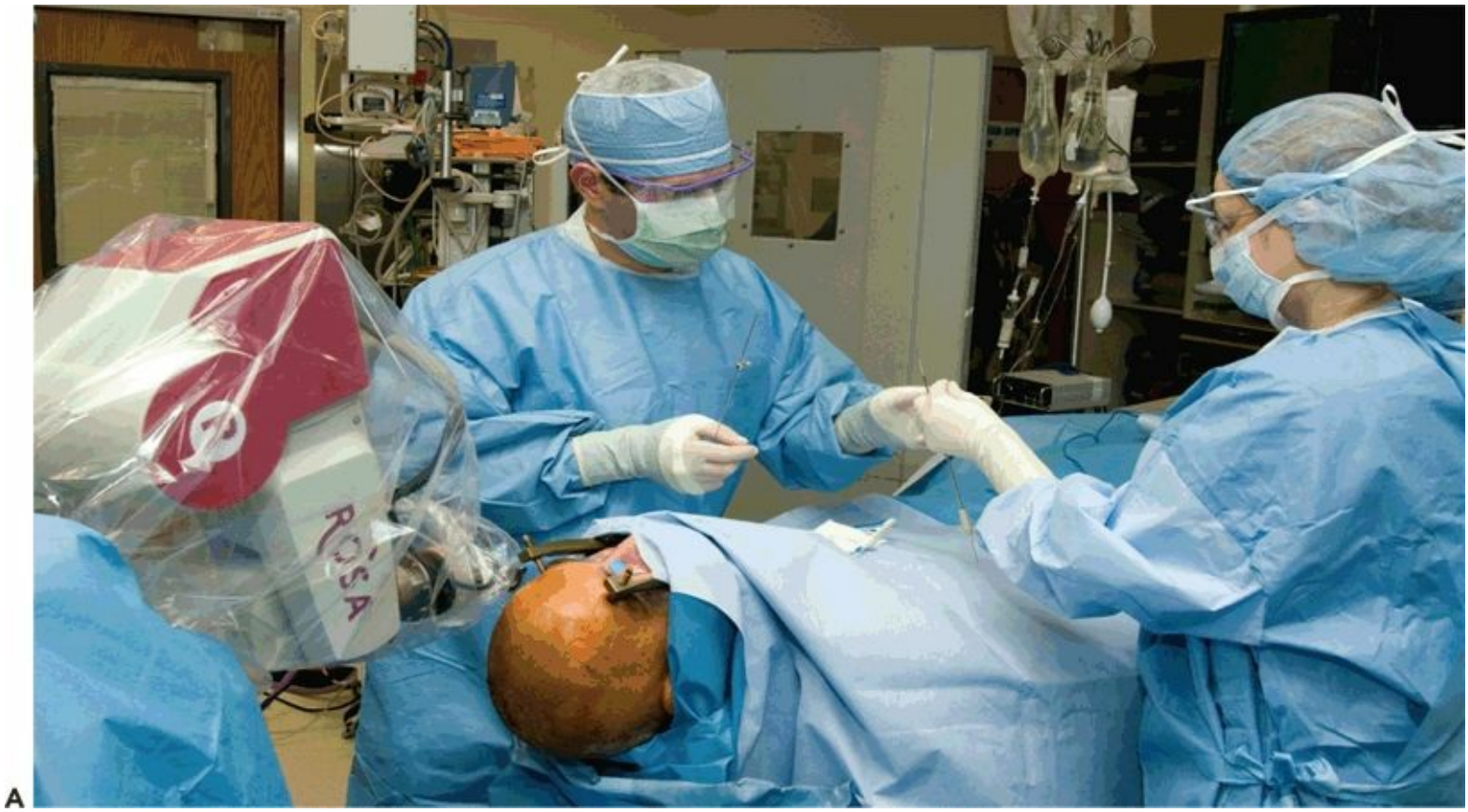
The development of an SEEG implantation plan requires the clear formulation of a specific anatomoelectrofunctional hypothesis to be tested. This hypothesis is typically generated during the patient management conference based on the results of various noninvasive tests. At Cleveland Clinic, a final tailored implantation strategy is generated during a separate presurgical implantation meeting. Depth electrodes sample the anatomic lesion (if identified), the more likely structure(s) of ictal onset, the clinically active regions, and the possible electrical pathway(s) of seizure-onset propagation (functional networks). The EZ may correspond to the first clinical sign or may reflect a spread area from a “clinically silent” ictal onset zone within a functional network. For these reasons, a three-dimensional “conceptualization” of the network nodes upstream and downstream from the hypothesized clinical onset region is an essential component of the presurgical implantation strategy. The desired targets are reached using commercially available depth electrodes in various lengths and variable number of contacts, depending on the specific brain region to be explored. The electrodes are implanted using conventional stereotactic technique through 2.5-mm diameter drill holes. Depth electrodes are inserted using orthogonal or oblique orientation, allowing intracranial recording from lateral, intermediate, or deep cortical and subcortical structures in a three-dimensional arrangement, thus accounting for the dynamic, multidirectional spatiotemporal organization of the epileptic pathways.

As part of our routine practice, the patient is admitted to the hospital on the day of surgery. The day before surgery, a stereo contrasted volumetric T1 sequence MRI is performed. Images are then

transferred to our stereotactic neuronavigation software (iPlan Cranial 2.6, Brainlab AG, Feldkirchen, Germany) where trajectories are calculated the following day. The day of surgery, while the patient is under general anesthesia, the Leksell stereotactic frame (Elekta, Stockholm, Sweden) is applied using standard technique. Once the patient is attached to the angiography table with the frame, a stereo DynaCT and a three-dimensional digital subtracted angiogram are performed. The preoperative MR images, the stereo DynaCT, and angiographic images are then digitally processed using a dedicated fusion software (syngo XWP, Siemens Healthcare, Forchheim, Germany). These fused images are used during the implantation procedure to confirm the accuracy of the final position of each electrode and to insure the absence of vascular structures along the electrode pathway, which may not be noted on MRI with contrast. Following the planning phase using the stereotactic software, trajectories' coordinates are recorded and transmitted to the operating room. Trajectories are in general planned in orthogonal orientation in relation to the skull's sagittal plane in order to facilitate implantation and later on interpretation of the electrode positions. Using the Leksell stereotactic system, coordinates for each trajectory are then adjusted in the frame and a lateral view fluoroscopic image is performed in each new position. Care is taken to assure that the central beam of radiation during fluoroscopy is centered in the middle of the implantation probe in order to avoid parallax errors. If the trajectory is aligned correctly, corresponding to the planned trajectory and passing along an avascular space, the implantation is then continued, with skull perforation, dura opening, placement of the guiding bolt (AdTech, Racine, WI; Integra, Plainsboro, NJ), and final insertion of the electrode under fluoroscopic guidance. If a vessel is recognized along the pathway during fluoroscopy, the guiding tube is manually moved a few millimeters until the next avascular space is recognized and implantation is then continued. The electrode insertion progress is observed under live fluoroscopic control in a frontal view to confirm the straight trajectory of each electrode. For additional guidance, a coronal MRI slice corresponding to the level of each electrode implantation is overlaid onto the fluoroscopic image.

A postimplantation DynaCT scan is performed while the patient is still anesthetized and positioned in the operating table. The reconstructed images are then fused with the MRI dataset using the previously described fusion software. The resulting merged datasets are displayed and reviewed in axial, sagittal, and coronal planes allowing verification of the correct placement of the electrodes (21).

Following the surgical electrode implantation, patients are transferred to the epilepsy monitoring unit (EMU). The duration of admission at the EMU varies from patient to patient and depends on several factors including number and quality of recorded ictal and interictal patterns. In the last 4 years, patients undergoing SEEG implantation at Cleveland Clinic stayed on average 7 days (range from 3 to 28 days). After obtaining the necessary information, electrodes are removed in the operating room, in a procedure performed under local anesthesia and sedation. The results of the SEEG evaluation are discussed during another patient management conference, and recommendations for surgical resection are made. Patients are discharged the next morning, and resective surgery is scheduled 2 to 3 months following SEEG electrode removal (Fig. 81.2).



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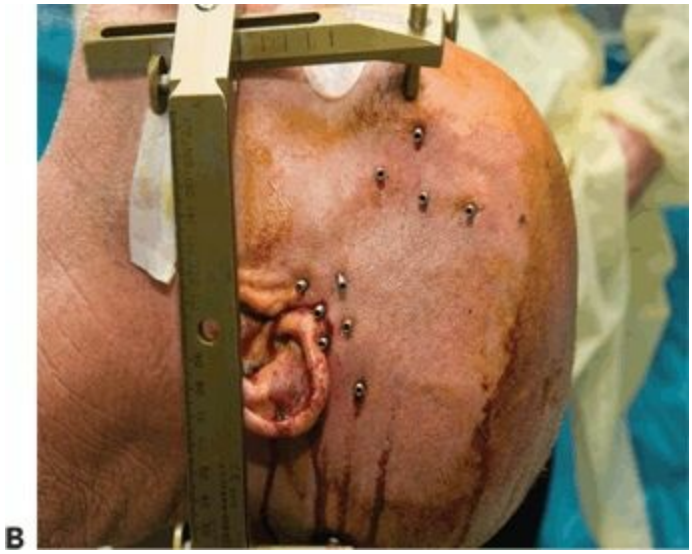

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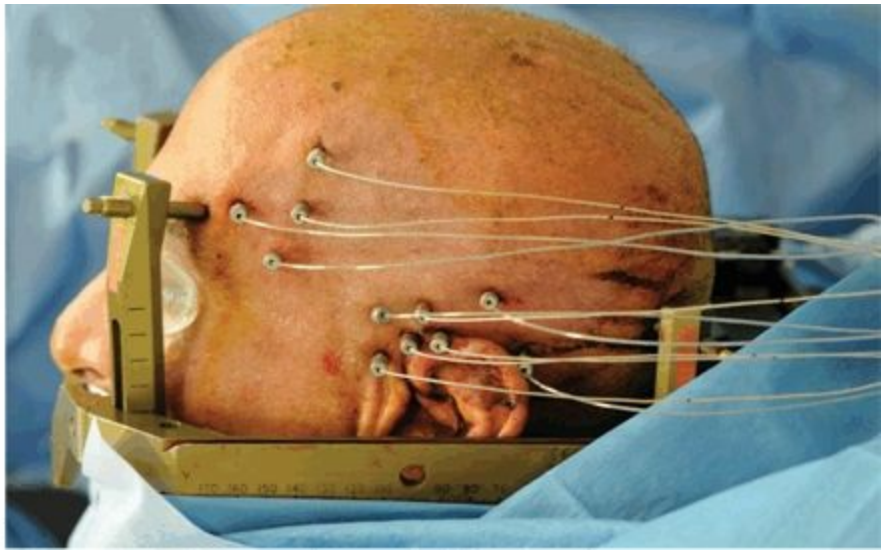

C

Figure 81.2. SEEG technique of implantation. **A:** General aspect of robotic implantation of SEEG electrodes, with the patient in supine

position with the stereotactic robotic arm guiding the electrode implantation. **B:** Intraoperative picture, showing bolts implanted in stereotactic fashion, without the placement of electrodes. **C:** Final aspect of SEEG implantation, with electrodes placed in their final position.

INDICATIONS OF SEEG ELECTRODE PLACEMENT

In addition to the general indications for invasive monitoring, specific indications can be considered to choose SEEG in detriment to other methods of invasive monitoring. These criteria include:

1. The possibility of a deep-seated or difficult-to-cover location of the EZ in areas such as the mesial structures of the temporal lobe, opercular areas, cingulate gyrus, interhemispheric regions, posterior orbitofrontal areas, insula, and depths of sulci
2. A failure of a previous subdural invasive study to clearly outline the exact location of the seizure-onset zone. The failure to identify the EZ in these patients may be due to multiple reasons that include the lack of adequate sampling from a deep focus or a clinically silent focus upstream from the EZ
3. The need for extensive bihemispheric explorations (in particular in focal epilepsies arising from the interhemispheric or deep insular regions)
4. Presurgical evaluation suggestive of functional network involvement (e.g., limbic system) in the setting of normal MRI (Table 81.1)

Table 81.1 Selection Criteria for Different Methods of Invasive Monitoring in Medically Refractory Focal Epilepsy

Clinical scenario	Method of choice	Second option
▪ Lesional MRI: Potential epileptogenic lesion is superficially located near or in the proximity of eloquent cortex.	SBG	SEEG
▪ Nonlesional MRI: Hypothetical EZ located in the proximity of eloquent cortex.		
▪ Lesional MRI: Potential epileptogenic lesion is located in deep cortical and subcortical areas.	SEEG	SBG with depths
▪ Nonlesional MRI: hypothetical EZ is deeply located or located in noneloquent areas.		
▪ Need for bilateral explorations and/or reoperations	SEEG	SBG with depths
▪ After SDGs failure	SEEG	SBG with depths
▪ When the AEC hypothesis suggest the involvement of a more extensive, multilobar epileptic network	SEEG	SBG with depths
▪ Suspected frontal lobe epilepsy in nonlesional MRI scenario	SEEG	SEEG

In these scenarios, the SEEG methodology may be considered as a more appropriate and safer option. As mentioned above, the SEEG methodology has the advantages of allowing extensive and precise deep brain recordings and stimulations with minimal associated morbidity. A majority of patients undergoing reoperations may have failed epilepsy surgery during preceding subdural evaluations because of difficulties in accurately localizing the EZ. These patients pose a significant dilemma for further management, having relatively few options available. Further open SDG evaluations may carry the risks associated with encountering scar formations and still having limitations related to deep cortical structure recordings. A subsequent evaluation using the SEEG method may overcome these limitations, offering an additional opportunity for seizure localization and sustained seizure freedom (28) . The main disadvantage of the SEEG method is the more restricted capability for performing functional mapping. Due to limited number of contacts located in the superficial cortex, a contiguous mapping of eloquent brain areas cannot be obtained as in the subdural method mapping. In order to overcome this relative disadvantage, the functional mapping information extracted from the SEEG method is frequently complemented with other methods of mapping, such as diffusion tensor imaging (DTI) images or awake craniotomies (21).

INVASIVE MONITORING MORBIDITY

In the Cleveland Clinic SEEG series, the total complication rate was 3%. Other groups reported similar results. Cossu et al. reported a morbidity rate of 5.6%, with severe permanent deficits from intracerebral hemorrhage in 1% (36). In our series, all three complications were hemorrhagic, which has been reported in several studies to be the most common complication in the setting of depth electrode placement (21,36). Other published series reporting complications across invasive monitoring procedures (SDGs and depth electrodes) documented rates ranging from 0% to 26% (32,40,41). SDG electrode implantation has historically been shown to have low permanent morbidity (0% to 3%) compared with depth electrodes (3% to 6%) since there is no intraparenchymal passage. Although it is difficult to compare morbidity rates between SDGs and SEEG due to the variability in patient selection, different institutions, and variable number of implanted electrodes, our early experience suggests that the SEEG method provides at least a similar degree of safety when compared with SDGs or strips. This impression is also shared by others (34,36,42,43).

CONCLUSIONS

The goals of invasive monitoring in pharmacoresistant focal epilepsy may include (i) the need for better anatomical localization and spatial delineation of the extent of the EZ and (ii) the need for the definition of cortical and subcortical functional brain areas. Extraoperative mapping with the subdural method (which includes SDGs and strips) has the advantage of allowing an optimal anatomical and contiguous coverage and sampling of adjacent cortex leading to accurate functional mapping. In addition, from a surgical perspective, subdural implantations are open procedures, with better management of possible intracranial hemorrhagic complications. The disadvantages of the subdural method are related to the inability to record and stimulate deep structures such as the insula, posterior orbitofrontal, cingulate gyrus, depths of sulci, etc. In these scenarios, the SEEG methodology may be considered as a more adequate and safer option. SEEG has the advantages of allowing extensive and precise deep brain recordings and stimulations with minimal associated

morbidity.

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SECTION B EPILEPSY SURGERY IN DIFFERENT CLINICAL SETTINGS

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CHAPTER 82 SURGERY FOR MEDICALLY REFRACTORY TEMPORAL LOBE EPILEPSY

SUMEET VADERA, WILLIAM E. BINGAMAN, AND IMAD M. NAJM

INTRODUCTION

Temporal lobectomy is commonly utilized for patients with medically intractable epilepsy and mesial temporal sclerosis (MTS), but this procedure can also be utilized for a variety of other epileptogenic lesions including malformations of cortical development (MCD) as well as neoplastic and vascular lesions of the temporal lobe (1). Although the term "standard temporal lobectomy" is used in the medical literature to describe removal of the lateral and mesial temporal lobe structures, there are significant variations in the technique based upon institutional practices and surgeon preference. The authors will discuss indications for this procedure and then describe techniques involved with resection.

INDICATIONS FOR TEMPORAL LOBECTOMY

As with all resective epilepsy surgery, prior to consideration for temporal lobectomy, patients must demonstrate (i) concordance of noninvasive data implicating the temporal lobe and (ii) medically intractable epilepsy after an adequate trial of anticonvulsants (2). It is important to keep in mind that as patients fail anticonvulsant medications, the likelihood of seizure freedom on medication alone falls precipitously with each additional medication trial. A study by Kwan and Brodie (3) showed that in patients with newly diagnosed epilepsy, only 47% became seizure free with administration of the first AED and only 14% with the second AED. Several studies have shown that temporal lobectomy is safe and superior to medical treatment, so the authors advocate for early surgical consideration in all patients with focal temporal lobe epilepsy who fail two anticonvulsant medications (4–6).

PRESURGICAL EVALUATION

There are several steps involved in the presurgical evaluation of patients prior to consideration for temporal lobectomy. Figure 82.1 shows a typical presurgical evaluation algorithm. Once the history, examination, video electroencephalography (vEEG), and magnetic resonance imaging (MRI) are obtained, the remainder of the workup is tailored entirely to the patient's clinical presentation (2,7–9). Therefore, not all studies are performed on all patients.

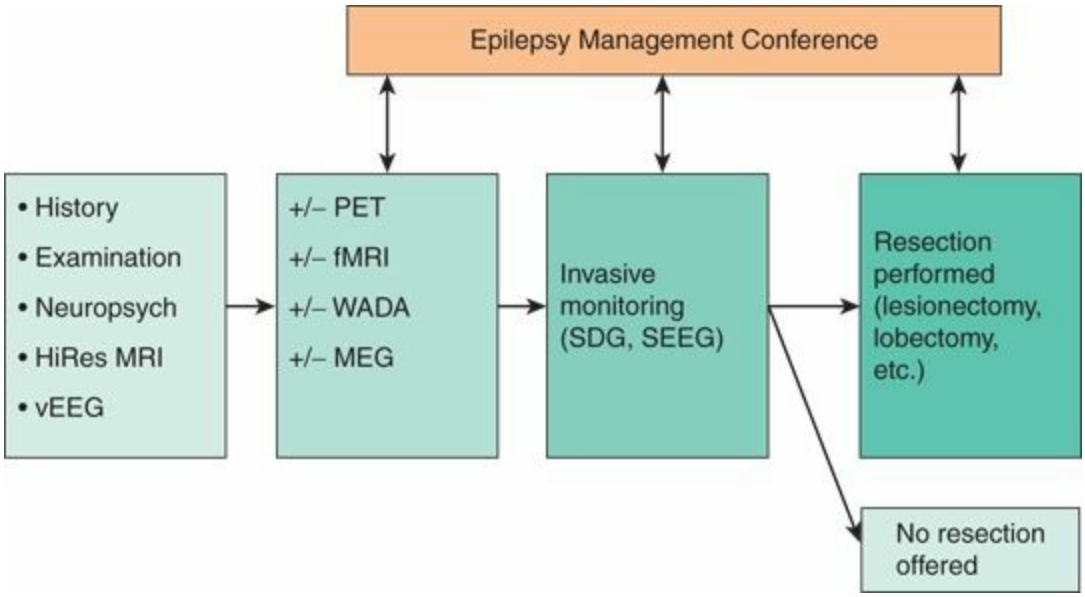

Figure 82.1. Typical presurgical evaluation algorithm for patients being considered for temporal lobectomy.

History and Neurologic Examination

The first step in evaluating any patient for temporal lobectomy is a thorough history and physical examination by a trained and experienced epileptologist. The history can assist with localizing the epileptogenic region and the possible underlying etiology. The history should specifically include any perinatal complications, history of childhood febrile convulsions, descriptions of auras, speech abilities during seizures, and whether the patient has any memory/naming difficulties. Physical examination is important to document any preoperative motor deficits and can be helpful if extratemporal (i.e., frontal lobe) epilepsy is suspected.

vEEG Monitoring—Semiology and EEG Patterns

Patients should undergo prolonged vEEG in a dedicated epilepsy monitoring unit to confirm the diagnosis and type of epilepsy (2,7). vEEG allows for a noninvasive method to evaluate the approximate localization and lateralization of the epileptogenic region. The ictal and interictal discharges help localize the region of interest, while the video recordings allow for a better understanding of seizure semiology and may assist with lateralization and localization.

Mesial Temporal Lobe Epilepsy

In adults with temporal lobe epilepsy undergoing temporal lobectomy, MTS is one of the most common pathologies and has been shown to be as high as 75% in some studies (10). Classically, patients describe an aura of a rising abdominal sensation, which often progresses to hand and mouth automatisms such as "picking" at their clothing or surroundings. They may also demonstrate contralateral dystonic hand movements during ictal onset. EEG recordings in patients with MTS typically show ipsilateral interictal anterior temporal lobe sharp waves and slowing. Sharp waves in the contralateral anterior temporal lobe have been described in patients with MTS but not in patients with other mesial temporal lobe lesions. Presence or absence of language function during a seizure can also be very helpful when attempting to lateralize language function and cerebral dominance (11).

Neocortical Temporal Lobe Epilepsy

Patients with neocortical temporal lobe epilepsy often present with different semiologies and EEG patterns than those with MTS. Motor phenomena may be more pronounced and are commonly seen earlier than in patients with MTS. EEG typically shows lateral and posterior distribution of ictal and interictal patterns (T7/8, P7/8) (1,12). Dual pathology can also be present, and there are several studies in the literature that describe lesions in the lateral temporal lobe (i.e., MCD and cavernomas) with associated MTS (13). To adequately assess the involvement of the mesial temporal lobe in these patients with "dual pathology," invasive electrode recordings may be considered prior to resective surgery.

Imaging Studies

High-resolution (1.5 or 3.0 T) MRI of the brain is the most important study to evaluate structural lesions in patients with temporal lobe epilepsy. At our institution, a dedicated epilepsy protocol MRI study is obtained on all patients evaluated for temporal lobe epilepsy. This includes thin-slice coronal T1-weighted magnetization prepared rapid gradient echo imaging, fluid attenuated inversion recovery (FLAIR) coronal sequences, and T2-weighted coronal sequences (Table 82.1). Contrast may be administered if a neoplasm is suspected. If available, 3.0 T MRI allows for better signal-to-noise ratio and should be utilized whenever possible to visualize subtle lesions such as MCD.

Table 82.1 Sequences for Epilepsy Protocol MRI

MRI epilepsy protocol (+/– gadolinium)
Volumetric coronal T1
Volumetric coronal and axial FLAIR
Coronal and axial T2

The epilepsy protocol utilizes several coronal sequences because these studies are best able to compare the size and shape of the hippocampi when evaluating for MTS. Hippocampal sclerosis also commonly exhibits increased signal intensity on FLAIR and T2 imaging. When MTS is noted, it is important to look for other temporal lobe lesions (i.e., MCD) as they may coexist with MTS and have been shown in up to 30% of these cases (2,14). This dual pathology may manifest itself as irregularities within the cortical ribbon or blurring of the gray–white junction. As mentioned previously, 3.0 T MRIs allow for increased resolution to detect structural lesions and should be considered in patients with no findings on 1.5 T MRI studies (15).

When evaluating language location in patients with temporal lobe epilepsy, the authors believe that functional MRI (fMRI) studies offer advantages over intracarotid sodium amobarbital testing (Wada tests) and now frequently use fMRI as the study of choice. One major advantage is that fMRI is noninvasive and does not put the patient at risk of periprocedural intracranial emboli that Wada testing may cause. Recent studies also suggest that fMRI is able to predict postoperative memory deficits with good accuracy (16,17).

Other studies such as fluorodeoxyglucose photon emission computed tomography, subtraction (ictal minus interictal) radionuclide blood flow studies, and magnetoencephalography are important

to utilize in the noninvasive presurgical evaluation and will be discussed elsewhere.

Neuropsychological Preoperative Evaluations

Neuropsychological testing and psychosocial and psychiatric evaluations are important during the presurgical evaluation period as the temporal lobe is involved in emotion, language, and memory. Oftentimes, patients will complain of difficulty remembering grocery lists or names of acquaintances, and this may prompt the patient to seek out a surgical evaluation. Although these complaints can be confounded by medication side effects, they are still very helpful in evaluating for baseline memory function and can help explain to the patient what to expect with regard to their memory after surgery. Formalized neuropsychological testing is also important to gain a baseline measure of overall intellectual functioning as well as verbal and visuospatial memory scores. The patient undergoes a litany of standardized neuropsychological tests, which are repeated 6 months after surgery. Postoperative memory outcomes are related to preoperative function and temporal lobe dominance. It is very important to discuss likelihood of postoperative memory decline in patients at risk. Invasive monitoring can also be utilized in patients who are high functioning with dominant temporal lobe epilepsy to attempt to preserve mesial structures and memory function.

When the presurgical evaluation has been completed, a multidisciplinary Epilepsy Management Conference should meet to evaluate all the data and decide upon the appropriate course of action. Ideally, this conference should consist of epileptologist(s), neurosurgeon(s), neuropsychologists, psychiatrists, neuroradiologist(s), nurses and midlevel providers, EEG technicians, and social workers. This conference is very important because a multidisciplinary approach to epilepsy surgery allows for the best care of patients with medically intractable epilepsy by creating a hypothesis of the location of the epileptogenic zone as well as an appropriate surgical strategy (see Fig. 82.1) (8,18,19).

ANATOMY OF THE TEMPORAL LOBE

An excellent understanding of the structural and functional anatomy of the temporal lobe is crucial when performing temporal lobectomy. The anterior, lateral, mesial, and basal surfaces are all well defined, while the posterior border is continuous with the parietal and occipital lobe. Mesial structures include the amygdala, hippocampus, parahippocampal gyrus, and the uncus. There are five gyri and four associated sulci in the temporal lobe (Table 82.2).

Table 82.2 Temporal Lobe Gyri and Sulci in Descending Order

Gyrus (superior to inferior)	Sulcus (superior to inferior)
Superior temporal gyrus	Superior temporal sulcus
Middle temporal gyrus	Inferior temporal sulcus
Inferior temporal gyrus	Occipitotemporal sulcus
Fusiform/occipitotemporal gyrus	Collateral sulcus
Parahippocampal gyrus	

Within the temporal horn, important anatomic structures include the inferior choroidal point

(anterior choroidal artery enters the choroid plexus here), the hippocampus occupying the mesiobasal portion of the ventricle, the fornix, the choroid plexus, the choroidal fissure, and the amygdala in the anterosuperomedial portion of the ventricle. Other important surgical landmarks during temporal lobectomy include the sylvian fissure, the vein of Labbé, the brainstem, posterior cerebral artery, basal vein of Rosenthal, and the third and fourth cranial nerves (20).

Aside from anatomic landmarks, there are also several important functional regions in the temporal lobe that must be considered. These include visual field fibers (Meyer loop), which cause contralateral upper quadrantic visual field deficits when removed ("Pie in the Sky" deficits), as well as important memory and language centers when operating on the dominant hemisphere. The exact location of language cortex in the dominant temporal lobe can vary significantly, and if necessary, intra- and extraoperative studies may be required to specifically localize language if a generous temporal lobectomy is planned. This includes awake craniotomy and direct cortical stimulation to test for language intraoperatively or invasive electrodes and functional stimulation to test for language extraoperatively. Some studies have shown that a small percentage of patients have language areas in the superior temporal gyrus (STG) as well as the basal temporal lobe, and as such, some centers will not remove the STG during temporal lobectomy, although no study has shown performing STG resection leads to long-term language deficits (12,21).

Meyer loop is located in the temporal lobe as the visual fibers extend from the lateral geniculate body before looping posteriorly to the calcarine cortex. These fibers are located in the roof of the temporal horn, and standard temporal lobe resections injure these fibers in as many as 50% of cases causing "Pie in the Sky" visual field deficits (22). When counseling patients, one can emphasize that this should not affect driving or other activities of daily living and that patients generally learn to ignore the deficit over time.

TEMPORAL LOBECTOMY PROCEDURE

In performing a temporal lobectomy, it is important to keep in mind whether the dominant or nondominant temporal lobe is being resected as this impacts the extent of posterior resection that can be performed. In dominant temporal lobe surgery, the posterior cut along the STG should be no more than 4.5 cm as measured from the temporal pole to avoid language deficits. In nondominant temporal lobe surgery, it is safe to extend this farther than 5.5 cm. It is important to visualize the vein of Labbé as this can limit posterior resection, especially when performing nondominant resections. Overly aggressive posterior resections can injure the geniculocalcarine tract leading to complete homonymous hemianopsia. If the surgical plan includes a generous temporal lobectomy, it is important to counsel the patient about this risk (23).

Standard preoperative measures are utilized including antibiotics, general anesthesia, arterial lines, IV access, and sterile preparation of the operative field. Hyperventilation and mannitol may be used for brain relaxation. A shoulder roll is used to limit neck rotation, and the head is placed in pins and turned 30 degrees from the midline so the operative site is accessible. The neck is gently extended to allow for the sylvian fissure to become perpendicular to the surgical approach, and finally, the vertex is rotated downward so that the temporal lobe falls away from the floor of the middle fossa to assist with the surgical approach. The ideal position will allow for the mesial structures to be readily visible and easily accessible to the surgeon once lateral temporal lobectomy is performed. Stereotactic navigation is optional and is not routinely used at our institution.

A small amount of hair is clipped along the surgical region, and a "reverse question mark"

incision is made 1 cm anterior to the tragus at the level of the zygoma, extending to the posterior part of the pinna and then curving anteriorly just above the insertion of the temporalis muscle. The temporalis is then sharply cut in a "T" manner ensuring that a cuff of muscle is left to suture the muscle back to. The anterior end of the "T" should go toward the anatomic "keyhole," and the inferior end of the "T" should go to the root of the zygoma. The muscle is then elevated from the bone and retracted from the surgical field.

Burr holes should be placed at the root of the zygoma and at the anatomic "keyhole" to give adequate exposure to middle fossa floor and superior aspect of the temporal lobe, respectively. Frontal lobe exposure is not necessary and should be minimized. Extending the craniotomy as anterior as possible and removing some of the sphenoid wing assist with the temporal lobectomy and are recommended. If air cells are noted at the bone edges, bone wax may be used to seal them off and prevent postoperative cerebrospinal fluid (CSF) leakage.

There are often several large arteries on the dura, including the middle meningeal branch, that may cause significant bleeding. These should be coagulated as proximal as possible to avoid shrinkage of the dura. The dural flap is reflected anteriorly and the temporal lobe visualized. An appropriately sized craniotomy should include the sylvian fissure along the superior limit of the bony edge, and the floor of the middle fossa should be visualized with minimal retraction of the inferior temporal gyrus. The sylvian fissure and floor of the middle fossa should be readily visible without brain retraction, and the temporal pole should be within 1 to 2 cm of the anterior bony edge of the craniotomy. Excess brain swelling may be treated with head elevation, mannitol, and/or hyperventilation.

The posterior limit of resection along the STG is now measured with a Penfield #1 dissector placed so the curve of the instrument follows the curve of the temporal pole and the instrument follows the STG. The appropriate length is decided based upon the laterality as well as any associated vessels. Vessels supplying the posterotemporal lobe should be preserved to avoid strokes along the edge of the resection cavity. On the other hand, vessels supplying the anterior temporal lobe are usually safe to ligate because the tissue they supply will eventually be removed.

Once the posterior line of resection is marked, dissection begins along the STG a few millimeters inferior to the sylvian fissure. This is done with bipolar coagulation and sharply dividing the pia followed by subpial aspiration of the cortical tissue. This allows exposure of the temporal pia of the sylvian fissure and the underlying insula and middle cerebral arteries. Large MCA branches should be visible through the temporal pia of the insula, which can help distinguish the correct plane. Dysplastic tissue often can be lifted off the pia very easily and requires minimal coagulation. The pia will end at the inferior circular sulcus of the insula, and this is also where the temporal stem begins. Avoid going deep to the plane of the pia past the inferior circular sulcus as this can cause inadvertent injury to vital structures including the basal ganglia and brainstem. Extend the resection anteriorly until the dura anterior to the temporal pole is reached. The posterior cut continues inferiorly at the premeasured point previously determined (3 to 4.5 cm left, 5.5 cm right). The posterior line of resection extends from just below the sylvian fissure at the STG angling posteriorly along the middle and inferior temporal gyrus so that slightly more inferior temporal gyrus is removed than STG. To avoid excessive bleeding, all pial edges should be coagulated and divided sharply during this portion of the procedure. The cortical tissue is aspirated down to the depth determined by exposure of the inferior circular sulcus. The basal temporal lobe is divided in line with the posterior cut as the fusiform gyrus is aspirated to expose the collateral sulcus. This dissection should be continued as long as the floor of the middle fossa is visible. As you perform this procedure, continue to look for

the edge of the tentorium as this will provide an important anatomic landmark later on in the case. If the edge of the tentorium is encountered, it is likely that the collateral sulcus has already been divided. The collateral sulcus is an important landmark as it facilitates controlled entry into the inferior horn of the lateral ventricle. As the inferior resection is continued, the ventricle should be encountered by gently aspirating the white matter near the end of the collateral sulcus. In patients with severe hippocampal sclerosis, sometimes the hippocampus can go unnoticed during the lateral temporal lobe dissection. To avoid complications in these cases, it is important that you utilize the tentorium as an anatomic boundary and use the above techniques to find the ventricle and the hippocampus. Once the ventricle is encountered, a cotton patty can be placed within the ventricular space to serve as a landmark and assist with the completion of the lateral temporal lobectomy. The ventricle can be opened further with gentle aspiration and coagulation directly over the patty. The hippocampus and amygdala will be readily visible once this is opened in entirety. The final cut involves connecting the anterior and posterior cuts by following the lateral ventricular sulcus. When this is complete, the lateral temporal lobe can be removed in entirety. Prior to removal, ensure that all draining veins are coagulated as this can cause excess bleeding. Also, note that bradycardia is sometimes encountered when coagulating along the floor of the middle fossa, and if this is noted, immediately stop coagulating and wait until this resolves. Finally, avoid excessive coagulation along the middle fossa floor as the heat may disseminate and cause injury to the fourth nerve, which runs immediately under the dura.

The resection of the mesial structures can be performed with loupe magnification or operating microscope. The operating microscope allows for improved magnification and illumination. The anatomy in this region is complex, and it is recommended that the operating microscope be utilized until a level of comfort is reached at which point loupes may be considered. Careful removal of the parahippocampus, hippocampus, and amygdala requires a thorough understanding of the relationships existing between these structures in the perimesencephalic cistern, the hippocampal sulcus, and the choroidal fissure and point. Failure to respect important landmarks at this point can lead to serious complications and patient harm. The next two steps may be performed in series or in parallel. The first step is removal of the amygdala and the uncus, and the second step is removal of the hippocampus and parahippocampus. It is important to respect the pial planes as they will protect the underlying structures from injury, especially along the perimesencephalic cistern. This can be done using subpial aspiration and minimal bipolar coagulation.

To remove the amygdala, begin by identifying the choroidal point as this serves as the uppermost border of the resection. This point is where the anterior choroidal artery enters the temporal horn and supplies the choroidal plexus. It is very important that this artery is not injured and that choroidal plexus coagulation is limited as this can lead to anterior choroidal artery territory strokes, which can be devastating. To find a safe plane to resect the amygdala, place a cottonoid patty such that it connects the choroidal point to the MCA branches that are visualized through the anterior sylvian pia. One may also utilize the roof of the ventricle as the uppermost border for resection. Continue to deepen this cut straight downward until mesial pia is reached. It is very important that this cut is not extended superiorly as the upper amygdala merges with the globus pallidus and can cause injury to the patient. As mentioned before, it is also important that the anterior choroidal artery is not coagulated as this can lead to hemianopsia and hemiplegia secondary to an anterior choroidal territory stroke. This cut is continued until the pial plane is reached, which overlies the brainstem, third nerve, and PCA. The remainder of the amygdala/uncus complex can be removed by gently separating the tissue from the pia. Finally, the posterior cut is made at the amygdalohippocampal

sulcus, and this should allow for removal of the amygdala/uncus complex. If the anterior edge of the tentorium, third nerve, and anterior PCA are not visualized, the amygdala complex has not been removed entirely.

The next step is to perform the hippocampal resection, and this is done first by gently aspirating any residual parahippocampal tissue, which is visible mesial and deep to the collateral sulcus. When this is removed, the hippocampus can be retracted toward the floor of the middle fossa with minimal retraction on the roof of the ventricle. The ventricle is opened up further until the tail of the hippocampus is visible as it extends around the brainstem. Care must be taken to avoid retraction upward along the roof of the ventricle or posteriorly along the edge of the remaining dominant temporal lobe as this can lead to hemiparesis and language deficits, respectively.

Once the parahippocampus is removed, the choroidal fissure is exposed by gently retracting the choroid plexus superiorly with the use of a cottonoid patty. Aspiration of the fornix of the hippocampus and dentate gyrus allows for the exposure of the underlying hippocampal sulcus. Tiny vessels in the hippocampal sulcus will be visualized and should be coagulated and cut sharply while leaving an arterial tail that is easily accessible. If this is not performed correctly, the stump can sometimes retract into the perimesencephalic cistern and cause a large subarachnoid hemorrhage, which is difficult to control and leads to a suboptimal result. Once the hippocampal sulcus is divided, the hippocampus and any remaining parahippocampus can be gently peeled off the underlying pia, and finally, the tail of the hippocampus can be amputated as it extends around the brainstem. The hippocampus can now be removed and sent to pathology for study. The mesial resection is then assessed and any remaining accessible posterior hippocampus removed. The posterior cut across the tail of the hippocampus should ideally allow for 3 to 4 cm of hippocampus to be removed.

At this point, hemostasis should be obtained with a combination of irrigation, hemostatic agents, and time. Coagulation should be used sparingly especially on the pial surfaces as this can cause heat spread and injury to underlying structures. The cavity is then filled with saline and the dura closed in watertight fashion. The craniotomy flap is attached with titanium fixation and the muscle sewn together and re-approximated to the residual cuff. The skin is then closed in anatomic layers over a subgaleal drain to reduce postoperative swelling.

OUTCOMES AND COMPLICATIONS

The best method to evaluate whether surgery is successful is by allowing the passage of time to dictate whether seizure freedom was achieved. Temporal lobectomy for medically intractable focal epilepsy, especially in patients with MTS, has been shown to have the best long-term seizure-free outcomes of any epilepsy surgery. The literature quotes seizure-free rates between 60% and 80%, although there is a decline over time, which is related to late-onset seizure recurrence (24–27). There is some controversy over whether normal MRI findings suggest worse seizure-free outcomes (24). One interesting finding noted during the postoperative period has been described as the “running-down” phenomena. This has been noted in up to 33% of patients and involves rare postoperative seizures after surgery, which essentially stops after approximately 6 months. It is hypothesized that this is related to a small residual focus of epileptogenic zone that has been debulked but not entirely removed. In this case, either this area loses the ability to create seizures or anticonvulsant medications are able to control the region (26).

Although hippocampal sclerosis is most common in adults, one study showed similar good outcomes relating to pediatric patients with hippocampal sclerosis, with an overall Engel grade 1 or

2 score of 84% (28).

Temporal lobectomy has the benefit of a high seizure-free rate as well as a very low rate of complication. Risks related to the procedure are very low and include infection (wound, craniotomy, meningitis, urine), hemorrhage (wound, epidural, subdural, intracerebral), red blood cell transfusion related to acute blood loss anemia, deep venous thrombosis, and anesthetic complications. Death after temporal lobectomy is exceedingly rare (26,28).

Aside from the complications that have already been discussed (visual field deficits, language and naming problems related to the dominant temporal lobe, cranial nerve palsies, and paresis and plegia), there are other common conditions that should be discussed with the patient that are not considered complications of the surgery. These include headaches, depression, swelling of the eye and face, jaw pain and difficulty eating (related to temporalis manipulation), and cosmetic deformity. Patients should be counseled that these conditions improve with time, although headaches and depression can make the patients feel very uncomfortable and anxious. Patients with a history of headaches, depression, and anxiety can sometimes find these are exacerbated after surgery.

Postoperative aphasia can be noted after dominant temporal lobe resection, although this is fortunately fairly uncommon. Patients may perseverate, have naming difficulty, or wake up with global or mixed aphasias. This can be very distressing for the patient and family members, and they should be counseled that language will likely return to baseline after an MRI is performed, which shows no stroke in the posterior dominant temporal lobe. Language function usually returns or improves within 24 to 48 hours. Steroids and speech therapy may be started during this period to assist with recovery. To minimize this complication, it is very important to avoid retraction on the posterotemporal lobe in the dominant hemisphere and preserving all vasculature that supplies the residual temporal lobe.

NEUROPSYCHOLOGICAL OUTCOMES

Patients often complain about cognitive dysfunction during the preoperative and postoperative period. Preoperatively, this can be related to medication effects on normal tissue as well as damage to the mesial structures with repeated seizure activity. Neuropsychological testing is important in the preoperative period to assist with counseling the patient on what to expect postoperatively. As mentioned earlier, patients at high risk for memory decline after dominant temporal lobectomy may benefit from invasive monitoring to assess the involvement of mesial structures. As one might expect, postoperative memory decline has been shown to be related to dominant temporal lobectomy, normal hippocampal size, normal baseline neuropsychological testing, and late onset of epilepsy. Although discussion has mainly focused on risks associated with dominant temporal lobectomy, surgery on the nondominant temporal lobe is associated with decline in visuospatial memory on repeat neuropsychological testing, but this is rarely clinically significant.

CONCLUSION

This chapter describes several variations on the “standard temporal lobectomy” across institutions and based upon surgeon preference, but interestingly, reported outcomes are universally quite good. The surgical treatment of medically intractable temporal lobe epilepsy is safe and effective and should not be delayed in patients that fail appropriate medical treatment. The preoperative workup should be completed at an epilepsy center that utilizes a multidisciplinary approach and is

comfortable with the surgical treatment of epilepsy.

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CHAPTER 83 SURGERY FOR FOCAL CORTICAL DYSPLASIAS

IMAD M. NAJM, ANDRE PALMINI, AND WILLIAM E. BINGAMAN

INTRODUCTION

The term "focal cortical dysplasia" was first used to describe a specific malformation of the brain that consisted of disorganized cortex with enlarged irregular/disoriented neurons (1) and enlarged ballooned cells (2). Since then, FCD has been increasingly recognized as a cause of pharmacoresistant epilepsy that carries a less favorable prognosis for a seizure-free outcome following surgical resection (3–7). The increased incidence of FCDs reported in surgical series has been attributed to better preoperative identification of the lesions through improved magnetic resonance imaging (MRI) resolution, a better understanding of the electroclinical characteristics of various FCD subtypes, and reports of more favorable postoperative seizure outcomes.

This chapter reviews the pathologic subtypes of FCDs in light of the recently reported clinical, electrical, imaging, and functional observations since the last International League Against Epilepsy (ILAE) revision (8). We also discuss the presurgical evaluation and surgical management of FCDs in the setting of pharmacoresistent epilepsy.

HISTOPATHOLOGY OF FCDS

It is useful to think about the cerebral cortex along architectural and cellular axes. Normal cortex has a laminar distribution (architecture) of granular and pyramidal neurons (cells) along six layers. The hallmark of FCDs is an abnormal cortical microarchitecture, with loss of the laminar neuronal distribution. Furthermore, some types of FCD also have abnormal cell types, specific for this disorder. These have increased volume, are haphazardly distributed over the dyslaminated cortex, and are of two main types: dysplastic neurons and ballooned cells. Thus, a focal dysplastic lesion may feature abnormalities only in the architectural axis or in both, the architectural and the cellular axes. This understanding is crucial to correctly interpret the histopathologic classifications of FCDs.

The original histopathologic classification of FCDs that was introduced in 2004 addressed many practical aspects for the everyday presurgical evaluation and surgical management of patients with pharmacoresistant epilepsy due to FCDs (Fig. 83.1) (9). The original classification was recently revised by an ad hoc task force of the ILAE (8), which kept the core features of the original classification (10) and added a third FCD type. Thus, currently, FCDs are divided into three pathologic FCD subtypes: FCD ILAE type 1 is histopathologically characterized by architectural disorganization (i.e., dyslamination) at the columnar (type 1a), laminar (type 1b), or both (type 1c) levels. Focal cortical dysplasia ILAE type 2a is characterized by dysmorphic neurons in the setting of architectural disorganization, while type 2b included the changes seen in type 2a in addition to balloon cells. A third type of FCD was introduced (type 3) that dealt with other (principal)

pathologies associated to FCD, particularly FCD type 1. Five subtypes were included under FCD type 3: 3a, hippocampal sclerosis; 3b, tumor pathology; 3c, vascular malformations; 3d, occurring in the setting of any other brain lesions acquired during early life, that is, trauma, ischemic injury, or encephalitis; and type 3NOS (Not Otherwise Specified) in which an associated pathology is suspected based on imaging data but surgical material for pathologic examination and verification of diagnosis is not available. There is much to be learned on the independent epileptogenic potential of the dyslamination (i.e., FCD) associated with these principal pathologies and whether such associations should be considered as a single or dual pathology (11).

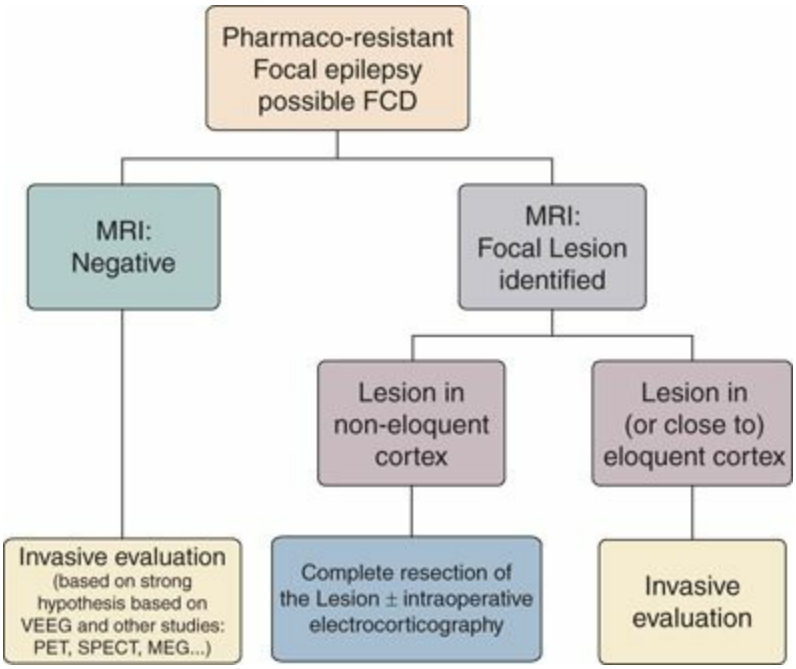
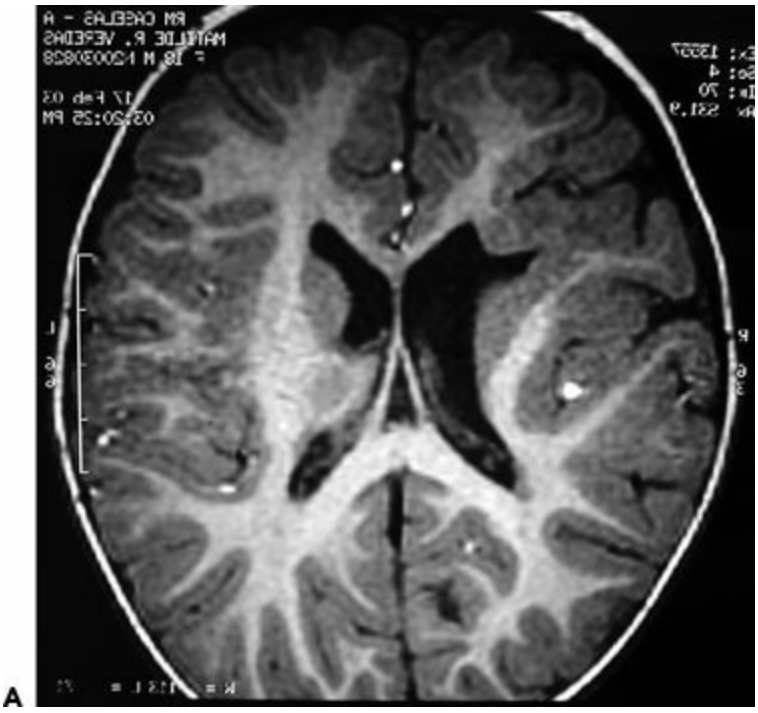


Figure 83.1. Proposed presurgical approach to pharmacoresistant epilepsy due to FCDs. (MRI, magnetic resonance imaging; VEEG, video EEG monitoring; PET, positron emission tomography; SPECT, (ictal) single-photon emission computed tomography; MEG, magnetoencephalography.)

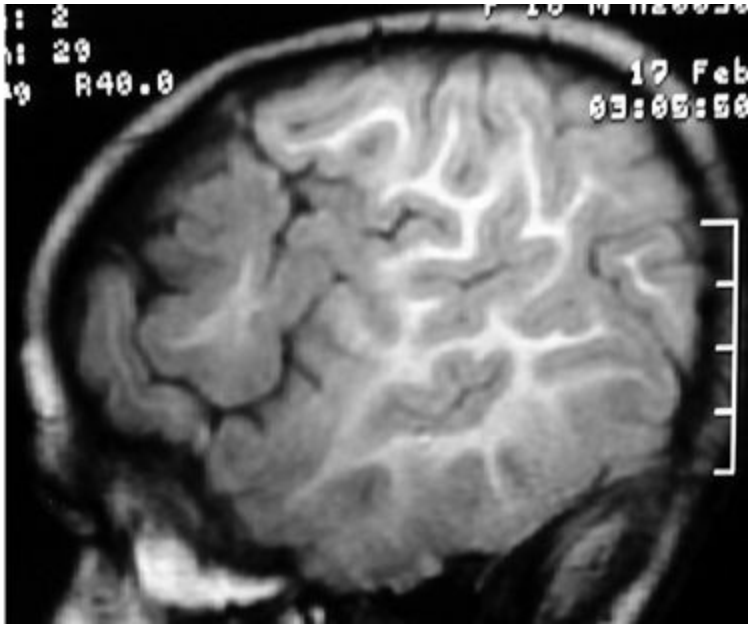
IMAGING CHARACTERISTICS OF FOCAL CORTICAL DYSPLASIAS

MRI techniques have provided a noninvasive window for the identification, localization, and some definition of the extent of some forms of FCDs.

FCD type 1: Nonspecific MRI changes were described for type 1. These include white matter volume reduction and subtle increased signals on fluid attenuated inversion recovery (FLAIR) and T2-weighted images. However, MRI is normal in the majority of patients with type 1 FCD (12,13). Nevertheless, it is important to seek very carefully for asymmetries in the cortical–white matter interdigitations, or in the white matter volume, because subtle changes may prove relevant and aid decision making (Fig. 83.2).



A



B

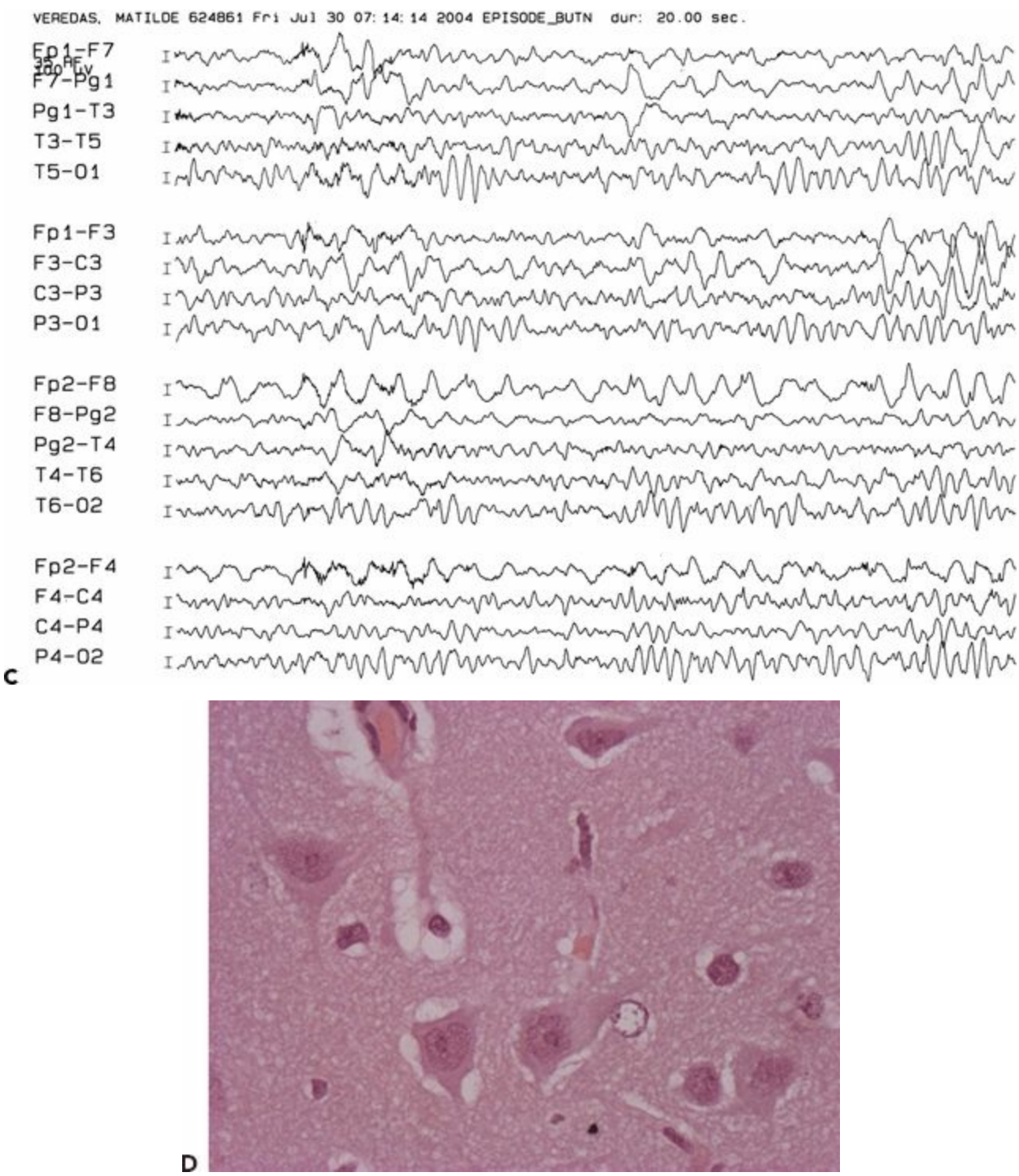


Figure 83.2. Two-year-old girl with frequent partial seizures, secondary generalization, and severe developmental delay. Sagittal **(A)** and axial **(B)** MRI sections showing a grossly dysplastic lesion in the right frontocentral region. Ictal EEG **(C)** suggested right frontal seizure onset. Following extensive frontocentral resection, the patient was seizure free for 30 months, when attacks recurred in the form of frequent startle-induced seizures with drop attacks. There was dramatic psychosocial regression. In **(B)**, note asymmetry of the white matter in the posterior quadrant, suggesting that the lesion was more considerably extensive than previously thought. Histopathology was FCD type 1 **(D)**.

FCD type 2: The most commonly reported abnormalities in FCD type 2 consist of focal changes in the cortical thickness, signal increase (mainly on FLAIR and T2-weighted sequences), and gray–white matter blurring, and in type 2b, the additional presence of a "transmantle" sign (a linear track of increased signal, extending from the periventricular region to the cortical mantle) (12–16). Recent observations show that type 2b dysplasia may show two distinct imaging patterns: (i) Mild to moderate FLAIR signal increase associated with increased thickness of the gray matter. These lesions tend to occur in the depth of sulci, in particular the precentral sulcus, superior frontal sulcus, and the

anterior extent of the sylvian fissure (frontal operculum) (17). (ii) A second group of balloon cell–containing FCD lesions is characterized by a "tuber-like" or "tumor-like" dense FLAIR signal increase in the center of the pathologic lesion surrounded by areas of variable FLAIR signal intensities (18), thickening of the cortical mantle, and gray–white matter blurring in association with transmantle signal increase pointing to the periventricular region (14,19,20). Less commonly described abnormalities such as cortical dimple, and hemispheric atrophy have been described in type 1 FCDs (21).

FCD type 3 lesions share the typical features of the associated lesions (HS, tumors, vascular malformations, scars) (22).

EPILEPTOGENICITY OF FCDS

The intrinsic in situ epileptogenicity of FCDs was previously reported by (4) using intraoperative electrocorticography (ECoG). Ictal or continuous epileptogenic discharges were mostly recorded from electrodes overlying dysplastic gyri. Direct cortical recordings demonstrated in situ epileptogenicity in FCD types 1, 2a, and some type 2b lesions (23,24) and showed various types of interictal epileptic activities (ranging from isolated spikes, polyspikes, repetitive spiking, to paroxysmal fast activities) and multiple ictal epileptic patterns (24). Some reports seem to suggest possible specific epileptic patterns in FCDs type 2, particularly repetitive, virtually continuous spikes (4,25,26). More recent data further suggested the in situ epileptogenicity of FCD through the recording of high-frequency oscillations (27).

The specificity of some interictal patterns as possible predictors of the area of ictal seizure onset has been reported, and focal continuous rhythmic discharges, repetitive spiking, and paroxysmal fast activities have been suggested as possible predictors of the ictal onset zone and early postoperative seizure outcome after resection of the area of focal electrical abnormalities (28).

We previously showed a differential distribution of the epileptic activities in balloon cell–containing lesions (type 2B) that display "tuber-like" or "tumor-like" high FLAIR signal intensities. The subregion within the balloon cell–rich FCD (mainly at the center of the MRI tuber-like abnormality) shows the least epileptogenicity, while the surrounding dysplastic cortical area containing few or no balloon cells (FCD type 1 or more often 2A) shows evidence of significant in situ epileptogenicity (24). On the other hand, deep sulcus balloon cell–containing lesions display intrinsic epileptogenicity (within the MRI-identified abnormality).

FUNCTIONAL STATUS OF FCDS

As a significant number of focal dysplastic lesions (FCDs) preferentially involve the frontal and temporal lobes, the issue of functional mapping and its potential overlap with epileptogenic cortex is the main challenge in the process of presurgical management of these patients (28). Dysplastic cortex has been shown to retain motor, sensory, or even language-related functions (29). Various electrical stimulation studies have shown that the dysplastic neocortex may conserve temporal and frontal language sites (30), but may display atypical motor homunculi (31,32). These studies demonstrate that function in dysplastic cortex could be preserved but may be reorganized and differences in functional expression may be dependent on the histopathologic subtype and spatial extent of the FCD. Some evidence is also provided by surgical intervention in high-functioning areas, in which a complete lesionectomy did not lead to motor deficit (33). What can be said, however, is that in FCD 2b, the

areas with the brightest signal changes most likely do not contain functions (and are less epileptogenic!) (33). These data lead to this rather provocative (and to a large extent hypothetical) question: Could incomplete resections of balloon cell-containing regions be an option considering their lack of epileptic potential and their possible protective effect against the seizures?

PREOPERATIVE EVALUATION AND SURGICAL MANAGEMENT OF PATIENTS WITH FCD: DIFFERENT SCENARIOS, VARIABLE APPROACHES

The precise anatomical localization and mapping of eloquent cortex and its relationships with a well-defined epileptogenic area are the most important components of any presurgical evaluation. They will facilitate the surgical planning and optimize the chances for a safe resection of the epileptogenic region (thus maximizing the chances for seizure freedom and minimizing the risks of neurologic deficits). Based on our current knowledge regarding FCDs, we suggest the following processes of presurgical evaluation and surgical management in patients with pharmacoresistant epilepsy.

The Preoperative Identification and Localization of FCD Lesion

MRI remains the gold standard and the most sensitive noninvasive window to the brain anatomy in the process of investigating the cause of epilepsy. As discussed above and elsewhere in this book, the identification of a lesion significantly enhances surgical candidacy, simplifies presurgical workup, and often improves seizure outcome. Furthermore, high-resolution MRI may help in the formulation of a hypothesis on the pathologic subtype of FCD (34). Interestingly, despite all advances in MRI, there remains a significant number of patients with FCDs (in particular FCD type 1) whose MRIs remain normal. A recent study found that more than 40% of patients with MRI-negative epilepsy harbor pathologic-confirmed FCD, the majority FCD 1 (35). However, apparently normal MRIs of children with severe epilepsies and mental retardation, with focal or multifocal discharges associated with secondary bilateral synchrony, should be examined with utmost care, seeking for asymmetries in the cortical–white matter interdigitations or in the white matter volume. Subtle changes may be a clue to a specific type of FCD type 1 that deserves aggressive surgical management (34,36,37).

Additional postprocessing techniques such as voxel-based MRI postprocessing using a morphometric analysis program (MAP) may help in the identification of some of these lesions: MAP abnormalities were found in 48% of the MRI-negative epilepsy patients (38).

Localization of the Epileptogenicity, Definition of Its Extent and Functional Mapping

Video electroencephalography (VEEG) would help in the identification of the network structures that may be involved in seizure generation and progression (through analysis of the recorded seizure semiology), therefore leading to the formulation of a clear anatomoelectroclinical hypothesis. Further validation of the anatomic hypothesis is achieved through imaging (the identification of lesion on MRI), with or without metabolic imaging (including FDG-PET hypometabolism that may point to

focal regions of cortical dysfunction). Other studies that may include ictal SPECT (SISCOM), MEG, and EEG-fMRI would further point to areas of dysfunction within a network or identify the three-dimensional localization of interictal epileptogenic regions, respectively.

Noninvasive studies achieve the goal of identification of the epileptogenic area and its possible anatomical cause in a sizable number of surgical patients (39–42). In many, however, formulation of a clear anatomoelectroclinical (AEC) hypothesis may not be possible, or an AEC hypothesis is generated but the exact location of the epileptogenic area within the network, its extent, and/or its overlap with functional (eloquent) cortex remain unclear (43–46).

The localization of functional areas in the brain, mapping of their extent, and their potential spatial overlap with the epileptogenic zone (EZ) are essential parts in the process of developing an adequate and individualized resective surgical strategy (39,47,48). As focal cortical dysplastic lesions (FCDs) are differentially located in the frontal and temporal lobes (therefore in potentially eloquent cortex), an understanding of the functional status of the involved region(s) and its anatomical and pathologic correlations are essential (39,49).

The pathologic differences and variable imaging characteristics in addition to the lack of known in situ biomarker(s) for the localization and mapping of the intrinsically epileptogenic dysplastic cortex constitute major challenges in the presurgical evaluation and surgical treatment of patients with FCDs (50,51). The main indications for an invasive evaluation in focal pharmacoresistant epilepsy due to suspected FCD (with the main purpose of direct cortical recording) are to address the main challenges and limitations of various noninvasive techniques. We recently recommended that an invasive evaluation should be considered in any one of the following cases (18):

1. The MRI does not show a cortical lesion in a location that is concordant with the electroclinical/functional hypothesis generated by the VEEG recordings (so-called MRI-negative cases).
2. The anatomical location of the MRI-identified lesion (and at times the location of a clearly hypometabolic focal area on PET) is not concordant with the electroclinical hypothesis. These include selected cases of deeply seated brain lesions such as deep sulcal lesions.
3. There are two of more anatomical lesions with the location of at least one of them being discordant with the electroclinical hypothesis, or both lesions are located within the same functional network, and it is unclear if one (or both) of them is (are) epileptic.
4. The generated anatomoelectroclinical hypothesis (MRI-negative or MRI-identifiable lesion) involves a potentially highly eloquent cortex (52–54).

In these instances, an invasive evaluation would lead to the formulation of a resective surgical strategy. The recommendation for an invasive monitoring and its type should be made during a multidisciplinary patient management meeting that includes neurologists, neurosurgeons, neuroradiologists, and neuropsychologists. Areas and networks of coverage/sampling should be determined based on a well-formulated AEC hypothesis (based on the results of all available noninvasive studies).

For this purpose, one intraoperative recording technique (ECoG) and two extraoperative invasive methods with chronic recordings—subdural grid electrodes (SDG) and stereotactically placed intracerebral electrodes (SEEG)—have been used to accomplish these goals.

Intraoperative recording is a limited option as it only provides information restricted to interictal activity. However, this type of recording may prove very useful when continuous repetitive

discharges are seen from involved cortex, as these have been shown to significantly correlate with the ictal onset zone (4,49,55). Furthermore, acute ECoG with carbon-ball electrodes may be performed in sequential stages during the resection, allowing electrical activity from depths of gyri and adjacent cortical regions to be repetitively probed (55). The influence of anesthetic agents on EEG activity may alter thresholds of afterdischarges and motor responses (52), although this has not been a universal observation and is often not relevant for the localization purposes of the study. Additionally, intraoperative language mapping often requires a cooperative patient who can tolerate being awake during surgery under local anesthesia. This is particularly difficult in the pediatric population.

Extraoperative mapping with subdural grid electrodes (SDG) has the main advantage of allowing an optimal coverage of the subdural space adjacent cortex with adequate and continuous superficial functional mapping capabilities (32,56–58). A major strength of subdural electrodes consists in the comprehensive anatomical coverage of cortical surfaces therefore allowing accurate anatomical electrical and functional mapping of the areas of coverage. Limitations of SDGs include the inadequate/partial/incomplete intrasulcal and interhemispheric coverage (59) and the need for craniotomy in order to implant. These characteristics are highlighted in the published results on the successes and failures following SDG implantation (60). Previous outcome studies showed that the best results following SDG implantation are achieved in patients with clear cortical lesions (in particular tumors), those who underwent lobar resections, and those patients in whom functional mapping was the main purpose of SDG implantation (49,60). These observations suggest that the best candidates for extraoperative invasive evaluation with SDG are those patients with clear FCD surface lesion(s) (excluding the interhemispheric, cingulate gyrus, deep sulcal, and mesial frontotemporal regions). A modified implantation approach of SDG and manually implanted depth electrodes has been used for the last 10 years at some epilepsy surgery programs. This modified approach has the main advantage of combining the two recording methods and thus allowing for excellent cortical coverage and some sampling of deeper lesions. But this modified approach does not allow extensive network coverage of functional networks and lacks the accuracy of the SEEG methodology.

Extraoperative recording with (SEEG) is indicated in patients with deep-seated lesions or in areas that are difficult to cover with SDG such as the interhemispheric regions (frontal, parietal, and occipital, in particular the paracentral lobule), opercular areas, cingulate gyrus, posterior orbitofrontal areas, insula, and depths of sulci. SEEG takes advantage of the more accurate anatomical presurgical workup and the possibility to stimulate into the depth of the sulcus and the subcortical pathways. There is at times a need for a complementation of the electrical localization with other methods of functional mapping such as diffusion tensor imaging, functional MRI, and intraoperative functional mapping (54). Limitations in SEEG include the need for more expensive testing preoperatively and specialized equipment in the operating room. The major risk of SEEG implantation is the higher risk of intracranial hemorrhage (3%) with associated permanent neurologic morbidity when compared to SDG implantation.

RESECTIVE STRATEGY IN FCD

The main principle that governs epilepsy surgery and in particular resection of FCDs is the “complete” resection of the EZ while preserving normal brain and function. This should be based on a clear definition of the anatomical, epileptic, and functional boundaries of the lesion and an accurate

hypothesis regarding the extent of the EZ. Every effort should be made to resect the lesion and the areas of ictal onset (from which ictal epileptic patterns were recorded). This is particularly important in patients with tuber-like FCD type 2b lesions, where an incomplete resection of areas adjacent to the visible lesion may exacerbate the epilepsy and results in acute postoperative refractory status epilepticus (61). What remains a subject of debate is the issue of recorded interictal patterns that are at times spatially distinct from the areas of ictal onset. As previous studies showed that some interictal patterns are highly predictive of ictal onset (such as continuous rhythmic discharges and paroxysmal fast activities) (4,28), we do recommend an extension of the margin of the resection to these areas. The significance of single spikes in the planning of the resection remains unknown, and although every effort should be made to resect these regions, their frequent location in regions that are noncontiguous with the lesion and the ictal onset zone precludes their complete resection.

Surgical strategy involves resection of involved cortical tissue while preserving blood supply. This is best accomplished by using a subpial resection technique to spare cortical vessels that may be passing through to irrigate noninvolved cortex. The involved cortex has often a more firm consistency, which allows surgical resection by following the plane between the softer normal cortical tissue and the firmer dysplastic tissue. In many of the type 2 FCD cases, the dysplastic cortex can be followed down into the white matter as one might follow the root of a plant into the Earth. It remains unknown whether resecting this deeper firm "tail" or "root" is clinically significant. When functional cortex is involved, the surgical approach must take into account the anticipated effect of operating in or near the functional cortex. Risks should be carefully detailed preoperatively so that postoperative expectations are clear. Intraoperative surgical techniques to identify and preserve function are the same as applies in other fields of neurosurgery and include cortical stimulation and surgery under awake conditions. Resection of some functional areas is well tolerated and should be undertaken when necessary and after proper informed consent to effect a cure from seizures. In general, surgery for FCD involves larger resections and outcomes improve when larger pieces of cortex are removed.

A final word is needed on the surgical strategies for children with severe epilepsies and mental retardation, in whom the association of (i) subtle asymmetries of gray–white matter volume (see Fig. 83.2) and (ii) focal or multifocal EEGs with frequent secondary bilateral synchrony (often wrongly suggesting symptomatic generalized epilepsies, yet due to unilateral pathology) indicates a specific kind of FCD type 1 causing epileptic encephalopathy (34,36). These are usually extensive lesions, involving either a quadrant or a whole hemisphere and should be completely resected as soon as possible. Resections are usually extensive and hemispherectomy may be needed, either as the initial or a second stage (36). When motor function is preserved, the central area and its connections may be spared by a technique known as "everything but motor" resection (62).

OUTCOMES OF EPILEPSY SURGERY IN PATIENTS WITH FCDS

Longitudinal outcome studies have shown that surgical treatment of pharmacoresistant epilepsy due to FCD yields less favorable results as compared to other well-recognized epileptic pathologies (63). Unfortunately, even if different subtypes of FCDs harbor clearly dissimilar anatomoelectroclinical features (especially types 1 and 2), surgical results, procedures, and outcomes are globally considered, not reflecting the enormous range in seizure freedom varying from 43% in type 1 to 75%

in type 2 (23).

A favorable long-term outcome with seizure freedom can be achieved in 47% to 79% of patients (13,23,64–70). Even in the more difficult cases that require invasive evaluation, epilepsy surgery in patients with medically intractable epilepsy due to FCD achieves favorable seizure outcome in a sizable number of patients. A recent long-term outcome study on patients who underwent invasive evaluation with subdural grids showed that complete seizure freedom was 61% at 1 postoperative year, 47% at 3 years, 42% at 5 years, and 33% at 10 years (60).

A recent study from the Cleveland Clinic reported on the longitudinal seizure outcome in a large series of patients with medically intractable epilepsy due to different types of FCD who underwent surgical resection following the implantation of intracranial electrodes (SDG, depth electrodes, and/or SEEG). This study identifies two patterns of epilepsy surgery failures that are likely due to two distinct causes: Most seizure recurrences (63%) were observed in the first 6 months after surgery. These early failures are due to an incomplete resection of the identified ictal onset zone, and late failures are dependent on the FCD pathologic subtype.

A favorable seizure-free outcome was achieved in half of the patients. Another previous study from the same institution on a smaller series of patients (n = 48) with FCD who underwent subdural electrode recordings between 1990 and 2004 showed a seizure-free outcome of 45% (28).

Long-term seizure control mainly depends on the pathologic subtype; whereas patients with type 2 FCDs show the best outcome, patients with type 1 FCD showed the least favorable outcome (60,71).

Isolated FCD 1 was observed in 31% of the patients, characterized by frequent seizures, negative MRI, and frequent frontal or multilobar involvement. In comparison to patients with FCD 1 associated with hippocampal sclerosis, other types of FCD, or tumors, the patients with isolated FCD 1 had a worse postsurgical outcome (46% in class 1) (64). This is also the case in children with epileptic encephalopathy associated with extensive unilateral FCD type 1 (36,37).Type 2 FCDs seem more prone to achieve long-term seizure freedom by the surgical treatment; moreover, FCD type 2b has an even better outcome reaching 88% of patients in class Ia (13,26).

RESULTS OF SURGICAL INTERVENTION IN PATIENTS WITH FCDS IN ELOQUENT CORTEX

Seizure freedom can be achieved in a significant number of patients with FCDs involving the eloquent cortex following a meticulous presurgical evaluation. Pondal-Sordo et al. (72) described an Engel I to III outcome in 73% of the 52 patients studied. However, only six patients had FCD. Surgical successes were also reported by Sandok and Cascino (73) in 14 patients with perirolandic lesion epilepsy where 78% were seizure free and only one patient suffered from a monoparesis: FCD was noted in only one patient in this cohort. Lehman et al. (74) reported 20 patients with lesions in the face area, with FCD pathology in only one patient. Seizure improvement was achieved in 90%, but six patients needed a reoperation.

Seizure-free outcome may be achieved in a significant number of patients with FCDs involving functional cortical areas (61,75). Devaux et al. (75) showed that seizure outcome was significantly associated with etiology in patients with epilepsy arising from functional areas (sensorimotor and supplementary motor areas, parietooccipital, insula, and language areas): 93% of Taylor-type FCD, whereas only 40% of cryptogenic epilepsies were in class I (75). Postoperative deficits were observed in 61% of patients but resolved completely in more than half of them (53%).

Another outcome study in patients with FCDs reported a successful seizure outcome and reduced seizure frequency in 88% of the patients (including an Engel class I in 59% of patients) with an incomplete resection and postoperative abnormalities on EEG representing the main recurrence risk factors for the type 2b FCD subgroup (61). However, deficits were noted in 59% of the patients. An intriguing finding in patients with type 2b FCD is the reported occurrence of focal status epilepticus in the immediate postoperative period (in 3 out of 8 patients). However, once a more aggressive surgical resection was performed, seizure freedom was achieved in all 3 patients.

These results show that a favorable seizure outcome can be achieved in a sizable number of patients with pharmacoresistant focal epilepsy due to FCD and arising from eloquent/functional cortex. The seizure outcome predictors in these patients depend on the type of the FCD lesion and its overlap with functional cortex. Patients with type 2 FCD have better surgical outcome and less functional deficit than those patients with type 1 FCDs. An overlap between function and in situ epileptogenicity is a predictor of a worse seizure outcome if the epileptogenic region is not completely resected.

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CHAPTER 84 HEMISPHERECTOMY: INDICATIONS, PROCEDURES, AND OUTCOME

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Hemispheric resections or disconnections are performed successfully to treat medically intractable hemispheric epilepsy in children and sometimes in adults, often resulting in remarkable improvement in seizure outcome and quality of life. New techniques are being constantly added to the surgical armamentarium of hemispheric disconnections, with the aim to minimize complications and improve outcome. In this chapter, we review the various aspects of hemispheric resections and disconnections, including a historical perspective, selection criteria, surgical methods, and outcome.

HISTORICAL PERSPECTIVE

Walter Dandy, in 1928, was the first to perform hemispherectomy for a patient with glioblastoma (1). Ten years later, McKenzie attempted to perform hemispherectomy in a patient with intractable epilepsy (2). In the 1940s, Krynauw systematically performed hemispherectomies in patients with intractable seizures and infantile hemiplegia (3). Only then, the technique gained acceptance in the management of handicapped patients with intractable epilepsy. Oppenheimer and Griffith, in 1966, reported delayed complications after anatomic hemispherectomy such as superficial hemosiderosis of the brain and obstructive hydrocephalus (4). Recurrent hemorrhage inside the operative cavity was considered the chief mechanism of these complications.

Further modifications of hemispherectomy were developed in order to prevent the late complications. Complete removal of the hemisphere was thought to increase the risk of repeated hemorrhages, and the idea of leaving some brain tissue in the cavity to "splint the brain" emerged. Subtotal hemispherectomies were attempted with poor results on seizure control. In 1983, Rasmussen described the so-called functional hemispherectomy—which involves resection of central and temporal lobes and disconnection of the anterior frontal and parietooccipital lobe; the residual disconnected tissue was left in place, to avoid late complications (5–7). Other techniques included the Oxford variation (or Adam modification, 1983), which included an anatomical hemispherectomy along with tacking the dura to the falx and tentorium to collapse the subdural space at the expense of a large epidural space (8), and hemidecortication aimed at removal of cortex leaving most of the subcortical structures including a rim of white matter around the ventricles (9).

The term "hemispherotomy" was first coined by Delalande in 1992 to describe a modified functional hemispherectomy, in which cortical resection was further minimized using a vertical parasagittal approach (10). Other modified techniques include the peri-insular hemispherotomy of Villemure and Mascott (11) and the transsylvian functional "keyhole approach" hemispherotomy of

Schramm et al. (12). All these variants of functional hemispherectomy represent attempts to perform a complete disconnection of the epileptogenic hemisphere with minimal tissue removal. In this chapter, the term hemispherectomy denotes to all forms of hemispheric disconnection unless otherwise specified.

SELECTION CRITERIA

Typical hemispherectomy candidates satisfy the following criteria: (i) medically refractory focal epilepsy; (ii) electroclinical evidence consistent with epilepsy from the affected hemisphere; (iii) large unilateral hemispheric lesions (e.g., encephalomalacia due to remote infarct, Rasmussen encephalitis, hemimegalencephaly (HME), multilobar dysplasia, Sturge–Weber syndrome); (iv) preexisting deficits ascribed to the diseased hemisphere, most commonly hemiplegia (loss of hand function in particular), cognitive delays, and sometimes visual field defect; and (v) minimal to no risk for new deficits after surgery deemed unacceptable to the patient, physician, or both. Most of these can be easily confirmed by a careful history and neurologic examination, video–EEG monitoring, and brain MRI. Values of additional tests such as PET and ictal SPECT are limited in catastrophic epilepsy due to large hemispheric lesions (5–16).

The majority of patients undergoing hemispherectomy satisfy the above-mentioned criteria, but a few exceptions may occur as outlined here. Firstly, abundant generalized EEG abnormalities may be noted in nearly a quarter of patients with congenital or early brain lesions. Sometimes, EEG abnormalities patients with large hemispheric encephalomalacia may appear higher over the healthy hemisphere. Successful hemispherectomy with good outcome despite generalized or contralesional maximum ictal and interictal EEG patterns has been reported (16). Second, we have also noted that structural abnormalities on the contralateral hemisphere are common in patients undergoing hemispherectomy (17). Hence, presence of bilateral MRI abnormalities or generalized EEG abnormalities should not be used as exclusion criteria for surgery. Lastly, although hemispherectomy is usually undertaken in patients with no useful preoperative hand function, high seizure burden and extremely poor quality of life may sometimes force families and patients to choose hemispherectomy even though it will result in a new or significantly worsened postoperative hemiparesis.

TIMING OF SURGERY

Many well-established epilepsy centers recommend early intervention to stop seizures and maximize chances for neurodevelopment (18–26). If the selection criteria (as outlined earlier) for hemispherectomy are met, surgery should be done as soon as possible.

In hemispherectomy for young infants, risk of perioperative morbidity and mortality should be carefully weighed against the risks of ongoing seizures by delay in surgery. In general, for noncatastrophic epilepsy, we consider a body weight of 10 kg or above acceptable. For catastrophic hemispheric epilepsy, surgery may be performed earlier with appropriate informed consent on the risks of excessive blood loss and mortality (14). Hemispherectomy has been safely performed at our center (Cleveland Clinic) for infants weighing as low as 5 kg at 2 months of age.

Surgery at younger age potentially offers maximum chances of neural plasticity to aid recovery of some key functions. In most right-handed subjects and a large proportion of left-handed subjects, the left hemisphere is dominant for language function. In patients with left hemispheric epilepsy due to early brain injury, hemispheric dominance may be atypical with the opposite hemisphere harboring

language abilities. Hemispherectomy is unlikely to have any impact on such patients especially when the preexisting damage is extensive. Surgery performed at a younger age (typically before 6 years) may lead to clinically significant functional recovery, even if the affected hemisphere harbored some language function (13). The intracarotid sodium amytal test may not be feasible and are not routinely performed at our center in such young patients with early brain injury. In older patients with later-onset brain injury, the need for language lateralization should be carefully reviewed before surgery.

ANATOMICAL REMARKS AND SURGICAL TECHNIQUES

Several techniques of hemispherectomy, hemispherotomy, and other hemispheric disconnections have been described. All these procedures have four common principles: (i) disruption of the descending and ascending fibers through the corona radiata and internal capsule, (ii) removal of the mesial temporal structures, (iii) complete callosotomy, and (iv) disruption of the frontal horizontal fibers, including the occipitofrontalis fasciculus and uncinate fascicle (27,28), The main difference among the various techniques lies in how the lateral ventricle is accessed—whether access starts from the temporal horn or from the body of the lateral ventricle—and the extent of brain resection necessary to gain access to the ventricular system. Other differences include the removal or preservation of the insula and the preservation or ligation of branches of the middle cerebral artery. In the following paragraphs, we simplistically describe the differences in the several techniques.

Anatomical Hemispherectomy

Anatomical hemispherectomy refers to complete removal of frontal, temporal, parietal, and occipital lobes preserving the thalamus and basal ganglia. Patient positioning is optimized to allow access to the lateral surface of the affected cerebral hemisphere and to minimize neck torsion. The head may be positioned in rigid point fixation or resting on a head support, depending on the patient's age. The head is turned 90 degrees with ipsilateral shoulder support and the vertex slightly down to allow access to the mesial temporal lobe structures and interhemispheric fissure (Fig. 84.1).

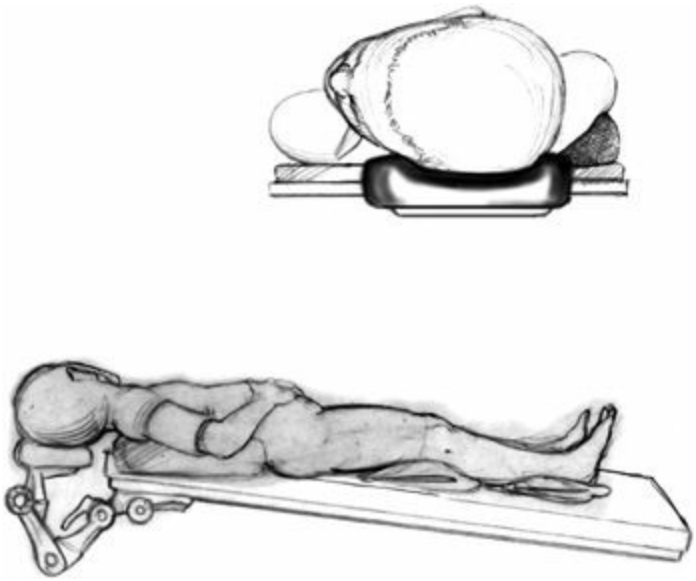


Figure 84.1. Patient's position for anatomical hemispherectomy.

The head is then shaved and a "T"-shaped incision planned to allow access from the floor of the middle fossa to the midline of the head. Superficial landmarks useful for incisional planning include anatomic midline from nasion to inion, the lateral edge of the anterior fontanelle, the transverse sinus location, the greater wing of the sphenoid bone, and the zygomatic arch (Fig. 84.2).

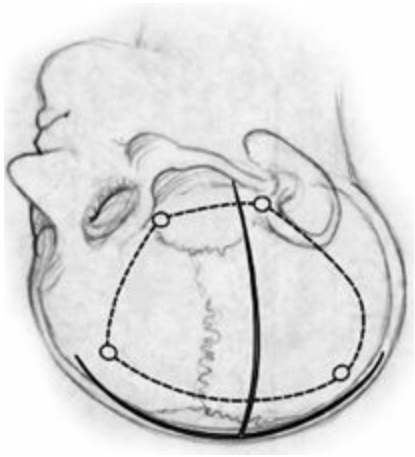


Figure 84.2. Important superficial landmarks, "T" incision and planned.

The T incision is designed by a line at least 0.5 cm from midline and a perpendicular line from the zygomatic root just anterior to the tragus. The midline incision extends from the hairline to a point 4 to 5 cm above the inion. The incision is made with caution in the younger patient with an open anterior fontanelle to avoid inadvertent sagittal sinus injury. The skin edges are then reflected and periosteum and temporalis muscle fascia visualized. The muscle is mobilized off the underlying bone with a "T" incision, reflecting each muscle cuff inferiorly. Burr holes are done at the keyhole, the floor of the middle fossa just above the zygomatic arch, and lastly along the parasagittal areas just off the midline to avoid sagittal sinus injury (if anterior fontanelle is closed). The optimal craniotomy flap allows exposure to the midline, orbitofrontal base, floor of the middle fossa, and total length of the sylvian fissure. The craniotomy flap is carefully removed with a high-speed air-drill craniotome.

After the dura mater is opened in an H fashion, the sylvian fissure is identified and venous drainage patterns inspected. The distance from the superior craniotomy edge to the interhemispheric fissure is verified. The locations of major draining veins to the sagittal sinus are noted and carefully protected until later in the procedure to avoid early and often devastating blood loss. The orbitofrontal region is inspected and the position of the olfactory tract visualized as an anatomic guide to the gyrus rectus and midline structures (Fig. 84.3).

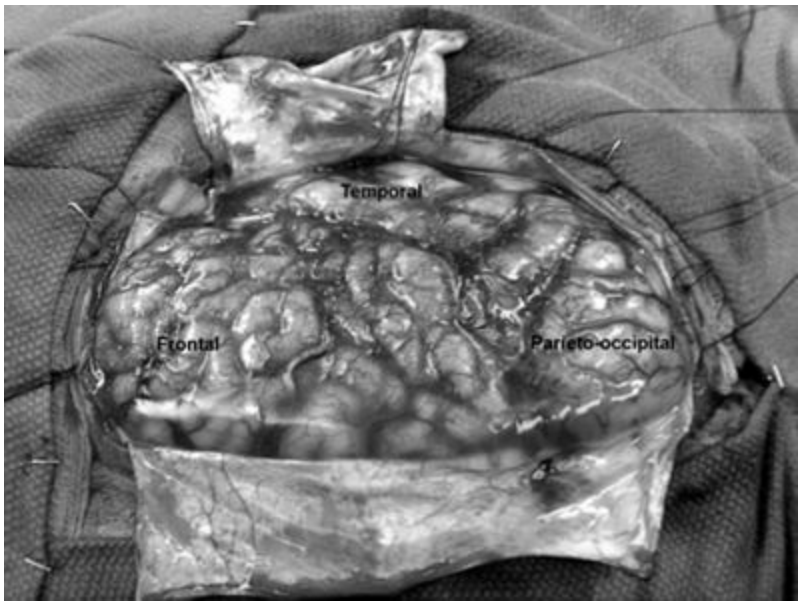


Figure 84.3. "H" dural opening and hemimegalencephalic brain.

The dissection of the sylvian fissure begins with early exposure and control of the middle cerebral artery trunk in the sylvian fissure just distal to the lenticulostriate branches. The sylvian fissure is split along its entire length using bipolar electrocautery, suction, and sharp microdissection (loupe magnification is preferred for this portion of the procedure). This should be done carefully to minimize bleeding, but cortex can be aspirated as necessary to aid in exposure. Once opened, the insular cortex including the inferior and superior circular sulci should be visualized along the length of the sylvian fissure.

The middle cerebral artery is then ligated with bipolar cautery and surgical hemostatic clips (Fig. 84.4). The inferior circular sulcus is identified and the white matter of the temporal stem is localized just deep to the sulcus. Using suction aspiration, the white matter is removed along the temporal stem, and the temporal horn of the lateral ventricle is entered. A cottonoid patty is placed here to protect the choroid plexus and prevent blood from entering the ventricular system. The pial dissection along the anterior (temporal) aspect of the sylvian fissure is carried below the main sylvian vein to the floor of the anterior aspect of the middle fossa. The anterior temporal pole is then aspirated to expose the edge of the tentorium. The white matter dissection of the temporal stem is then continued posteriorly to achieve exposure of the temporal horn from the anterior aspect to the trigonal region (Fig. 84.5). A long, thin cottonoid is then placed posteriorly into the ventricle passing from the trigone up into the lateral ventricle.

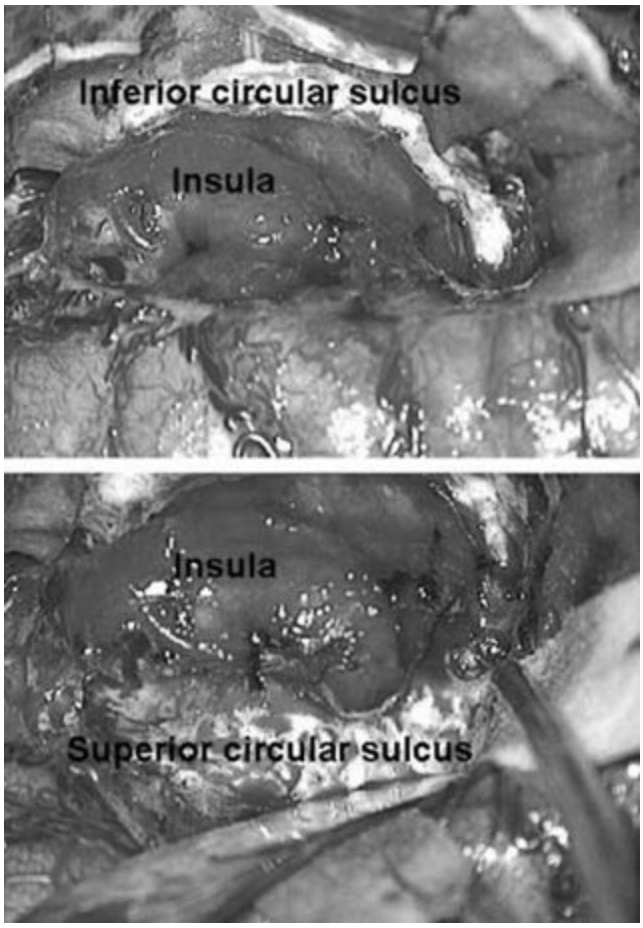


Figure 84.4. Exposure of superior and inferior circular sulcus surrounding insula.

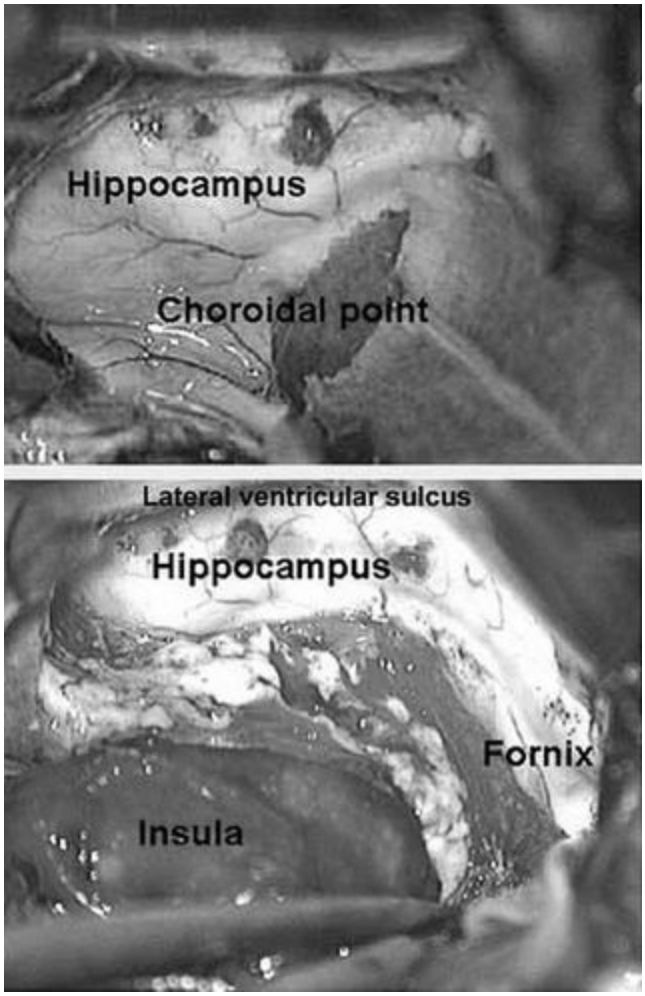


Figure 84.5. Temporal horn access through inferior circular sulcus and identification of important landmarks for mesial structures dissection.

The posterior trigonal area is then plugged with a large cotton ball to prevent blood from entering the lateral ventricle. Exposure of the tentorial edge and basomesial temporal pia is then achieved by dissection of the lateral ventricular sulcus (collateral eminence) from within the temporal horn, just lateral to the hippocampus. This can be done with bipolar coagulation and suction or ultrasonic aspiration. In either case, the amygdala, hippocampus, and choroid plexus are protected from injury with cottonoid patties. Once the mesiobasal pia is identified just lateral to the parahippocampal gyrus, the dissection can be extended anteriorly to meet the prior pial dissection at the floor of the anterior middle fossa. The parahippocampus is then aspirated to identify the tentorial edge. The tentorial edge is then followed from anterior to posterior, curving back behind the mesencephalon. At this point, the posterior cerebral artery branches can be ligated as they pass from the perimesencephalic cistern over the tentorial edge to the temporooccipital cortex. At the conclusion of this phase of the operation, the temporal lobe lateral to the parahippocampal gyrus has been disconnected and the posterior cerebral artery branches divided. The amygdala, hippocampus, and a remnant of the parahippocampal gyrus remain in place.

Suprasylvian dissection through the superior limiting (circular) sulcus of the insula takes place to divide the coronal radiata and expose the lateral ventricle along its length. This can be done by careful dissection from above the insula or by following the previous trigonal ventricular opening around the posterior aspect of the insula to the lateral ventricle (Fig. 84.6). Dissection is facilitated by dividing the posterior branches of the MCA at the end of the sylvian fissure. Once the corona radiata is divided, the entire length of the lateral ventricle is opened and the foramen of Monro plugged with a small cotton ball to prevent blood from entering the dependent ventricular system. Care should be taken to protect the choroid plexus to avoid unnecessary bleeding. Similarly, basal ganglia disruption can be prone to bleed and is best controlled by the application of hemostatic agents to the exposed surfaces.

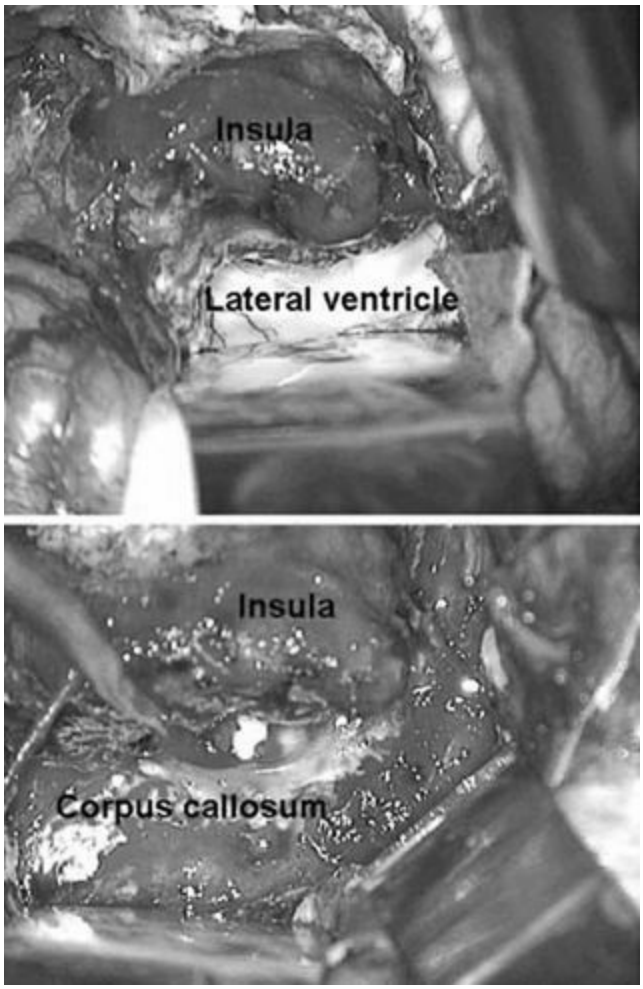


Figure 84.6. Opening of lateral ventricular system and corpus callosotomy. (Tip of the shunt from the opposite hemisphere is also seen.)

The corpus callosum is identified from within the ventricle at the junction of the septum pellucidum and the roof of the lateral ventricle. Aspiration of the roof of the lateral ventricle just above this area leads to the gray matter of the ipsilateral cingulate gyrus and falx cerebri. This is meticulously aspirated to prevent injury to the contralateral cingulum. Once this area is exposed, identification of the pericallosal arteries and corpus callosum proper is easily achieved. The corpus callosum and ipsilateral cingulate gyrus are then aspirated from the genu to the splenium. Complete sectioning is important to achieve and can be accomplished by following the pericallosal artery as it closely follows the characteristic course of the callosum. Special attention should be given to the genu and splenium to assure complete disruption of the horizontal fibers. Additional assistance is achieved by removal of the cingulate gyrus and identification of the inferior edge of the interhemispheric falx. Finally, the ipsilateral fornix is disrupted by aspiration at a point just anterior to the splenium. Next, the mesial dissection should continue anteriorly coagulating and dividing the pia of the ipsilateral mesial frontal lobe including the arterial branches from the anterior circulation. This mesial frontoparietal disconnection is followed anteriorly to the base of the frontal lobe just above the olfactory nerve (frontal pole). Posteriorly, the edge of the falx is followed as it transitions to the tentorium. This mesial parietooccipital resection should connect with the basal temporal disconnection below the sylvian fissure, which was performed earlier. At this point, the callosum is disconnected and the pia along the mesial aspect of the entire hemisphere is coagulated and divided. The only remaining portion of the hemisphere in place is the basal–frontal lobe below the genu and the draining veins to the venous sinuses.

The last remaining pia to be divided extends from the anterior aspect of the sylvian fissure down along the posterior–basal–frontal lobe. This pia is coagulated and divided along with the MCA branches to the frontal cortex. The posterior–basal–frontal lobe is aspirated, maintaining a plane just anterior to the anterosuperior insula (Fig. 84.7).

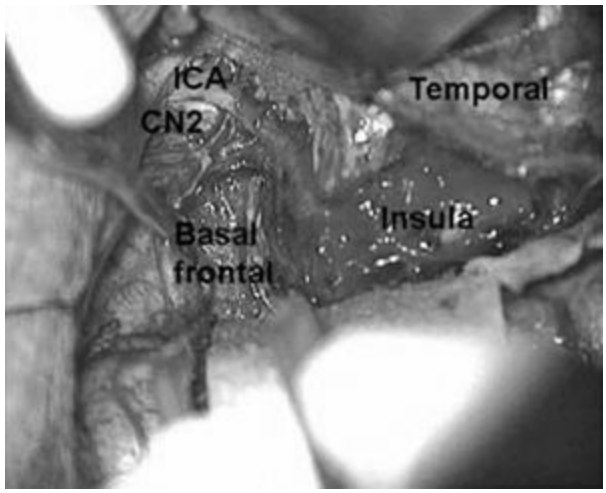


Figure 84.7. Important surgical landmarks of right frontobasal disconnection.

The orbitofrontal pia is then coagulated and divided down to the olfactory nerve, and the pia overlying the gyrus rectus is identified and divided. The gyrus rectus is then aspirated to expose the contralateral gyrus rectus and a cottonoid patty placed to mark the midline. The pial dissection along the olfactory nerve is then carried anteriorly to avoid disruption of the nerve. The remaining gyrus rectus is then aspirated with the posterior removal limited by the internal carotid artery. The deep white matter and mesial frontal gyri are removed in subpial fashion by a dissection plane marked by the anterior aspect of the frontal horn starting below the prior dissection of the genu of the corpus callosum. This dissection is carried out through the caudate nucleus along the course of the anterior cerebral artery to where it joins the internal carotid artery. Special care should be taken after the hemisphere is removed to ensure complete removal of the basal–posterior–frontal lobe. Once all the pial surfaces and white matter tracts have been cut, the draining veins to the sinuses are circumferentially coagulated and divided and any bleeding points packed with hemostatic agent. At this point, the entire hemisphere can be removed in one anatomic piece and sent for pathologic study. The remaining amygdala–hippocampus bloc is then removed as the last portion of the procedure.

The insular cortex can be removed if so desired by subpial aspiration using the ultrasonic aspirator or suction coagulation. As the middle cerebral artery has already been controlled, arterial injury is of less concern than in the functional hemispherectomy operation. Care must be taken to limit resection to the insular gyri to avoid injury to deeper subcortical structures. Perhaps stereotactic imaging would be useful at this stage, although a practical approach is to stop the dissection when underlying white matter is reached.

Adams Modification of Anatomic Hemispherectomy

Adams modification was an attempt to avoid the complications of hemosiderosis and hydrocephalus. The classic anatomic hemispherectomy is supplemented by a muscle plug in the foramen of Monro on the resection side and by folding down the stripped dura of the convexity bone onto the falx, central

block (composed by basal ganglia and thalamus and middle fossa cavity). The subdural space is occluded and outflow of cerebrospinal fluid from the opposite side is prevented. Using this technique, there seems to be a higher rate of infection, but the rate of hydrocephalus seems to be reduced, compared to the classic anatomic resection (8).

Functional Hemispherectomy and Other Disconnection Techniques

Classic Functional Hemispherectomy

Rasmussen et al. proposed "functional hemispherectomy," minimizing tissue resection (5–7). The overall goal of the functional hemispherectomy is to disconnect the frontal lobe (through an incision placed just anterior to the genu of the corpus callosum) and to disconnect the parietal and occipital lobe (through a posterior incision) and remove the temporal lobe and central part of the frontal and parietal lobe. The fiber tracts projecting from the remaining parts of the frontal, parietal, and occipital lobes to the brainstem and spinal cord are then transected. The blood supply to the disconnected cortical regions is kept intact.

In the functional hemispherectomy procedure, T-shaped scalp incision (similar to one described under anatomic hemispherectomy) is performed. The craniotomy is smaller than in the anatomical hemispherectomy, especially in the anterior–posterior orientation, and is mainly centered in the topographic location of the insula. The dura is opened in the same manner as it has been described for the anatomical hemispherectomy.

The first cortical incision is made along the upper margin of the sylvian fissure, by coagulating and incising the pia and its blood vessels, dissecting down into the frontal and parietal operculum, down to the plane of the insular cortex. From the anterior and posterior ends of this dissection, a central resection is performed, exposing the entire sulcus limitans of the insula and, consequently, the insula cortex. The incisions are extended to the medial surface to the level of the cingulate gyrus, which is preserved at this stage to protect the pericallosal artery, but removed later. By deepening the dissections in the superior sulcus limitans of the insula, the body of the lateral ventricle is entered and the central bloc of tissue removed.

The temporal lobe is removed by coagulating and dividing the pia and its vessels along the superior temporal gyrus, back to the posterior limb of the upper resection, and anteriorly around the temporal pole, down to the uncus. The roof of the temporal horn is entered and then the lateral portion of the temporal lobe is removed through the collateral sulcus. The hippocampus is dissected and removed through the coagulation of the hippocampus sulcus. The hippocampus is dissected free, and the amygdaloid nucleus is removed.

The deep white matter of the medial and inferior aspects of the frontal lobe is divided in the coronal plane, from the central resection area to the most basal and posterior area of the frontal lobe, just rostral to the anterior perforated substance and medial and lateral olfactory striae. The anterior portion of the corpus callosum is also divided, from its body to the knee and rostrum portions, stopping at the level of lamina terminalis. In the same way, the white matter of the parietal lobe is divided posterior to the splenium from the ventricular ependyma, from the body and atrium of the lateral ventricle to the pia overlying the falx and the floor of the middle fossa. Following subpial dissection, the cingulate gyrus is removed. In the same way as the anterior callosotomy, the posterior corpus callosum is also divided, from the topography of the central resection to the splenium. Just anterior to the splenium, the fimbriae and fornices from both hippocampus formations join, forming

the hippocampus commissure, which will need to be completely disconnected. After irrigation, the craniotomy is closed as previously described for anatomical hemispherectomy.

Hemidecortication

It is based on the principle that only the epileptogenic cortex needs to be removed in order to achieve seizure freedom. The concept was first delineated by Ignelzi and Bucy in 1968 (9). The integrity of the lateral ventricle is largely preserved, except at the temporal lobe, where removal of the hippocampus requires opening of the temporal horn. Although the main aim is to avoid opening the ventricular system, removal of the hippocampus makes opening of the temporal horn a necessary step. In this procedure, a large wound surface is created, and, in cases of HME, where dysplastic ectopic gray matter is located in the white matter, orientation can be difficult.

Transsylvian, Transventricular Functional Hemispherectomy

This approach was developed and refined by Schramm and colleagues (12). The key features of this approach are (i) small craniotomy and transsylvian exposure of the insular cortex; (ii) anterior mesial temporal lobe resection, including amygdala and hippocampus; (iii) transcortical access to the ventricular system through the limitans sulcus of the insula, from the tip of the temporal horn to the tip of the frontal horn; (iv) frontal–basal disconnection anterior to the anterior cerebral artery; (v) mesial disconnection following the anterior cerebral artery through the anterior portions of the corpus callosum to the splenium; and (vi) posteromedial disconnection in the ventricular trigone following the outline of the falcotentorial border to the temporomesial resection cavity. This procedure is especially suited for cases with enlarged ventricles, porencephalic cysts, and marked atrophy of the insula–basal ganglia block or for cases with larger ventricle and cisterns.

The size of the craniotomy is chosen guided by the length of the corpus callosum, the anteroposterior diameter of the basal ganglia thalamus–insula block (limen insulae to pulvinar), and the degree of ventricular enlargement. The sylvian fissure is then opened, and the circular sulcus is exposed, taking advantage of the fact that the temporal operculum is overlying the inferior limb of the limitans sulcus only about 0.5 to 1 cm, whereas the frontal operculum can overlie the frontal limb of the circular sulcus up to 3 cm. Access to the temporal horn is gained through the inferior circular sulcus approach. The uncus and the lateral parts of the amygdala are removed, and the hippocampus also is taken out either by suction or en bloc. Sparing the major branches of the middle cerebral artery, the ventricular system is then opened all around the insular cortex. From inside the anterior horn of the lateral ventricle, a dissection line is now created by suction and bipolar coagulation from the frontal horn floor, just anterior from the foramen of Monro, down to the basal arachnoid, just anterior to the middle and anterior cerebral arteries. The mesial disconnection can now be continued around the corpus callosum following the anterior cerebral artery. Callosotomy is then performed within the ventricle, back to the area of the splenium. The fornix and the hippocampus tail are disconnected and resected, until the mesial temporal lobe resection cavity is reached.

According to Schramm and colleagues (12), the transsylvian–transventricular hemispherectomy with only a minimal mesial temporal lobe resection should not be used for HME cases, even if ventricles are enlarged, for two reasons: the insular cistern may be atypically configurated and the transsylvian approach can be more difficult even with enlarged hemisphere. In HME, the transsylvian–transventricular hemispherectomy should be combined with resection of the entire temporal lobe or with resection of the frontal operculum to the level of the insular cortex. This

resection facilitates the transcortical access from the limitans sulcus of the insula to the lateral ventricle and creates room for postoperative swelling.

According to Bonn series, possible disadvantages of this procedure include problems identifying anatomical landmarks due to the limited exposure. Hydrocephalus, possibly induced by the large wound surface and the transventricular approach, was not seen in the transsylvian "keyhole" hemispherectomies for all causes so far. No case of incomplete disconnection toward the midline was detected, but too anteriorly placed disconnections were seen.

Peri-Insular Hemispherotomy

Peri-insular hemispherotomy was initially developed by Villemure and Mascott (11). The main features of this approach are (i) medium-sized craniotomy exposing the frontal, parietal, and temporal operculum in the whole length of the sylvian fissure; (ii) resection of the frontal and parietal operculum and underlying white matter, opening the whole lateral ventricle through the anterior and superior limitans sulcus of the insula and disconnection of the frontobasal area through the intraventricular approach; (iii) resection of the temporal operculum (T1 gyrus and underlying white matter) and exposure of the temporal horn through the inferior limitans sulcus of the insula; (iv) mesial disconnection through the corpus callosum, from the rostrum and knee to the splenium; and (v) temporomesial disconnection with only anterior resection of the amygdala, anterior aspect of the hippocampus and uncus.

Peri-insular hemispherotomy is best indicated in patients with enlarged ventricle and certain degree of atrophy, and because of the more extensive resection of the operculum and underlying white matter, it can be also applied for HME cases. Kestle et al. used this technique in 11 of their 16 cases. Estimated blood loss was 462 mL, compared to 1.3 L for decortication, 73% of their patients needed a transfusion, and there was no need for shunts (29).

Vertical Parasagittal Hemispherotomy

This approach was first described by Delalande et al. in 1992 (10). It includes initially a small parasagittal craniotomy, followed by complete callosotomy with opening of the roof of the lateral ventricle. Once the entire lateral ventricle is unroofed, posterior disconnection of the hippocampus is achieved by cutting the columns of the fornix at the level of the ventricular trigone. The vertical incision is performed lateral to the thalamus, choroid plexus, and choroidal fissure of the temporal horn, then following the temporal horn from the trigone to the most anterior part of the ventricle, keeping the incision in the white matter. The callosotomy is then completed by resecting the genu and the rostrum of the corpus callosum to the anterior commissure. The next step is the resection of the posterior part of the gyrus rectus, which will allow the visualization of the anterior cerebral artery and optic nerve and provide enough space for the last disconnection step, which is a straight incision anterolaterally through the caudate nucleus from the rectus gyrus to the anterior temporal horn.

ANATOMICAL HEMISPHERECTOMY VERSUS FUNCTIONAL HEMISPHERECTOMY AND OTHER DISCONNECTION TECHNIQUES

The discussion about what would be the appropriate surgical technique for treatment of intractable hemispheric epilepsy is controversial. The literature is full of personal series, specifically reporting seizure outcome and complications related to one specific technique. In addition, most of the studies are retrospective in nature, reporting results in populations that differ in age, severity of seizure, and pathologic substrate. There are no studies that directly compare functional versus anatomical hemispherectomy. In the largest series of patients treated with anatomical hemispherectomy, the surgical outcome is similar to that for functional disconnection (25,29–34). The group at Johns Hopkins reviewed their experience with anatomical hemispherectomy in infants and children (18,22). Of 21 patients with cortical dysplasia, 8 (38%) were seizure free and an additional six (29%) had mild seizures after surgery. In contrast, surgical series after functional hemispherectomy for CD report 50% to 67% of seizure-free rate with an additional 11% to 33% having only rare seizures. Although number are small in all these studies and the radiologic involvement of CD is not well outlined in some of these reports, these results suggest that functional hemispherectomy is at least as effective as anatomical hemispherectomy. The frequency of complications may also be lower after functional hemispherectomy. In one series, of five patients with HME who continue to have seizures after functional hemispherectomy, three had seizures that arose from the operated hemisphere and two had seizures arising from the contralateral hemisphere. These results suggest that anatomic hemispherectomy may be more effective in patients with HME and that functional hemispherectomy may be better suited for patients with more restricted hemispheric cortical dysplasia. At the Cleveland Clinic, we believe that anatomical hemispherectomy provides a better seizure outcome in patients with cortical dysplasia and HME. In a series of patients with catastrophic epilepsy in young ages, incomplete disconnection was the only variable statistically associated with persistent seizures after surgery (14). In a total of 18 patients, 6 patients had persistent seizures after surgery. Two patients had the diagnosis of HME and four had cortical dysplasia. From this group, four patients had incomplete disconnection, always located in the posterior basal–frontal areas. All four patients underwent reoperation, converting the procedure to anatomical hemispherectomy. All four patients achieved seizure freedom. In our studied group, we found that for patients with HME, anatomical hemispherectomy is a better option. In general, the lateral ventricle from patients with HME is characterized by an irregular shape, a relative hypoplasia of the temporal horn. Such anatomical peculiarities, together with irregular and abnormal thickness of the cerebral mantle, deep heterotopic gray matter, distorted trajectory of the anterior cerebral arteries, abnormal large veins at the level of the malformed sylvian fissure, and the possible interdigitation of the mesial aspect of the hemispheres, make the functional hemispherectomy a technically difficult procedure in this group of patients. In our surgical series, all patients with HME who underwent functional hemispherectomy resulted in uncontrolled seizures after surgery; the conversion to anatomical hemispherectomy resulted in seizure freedom in all patients (14).

Although several authors reported higher complications rates in anatomical hemispherectomy (5,35–37), particularly hemosiderosis and secondary hydrocephalus, we did not observe such findings in our patients. With specific regard to hemosiderosis associated with anatomic hemispherectomy, one could speculate whether late mortality from hemispherectomy was caused by the effects of chronic deposition of Fe^{2+} on the cerebral parenchyma, from repeated intracranial hemorrhages, or it was simply the outcome of hydrocephalus, which escaped detection before the introduction of computerized tomography (CT). It is worth noting that reports concerning hemosiderosis have been practically absent in the literature since the 1970s; nevertheless, hemosiderosis is still cited as a common reason for avoiding anatomic hemispherectomy.

OUTCOME AFTER HEMISPHERECTOMY

There are different perspectives in assessing outcome after hemispherectomy. Seizure outcome is the primary concern, but the long-term functional outcome is equally important in improving the quality of life. Additionally, morbidity associated with the different procedures has to be considered.

Seizure Outcome After Hemispherectomy

In various cross-sectional studies on outcome after hemispherectomy, the seizure-free rates range from 52% to 80% (38–43). We recently examined longitudinal outcome of 170 children who underwent hemispherectomy over a 10-year period at the Cleveland Clinic (38). At a mean follow-up of 5.4 years, 66% of children were seizure free (Engel 1a). Of 58 patients with seizure recurrence, 8 had late remission (seizure free for 1 year or more at last follow-up) and another 16 patients had >90% reduction in seizures (38). Overall, 80% of children were either seizure free or had major improvement after hemispherectomy. Similar seizure outcome has been reported after hemispherectomy in adults with refractory epilepsy due to large middle cerebral artery infarct or cortical malformation (44).

In the Cleveland Clinic hemispherectomy series, age at seizure onset, age at surgery, epilepsy duration, etiology, presence of generalized epileptiform abnormalities, bilateral abnormalities on brain MRI, and type or side of hemispherectomy had no effect on seizure outcome. Prior hemispheric surgery, nonlateralized ictal EEG, acute postoperative seizures, and bilateral abnormalities on PET were predictive of poor seizure outcome on univariate analysis. On multivariate analysis, only the latter two emerged as independent predictors of poor outcome. In one of the earlier reports, children with malformation tended to have poor seizure outcome; we did not find etiology as a predictor in our study. At our center, we favor more tissue resection, not infrequently anatomic hemispherectomy, in children with HME for reasons cited in the earlier section. Head-to-head comparison between different techniques of hemispherectomy is not feasible as most centers tend to do favor one particular technique. Overall, the reports from various centers do not suggest a major difference in seizure outcome with different techniques.

Seizure recurrence after hemispheric disconnection procedure indicates either continued seizures from operated side due to incomplete disconnection or independent epilepsy arising from the opposite hemisphere. Seizure semiology, interictal and ictal EEG findings, and MRI may assist in differentiating in some patients. However, in our experience, EEG findings after disconnective hemispherectomy are complicated and may be unhelpful. It is difficult to reliably confirm the completeness of resection by MRI as well. At our center, in many such cases with failed functional hemispherectomy, we proceed to perform removal of residual tissue on the operated side (thereby converting to anatomic hemispherectomy) to ensure effective hemispherectomy. This strategy has helped in achieving seizure freedom in a third of patients and major improvement with >90% seizure reduction in as high as two-thirds of patients (38,45).

Functional Outcome After Hemispherectomy

Several studies in the past addressed the functional outcome after hemispherectomy. Although most studies do not have a comparative group to study the effects of the surgery per se, most clinicians firmly believe that successful hemispherectomy improves functional outcome as well (46,47). From a practical standpoint, the alternative course of persistent daily seizures and continued worsening of

neurologic status is unacceptable to most families.

We recently reported the functional status of 115 children who underwent hemispherectomy at the Cleveland Clinic (47). In our cohort of 115 children, 92% were able to walk independently or with assistance (Fig. 84.8). Children with bilateral motor deficits (worse on the side concordant with surgery) or MRI abnormalities in the unoperated hemisphere or seizure recurrence were more likely to have poor motor outcome. Over two-thirds of children in this series had spoken language skills sufficient for regular conversation; nearly half of these children had age-appropriate language abilities as perceived by their families. Preoperative language delay, bilateral MRI abnormalities, and seizure recurrence were associated with poor language outcome. Age at seizure onset and left-sided surgery had no significant impact on the language outcome in this cohort. Reading abilities were poor in 59% of children and only 18% of children had age-appropriate reading ability. Per parental report, 73% of patients had minimal to no behavioral problems; the rest had significant problems in home and school environment. Children with postoperative seizure recurrence were more likely to have behavioral problems. Although visual field defect is expected to be present in every patient, families did not perceive it as a major handicap. Patients were accustomed to the defect and were able to take precautions to avoid major mishaps (47).

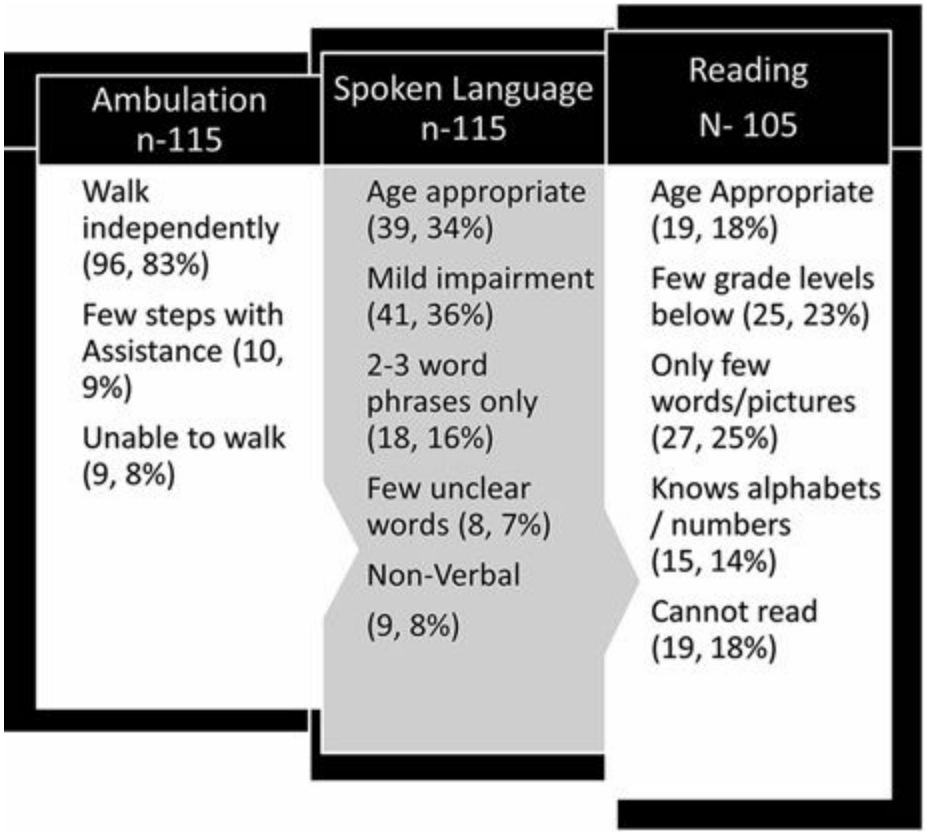
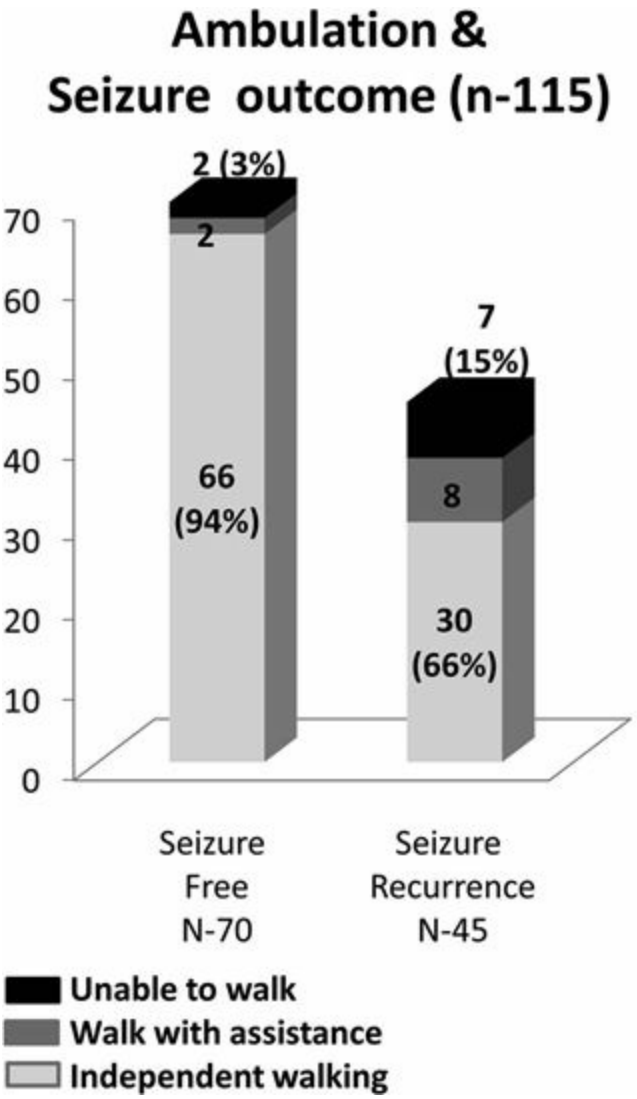
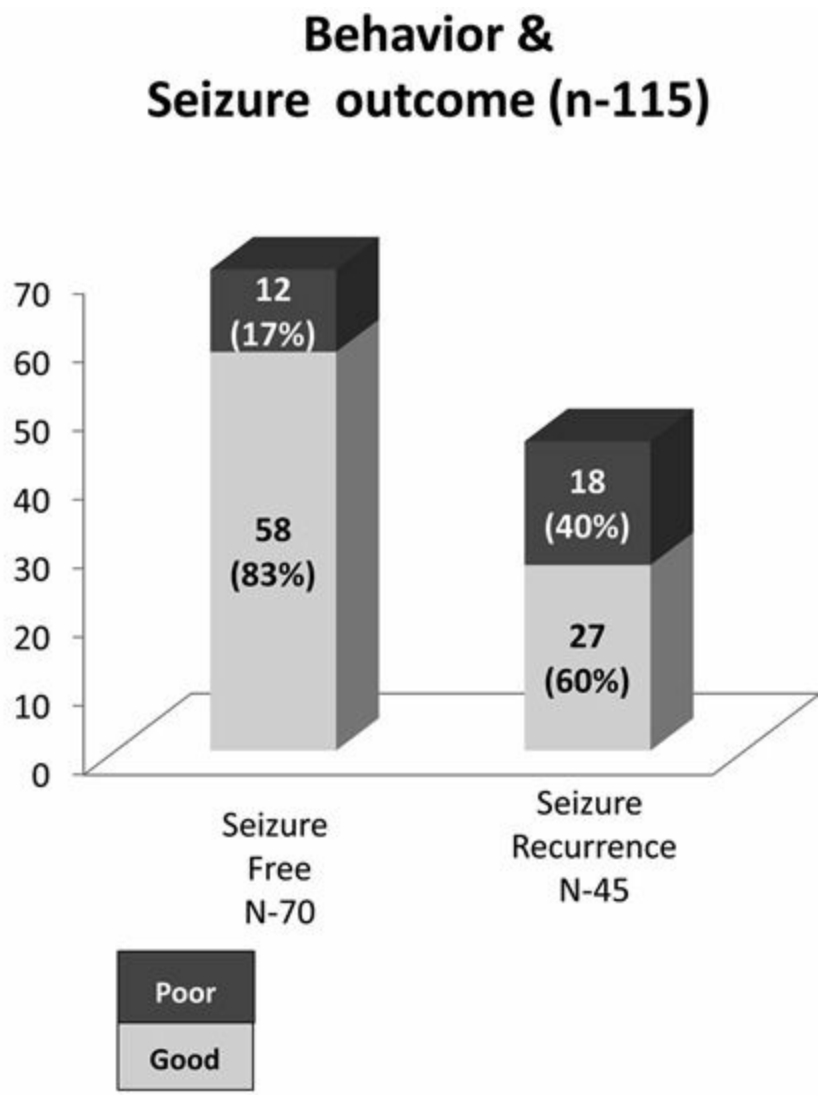


Figure 84.8. Functional outcome after hemispherectomy in 115 children. Mean age at follow-up was 12.7 (±6) years. Reading status was assessed in children older than 6 years (n = 105).

Seizure outcome emerged a single most important predictor of functional outcome. Seizure freedom improved the odds of good outcome in ambulation, behavior, spoken language, and reading skills (Fig. 84.9). This observation may suggest that hemispherectomy improves functional outcome by providing seizure freedom (47).


Ambulation &
Seizure outcome (n-115)
2 (3%)
2
66
(94%)
7
(15%)
8
30
(66%)
70
60
50
40
30
20
10
0
Seizure
Free
N-70
Seizure
Recurrence
N-45
Unable to walk
Walk with assistance
Independent walking


Behavior &
Seizure outcome (n-115)
12
(17%)
58
(83%)
18
(40%)
27
(60%)
70
60
50
40
30
20
10
0
Seizure
Free
N-70
Seizure
Recurrence
N-45
Poor
Good

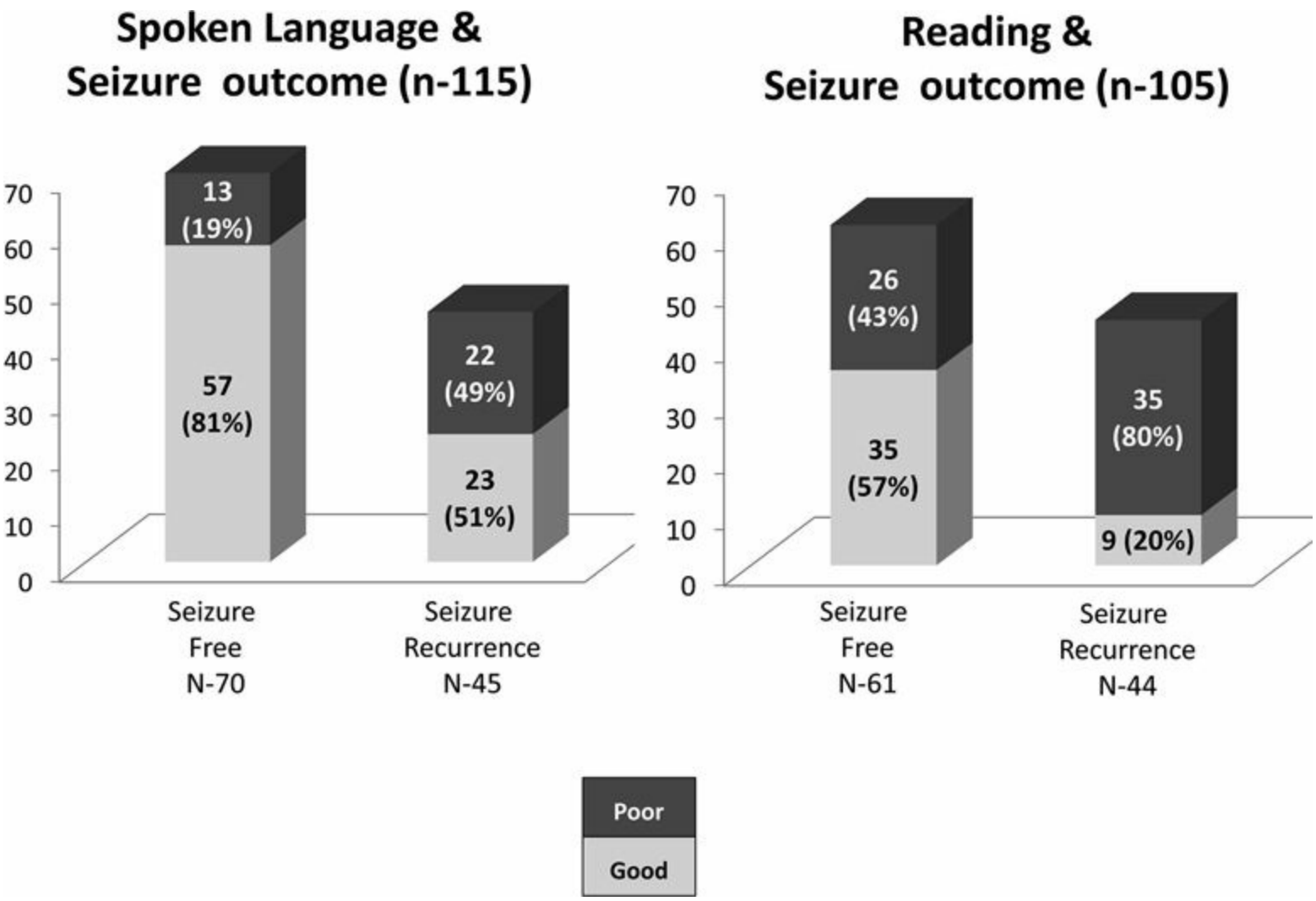


Figure 84.9. Positive impact of seizure freedom status on functional outcome.

Complications: Acute and Delayed

Hydrocephalus in the early postoperative period is a common complication across all surgical series. In a recent large multicenter study of 690 patients undergoing hemispherectomy, 23% required treatment for hydrocephalus (48). Anatomic hemispherectomy and prior brain surgery were identified as risk factors for hydrocephalus. A quarter of the hydrocephalus may evolve 3 months postsurgery, highlighting the importance of continued surveillance. Mortality rate in various series has ranged from 0 to 3% (18,38–42,49). Postoperative fever is common, in as high as 82% of children after hemidecortication (50). Chemical meningitis is a common cause of postoperative fever but careful exclusion of infectious causes is warranted. Other complications such as subdural and epidural hematomas also may occur infrequently.

Superficial hemosiderosis of the brain after hemispherectomy appears to be very rare with no published reports in the past three decades. A fall in delayed worsening after hemispherectomy may be related to decreased incidence of superficial siderosis of brain secondary to modifications in the hemispherectomy techniques as well as improvement in treatment hydrocephalus in the post-CT era.

CONCLUSION

Hemispherectomy and other disconnection procedures for intractable epilepsy provide excellent and dramatic results with a satisfactory complication rate. Modifications in surgical techniques and better

perioperative care has improved the outcome in the last 60 years. Despite this, discrepancies related to complication rate and seizure outcome among different techniques are still unresolved. A large prospective multicenter study is necessary to indicate the better surgical technique for a specific pathology and population group. Nevertheless, early surgery in patients with catastrophic epilepsy seems to be associated with better seizure control and cognitive prognosis.

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CHAPTER 85 SURGICAL APPROACH IN MULTILESIONAL OR MULTILOBAR EPILEPSIES

ELIA M. PESTANA KNIGHT, AJAY GUPTA, AND ELAINE WYLLIE

Multilesional epilepsy, by definition, involves more than one lesion that is distributed noncontiguously in one or both hemispheres. One or more lesions may be responsible for the generation of seizures. A typical example is seen in patients with tuberous sclerosis. While the presence of multiple brain lesions does not necessarily indicate multiple ictal onset zones or multifocal epilepsy, this poses additional challenges in presurgical evaluation.

Multilobar epilepsy, for purpose of this chapter, involves an epileptogenic zone that extends into multiple lobes of one hemisphere, with or without a lesion seen on MRI. The area is contiguous with homogenous or heterogeneous brain MRI findings in the regions/lobes of interest. This chapter focuses on lesional cases. The surgical approach to nonlesional cases in focal, multifocal, unilobar, or multilobar epilepsy will be covered in Chapter 86.

The topic of multilesional and multilobar epilepsy has been sparsely addressed in the epilepsy-related literature. Data regarding the evaluation, indications for surgery, and surgical outcomes in these patients are often buried in single-center descriptive studies. Multiple cohort data are combined with cases of extratemporal epilepsy or in series dedicated to pediatric or adult populations or to a specific epilepsy etiology (1–7), making it difficult to determine the real incidence and prevalence of multilesional and multifocal epilepsy.

Multilesional and multilobar resections range from 3% to 22% of the epilepsy surgeries reported in the medical literature in different centers (8–12). The number of multilobar resections is higher in the pediatric epilepsy population than in the adult population.

Patients with multilobar and multilesional epilepsies often have medically intractable epilepsy, or catastrophic epilepsies in the case of children. Multilobar resections account for 9% of the surgeries in children with infantile spasms (13) and 16% to 20% of the surgeries in infants with catastrophic epilepsy (14,15). Approximately 35% of the reoperations in patients with epilepsy result in multilobar resections (16).

This chapter will focus on:

- The selection of surgical candidates from patients with multilobar and multilesional epilepsy
- The selection of the surgical procedure
- Outcomes of multilobar and multilesional epilepsy

Figure 85.1 is a proposed algorithm for the evaluation of patients with multilobar and multilesional epilepsy to determine what type of procedure should be performed. We follow this algorithm for the discussion in this chapter. At the end of the chapter, the reader can find four cases illustrating the use

of algorithm for surgical decision making.

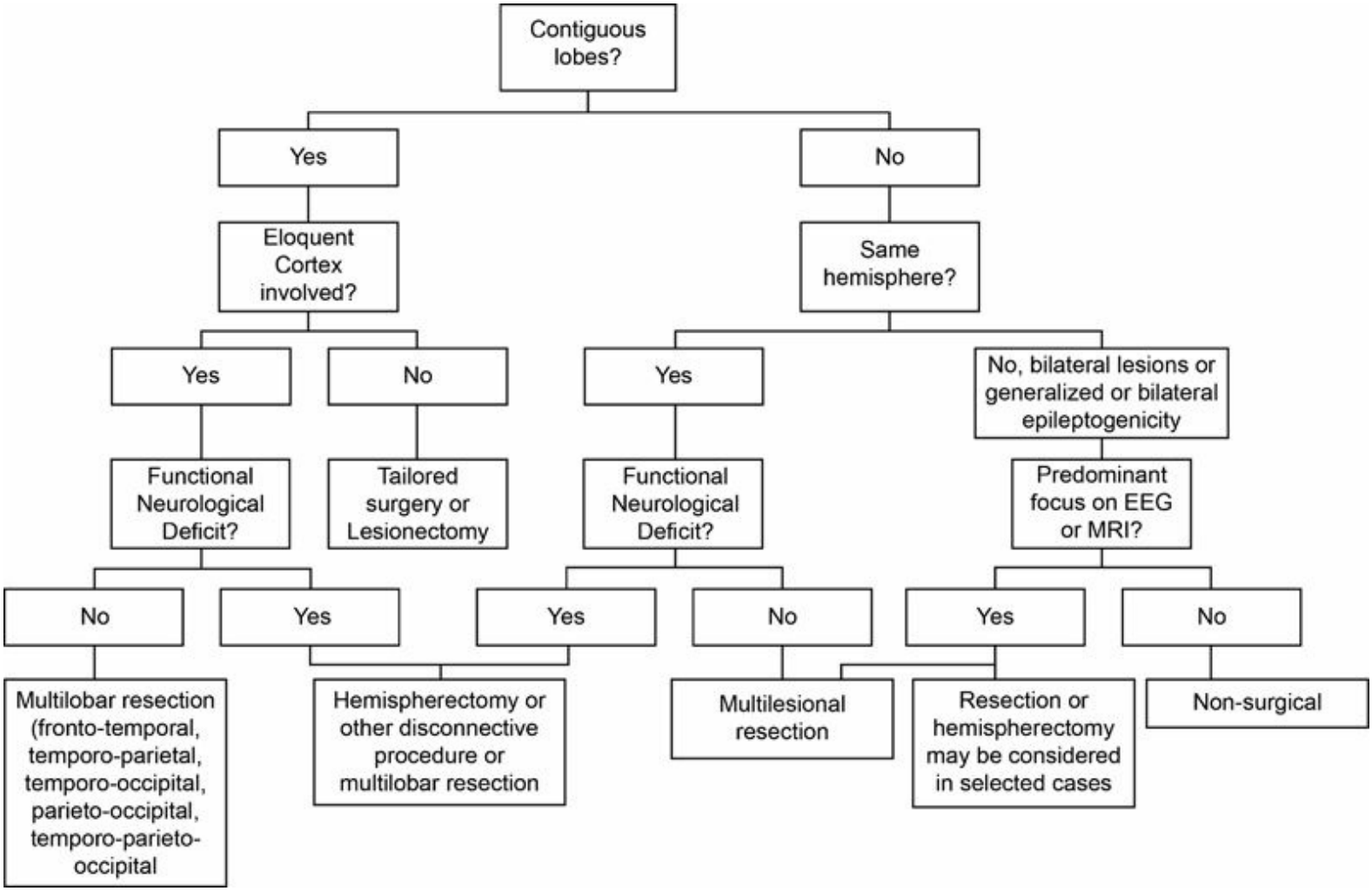


Figure 85.1. Proposed algorithm for the evaluation of patients with multilobar and multilesional epilepsy. The algorithm departs from the findings in the brain MRI. The first element to consider is whether lesions in contiguous lobes or not. Contiguous lesion algorithm continues on the left side of the scheme with next step focused in the relationship of the lesion with the eloquent cortex and the presence of functional neurologic deficit. Noncontiguous lesions follow the path of the right side of the scheme with the next step determining if the lesions are noncontiguous in the same hemisphere or bihemispheric and the presence or not of functional neurologic deficit or involvement of the eloquent cortex. Cases illustrating the use of the algorithm can be found at the end of the chapter.

SELECTION OF CASES WITH MULTILOBAR AND MULTILESIONAL EPILEPSY FOR SURGICAL CANDIDATES

The selection of surgical cases from patients with multilobal and multilesional epilepsy is based on several factors: brain MRI findings, VEEG, other neuroimaging techniques, and clinical data, including seizure semiology and findings of the clinical exam.

MRI FINDINGS

The role of the MRI in the identification of surgical candidates has been well established. The proposal from the Pediatric Epilepsy Surgery Subcomission (17) and the practice parameters of the Quality Standards Subcommittee of the American Academy of Neurology (18) mandate a brain MRI

using a specified epilepsy protocol as part of the minimal presurgical evaluation of children and adults for temporal lobe and neocortical epilepsies. Brain MRI is a diagnostic tool that is readily available in most epilepsy centers around the world, particularly those in developed countries (19).

The definitions of multilobar and multilesional epilepsies used in this chapter will be based on brain MRI findings. The results of the brain MRI are the first step at the beginning of the algorithm proposed in Figure 85.1. A brain MRI will identify the type, etiology, and location of a lesion. Although the etiology of the lesion is important in following the algorithm, for surgical planning purpose, the location of the lesion is equally important.

Etiology of the Lesion

The MRI findings in multilobar epilepsies include dysplasias, hemimegalencephalic syndromes, Sturge–Weber syndrome, Rasmussen encephalitis, polymicrogyria, periventricular encephalomalacia, or other encephalomalacias from trauma, stroke, tumors, etc.

MRI substrates in multilesional epilepsies include tuberous sclerosis complex, inflammatory and postinfection lesions, bilateral strokes or watershed infarcts, tumors, and vascular malformations.

All these etiologies are discussed in detail in Section B of this book. The frequency with which these lesions are seen in tertiary epilepsy centers has been extensively discussed in the medical literature. Cortical dysplasia remains the most common of all multilobar and multilesional epilepsies. Nevertheless, one community-based epidemiologic study of lesions identified by brain MRI in children with epilepsy found that 16% of the children (82 out of 518) had abnormalities in the brain that could be responsible for their epilepsy (20). 37% of the patients in this group had pre- and perinatal-acquired cerebral injuries, 27% had cortical dysplasia, 22% had other discrete lesions such as tumors, and 15% had lesions associated with genetic conditions.

Location and Extent of the Lesion

The brain MRI will help to determine whether the lesions are located within one hemisphere or are bilateral, and whether the lesion(s) is unilobar or multilobar. The brain MRI also determines whether the lesion is cortical, subcortical, or both and its relationship with the eloquent cortex. Cortical lesions located near the eloquent cortex, as well as lesions located near the major tracks (pyramidal tract, optic tract, arcuate fasciculus, etc.), put the patient at risk for neurologic deficit during surgical resection. Adding Diffusion Tensor Imaging (DTI) sequences could help with the surgical planning in such cases (21,22).

Forty-six percent of the cases in a community-based study involved bihemispheric brain lesions (20). We have learned in recent years that bilateral lesions do not preclude successful epilepsy surgery (23).

In addition to brain MRI, surgical decision in patients with multilobar and multilesional epilepsy includes data from other imaging modalities such as PET, SPECT, and DTI. In some patients MRI postprocessing are needed. The role of these techniques in the evaluation of epilepsy surgical candidates is covered in Chapters 75, 77, and 78.

Refractory Epilepsy

Since our surgical selection algorithm is based on brain MRI findings, this chapter minimally discusses the role of refractory epilepsy and incidental findings in patients with nonsurgical epileptic

syndromes or patients with epilepsy-related findings in brain MRI who never have had a seizure.

Refractory epilepsy is defined as the failure of two to three drugs that are used appropriately and adequately for the seizure type, although some variations on time of seizure freedom and time required from onset of seizures to time of evaluation have been used for research purposes (17,18,24,25). While brain MRI opened a new era in epilepsy surgery, its results must be interpreted with caution and in the appropriate clinical setting before referring the patient for epilepsy surgery. One study reported incidental brain abnormalities in 23% of normal children (26). A study of candidates for cochlear implants found incidental or unexpected brain abnormalities in 18% of the sample, including a few cases of periventricular nodular heterotopia (27). The incidental findings of brain lesions led to additional investigation and sometimes to surgeries—for example, in cases with brain tumors. A more complicated situation occurs when the patient has a history of epilepsy or seizures. Incidental brain abnormalities have been described in 3% of children with idiopathic epileptic syndrome and 10% of children with nonidiopathic epilepsy, normal neurologic exams, and nonpharmacoresistant epilepsy (20). Thus, the definition of refractory epilepsy is necessary but not indispensable for the referral for epilepsy surgery. A community study found that 6 of the 82 children with epilepsy as well as brain abnormalities and brain tumors (4 neoplasias and 2 DNETs) underwent surgeries even when their epilepsy was not pharmacoresistant (20).

Clinical Aspects: Semiology, Exam Findings, Weight, and Age

Semiology

The semiology of the seizures, specifically early in the course of seizures, is very important when considering epilepsy surgery. The presence of focal features can point to a specific brain region or location (15,28–32). Auras, lateralizing signs, and postictal symptoms are also very important in assigning both hemispheric and lobar localizations (28,30,33).

Semiology is even more critical in patients with multilobar or multilesional substrates. In multilobar cases, semiology may help predict early seizure spread in relationship to a large lesion. For example, in patients with posterior quadrant dysplasia, limb clonic or versive seizures at the onset may suggest anterior ictal spread. Hypomotor semiology may suggest a posterior spread. In multilesional patients, semiology may help narrow down the inventory of lesions that could possibly result in the semiology. More than one semiology during VEEG may suggest multiple ictal-spread patterns from one region or multiple independent seizure-onset zones. Hence, a critical review of history and VEEG with an appropriate sampling of seizure data is vital to building an effective surgical strategy.

Age-related syndromes in infants and children, such as epileptic spasms or Lennox–Gastaut-type seizures, could be the manifestation of focal epilepsy secondary to a focal, unilobar, multilobar, or hemispheric lesion (15,32,34,35). Seizures characterized by arrest of activity with very subtle limb movements and/or automatisms are also seen in this group, and some seizures with clear asymmetric features fail to point to a generalized or a focal epilepsy (15,36). Detailed evaluation of seizure semiology during VEEG becomes very important in these cases.

Clinical Exam

The clinical exam is equally important when determining the type of brain surgery to be performed. In

addition to the proximity of the lesion to the eloquent area, the presence of motor deficit, hemianopsia, neglect, etc., are important when deciding the extension of the surgery. The degree of motor deficit is equally important. The possibility of a new neurologic deficit is a deterrent to patients and relatives when considering epilepsy surgery, and worsening of an existing neurologic deficit is also not desired. Risk of neurologic deficit was the cause for refusing resection in seven of nine children with subdural grids who were studied at the Cleveland Clinic (37). In these cases, an early consent discussion that includes clearly defined risks and benefits could lead to alternative or palliative treatments. In some patients, assessment of hemiparesis may be difficult because it fluctuates with acute worsening and recovery over weeks to months. Such phenomenon is seen in Rasmussen's. This is also reported in Sturge–Weber syndrome where a component of ischemia makes a pattern of observation over time more important rather than one-time assessment. Occurrence of epilepsia partialis continua in patients of Rasmussen's, poststroke cases, and rarely in focal cortical dysplasia makes this even harder as the patient may not be able to cooperate or part of the deficit could be ascribed to Todd paralysis.

Weight and Age

These are important factors in scheduling surgery. Infants as young as 1 month and weighing 4 kilograms have undergone surgery for catastrophic epilepsy (14,15,38). Although operative risks are greater in very small infants or the elderly, there are no absolute age or weight limitations for epilepsy surgery if seizures are difficult to control. The expertise and comfort of the neurosurgeon and the hospital team are the ultimate determining factors.

THE SELECTION OF THE SURGICAL PROCEDURE

Multilobar Resection/Disconnection

Patients with multilobar and multilesional epilepsy involving contiguous lobes and located in or near eloquent cortex are candidates for multilobar resection or disconnection, assuming the absence of a significant preexisting neurologic deficit. These cases may require additional invasive evaluation if a more tailored surgery is possible or desired.

A variety of multilobar resections or disconnections can be performed, depending upon the location of the lesion and information provided from the presurgical and invasive evaluations. Types of multilobar resections or disconnections include occipital plus, frontotemporal (FT), temporoparietal (TP), and frontoparietal (12,39,40).

The most common type of multilobar resection or disconnection is the occipital plus or posterior quadrant surgery. The posterior quadrant resection/disconnection includes temporoparietal–occipital (TPO), parietooccipital (PO), and temporo-occipital surgeries. The most common of these procedures is the TPO, which accounts for 21% to 46% of the multilobar resections or disconnections (12,39,40). In adults, TPO is less commonly performed and only accounts for approximately 5% of the surgeries (12,41,42). The TPO is selected when data support the fact that the frontal lobe is free of lesions, is not epileptogenic, and can be preserved. It is also the procedures of choice when there is need to preserve the motor and sensory cortex.

The decision to perform a multilobar resection versus a disconnection depends on the experience and expertise of the center. Daniel et al. described a series of patients in which the selection of the

technique changed over the years. Earlier surgeries included anatomical posterior quadrantectomy or TPO resection; years later, the predominant procedure was the functional posterior quadrantectomy or extended temporal lobectomy with PO disconnection. Peri-insular posterior quadrantectomy has been described as the latest approach for posterior quadrant epilepsy (43). This technique includes disconnection of the temporal lobe followed by disconnection of the PO lobes during the same surgical procedure (39,42,43). Other approaches— rationale of this is not clear—such as a two-stage procedure with PO lobectomy followed by a temporal lobectomy in a separate surgery were used in some of the patients (43). Etiologies for occipital plus resections include malformation of cortical development, sequels of stroke or other vascular injuries, tumors, tuberous sclerosis, and Sturge–Weber syndrome. In general, occipital plus resection has a better long-term outcome than FT and TP resections.

Variations of focal resections with or without multiple subpial transections have been described in patients with perirolandic epilepsy (44). Nevertheless, seizure outcome with complete seizure freedom has been reported only in 31% of the cases with new neurologic deficits present in up to 23% of the cases. In other patients with multilobar lesions in which sparing of the motor cortex is desired, proposed surgery includes the premotor resection of the frontal lobe combined with a TPO resection (44,45). This technique provides seizure improvement but not freedom. Random cases with multifocal epilepsy can have improved quality of life when the resection is targeted toward the region producing more disabling or frequent seizures (46).

Hemispherectomy, Hemispherotomy, and Other Disconnective Procedures

Patients with epilepsy secondary to large multilobar brain lesions generally undergo hemispherectomy, although there are some exceptions, particularly when the surgical procedure is risking a new neurologic deficit.

Hemispherectomy or other disconnective procedures may be indicated for patients with multilobar and multilesional epilepsy involving contiguous lobes and located in or near the eloquent cortex who have a preexisting significant, complete or nearly complete neurologic deficit (47,48). In some patients with this scenario, the benefits from hemispherectomy may outweigh the risks of continuing seizures, hence favoring a more aggressive approach. In some patients with Rasmussen syndrome, hemispherectomy may be preemptively done due to anticipated deficits. Although quite controversial and not a widely accepted practice, there is a school of specialists who believe patients with Sturge–Weber syndrome should get early hemispherectomy rather than a focal resection. Etiologies for patients with epilepsy who require hemispherectomy include Rasmussen encephalitis, vascular or posttraumatic encephalomalacia, in particular perinatal infarction, cortical dysplasia, and hemimegalencephaly. Pathologic analysis of samples from 34% of patients with encephalomalacia found additional abnormalities consistent with cortical malformation (48). Functional or anatomical hemispherectomy is a procedure that is very well tolerated in infants and young children with catastrophic epilepsy (49). Compelling data indicate that the presence of mild or moderate MRI abnormalities in the hemisphere contralateral to the one with the main MRI abnormality is not a contraindication for epilepsy surgery. Surgery in these cases has a short-term positive outcome of 79%, compared to results in patients who did not have contralateral abnormalities (23). Similarly, patients with generalized epilepsy and generalized or contralateral EEG findings, who had congenital, perinatal, or early-acquired brain lesions on MRI, underwent successful epilepsy surgery

(35,50). Sixty-four percent of patients in the series reported by Wyllie et al. received a hemispherectomy, and 14% had a posterior quadrant or occipital plus resection. Seven out of the 10 patients with bilateral EEG abnormalities in the series reported by Gupta et al. underwent hemispherectomy; 5 out of the 7 patients were completely free of seizures at follow-up (50). Six out of 27 (22%) patients with Lennox–Gastaut syndrome underwent hemispherectomy, with Engel class I archived in 5 out of the 6 patients (51).

Multilesional/Multifocal Resections and Multistage Surgeries

Following a complete presurgical evaluation, multilesional and multifocal resections are performed in patients with multiple epileptogenic lesions or multiple ictal onset zones. The medical literature covering this topic is limited because patients with multilobar surgeries are often lumped together with those requiring multifocal /multilesional surgeries. The indications for evaluation and outcomes of the surgical procedures are, therefore, difficult to determine. Another limitation is that documentation of the success of multifocal epilepsy surgery is sometimes limited to case reports.

Tuberous sclerosis (TS) is the most common etiology for a multilesional resection. Other etiologies include cortical dysplasias, postinfectious encephalitis, posttraumatic epilepsy, vascular injuries, tumors (in particular, brain metastases), postradiation epilepsy, etc. Some patients have dual pathologies that include malformations of cortical development and mesial temporal sclerosis (52,53). Multiple pathologies are reported in up to 10% of the specimens from patients with medically refractory epilepsy studied in one anatomopathology laboratory (54).

In the past, patients with multifocal ictal onset zones were considered nonsurgical candidates. Multifocal ictal onset zones were the reason for not performing resections in four out of nine children studied with subdural electrodes and reported by Pestana Knight et al. (37). One study in adult patients with epilepsy documented that resections were not performed after invasive evaluation in 10 out of 22 patients because of diffuse or multifocal ictal onset zones (52). Another study reported poorly localized epilepsy in 9 out of 17 cases in which resections were not performed after invasive monitoring (55). Currently, patients with multifocal epilepsy who were deemed ineligible for surgery on the basis of evaluations with subdural grids alone, or subdural grids in combination with a few depth electrodes, are benefitting from stereo-electroencephalographic (SEEG) evaluation (56,57). Vadera et al. reported 14 patients who failed subdural grid evaluation and received a second evaluation with SEEG. Ten of these patients had resections after SEEG placement. At 11 months, 60% of the patients were seizure free (56). SEEG offers some advantages to patients with multifocal, unilateral, or bilateral epileptogenic foci or lesions. These include the possibility of studying epileptogenicity in deep gyri, sulci, and bilateral brain structures when noninvasive or invasive studies had failed to localize the epileptogenic zone (57,58).

Some patients with multifocal or multilesional epilepsy may also benefit from multistage procedures. Implantation of electrodes is followed by resection and reimplantation of electrodes with further evaluations and resections, depending upon the patients' characteristics (45,55,59). Multistage procedures have been performed in patients who require up to four admissions and two to three operations at each admission (55), with a relatively low complication rate (45,55,59). Staged and bilateral invasive evaluations have changed the outcomes for seizure control for patients with TS and those with lesions involving the motor cortex (60,61). Chapter 30 also discusses surgical strategy in patient with tuberous sclerosis complex.

Other Surgical Procedures

Multiple Subpial Transections

Some patients are candidates for limited brain resection as a palliative, more than a curative, treatment. Multiple subpial transection is another technique that has been used in cases with lesional or nonlesional epilepsy. The technique has been used alone or in combination with lesionectomies, lobectomies, or multilobar resections (61,62) and is discussed further in Chapter 88.

Limited Resection for Extensive Lesions

Catenoix et al. (63) studied seven patients with large multilobar lesions and seizure semiology consistent with mesiotemporal epilepsy who underwent temporal lobectomies. All patients became free of seizures after the surgery and remained so after a mean follow-up period of nearly 3 years. The researchers concluded that patients with ictal symptoms that are consistent with temporal lobe epilepsy have excellent seizure outcomes following temporal lobectomy, regardless of the size or extent of the brain lesions. This study analyzed only a limited number of patients with a very specific seizure semiology.

Seizure outcome of 75% at follow-up was also described in a series of four patients with infrasylvian multilobar polymicrogyria who underwent partial resection of the polymicrogyria (3/4 patients) combined with anterior mesial temporal resection. These patients had complex malformations that include polymicrogyria, squizencephaly, focal cortical dysplasia, and hippocampus malrotation (64).

Nonsurgical Candidates

Some patients do not receive epilepsy surgery because of the extent of the lesion, high risk for new postsurgical deficits, or the suspicion of multifocal epilepsy. Selwa et al. (65) followed patients for 4 years who were not surgical candidates. Twenty-one percent of the patients were seizure free at follow-up; others reported reduced seizure frequency. Roth et al. (55) reported on seven patients who became seizure free after invasive monitoring alone, without epilepsy surgery. Particular cycling of the epilepsy could possibly explain the findings that seizure freedom in these two different patient groups is possible in some refractory cases.

Some other cases considered not surgical candidates could benefit from palliative procedures such as corpus callosotomy or neurostimulation.

OUTCOME OF MULTILOBAR AND MULTIFOCAL EPILEPSY

There are data supporting the position that complete resection obtains the best seizure control after surgery and that incomplete resection of the lesion is a predictor of poor outcome. Seizure outcomes in patients with epilepsy due to large hemispheric or multifocal lesions who underwent small or limited resections are not well known.

Sarkis et al. (12) from the Cleveland Clinic reported 71% seizure freedom at 6 months in 63 patients who underwent multilobar epilepsy surgery. Seizure-free outcome was reduced to 52% at 5

years and 41% at 10 years after surgery. They did not study patients with extensive brain lesions who underwent limited resections. Bulacio et al. (66) (Fig. 85.2) reported a probability of a little above 0.1 of seizure freedom at 10-year follow-up for patients who underwent multilobar resection. This population included patients who had invasive evaluation only, which is not representative of current trends in pediatric epilepsy surgery in some tertiary care centers.

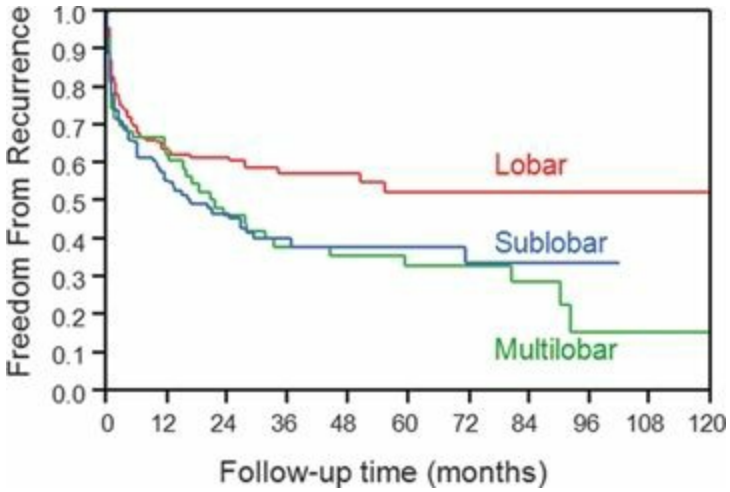


Figure 85.2. Probability of seizure freedom for the lobar, sublobar, and multilobar resections.
(Modified from Bulacio JC, Jehi L, Wong C, et al. Long-term seizure outcome after resective surgery in patients evaluated with intracranial electrodes. Epilepsia. 2012;53(10):1722–1730.)

CONCLUSIONS

Patients with multilobar and multifocal epilepsy are a heterogeneous group with different etiologies and epilepsy locations. Refractory epilepsy is common in these cases and catastrophic epilepsy is commonly seen in younger children. Therefore, many of these patients represent a treatment challenge. Some of these cases need presurgical and invasive evaluations tailored to individual needs. Novel surgical strategies and improved perioperative care have improved seizure outcome and lowered surgical risk in these patients. Overall, they can expect improved quality of life for these surgeries. Although it is difficult to group these cases for outcome analysis, further understanding of the epilepsy outcomes is needed.

ANNEX

Figures 85.3 through 85.7 show cases illustrating the decision making of the algorithm for the evaluation of patients with multilobar and multilesional epilepsy, shown in Figure 85.1.

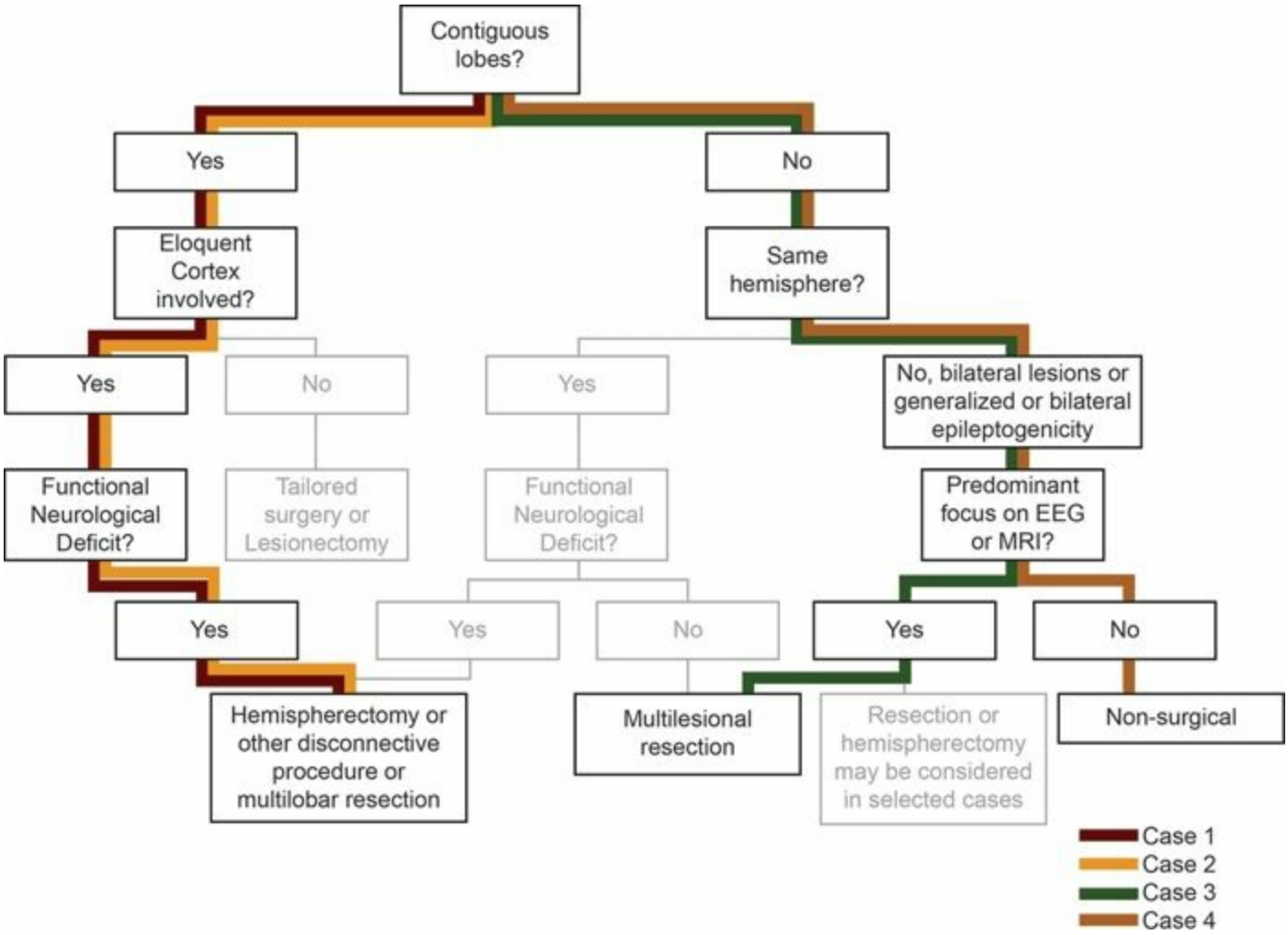
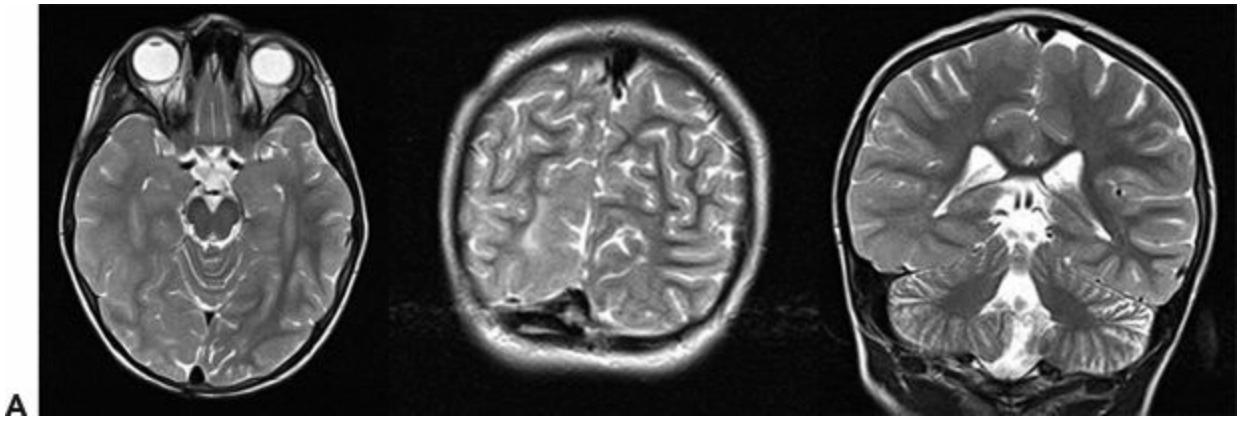
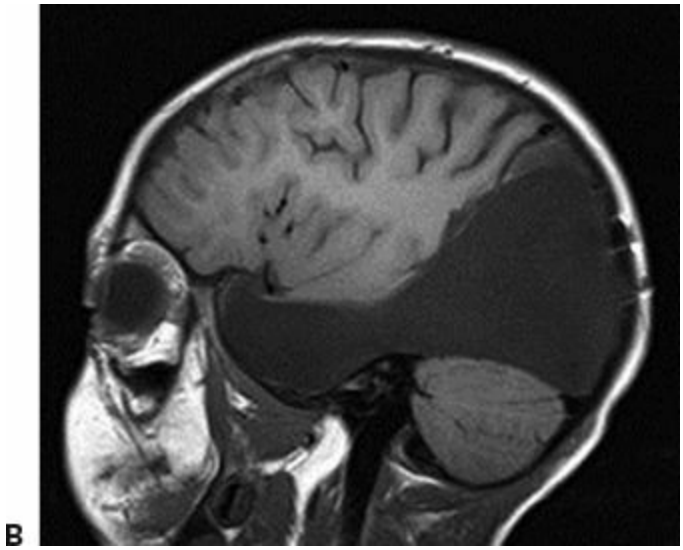
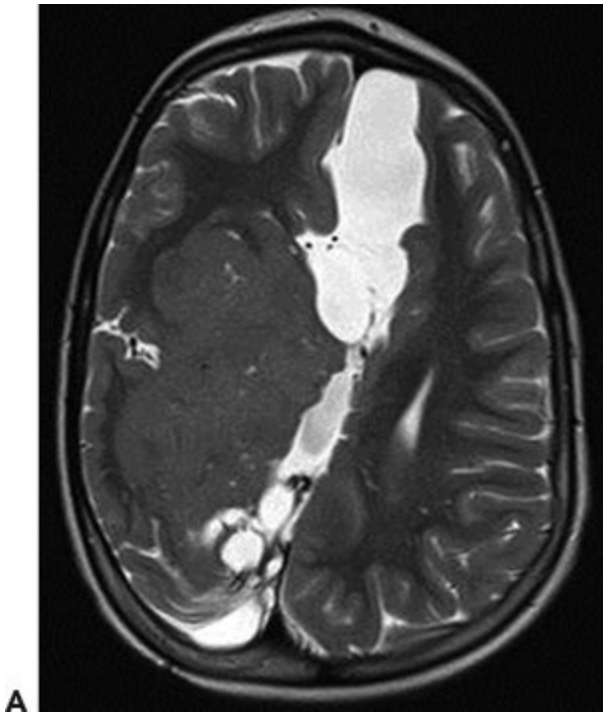


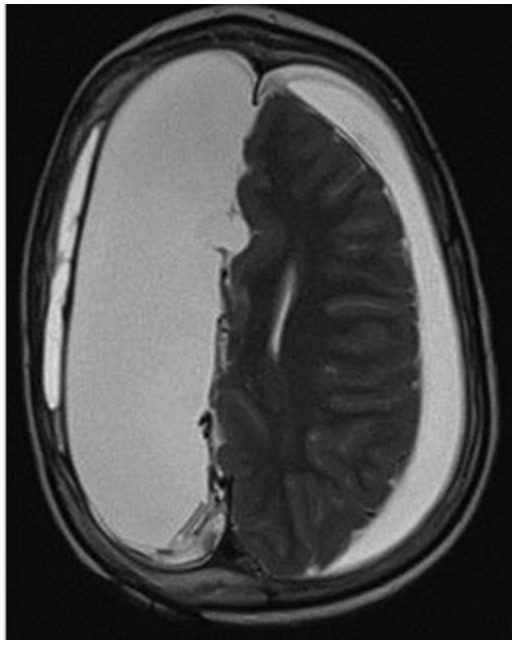
Figure 85.3. Progression in the proposed algorithm for the evaluation of patients with multilobar and multilesional epilepsy in four patients with different clinical scenarios. Each case is color coded in the figure key: Case 1 in red, Case 2 in yellow, Case 3 in green, and Case 4 in orange.



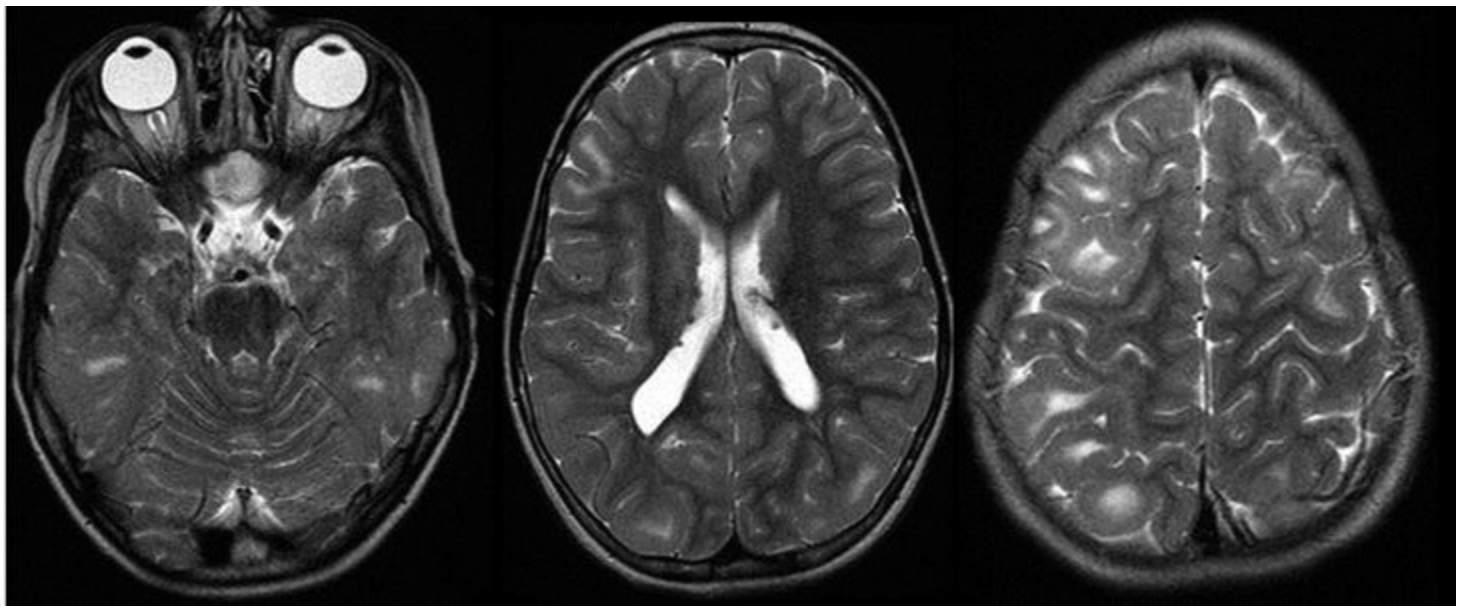


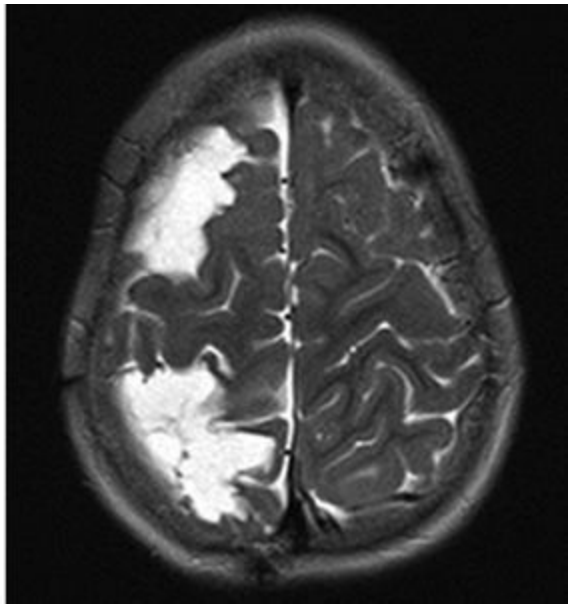
A:Brain MRI axial and coronal T2 images on Case 1. The figure documents the presence of extensive cortical dysplasia in the right TPO region with blurring of the gray–white matter junction. Case 1 is a 5-year-old right-handed male with seizure onset at age 2 months. Initial seizures were infantile spasms that responded to ACTH therapy initially. At the time of the presurgical evaluation, he was having multiple daily seizures described as behavioral arrest (hypomotor seizures) and bilateral asymmetric tonic seizure. On examination, there was evidence of delayed cognition for age, left hemineglect, mild left hemiparesis, and a possible left hemianopia. He was receiving treatment with felbamate, lacosamide, and rufinamide. Previous antiepileptic drugs included ACTH, clonazepam, levetiracetam, oxcarbazepine, and topiramate. He had a vagus nerve stimulator implanted. Interictal findings on video–EEG evaluation were right hemispheric sharp waves, right bioccipital sharp waves with maximum right and rare left occipital sharp waves. There were generalized polyspikes during sleep and continuous slow activity over the right hemisphere. Hypomotor seizures had an ictal onset in the right occipital region or right hemisphere. Figure 85.3 showed the decision making for this case in color red. **B:**Postoperative brain MRI sagittal FLAIR image of Case 1. The figure shows a multilobar resection that included right TPO lobe. Case 1 has been seizure free for 14 months after this surgery.





A:Brain MRI axial T2 image on Case 2. The figure documents the presence of severely dysmorphic brain with massive right hemisphere cortical dysplasia, callosal dysgenesis, and complex supraventricular midline cyst. Case 2 is a 7-year-old right-handed male with chromosomal abnormality 8p21.3 duplication and 4q13.3 deletion (unknown clinical significance) who had seizure onset at age 11 months. His initial and ongoing seizures were hypomotor seizures that often time were not identified by his relatives. He also had left arm clonic status epilepticus lasting several hours to a day and occurring around three times per year. On examination, he had a left hemiparesis with no fine motor movements in the left hand and left hemineglect. He was taking oxcarbazepine and topiramate. Rectal diazepam failed to control episodes of partial status epilepticus. Previously, he was taking levetiracetam. He had a ventriculoperitoneal shunt placed at birth due to complex midline cyst and hydrocephalus. Interictal activity on video–EEG was characterized by right centroparietal and right frontocentral sharp waves. There was continuous slow in the right hemisphere with asymmetric background. Several hypomotor seizures were recorded with onset in the right centroparietal region. Figure 85.3 shows the decision making for this case in color yellow. **B:**Postoperative brain MRI T2 axial image on Case 2. In this case, the complexity of the malformation did not allow for a functional hemispherectomy. Case 2 has been seizure free for 12 months after anatomic hemispherectomy.





A:Brain MRI Axial T2 images of Case 3. Case 3 is a 12-year-old right-handed female with TSC2 mutation. Her seizures began at age 2 weeks. Initial seizures were infantile spasms that improved but nor resolved with ACTH therapy. Before surgery, she had multiple seizures per day that were described as complex motor behavior evolving to hypomotor seizures (behavioral arrest) and then followed by epileptic spasm. She also has generalized tonic seizures. On examination, she has cutaneous tuberous sclerosis stigmata and clinical/behavioral features consistent with cognitive impairment and pervasive developmental disorder. She was nonverbal and had left hemineglect. Systemic evidence of TSC included left eye astrocytoma and bilateral renal angiomyolipomas. At the time of the presurgical evaluation, she was taking zonisamide, valproic acid, levetiracetam, and clonazepam. In the past, seizures were refractory to ACTH, pyridoxine, topiramate, oxcarbazepine, lamotrigine, and carbamazepine. Interictal abnormalities on video–EEG included continuous slow activity lateralized right hemisphere maximum right centroparietal region, multiregional sharp waves right more than left hemisphere, generalized polyspikes, and generalized spike and wave complexes. Typical clinical seizures and electrographic seizures were recorded with an ictal onset in the right centroparietal region. Hypomotor seizures had nonlocalizable onset. Figure 85.3 shows the decision making for this case in color green. **B:**Postoperative brain MRI Axial T2 images of Case 3. Case 3 had right-side multilesional resection with sparing of the motor cortex. Surgery was done with cortical stimulation studies and electrocorticography. At last outcome, 5 years after the surgery, Case 3 has had a seizure reduction of 80% compared to her presurgical baseline. She has occasional tonic seizures and isolated tonic spasms mainly when she is ill.

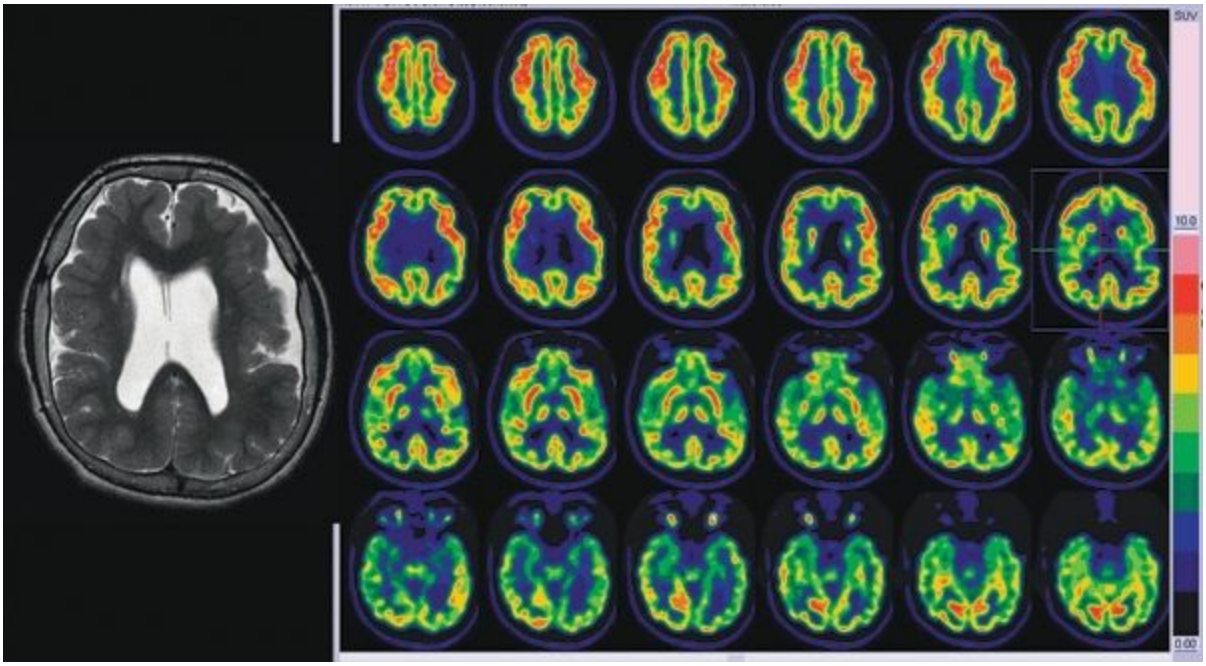


Figure 85.7. Brain MRI Axial T2 image and PET scan of Case 4. MRI shows bilateral polymicrogyria. PET scan shows bilateral extensive and multilobal hypometabolism. Case 4 is a 16-year-old right-handed male with seizure onset at age 7 months. His seizures are axial spasms, myoclonic seizures, and atypical absence seizures. He has multiple seizures daily. On examination, he has clinic features consistent with moderate cognitive impairment and spastic quadriparesis with lower extremity predominance. Current

medications are topiramate, vigabatrin, clobazam, clonazepam. Rescue medication is rectal diazepam. Previous medications included lacosamide, lamotrigine, levetiracetam, rufinamide, valproate, and ketogenic diet. He also had a vagus nerve stimulator implanted. On video–EEG, he has continuous slow generalized and axial spasms and myoclonic seizures both with generalized onset. This case is not a surgical candidate. Figure 85.3 shows the decision making for this case in color orange. In patients like Case 4, palliative procedures such as callosotomy could be considered to reduce the daily seizure burden.

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CHAPTER 86 SURGICAL APPROACH IN NONLESIONAL CASES

DEEPAK LACHHWANI AND JORGE ALVARO GONZÁLEZ-MARTÍNEZ

INTRODUCTION

Nonlesional refractory focal epilepsy cases invariably lead to a challenging path toward curative epilepsy surgery. The identification of a pathologic substrate on magnetic resonance imaging (MRI) is useful for an appropriate surgical strategy and most predictive of long-term seizure outcome. Patients with nonlesional MRI on the other hand require a more rigorous pre surgical evaluation and often end up with a disappointing surgical outcome (1).

For example, a long-term study involving 85 patients with extratemporal epilepsy and normal MRI showed only 11% (9/85) were seizure free with 10 or more years of follow-up. These 9 patients belonged to the subgroup of 24 who had had received surgical resection (38% seizure free) (2). Therefore, while surgical treatment provided hope for 38% in this study, the alternative of medical management only was uniformly dismal with respect to seizure outcome. Interestingly, this study found the scalp EEG to be the most useful test to identify patients who were likely to have an excellent outcome, while the presence of a localized SISCOM did not predict surgical outcome. Nonlesional temporal lobe epilepsy patients have a slightly better outlook after surgery. Reports of excellent surgical outcome range from 41% to 65% (3–6).

Therefore, nonlesional refractory focal epilepsy is a challenge eagerly awaiting a solution. Despite years of advances in imaging modalities such as positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance spectroscopy, magnetoencephalography (MEG), etc., none of these tests have shown independent predictive value in formulating surgical strategy in this cohort of patients. Presurgical management begins with a sound clinical hypothesis based on epilepsy history, seizure semiology, and a corroborating video–EEG evaluation involving scalp EEG. By definition, nonlesional epilepsy means that an MRI fails to reveal a plausible epileptogenic substrate. At this juncture, revisiting the initial hypothesis of seizure origin is critical before employing additional imaging techniques in the face of a normal MRI. For the epileptologist, each one of these imaging techniques holds the promise to better define the epileptogenic zone (EZ). Due to lack of convincing published data regarding predictive value of these tests, the answers yielded by these modalities may benefit if it supports a localizing hypothesis. Concordance of the initial clinical hypothesis and data from carefully chosen tests segues to an invasive evaluation directed toward a tailored resection. This chapter focuses on methods that share center stage in evaluating nonlesional epilepsy cases followed by available invasive evaluation techniques.

IS THE MRI TRULY NORMAL?

"The eye sees only what the mind is prepared to comprehend." Henri-Louis Bergson (1859–1941)

In nonlesional cases, it may be especially relevant to paraphrase Bergson in that the eye sees only what the mind is prepared to comprehend and what an MRI can reveal. Two critical steps can sometimes reveal an MRI answer hidden in plain sight: correct MRI technique and an expert review of the MRI. Before labeling an MRI as normal, it is essential to ensure that the proper technique was used to obtain the MRI and an expert reviewed the images within the clinical context. Standard MRIs may fail to detect 57% of focal epileptogenic lesions, while dedicated MRI protocols to evaluate epilepsy patients may show focal lesions in 85% of patients with "nonlesional" standard 1.5 T MRI (7). In the same study, authors found the sensitivity for detection of focal lesions of "nonexpert" reports of standard MRI was 39%, while that of "expert" reports of epilepsy specific MRI was 91%.

Advanced techniques utilizing 3-T or higher-strength magnets have provided additional insight in studying anatomic details crucial for surgical planning (8,9). Phased array surface coils performed at 3 Tesla (3 T PA-MRI) interpreted by experienced, unblinded radiologists yielded useful information in 48% of the studies previously performed with a 1.5-Tesla magnet (9). In 65% of the 1.5-Tesla studies reported as normal, 3-T PA-MRI was able to appreciate a new lesion. In 33% of the 1.5-Tesla identified lesions, 3-T PA-MRI provided better anatomic boundaries of the lesion (9). Overall, 3-T PA-MRI techniques influenced decision making in 38% of the patients in this group, mostly affecting the decision to perform surgery. Advances in MRI techniques have improved the signal-to-noise ratio, reduced scan time, and increased spatial resolution as well as contrast-to-noise ratio.

Moreover, in very young patients, the timing of MRI can have a significant influence on yield. Throughout infancy, as axons myelinate, their T2 signal shifts from being brighter than surrounding cortex to darker than surrounding cortex. Due to these maturational changes, focal lesions are best appreciated before 6 months of chronologic age. A normal MRI study obtained between 9 and 18 months of age should be repeated after 2 years to account for a lesion that may be present but not evident during transitional signal changes (10). Appropriate MRI techniques and protocols for patients suspected to have focal epilepsy are well described in the literature (10,11).

PET

[18F]FDG-PET is the most frequently used nuclear functional imaging technique in patients with focal epilepsy. The uptake of radiotracer during the interictal state provides dynamic information regarding regional and general metabolism of the brain. After injection of a radiotracer, the subject is monitored with simultaneous EEG recording. The characteristic finding is a regional hypometabolism in the interictal state of patients with focal epilepsy. A meta-analysis of studies from 1992 to 2006 found that ipsilateral PET hypometabolism shows high concordance and good predictive value for seizure-free outcome even in cases with normal MRI (12). Ictal activity can have a variable influence on glucose uptake. Therefore a PET study needs to be interpreted with caution if EEG monitoring during uptake of radiotracer demonstrates a seizure or frequent spiking on EEG.

[18F]FDG-PET correctly identifies the diseased temporal lobe in >86% of nonlesional TLE patients (5). It is not uncommon for PET hypometabolism to be more widespread when compared to hypometabolism seen in patients with HS on MRI (12). The degree of hypometabolism may vary and is more often subtle in patients with type I dysplasia (13), one of the presumed substrates in nonlesional MRIs. A subtle abnormality on PET coupled with the poor resolution of the PET images raises the risk of overlooking a milder yet telling FDG-PET abnormality. A useful technique is to

coregister the patient's FDG-PET images to the MRI. Coregistration of the FDG-PET to the patient's MRI may enhance the detection of subtle hypometabolic areas and guide subsequent surgical strategy (14). In a cohort of patients where FDG-PET/MRI coregistration was included as a standard component of presurgical evaluation, this technique was especially useful in guiding surgery in 33% of patients with normal MRI and mild type I dysplasia (13).

Statistical parametric method analysis can be used as a complementary analytic tool for FDG-PET imaging, although a paucity of normative data in young patients poses a limitation and a visual evaluation is the mainstay in most epilepsy centers (15,16).

Alternate PET ligands such as [11]C-alpha-methyl-L-tryptophan (AMT) have shown promise particularly in evaluating patients with tuberous sclerosis. Their role in nonlesional MRI is not clear. One study found seizure outcome was poor in patients with normal MRI, with normal histopathology but abnormal AMT-PET, while it was better in patients with normal MRI and normal AMT-PET (17). The patient numbers were small, and additional data are needed to assess usefulness of AMT-PET in nonlesional MRI. Another technique, flumazenil (FMZ)-PET, helps to assess benzodiazepine receptor distribution. A prospective study found its usefulness in patients with bitemporal epilepsy as well as in patients with nonlesional MRI and FDG-PET–negative temporal lobe epilepsy (18). Recent studies showing seizure-related short-term plasticity of benzodiazepine receptors may help point to a potential avenue of FMZ-PET usefulness if performed within a few days in patients with normal MRI patients (19).

SISCOM

Interictal SPECT scan when compared with the ictal SPECT scan provides a snapshot of regional increase in blood supply keeping pace with the increased metabolic needs of the seizure-onset zone in patients with focal epilepsy. The subjective visual comparison of interictal and ictal SPECT images has been supplanted by digital subtraction of the images, followed by coregistration of the subtracted image to the patient's MRI (SISCOM, subtraction ictal single photon emission computerized tomography coregistered to MRI). The threshold of change included in the subtracted image is conventionally set at two standard deviations from the mean.

SPECT radio ligand injection needs to be timed early in the course of a seizure to capture the first and relatively restricted change in perfusion before the ictal activity spreads beyond the seizure-onset zone. This poses practical challenges, and despite best efforts, a late injection or a postictal injection (especially in brief seizures) may be unavoidable. The dynamic perfusion changes may transition from a relative increase from baseline (ictal) all the way to a reduction from baseline (post ictal). Interpreting subtracted SPECT images within the context of scalp EEG–confirmed time of injection is valuable in identifying a potential epileptic focus (hypo- or hyperperfused relative to baseline) in 77% of patients (20). Surgical outcomes are favorable when SPECT-provided information is incorporated in preoperative planning particularly when intracranial EEG data is concordant with the SPECT data (21). Thus, the role of SPECT is best as an adjunctive tool in nonlesional patients, with a contribution toward invasive implantation strategy.

MEG

Magnetic source imaging utilizes the magnetic fields associated with electric current dipoles to provide regional topography of the interictal epileptiform abnormalities. Bone and tissue are

transparent for the magnetic field, and hence magnetic signals are not attenuated when compared to the electrical (EEG) signals, which undergo significant attenuation, and small-amplitude spikes may not be visible on surface EEG. MEG is more sensitive in detecting interictal epileptiform discharges when compared to EEG (22). Postprocessing of magnetic dipoles offers a clear three- dimensional view of the epileptic discharges emanating from the cortical generators. In MRI-negative patients, MEG may serve as an adjunctive tool, and if the findings are in agreement with the initial hypothesis, MEG may facilitate planning for invasive evaluation. In a series of adult patients, who underwent MEG, the concordance between MEG spike cluster and findings on invasive recordings was 70% to 100% in 9/13 patients with no visible MRI lesions (23). The presence of MEG dipole clusters bode well for seizure-free outcome, while patients with poorly localized MEG spikes were not seizure free. Of note, the study found that complete removal of a MEG source cluster was not necessary for achieving seizure-free outcome (23).

Another retrospective study involving mostly nonlesional (15/22) pediatric patients noted that the number and density of preoperative clustered spike sources within the postoperative MRI-delineated resection bed is not associated with seizure-free outcome (24). There was no statistical difference in seizure-free outcome between the groups with >70% or <70% of MEG spike cluster removed. The role of MEG is attractive as an adjunctive tool to find convergent data in nonlesional patients. Additional data are needed to assess whether MEG may prove to be a better tool over other functional imaging modalities in the subset of nonlesional patients.

RATIONALE FOR THE USE OF INVASIVE MONITORING IN NONLESIONAL CASES

As an electroclinical concept, the localization of the EZ is done in the majority of cases through scalp EEG recordings. It is usually complemented by functional semiologic details of the ictal events (seizures). Additional anatomic, metabolic, and/or functional techniques would help to anatomically identify and localize the possible “epilepsy-producing lesion.” The gold standard techniques for the localization of the EZ (scalp EEG and video recordings of the seizure semiology) are sufficient to approximate the location of the EZ (25–28) and to generate an anatomoelectroclinical (AEC) network hypothesis. Nevertheless, scalp EEG only approximates the boundaries of the epileptic anatomic area to be resected. This is mainly due to the fact that scalp EEG detects only epileptiform activity that results from EEG synchronization of relatively large areas of cortex, estimated in some studies to be between 6 and 10 cm^2, and EEG recordings are affected by the smearing effect of the bone and other high-resistance structures (e.g., meninges and scalp) between the cortical generators and the recording electrodes (29).

More specifically, in patients with refractory focal epilepsy in the settings of nonlesional MRI, a thorough analysis of the seizure semiology and the sequence of ictal clinical manifestations would add a functional and clinical depth to the EEG data and therefore contribute to the generation of the AEC hypothesis. As described above, additional information may be afforded by PET, MEG, and other anatomic/functional/metabolic techniques. Finally, the localization of functional areas in the brain and mapping their extent and their potential spatial overlap with the EZ are essential components in the process of developing an adequate and individualized resective surgical strategy in patients with nonlesional MRI (27,30).

As focal cortical dysplastic (FCD) lesions are the most common pathologic substrates for focal

epilepsies and are differentially located in the frontal lobe (therefore in potentially eloquent cortex), an understanding of the functional status of the involved region(s) and its anatomical and pathologic correlations are essential (27,31,32). Mild forms of cortical dysplasia (FCD type I) frequently present with subtle or no MRI changes and may be functional and intrinsically epileptogenic (33,34).

Therefore, the precise anatomical localization and mapping of eloquent cortex and its relationships with a well-defined epileptic area are the two most important components of any presurgical evaluation. They will facilitate the surgical planning and optimize the chances for a safe resection of the epileptic region (thus maximizing the chances for seizure freedom and minimizing the risks of neurologic deficits). This is particularly important in patients with difficult to localize seizures associated with nonlesional MRIs, since the absence of the "epileptic lesion" makes the clear localization and anatomical delineation of the EZ much more challenging by noninvasive methods of localization. For these reasons, in specific clinical scenarios associated with nonlesional MRI, an extraoperative monitoring phase is needed.

INDICATIONS OF INVASIVE EVALUATION IN PATIENTS WITH NONLESIONAL MRI

The main indications for an invasive evaluation in focal pharmacoresistant epilepsy are to address the major limitations of various noninvasive techniques. Based on the limitations outlined above of the various noninvasive techniques, an invasive evaluation should be considered in nonlesional patients in any one of the following cases:

1. The MRI does not show a cortical lesion in a location that is concordant with the electroclinical/functional hypothesis generated by the video–EEG recordings (so-called MRI-negative cases).
2. The anatomical location of the MRI-nonidentified lesion (and the location of a clearly hypometabolic focal area on PET) is not concordant with the electroclinical hypothesis. In addition, scalp EEG recordings in 85% to 100% of patients with FCD not visible on MRI show interictal spikes that range in their distribution from lobar to lateralized, from difficult to localize to diffuse (35,36).
3. The generated AEC hypothesis in MRI-negative cases involves a potentially highly eloquent cortex. The identification of the EZ, mapping of its extent, and/or its relationship with potentially eloquent cortex are not typically resolved in these cases. These include patients with suspected focal cortical dysplasia as the possible pathologic substrate for the epilepsy (33,37–39).

In these instances, an invasive evaluation would lead to the formulation of a clear resective surgical strategy. The recommendation for invasive monitoring is made during a multidisciplinary patient management session that include neurologists, neurosurgeons, neuroradiologists, and neuropsychologists. Areas and networks of coverage/sampling are determined based on a well-formulated AEC hypothesis based on the results of the noninvasive studies. Two extraoperative invasive methods have been used to accomplish these goals: subdural grid (SDG) electrodes and stereotactic placement of depth electrodes (stereoelectroencephalography, SEEG).

PRINCIPLES AND INDICATIONS OF SUBDURAL ELECTRODES PLACEMENT

Extraoperative mapping with the subdural electrodes (which includes SDGs and strips) has the main advantage of allowing an optimal coverage of the subdural adjacent cortex with adequate and continuous superficial functional mapping capabilities (33,40,41). A major advantage of subdural electrodes consists in the comprehensive anatomical coverage of cortical surfaces, therefore allowing accurate anatomical electrical and functional mapping of the areas of coverage. Limitations of SDG electrodes include an inadequate/partial/incomplete intrasulcal, deep brain and interhemispheric coverage, and the relative difficulty in multilobar, three-dimensional, and large functional network sampling (42). These characteristics are highlighted in the published results on the successes and failures following SDG implantation (43). The best resective surgical outcomes following SDG implantation are achieved in patients with clear cortical lesions especially tumors and those patients in whom the SDG implantations were placed with the main purpose of functional mapping (32,43). On the other hand, the worst outcomes are seen in patients with no clear lesions on the MRI and nonspecific histopathology and those who underwent either a sublobar or multilobar resections.

These characteristics suggest that the best candidates for extraoperative invasive evaluation with SDG are those patients with clear cortical surface lesion(s) (excluding the interhemispheric, cingulate gyrus, deep sulcal, and mesial frontal/temporal regions), in particular those patients where the main indication for the invasive evaluation is electrofunctional/eloquent cortex mapping in the setting of a superficial cortical lesion. In nonlesional patients, the indication of SDGs and strips is likely reserved in patients where the hypothetical EZ is located in clear proximity to eloquent cortical areas.

INDICATIONS OF SEEG ELECTRODES PLACEMENT

In addition to the general indications for invasive monitoring specified above, specific indications can be considered to choose SEEG in detriment to other methods of invasive monitoring. These criteria included the following:

1. The possibility of a deep-seated or difficult-to-cover location of the EZ in areas such as the mesial structures of the temporal lobe, opercular areas, cingulate gyrus, interhemispheric regions, posterior orbitofrontal areas, insula, and depths of sulci.
2. A failure of a previous subdural invasive study to clearly outline the exact location of the seizure-onset zone. The failure to identify the EZ in these patients may be due to multiple reasons that include the lack of adequate sampling from a deep focus or a clinically silent focus upstream from the EZ.
3. The need for extensive bihemispheric explorations (in particular in focal epilepsies arising from the interhemispheric or deep insular regions).
4. Presurgical evaluation suggestive of a functional network involvement (e.g., limbic system) in the setting of normal MRI.

In these scenarios, the SEEG methodology may be considered as a more appropriate and safer option.

As mentioned above, the SEEG methodology has the advantages of allowing extensive and precise deep brain recordings and stimulations with minimal associated morbidity. In reoperations, mainly in patients who underwent a previous subdural evaluation, the possibilities are that the majority of these patients failed epilepsy surgery because of difficulties in accurately localizing the EZ. These patients pose a significant dilemma for further management, having relatively few options available. Further open SDG evaluations may carry the risks associated with encountering scar formations and still having limitations related to deep cortical structure recordings. A subsequent evaluation using the SEEG method may overcome these limitations, offering an additional opportunity for seizure localization and sustained seizure freedom (44). The main disadvantage of the SEEG method is the more restricted capability for performing functional mapping. Due to limited number of contacts located in the superficial cortex, a contiguous mapping of eloquent brain areas cannot be obtained as in the subdural method mapping. In order to overcome this relative disadvantage, the functional mapping information extracted from the SEEG method is frequently complemented with other methods of mapping, as DTI images or awake craniotomies (39).

CONCLUSION

Due to recent advances in numerous diagnostic modalities, nonlesional cases of refractory focal epilepsy have a better chance to be considered for a surgical treatment strategy than any other previous time. This is due to refinement of existing imaging techniques as well as adoption of less commonly used invasive techniques such as SEEG. Without a clear hypothesis to support the focal onset of seizures, invasive investigations are likely to mislead and should be avoided. However, when a priori hypothesis of focal onset of seizures is reasonably sound, initiating an invasive workup is recommended. Under such circumstances, the limitations of noninvasive investigations can be overcome with a carefully chosen technique of invasive evaluation (SDGs or SEEG). Outcome data are encouraging and support clinical judgment and judicious use of tools to explore surgery for this challenging subset of nonlesional cases.

CASE

A 15-year-old right-handed boy, with seizure onset at 8 years of age, had dialeptic seizures with automotor features, sometimes evolving to left head version followed by secondary generalized tonic–clonic seizure. Despite adequate medication trials, he was having one seizure/month to one seizure every 2 to 3 months. 3-T brain MRI was normal; MEG and FDG-PET did not provide further localizing information. Surface interictal and ictal EEG was consistent with right hemisphere epilepsy (Figs. 86.1 through 86.4). After careful deliberation at surgical conference, it was decided to undertake an SEEG evaluation focusing on the right frontal and perirolandic areas as well as right insula (Figs. 86.5 through 86.9). A tailored resection was based on the SEEG findings (Fig. 86.10) resulting in seizure freedom since surgery (>5 years). Histopathology did not show evidence of malformation.

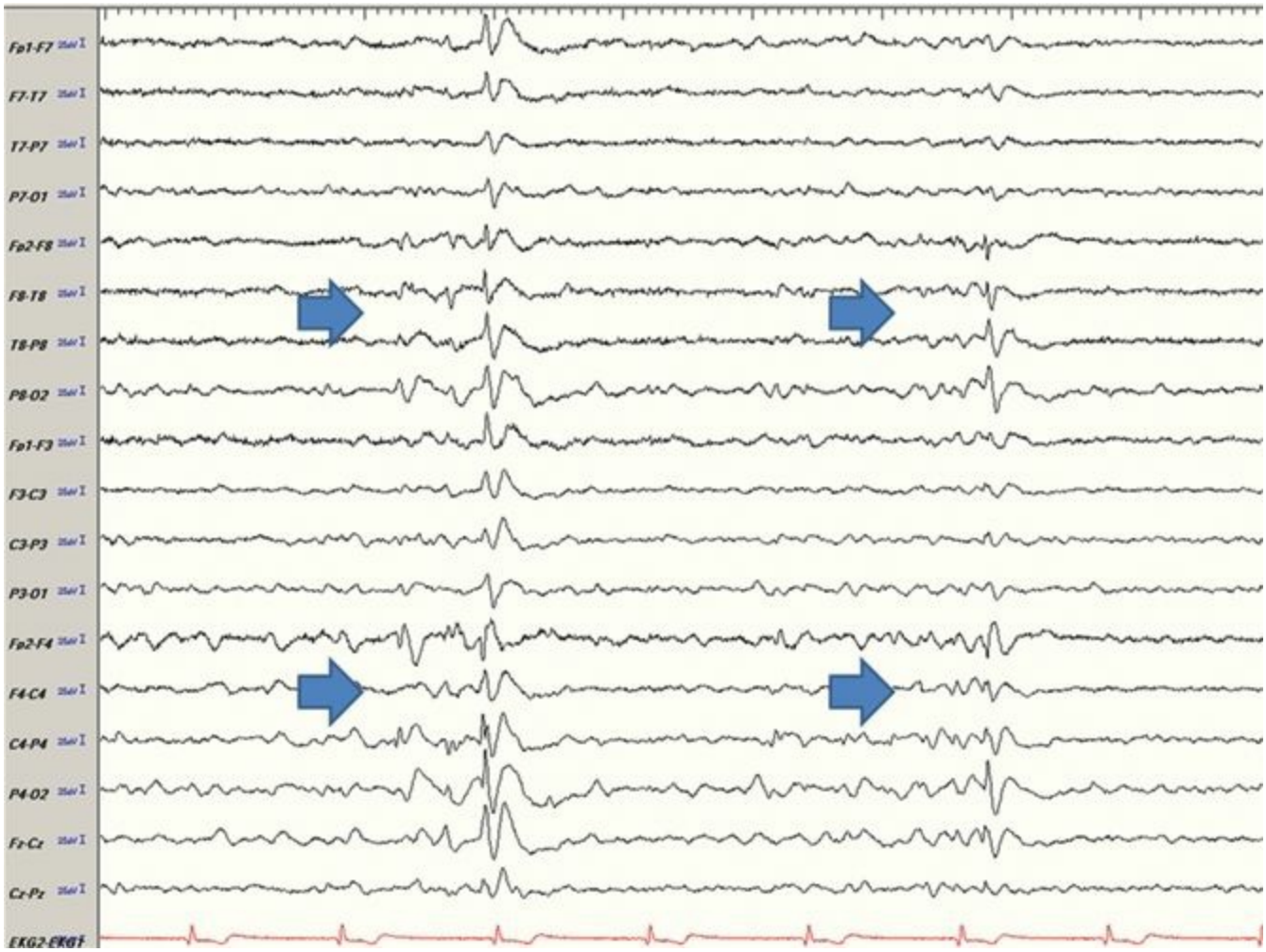

Figure 86.1. Surface interictal EEG. Arrows indicate spike-and-wave complexes generalized maximum right (45%).

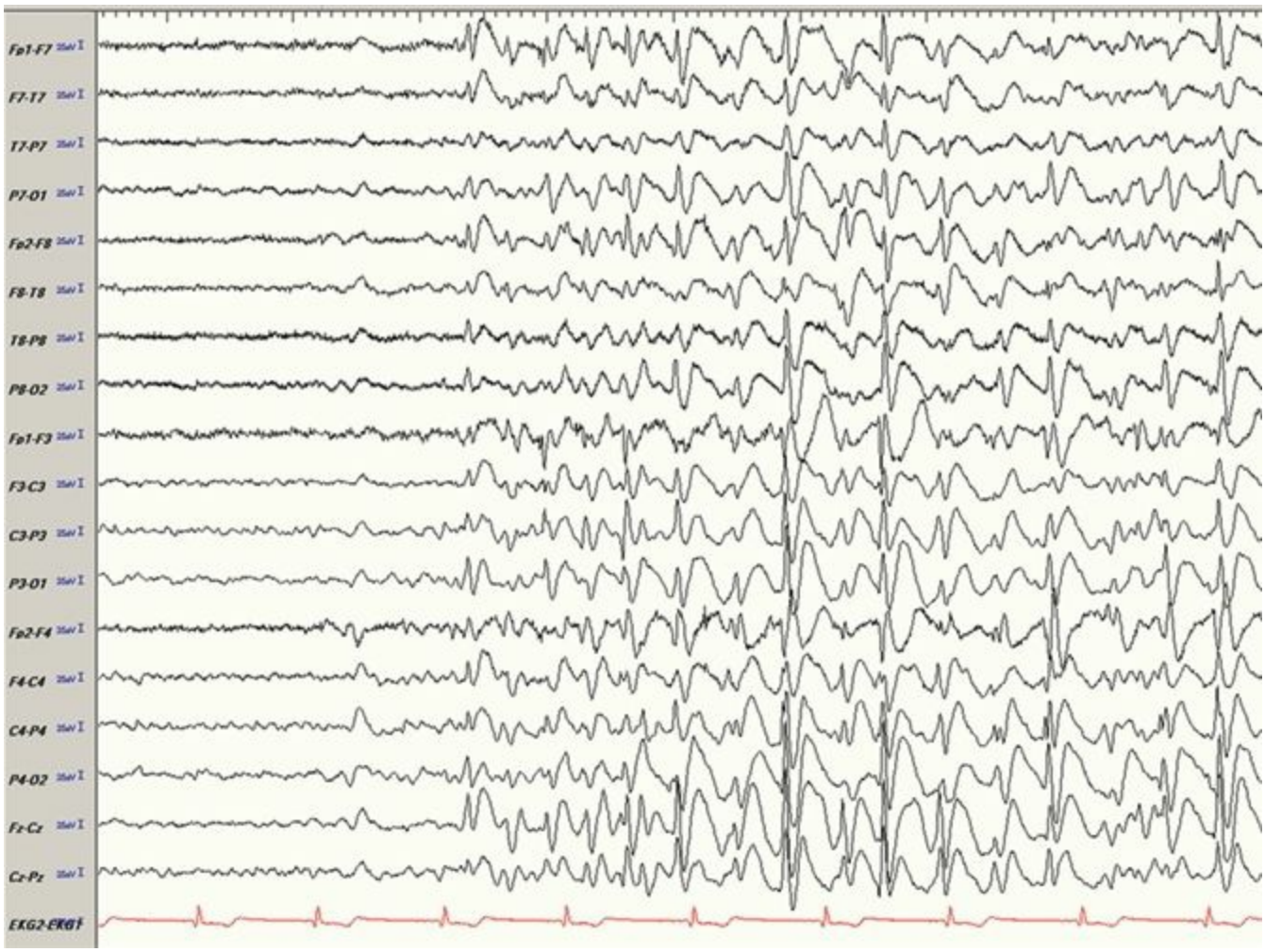

Figure 86.2. Surface interictal EEG. Spike-and-wave complexes generalized (50%). Rarely noted (not shown) spike-and-wave complexes regional, right parietooccipital (<1%), or spike-and-wave complexes generalized maximum left hemisphere (<1%).

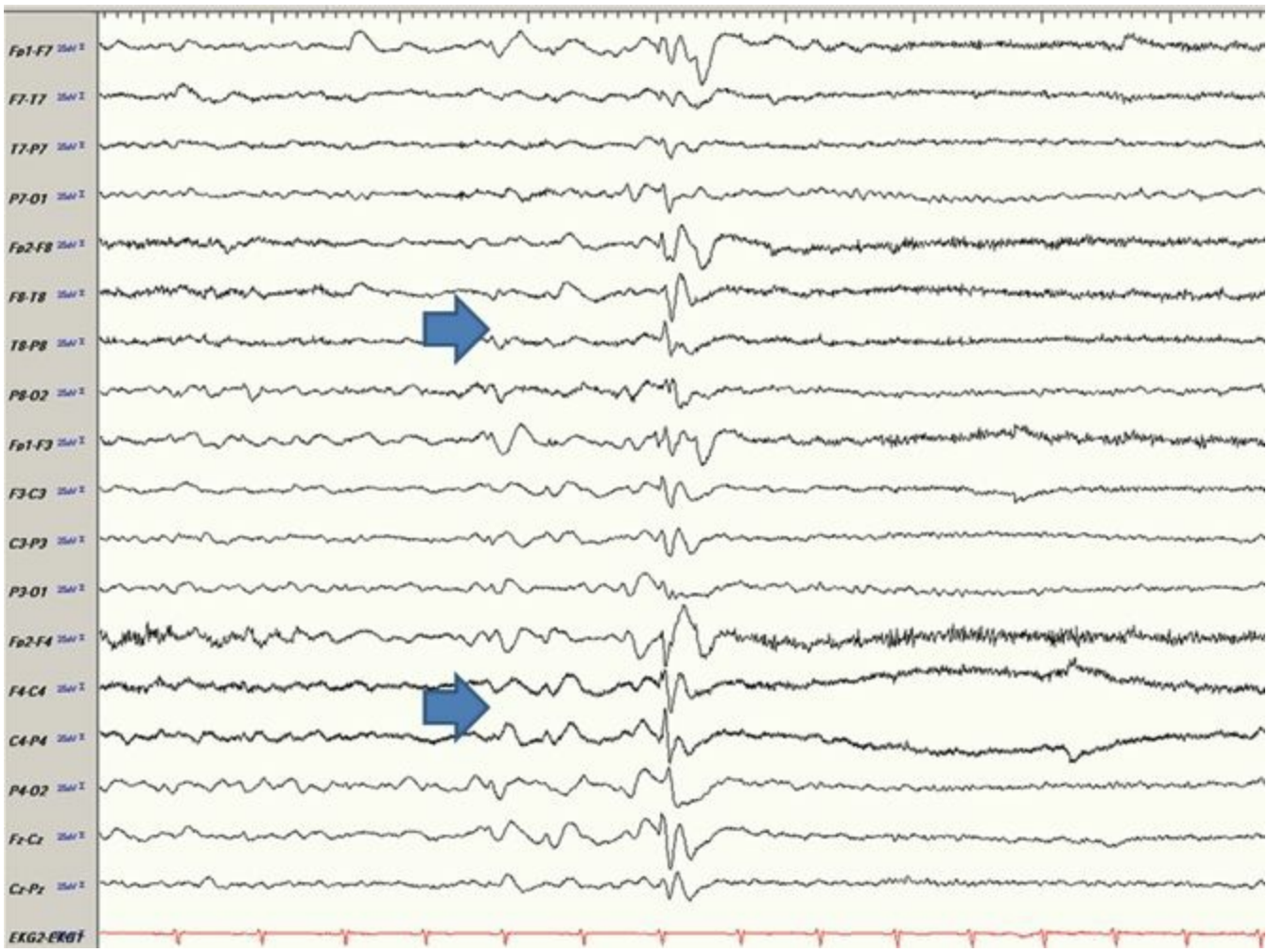

Figure 86.3. Surface ictal EEG (example 1). Generalized and lateralized right hemisphere (arrows).

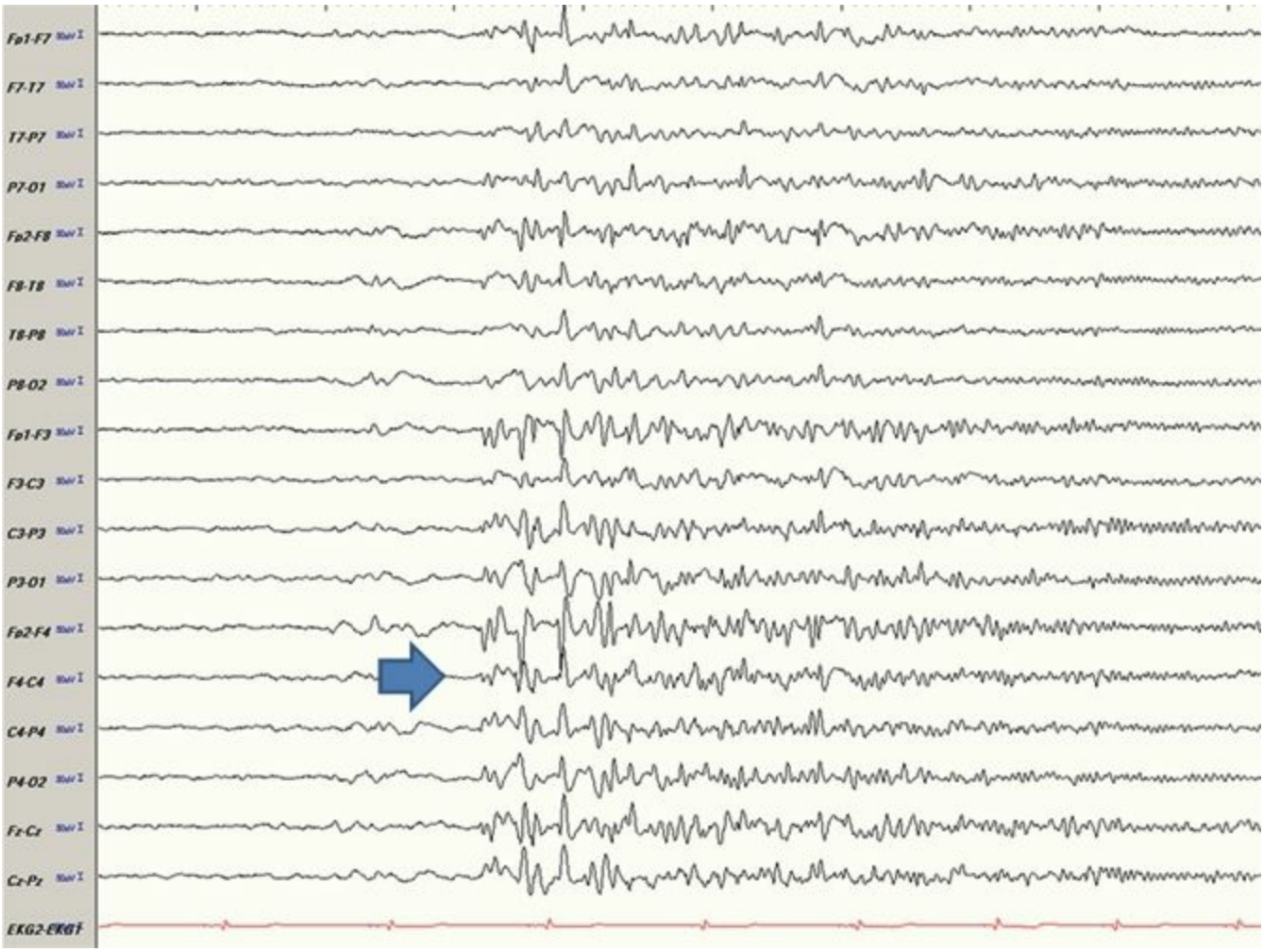

Figure 86.4. Surface ictal EEG (example 2). Generalized and lateralized right hemisphere (arrow).

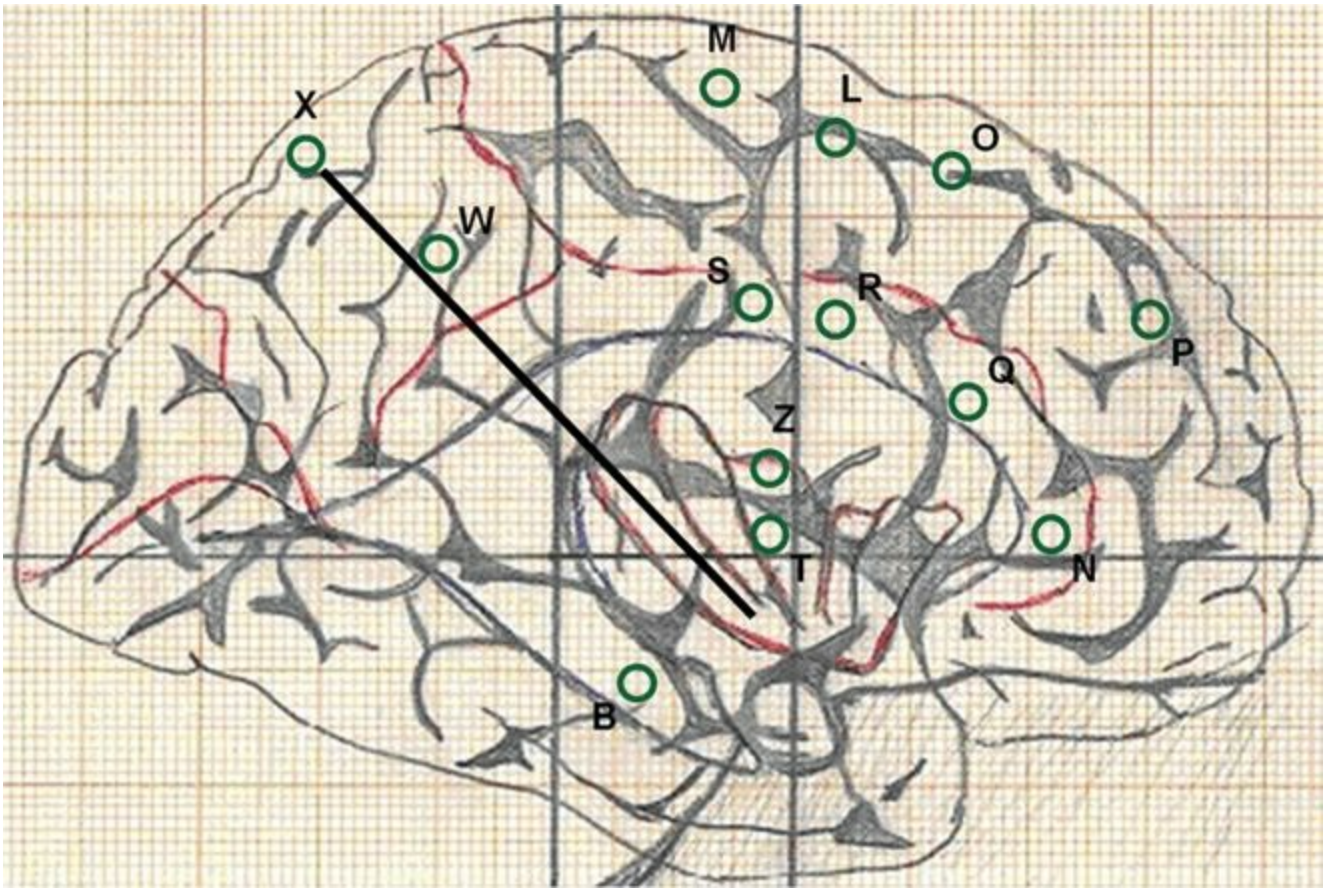

Figure 86.5. SEEG evaluation focusing on the right frontal and perirolandic areas as well as right insula.

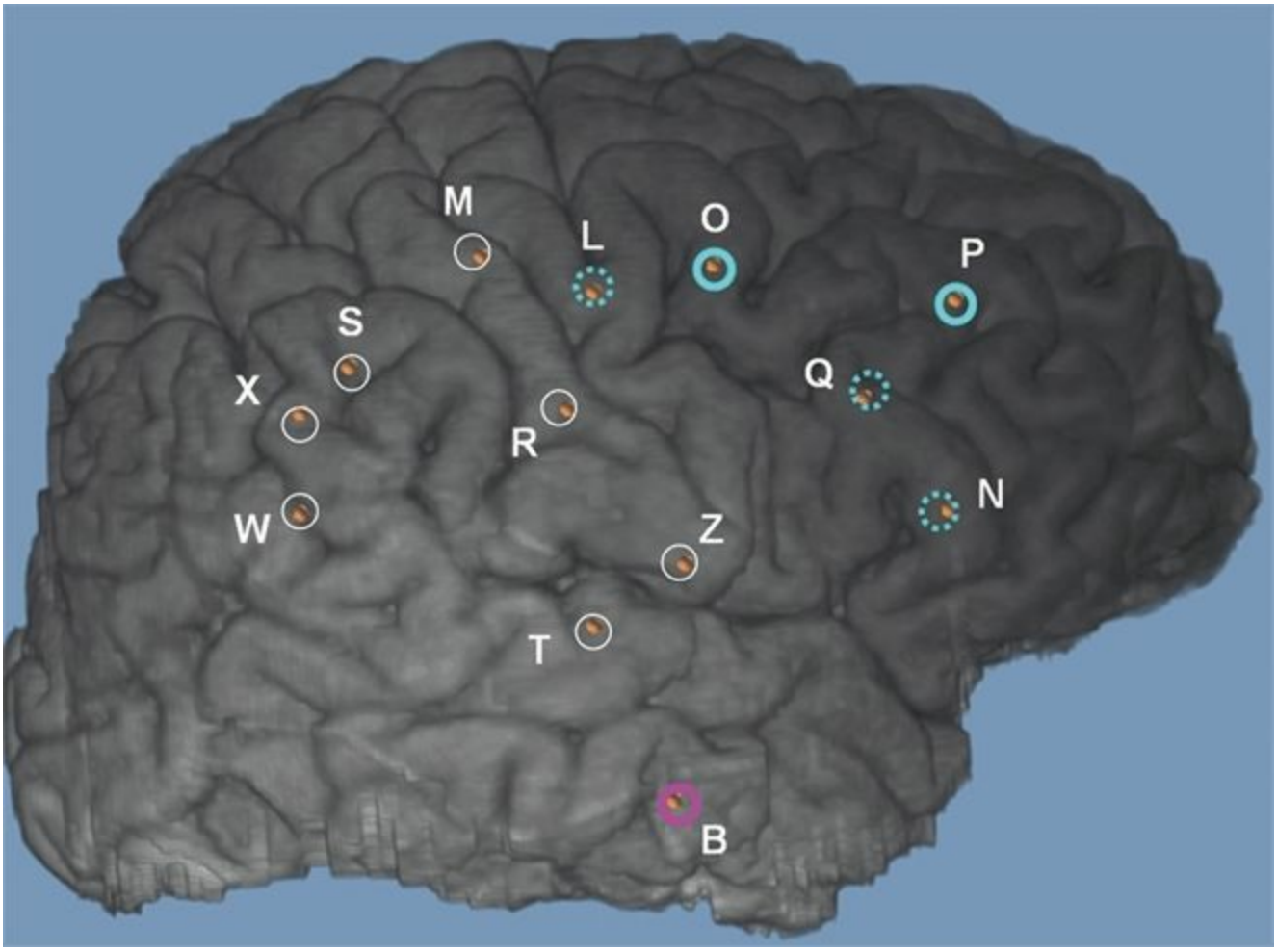

Figure 86.6. SEEG interictal findings best localized to “P” and “O” electrodes.

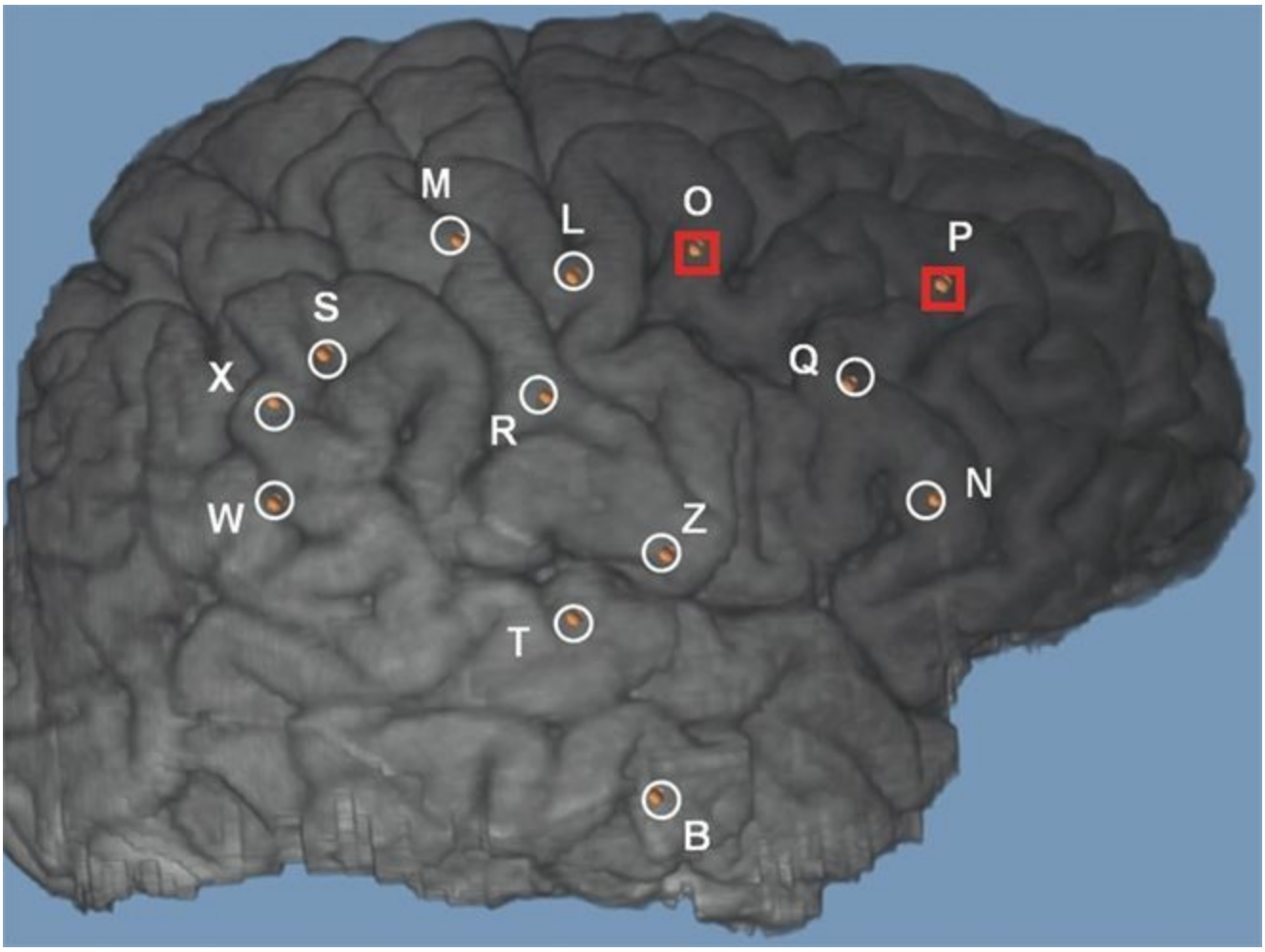

Figure 86.7. SEEG ictal findings best localized to “P” and “O” electrodes.

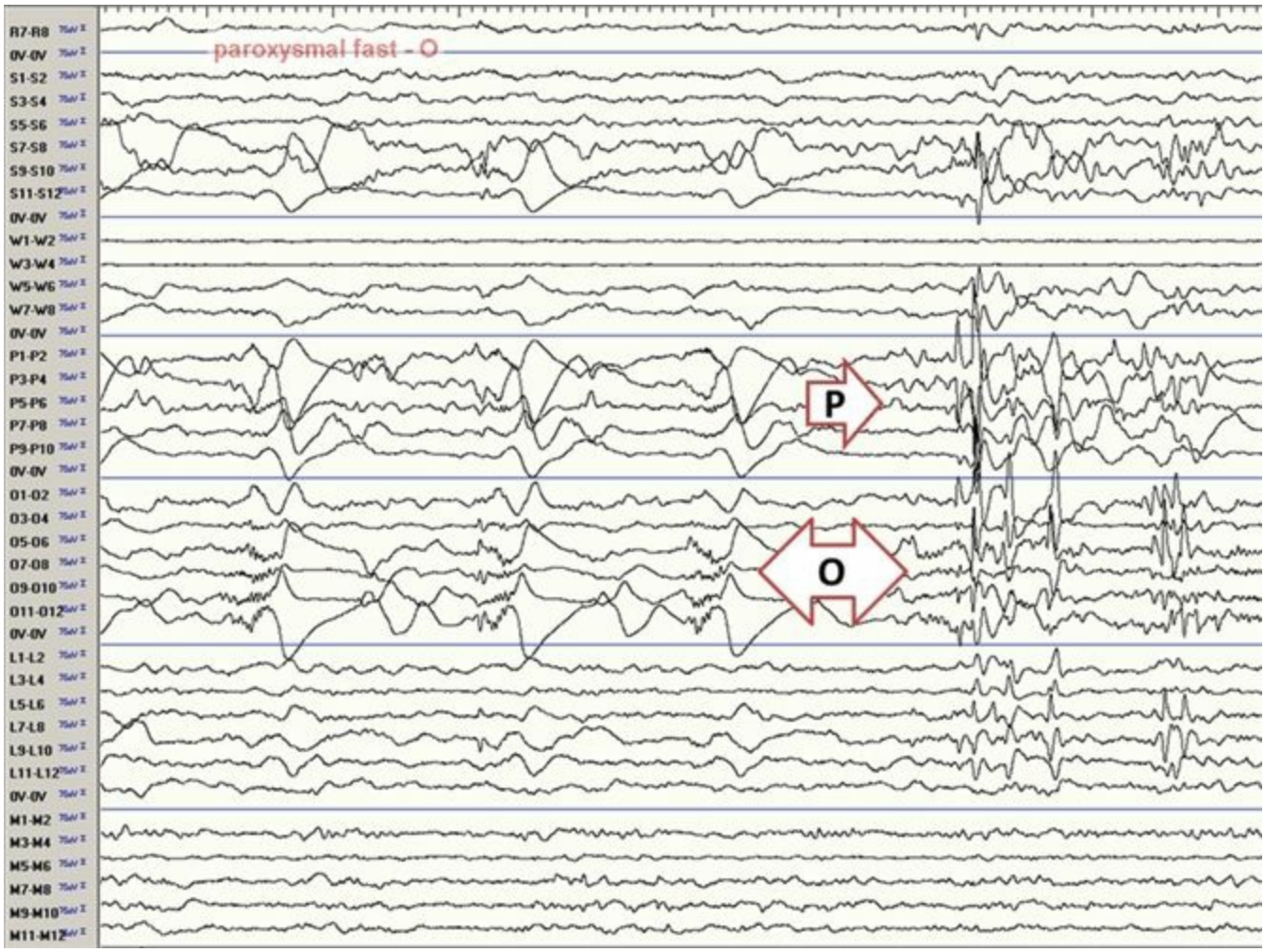

Figure 86.8. SEEG interictal EEG. 70% of interictal spikes and paroxysmal fast activity came from “P” and “O” SEEG electrodes.

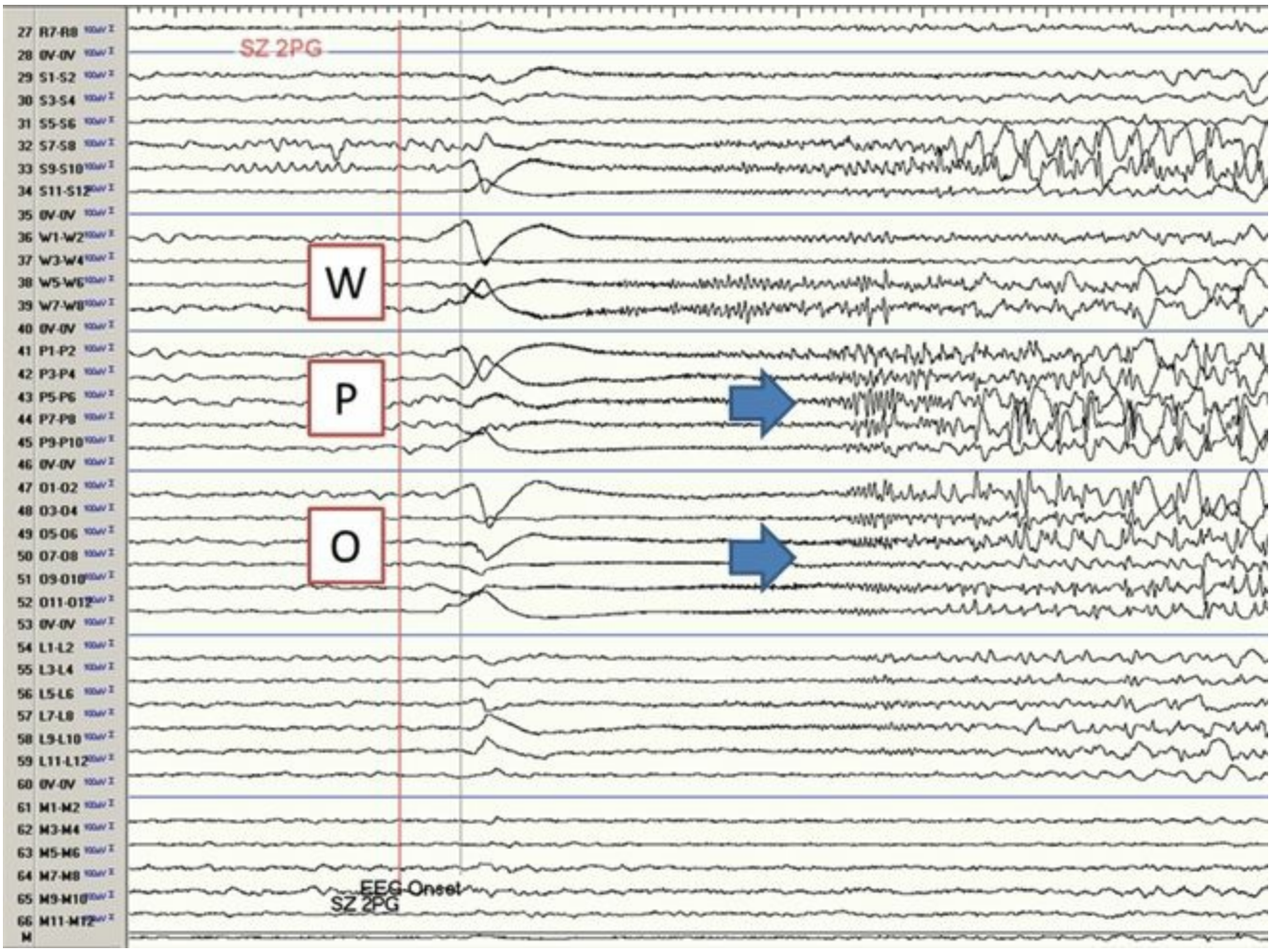

Figure 86.9. SEEG interictal EEG. Ictal EEG onset involved "P," "O," and "W" electrodes with best evolution in "P" and "O" electrodes (arrows).

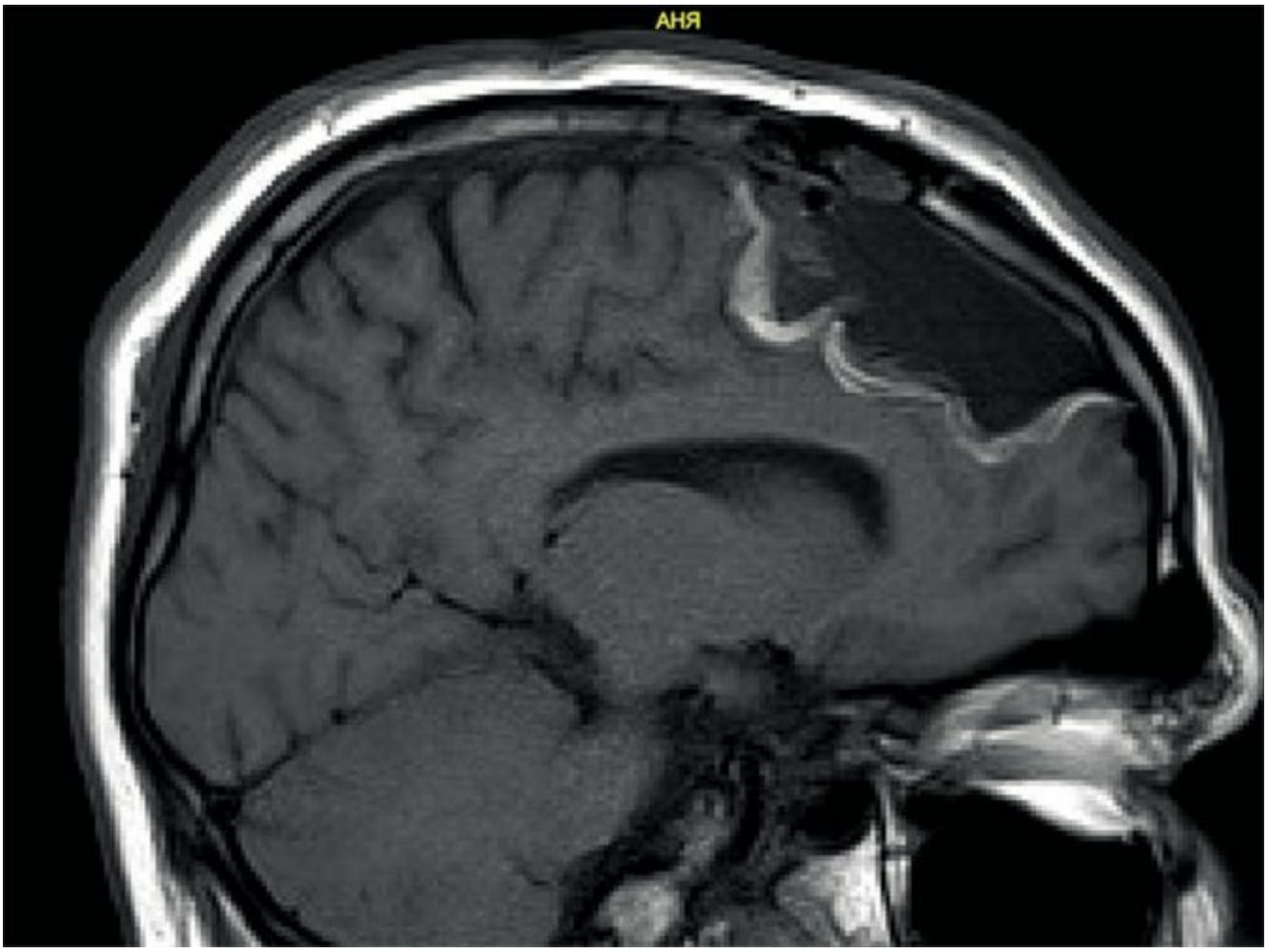

Figure 86.10. Immediate postoperative MRI.

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CHAPTER 87 HYPOTHALAMIC HAMARTOMA

JOHN F. KERRIGAN

Hypothalamic hamartomas (HHs) result in a rare but distinctive epilepsy syndrome. Clinical research over the past two decades has led to improved understanding of the diversity and complex natural history of this disorder, including the recognition that HHs are intrinsically epileptogenic. Multiple treatment options have emerged over the past 10 to 15 years, a revolutionary development for what was once considered an untreatable disease. The choice of a surgical treatment modality should be individualized to the patient's clinical course and lesion anatomy as shown by high-resolution magnetic resonance (MR) imaging. HH is the best human model for subcortical epileptogenesis and is an excellent clinical model for studying some of the fundamental questions associated with severe epilepsy in children, such as secondary epileptogenesis and epileptic encephalopathy. This chapter explores this unique form of epilepsy.

HISTORY

Pathologic laughter, most likely representative of gelastic (or laughing) seizures, was first described by Trousseau in 1877 (1). In 1950, Martin (2) drew attention to the floor of the third ventricle as a possible site of origin for gelastic seizures. List was the first to clearly identify the association between HH and epilepsy in 1958 (3). The neurologic features associated with HH, including treatment-resistant gelastic seizures beginning in infancy, and later development of additional seizure types, along with cognitive impairment and psychiatric symptoms, were delineated by Berkovic et al. in 1988 (4).

Since seizures usually arise from the cerebral cortex (including the hippocampus), it was initially assumed that the HH was a marker for epileptogenic abnormalities elsewhere in the brain. However, in 1994, using implanted intracranial electrodes for seizure monitoring, Kahane et al. (5) demonstrated that ictal discharges associated with gelastic seizures arise within the HH lesion itself. A host of subsequent reports have confirmed that the HH is intrinsically epileptogenic, and therefore a potential target for surgical treatment. Early efforts with subfrontal or subtemporal surgical resection were disappointing for most patients. The current era of HH treatment was initiated with the use of the transcallosal interforniceal approach for open surgical resection by Rosenfeld et al. in Melbourne in 2001 (6).

The last 10 years have seen a very rapidly moving landscape with the emergence of multiple surgical treatment options, including noninvasive techniques [gamma knife (GK) radiosurgery] and stereotactic ablation procedures. At this point, it is appropriate to say that no one treatment option is ideal for all patients with HH and epilepsy and that the choice of definitive therapy should be individualized to the patient's clinical course and pathologic anatomy. This chapter explores the clinical features that suggest the choice of one treatment option over another. However, an evidence-

based algorithm that guides the choice of treatment for individual patients is not yet possible.

CLINICOPATHOLOGIC SUBTYPES AND EPIDEMIOLOGY

HH lesions are associated with two distinct, though overlapping, clinicopathologic syndromes (7–11). Pedunculated HH lesions, also referred to as parahypothalamic HH, are associated with central precocious puberty (CPP). These patients usually do not have epilepsy or developmental and behavioral problems. The second subtype, known as sessile (or intrahypothalamic) HH, is associated with gelastic seizures, cognitive impairment, and psychiatric problems. Approximately 40% of these patients will also have CPP.

There are no recognized differences in the histopathology of resected HH tissue between these two subtypes. Rather, the differences are more likely related to the anatomy of lesion attachment to the hypothalamus. HH lesions associated with CPP have an attachment to the tuber cinereum, usually with a narrow stalk and base of attachment, while those associated with epilepsy have a more posterior, and broader, base of attachment in the region of the mammillary bodies (12,13). Patients with HH lesions that attach both to the tuber cinereum and the mammillary bodies (which correlates with large HH lesion size) are more likely to have both epilepsy and CPP. This chapter focuses on HH associated with epilepsy, unless otherwise stated.

HHs are relatively rare. The prevalence of HH with epilepsy is 1 in 200,000 children and adolescents in a Scandinavian population (14). There are no known racial or ethnic predilections for HH, although it may be slightly more common in males.

Most HHs are sporadic and are not associated with other congenital malformations or a positive family history. However, approximately 5% of all HH cases are associated with Pallister–Hall syndrome, which includes other malformations such as polydactyly, imperforate anus, and bifid epiglottis (15,16). Additional syndromes in which HHs can occur include Waardenburg syndrome (17), oral–facial–digital syndrome type IV (16,18), Bardet–Biedl syndrome (16), and, rarely, neurofibromatosis I (19).

NEUROPATHOLOGY

In comparison to other intrinsically epileptogenic tissues, such as mesial temporal sclerosis or focal cortical dysplasia of neocortex, HH has a relatively simple histopathology. As a hamartoma, the individual constituent cells appear normal, but cellular relationships and spatial organization are disordered. HH tissue consists of intermixed neurons and glia, although the relative proportion of these differs significantly from case to case (20). A universal feature of all epileptic HH lesions appears to be the tendency of neurons to cluster, although the abundance, size, and cellular density of these clusters vary significantly (21). The current mechanistic model for HH epileptogenicity hypothesizes that these clusters are the “functional unit” of HH tissue (22).

While the array of HH neuron phenotypes will undoubtedly become more diverse with further investigation, current studies have recognized two types, the small and the large HH neuron. Small HH neurons (generally <16 μm in diameter) have an interneuron-like phenotype, with expression of glutamic acid decarboxylase (GAD), the synthetic enzyme responsible for the presynaptic production of gamma-aminobutyric acid (GABA) (23). These cells are abundant (accounting for approximately

90% of all HH neurons) and have a relatively simple morphology with short, unbranched, aspiny dendrites (24). Functionally, these neurons also have intrinsic pacemaker-like firing activity with microelectrode recordings of perfused HH tissue slices or acutely dissociated single small HH neurons (23,25).

Large HH neurons (diameter >20 μm) are less abundant, have a pyramidal appearance more consistent with projection-type neurons, and do not show intrinsic pacemaker-like firing activity. However, they do have the interesting property of depolarizing and firing in response to pharmacologic exposure to $GABA_A$-receptor agonists, such as muscimol, in slice preparations obtained from freshly resected HH tissue (26,27). A working model for HH epileptogenesis is presented in Figure 87.1 (22).

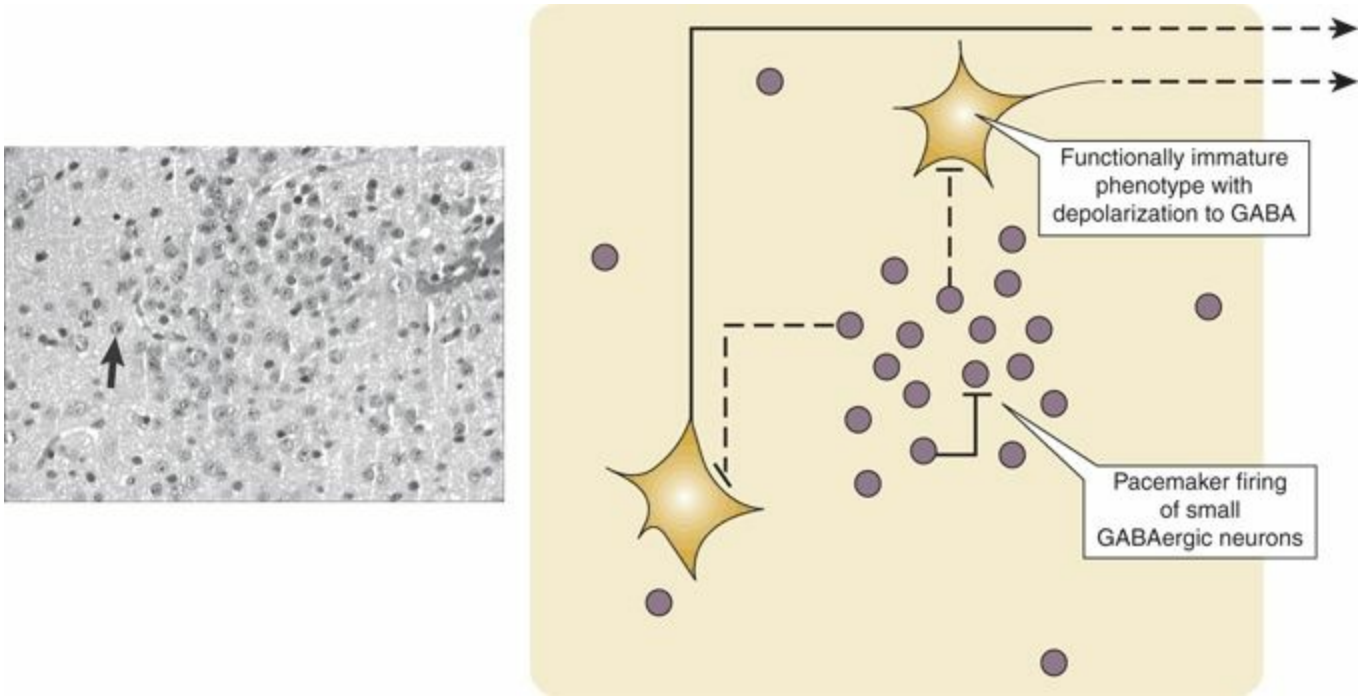

Figure 87.1. Preliminary cellular model for HH epileptogenesis based upon laboratory findings derived from surgically resected HH tissue [references (21–27); reviewed in (22)]. A photomicrograph of HH tissue is shown on the left side of the figure (hematoxylin and eosin stain). A small HH neuron (typically <16 μm in diameter) is indicated by the arrow, characterized by the well-defined nuclear membrane and densely staining nucleolus (21). A cluster of small neurons is seen immediately to the right of the arrow. The working model for epileptogenesis is shown on the right side of the figure. Small HH neurons tend to occur in clusters (21). They also express GAD and demonstrate intrinsic, spontaneous pacemaker-like firing activity in microelectrode recordings from freshly resected HH slice preparations (23). Their projections appear to be local, indicated by the solid line connecting two small HH neurons (24). Large HH neurons (typically >20 μm in diameter) have the morphology of projection neurons and may express excitatory neurotransmitters (24). These large neurons depolarize to GABA agonist administration (26,27). The evidence for structural and functional connections between small and large HH neurons is incomplete, indicated by the use of a dashed line. Small HH neurons within the cluster may be functionally connected by gap junctions (unpublished observation). The destination of the axonal projections of large HH neurons is unknown, also indicated by dashed lines. We hypothesize that clusters of small spontaneously firing HH neurons are linked in a functional network, resulting in the synchronized release of GABA, which has an excitatory effect on the larger projection neurons (22).

ETIOLOGY

Most HH cases are sporadic, and the underlying cause is unknown. However, HH is a cardinal feature of Pallister–Hall syndrome, known to result from haploinsufficiency of GLI3, a zinc finger transcription factor in the sonic hedgehog pathway. Somatic mutations (mutations present in the tumor only) in GLI3 are associated with HH in approximately 15% to 25% of sporadic cases, based upon

current genotyping technology (28,29).

While somatic mutations in GLI3 may be responsible for sporadic HH in some cases, other mutations are also likely to be discovered. At least two other susceptibility loci have been reported, specifically SOX2 and 6p25.1-25.3, a locus which includes FOXC1 (30,31). Like GLI3, SOX2 and FOXC1 are known to be transcription factors that are active during morphogenesis of the ventral forebrain. A project utilizing whole exome sequencing of DNA derived from HH compared to whole blood is currently under way (unpublished observation).

The specific molecular mechanisms controlling cellular proliferation that result in HH are unknown.

CLINICAL FEATURES

There is a great deal of diversity with respect to the age of onset, severity, and evolution of the neurologic symptoms in patients with HH and epilepsy (32). The tremendous clinical variability from case to case must be kept in mind when evaluating patients with a possible diagnosis of HH. These same clinical features, particularly the presence or absence of neurologic deterioration and the pace at which it is occurring, affect the decision-making process for deciding the type and timing of therapeutic intervention.

Epilepsy: Gelastic Seizures

Gelastic seizures are the most specific symptom associated with HH. They are usually brief, typically just a few seconds in duration, and usually last <30 seconds. They usually occur daily, with multiple seizures per hour in more severely affected patients. Gelastic seizures can be associated with little or no change in consciousness, particularly early in the clinical course, although making this determination in infants and young children can be challenging. Superficially resembling laughter, the patients generally do not experience mirth, and most family members can readily distinguish the gelastic seizure from true laughter. Not uncommonly, patients may have clinical events that more closely resemble crying rather than laughing (ictal crying or dacrystic seizures). Gelastic seizures can also be quite subtle. A purely subjective sensation, described as a pressure to laugh, can be described by communicative patients (33). They are commonly mistaken for other conditions, particularly during early infancy, including colic and gastroesophageal reflux disease (34).

Gelastic seizures associated with HH begin at an early age and are usually the first seizure type (35). In our experience, the clinical diagnosis is almost always delayed by months or even years. In retrospect, parents can identify the onset of peculiar laughing spells at a very early age. The mean age of onset for gelastic seizures in our series of HH patients with refractory epilepsy (N > 180) is 11 months, with onset before 1 month of age in 45% and before 1 year of age in 81%. However, in this series, seizures have presented as late as age 13 years, emphasizing the clinical diversity within the HH population. Gelastic seizures become less frequent during the first decade and may disappear entirely as other seizure types develop (36). Uncommonly, patients with HH may not develop gelastic seizures until early adulthood (37).

The EEG features associated with HH and gelastic seizures deserve emphasis, specifically because ictal recordings, obtained with the conventional placement of electrodes over the scalp, often show no change in the EEG from the ongoing background, which itself is often normal (38–40). Hence, clinicians need to be alert to this fact so as to not miss the correct diagnosis of epileptic

seizures. Alternatively, nonlocalizing ictal changes may be observed, such as relative flattening of the EEG background, generalized paroxysmal fast activity, or an absence of interictal spikes (4,32,41,42). There is limited utility to video–EEG seizure monitoring for most patients with HH and epilepsy (42).

Gelastic seizures do not usually respond to antiepilepsy drugs (AEDs). Consequently, the timing of surgical intervention (here, this term includes GK radiosurgery) is the major decision point facing the patient, family, and clinician. Brief, infrequent gelastic seizures are not disabling. If the child is making good developmental progress, a decision to withhold surgical intervention is appropriate. However, under these circumstances, the clinical course needs to be observed carefully for any adverse changes.

Epilepsy: Other Seizure Types

Seventy-five percent of patients with gelastic seizures and HH will develop other types of seizures (35,36). The age at which other seizure types will appear varies, but is most likely to occur between 4 and 10 years of age (4). Mullati et al. (36) have reported two to five seizure types for each patient with childhood onset of epilepsy due to HH, and virtually all seizure types have been reported, including infantile spasms accompanied by hypsarrhythmia (43). A review of the published reports regarding lifetime prevalence of seizure types in patients with HH suggests that complex partial seizures occur in 50% to 60% of patients, tonic–clonic seizures in 40% to 60%, atypical absence in 40% to 50%, tonic seizures in 15% to 35%, and "drop attacks" in 30% to 50% (32,35,36,44–46). Seizures associated with HH are usually refractory to management with AEDs (47).

When they occur, complex partial seizures often suggest temporal lobe localization (most frequently) or frontal lobe localization based upon seizure semiology and the results from conventional video–EEG seizure monitoring utilizing scalp electrodes. However, surgical outcomes following temporal lobe or frontal lobe resections in HH patients are universally poor (48).

Freeman et al. (49) have reported the presence of a symptomatic generalized epilepsy phenotype in 12 of 20 patients undergoing HH resection. Their cohort of patients demonstrated features of Lennox–Gastaut syndrome, including tonic seizures, and slow spike-wave and polyspike activities on interictal EEG. Seizure onset (gelastic seizures were the first seizure type in 92% of these patients) began between birth and 24 months of age (mean 0.3 years), while tonic seizures developed between 2 months and 9 years of age (mean 6 years).

The interictal EEG is frequently normal early in the natural history of epilepsy associated with HH, particularly when gelastic seizures may be the only seizure type (32,35,36,42). However, the appearance and subsequent evolution of abnormal EEG findings parallel the worsening of the epilepsy with the emergence of multiple seizure types (4,35,36,49). In the review of Tassinari et al. (35), EEG studies in HH patients with multiple seizure types showed normal results in only 2%, generalized spike or spike-wave findings in 47%, multifocal independent spikes in 18%, and focal spikes (most frequently over the temporal regions) in 33%. Localization of the epileptic process in HH is complex, as seizures (simple partial, complex partial, or secondarily generalized) can originate within the HH and spread to cortical regions. These seizures may or may not have a clinically apparent gelastic component at the onset.

However, the observed changes in seizure type and the evolution of EEG findings also suggest a process of secondary epileptogenesis, in which distant cortical structures begin to generate seizure events that are independent of the original seizure focus (in this case, the HH lesion) (50–53).

Initially, the new focus is dependent upon the presence of the original focus, such that removal of the HH will lead to a decrease in seizure frequency and eventually complete disappearance of seizures arising from the second focus (the "running-down phenomenon") (51). With time, however, usually over a period of years, the second focus becomes entirely independent of the original, inciting focus, such that its removal does not influence the independent epileptogenesis of the second focus. The original concept of secondary epileptogenesis was formulated in the context of temporal lobe epilepsy (54), but epilepsy associated with HH is also consistent with this model (46).

Video–EEG recordings with intracranial electrode implantation have demonstrated that seizure activity developing later in the course of the disease may not arise from the HH lesion (5,49,50,55). Approximately 10% of patients undergoing resective surgery for HH experience the running-down phenomenon, in which seizures of neocortical origin decrease in frequency and eventually stop over a period of weeks or months (56). The running-down phenomenon is observed in 21% to 40% of those HH patients who are ultimately seizure free following surgical resection (at least 1 year of postoperative follow-up) (56,57). Conversely, failure of surgical treatment in HH cases may be attributed to secondary epileptogenesis, as patients with 100% HH lesion resection may continue to have residual seizures in the absence of any other identifiable structural lesion (56).

Although the possibility that there are other cerebral abnormalities must be considered (58,59), most HH patients do not have observable structural abnormalities by high-resolution magnetic resonance imaging (MRI) (56,60–63). The cellular mechanisms for secondary epileptogenesis and the running-down phenomenon are unknown (53).

Cognition and Development

The clinical course of worsening epilepsy and increasingly abnormal EEG findings can also be accompanied by developmental regression and cognitive decline (4,32,64–67). There is a great deal of individual variability in this regard, but approximately 50% of HH patients with the onset of seizures during infancy will experience this deteriorating clinical course (47). Therefore, the degree of impairment demonstrated by any individual patient is a potentially moving target. There are no published series that document this natural history with longitudinal study of a large cohort of patients, but those detailed individual case reports that are available are compelling (64,68).

Cognitive impairment is common in HH patients, with or without the deterioration noted above, occurring in 80% or more of the patients with the intrahypothalamic subtype of HH (35,44,69). Cognitive problems correlate with the presence of epilepsy as a comorbid feature. Patients with parahypothalamic HH typically do not have epilepsy, and also have little or no cognitive impairment (70). The severity of cognitive impairment and developmental retardation correlates with an earlier age of seizure onset (47), and HH lesion size and subtype (69).

Behavior and Psychiatric Symptoms

Patients with epilepsy and intrahypothalamic HH lesions also have a high likelihood to develop clinically significant behavioral and psychiatric problems (4,44,71). These symptoms can present the most significant day-to-day problem for affected families and in some instances lead to placement outside the home. Mood lability and rage attacks are the most frequent symptoms. Patients can have poor frustration tolerance, with acting-out behavior and excessive reactivity to relatively minor stimuli, sometimes with destructive and aggressive features (72).

There is a strong positive association between the incidence of refractory epilepsy, cognitive impairment, and behavioral disturbance in HH patients (47). There is abundant descriptive literature that worsening seizures, cognitive decline, and behavioral deterioration occur simultaneously (4,64,65,73,74). HH is a clinical model for epileptic encephalopathy, although the basic mechanisms responsible for this are unknown.

TREATMENT

Rationale for the HH as the Therapeutic Target

There is now compelling evidence that gelastic seizures arise from HH tissue (66). This idea was slow to gain acceptance, since localization-related seizures were thought to arise exclusively from cortical structures (75,76). However, Kahane et al. (5,55) reported in 1994 that if ictal video–EEG recordings included intracranial monitoring with an electrode in the HH, then the ictal EEG pattern associated with gelastic seizures was initially seen in the HH lesion. This has subsequently been confirmed by multiple additional reports (50,71,77–79). Electrical stimulation of the electrode contacts within the HH can provoke the patient's habitual gelastic seizures (50,77,79). Functional imaging with single photon emission computed tomography (SPECT) has demonstrated increased perfusion in the HH with ictal SPECT imaging (77,80), and ictal imaging with flourodeoxyglucose positron emission tomography has also shown increased metabolism within the HH lesion (59,81). Perhaps, the most important evidences for the intrinsic epileptogenesis of HH lesions are the outcomes observed with surgical resection, in which gelastic seizures can be abolished with successful surgical removal or disconnection.

Absence of Controlled Treatment Trials

There are no controlled trials investigating treatment issues for HH and epilepsy. However, over the past decade, multiple uncontrolled treatment series have been published as HH cases became concentrated at multidisciplinary referral centers (56,57,61,63,82–89).

Antiepilepsy Drugs

There is broad consensus in the literature about the lack of efficacy of AEDs (47). It is likely that the number of medication-responsive patients is underestimated due to the ascertainment bias of epilepsy referral centers, and a small number of cases responsive to AEDs have been reported (8,33,81). However, probably <5% of patients with intrahypothalamic HH and epilepsy achieve complete and sustained seizure control with medications alone. AEDs are often reported to have little impact on the frequency of gelastic seizures but may be valuable by reducing the frequency of other seizure types (66). At this time, no AED has emerged as demonstrating superior efficacy for treating epilepsy associated with HH. As a consequence, AEDs are probably best chosen based upon other factors, including adverse event profile and ease of administration.

Presurgical Evaluation

Video–EEG seizure monitoring is a conventional component of the evaluation process for epilepsy

surgery. However, as the HH lesion is deep in the brain, the results of seizure monitoring with electrode placement over the scalp have limited utility, and these results should be used with caution when planning surgical interventions (42). In general, in HH cases, seizure monitoring is more likely to identify patterns of ictal spread, rather than localizing seizure onset. Even for those patients with secondary epileptogenesis, seizure activity arising from the second focus is dependent (for an undetermined time) upon the presence of the HH (see the discussion of the running-down phenomenon). Accordingly, for almost all patients with HH and epilepsy, the HH lesion is the most appropriate initial surgical target.

Invasive seizure monitoring, with electrodes implanted into the HH as well as multiple other brain regions, was necessary to prove seizure localization in HH cases. However, this type of implantation is technically challenging, has a low but definite risk of surgical complications, and rarely alters the decision-making process. Accordingly, we do not recommend intracranial monitoring for most HH patients.

The timing of surgical intervention is influenced by the emergence of multiple seizures types, often accompanied by cognitive and behavioral regression. Neuropsychological testing is recommended at yearly intervals, if possible, to monitor for changes that may not be immediately apparent in the classroom or in the home.

MRI is the most important modality for diagnosis and surgical planning. For HH patients, MRI should include a coronal T2 fast spin-echo (FSE) sequence with thin cuts and no imaging gaps through the hypothalamus. The presence or absence of structural abnormalities elsewhere in the brain must also be determined.

Surgical Resection/Disconnection

Patients with the parahypothalamic (or pedunculated) subtype of HH usually do not have epilepsy or cognitive disturbance and are medically treated with gonadotropin-releasing hormone agonists (such as leuprolide acetate). Accordingly, surgical resection is usually not indicated for this subgroup of HH patients (8,90).

However, some of the early case reports of resective surgery for patients with CPP secondary to HH happened to include children with gelastic seizures, and improvement in seizure control was noted (91,92). Subsequent reports with HH resection specifically for epilepsy indicated encouraging results for seizure control in some patients and suggested an improved outcome for cognitive and behavioral functioning (67,93,94).

The last decade has seen significant improvements in the operative techniques available for surgical resection and/or disconnection of HH lesions associated with epilepsy. The relative merits of one treatment approach over another are based upon the individual circumstances of each patient, including the surgical anatomy of the HH. The clinical course for each patient, particularly as it relates to any signs of regression or worsening, also influences the decision to use one treatment modality over another, as well as the timing of intervention.

HH Classification and Surgical Anatomy

When considering the surgical options, the classification of HH lesions must be refined beyond the binary model used thus far, specifically, intrahypothalamic and parahypothalamic HH subtypes. Several authors have proposed classification schemes for HH lesions, including Valdueza et al. (8),

Regis et al. (62), and Delalande and Fohlen (82,95). Regardless of the classification system that is used, our experience suggests that there is a relatively smooth continuum between these subtypes. However, while the advantages of one classification scheme over another are debatable, each of these schemes addresses an important issue: the surgical anatomy of the HH lesion. Currently, our preference is to utilize the Delalande classification system (82,95) (Fig. 87.2).

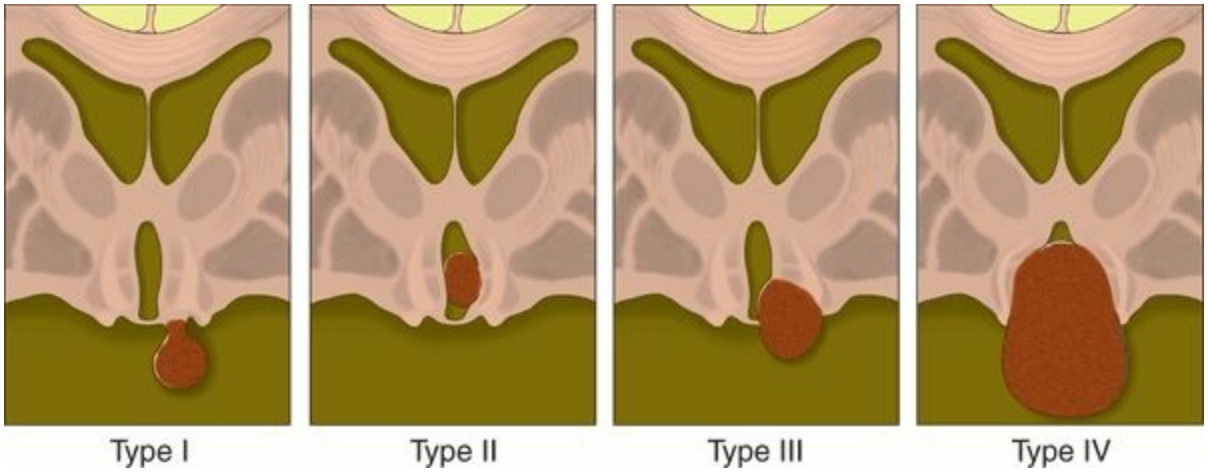

Figure 87.2. Classification system for HH, proposed by Delalande and Fohlen (95). Type I lesions have a horizontal base of attachment, below the normal position of the floor of the third ventricle. If attached by a narrow stalk to the tuber cinereum, they result in CPP, whereas more posterior attachment to the region of the mammillary bodies may result in epilepsy. Larger type I lesions can result in both CPP and epilepsy. Type II lesions have a vertical plane of attachment to the wall of the third ventricle, completely above the normal position of the floor of the third ventricle. Type III lesions may be unilateral or bilateral and have a plane of attachment that extends both above and below the floor of the third ventricle. Consequently, these lesions have both vertical and horizontal planes of attachment when viewed on a coronal sequence. Type IV lesions are termed "giant," though features clearly distinguishing them from type III lesions were not provided (95). (Copyright Barrow Neurological Institute, 2013.)

Selecting the optimal surgical approach must take into account the location and size of the HH lesion, and most importantly, the anatomy of its base of attachment to the hypothalamus (82,95–98). Type I lesions in the Delalande system are attached to the inferior (horizontal) surface of the hypothalamus. This type includes those HH lesions with a thin peduncle or stalk, often attached to the tuber cinereum, and associated with only with CPP, but can also include HH lesions with a broader or more posterior base of attachment that are associated with epilepsy. These lesions are best resected or disconnected by an inferior or pterional approach. Conversely, Delalande type II lesions have a vertical plane of attachment within the third ventricle and are best suited to a superior surgical approach to resection (transcallosal interforniceal or transventricular endoscopic [TE]), stereotactic thermal ablation, or GK radiosurgery. Delalande types III and IV have both vertical and horizontal planes of attachment (both above and below the normal position of the floor of the third ventricle). The superior approaches noted above may be adequate, but some of these cases may require a combined approach, with either simultaneous or staged resections.

Pterional Approach

Until 2001, resective surgery for HH was almost always performed with a surgical approach from below the lesion. As reported by Nishio et al. (94,99) and Machado et al. (67) in detailed case studies, resection of the HH via a pterional approach had the potential to control seizures and improve the patient's cognitive and behavioral level of functioning. Other surgical approaches for the HH lesion from below have also been reported, including orbitozygomatic (98), subfrontal (71), and

lamina terminalis approaches (71). In those instances where a complete resection via a pterional approach is possible, seizure outcomes are good (66% seizure free with complete resection of the lesion) (47,86). Pterional resection (in our hands usually an orbitozygomatic approach) is still the most appropriate means of resection for HH cases with epilepsy and type I lesions (86).

However, the pterional approach is not suited to the surgical anatomy of most HH cases, where a substantial component of the HH has a vertical plane of attachment within the third ventricle (Delalande types II to IV). Additionally, the complication rate, including stroke and cranial nerve injury, was substantial in earlier series (47,71). These approaches traverse territory with vascular structures, including the internal carotid artery, anterior and posterior communicating arteries, and their associated perforating branches. The optic tracts and chiasm and the third cranial nerve are also vulnerable (96).

Transcallosal Anterior Interforniceal (TAIF) Approach

Although utilized previously for other pathologies (100), Rosenfeld et al. (6,97) in Melbourne, Australia, were the first to utilize the TAIF approach to the third ventricle to resect HH lesions in patients with refractory epilepsy. This approach, utilizing microsurgical technique and intracranial guidance systems, allows for excellent direct visualization of the HH and its base of attachment within the third ventricle. Rosenfeld's modification of the transcallosal approach to the third ventricle, with a more anterior, transseptal trajectory, minimizes retraction of the columns of the fornix and also avoids injury to the internal cerebral veins, located more posteriorly (97).

The Melbourne group has published a series of 29 consecutive patients undergoing intrahypothalamic HH resection via the TAIF approach (57). Age at surgery ranged from 4 to 23 years (mean age 10 years). All patients had multiple seizure types, including gelastic seizures. Coexisting morbidities included a history of CPP in 13 (45%), intellectual disability in 21 (72%), and behavioral problems, most frequently rage and aggression, in 18 (62%).

At least 95% resection of HH lesion volume was achieved in 18 patients (62%). Postoperative follow-up for a minimum of 12 months showed 15 patients (52%) who were completely seizure free and 7 patients (24%) with at least a 90% improvement in seizure frequency. Surgical resection was generally well tolerated. Small, unilateral ischemic strokes of the thalamus and internal capsule occurred in two cases (7%), both with complete recovery, and transient third cranial nerve injury was reported in one patient. The majority of patients (55%) developed mild, asymptomatic hypernatremia postoperatively, but no patients had persistent disturbances in fluid or electrolyte homeostasis. Five patients (17%) required thyroid hormone replacement therapy following surgery. Increased appetite with weight gain was reported in 45% of patients but resolved in half of these with time.

Impairment of short-term memory was, however, a significant issue. The TAIF surgical approach, despite its more anterior trajectory, requires retraction of the columns of the fornix. Transient memory disturbance was noted in 14 patients (48%) during the immediate postoperative period, but residual difficulties were reported by only 4 (14%). Attention and behavior were noted to improve in many of the patients in this series, but further details were not available (57).

Very similar results were subsequently reported by Ng et al. (56) at the Barrow Neurological Institute in Phoenix. In this series of 26 consecutive patients undergoing TAIF, 54% were completely seizure free. The likelihood of complete seizure freedom (with at least 1 year of postoperative follow-up) had a positive correlation with the percentage of HH lesion volume that was successfully

resected ($P < 0.05$). The risk and type of surgical complications were also similar. Notably, transient short-term memory impairment was noted in 58% of the patients but persisted in only two patients (8%).

Transventricular Endoscopic Approach

Transcortical TE resection and/or disconnection is also a treatment option for HH patients with refractory epilepsy (61,71,82,85,95,101–104). Barrow has reported a series of 37 consecutive HH patients treated with endoscopic resection/disconnection for treatment-resistant seizures (61). All patients had at least 1 year of follow-up. The mean age at the time of surgery was 11.8 years (range 0.7 to 55 years). All patients had a history of gelastic seizures at some time point during their clinical course, and 29 (78%) had active gelastic seizures at the time of surgery. Twenty-eight patients (76%) had type II HH lesions by the Delalande classification, and the median lesion volume was 1.0 cm^3. (In comparison, in the Barrow series of transcallosal resections noted above, 42% had a type II lesion, and the median HH lesion volume was 2.4 cm^3, reflecting the different selection criteria for each approach (56).)

Median follow-up was at 21 months. Eighteen patients (49%) were completely seizure free, while seizure frequency was reduced at least 90% in an additional eight patients (22%). Twelve patients were determined to have 100% of their HH lesions resected. Of these, eight (67%) were 100% seizure free (61).

As observed with the TAIF approach, most patients tolerated endoscopic resection well. However, some differences from the TAIF approach were observed, with a significantly shorter total length of hospital stay in the endoscopic group (mean 4.1 days) versus the previously reported transcallosal group (mean 7.7 days, $P < 0.001$) (56,61). Only five patients (14%) experienced postoperative short-term memory loss, but this appeared to be a permanent residual problem (by history) in three (8%), which is comparable to the TAIF approach. No patients with endocrine disturbance, either transient or permanent, were observed. However, eleven patients (30%) showed small unilateral thalamic infarcts on diffusion-weighted MRI sequences. These were clinically asymptomatic in nine of eleven cases and the remaining two patients made a complete clinical recovery. These infarcts were attributed to disruption or injury to small thalamic perforators as a result of local brain movement with excursions of the endoscope.

Wethe et al. (105) at Barrow have recently reported the postoperative neuropsychological testing results for patients with HH and treatment-resistant epilepsy. Of the cohort of 32 patients, 63% underwent endoscopic resection. For the entire cohort, there was a statistically significant improvement in full-scale intelligence quotient (IQ), with a preoperative mean of 83.0 and postoperative mean of 91.3 ($P < 0.001$). For the entire cohort, there was no significant difference for preoperative and postoperative scores relating to learning and memory. Improvement in cognitive functioning was most likely to occur in patients who were younger at the time of surgery (and had a shorter lifetime duration of epilepsy) and in those with lower scores with preoperative testing (105).

For those HH patients who require surgical resection/disconnection from above, the factors that favor the endoscopic approach include smaller lesions, unilateral attachment, adequate space within the third ventricle to manipulate the endoscope, and adequate size of the lateral ventricle and foramina of Monro for safe instrumentation. Factors that are more favorable for the TAIF approach include a younger age at the time of surgery (the columns of the fornix and leaves of the septum tend to fuse with age), larger lesions, and bilateral attachment.

Gamma Knife Radiosurgery

GK radiosurgery is now established as an ablative therapy for patients with HH and treatment-resistant epilepsy (55,83,101,106–113). GK is noninvasive and can deliver a clinically effective dose of radiation to a small volume of tissue via a large number of independent trajectories, with little or no injury to surrounding brain.

Regis et al. (114) have described a series of 27 patients with intractable epilepsy and HH with at least 3 years of follow-up after GK therapy. GK delivers its maximal destructive energy to the interior of the targeted lesion, and the intensity of energy delivery falls off toward the periphery of the lesion. A dose of at least 17 Gy is ideally delivered to the entire lesion. The peripheral treatment margin (usually referred to as the 50% isodose margin) is matched to the outer edge of the HH lesion, but the dosimetry map may need to be modified in proximity to the optic tracts or other radiosensitive structures.

A maximal threshold of 10 Gy to the optic tracts and 8 Gy to the optic chiasm and optic nerve was utilized for treatment planning for this prospective treatment study (114). In this series, the median HH diameter was 0.95 cm (range 0.5 to 2.6 cm) and the median volume of the marginal isodose was 0.65 cm^3 (range 0.13 to 2.67 cm^3). The median radiosurgery dose to the 50% isodose margin was 17 Gy (range 13 to 26 Gy, mean 16.9 Gy). Of the 27 patients reported, 10 (37%) were completely seizure free and an additional 6 (22%) were substantially improved with only rare gelastic seizures.

Efficacy is delayed from the time of GK treatment. Initially after treatment, seizure frequency may be improved, or patients may continue to have seizures at their pretreatment baseline. Several months following therapy, an increase in seizure frequency, lasting for only a few days up to several weeks, may be observed. Subsequent to this, patients responding to treatment will experience progressively fewer seizures, with complete seizure control after a period of 6 to 24 months. Regis et al. recommend waiting 36 months from the time of treatment to assess final efficacy.

GK has an excellent adverse event profile. Most patients have no complications or side effects attributable to GK treatment. No patients among the 27 treated were reported to have a permanent complication (114). Three patients (11%) experienced transient poikilothermia. In contrast to side effects that may be seen with resective surgery, there were no patients in this series that experienced weight gain, endocrine disturbance, adverse changes in cognition, or short-term memory complaints. The disadvantage of GK is the delayed onset of action for controlling seizures and the more limited anatomical spectrum of HH lesions to which it is suited.

GK is an important treatment option for many patients with HH and epilepsy, and should be the preferred treatment modality for smaller lesions, particularly for patients who are clinically stable and capable of tolerating the delay in efficacy to obtain improved seizure control. It is a less desirable approach for those patients who are progressively worsening with their epilepsy or experiencing cognitive decline or behavioral deterioration with uncontrolled seizures. Additional study to define the optimal role of GK compared to other treatment modalities is required.

Stereotactic Thermal Ablation

Radiofrequency thermal ablation has been described in a relatively small number of patients (37,77,79,87,115–118). This technique involves stereotactic placement of a depth wire into the HH target and then causing a destructive thermal lesion by physically heating the probe tip. Most of these publications are single case reports.

Kameyama et al. (87) have reported a series of 25 HH patients undergoing stereotactic thermal ablation with a follow-up interval of at least 6 months. Mean age was 14.8 years (range 2 to 36 years) at time of treatment. All patients had at least daily gelastic seizures, and 22 (88%) had multiple seizure types. HH lesions were classified as intrahypothalamic in 10 (corresponding most closely to Delalande type II; 40% of treatment cohort), parahypothalamic in 6 (corresponding to Delalande type I; 24%), and mixed in 9 (corresponding to Delalande types III and IV; 36%).

The radiofrequency thermocoagulation probes were placed with MRI-guided stereotaxis and heated to 74°C for 60 seconds, resulting in a 5-mm spherical lesion. Targeting prioritized the HH lesion at the point of attachment, maximizing the potential for disconnection, along with the central region of larger lesions. Up to 4 lesions could be created by moving the probe within its track. Additional passes were required for most patients to ablate the intended target for each individual patient (mean lesions per patient 7.2 [range 1 to 18] and mean tracks per patient 3.8 [range 1 to 8]). Six patients (24%) required a second thermocoagulation procedure to obtain final results.

Complete freedom from seizures (Engel class I) is reported in 76%. Gelastic seizures disappeared in 92% of patients. Results were more favorable in the pediatric subgroup with complete seizure control in 16 of 18 patients (89% Engel I), whereas seizures were completely controlled in only 3 of 7 adults (43% Engel I). There were no permanent complications. Transient problems following thermocoagulation treatment included hyperthermia (n = 4 patients), hyperphagia (n = 2), hyponatremia (n = 4), Horner's syndrome (n = 3), and short-term memory disturbance (n = 2). There was a significant increase in IQ or developmental quotient postoperatively (preoperative mean 67.6 and postoperative mean 75.9; $P < 0.0001$).

Stereotactic thermal ablation is emerging as the preferred treatment modality for many HH lesions, but expertise is available in a small number of centers. Further research is required to define the boundaries within which stereotactic thermal ablation is the optimal surgical approach versus microsurgical or endoscopic resection.

A recent technical innovation on the use of stereotactic thermocoagulation utilizes laser energy to heat the tip of the stereotactic probe and has the added advantage of near real-time MRI thermography to follow the delivery of the treatment dose with predetermined safety parameters (119). Curry et al. (120) have reported two HH patients treated with this device, both of whom were completely free of seizures with brief follow-up (5 and 2 months, respectively) at the time of initial publication. This technique (MR-guided laser interstitial thermal therapy) appears promising, but thus far, a limited number of patients with HH have been treated worldwide. Additional peer-reviewed research reports with a larger cohort and long-term follow-up are anticipated (120).

Interstitial Radiosurgery

Interstitial radiosurgery with stereotactic implantation of ^{125}I radioactive seeds has also been proposed as an ablative therapy for HH associated with epilepsy (63,121). Schulze-Bonhage et al. (121) in Freiburg, Germany, have reported a series of 24 patients (mean age 21.9 years), all of whom had treatment-resistant gelastic seizures, in addition to other seizure types. Mean HH lesion volume was 1.2 cm^3.

The treatment plan was designed to deliver a dose of 60 Gy at the outer margin of the HH, followed by radioisotope seed removal. Thirteen of twenty-four patients (54%) required at least one reimplantation for a second course of therapy if the response to the initial course was unsatisfactory. With follow-up of at least 2 years, 12.5% were seizure free (Engel I outcome) while 41.7% had at

least a 90% improvement in seizure frequency (121). Treatment response is described as occurring within 8 weeks following treatment. No complications were noted, but follow-up MRI 3 months after treatment revealed local cerebral edema in five of twenty three patients (22%), in some instances associated with headache and fatigue. Neuropsychological testing prior to implantation and at least 1 year following treatment showed no significant changes with groupwise analysis of the treatment cohort.

Staged Procedures for Giant HH

For the purposes of this discussion, giant HH lesions are defined as exceeding a volume of 4 cm^3, as determined by measuring the diameter of the lesion in the three major axes and applying the formula for determining the volume of an ellipsoid [vol = π × height × length × width/6]. HH lesions of this size account for 12% of our surgical series (22 of 180 patients). These lesions are problematic as patients with giant HH are at higher risk for severe epilepsy (122), developmental impairment (69), and CPP (13,60).

They are also challenging lesions with respect to surgical therapy, relating more to the nature of their attachment to the hypothalamus rather than to their size alone. Most giant HH lesions have both vertical (above the normal position of the floor of the third ventricle) and horizontal (below the normal position of the floor of the third ventricle) planes of attachment, and consequently, no one approach, from either above or below, may enable the surgeon to safely visualize the plane of attachment and adjacent structures (Fig. 87.3).

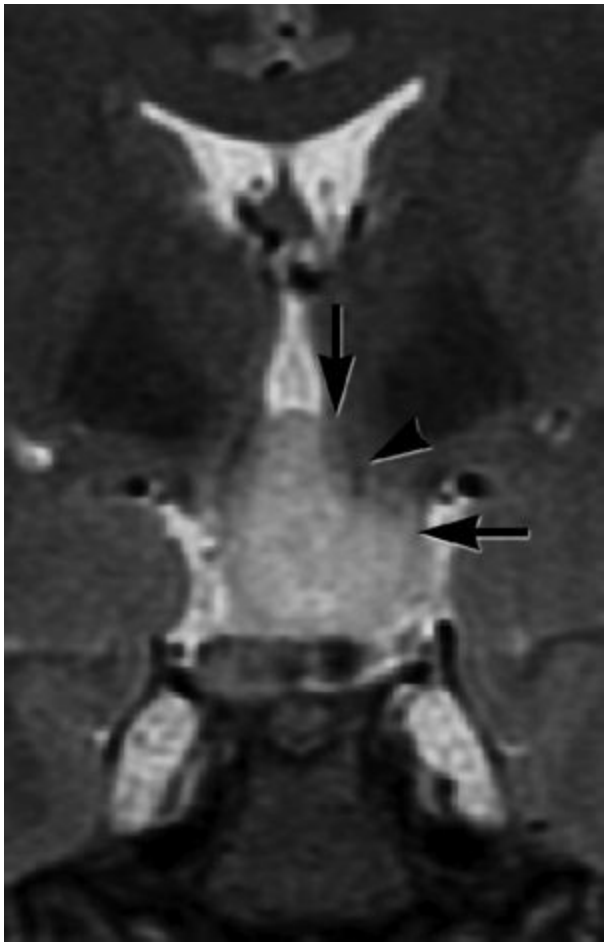

Figure 87.3. Delalande type IV (giant) HH, as shown on coronal T2-weighted FSE sequence, illustrating the complexity of attachment for these large lesions. There is a largely vertical plane of attachment within the third ventricle (vertical black arrow) and a largely

horizontal plane of attachment below the hypothalamus (horizontal black arrow). Note the dark signal corresponding to the left descending column of the fornix (black arrowhead), which partially traverses the HH to lead to the mammillary body (located posterior to this slice). (Copyright Barrow Neurological Institute, 2013.)

Gore et al. (123) described a "combined" approach in which two teams operated simultaneously, one approaching from above and one from below. This had the advantage of allowing the surgeons to visually meet as the lesion was resected and disconnected, but the logistics and need for space with two different surgical fields proved daunting. We now advocate a "staged" approach, in which two operations are planned roughly a week apart. The surgical modality (open microsurgical resection/disconnection, endoscopic resection/disconnection, or stereotactic thermal ablation) need not be the same for each stage but rather should be chosen based upon the unique surgical anatomy of each case.

Reoperation After Subtotal Surgical Treatment

Patients undergoing epilepsy surgery with unsatisfactory outcome may be candidates for a second operation. There are multiple possible causes for surgical failure, but incomplete removal of the primary epileptic focus is common (124). With respect to the treatment of HH, the complication rate from injuring normal hypothalamus and adjacent structures is high. Consequently, even with MR-guided intracranial navigation systems, the prudent neurosurgical approach is to err on the side of a more conservative resection and minimize the risk of injury to normal hypothalamus. In one representative study in this regard, Ng et al. (56) reported that only 9 of 26 (35%) of patients undergoing the transcallosal interforniceal approach had 100% resection when evaluated with volumetry on postoperative MR imaging (of these, 89% were seizure free).

For large HH lesions, disconnection, rather than complete resection, is an appropriate surgical strategy. However, the same principle applies: 100% disconnection is the goal, but real-world results may fall short of this target. In the series just mentioned, for those with residual tissue, only 4 of 17 (24%) had 100% disconnection with high-resolution postoperative imaging (56).

Pati et al. (125) have recently reported their experience with reoperation for HH. In this retrospective study, 21 of 157 consecutive HH patients (13%) underwent a second surgical procedure with the intent of removing or completely disconnecting residual HH. Subsequent to the second surgery, all patients had at least 6 months of follow-up: 2 patients (10%) seizure free, 4 (19%) with >90% improvement in seizure frequency, 10 (48%) with 50% to 90% improvement in seizure frequency, and 4 (19%) no change.

Currently, we consider GK radiosurgery as an attractive option for those undergoing a second procedure for residual HH after microsurgical resection or stereotactic thermal ablation.

Alternative Therapies

A limited number of HH patients have been reported following treatment with alternative therapies such as the ketogenic diet (KD) (74,126), vagus nerve stimulation (VNS) (14,127), corpus callosotomy (48,68,128), and deep brain electrical stimulation (DBS) (50,68,129–131). With the possible exception of corpus callosotomy, which should be discouraged in this patient population based upon unsatisfactory published reports, the other alternative therapies should be regarded as unproven therapeutic options (KD and VNS) or investigational treatment (DBS).

CONCLUSION

There has been tremendous progress in our understanding of HH over the past 15 years. Although uncommon, the intrahypothalamic subtype of HH can present with catastrophic epilepsy of early childhood. Many of these patients will experience a deteriorating course with worsening of seizures, cognitive functioning, and behavior. We now know that the HH itself is intrinsically epileptogenic and surgically treatable. A number of different therapeutic options are now available. While comparative trials have not been performed, it seems increasingly clear that no one treatment modality is appropriate for all HH patients. Treatment selection is based upon the individual circumstances of each patient, and each option is discussed with the family. The most important factors for consideration include the stability of the patient (seizure severity and the presence or absence of clinical deterioration) and the surgical anatomy of the patient's HH lesion.

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CHAPTER 88 CORPUS CALLOSOTOMY AND MULTIPLE SUBPIAL TRANSECTION

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Multiple subpial transection (MST) and corpus callosotomy share some common traits. Both are palliative surgical disconnection procedures that are effective in the treatment of medically intractable epilepsy in select patient populations. They both work by disrupting neuronal synchrony of epileptic activity in a critical population of neurons to stop the expression of seizures. MST breaks up the epileptic neuronal synchrony among cortical columns disrupting the epileptic focus itself by the transection of the horizontal fiber system disrupting the critical neuronal synchrony necessary to produce an epileptic spike. Corpus callosotomy disrupts the hemispheric synchrony that is critical in the expression of some generalized seizures such as atonic, tonic, and generalized tonic–clonic seizures. Both procedures are occasionally curative but effectively treat epileptic seizures that cannot be helped by focal cortical resection.

CORPUS CALLOSOTOMY

Corpus callosotomy was first introduced as a surgical treatment for medically intractable epilepsy by Van Wagenen and Herren in 1939 (1). The ultimate goal of callosal section is to abolish the bilateral synchrony (or near-synchrony) of cortical epileptiform activity, which can result in seizures with bilateral motor manifestations, such as atonic, tonic, myoclonic, and tonic–clonic seizures. However, as cited by Blume (2), synchronous corticofugal epileptic discharges can also disrupt brainstem mechanisms affecting posture and tone of proximal limb and axial muscles, leading to atonic or akinetic seizures. Here, we briefly review some of the more relevant studies that have played an important role in the development and refinement of the techniques used in corpus callosotomy.

Neurophysiologic Basis

The corpus callosum is the most important interhemispheric commissural connection in the brain, with approximately 180 million axons in humans (3). These axons connect homotopic as well as heterotopic cortical regions (4) and exert both inhibitory and excitatory effects (5). This latter property of the corpus callosum has been suggested as an explanation for the clinical reports of increased partial seizures after callosotomy in humans (6,7) and in animals (8). Studies in rhesus monkeys have shown that section of the anterior two-thirds of the corpus callosum resulted in the development of partial seizures five times faster than in nonbisected animals (9). In the amygdala kindling model of the cat, Wada and Sato (10) reported that section of the corpus callosum accelerated the final stages of generalized convulsions.

The corpus callosum provides interhemispheric connection, unifying of certain motor functions and sensory perceptions of the axial or midline visual and somatosensory world. Axons connecting

the frontal lobes occupy a rostral position, whereas those connecting parietal, temporal, and occipital cortices are positioned more caudally, in that order.

The role of the corpus callosum in epileptogenesis is evident from various studies in animals. In the feline model of generalized epilepsy, Musgrave and Gloor (11) demonstrated the loss of bilateral synchrony of spike and slow-wave discharges following the total section of the corpus callosum and anterior commissure. Callosal section in the photosensitive baboon, Papio papio, resulted in a decrement in the synchronization of epileptiform discharges and of seizures triggered by photic stimulation (12,13). In a study carried out on four monkeys by Kopeloff et al. (8) in 1950, seizures generated by unilateral application of aluminum oxide cream had a bilateral motor expression. Following callosal section, their clinical manifestations were restricted to a distribution contralateral to the seizure focus.

It must be remembered that although the corpus callosum may be the most important anatomic structure for the interhemispheric spread of epileptic activity, it is not the only one. Anterior and posterior commissures, thalamus, and brainstem structures may all play a role in the spread of discharge from one hemisphere to the other. Suppression of synchronized epileptic activity is routinely and repeatedly seen in acute models of generalized seizures. However, in most models of chronic epilepsy after callosotomy, some synchronized epileptic activity returns over the ensuing months. This suggests that the epileptic activity utilizes alternate pathways over time. In patients who demonstrate lateralized epileptic activity postoperatively, there is a general tendency for these discharges to synchronize again over the first postoperative year.

Studies in Humans

The first series of 10 patients was published in 1940 by Van Wagenen and Herren (1). However, the real interest in this procedure developed almost 30 years later when Wilson et al. (14) reported on the Dartmouth series of callosotomies. In general, clinical patient series have replicated animal studies, demonstrating the efficacy of callosotomy in treating seizures requiring bilateral synchrony for their clinical expression. In 1985, Spencer et al. (15) reported the abolition of a bilaterally synchronous ictal onset in 5 of 5 patients who underwent a complete section of the corpus callosum, but in only 5 of 10 patients who underwent a two-thirds anterior section. In contrast, interictal bisynchronous discharges persisted even after a complete section, albeit with a significantly lower frequency. A significant reduction in bisynchronous discharges has been reported in several other patient series (14,16–19). However, as with animal studies, there are a number of reports of an increase in partial seizures (2,20–24), and in some cases, the seizures are described as being more severe (25). Other authors report a conversion of generalized to partial seizures following callosotomy.

Indications

In 1985, Williamson suggested the use of corpus callosotomy to treat the following disorders: (i) infantile hemiplegia and its forme fruste, (ii) Rasmussen syndrome, (iii) Lennox–Gastaut syndrome, and (iv) frontal lobe epilepsy. However, its primary use has been in the treatment of patients with Lennox–Gastaut syndrome.

Efficacy

In general, the purpose of corpus callosotomy is to palliate the patient's intractable seizure condition by decreasing or abolishing the most incapacitating of generalized seizures and improving the patient's quality of life. Overall, 50% to 77% of patients with Lennox–Gastaut syndrome have been reported to have a satisfactory outcome, defined as seizure reduction of 50% to 80% or more in various reports. The best response has been observed in patients with "drop attacks" presenting as tonic and/or atonic seizures. However, there is evidence that patients with atonic seizures derived a greater benefit from the procedure than did those with tonic seizures (18,19,22,26–28). In 1996, Phillips and Sakas (29) reported the results of anterior callosotomy in 20 patients. They divided outcome into freedom from seizures and significant reduction (70%) of seizures. Using these criteria, 16 of 20 patients (80%) had significant improvement of at least a 70% decrease in seizure frequency. Patients with atonic seizures (11–13) had the best outcome, and favorable results were found in 14 of 18 patients with generalized tonic–clonic seizures.

Nei et al. (30) reported a series of 53 patients who underwent an anterior or complete corpus callosotomy. For those with generalized tonic–clonic seizures, almost 80% had ≥50% decrease in generalized tonic–clonic seizures and 60% had >80% reduction. Complications were seen in 21% with 3.8% of these being permanent. Gates et al. (31) reported that tonic seizures associated with an ictal electroencephalographic pattern consisting of an electrodecremental response were associated with a very good outcome in 92% of patients aged 10 years or older. However, this association of seizure type was not predictive of outcome in younger patients (16,31).

Corpus callosotomy has yielded a significant reduction of generalized tonic–clonic seizures in 50% to 80% of patients treated with the procedure (6). Oguni et al. (28) and Spencer et al. (7) have suggested that patients with secondarily generalized tonic–clonic seizures in the presence of electroencephalographic evidence of secondary bilateral synchrony and clinical or neuroradiologic evidence of focality derive greater benefit than do those with generalized tonic–clonic seizures without these characteristics. This view has not been universally accepted. Phillips and Sakas did not find neuroimaging or electroencephalographic findings to be predictive of outcome (29).

Patients with complex partial seizures are less likely to respond to this procedure; approximately 40% achieve a significant seizure reduction. Moreover, simple partial seizures are rarely affected by callosotomy. Corpus callosotomy had been used in patients with frontal lobe seizures in whom the seizure focus could not be lateralized because of very rapid spread of epileptiform activity. Clarke et al. (32) in 2007 found that a planned palliative corpus callosotomy may help identify a resectable epileptic focus. However, Purves et al. (33) reported six such patients who underwent a two-thirds anterior callosotomy without favorable results.

Jenssen et al. (34) reported nine patients with presumed idiopathic generalized epilepsy who underwent corpus callosotomy. Four patients had an 80% decrease in generalized tonic–clonic seizures, and eight had a 50% decrease in generalized tonic–clonic seizures.

Corpus callosotomy may be performed as a partial resection involving the anterior two-thirds (in the majority of cases) or a complete section. The decision to use one technique rather than the other remains controversial. Studies by Cendes et al. (35), Harbaugh et al. (27), and Reutens et al. (36) showed no differences in seizure control between complete and partial sections. However, Spencer et al. (7) reported elimination of generalized tonic–clonic seizures in 77% of patients who underwent a complete section of the corpus callosum, compared with 35% of patients who underwent a two-thirds anterior callosotomy. Rahimi concurred that in patients with secondarily generalized intractable epilepsy, complete callosotomy was superior to partial callosotomy (37). Following a reanalysis of 50 callosotomy patients, Spencer et al. (28) concluded that a two-thirds anterior section

should be considered for patients with tonic, atonic, or myoclonic seizures, whereas a complete section should be reserved for patients with incomplete response to the two-thirds anterior section. Maehara and Shimizu advocate a complete callosotomy, especially in children and in adults with widespread epilepsy (38). Jalilian et al. (39) reported on 27 children and adults and found that complete callosotomy results in a superior (class I–III) outcome of 91% versus anterior 2/3 callosotomy of 75% (class I–III) outcome. In any event, when a complete section is considered, it should be carried out as a two-stage procedure to minimize complications.

Impact on Quality of Life

Rougier et al. (40) reviewed the literature on the efficacy of corpus callosotomy and its effect on quality of life. They found a favorable outcome, defined as a 50% reduction of seizures reported in 60% to 80% of all patients with atonic and/or tonic seizures resulting in falls. Favorable outcomes for tonic–clonic seizures vary from 40% to 80%. Complex and simple partial seizures were significantly improved less often. Improvements in quality-of-life indices did not always correlate with reduction in seizure frequency. The length of time for which patients had refractory epilepsy and its deleterious effect on cognitive and social function were important variables in predicting quality-of-life improvements. In a study conducted at the Cleveland Clinic, 9 of 17 patients experienced a >80% reduction in their targeted seizures, and 15 of 17 reported satisfaction with the surgical outcome. However, improvements in alertness and responsiveness, not necessarily reduction in seizure frequency, were most closely associated with satisfaction with surgical outcome (41). Papo et al. (41) reviewed 36 patients with intractable seizures of mixed seizure types. Twenty-seven had an anterior callosotomy; eight had a complete callosotomy in two stages, and one had a posterior callosotomy. Of the 36 patients, 30 had adequate follow-up to report meaningful results. Fourteen had excellent results (defined as more than 90% reduction in targeted seizure type), five had good results (more than 50% reduction), six had poor results (<50% reduction), and five showed no change. Similar to other reports, global measures of quality of life did not always coincide with improvement of seizure frequency. In some patients with excellent seizure results, there was no clear change in quality of life. The authors suggest that this might be related to the long duration of uncontrolled seizures and their effect on cognitive function (41). In the series reported in 2013, Park et al. (42) concurred that there was a disconnect between corpus callosotomy's effectiveness in reducing seizures and improvement in quality of life in adults. Gilliam et al. (43) have also noted that overall clinical improvement did not always correlate with seizure reduction.

Asadi-Pooya et al. (44) document that corpus callosotomy's effectiveness and low permanent morbidity are demonstrated by over six decades of experience with this procedure. They note that besides seizure reduction, quality of life often improves.

VAGUS NERVE STIMULATION VERSUS CORPUS CALLOSOTOMY

While vagus nerve stimulation (VNS) is increasingly used for treatment of various seizure types in the Lennox–Gastaut syndrome, there have been a number of recent studies comparing VNS with corpus callosotomy. You et al. compared 14 patients with total callosotomy versus 10 patients with VNS implantation and followed them for more than 1 year. All patients had multiple seizure types, primarily atonic seizures and tonic seizures. Efficacy in seizure reduction was similar in the two

groups. They reported that 64.3% in the callosotomy group versus 70% in the VNS group had a 50% reduction in targeted seizures (45). The authors concluded the efficacy and safety of VNS and corpus callosotomy were comparable. This differs somewhat from Nei's report that compared corpus callosotomy (n = 53) with VNS (n = 25) with refractory generalized seizures (generalized tonic–clonic, tonic, and atonic). 79.5% in the corpus callosotomy group had 50% or greater response versus 50% in the VNS group. However, morbidity in the corpus callosotomy group was higher (21% vs. 8%), although only 3.8% of the complications in the corpus callosotomy group were permanent. The authors concluded that both procedures were efficacious, yet corpus callosotomy had greater efficacy, though with transiently higher morbidity (30).

Surgical Technique

Under general anesthesia, the patient is placed in the supine position with pressure points padded. The head is placed in pin fixation in neutral position with the neck slightly flexed. The hair is clipped and the skin prepped. A lumbar drain may be placed to aid in retraction of the midline. A variety of skin incisions may be used for anterior callosal sectioning, all of which give access to the anterior midline. A coronally oriented skin incision 2 cm anterior to the coronal suture exposing both sides of midline will give the needed exposure. Usually, this incision should expose more right side than left because approach from the right allows retraction of the nondominant hemisphere. Hodaie et al. (46) propose the use of image guidance in part to analyze the parasagittal veins in order to decide the side of entry. A craniotomy is performed just anterior to the coronal suture, crossing midline to expose the sagittal sinus. The procedure can be done without exposing the sinus, but retraction of the sinus is then not possible and sinus bleeding is more difficult to control if encountered. The dural flap is based on the sinus, and retraction of the dura allows retraction of the sinus. Although the exposure is anterior to the coronal suture, all but the most insignificant bridging veins should be spared. Planning the approach and exposure may be aided by examining preoperative magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA) scans (Figs. 88.1 through 88.3). If a bridging vein complex does not allow retraction because of a far lateral entry of the vein into the sagittal sinus, a dural incision may be made in the form of a triangle around the laterally entering vein to allow retraction of the dural flap without disturbing the vein.

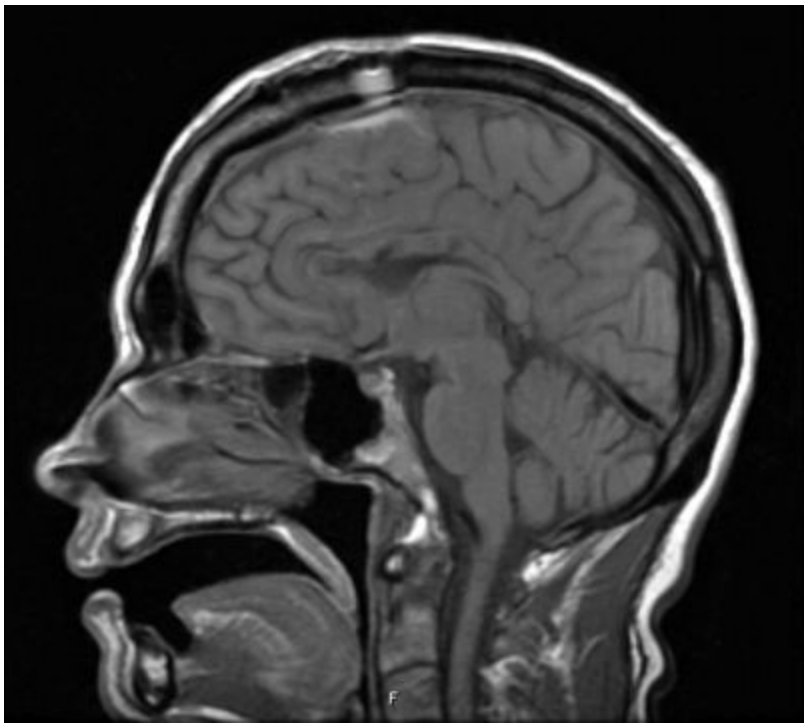

Figure 88.1. Sagittal T1 magnetic resonance image showing an anterior two-thirds callosotomy.

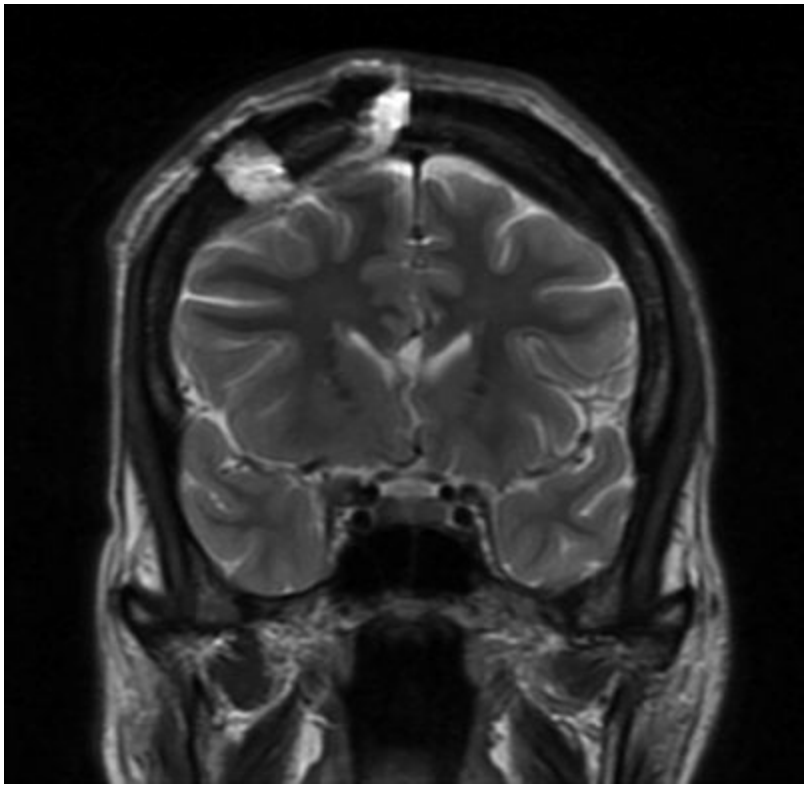

Figure 88.2. Coronal T2 magnetic resonance image showing the position of the craniotomy and the division of the genu into the midline cavum.

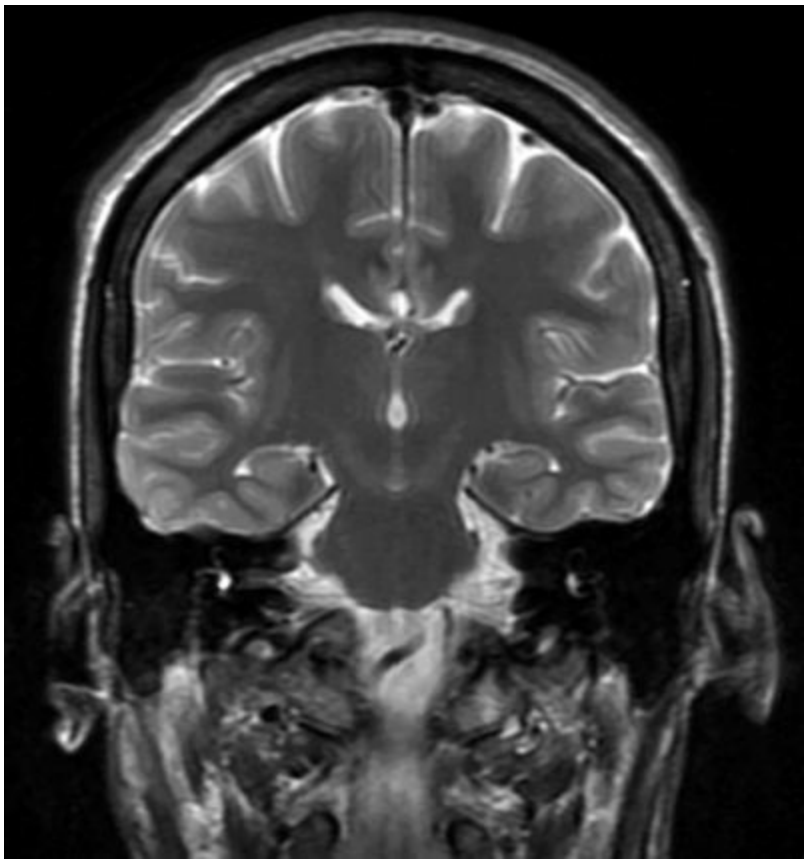

Figure 88.3. Coronal T2 magnetic resonance image showing division of the posterior body of the corpus callosum. Note the position of the fornices below the corpus callosum.

Once an unencumbered view of the intrahemispheric fissure is obtained, the medial aspect of the exposed frontal lobe is covered with moist cottonoids, and self-retaining retractors are gently advanced. The falx is followed down the midline until the cingulate gyri are encountered. An error that is sometimes made is to mistake this view of the adherent cingulate gyri for the corpus callosum. The cingulated gyri are separated under magnification in the midline, exposing the corpus callosum and the pericallosal arteries. Once this view is obtained and the retractors are set, a final check of the anterior exposure confirms the exposure of the anterior corpus callosum if the genu is visible.

The actual division of the anterior corpus callosum is done with a microdissection instrument and gentle suction. This should begin in the midline of the callosum just posterior to the genu. Great care is taken to separate, but not disturb, the pericallosal arteries. At this level, certain landmarks, such as the cavum of the septum pellucidum, are visible beneath the corpus callosum, even if it is only a potential space in the individual patient. This midline landmark is valuable, if found, because it confirms the complete transection of the callosal fibers and it allows one to stay out of the lateral ventricles. If the lateral ventricle is entered, intraoperative or postoperative bleeding may cause hydrocephalus. The transection is then carried forward into the genu and the rostrum of the corpus callosum. The disconnection is carried out downward following the A2 branches as they approach the anterior communicating artery complex. The extent of posterior callosal sectioning is decided preoperatively. Some surgeons advise a simple one-half callosal sectioning, which can be measured by comparing the intraoperative transection to the length of the callosum on the preoperative sagittal MRI. This and other techniques, such as intraoperative plain films and stereotaxy, have been described to confirm the length of callosotomy (47). Other authors advocate a three-quarter sectioning, as there is some indication that seizure control may be more complete. Jalilian et al. (39) reported that an upfront complete corpus callosotomy should be considered in children with lower

functional status. Bower et al. (48) reported that the majority of patients in their series that underwent an anterior two-thirds callosotomy derived significant benefit without requiring a completion of the callosotomy.

If a complete corpus callosotomy is to be performed, the sectioning may be done with a microdissector or suction aspiration to the splenium. A complete posterior sectioning is confirmed by viewing the arachnoid covered vein of Galen in the posterior midline. If only an anterior transection is planned, an MRI-compatible marker should be placed at the posterior border of the anterior transection in order to see it on imaging studies and to note on reoperation, if necessary, the extent of the first procedure. Hemostasis is obtained, and any entry into a lateral ventricle is covered with Gelfoam. A standard craniotomy closure is performed.

Over the past few years, there have been increasing reports in the use of radiosurgery or gamma knife to perform a corpus callosotomy (49–51). While the numbers in each series were small, efficacy was comparable to traditional surgical callosotomy (49–51). Moreno-Jimenez et al. (52) reported that DTI acquired after callosal radiosurgery showed progressive decrease in fractional anisotropy compared to controls. Falowski and Byrne (53) reported in 2012 CO_2 laser suction device versus bipolar electrocautery to improve midline dissection and decrease the likelihood of entering the ventricles.

Complications

Complications unique to corpus callosotomy as a surgical procedure are often neuropsychological in nature. Well-described acute and chronic neuropsychological sequelae are possible after callosotomy (54,55). Varying degrees of acute disconnection syndrome are commonly seen. This syndrome is characterized by a lethargic, apathetic mutism during the first few days after surgery. For most, this is always transient. The predictors of this transient state are related to the extent of callosal sectioning, baseline cognitive impairments, and the amount of traction necessary to gain access to the corpus callosum. Other early complications of the acute syndrome are incontinence, bilateral Babinski sign, and apraxia.

Chronic disconnection syndrome was initially not well recognized when callosotomy was first described (1). Detailed neuropsychological testing reveals deficits that are common after callosotomy but are not usually clinically significant. The majority of neuropsychological alterations, other than mutism, occur with posterior callosotomy. This is caused by disruption of communication between visual and tactile cortical sensory functions and verbal expression. Because of the disconnection between the hemispheres, an object placed only in the left visual field of a left hemisphere–dominant patient will be seen by the right hemisphere, but the information will not be transferred to the left hemisphere for speech production. Thus, the patient recognizes the object but cannot name it. Similarly, an object placed in the left hand, but not seen, may be recognized by its shape and size, but it will not be named. This is interesting but not clinically disabling to the patient because objects are normally seen by both hemispheres and can be felt with either hand. If a patient has bilateral speech representation, dysphasia may be a postoperative complication. This should be considered before complete callosotomy is performed on a patient with mixed speech dominance.

A disturbing complication known as alien hand syndrome has been reported (55). In this syndrome, poor cooperation or even antagonistic behavior between the left and right hand is noted. The verbal-dominant hemisphere may express displeasure with the actions of the ipsilateral extremities. This phenomenon is usually short lived and is usually seen only in the immediate

postoperative period; however, on rare occasions, it may persist. Performing only an anterior callosotomy can minimize the likelihood and the extent of these neuropsychological sequelae. If the anterior callosotomy is unsuccessful in controlling seizures, completion of the callosotomy may be performed at a later time.

Other observed complications are related to frontal lobe retraction: cingulate gyrus injury, injury to the pericallosal arteries, bridging veins or superior sagittal sinus, and hydrocephalus following entry into the lateral ventricle. Postoperative hydrocephalus secondary to entry into the ventricular system and a subsequent ventriculitis has been dramatically reduced by using an operative microscope and carefully respecting ventricle boundaries. Transient mutism may be reduced by minimizing the retraction of frontal cortex and retracting the nondominant frontal lobe, if possible. Despite this, mutism may occur transiently in up to 30% of patients.

Spencer et al. (7) reported a meta-analysis of long-term neurologic sequelae of both anterior and complete corpus callosotomy. They found that motor sequelae were reported in 56% of complete and 8% of anterior callosotomy patients; language impairments in 14% and 8%, respectively; and both cognitive impairment and behavioral impairment in 11% and 8%, respectively.

Some authors have suggested certain contraindications to corpus callosotomy. Spencer et al. (7,15) found that patients with severe mental retardation (IQ lower than 45) did not derive any benefit from the procedure. Other studies, however, have not found any relationship between IQ and outcome (32,33,56–58). A relative contraindication has been proposed concerning patients whose hemisphere of language dominance is not that of hand dominance (59). Speech difficulties, with sparing of writing, have been identified in patients who are right hemisphere dominant for speech and are right-handed, and dysgraphia with intact speech has been identified in left-handed patients with a dominant left hemisphere.

In conclusion, corpus callosotomy is an effective surgical technique for the treatment of selected pharmacoresistant epileptic syndromes, particularly certain types of seizure (i.e., atonic seizures). Over the past 10 years, its use has decreased as a result of the introduction of new antiepileptic drugs, especially lamotrigine and topiramate, and a rekindling of interest in the ketogenic diet. The vagus nerve stimulator has clear benefit for atonic/tonic seizures, and cortical stimulation may be beneficial for “drop” seizures, but no conclusive data are yet available. Certain epilepsy centers in the United States are routinely performing VNS before considering corpus callosotomy. In general, anterior corpus callosotomy is still an underutilized procedure, especially for patients with intractable atonic seizures associated with recurrent falls and subsequent head injury. Radiosurgery has been proposed as an alternative to surgical callosotomy by Pendl et al. (60). Although this is a promising approach, several questions about volume–dose analysis and long-term efficacy are yet to be fully answered (61,62).

MULTIPLE SUBPIAL TRANSECTION

Focal-onset medically intractable epilepsy has been surgically treated for 70 years by location of the seizure focus and resection of the involved cortex. A certain proportion of patients who undergo evaluation for possible surgical resection are found to have an epileptogenic zone originating in, or overlapping with, eloquent cortex. These patients traditionally have been denied surgery because resection of primary speech, motor, sensory, or visual cortex would result in unacceptable deficits. MST was developed specifically to address this problem. The purpose of this technique is to disrupt the intracortical horizontal fiber system while preserving the columnar organization of the cortex (i.e.,

its vertically oriented input and output systems and vascular supply) (63). The transection of horizontal fibers is aimed at preventing the propagation of epileptic discharges, thus averting the synchronous neuronal activation that ultimately results in the development of clinical seizures. The preservation of the columnar organization of the cortex prevents or minimizes the disruption of the functional state of the transected cortex.

The development of this technique was derived from three sets of experiments, each unrelated to the others or to the field of epilepsy surgery. The first set of experiments by Asanuma and Sakata (64), Hubel and Wiesel (65), and Mountcastle (66) demonstrated that the vertically oriented micro- and macrocolumns (with their vertically oriented input, output, and vascular supply) are the organizational unit of functional cortical architecture. The functional role of the intracortical horizontal fiber system is yet to be firmly established. However, this system is composed of fibers responsible for recurrent inhibition and excitation underlying neuronal plasticity. In the second set of experiments, Sperry (67) demonstrated that surgical disruption of the horizontal fiber system in the visual cortex of the cat, while sparing its columnar organization, does not affect its testable functional status. Tharp (68) postulated to the importance of the horizontal fiber system as a "critical component in cortical circuit necessary for generation and elaboration of paroxysmal discharges." Epileptic activity in the form of spikes or sharp waves requires a synchronous neuronal activation of a contiguous cortical surface of at least 12 to 25 mm^2 (68,69). Tharp found that epileptic foci would synchronize their activity if the distance between them was 5 mm or less, and disrupting the neuropil between the foci would desynchronize the epileptic activity.

With this information, Morrell et al. (63,70) hypothesized that sectioning of the intracortical horizontal fibers at 5-mm intervals, while preserving the columnar organization of the cortex, could abolish epileptic activity yet preserve the functional status of the transected cortex. Testing this hypothesis in the monkey, Morrell produced an epileptic focus with aluminum gel lesions in the left precentral motor cortex, which resulted in the development of focal motor seizures. Using a small wire, he disconnected the horizontal fibers at 5-mm intervals throughout the epileptogenic zone. This procedure, the first subpial transection for epilepsy, stopped the seizures, and the monkey suffered no motor deficits from the procedure. To confirm that what he had transected was motor cortex, 1 year later, Morrell surgically removed the transected area, resulting in the expected hemiparesis. With this experimental evidence, Morrell et al. moved forward into the treatment of intractable human neocortical epilepsy arising in or overlapping eloquent cortex.

Indications for Multiple Subpial Transection

MST is indicated in any patient in whom the epileptic zone arises from or overlaps with eloquent cortex. The procedure is performed after a detailed presurgical evaluation, which includes closed-circuit television/electroencephalographic recording of habitual seizures using scalp and intracranial electrodes, mainly subdural grids. In addition, detailed functional mapping to identify eloquent cortex by electrical cortical stimulation and evoked potentials is performed. Neuropsychological testing and intracarotid amobarbital tests, as well as functional neuroimaging studies, all assist in defining the baseline function and risks of the procedure. Magnetoencephalography studies have also been very useful in the evaluation of children with an acquired epileptic aphasia of childhood or Landau–Kleffner syndrome (LKS) (71). It allows more accurate identification of the source of the dipole, especially its depth within a sulcus.

MST can be performed as the sole procedure or in conjunction with resection of noneloquent

cortex, depending on the extent to which the epileptogenic zone involves eloquent cortex. Most cases of MST occur in conjunction with a cortical resection. Candidates are typically patients with dominant temporal neocortical epilepsy, dominant frontal lobe epilepsy, or primary sensory, motor, or visual cortex involvement. In patients undergoing resection/transection, resection of noneloquent cortex is performed to within 1.5 cm of the identified eloquent cortex. We recognize that this patient group is problematic for the evaluation of the clinical effectiveness of MST.

Cortical Surgical Anatomy

Human cortex is arranged in a gyral pattern, which is fairly constant between individuals. However, the microgyral patterns of individual gyri may considerably vary. These cortical variations must be taken into account in a procedure where transections are being made perpendicular to the long axis of a gyrus. Thus, careful inspection of each gyrus prior to the procedure is important. Gray matter is, on average, 5-mm thick over the crown of a gyrus. However, the depth of each sulcus differs by individual.

These points are critical in subpial transection procedures because the objective is to divide the neuropil into 5-mm intervals perpendicular to the long axis of the gyrus while preserving the overlying pia with its blood vessels and the underlying white matter tracts and U fibers.

Approximately a quarter of our patients have undergone MST as their primary procedure. These patients mainly had epilepsia partialis continua due to Rasmussen encephalitis or LKS. In the patients with Rasmussen syndrome, the epileptogenic zone arose from primary language and/or motor cortex, whereas in patients with LKS, it involved posterior language cortex.

Operative Procedure

Patients are given preoperative antibiotics and often steroids and are positioned so that the surgical site is at the highest point in the operative field. This makes intraoperative electrocorticography (ECoG), resection, and transection easier. The head is held in Mayfield head fixation, and all pressure points are padded. If the operation is done with the patient awake, the patient's comfort is especially important.

Anesthesia is accomplished with intravenous methohexital and a generous amount of local anesthesia. Although methohexital has been shown to activate interictal epileptiform activity, such activation does not extend beyond the epileptogenic zone (72). Furthermore, the degree of activation of epileptiform activity can be minimized by lowering the infusion rate of methohexital. At our center, we perform intraoperative ECoG in all cases, even when mapping with subdural grids has been done, to ensure that the initial transections result in the desired abolition of epileptic activity.

Transections

Before performing the transections, careful inspection of the gyri, microgyral pattern, sulci, and vascular supply is carried out. Transections are first performed in the more dependent areas to avoid the problem of subarachnoid blood obscuring the other areas. At the edge of the visible gyrus, in an avascular area, a 20-gauge needle is used to open a hole in the pia. The tip of the subpial transection hook is introduced into the gray matter layer and advanced to the next sulcus in a direction perpendicular to the long axis of the gyrus. The tip of the hook is held upward and is visible immediately beneath the pia. It is important that the pia be left undisturbed to minimize vascular injury

and scarring. The transection hook is designed with a handle, a malleable shaft, and a tip that is 4-mm long (paralleling the cortical width) and 1-mm wide. If the 4-mm tip is introduced just below the pia, it should remain in the gray matter layer, leaving the white matter undisturbed. The tip is angled at 105 degrees and is blunt. These two features make snagging or injuring a vessel less likely. However, it is important to avoid crossing a sulcus where buried vessels are unprotected. While this procedure is simple in principle, we have found that to master it requires considerable experience.

After the first transection is completed, bleeding from the pial opening is controlled with small pieces of Gelfoam and a cottonoid. The 4-mm tip is then placed up against the cortex next to the transection so as to select the next transection site 5 mm from the first. This is repeated until the identified epileptogenic zone is transected. Over a few minutes, the lines take on a striped appearance from the petechial hemorrhages along the lines. Minimal bleeding is encountered if the transections are done properly. ECoG is repeated at the conclusion of the transections. The transected area displays a significant attenuation of the background activity with elimination of the spikes. In cases of persistent epileptiform activity, the possibility that activity is coming from the depth of a sulcus or from remote areas must be considered. On rare occasions, when persistent activity is clearly identified as originating in an area that has been transected, transecting down into the sulcus may be done. In order to perform this safely, the tip of the probe should be turned away from the sulcus as the instrument is advanced.

Favorable outcomes using alternative instruments and methods of transection have been described by neurosurgeons (73,74). Ntsambi-Eba et al. (75) reported a large series utilizing radial MST from a single cortical entry point.

Seizure Outcome

Evaluation of seizure outcome should be carried out in patients who underwent MST without additional cortical resection. We have previously reported our series of patients with partial epilepsy with 37.5% of patients becoming seizure-free at 2-year follow-up with an additional 37.5% having a worthwhile outcome (class II–III). However, as has been reported by other centers, there is a late reoccurrence rate in seizures following MST (76). Orbach et al. (77) reported a relapse rate of 18.6% over several years. Schramm et al. reported on the efficacy of MST alone in 20 patients with drug-resistant epilepsy. One patient had a previous temporal resection; there were two cases each of LKS and electrical status epilepticus of sleep (ESES). In this series, 10% had a class I outcome and 45% had a class II–III outcome. They also noted the relapse in seizures over time (78). Zhao et al. reported on 80 patients treated with MST alone as part of his larger series. He reported 51.7% seizure freedom in patients with at least 1-year follow-up (79).

Ntsambi-Eba et al. reported on 62 patients, using radial MST. Twelve patients were MST alone. Reduction in seizures by 50% was seen in 79%. Forty-two became seizure free and 33% of the MST alone group (75).

In a meta-analysis of MST with or without additional cortical resection, Spencer reviewed 211 patients who underwent MST for intractable epilepsy and found an excellent outcome (>95% reduction in seizure frequency) in 87% of patients who had generalized seizures and 68% of patients with simple and complex partial seizures (80). Zhao et al., in the largest series reported to date, reported on 200 patients (80 MST alone) treated with MST for intractable partial epilepsy involving eloquent cortex between 1991 and 2000. They found complete control of seizures in 62.5% with another 20% of patients having a significant reduction (>75%), with 160 patients having at least 1-

year follow-up (79).

Pondal-Sordo et al. published the neurosurgical experience of London, Ontario, with perirolandic epileptic foci with cortical resection with or without additional MST. The most common etiology was neoplastic. Average follow-up was 4.2 years. At follow-up, 46% had worthwhile outcome (Engel class I, 31%; Engel class II, 15%). Residual deficits were seen in 50% but were mild in half. Those patients whose postoperative ECoG showed infrequent or no epileptiform activity had better surgical outcomes (81).

In pediatric patients, Shimizu and Maehara (82) analyzed 25 cases where MST was utilized with 10 out of 25 having an Engel class I or II outcome. In 2006, Benifla et al. reviewed two studies of MST efficacy that included 60 patients (10 MST alone). They found that between 33% and 46% of patients in the respective series had Engel class I or II outcomes (83).

MST had been used to treat hippocampal epilepsy and preserve verbal memory. Shimizu and Maehara reported a case series of 21 patients who underwent multiple transections of the pyramidal layer of the hippocampus under the alveus using a modification of the MST procedure. Of the 21 patients, 17 were followed for more than 1 year. Fourteen patients (82%) became seizure-free and two (12%) had rare seizures. Eight patients underwent a full postoperative battery of neuropsychological testing of verbal memory. Verbal memory was completely spared in seven, with one patient having a transient worsening that cleared over 6 months (84). The authors were encouraged with the above results; however, a longer follow-up and greater numbers of patients are required before transection of hippocampus is confirmed to be efficacious and sparing of verbal memory function.

Patil and Andres assessed 15 patients with 2- to 5-year follow-up who underwent multiple hippocampal transection. In this series, a transcortical approach exposed the hippocampus and shallow transections were made on the hippocampus. Further transections were also performed on the temporal lobe in some patients. Results were excellent with 94.7% class I and 5.3% class II. Verbal memory was preserved (85).

MST had been used to treat LKS for the past 15 years at our institution. Kanner et al. reviewed the outcome of 24 patients with classic LKS. Thirteen of the 24 had MST alone and 7 had resection and MST (86). All had continuous spike and wave in slow-wave sleep from a unilateral perisylvian source, and all had been mute for at least 2 years. After MST of the perisylvian epileptic abnormality, follow-up revealed that two-thirds of children speak in complex sentences at their last formal speech evaluation with significant improvement of language coming within the first 6 months postoperatively. Nine of these children had achieved complete recovery of language and were not requiring any speech therapy (86).

Irwin et al. reported five cases of classic LKS who underwent MST. All had ESES, clinical seizures, severe language dysfunction or no language, and a behavioral disorder. The frequency of seizures and behavioral disorders were significantly improved in all; however, improvement in language function was not dramatic. This might be related to the duration of the epileptic abnormality prior to surgery (87). The mean duration was 4.6 years, and studies have suggested that duration over 3 years is a predictor of the severity of chronic language disturbance, even with treatment (87).

MST with cortical resection has also been used in patients with multifocal multilobar epilepsy with clinical seizures and developmental regression. In reports by Patel and Devinsky (88), a moderate improvement in language, social, and behavioral function with a significant improvement in seizure frequency was found.

MST had been used in Rasmussen encephalitis in seven patients from Morrell's series. In four

patients, the targeted seizures were eliminated but the progression of the disease continued. In three of seven, MST did not eliminate the epileptic process due to the fact that it arose from the depth of the sulcus (63). MST had also been used in patients with refractory status epilepticus that involved eloquent cortex. In both cases, MST successfully stopped the status epilepticus (89,90). MST has also been utilized in intractable infantile spasm with some improvement in seizures and developmental delay. (91)

Surgical Morbidity

Acute Postoperative Morbidity

Cerebral edema is expected after MST, peaking on the 3rd to 4th postoperative day. Consequently, patients are expected to experience transient dysfunction of transected cortex, with ensuing neurologic deficits lasting for 2 to 3 weeks. Sometimes, mild deficits may persist for several months. Similar observations have been made at the other centers where MST is performed (see the following section).

Chronic Morbidity

The incidence of chronic morbidity varies, in part, with the experience of the neurosurgeon performing the MST procedure. We have reported previously a neurologic complication rate of 15% with 7% suffering a permanent deficit. These included foot drop in 2%, language deficit in 2%, and a parietal sensory loss in 1%. Mild, but clear, diminution in rapid skilled movements was seen in the majority of those undergoing MST of the parietal sensory cortex.

In the meta-analysis of 211 patients by Spencer, the highest morbidity with new neurologic deficits was found in 19% of those with pure MST including 4 with memory decline, 5 with hemiparesis, and 1 with partial visual field defect. A total of 23% of the patients with resection and MST had persistent neurologic deficit (80). Schramm reported transient neurologic deficit in 29% of the 20 cases of pure MST, but all deficits resolved to the point that they would not be noted on standard clinical exams (78). In Zhao et al.'s (79) larger series of 200 patients, 80 MST alone, he reported transient neurologic deficits in just 3%. Likewise, in review of pediatric MST, Benifla et al. (83) reported no permanent language or motor disabilities after MST. Ntsambi-Eba et al. (75) using the modified radial MST had permanent neurologic deficits in 64% with 3.2% permanent deficits, directly attributed to the MST.

CONCLUSIONS

Corpus callosotomy and multiple subpial transaction are different surgical techniques, yet both are fundamentally disconnection procedures. Both offer therapeutic options in patients previously rejected for more traditional resective surgery. The efficacy of corpus callosotomy has now been demonstrated in multiple centers around the world. MST, while used with increasing frequency in epilepsy centers worldwide, has yet to gain universal acceptance. Additional experimental and clinical studies are needed before this surgical procedure is fully integrated into the therapeutic armamentarium at all major epilepsy centers. Much of the success of both procedures depends on the proper selection of patients and the experience of the neurologic and neurosurgical teams. A learning

curve should be expected whenever these procedures are newly implemented at a center.

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CHAPTER 89 SPECIAL CONSIDERATIONS IN CHILDREN

AJAY GUPTA AND ELAINE WYLLIE

Surgery is a well-established treatment for children with medically intractable seizures (1–5). With training of pediatric neurology practitioners, broad acceptance of surgery as a therapeutic option, and improved safety of pediatric anesthesia, neurosurgery, and intensive care techniques, pediatric epilepsy surgery has truly emerged to be a mature discipline with growth of academic programs in most developed and some developing countries (6–8). There have been collaborative efforts to study pediatric epilepsy surgery outcomes from programs in the United States, Europe, and Australia (9) as well as health system studies to improve children's access to epilepsy surgery (6). Consequently, surgical experience and seizure outcome data after surgery in children have now been published from several centers around the world, and results are encouraging from pediatric series involving infants and young children (1,10–18) and adolescents (19–24). However, identification of appropriate pediatric surgical candidates, especially infants and children, remains a challenge because of complex interactions of several unique and age-related factors (3,10,25).

In this chapter, we focus on these unique and age-related differences that interplay in the management of children who are likely to benefit from the surgical treatment of epilepsy. The step critical to surgical strategy in children as well as adults is the identification of a focal, resectable epileptogenic zone. Clues to the epileptogenic zone are found in seizure symptomatology, electroencephalography (EEG), and neuroimaging results. Some aspects of these features are similar to those in adult candidates, whereas others are unique to infants and children.

Table 89.1 compares common findings during diagnostic evaluation of pediatric and adult patients for epilepsy surgery.

Table 89.1 Commonly Encountered Differences During Diagnostic Evaluation and Surgical Decision Making in Pediatric and Adult Patients

Characteristic findings	Infants/young children	Adult patients
History, seizure semiology, and examination		
Specific auras	Rare (unable to communicate)	Common
Seizure semiology	Stereotypic (like "epileptic spasms" or "bland stare")	May indicate symptomatogenic zone
Clinical seizure onset, ictal examination, postseizure recall	Unable or difficult to confirm	Easier
Ictal lateralizing features	Uncommon or unreliable	Common and reliable
Neurologic deficit on examination	Difficult to elicit (mild hemiparesis, visual fields)	Easy to elicit
Neuropsychological testing for surgical risk	Less objective (due to age, severe cognitive and behavioral difficulties)	Helpful in pointing to specific deficits
Scalp EEG patterns		
Confounding factor of developmental EEG evolution	Present	Absent
Stereotypic and nonlocalizing interictal and ictal patterns	Common (hypsarrhythmia, generalized discharges)	Absent or uncommon
Imaging and pathologic substrates		
Confounding factor of developmental brain MRI changes	Present	Absent
Ictal SPECT	Difficult (brief frequent seizures, clusters, difficult ictal onset)	Easier
Common location and extent of lesions	Extratemporal large lesions	Temporal, smaller lesions
Common etiologies	Congenital (cortical dysplasia, malformation, tumor, perinatal stroke)	Hippocampal sclerosis, focal cortical dysplasia
Surgical considerations		
Morbidity and mortality	Higher (due to age, weight, larger resections, coexisting disabilities)	Lower
Timing and best techniques for surgery	More controversial and require planning and experience	Less controversial
Invasive mapping (intracranial grids or depth electrodes)	Not practical in most infants and young children	Possible
Intraoperative neurophysiologic techniques	Limited utility, more challenging in infants	Very useful
Goals of surgery/successful seizure control	Cognitive improvement, schooling, behavior, productive adult life	Job, driving, independence

SEIZURE SEMIOLOGY DURING VIDEO–EEG IN INFANTS AND CHILDREN

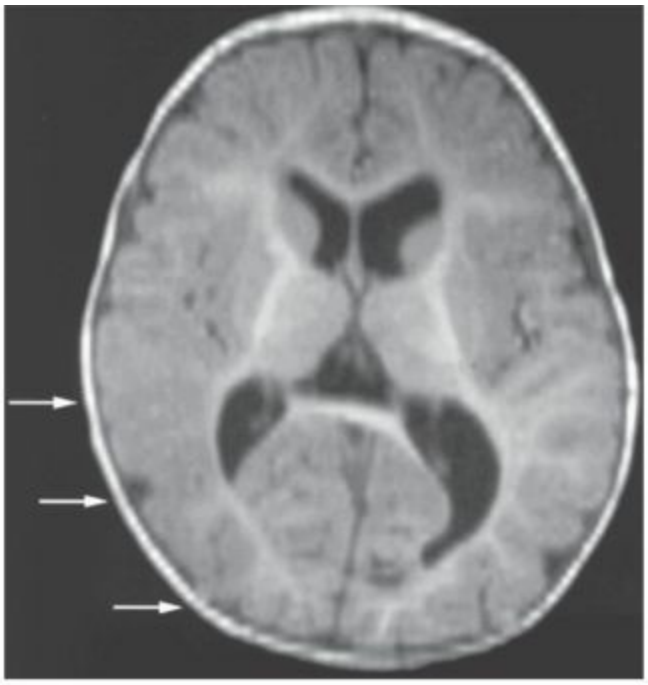
Clinical features of focal seizures may differ in pediatric and adult surgical candidates. Independent studies (26–29) of videotaped seizures from patients at separate institutions indicated that the classification of epileptic seizures of the International League Against Epilepsy (29), originally reflecting experience in older patients, was not applicable to infants younger than 3 years of age. In one study (26), only 3 of 21 infants had unmistakable characteristics of localized seizure onset, including clonic jerking of one extremity. In the remaining patients, seizures consisted of a decrease in motor activity with indeterminate level of consciousness and minimal or no automatisms, arising from temporal or temporoparietal regions, or bilateral tonic stiffening sometimes preceded by bilateral eyelid blinking, arising from frontal or frontoparietal regions. In another study of 77 children with temporal lobe epilepsy examining the relationships between etiology, age at onset, and electroclinical findings, auras were typically clear after the age of 6 years, and initial ictal symptomatology consisted of staring with behavior arrest, lip cyanosis, and bland or subtle oral

automatisms again reiterating the lack of clear lateralizing or localizing semiology (30). Other authors (27,31) have also noted bilateral motor phenomena during partial seizures in infants. The mechanism is unknown but may include ictal activation of subcortical regions or of the supplementary sensorimotor area. A localized EEG seizure pattern clarifies the focal nature of the epileptogenic process.

Seizure characteristics signaling localized onset in older patients may be absent or unidentifiable in infants. For example, an aura is an important clue to focal onset in older children and adults, but sensory phenomena are difficult to detect and are rarely observed during video–EEG studies in infants (26). Clinical seizure onset may be difficult to notice, especially in mentally impaired young children, and this may create a challenge during diagnostic evaluation like video–EEG and ictal single photon emission computer tomography (SPECT) (32,33). Complex gestural automatisms and altered awareness are hallmarks of many partial seizures in older patients, but assessment of the ictal level of consciousness in infants is fraught with problems, and automatisms, when present, tend to be simple, bland, and predominantly oral. In infants, distinguishing automatisms from normal background behavioral activity can be difficult (26,27).

SCALP EEG PATTERNS, INFANTILE SPASMS, AND FOCAL CORTICAL LESIONS

Within the first 2 years of life, focal cortical lesions may manifest as infantile spasms and hypsarrhythmia (12,34–36). The spasms may be intermixed with partial seizures (Fig. 89.1) or may replace a previous partial seizure type altogether, becoming the only active seizure type (Fig. 89.2). The mechanism is unknown, but a clue may be the relationship between age of onset of spasms and location of the lesion. Koo and Hwang (37) found that spasms began earliest in patients with occipital lesions (mean age, 3 months), appeared later in patients with centrotemporoparietal lesions (mean age, 6 months), and occurred latest in patients with frontal lesions (mean age, 10 months). This timing coincides with maturation in those regions, rapid increases in synaptic density, and sequential myelination that proceed from the back to the front of the brain. Infantile spasms appear to result from an age-related pathologic interaction between a focal cortical lesion and normal developmental processes.



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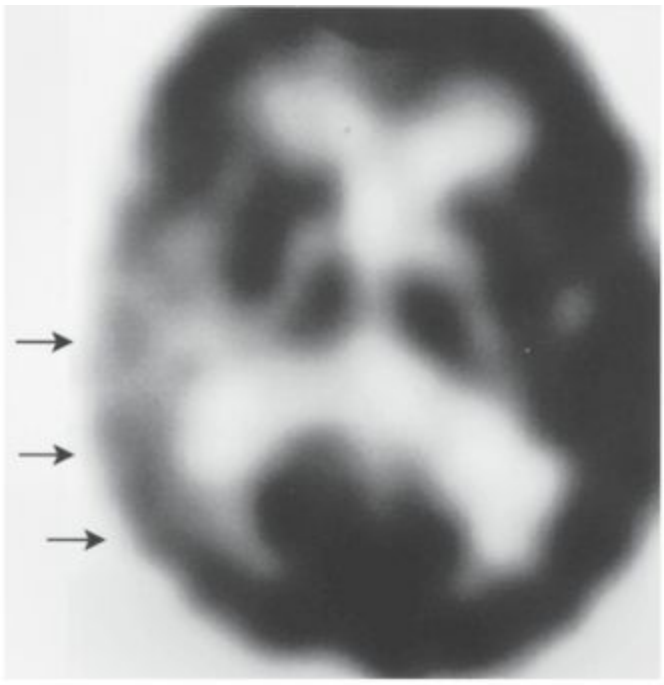

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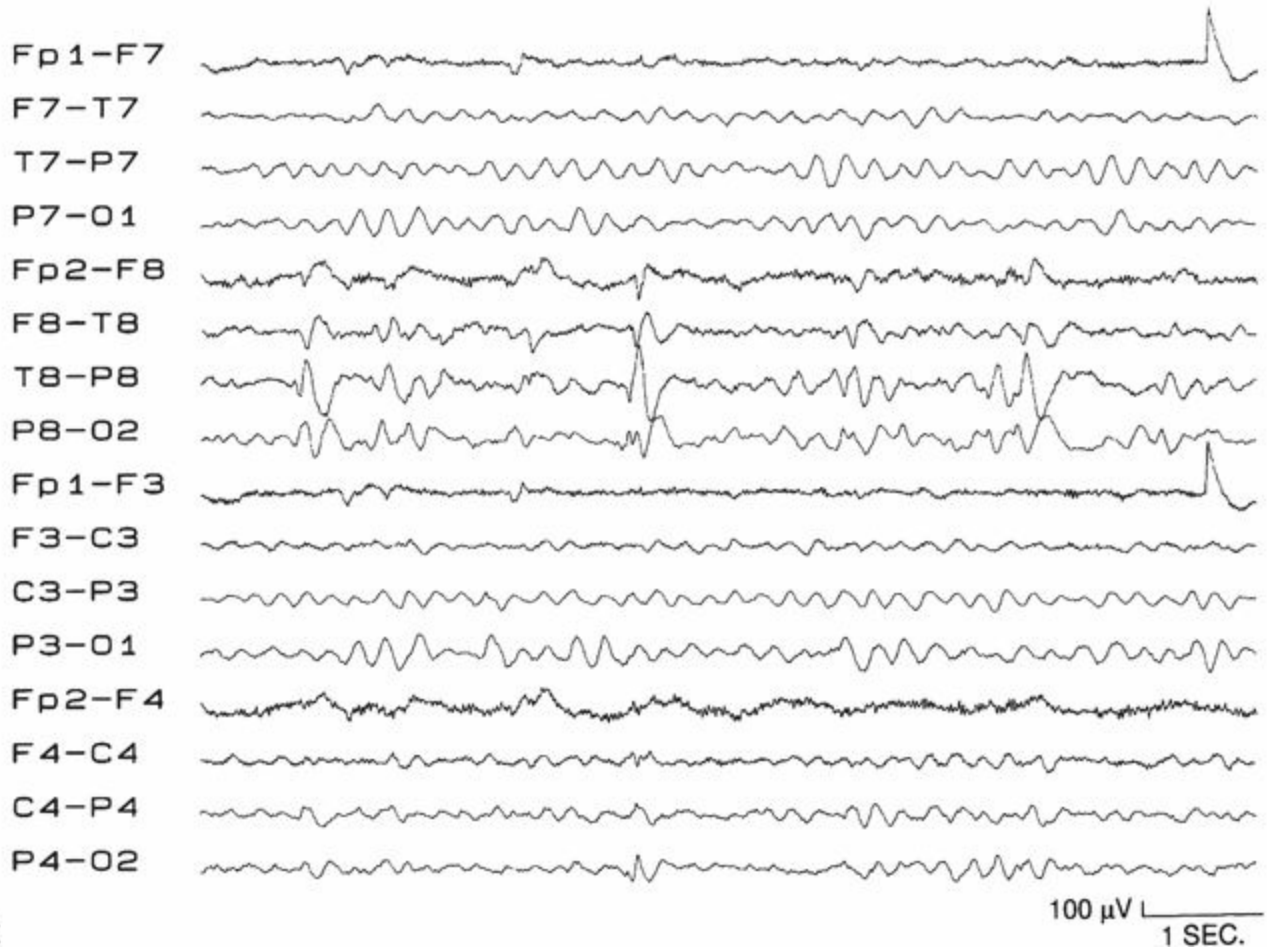
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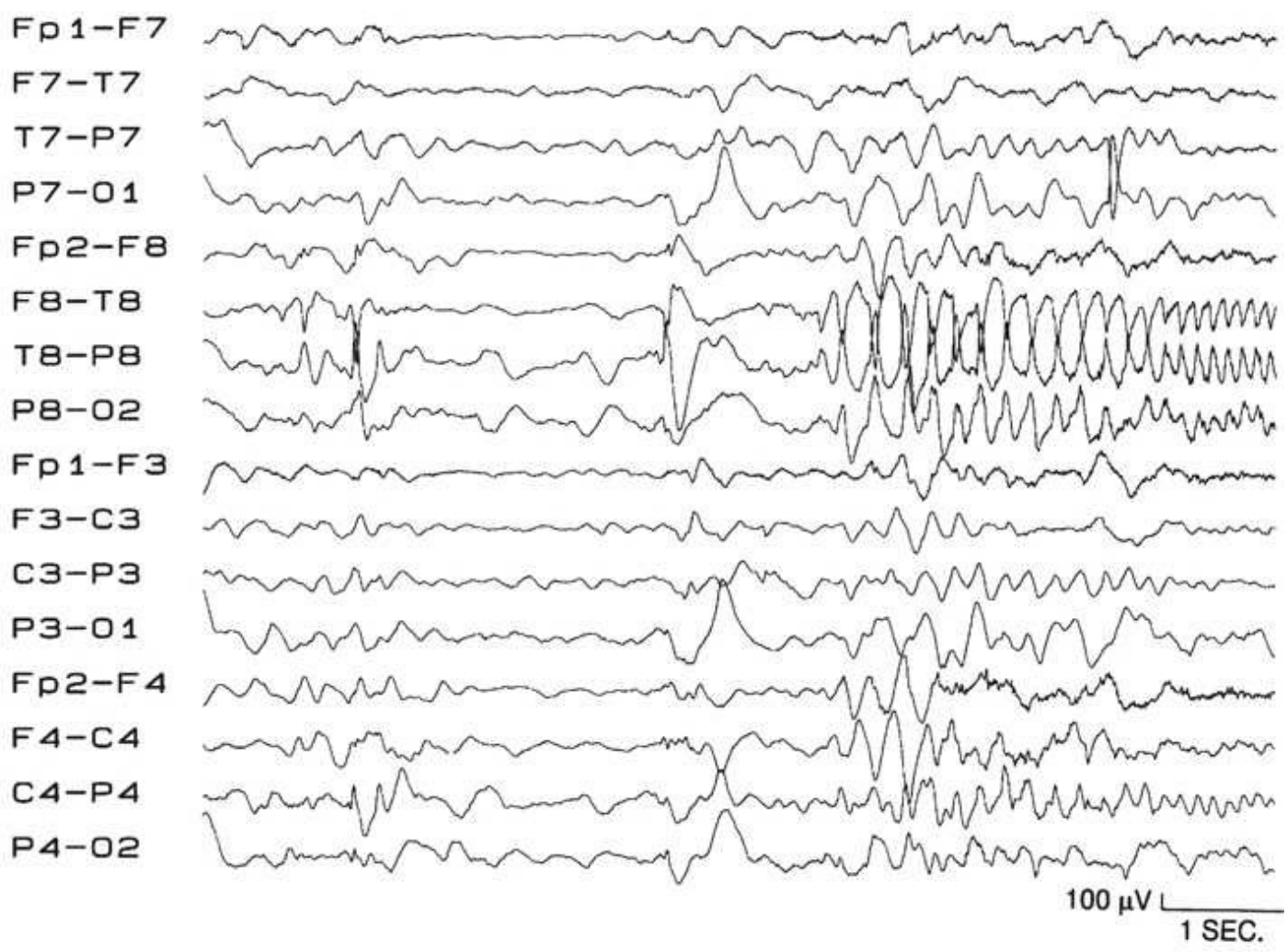
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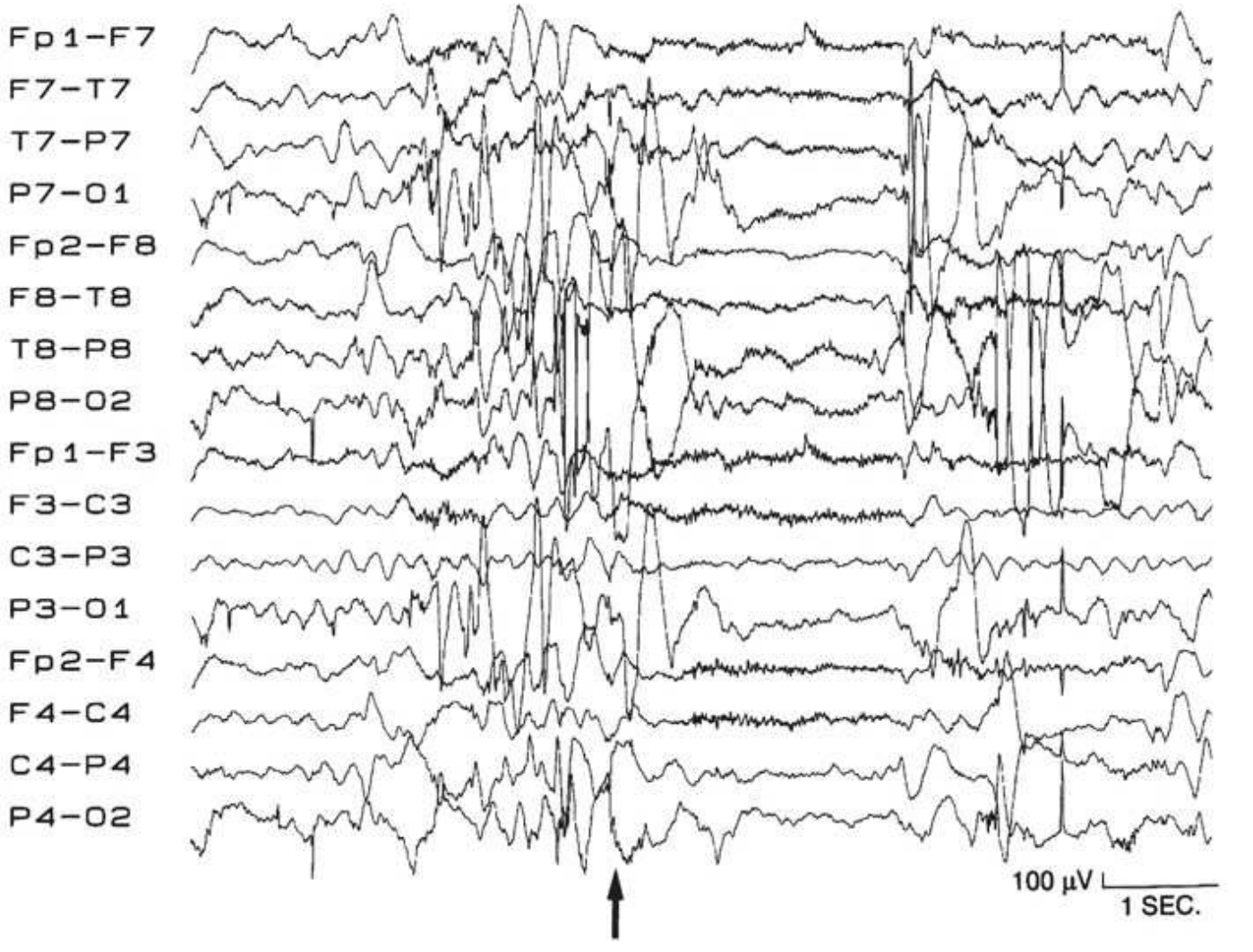
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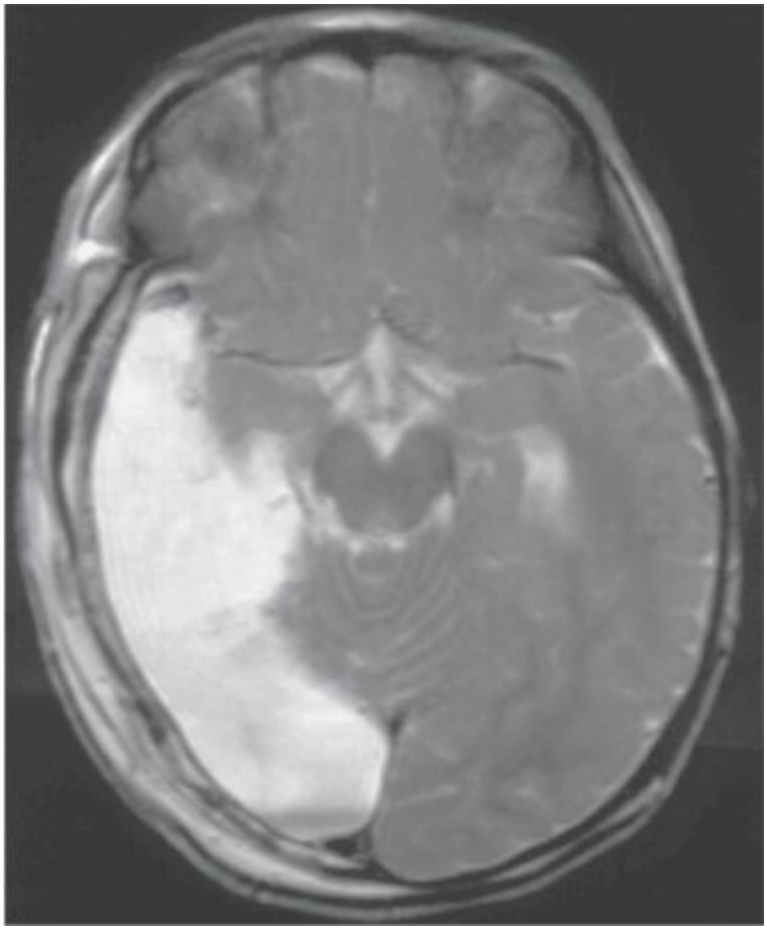


Figure 89.1. Case 1. (All images are of the same patient.) **A:** Axial magnetic resonance image from an 8-month-old boy, showing focal malformation of cortical development in the right temporo-occipital region (arrows). Findings were subtle and included decreased arborization of the white matter and thickened, poorly sulcated cortex. Seizures began 14 hours after an unremarkable term birth and occurred 20 to 30 times per day. The boy was otherwise normal except for developmental delay. **B:** 2-[^{18}F]fluoro-2-deoxy- D-glucose PET scan at age 8 months, showing glucose hypometabolism in the right temporo-occipital region (arrows) . **C:** Interictal electroencephalogram at age 8 months, showing right posterotemporal sharp waves (maximum at the T8 and P8 electrodes), slowing, and decreased background activity. **D:** Ictal electroencephalogram at age 8 months with seizure pattern maximum in the right posterior temporal region (T8 electrode). Seizures involved bilateral clonic eyelid blinking, rhythmic interruption of crying, and bilateral clonic arm twitching. **E:** Ictal electroencephalogram at age 8 months, showing diffuse electrodecrement (arrow, preceded and followed by movement artifact) during an asymmetric spasm with extension and elevation of both arms (left more than right) and tonic closure of the left eyelid. **F:** Magnetic resonance image showing the right temporo-occipital resection performed at age 22 months. Fourteen months later, the child still has developmental delay but remains free of seizures off all antiepileptic medication. (**A** and **C–F** are from Wyllie E. Surgical treatment of epilepsy in infants and children. Can J Neurol Sci. 2000;27:106–110, with permission.)

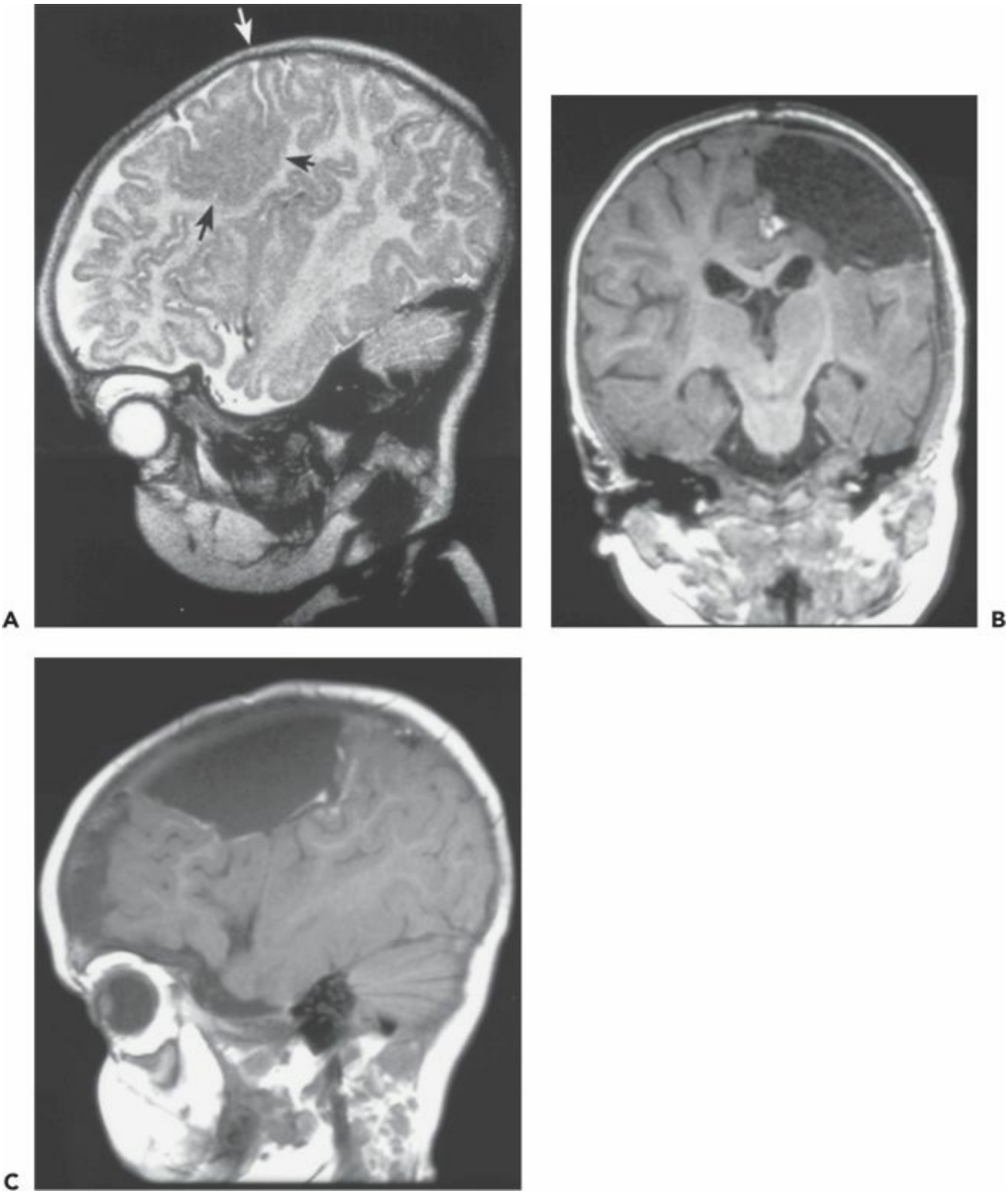
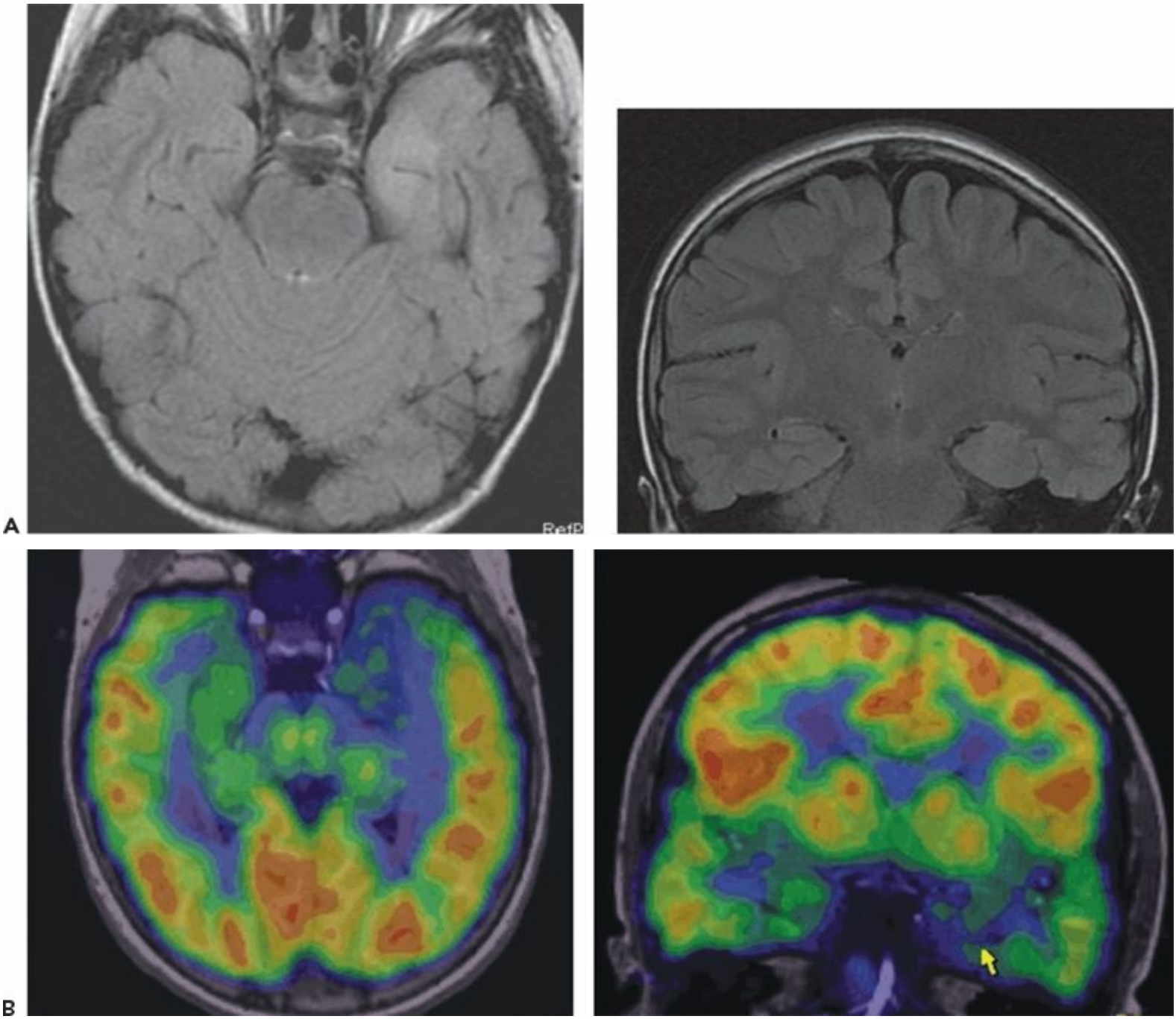


Figure 89.2. Case 2. **A:** Sagittal magnetic resonance image showing focal malformation of cortical development cerebral dysgenesis (black arrows) in the left posterior frontal lobe extending across the central sulcus (white arrow) into the anterior portion of the postcentral gyrus. The boy was 4 months old at the time of the MRI, with intractable daily seizures since the first day of life after an uncomplicated full-term delivery. Seizures involved clonic jerking of the right arm and leg, with eye deviation toward the left, or opisthotonic posturing with stiffening and extension of all extremities. Ictal and interictal epileptiform discharges were localized to the left central region. Moderately severe right hemiparesis and mild developmental delay were also present. **B:** Coronal and **(C)** sagittal scans performed 2 days after cortical resection at age 9 months. Prior to resection, electroencephalographic seizure was recorded over the lesion with intraoperative electrocorticography, and primary hand motor cortex was identified in the same area by intraoperative cortical stimulation. Postoperatively, the hemiparesis was transiently minimally worse, returning to preoperative baseline within days. Twenty-two months later, the child is making developmental progress and has had no seizures on a reduced dose of antiepileptic medication. (A from Wyllie E. Surgical treatment of epilepsy in children. Pediatr Neurol. 1998;19:179–188, with permission.)

Chugani et al. (13,38,39) first emphasized the role of positron emission tomography (PET) and magnetic resonance imaging (MRI) in identifying focal cortical lesions in children with infantile spasms and hypsarrhythmia, describing several patients with cessation or dramatic reduction of seizures after cortical resection or hemispherectomy. Their experience has been replicated elsewhere (2,35,40). Sixty-five percent of affected children are free of seizures after surgery (12), and infantile spasms are not predictive of poor outcome. However, the identification of appropriate surgical candidates may be complicated by the absence of focal EEG seizure patterns in the setting of spasms with diffuse electrodecrements (17,40).

The goal of the presurgical evaluation in patients with infantile spasms is to identify a region of cortical abnormality. The most common finding for surgical planning in this setting is a unilateral lobar, multilobar, or a hemispheric epileptogenic lesion on MRI or PET, usually a malformation of cortical development or encephalomalacia following perinatal cerebral infarction or ischemia. Helpful EEG findings may include a predominance of interictal sharp waves over one region; localized slowing, decreased background activity, or absent sleep spindles over the affected region or hemisphere; unilateral electrodecremental events; asymmetric EEG seizures; or a history of partial seizures (3). Neurologic examination may show evidence of unilateral hemispheric dysfunction with decreased spontaneous movement of one arm (hemiparesis) or gaze preference to one side (homonymous hemianopia).

Generalized epileptiform discharges on scalp EEG in the presence of a congenital or early-acquired focal lesion are not limited to infants. Recently, two reports from Cleveland Clinic described older children and adolescents with a unilateral or strongly asymmetric focal or hemispheric epileptogenic lesion who presented with generalized interictal abnormalities and ictal scalp EEG patterns (41,42). Initially, many of these children were rejected for surgical treatment owing to the presence of generalized EEG findings and lack of localizing EEG data. Because of a high burden of seizures, failure of most treatment modalities, and minimal risk of new postoperative side effects, surgical treatment was generally offered as a last resort with resection of the brain MRI lesion or hemispherectomy in each case. Seizure-free outcome was obtained for 70% of these children with generalized or contralateral EEG abnormalities, and these results were similar to those in a comparison group of children with similar MRI lesions and localized EEG findings. On further analysis of the group with generalized video–EEG abnormalities, the rate of seizure freedom after resection of the lesion was invariable regardless of the presence or absence of focal ictal semiology, generalized slow spike-and-wave complexes, and proportion (30% to 100%) of the generalized or contralateral ictal and interictal epileptiform discharges (42). Postoperative EEG in seizure-free children typically showed resolution of the generalized or contralateral epileptiform discharges, which were often nearly continuous on preoperative EEG, especially during sleep (Fig. 89.3).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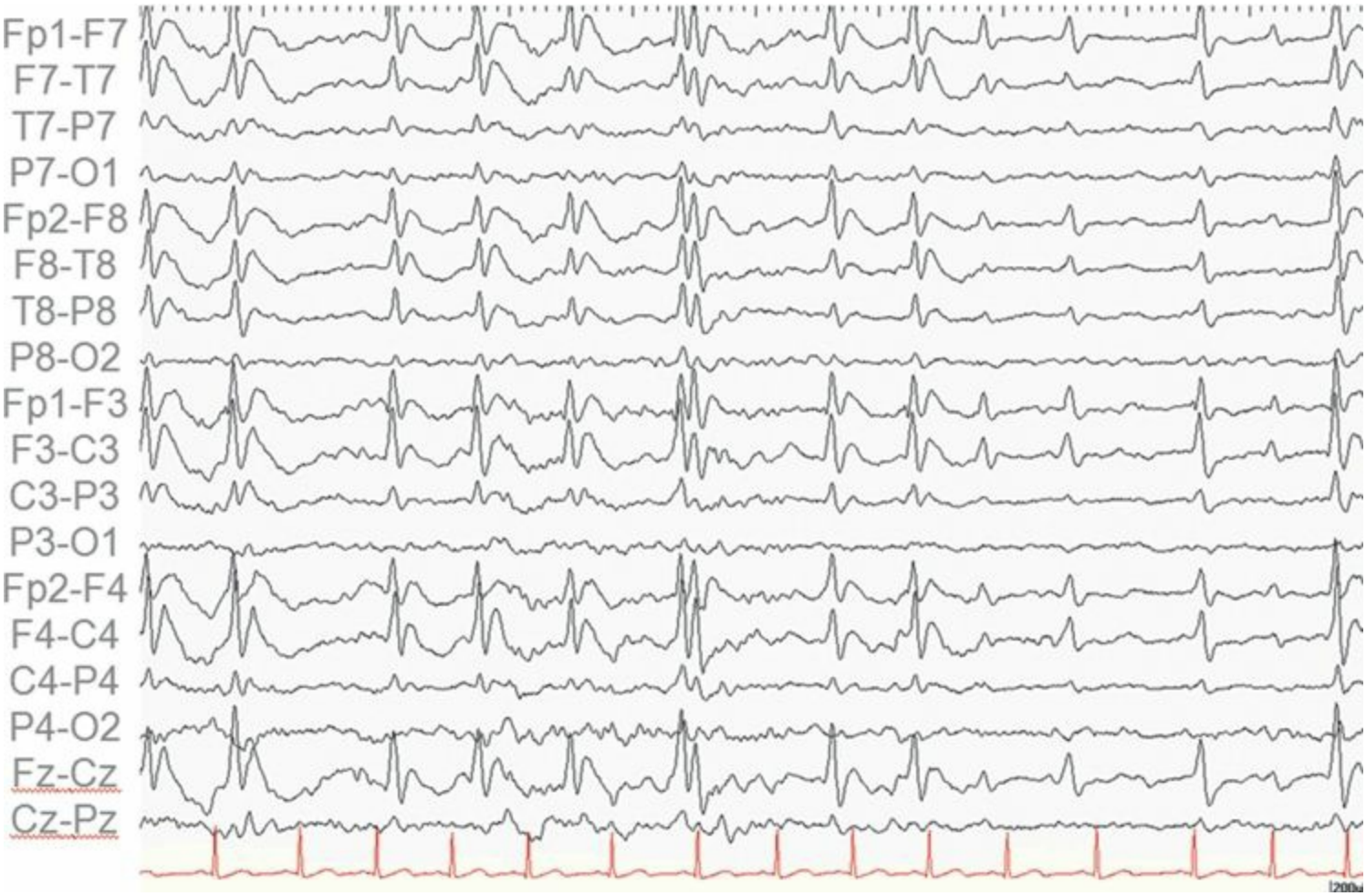


Figure 89.3. Case 3. (All images are of the same patient.) **A:** MRI showing left anteromedial temporal malformation of cortical development in an 11-year-old girl with history of left temporal lobe seizures from 5 to 7 years of age and then severe epileptic encephalopathy. **B:** FDG–PET showing severe left anteromedial hypometabolism in the region of the malformation seen in **A**. **C:** EEG at 11 years of age showing nonlocalized slow spike-and-wave complexes, nearly continuous during sleep (CSWS pattern). After left anteromedial temporal resection, she was free of seizures with resolution of her epileptic encephalopathy. Postoperative EEG showed no epileptiform discharges while awake or asleep.

A unifying feature in the Cleveland Clinic studies with generalized EEG was the early timing of the occurrence of the lesion seen on MRI, most commonly a malformation of cortical development or encephalomalacia following ischemia, infection, or trauma (41,42). Lesions were congenital or perinatal in 75% of patients and acquired within the first 2 years of life or earlier in 90%. The latest timing of lesion acquisition in the series was at age 5 years. In contrast, the age at evaluation for surgery ranged widely from infancy through young adulthood, with median at 8 years (42). Although mechanisms are unknown, the generalized epileptiform discharges seen later in childhood appear to result from complex early interactions between the epileptogenic lesion and the developing brain (41,42). These studies (41,42) highlight the limitations of scalp video–EEG in children, emphasize the importance of a brain MRI lesion, and show practical difficulties in establishing proof of focal epileptogenicity in some children before surgery. Therefore, in every child, the location of the focal epileptogenic zone must be preoperatively defined, whenever possible, by a convergence of results from clinical examination, video–EEG, anatomic and functional neuroimaging, and other testing, while recognizing that in carefully selected cases with early MRI lesions, generalized EEG patterns may not contraindicate surgery (3,25).

ANATOMIC AND FUNCTIONAL NEUROIMAGING

Neuroimaging is a critical component of surgical strategy at every age. A focal epileptogenic lesion on the MRI seems to indicate a better prognosis for seizure-free outcome. In the Cleveland Clinic pediatric series from 1990 to 1996 (2), 54% of patients were seizure free and 19% had only rare seizures after extratemporal or multilobar resections. In contrast, in the Montreal Neurological Institute pediatric series (43) (excluding tumor cases) during the pre-MRI era between 1940 and 1980, only 27% had few or no seizures after frontal resection. The more favorable results from the Cleveland Clinic may be due to identification of a focal epileptogenic lesion on preoperative MRI in 85% of patients. Almost identical results were reported in an adult series of extratemporal resections performed in Bonn, Germany, from 1987 to 1993, with 54% of patients free of seizures after surgery (44). Seizure-free outcome in that series was significantly more common in lesional than nonlesional cases, with 82% of lesions identified preoperatively by MRI. The absence of MRI localization appears to be an unfavorable prognostic sign, although some patients may have good outcome after EEG-guided cortical resection. The yield of brain MRI, particularly in neocortical frontal and temporal lobe epilepsy, could be enhanced by use of high-resolution imaging with 3-T magnets, specialized protocols with thin sections and surface coil MRI, and experience of the reader (5,45).

PET is also an important neuroimaging tool for pediatric epilepsy surgery. Chugani et al. found that a localized region of hypometabolism may identify focal cortical dysplasia even without abnormal features on MRI (12). This is especially helpful in infants because immature myelination challenges identification of subtle dysgenetic abnormalities of the gray–white junction on routine brain MRI protocols. In a recent study, brain PET was also found to be a useful predictor of seizure outcome after hemispherectomy, with bilateral PET abnormalities being associated with postoperative seizure recurrence (46). PET scans using special tracers have been reported to be useful in some children with tuberous sclerosis (47). Ictal SPECT remains a challenging modality to use in children; however, it has been increasingly used in many centers in selected pediatric cases (32,48,49). Acquisition and interpretation of ictal SPECT in children are complicated as a result of several factors (32). First, interictal SPECT may be difficult to obtain owing to multiple daily seizures in this group of patients. Second, difficulty in promptly recognizing the clinical onset of ictal behavioral changes because of age and coexistent mental retardation may result in a late injection for an ictal SPECT. Third, some extratemporal seizures may be brief and spread rapidly. Fourth, children may require sedation on two occasions to obtain interictal and ictal scans. Newer noninvasive presurgical procedures, such as magnetoencephalography and functional MRI (fMRI), are increasingly being used in children for source localization of interictal spikes (50–53) and mapping of language and motor function (fMRI) using standardized protocols (54,55). However, it remains to be seen if these techniques will independently expand the selection of pediatric surgical candidates, obviate the need for invasive video–EEG recordings, and improve the long-term surgical outcome in children.

ETIOLOGIES AND PATHOLOGIC SUBSTRATES OF EPILEPSY IN PEDIATRIC PATIENTS

Causes of epilepsy differ in children and adults. Figure 89.4 depicts the usual age of onset and common etiologies/pathologic substrates encountered in children with epilepsy. Hippocampal sclerosis, the most common etiologic factor in adult candidates for epilepsy surgery, is uncommon in children. In contrast, in a pediatric epilepsy surgery series from the Cleveland Clinic Foundation (2),

hippocampal sclerosis was the cause in only 12% of 62 children (3 months to 12 years of age) and in 15% of 74 adolescents (13 to 20 years of age). Although hippocampal sclerosis may begin in childhood, the typical presentation for surgical evaluation is in early adulthood. When hippocampal sclerosis occurs in pediatric candidates for epilepsy surgery, the clinical and EEG features may be similar to those in adults (56). However, pediatric patients appear to have an especially high incidence of dual pathology with cortical dysplasia in addition to the hippocampal sclerosis (56).

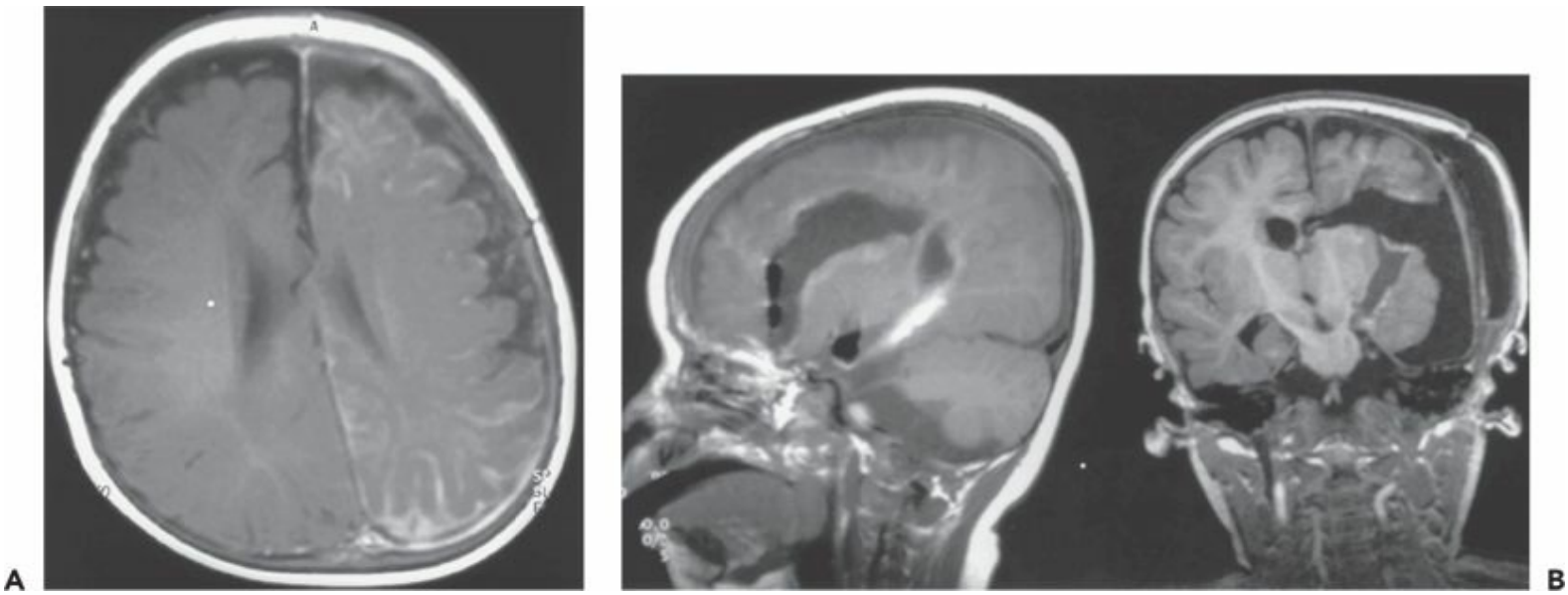
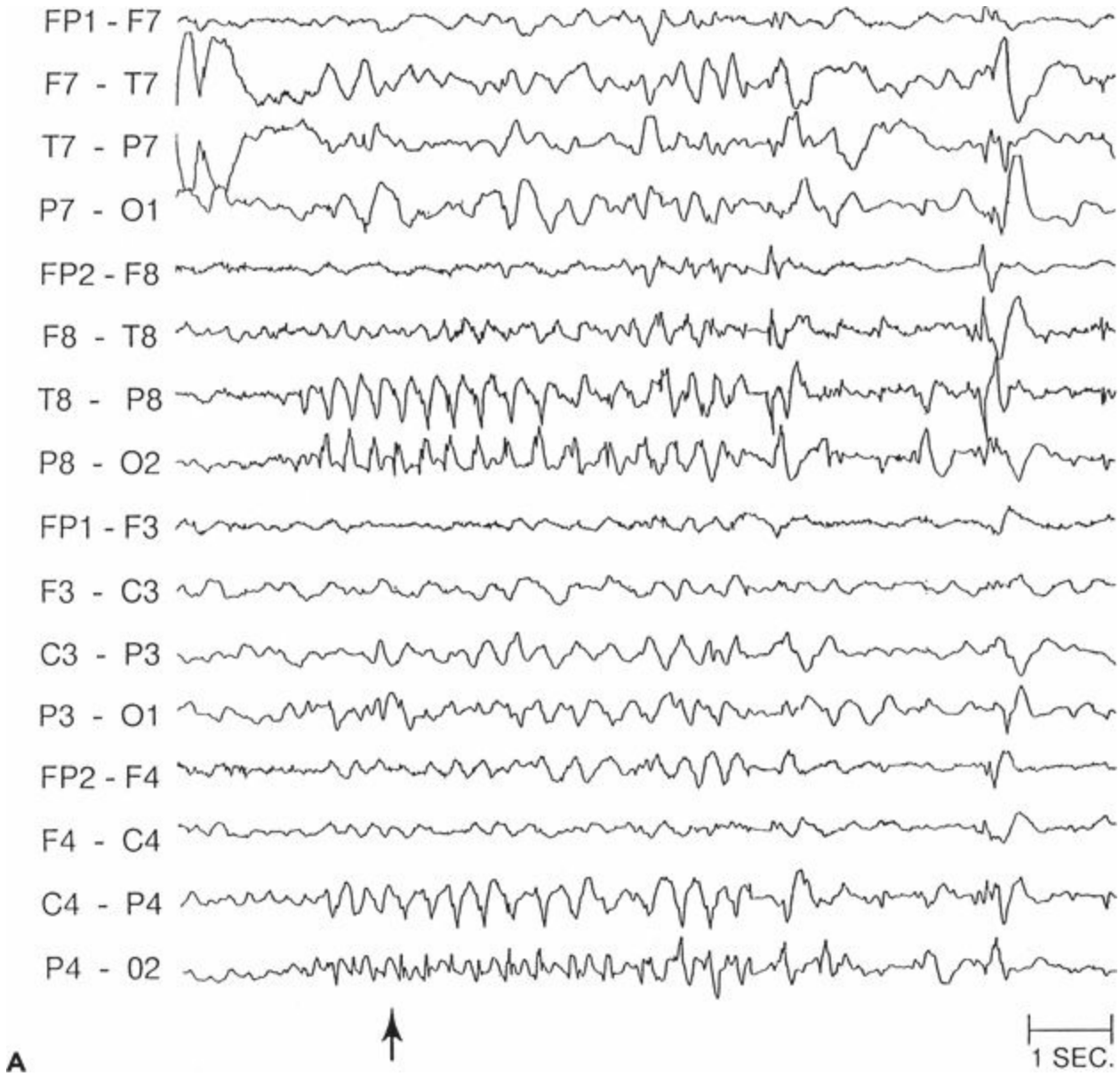


Figure 89.4. Case 4. **A:**Axial magnetic resonance image at age 12 months, showing Sturge–Weber malformation with left hemispheric atrophy and pial angiomatosis. Starting at age 2 months, seizures occurred once or twice per day characterized by jerking of the right arm or decreased behavioral activity with bilateral eye blinking and lip smacking. Physical examination revealed right hemiparesis, right hemianopia, and developmental delay. Ictal and interictal epileptiform abnormalities were seen in multiple areas of the left hemisphere. **B:**Sagittal (**left**) and coronal (**right**) magnetic resonance images showing the left hemispheric disconnection performed at age 12 months. No seizures occurred during the 8 months since surgery on a reduced dose of antiepileptic medications. Surgery did not worsen neurologic deficits, and the child has progressed developmentally.

In pediatric candidates, the predominant etiologic factors are focal, multilobar, or extensive hemispheric malformation of cortical development (cortical dysplasia) (Figs. 89.1, 89.5, and 89.6) and low-grade tumor (2,3,57). These were the cause of the epilepsy in 57% of adolescents, 70% of children, 90% of infants younger than 3 years in the Cleveland Clinic series (2), and 90% of infants treated surgically in the series of Duchowny et al. (1). Less common causes are vascular malformation, arachnoid cyst, and localized injury due to infarction, trauma, or infection (1,2,57).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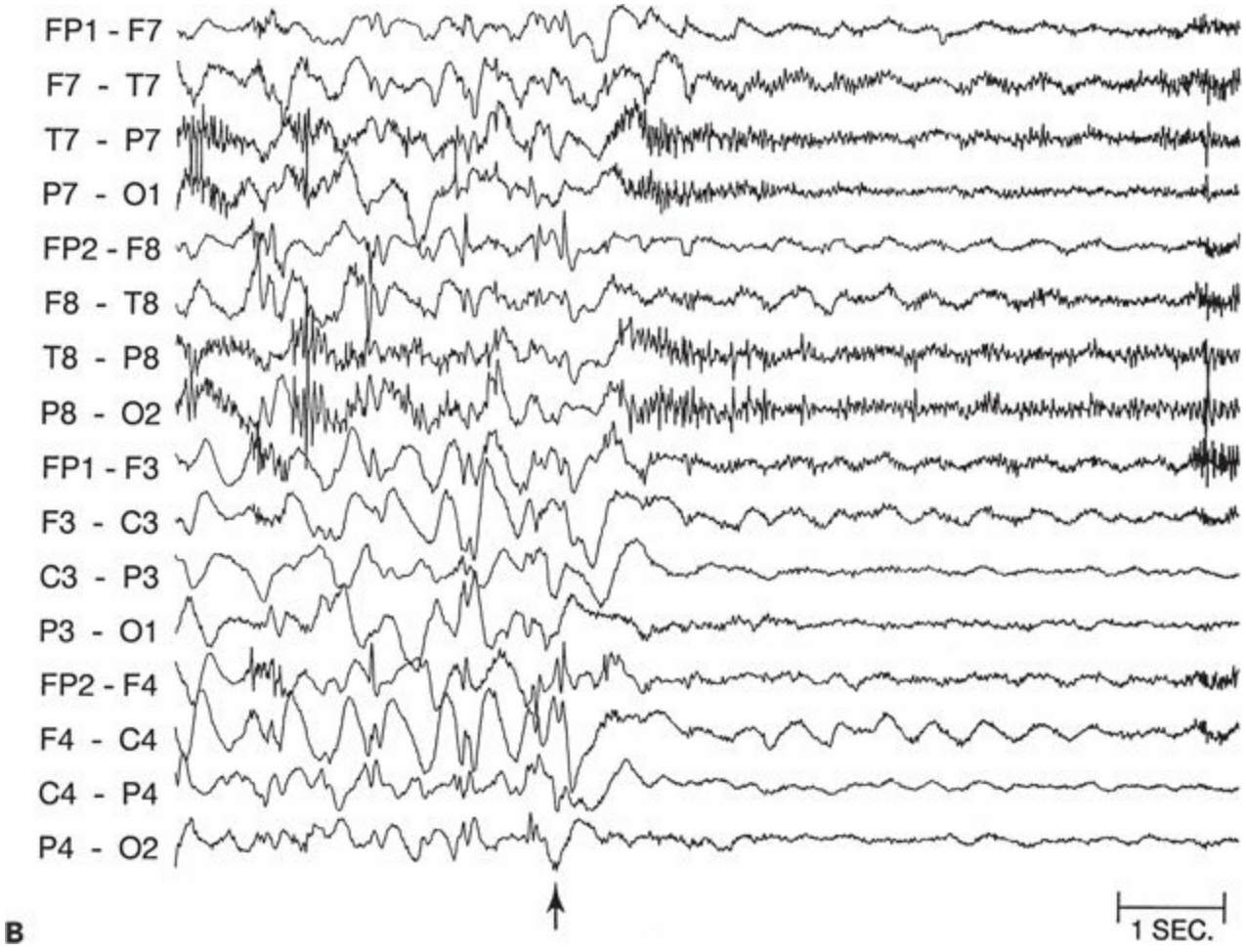
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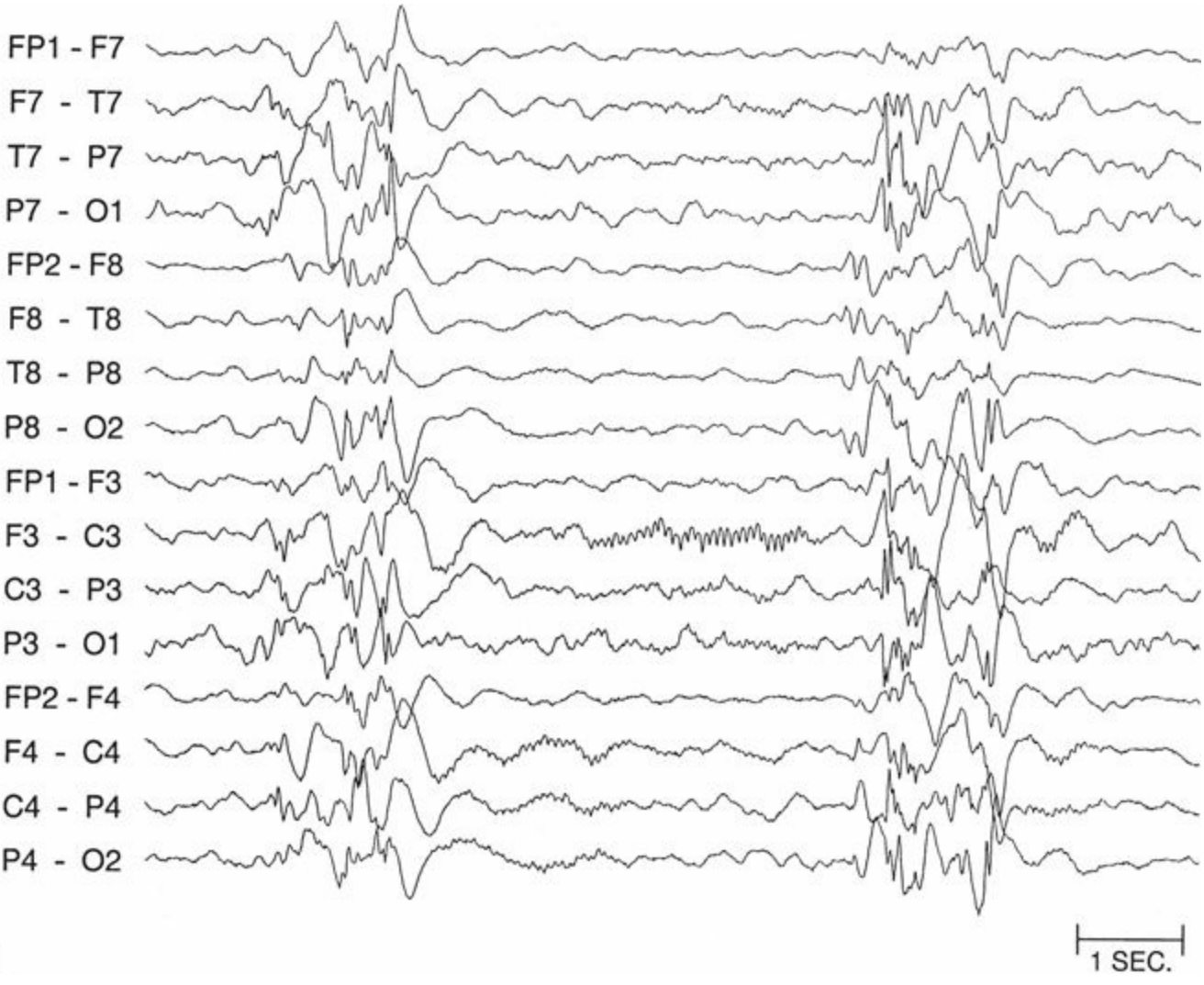
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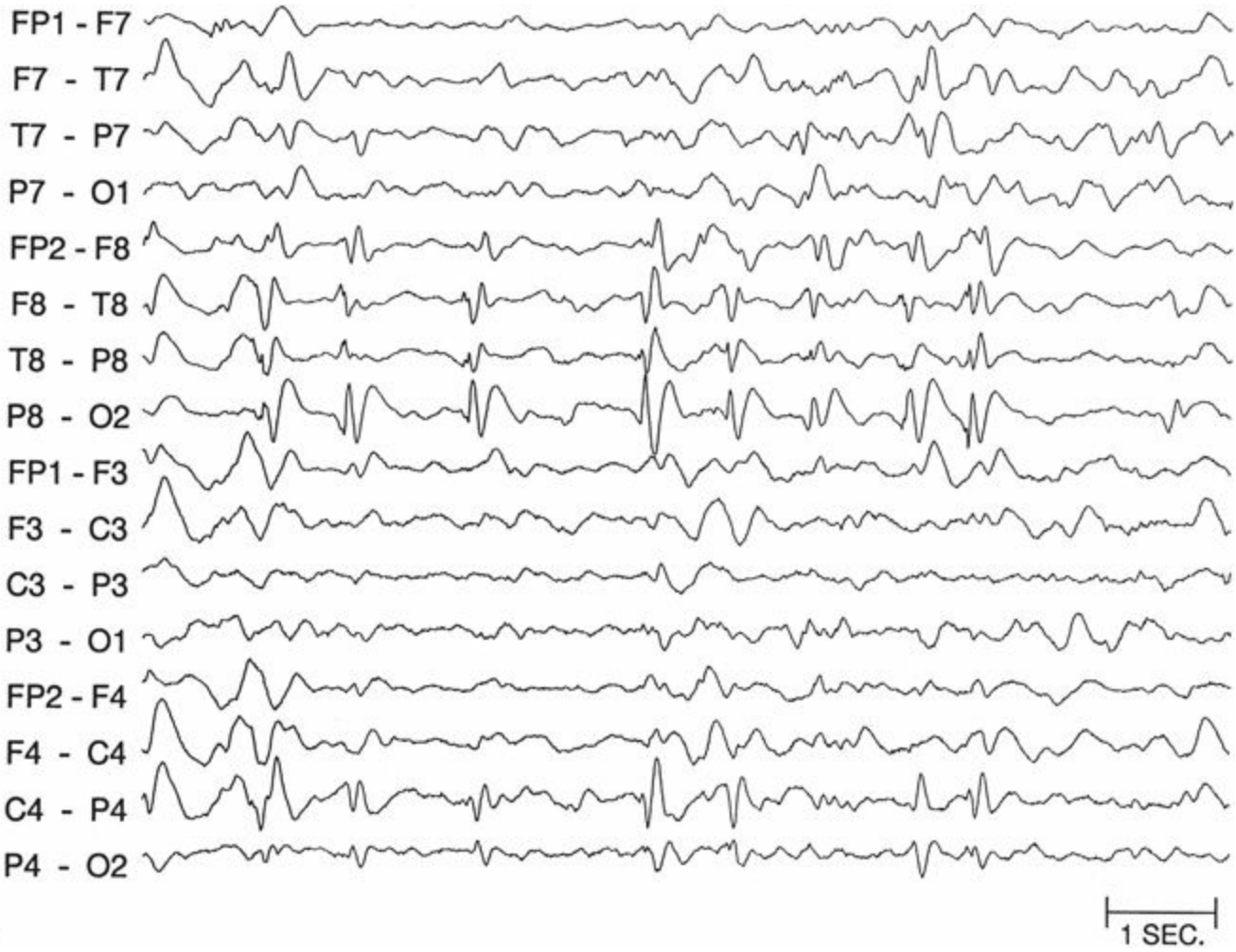
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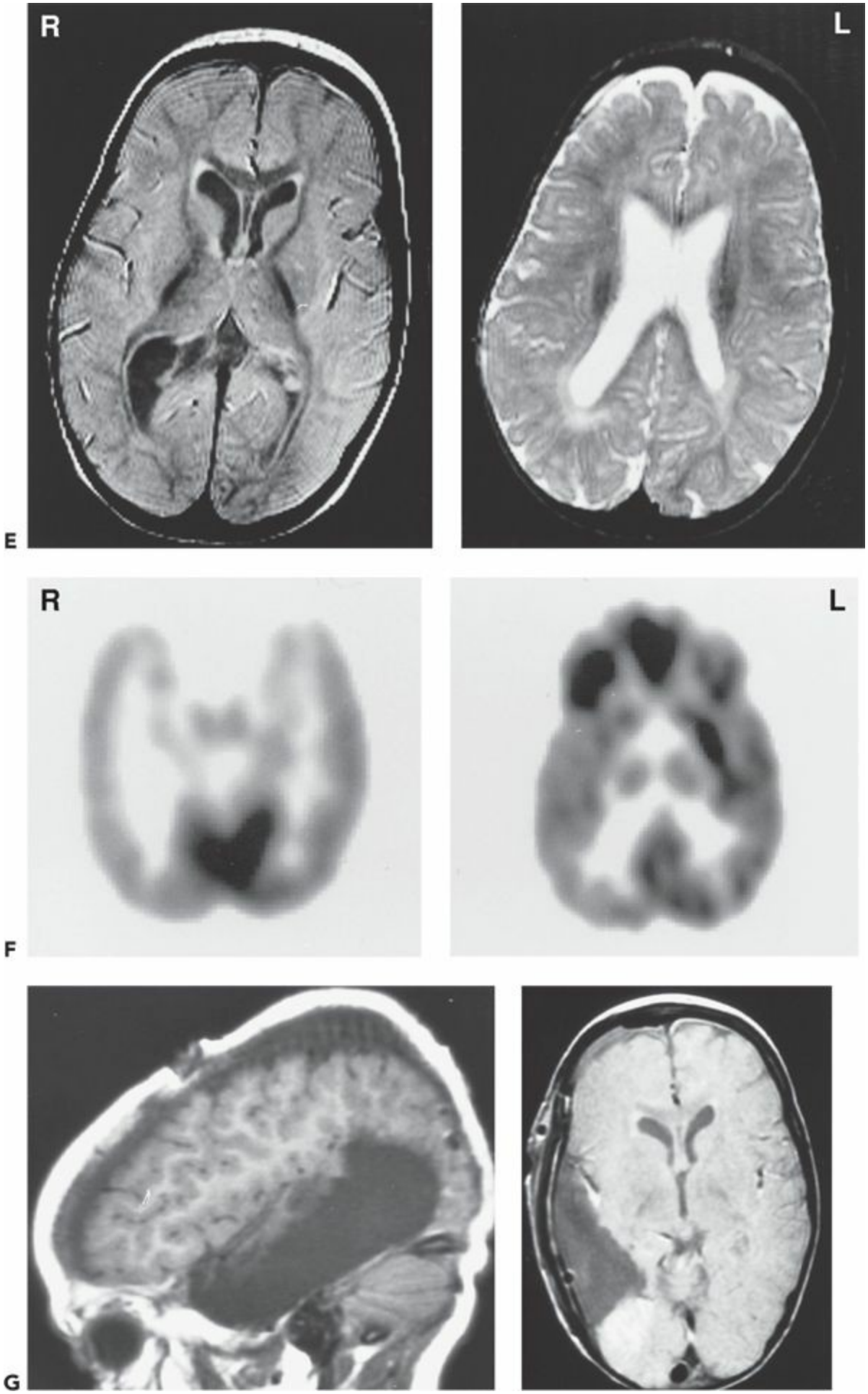

Figure 89.5. Case 5. (All images are of the same patient.) **A:** Ictal electroencephalogram from a 4.5-month-old infant (patient 2089) showing right parietal onset of a partial seizure (arrow). Seizures began at age 2 months and occurred several times a day. **B:** Ictal electroencephalogram at age 13 months, showing hypsarrhythmia with diffuse electrodecrement at the onset of an infantile spasm

(arrow). Evolution from partial seizures to infantile spasms occurred at age 7 months. The infant had delayed cognitive development and reduced visual attentiveness but no motor deficits. **C:** Sleep spindles were consistently reduced over the right hemisphere, providing further evidence of right hemisphere dysfunction. **D:** This carefully selected segment of the interictal electroencephalogram shows that spikes were sometimes predominant over the right parietal region, despite the diffuse hypsarrhythmic pattern during most of the recording. Normal faster frequencies were reduced in that area. **E:** Magnetic resonance imaging (MRI) at 13 months showed bilateral periventricular leukomalacia, worse in the right parietal region. The findings could have resulted from intrauterine right germinal matrix hemorrhage several weeks before the uneventful term birth. No cortical dysplasia or gyral abnormality was evident on MRI. **F:** Interictal 2-[^{18}F]fluoro-2-deoxy-D-glucose PET at 13 months showing right parietooccipitotemporal hypometabolism. **G:** Postoperative MRI showing the right parietooccipitotemporal resection performed at age 15 months. Histopathologic analysis of resected tissue revealed microscopic cortical dysplasia, possibly as a result of disturbance of late neuronal migration at the time of the intrauterine intraventricular hemorrhage. The infant remains free of seizures 17 months after operation and has made "catch-up" developmental progress. (**A**, **B**, **E**, and **F** are from Wyllie E, Comair Y, Ruggieri P, et al. Epilepsy surgery in the setting of periventricular leukomalacia and focal cortical dysplasia. Neurology. 1996;46:839–841, with permission; **A** and **G** are from Wyllie E, Comair YG, Kotagal P, et al. Epilepsy surgery in infants. Epilepsia. 1996;37: 625–637, with permission.)

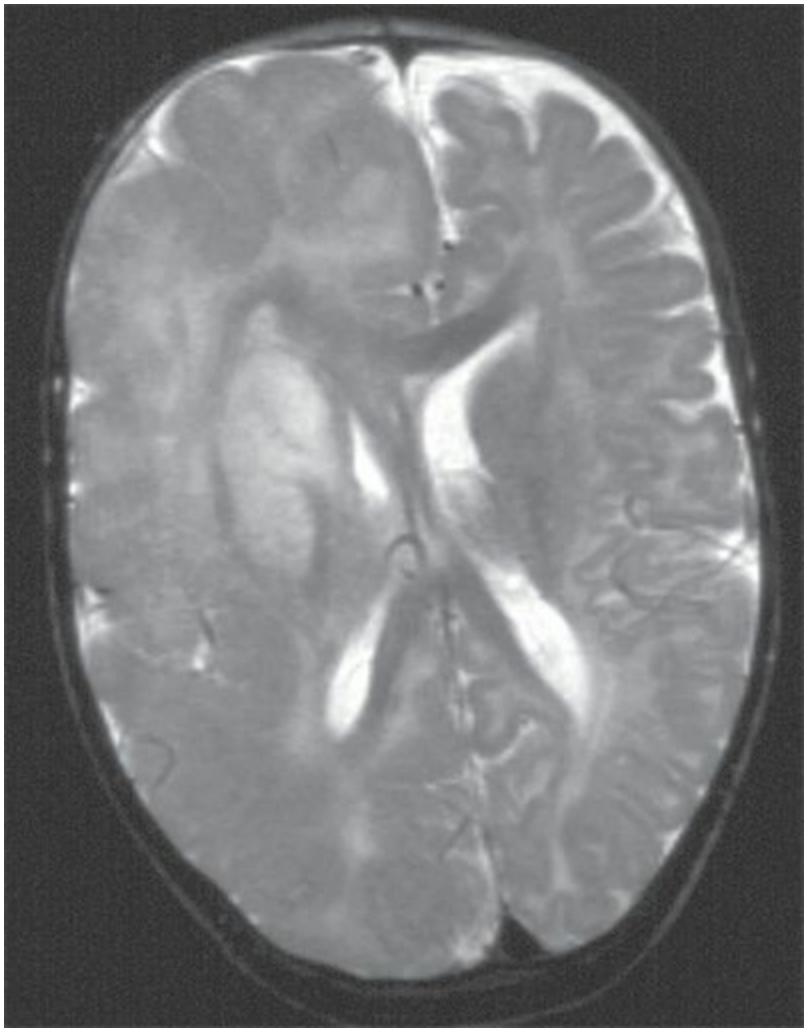

Figure 89.6. T2-weighted sagittal image of "typical" hemimegalencephaly showing diffuse right hemispheric enlargement and dysplasia. Midline shift with bulging of anterior falx to the left and compression of the right lateral ventricle suggests a mass effect as a result of increased volume of the brain parenchyma. Dysplastic changes are diffuse, with thick and disorganized cortex, poor gray–white matter differentiation, and abnormal signal in the white matter. Note that the basal ganglia are also dysplastic with abnormal increased signal.

Hemispheric syndromes are also important etiologies in children undergoing epilepsy surgery in the form of hemispherectomy (46,58). Hemispheric malformations of cortical development like hemimegalencephaly (see Fig. 89.6), Sturge–Weber syndrome, and perinatal unilateral cerebral ischemic insults are the most common etiologic factors in children and adolescents who had

hemispheric ablation procedures, with Rasmussen chronic focal encephalitis occurring less frequently (46,58,59).

The age-related differences in etiology result in an age-related spectrum of surgical procedures. Anteromesial temporal resections predominate in adults but not in children. In pediatric series, extratemporal or multilobar resections or hemispherectomies composed 44% of the surgeries in adolescents, 50% in children, and 90% in infants (1,2).

SURGICAL CONSIDERATIONS IN PEDIATRIC PATIENTS

Identification of Candidates: The Timing of Surgery

Critical features of surgical candidacy at any age include intractable epilepsy interfering with quality of life or development, clear identification of a localized epileptogenic zone, and low risk for new postoperative neurologic deficits. However, for each of these factors, age-related issues must be considered in light of results from an extensive presurgical evaluation. The risk of proceeding with surgery must be weighed against the risk of continuing with uncontrolled seizures treated medically. If careful analysis yields a favorable risk–benefit ratio for surgery, then the available data suggest that it is appropriate to proceed regardless of age.

The usual delay from onset of seizure intractability to surgery is still in the range of 12 to 15 years at most centers, reflecting a reluctance to consider surgery during childhood. Results from pediatric series do not justify this reluctance but instead suggest that children should be referred for surgical evaluation at whatever age they present with severe focal epilepsy. Complicated cases warrant referral to specialized centers with extensive pediatric experience. Improving access to centers with pediatric epilepsy surgery experience is also critical (6). Evidence is also emerging to support the long-held notion—"sooner the epilepsy surgery in children better is the prognosis for seizure outcome" (60).

Goals of Epilepsy Surgery in Children and Adolescents

The goals of epilepsy surgery may vary according to age. In adolescents and adults, the main goals are usually related to driving, independence, and employment, and their achievement requires complete postoperative freedom from seizures. For infants and children, the goals often center on relief of catastrophic epilepsy, resumption of developmental progression, and improvement in behavior. These goals may sometimes be reached even in the absence of complete freedom from seizures. For infants and young children with many daily seizures and developmental stagnation or regression, a postoperative outcome with rare or infrequent seizures and resumption of developmental progression may be gratifying. Even in the less-favorable-outcome group with malformation of cortical development, 68% of patients in the Cleveland Clinic series had few or no seizures after surgery (2).

In pediatric practice, developmental outcome is of paramount importance. Developmental delay is common in pediatric epilepsy surgery candidates, especially infants. Duchowny and associates noted normal preoperative development in only 20% of infant candidates for epilepsy surgery, whereas the remainder had moderate (52%) or severe (28%) delay (1). Postoperatively, the

developmentally normal infants remained normal after surgery, whereas the severely delayed infants remained severely delayed. Parents reported cognitive and social gains in children with seizure-free outcome, although these were difficult to appreciate on examination (1). Other researchers have made similar observations (12,36,61,62).

In a series of infants who had epilepsy surgery at the Cleveland Clinic (63), the developmental quotient indicated modest postoperative improvement in mental age. Developmental status before surgery predicted developmental function after surgery, and patients who were operated on at younger age and with epileptic spasms showed the largest increase in developmental quotient after surgery (63). In a recent large series on long-term functional outcome of patients after hemispherectomy, seizure recurrence after hemispherectomy and contralateral hemisphere abnormalities on MRI were the major predictors of poor outcome in ambulation, spoken language, and reading abilities (64). These results suggest that early surgery for refractory epilepsy as well as postoperative seizure freedom may offer an opportunity for improved developmental outcome.

Seizures that begin in the first few years of life, regardless of etiology, constitute a risk factor for mental retardation (65,66). Early surgical intervention may reduce this risk, but quantitative and prospectively collected data are scant. Asarnow et al. (67) studied results of the Vineland assessment in 24 patients with infantile spasms who underwent focal cortical resection or hemispherectomy at a mean age of 21 months (67). Raw scores 2 years after surgery increased significantly compared with preoperative levels, although only four children had a normal rate of development. The Adjusted Behavioral Composite scores were significantly higher for children who had higher preoperative scores or earlier surgery. Surgery within the first year of life may therefore maximize developmental outcome by allowing resumption of developmental progression during critical stages of brain maturation (67). Another study (68) on cognitive outcome of hemispherectomy in 53 children who underwent presurgical and postsurgical testing reported moderate cognitive and behavioral improvement in most patients. The most significant predictor of cognitive skills after surgery was etiology, with dysplasia patients scoring lowest in intelligence and language but not in visual–motor skills (68). Other studies have also reported similar improvements in the cognitive and behavioral spheres after hemispherectomy (64,69–71).

Psychosocial outcome may also be better after earlier surgery. At the advent of epilepsy surgery, Falconer urged that adolescents be considered for operative treatment before the end of secondary school so that they could pass more normally through the maturational stages of early adulthood (20). In patients who had temporal resection for childhood-onset epilepsy and were studied after a mean interval of 15 years, Mizrahi et al. noted that later surgery was associated with greater permanent psychosocial, behavioral, and educational problems (72). Delaying surgery for childhood-onset epilepsy may have disadvantages.

Age-Related Risks of Epilepsy Surgery

The extensive multilobar and hemispheric surgeries performed in children and adolescents may carry some risk. In the Cleveland Clinic series (2), two of 149 patients (1.3%) died immediately after surgery, and Paolicchi et al. (16) reported one postoperative death among 83 patients (1.2%) in a pediatric series from Miami Children's Hospital. Mortality may be slightly higher for infants, in part because of their small blood volumes. One or two infant deaths were reported in surgery series from UCLA (38), Johns Hopkins Medical Center (73,74), and Miami Children's Hospital (1,16). These results emphasize the need to reserve surgery for infants with severe epilepsy. Risk may be reduced

by a dedicated team of pediatric anesthesiologists, intensivists, and surgeons.

At any age, the mortality from epilepsy surgery must be weighed against the mortality from uncontrolled seizures treated medically. Nashef et al. (75) found this risk to be 1:295 per year in children and adolescents with severe epilepsy and learning disabilities. In a population-based cohort study in children (76) (1 to 16 years of age) who developed epilepsy between 1977 and 1985, 26 (3.8%) of 692 children died by the year 1999. The majority (13/26) who died had secondarily generalized seizures. Neurologic deficit was the only independent factor that determined mortality. In this study, mortality in children with comorbid neurologic deficits (15/1000 person-years) was higher than in those without any deficits (0.7/1000 person-years). Mortality in the children with seizures and no neurologic deficits was no different from that in the reference nonepileptic population. A Dutch study has reported similar results (77,78). These epidemiologic data reinforce consideration for early surgical intervention, as children with catastrophic partial epilepsy who are candidates for surgery often have neurologic deficits and secondarily generalized seizures. The increased long-term mortality from epilepsy in children can also be seen in outcome studies of epilepsy surgery. During long-term follow-up, late death occurred in 2% of the Cleveland Clinic series (2) and in 11% of a series from Guldvog et al. (21) involving patients with persistent seizures.

Other risks of epilepsy surgery, including new postoperative neurologic deficits (e.g., hemiparesis or language impairment), may be reduced in pediatric patients as a result of developmental plasticity. Language may transfer to the right hemisphere during the course of destructive processes such as Rasmussen chronic focal encephalitis or may develop in an unusual region of the left hemisphere in a congenital left frontal or posterotemporal tumor (79,80). In these cases, the epileptogenic lesion may be resected or disconnected without producing new language deficits. Motor function may also partially develop outside a damaged or malformed rolandic region, so that resection of a peri-rolandic lesion results in little or no additional postoperative motor deficit (see Fig. 89.5). Factors favoring developmental plasticity include early onset of the lesion (e.g., perinatal infarction or congenital malformation) and surgery performed within the first few years of life.

Decrements in postoperative verbal memory scores may follow left mesial temporal resection in adults, especially in individuals with high preoperative scores (81,82). Little is known about this potential complication in children, although similar risk factors were identified in a small pediatric series examining cognitive outcome after temporal lobe resection (83). It is not known whether the intracarotid amobarbital procedure can accurately predict this complication in children. Low memory retention scores may occur during this testing in a significant proportion of children (84), and withholding mesial temporal resection from otherwise favorable candidates on the basis of this finding alone may not be appropriate.

Seizure Outcome after Epilepsy Surgery

Published studies on surgical outcome are reliable but difficult to compare owing to the inclusion of patients with diverse pathologic conditions, use of different evaluation and surgical techniques, and variable definitions of postoperative outcome and follow-up. Good postoperative outcomes with rare or no seizures occur with similar frequencies at all ages, according to recent series in infants, children, adolescents, and adults, despite age-related differences in causes and surgery types (1,2,16,36,85). The likelihood of a favorable seizure outcome postoperatively does not diminish significantly, even in infancy. These results compare favorably with those achieved during controlled

trials of new antiepileptic drugs, in which the rate of "responders" (at least 50% improvement in seizure frequency) was 20% to 40% and seizure freedom was fairly rare (86). More recent studies show only modest chances of seizure freedom (<5%) after failure of two antiepileptic medications and report no difference between established and newer antiepileptic drugs used as initial monotherapy (87).

Certain subgroups appear especially likely to be free of seizures after surgery. In the Cleveland Clinic pediatric series (2), this outcome was significantly more common in patients who had temporal resection (78%) than in those who had extratemporal or multilobar resection (54%). However, this difference based on surgery type disappeared when results were analyzed by etiologic factors. Significantly more patients with low-grade tumor (82%) than patients with malformation of cortical development (52%) were seizure free, regardless of whether the surgery was temporal (86% for tumor vs. 56% for dysplasia) or extratemporal/multilobar (75% for tumor vs. 50% for dysplasia). Duchowny et al. (1) noted that it is relatively meaningless to consider pediatric patients treated with temporal resection as a special outcome subgroup because of the varied etiologic factors in younger patients. In children, surgically managed temporal lobe epilepsy is not synonymous with hippocampal sclerosis. However, in the pediatric patients who have hippocampal sclerosis, postoperative seizure outcome appears similar to that in adults. In a series of 34 children and adolescents with hippocampal sclerosis who had anteromesial temporal resection at the Cleveland Clinic for intractable temporal lobe epilepsy, 78% of patients were free of seizures after surgery (56). Published series (46,59,69,70) in children who underwent hemispherectomy for any indication report seizure freedom rates in the range of 50% to 65% after a postoperative follow-up of 3 months to 22 years (Chapter 84).

CONCLUSIONS

All children with catastrophic epilepsy, regardless of age, must be promptly evaluated for diagnosis and surgical candidacy. The risk–benefit ratio should then be cautiously weighed for every child in light of several complex age-related issues discussed in this chapter. Young age entails special challenges for presurgical evaluation, but it also provides a great opportunity to attain early freedom from daily seizures and to achieve the maximum cognitive potential. Even in some older children, it is now evident that surgically treatable epilepsy due to focal congenital or early-acquired lesion may manifest with a "generalized EEG phenotype" and global epileptic encephalopathy posing challenges for surgical selection. Evaluation and treatment of complex cases are best done at specialized centers with extensive experience in pediatric epilepsy surgery.

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CHAPTER 90 OUTCOME AND COMPLICATIONS OF EPILEPSY SURGERY

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The effectiveness of epilepsy surgery in the treatment of intractable focal epilepsy is currently widely accepted. With Engel class I evidence showing obvious therapeutic superiority of temporal lobectomy (TL) over medical treatment with comparable complications (1), and multiple series replicating similar results with up to 50% to 55% of patients remaining seizure free as late as a decade after surgery (2,2–9), little doubt remains that once the determination of medical intractability has been made, a patient with temporal lobe epilepsy (TLE) should undergo an evaluation for surgical candidacy (10). Several studies have also shown encouraging, albeit less dramatic, results following extratemporal epilepsy surgery with chances of seizure freedom at 5 to 10 postoperative years ranging from 30% to 50% (11–22).

Our understanding of "favorable" surgical outcomes has evolved significantly over time. We know now that postoperative seizure outcome is a dynamic state with chances of ongoing seizure freedom dropping steadily after surgery (3,6,8,23). Conversely, up to 20% to 30% of TL patients have intermittent seizures within the few months following surgery only to become seizure free later (3,7,24–26). So, assessing the "success" of surgery few months postoperatively represents a simplistic approach of limited long-term usefulness. Furthermore, while seizure outcome is indeed the most important determinant of quality of life (QOL) after surgery (27), it is not the only one, such that a comprehensive view of a surgical outcome should include consideration of neurocognitive, social, psychiatric, and functional implications of surgery, as well as its potential complications. Lastly, recent clinical research on postoperative seizure outcomes has generated the conceptual framework for translational research aimed at understanding and modifying the mechanisms of seizure recurrence after surgery (20,28–30).

This chapter provides an overview of the currently available information on surgical outcomes following the most commonly performed types of epilepsy surgery.

AVAILABLE OUTCOME MEASURES AND PITFALLS OF OUTCOME STUDIES

Definitions of "seizure free" vary. Two major seizure outcome classification systems are currently available. Traditionally, most studies have used Engel's classification (Table 90.1), reporting favorable seizure outcomes as being either "excellent," reflecting freedom from disabling seizures (Engel class I), or "good" with the additional inclusion of patients having rare seizures (Engel classes I and II). Disadvantages of this system include the following: (i) Certain outcome criteria, such as "worthwhile improvement," are very ambiguous, leading to variation in interpretation among different centers; (ii) comparison to antiepileptic drug (AED) trials is virtually impossible as those

typically use "≥50% seizure reduction" as their outcome measure; and (iii) the "seizure-free" category (Engel class I) is not restricted to patients who are truly completely seizure free after surgery (Engel class IA); it also includes those with persistent auras, simple partial seizures, and generalized convulsions upon AED withdrawal (Engel classes IB to ID). Because most studies do not usually report outcome using Engel's classification subcategories, the independent evaluation of truly seizure-free patients is not always possible.

Table 90.1 Engel's Classification of Postoperative Outcome

Class I: Free of disabling seizures[a]
A: Completely seizure free since surgery
B: Nondisabling simple partial seizures only since surgery
C: Some disabling seizures after surgery, but free of disabling seizures for at least 2 y
D: Generalized convulsions with AED discontinuation only
Class II: Rare disabling seizures ("almost seizure free")
A: Initially free of disabling seizures but has rare seizures now
B: Rare disabling seizures since surgery
C: More than rare disabling seizures since surgery, but rare seizures for the last 2 y
D: Nocturnal seizures only
Class III: Worthwhile improvement[b]
A: Worthwhile seizure reduction
B: Prolonged seizure-free intervals amounting to greater than half the followed-up period, but not <2 y
Class IV: No worthwhile improvement
A: Significant seizure reduction
B: No appreciable change
C: Seizures worse

[a]Excludes early postoperative seizures (first few weeks).
[b]Determination of "worthwhile improvement" will require quantitative analysis of additional data such as percentage seizure reduction, cognitive function, and QOL.

To address the above issues, the International League Against Epilepsy (ILAE) issued a commission report proposing a new outcome classification scheme (Table 90.2). Completely seizure-free patients are classified separately; seizures are quantified in each category and compared to a well-defined baseline frequency, and results can be easily compared to AED trials. To date, only one study (26) compared both systems in its outcome assessment and found similar results at the last available follow-up.

Table 90.2 Proposal for a New Classification of Outcome with Respect to Epileptic Seizures

Outcome classification	Definition
1	Completely seizure free[a]; no auras
2	Only auras[b]; no other seizures
3	1–3 seizure days per year; ± auras
4	4 seizure days[c] per year to 50% reduction of baseline seizure days[d]; ± auras
5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ± auras
6	More than 100% increase of baseline seizure days; ± auras

[a]"Neighborhood seizures" in the first postoperative month are not counted.
[b]Auras are only counted if they are short in duration, and similar or identical to the preoperative ones.
[c]A "seizure day" is a 24-hour period with one or more seizures. This may include an episode of status epilepticus.
[d]"Baseline seizure days" are calculated by determining the seizure-day frequency during the 12 mo before surgery, with correction for the effects of AED reduction during diagnostic evaluation.

Some centers reported their outcomes using internally validated scoring systems (24,31,32). Others chose a prespecified period of seizure freedom—usually 12 to 24 months—as reflecting a favorable outcome (4,33,34).

This wide variation in outcome measures is only one of many pitfalls complicating the interpretation and comparison of the results among different surgical series. Other issues comprise (i) including patients with heterogeneous disease pathologies and surgeries in the same study limiting the validity of the results for any one group; (ii) using cross-sectional methods of analysis, which, by definition, are inaccurate in analyzing longitudinal dynamic time-dependent outcomes like postoperative seizure freedom; and (iii) the lack of studies comparing the usefulness of various surgical diagnostic (e.g., invasive subdural vs. depth recordings) or treatment techniques (e.g., resective vs. radiosurgery vs. thermo- or laser ablation). The final limitation of our current outcomes understanding remains our inability to "individually" predict the chances of success for potential surgical candidates.

TEMPORAL LOBE SURGERY

Rate and Stability of Postoperative Seizure Freedom

TL is the most common type of resective epilepsy surgery performed. One randomized controlled trial (1) showed that only two intractable epilepsy patients need to be treated surgically for one patient to become free of disabling seizures. Table 90.3 summarizes the seizure outcomes of most major centers, showing relatively comparable results with about two-thirds of the patients becoming seizure free postoperatively, compared to 5% to 8% with medical therapy. More than 50% of patients remain seizure free beyond 10 years after anterior temporal lobectomy (ATL) reflecting a sustained

benefit (3,5,35–38).

Table 90.3 Surgical Outcome in Major Studies Evaluating Pure Cohorts of Patients with Hippocampal Sclerosis

Author[a]	Study period	Years of follow-up: mean (range)	N	Surgery	Outcome measure used		Percentage of favorable outcome at: 1 year	2 years	5 years	>5 years	Date of last follow-up
Paglioli et al. (25)		6.7 (2–11)	80	ATL	Engel I						72%
		4.5 (2–11)	81	SAH	Engel I						71%
Jeha et al. (4)	1990–2000	5.5 (1–14.1)	371 (219 with MTS)	ATL or SAH	ILAE 1	All		78%	66%	53% at 10 y	63%
					ILAE 1	MTS		71%	64%	55% at 10 years	70%
Jeong et al. (5)	1994–2000	4.6 (1–n/a)	227	ATL	Engel I		81%		75%		
Spencer et al. (8)	1996–2001	4.6 (2–7.3)	339 (297 with MTS)	ATL	2-year remission from seizures ± auras			46%	69%		MTS 68% Neocortical 50%
Janszky et al. (2)	1993–2002	n/a (0.5–n/a)	171	ATL	Complete seizure freedom to last follow-up or for "≥2 y at time of outcome assessment"			71%	58%		
Salanova et al. (26)	1984–2002	n/a	262	ATL	Engel I						65%
Paglioli et al. (7)	1992–2000	5.47 (2–11)	135	ATL or SAH	Engel IA		85%	77%	74%	66% at 10 y	
Urbach et al. (27)	1999–2000	2	209	n/a	Engel IA		73%				
McIntosh et al. (6)	1978–1998	9.6 (0.7–23)	325	ATL	Engel I (a, b, d)	All	61%	55%	48%	41% at 10 y, 37% at 15 y	
						HS	68%	62%	54%	47% at 10 y 43% at 15 y	
Yoon et al. (28)	1972–1992	8.4 (3.1–20)	175	n/a	"Continuous l-year seizure-free"		51%				
Jutila et al. (29)	1988–1999	5.4 (3 mo–10.5 y)	140	ATL or SAH	ILAE 1		64%	58%	50%	50% at 9 y	58%
Wieser et al. (19,30)	1975–1999	7.2 (1–24)	369 (with MTLE, 151 with HS)	SAH	Engel I		71%	70%	65%	62%	66.9%
Hennessy et al. (24)	1975–1995	5.2 (n/a)	116	ATL	ILAE class 1a 12 consecutive months of absolute seizure freedom ± auras		56%	50%	38% 67%	34% at 10 y	57.1%

[a]Bold: Prospective studies; italic: all TLE (not distinguishing MTLE from neocortical).

If a patient is seizure free at 1 year postoperatively, the likelihood of remaining seizure free is 87% to 90% at 2 years, 74% to 82% at 5 years, and 67% to 71% at 10 years (3,5, 35–39). If a patient is seizure free for 2 years postoperatively, chances of seizure freedom increase up to 95% at 5 years, 82% at 10 years, and 68% at 15 years (8,40). So, seizure freedom for 2 years might be a better predictor of long-term outcome, although both the 1-year and the 2-year conditions correlate fairly well with subsequent seizure-free status.

In surgical failures, more than half of seizure recurrences start within 6 postoperative months, and more than 95% recur within 2 to 5 postoperative years (8,41). There is therefore an initial phase of steep recurrence, followed by a relapse rate of 2% to 5% per year for 5 years with subsequent more stable seizure freedom (6,8,36). Recent data suggest that prognostic factors affecting those two phases of recurrence are distinct (8,28,29,33,42,43), possibly reflecting different mechanisms for early versus late relapses. "Early recurrences" occurring within 6 to 12 months of surgery may be due to incomplete removal of the initial epileptogenic zone, whereas later relapses may reflect an underlying diffuse epileptogenicity or progression of an "age-dependent" etiology such as mesial temporal sclerosis (2,4,28,29,36,39,44,45). The main implication of this mechanistic perspective is the idea that improving seizure outcomes necessitates both optimal localization and resection of the epileptic focus AND strategies aimed at preventing future epileptogenesis.

The counterpart of late seizure relapses also exists. In the "running-down" phenomenon, defined as the late remission of postsurgical seizures and occurring in 3.2% to 20% of TLE surgery cases, the frequency of seizures during the running-down interval may be up to several per month, but a seizure-free state is usually achieved within 2 years (44,46). The most accepted explanation for this phenomenon is a dekindling effect, the converse process to secondary epileptogenesis, where the induced synaptic dysfunction gradually declines in the surrounding epileptogenic cortex after pacemaker resection, and eventually "runs itself down" (46).

Predictors of Recurrence

Clinical Variables and Seizure Outcome

Age at Onset of Epilepsy.

Patients with an earlier age at onset of epilepsy (usually <5 years) or at the time of the initial neurologic insult may be up to three times more likely to have a favorable postoperative outcome (5,37). However, some investigators proposed that this variable actually predicts hippocampal sclerosis (HS), which is the actual good prognostic indicator (34,47). This hypothesis is supported by the observation that those patients were more likely to have features typical of HS such as unilateral hippocampal atrophy on MRI (48) and focal ictal electroencephalogram (EEG) with predominantly partial seizures (37) and by the fact that age at onset per se was of no prognostic value in studies evaluating pure cohorts of HS (34,47) or controlling for pathology (4,6,8).

Duration of Epilepsy.

A long history of seizures correlated with worse outcome in multiple studies on univariate analysis (24,41,44). In some of those same cohorts, this influence disappeared when multivariate analysis was performed adjusting for other more solid indicators of outcome (6,7). Furthermore, many more recent studies found no correlation of epilepsy duration with outcome (4–6,34,47,49). Various hypotheses have been proposed to explain those findings, including secondary epileptogenesis occurring with a long seizure history, varying degrees of maturation of different epileptogenic foci, and the increased development of generalized seizures with longer epilepsy duration (44).

Age at Surgery.

Most studies found no correlation between age at surgery and seizure outcome (5,6,8,34), although one longitudinal study in HS patients found that patients who were ≤24 years old at surgery were about four times more likely to be seizure free at 5 postoperative years when compared to the older surgical group (36 years or older) (7). Few other studies found similar results (44).

One should note here that successful and safe ATLs have been performed in the elderly (>50 years old), with few reports suggesting slightly lower chances of seizure freedom albeit without increased risks of neuropsychological deficits (44). Therefore, older age by itself should not be a deterrent from surgery.

Absence of Secondarily Generalized Tonic–Clonic Seizures.

Only 57% of mesial TLE patients with secondarily generalized tonic–clonic seizures (SGTCS)

achieved a 1-year remission compared to 80% remission rate in those who had only partial seizures in one study (34). Patients who had no generalized tonic–clonic seizures (GTCS) were 2.2 times more likely to be seizure free 5 years after surgery in another study (7). This effect may be most significant when GTCS are frequent (more than two per year) and occurring within 3 years of surgery (6). The prognostic significance of SGTCS was confirmed in a prospective multicenter trial (4).

The occurrence of SGTCS in TLE correlates with more extensive HS, multifocal irritative areas, and extended positron emission tomography (PET) hypometabolism suggesting a diffuse potential epileptogenic zone with worse expected surgical outcome (44).

Other.

Clinical variables where some studies suggested a favorable prognostic significance include low baseline seizure frequency and a history of febrile seizures. This, however, was not consistently confirmed. No correlation between occurrence of auras and outcome was proven (8).

Imaging Variables and Seizure Outcome

Magnetic Resonance Imaging.

A consistently identified favorable outcome predictor has been the presence of a unilateral temporal lobe abnormality on MRI (4,44,47). Patients with MRI evidence of unilateral HS had a 54% chance of seizure freedom at 10 years after ATL compared to 18% if MRIs were normal in one longitudinal study (6). However, recent data suggest that such a favorable prognostic significance is actually conferred by ANY unilateral temporal MRI lesion, and not necessarily by HS, especially with concordant ictal and interictal EEG findings (44).

Although a normal MRI was traditionally considered an automatic correlate to surgical failure (40,41), recent data have actually shown seizure-freedom rates of up to 41% to 48% as long as 8 years after ATL (18,50–54). While some data suggest that these patients may actually have "MRI-negative" or undetected HS (44), other studies concluded that most cases of normal-appearing hippocampi on high-resolution MRI have neocortical TLE since they had less febrile seizures, more delta rhythms at ictal onset, and more extensive lateral neocortical changes on PET with surgical outcomes still comparable to those of HS obvious in MRI (51,53). It should be emphasized, though, that surgery was successful in nonlesional patients typically when performed in context of concordant EEG and PET data (18,51,53). "Normal" MRIs correlating with bad outcomes in older studies using lower quality imaging may have included patients with extratemporal or contralateral pathology, findings that would currently exclude viable surgical options (18,51,53). Lack of SGTCS and low preoperative seizure frequency correlate with more favorable surgical outcomes in nonlesional TLE, similar to lesional TLE (18).

Bilateral MRI lesions, including grossly bilateral HS, reflect multiple potentially epileptogenic foci and correlate with a worse surgical outcome: 58% seizure free at 2 years compared to 78% when compared to unilateral lesions or even normal MRI (8,44). Subtle hippocampal asymmetries only detected using volumetric analyses were less predictive of outcome (44).

Nuclear Imaging.

Unilateral temporal hypometabolism on FDG-PET is a good predictor of seizure freedom in patients with mesial TLE, independent of pathologic findings and regardless of whether the MRI is normal

(55). In a recent review of the literature, Casse (55,56) found that 86% of patients with unilateral temporal hypometabolism ipsilateral to the side of surgery had a good outcome as defined by more than 90% reduction in seizure frequency or Engel class I or II, with those chances slightly reduced to 82% if the MRI was normal. This number significantly dropped to 62% when PET was normal and to 50% when it showed bitemporal hypometabolism (56). With extratemporal hypometabolism, chances of seizure freedom are even worse: Complete seizure freedom at last follow-up (mean 6.1 years) was seen in 45% of patients with extratemporal cortical hypometabolism confined to the ipsilateral hemisphere and only 22% with contralateral cortical hypometabolism (57).

Abundant data support the usefulness of ictal SPECT in localizing the epileptogenic zone in TLE, with 70% to 100% of ictal SPECTs being correctly localizing and only 0% to 7% incorrectly localizing (44). However, while the prognostic value of such localized SPECT findings is clear in extratemporal or poorly localized nonlesional temporal epilepsy (58,59), its role in clear lesional TLE cases is less defined. In a recent analysis of patients with unilateral HS visible on MRI, surgical outcome was not influenced by contralateral increased flow on ictal SPECT (60). One hypothesis is that due to their low temporal resolution, ictal SPECT hyperperfusion patterns often contain both the ictal-onset zone and propagation pathways. These patterns often have a multilobulated "hourglass" appearance with the largest and most intense hyperperfusion cluster often representing ictal propagation and not necessarily requiring resection to render a patient seizure free (61,62). Results for interictal SPECT suggest that it is relatively poor at localizing the seizure focus (44).

Neurophysiologic Variables and Seizure Outcome

Noninvasive EEG.

Focal interictal EEG predicts a favorable outcome when lateralized to the side of surgery or when highly localized to the resected temporal lobe. Patients whose interictal EEGs showed ≥90% predominance on the operated-on side had an 80% chance of complete seizure freedom after a mean 5.5 years of follow-up versus 54% in those with lesser degrees of lateralization in one prospective study (5). In general, interictal evidence of a diffuse irritative zone predicts a worse outcome: Postoperative seizure freedom is worse when interictal spiking was posterior temporal, extratemporal, or bitemporal (44). Posterior temporal and extratemporal spiking in patients with pathologically confirmed HS may reflect diffuse epileptogenicity or "dual pathology" with associated neocortical epileptogenic zones, thereby explaining the associated worse prognosis (34,63). However, prognostic implications of bitemporal interictal spiking on surface EEG deserve more careful consideration, as it does not automatically preclude postoperative seizure freedom. One study found that if ≥90% of surface interictal bitemporal spikes arise from one temporal lobe, excellent outcome is possible (92% seizure free in the second postoperative year vs. 50% if <90% lateralization), and further evaluation with depth EEG electrodes may not even be indicated (64). With a unilateral MRI temporal lesion, and with lateralizing WADA or neuropsychiatric testing, up to 64% of patients with bilateral interictal spikes achieved complete seizure freedom at ≥1 year postoperatively when seizure onset was strictly unilateral on invasive evaluation (65). Other findings consistent with unilateral HS, such as a history of febrile seizures or early onset of epilepsy (prior to age 3 to 6 years), also correlated with favorable outcome in patients with bitemporal interictal spikes suggesting that contralateral spiking may simply be spread from a surgically treatable hippocampus (44). However, if the MRI is normal or shows widespread abnormalities, then seizure recurrence is

the rule as either an extratemporal focus spreading to both temporal lobes or bitemporal epilepsy becomes more likely (65).

Similar concepts apply to the prognostic value of ictal EEG. Again, focal or anterior ictal EEG correlates with a more favorable outcome, and patients who had bitemporal ictal onsets on surface EEG still achieved seizure-freedom rates of up to 64% at 1 postoperative year if seizures were exclusively unilateral with depth recordings and imaging or neuropsychological testing were also consistent with unilateral temporal dysfunction (44,65).

Intracranial EEG.

Depth electrode evaluations have traditionally been used to clarify lateralization of the epileptogenic zone in patients with suspected bitemporal or falsely lateralized TLE, whereas subdural recordings and stereoelectroencephalography (SEEG) are useful in neocortical epilepsy for extraoperative functional mapping and definition of the extent of the epileptogenic zone. Those modalities are therefore reserved for patients with a poorly defined epileptogenic zone, which may explain poorer outcomes seen in cases that required invasive recordings preoperatively compared to those that did not (8,38,44,66). Outcomes are particularly worse in patients who had prior temporal lobe resections (67). Yet, specific findings obtained with such invasive evaluations may provide useful prognostic information. During depth recordings, more favorable outcomes are seen with exclusively unilateral seizure onset and ictal spiking as opposed to low-voltage fast activity, electrodecrement, or any other rhythmic sustained activity at seizure onset, whereas evolution into distinct contralateral electrographic seizures lowered seizure freedom from 84% to 47% at 1 postoperative year (44). Short interhemispheric propagation times ranging from <1 second to <8 second, a short duration between EEG and clinical seizure onset, and diffuse or posterior temporal onset as opposed to anterior and/or middle basal temporal ictal onset have all been also identified as predictors of seizure recurrence after surgery (44).

Surgical Technique and Seizure Outcome

Similar seizure-freedom rates have been observed with selective amygdalohippocampectomy and anterior TL (8,68,69). Many studies failed to correlate the extent of temporal resection (37), the extent of hippocampal resection (38), or having a mesial versus neocortical resection (8,70) to outcome. Those studies, however, did not evaluate patients with mesial TLE separately. In the presence of unilateral mesial TLE with HS, the extent of mesial resection becomes a more significant predictor of postoperative seizure freedom (44). In a prospective, randomized, blinded clinical trial, Wyler et al. (71) found that only 38% of patients in whom the hippocampal resection was limited posteriorly by the projection of the lateral mesencephalic sulcus (partial hippocampectomy) were seizure free at 1 year, compared to 69% of those in whom the hippocampus was removed further, to the level of the superior colliculus (almost complete resection). The amount of amygdala that must be resected to achieve seizure freedom is unclear, although one study found no correlation between residual amygdalar tissue and surgical outcome (72). The ideal extent of lateral temporal resection also remains to be defined with conflicting data currently available (44).

In the presence of a well-circumscribed lesion, such as a tumor or a vascular malformation, a lesionectomy plus resection of the nearby adjacent cortex might suffice unless there is associated hippocampal atrophy. In such cases of dual pathology, complete seizure freedom after a mean follow-up of 37 months was lowered from 73% with lesionectomy plus mesial temporal resection to 20%

with mesial temporal resection alone and 12.5% with lesionectomy alone (44,73,74).

Etiology, Pathology, and Seizure Outcome

When pathologic findings in the resected temporal lobe were restricted to nonspecific gliosis, poor short- and long-term outcomes have consistently been observed (44). In a longitudinal study of 371 ATL patients, 44% of cases who only had gliosis were seizure free 8 years after surgery, compared to 64% if a specific pathologic diagnosis was identified (8). However, once a specific pathologic abnormality is identified, it is not entirely clear that its nature is relevant for seizure outcomes. While the older literature has suggested more favorable outcomes with HS, seizure-freedom rates were similar between HS and other types of lesions in many recent (6,8) or prospective studies (4,70,75). One hypothesis is that outcome depends not only on the presence of HS but also on its severity: Worse disease may predict better outcome. One group found that 84% of patients with classical HS, as defined by neuronal loss and sclerosis in CA1, CA4, and the granule cells of the dentate gyrus, achieved at least 95% seizure reduction at last follow-up, compared to only 29% of those where cell loss was restricted to the dentate gyrus and/or CA4 (53). Another group also found that rates of Engel class I outcomes at last follow-up increased from 60% to 76% to 89% as the pathologic severity of HS ranged from mild to moderate to severe (26).

FRONTAL LOBE SURGERY

Rate and Stability of Postoperative Seizure Freedom

Frontal lobectomy (FL) accounts for 6% to 30% of all epilepsy surgeries and represents the second most common procedure performed to treat intractable focal epilepsy after TL. However, reported seizure-freedom rates with frontal resections have varied from 13% to 80% (11,15,17,54, 76–82), suggesting, in general, significantly lower success rates than those observed with temporal resections. Only few studies evaluated seizure freedom after FL longitudinally and can therefore provide useful information related to rate and stability of seizure outcome over time (11,77,83). In a retrospective study evaluating 97 adults who underwent resective FL surgery between 1991 and 2005, Elsharkawy et al. (77) found that the probability of an Engel class I outcome was 54.6% at 6 months, 49.5% at 2 years, 47% at 5 years, and 41.9% at 10 years. In a study reviewing patients operated at Cleveland Clinic between 1995 and 2003, and using a stricter "favorable outcome" definition (complete seizure freedom since surgery), we had previously identified a seizure-freedom rate of 55.7% at 1 postoperative year, 45.1% at 3 years, and 30.1% at 5 years and beyond (11). Outcomes were somewhat more favorable, closer to the 40% seizure-free range in a more recent series (20). Eighty percent of seizure recurrences occur within the first 6 postoperative months, and although late remissions and relapses may occur, those are usually rare (11). One study showed that although a postoperative reduction in seizure frequency often occurred in patients who failed to become completely seizure free after surgery, this improvement was sustained until the last follow-up in only 35%, with seizure frequencies eventually returning to preoperative levels in the remainder (11). The running-down phenomenon previously described may occur following FL, but at a rate of <15%, also significantly less than that seen after TL (77).

Similar to TL, however, seizure freedom at 6 months to 2 postoperative years seems to be a very good predictor of a long-term seizure-free state. If a patient is seizure free at 2-year follow-up, the

probability of remaining seizure free up to 10 years may increase up to 86% (77).

Predictors of Seizure Recurrence

Mechanistically, proposed hypotheses to explain the generally lower rates of seizure freedom following FL include (i) difficulty localizing the epileptogenic zone with EEG data secondary to rapid ictal spread through the frontal lobe, (ii) difficulty achieving a complete surgical resection secondary to proximity of functional/eloquent cortex, and (iii) a preponderance of cortical dysplasia, often invisible on MRI, as the epilepsy etiology in the frontal lobe as opposed to clearly localized HS in the temporal lobe (14,79,84). Practically, identified predictors of postoperative seizure recurrence have included incomplete resection of the epileptic lesion (11,22,77,85,86), the need to perform an invasive EEG evaluation (11,77), the occurrence of acute postoperative seizures (11), the persistence of auras postoperatively (11,77), a history of febrile seizures (79), predominantly generalized or poorly localized ictal EEG patterns on surface EEG prior to surgery—especially in the adult population (11,13,17,77) —and the lack of a distinct single MRI lesion (11,13,77,85). Of all the above prognostic indicators, the two most consistently reported and strongly predictive of postoperative seizure freedom are the presence of an MRI lesion and completeness of resection (Figs. 90.1 and 90.2). A short epilepsy duration (<5 years) is associated with significantly improved outcomes, regardless if patients are lesional or not, a finding that highlights the urgency and importance of early surgical referral in patients with FLE (20).

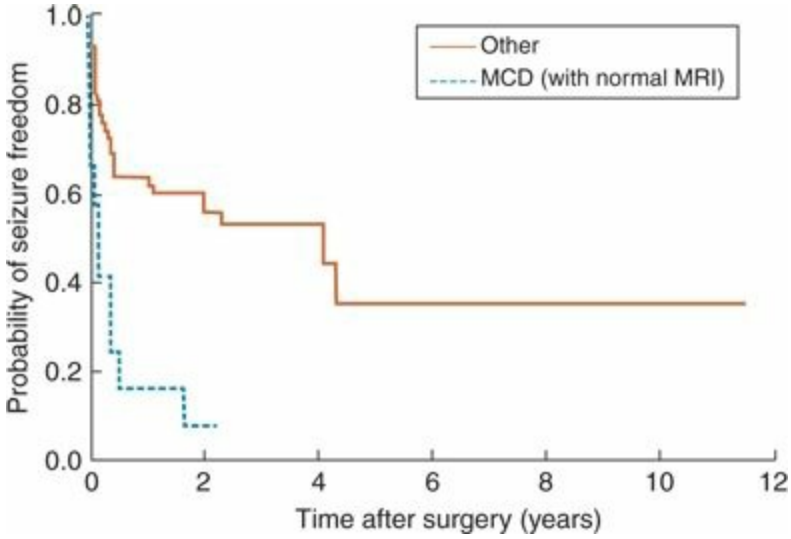

Figure 90.1. Survival curve illustrating lower long-term rates of seizure freedom in patients with normal MRI as opposed to lesional cases following frontal lobe resection. (Adapted from Jeha LE, Najm I, Bingaman W, et al. Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. Brain. 2007; 130(Pt 2):574–584.)

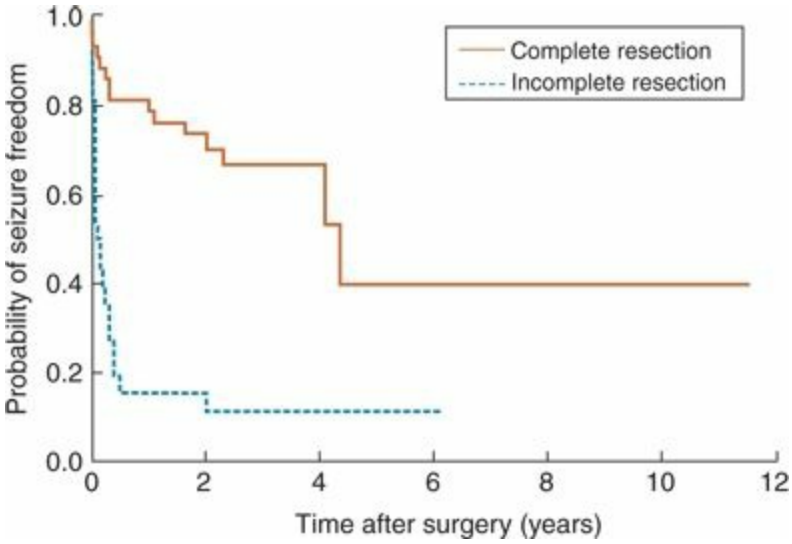

Figure 90.2. Survival curve illustrating lower long-term rates of seizure freedom in patients with incomplete resection as opposed to complete resections following frontal lobe resection. (Adapted from Jeha LE, Najm I, Bingaman W, et al. Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. Brain. 2007; 130(Pt 2): 574–584.)

MRI and Seizure Outcome

A normal MRI in a patient undergoing FL has consistently been found to predict a worse outcome. Twenty-five percent of the patients with negative MRI studies and 67% of those with neuroimaging abnormalities restricted to the frontal lobe were seizure free at a minimum duration of follow-up of 1 year in one study (87). A focal MRI abnormality was the only variable significantly associated with a favorable surgical outcome in another report (88). Only 41% of nonlesional FLE patients had an excellent outcome versus 72% when MRI abnormality was present in yet another retrospective analysis (79). Most such "nonlesional" FLE cases are thought to have an underlying malformation of cortical development (MCD) (13,85). In one series, all patients with normal MRI and pathologically proven MCD had recurrent seizures by 3 postoperative years (11). Knowing that milder forms of MCD such as microdysgenesis, cortical dyslamination, or focal MCD are often missed, even on high-resolution MRI may explain why one cannot "see" the extent of the epileptogenic tissue in those MRI-negative MCD cases making adequate surgical treatment harder. The particular pathologic MCD substrate in fact was critical in determining surgical outcome in another more recent series with the worst outcomes in type I MCD (19).

Techniques such as ictal SPECT imaging, FDG-PET, and subdural grid or SEEG monitoring are often used to better localize the epileptogenic zone in nonlesional FLE cases. A study reporting on 193 patients with neocortical focal epilepsy (including 61 with FLE) showed that correct localization by FDG-PET was an independent predictor of a good outcome (13), and other case reports highlighted the usefulness of ictal SPECT in identifying a potential epileptogenic zone in nonlesional FLE (84). A recent analysis, however, found that while MRI, PET, and ictal SPECT all had good positive predictive values with correspondingly acceptable negative predictive values in correlating with the ictal-onset zone as later defined by invasive EEG recording, there was no significant relationship between the diagnostic accuracy of any of these modalities and surgical outcome, with the exception of MRI ($P = 0.029$) (15). So, the translation of "accurate" and "correct localization" of epileptic foci using either PET or SPECT into actual improvements in seizure outcome for nonlesional FLE has not always been consistently reproducible. The interpretation of the role of intracranial EEG monitoring is another delicate issue. In a cross-sectional study of 51 nonlesional,

mostly FLE, cases operated on between 1992 and 2002, Wetjen et al. (76) found that 35.7% of the 28 patients who eventually underwent a focal resection after intracranial EEG recording became seizure free with high-frequency oscillations at ictal onset being predictive of seizure freedom. Since this study's patient population included cases operated on prior to the advent of FLAIR imaging and other high-resolution neuroimaging techniques, an unknown proportion of its cases may have had subtle structural abnormalities, which potentially could have been detected using current imaging modalities. A longitudinal study of FLE patients imaged and operated on more recently found that 66% were seizure free at 1 postoperative year, and 44% (95% CI = 39 to 49) at 5 years and beyond, including nonlesional cases (20). In summary, while nonlesional FLE cases seem to be as a whole less than ideal surgical candidates for resective epilepsy surgery, efforts to identify the specific subgroup that might benefit from surgery while pursuing nonsurgical treatment options for the rest are still required. Early referral for a presurgical evaluation is essential (20).

Any extrafrontal MRI abnormality also confers a poor prognosis. Favorable outcomes occurred in either none of the patients with multilobar MRI abnormalities (87) or at best in 10% to 14% (11,89). Tumors, well-circumscribed pathologies, usually have the best outcome with up to 62% seizure free at last follow-up in one report (11) and 65% Engel class I or II at last follow-up in another series (14).

European series from centers using stereo–EEG evaluations report more favorable outcomes in nonlesional extratemporal epilepsy (90,91), highlighting the importance of adequately developing a preimplantation hypothesis prior to exploration of these patients for resective surgery.

Extent of Resection and Seizure Outcome

Complete resection of the epileptogenic lesion has consistently been found to predict seizure freedom. In one report, of patients who had complete removal of their epileptogenic lesions, 81% were seizure free at 1 year and 66% at 3 years, compared to 13% and 11%, respectively, of those who did not (11). Complete removal of neuroimaging abnormalities (76,85,92) and abolition of residual ECoG spiking (93) or seizures (94) have also been linked with the most favorable outcomes following FLE surgery. Major challenges that hinder a complete resection in all cases include frequent proximity or overlap with eloquent cortex and difficulties identifying the true edges of the "abnormal" tissue in MCD cases where the MRI-visible portion of the dysplasia may be surrounded by microscopically abnormal tissue that seems normal on imaging (11).

In summary, while the rates of seizure freedom are low, in general, following frontal resections, very successful seizure outcomes are possible in a selected group of patients, mainly those with a clear MRI lesion that is completely resectable.

POSTERIOR CORTEX SURGERY

Rate and Stability of Postoperative Seizure Freedom

Resections in the posterior cortex represent <10% of all epilepsy surgeries, with reported postoperative seizure- freedom rates varying from 25% to 90% (12,85,95–98). In a longitudinal analysis of a cohort of posterior cortex resections, the estimated chance of seizure freedom was 73.1% at 6 postoperative months, 68.5% at 1 year, 65.8% between 2 and 5 years, and 54.8% at 6 years and beyond. The median timing of recurrence was 2.0 months with 75% of the seizure

recurrences occurring by 6.4 months, and late recurrences were rare with the latest being at 74 months (12). Similar rates of seizure freedom have been reported in another longitudinal analysis of 154 adult patients who underwent various types of extratemporal resections (about 40% frontal and the remaining being posterior cortex surgeries), with an Engel class I at 2 postoperative years being correlated with an 88% chance of remaining seizure free 14 years after surgery (83). These findings suggest that in posterior cortex resections, we can expect an initial rate of seizure recurrence that is as fast as following FL, allowing a relatively early identification of surgical failures, but with a more optimistic long-term outlook with late seizure-free rates comparable to those following temporal resections. Figure 90.3 illustrates the longitudinal rates of seizure freedom in posterior quadrant resections in a cohort evaluated at Cleveland Clinic recently.

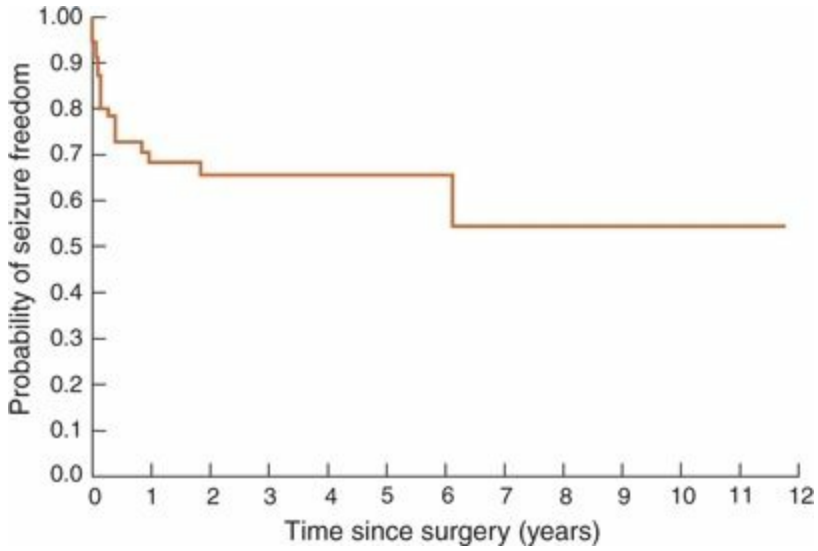

Figure 90.3. Survival curve illustrating long-term rates of seizure freedom following posterior quadrant surgery. (Adapted from Jehi LE, O'Dwyer R, Najm I, et al. A longitudinal study of surgical outcome and its determinants following posterior cortex epilepsy surgery. Epilepsia. 2009;50(9):2040–2052.)

Predictors of Seizure Recurrence

Patients with well-circumscribed focal lesions (tumors or MRI-visible MCD), who have more extensive resections (lobectomies or multilobar resections as opposed to lesionectomies), no preoperative evidence of extralobar epileptogenicity extending to the ipsilateral temporal lobe (temporal spiking or auditory auras), and no postoperative evidence of residual epileptogenicity (spiking on 6 months postoperative EEG) had the most favorable outlook in most series of posterior cortex resections (12,83,85,95–98).Other less consistently reported predictors of seizure freedom include lateralizing seizure semiology (95), focal ictal EEG (99), and shorter epilepsy duration (100).

In a series of 57 patients with posterior cortex resections, only a quarter of patients with either a tumor or lesional MCD had postoperative seizure recurrence, as opposed to more than half of the patients who had other pathologies after a mean follow-up of 3.3 years (12). Completeness of resection of such epileptogenic lesions was identified, among others, by Barba et al. (99) in 2005 to be the strongest predictor of postoperative seizure freedom. The challenge though is that while it is easily understood that larger resections have a better chance of achieving seizure freedom, this may not always be possible secondary to risks of injury to eloquent cortex, especially in the dominant hemisphere. We found that a lesionectomy achieved seizure freedom in 67% of cases in tumor or

MCD but in only 20% of other etiologies, suggesting that attempting a "smaller surgery" to avoid injuring eloquent cortex may be appropriate in selected cases of tumor/MCD but is rather ill-advised with other "unfavorable etiologies" (12). Invasive EEG recordings with subdural grids or depths or the use of stereo–EEG are more extensively used for better delineation of the epileptogenic zone and for extraoperative functional mapping optimizing resections with multiple reports showing very promising seizure outcome data. Caicoya et al. (101) found that five of seven occipital lobe epilepsy patients who underwent tailored resections guided by subdural EEG data were seizure free after a mean follow-up of 24.3 months. Cukiert et al. (102) reported on 16 patients with intractable extratemporal epilepsy who had either normal or "nonlocalizing" MRI, finding that 13/14 were rendered seizure free with resections that used subdural EEG information. The use of preoperative invasive monitoring has even been shown in one report to actually correlate with a more favorable outcome in a large cohort of extratemporal resections, consisting mostly of posterior cortex surgeries (83).

PSYCHIATRIC OUTCOMES AFTER EPILEPSY SURGERY

Epilepsy surgery, especially when successful, appears to reduce the prevalence of commonly observed psychiatric comorbidities of epilepsy, including depression and anxiety. Kanner et al. (103) reported a total remission rate off psychotropic medication in 45% of patients who underwent epilepsy surgery. The impact on psychotic disorders, however, is less clearly defined: It varied from unchanged in most cases to improved psychotic status/and or level of functioning (103). Conversely, patients may undergo an exacerbation of an underlying psychopathology or develop de novo psychopathology after surgery. In a study by Wrench et al. comparing the psychiatric outcomes following temporal versus extratemporal resections over a 3-month period, it was found that although both groups had similar baseline rates of depression and anxiety, and more patients were seizure free after a temporal than after an extratemporal resection, the psychiatric outcome was significantly worse in the temporal resections group: At 1 month after surgery, 66% of TL versus 19% of ETL patients reported symptoms of anxiety or depression, which persisted until the 3-month follow-up in 30% of TL and 17% of ETL. In addition, by the 3-month follow-up, 13% of ATL patients had developed a de novo depression as opposed to none in the ETL group. More notably, the occurrence of any of those psychiatric comorbidities was not related to seizure freedom (104). This reinforces the need to carefully evaluate and consider psychiatric outcomes after epilepsy surgery as an independent—albeit intimately connected—entity to the seizure outcomes.

PSYCHOSOCIAL OUTCOMES AFTER EPILEPSY SURGERY

The goals of surgery, as identified by epilepsy patients, extend beyond seizure control, to include driving, regaining or improving employment, and overall independence (104). Intimately linked to these goals is the absence of any "functional" worsening due to surgery, as might occur with a new neurologic deficit, memory loss, or language disturbance. A "successful" surgery is one where seizures are controlled and where the patients' psychosocial goals materialize into an improved QOL. Several studies have found that for optimal improvement in QOL measurements, complete

seizure freedom (even from auras) is required (41,105). Other possible predictors of an improved QOL include a higher presurgical IQ score, younger age at surgery, and a more stable mood at baseline (105). Studies evaluating the psychosocial and educational impacts of surgery in the pediatric population are very limited, but do suggest meaningful improvements in educational attainments and later employment (105).

SURGICAL COMPLICATIONS AFTER FOCAL EPILEPSY SURGERY

The main goal of the pre- and intraoperative evaluation for epilepsy surgery is to identify possible candidates in whom surgical intervention will totally or partially control seizures without increasing neurologic deficits or general morbidity.

In general, we can divide complications in focal neocortical epilepsy surgery based on pathophysiologic mechanisms into

Surgical Complications:

- Infection
- Hematoma
- Brain swelling
- Hydrocephalus
- Vascular compromise (arterial or venous)

Injury to Eloquent Areas of the Brain Causing Neurologic Impairment:

- Hemiparesis
- Hemiplegia
- Visual field defect
- Aphasia
- Alexia
- Neuropsychological impairment (deficits in cognition, memory, language, attention, and concentration)

Psychosocial Impairment:

- Family and interpersonal relationships
- Self-esteem
- Vocational/educational

Psychiatric Impairment:

- Depression
- Anxiety
- Psychosis

In regard to surgical procedures related to neocortical focal epilepsy, we can classify complications

due to focal neocortical resections as follows:

Diagnostic Procedures:

- Complications associated with subdural grid and strip electrodes, depth electrode, and SEEG

Therapeutic Procedures—Resective Surgery:

- Complications associated with frontal (mesial and lateral) resections
- Complications associated with temporal lobe resections
- Complications associated with parietal and occipital resections

Diagnostic Procedures

Subdural Grids/Strip Electrodes, Depth Electrode, and SEEG Complications

When noninvasive studies remain nonconcordant or inconclusive regarding the localization and the extent of the seizure- onset zone and/or the eloquent cortex, invasive studies using subdural grids, strips, or depth electrode may be needed (106). Jayakar et al. proposed the following relative indications for the evaluation with invasive monitoring: Normal structural imaging, extratemporal location, divergent noninvasive data, and encroachment on eloquent cortex, tuberous sclerosis, and cortical dysplasia (106). Rosenow and Lüders (107) recommended the use of invasive monitoring only in patients with focal epilepsy (single focus) in whom there is a clear hypothesis regarding the location of the epileptogenic zone (derived from noninvasive studies).

The intracranial placement of subdural grid electrodes via craniotomy has received increasing acceptance over the past decade. Invasive EEG monitoring by subdural grid electrodes facilitates prolonged electrographic assessment as well as extraoperative functional brain mapping of the superficial cortex. Also, it is particularly important in pediatric cases in which awake surgery and intraoperative functional mapping are often difficult.

The principal complications of grid electrode implantation include infection and subdural hematoma formation, which may be associated with neurologic deficits, elevations of intracranial pressure (ICP), and even death (108–110). Other complications may include brain swelling and arterial or venous infarctions (Fig. 90.4). In a recent series, of the 228 cases from 9 centers, the reported complications included infection, hemorrhage with transient deficit, increased preexisting hemiparesis, aseptic necrosis of the bone flap, and transient elevations in ICP (111). In an individual series from the Cleveland Clinic, an initial infection rate of 22% declined to 7% when subcutaneous tunneling of electrode cables was instituted (112). More recently, routine use of perioperative antibiotics and watertight dural closure with sutures at cable exit sites has been advocated in our group (Awad, personal communication, 1992). Since these modifications were introduced, the infection rate has declined markedly.

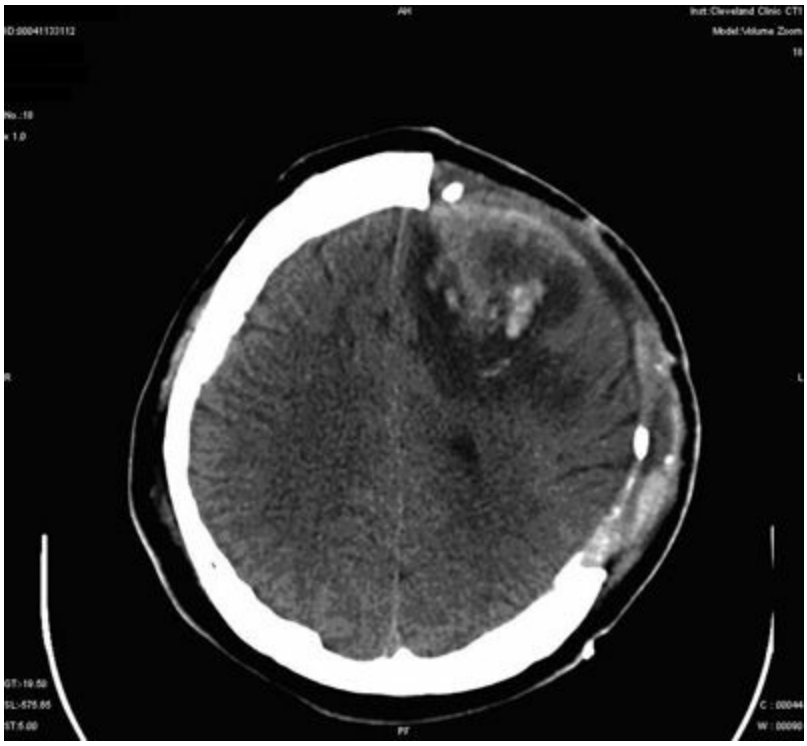

Figure 90.4. Complication of subdural grid placement: Venous infarction located in the left frontal lobe region after subdural grid placement. Postoperative CT after subdural grid removal and bone decompression.

In the absence of a multicenter, prospective complications survey, anecdotal reports of subdural hematoma formation, increased ICP, and death following grid placement have been documented in the literature. Some centers recommend routine, perioperative dexamethasone, and mannitol administration over 2 to 3 days after surgery, dural grafting, or leaving out the bone flap during the period of monitoring as responses to the threat of increased ICP. Circumferential dural incision, lining of the outer grid surface with hemostatic agents, and tapering of valproic acid are also recommended to reduce hematoma formation. There is no data with respect to the relative value of any of these practices in preventing individual complications.

Regarding subdural strip electrodes, epilepsy surgery literature suggests that insertion may be safer than depth electrode placement (109,113). No examples of significant hemorrhagic complications associated with prolonged neurologic deficit or death have been reported so far. Localized infections occur at a slightly lower frequency when compared with depth recordings and usually respond to antibiotic therapy alone. In a recent series of 350 patients, 2 cases of meningitis, 1 brain abscess associated with hemiparesis, and 3 superficial wound infections were reported (114). In two additional reports studying 122 patients, no hemorrhagic, neurologic, or infectious complications occurred following strip electrode placement (115).

Regarding the SEEG method, the total complication rate was 3% in a recent report from the Cleveland Clinic (116). Other groups reported similar results. Cossu et al. (90) reported a morbidity rate of 5.6%, with severe permanent deficits from intracerebral hemorrhage in 1% (90). In our reported series, all complications were hemorrhagic, which has been reported in several studies to be the most common complication in depth electrodes placement (90,116). Other published series reporting complications across invasive monitoring procedures (subdural grids and depth electrodes) reported rates ranging from 0% to 26% (114,117,118). Subdural grid electrodes implantation has historically been shown to have low permanent morbidity (0% to 3%) compared with depth electrodes (3% to 6%) since there is no intraparenchymal passage. Although it is difficult to compare

morbidity rates between subdural grids and SEEG due to the variability in patient selection, institutional preferences, and variable numbers of implanted electrodes, our experience suggests that the SEEG method provides at least a similar degree of safety when compared with subdural grids or strips; an impression also shared by others (90,119,120).

Different techniques of invasive monitoring exist, and each has its advantages and disadvantages. Chronically implanted subdural electrodes allow recording from large superficial cortical areas, but they provide limited coverage of deeper structures, such as the hippocampus, the interhemispheric region, or the cortex within sulci. Intracerebral electrodes have the advantage of excellent sampling from mesial structures and from deep cortical areas, providing a three-dimensional view of the epileptogenic network, with the disadvantage of providing information from a limited volume of tissue. Combined use of subdural and intracerebral electrodes also has been advocated. In a recent publication, Cossu et al. presented a retrospective study of a large series of patients (211 patients) who underwent SEEG evaluation. SEEG provided additional guidance toward epileptic focus resection in 183 patients (87%), resulting in seizure-free outcome in 44% of the cases and an overall significant improvement in 82%.

As highlighted by others, important issues relating to the stereotactic placement of depth electrodes and associated complications include (i) the relative safety of lateral, parasagittal, and tangential methods of insertion; (ii) the relative safety of flexible versus rigid electrodes; (iii) the role of computer- assisted work stations in the improvement of stereotactic accuracy and the reduction of vessel injury; and (iv) the effect upon infectious complications of length of monitoring, antibiotics prophylaxis, tunneling of electrode leads, and methods of electrode removal.

Therapeutic Procedures

Complications of Temporal Neocortical Focal Resections

In general, there are at least four different surgical approaches to treat mesial TLE. These approaches include (i) en bloc temporal resection or standard TL, (ii) awake TL with tailored resection, (iii) amygdalohippocampectomy, and (iv) radical hippocampectomy. Each technique represents a different approach to the identification and resection of the epileptogenic zone. Because this chapter is focused on complications in neocortical epilepsy surgery, complications related to amygdalohippocampal resections will not be discussed.

In an extensive review of the literature performed by Pilcher and Ojemann regarding complications of anterior TL, mortality occurred in <1%, mainly caused by hemorrhage, infarction, pulmonary complications, and sudden death. Other complications included hemiparesis (transient or permanent) in 2% to 4%, minimal visual field defects in more than 50%, and severe field defects (hemianopsia) in 2% to 4%. Infections (meningitis, abscess), epidural hematoma, and III nerve palsy (transient) occurred in <2%. Neurobehavioral complications included transitory anomia (<1 week) in 20% of the patients, persistent dysphasia in 1% to 3%, and transitory psychosis/depression in 2% to 20%.

Penfield reported a 2.5% hemiplegia in an early Montreal Neurological Institute (MNI) series. He attributed this complication to excessive manipulation of branches of the middle cerebral artery during the transsylvian resection of insular cortex (121). Alternative explanations included direct capsular injury with insular resection as well as compromise of the lenticulostriate vessels and the anterior choroidal artery.

Visual field deficits occur following temporal lobe resections in approximately 50% of operated patients. These deficits are often incongruous or worse in the ipsilateral eye, due to the anterolateral location of ipsilateral fibers overlying the anterior portion of the temporal horn (Meyer loop). Severe visual field deficits considered disabling by patients are less frequent and were reported in 8% in our previous series (112). Rasmussen et al. suggested that by limiting the extent of the superolateral ventricular opening to 1 cm, quadrantic deficits could be avoided entirely. Other studies also suggested that the magnitude of the visual field deficit was entirely related to the extension of the ventricular opening, mainly in the ventricular roof in the temporal horn. Alternatively, direct surgical injury to the optic tract, lateral geniculate nucleus, or optic radiation in the posterior temporal lobe white matter can also cause visual field deficits.

Postoperative anomia or dysphasia is not uncommon following dominant TL. These aphasias are largely resolved after 1 week. Transitory dysphasias are reported in up to 30% of operated patients in the setting of awake surgery with intraoperative language mapping. Removal of the anterior temporal or inferior basal language sites may explain this phenomenon (122). Other explanations include resection of cortex within 1 to 2 cm from essential language areas, brain retraction, and disruption of white matter pathways connecting language areas. According to Crandall et al., persistent language disorders were found in three of 53 patients undergoing temporal lobe resection. In another series, 5 of 25 patients were aphasic at the time of discharge (123). In the MNI series, using intraoperative language mapping, 2 of 250 patients were reported to have long-lasting aphasia after surgery (124,125). In both cases, aggressive resection near essential speech areas was performed. In the Seattle series, removal of brain within 1 to 2 cm of essential sites established by intraoperative mapping was associated with mild language deficits (126,127).

The “tailored operation” is designed to use language-mapping techniques to identify and protect neocortical language sites. In a comparison of “standard” versus tailored TLs performed by a single surgeon, a slight increase in postoperative dysnomia was identified 6 months after surgery following a “standard” operation (128).

Complications of Extratemporal Neocortical Focal Resections

The extratemporal epilepsies considered for resective therapy are less frequent, more variable in their presentation, and the epileptogenic zone is more likely to involve eloquent cortex, and intraoperative or extraoperative brain mapping is often necessary. All of these facts have a direct impact upon the complications of extratemporal neocortical focal resections, most important of which are the functional consequences of adequate removal of the epileptogenic zone in a particular brain area. In a systematic fashion, we can divide extratemporal focal resections in frontal, central, parietal, and occipital resections.

Frontal Resections.

Anatomically, Broca area is located in the inferior frontal gyrus at pars triangularis and pars opercularis of the dominant frontal lobe, and this region is generally avoided when dominant frontal resections are performed under general anesthesia. The pattern of frontal language localization may be quite variable, and many centers rely upon brain-mapping techniques to tailor frontal resections and avoid language complications. These investigations may identify zones of language cortex quite separate from Broca area within the middle, superior, and even parasagittal frontal cortex in the region of the supplementary motor area (SMA).

Transitory aphasic syndromes are often caused when resections are carried within 1 to 1.5 cm of these essential language areas (126,127). Long-lasting expressive aphasia can follow resection of language sites in the posterior inferior frontal gyrus or vascular compromise with postoperative ischemic injury to the region. Resections involving frontal cortex (superior frontal gyrus) may cause compromise of draining frontal veins with associated postoperative edema, venous infarction, as well as potential language and motor deficits.

The SMA is located in the mesial surface of the superior frontal cortex, superior to the cingulate gyrus. Functional studies have shown that this area is activated during initiation of movement and vocalization. Stimulation of this area leads to a fencing posture with bilateral motor movement. Unilateral responses are rare. The SMA is extensively and somatotopically connected through the corpus callosum, resulting in fast spread of the ictal discharges to the contralateral side, making lateralization of the ictal-onset zone difficult (129). Resection of the SMA located in the mesial frontal lobe may produce supplementary motor cortex syndrome characterized by mutism, contralateral neglect or hemiparesis, and diminished spontaneous movement, which gradually resolves over several weeks (130). On long-term follow-up, gross motor deficits are rare.

The orbitofrontal area is limited laterally by the horizontal ramus of the sylvian fissure, medially by the olfactory sulcus, and posteriorly by the anterior perforated area. The orbitofrontal cortex is extensively connected with the anterior and mesial temporal lobes, cingulum, and opercular area and, for this reason, frequently misdiagnosed as anterior temporal seizures (131). Adequate sampling of these structures using invasive electrodes is recommended. The cognitive effects of extensive nondominant frontal resections are thought to be of minimal consequences in daily life activities (132). Furthermore, provided that a careful subpial technique is employed, with preservation of the vascular supply to motor cortex, frontal excisions may be safely carried up to the pial bank of the precentral gyrus. Care must be taken, however, not to undermine the motor cortex if the resections are extended into the white matter.

Central Resections.

Central-type epilepsy or seizures arising from the primary motor and sensory area are infrequent. Patients with preserved motor function present considerable challenges. A more aggressive approach to the peri-Rolandic epilepsies is gaining acceptance in which extraoperative functional mapping of central cortex is supplemented by intraoperative remapping of this area by direct cortical stimulation, often under awake conditions.

Resection of the facial motor cortex.

The partial resection of the nondominant face motor cortex may be safely performed, resulting in a transitory contralateral facial asymmetry. Complete removal may be associated with perioral weakness in some patients. The superior resection margin should extend no higher than 2 to 3 mm below the lowest elicited thumb response. In the dominant hemisphere, some surgeons report postoperative dysarthrias and dysphasias following face motor cortex excision. Nevertheless, Rasmussen et al. reported that complete removal of dominant face motor and sensory cortex may be safely performed, provided that manipulation of underlying white matter or ascending vascular supply is avoided (124,125).

Resection of the hand/leg motor cortex.

The resection of the primary hand motor cortex produces a permanent deficit of fine motor control and should be avoided if useful hand function is present preoperatively. Resection of the primary leg motor cortex will elicit an immediate flaccid leg paralysis followed by gradual partial recovery of ambulatory capacity over months (124,125). Proximal limb function is likely to recover; however, distal ankle and foot permanent weakness are often present, requiring use of orthoses for safe ambulation.

Resection of the sensory cortex.

The resections of leg or face sensory cortex cause permanent but clinically insignificant deficit of proprioception in the leg or two-point discrimination in the lower face (132). In contrast, resection of hand sensory cortex is followed by important functional impairment, with the majority of patients showing deficits of pressure sensitivity, two-point discrimination, point localization, position sense, and tactual object recognition, which makes functional use of the involved hand difficult (132).

Parietal Resections.

Very few articles reporting complications in parietal resections are available in the literature. Salanova et al. (97) reported the MNI experience of 79 patients with nontumoral parietal lobe epilepsy. Of these, 45.5% were seizure free, 19% had rare seizures, and 21.5% had worthwhile improvement. Persistent dysphasia was noted in two patients, Gerstmann syndrome in one patient, and contralateral weakness in three patients.

Large parietal resections may be undertaken posterior to the central cortex in the nondominant hemisphere without causing a sensorimotor deficit and with a rate of hemiparesis of approximately 0.5% (124,125). A nondominant parietal syndrome may follow these resections in some individuals. In the dominant hemisphere, language mapping must be used to avoid postoperative language deficits if resections extend to the inferior parietal lobule. When resections are extended into the parietal operculum, contralateral lower quadrantic or hemianopic visual field deficits (rare) may occur as resections are performed beyond the depths of the sulci into the white matter (111,124,125).

Occipital Resections.

In patients with hemianopsia, resective occipital surgery carries minimal risk. On the dominant hemisphere, the speech-related cortex should be identified and spared. The management of patients with intact vision is challenging. When a circumscribed lesion is found, lesionectomy can yield satisfactory results. In nonlesional cases, the ictal-onset area should be precisely localized using invasive electrodes (80,133). These are used in addition to mapping of the calcarine cortex and speech-related cortex. With this strategy, visual deficits can be minimized. Resections of the dominant basal temporal lobe should be carefully planned as this can yield to an alexia without agraphia deficit (122).

Contralateral homonymous hemianopsia may follow resections in this area. If vision is intact preoperatively, calcarine cortex and optic radiations must be spared as much as possible. The use of intraoperative visual evoked potential, intraoperative direct stimulation, and radiologic techniques as diffuse tensor images is still under investigation.

If adequate data from invasive monitoring are available to suggest that the superior calcarine gyrus may be spared, an inferior calcarine gyrus resection with or without an aggressive resection of mesial temporal lobe structures will result only in a superior quadrantic deficit associated with

minimal disability. Excision to within 2 cm of Wernicke area in the dominant hemisphere may elicit persistent dyslexia (124,125). Therefore, exposure at craniotomy should be adequate to provide access to the postcentral gyrus and parietotemporal language areas, which will serve as the anterior limits of resection.

CONCLUSIONS

A valid appreciation of the complications of epilepsy surgery is fundamental to balance the risks and benefits of diagnostic and therapeutic procedures. Unfortunately, the actual literature available in this topic does not reflect contemporary surgical practice. Available data are derived from the surgical experience of a few highly experienced surgeons who worked in a few well-established comprehensive epilepsy centers and used patient selection criteria and operative approaches, which have since been modified or radically changed. A prospective multicenter study is necessary to determine the contemporary risks for invasive monitoring, the role of awake craniotomy with intraoperative mapping for speech mapping, and the complications rate in the epilepsy population.

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CHAPTER 91 ELECTRICAL STIMULATION FOR THE TREATMENT OF EPILEPSY

WEI HU, S. MATTHEW STEAD, AND GREGORY A. WORRELL

Electrical stimulation has a long history as a diagnostic and therapeutic modality for epilepsy (1,2). The application of electrical stimulation for mapping cortical function in animals was first reported by Fritsch and Hitzig in 1870 (3), and the first report in humans by Bartholow (4) followed in 1874. Krause and Foerster extended the clinical application of electrical stimulation for localization of brain function in patients undergoing surgery for epilepsy (5). These studies culminated in the seminal work of Penfield and Jasper (6) who established the routine clinical use of electrical stimulation for localization of cortical function in epilepsy surgery. In the 1970s, the concept of therapeutic electrical stimulation for epilepsy emerged and has remained an area of active clinical research. Only recently, however, have well-designed clinical trials yielded class I evidence for efficacy.

THERAPEUTIC STIMULATION FOR THE TREATMENT OF EPILEPSY

Cooper first began implanting cerebellar stimulators in patients with intractable epilepsy in the 1970s (7,8), but the idea of electrical stimulation as a treatment for epilepsy is much older (2). Cooper et al. (7,9) reported significant reductions in the number of seizures with chronic cerebellar stimulation. However, later controlled trials did not confirm a dramatic therapeutic effect (10). The failure of a controlled trial to confirm the efficacy reported in an uncontrolled trial was later repeated for centromedian nucleus (CMN) of thalamus stimulation (11). These examples underscore the need for well-designed clinical trials to establish the efficacy of electrical stimulation before they can be recommended in routine clinical practice. Recent reviews have summarized the research in humans and animal models and have laid the framework for future research and clinical trials of brain stimulation for the treatment of epilepsy (2,12). Advances in neural engineering are now poised to deliver new treatments for a range of neurologic diseases. In epilepsy, active areas of research include the development of devices that modulate epileptogenic brain to prevent seizures, devices that directly detect seizures and deliver electrical stimulation to abort seizures, and devices that identify periods of increased probability of seizure occurrence (2,8). Two first-generation devices using electrical stimulation for the treatment of epilepsy have been recently completed in multicenter trials and are discussed below in detail.

Clinical Trial Design

Determining the efficacy of an epilepsy therapy is challenging. Epilepsy is characterized by unprovoked, paroxysmal, seizures that leave no lasting objective evidence of their occurrence. This can be contrasted with other neurologic diseases or disorders that have clear magnetic resonance

imaging (MRI) abnormalities or neurologic exam findings that can be tracked, for example, brain tumor, stroke, multiple sclerosis, amyotrophic lateral sclerosis, and peripheral neuropathy. Determining the efficacy of an epilepsy therapy requires tracking the occurrence of seizures. Unfortunately, until recently, this has only been possible with self- (or observer) reporting of seizures. Patient diaries, however, are imperfect, and their limitations are well known (13). A recent study showed very poor correlation between recorded seizures and patient diaries in 15 patients implanted with a device recording continuous intracranial electroencephalographic (iEEG) (14). Clinical trials investigating treatment efficacy of medications or brain stimulation typically use reduction in seizure frequency as the primary outcome measure. Well-designed clinical trials have control and active therapy arms (Fig. 91.1) with patients randomized to therapy ON or OFF. The patient and treating physicians are blinded to this information in order to limit bias. Nonetheless, because seizures occur sporadically without lasting objective evidence of their occurrence, the measure of treatment success has depended on the seizure diaries.

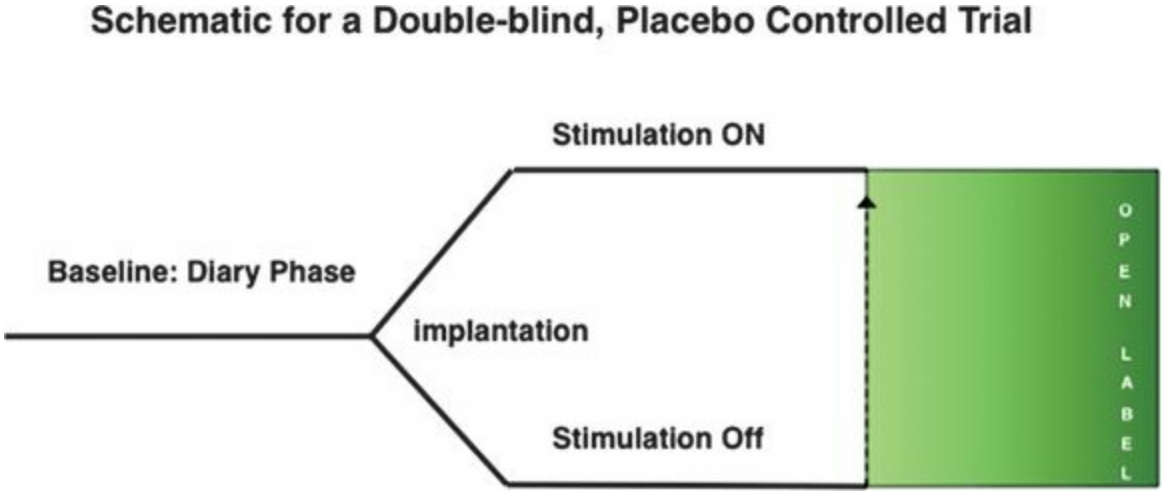
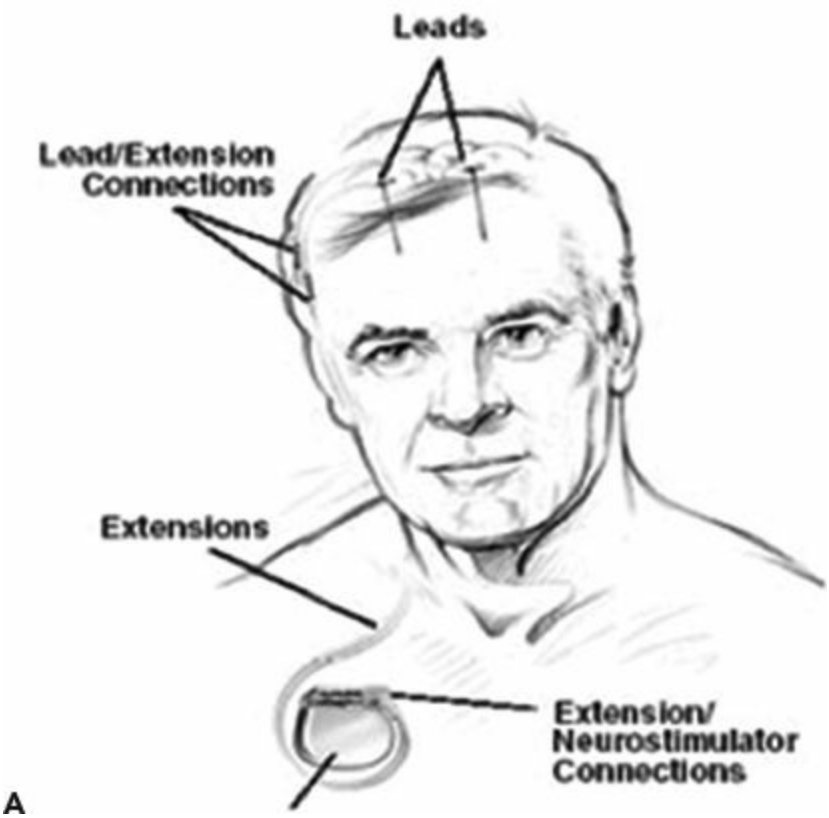
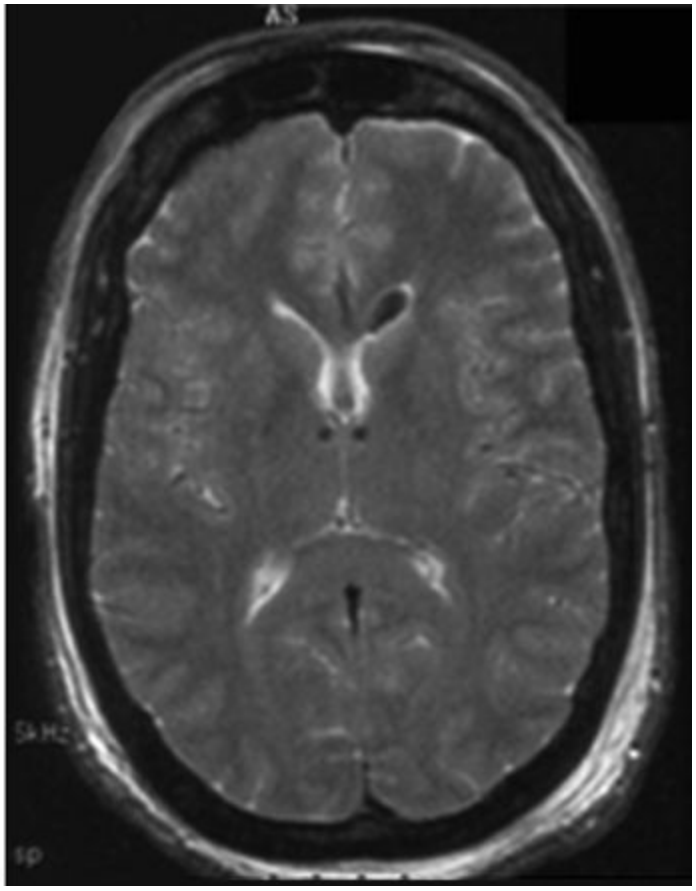


Figure 91.1. A schematic for a double- blind, placebo-controlled trial that has been adopted for two recent multicenter brain stimulation trials (Medtronic stimulation of the anterior nucleus of the thalamus [SANTE] trial and NeuroPace responsive neurostimulator system [RNS] trial). Specifically, well-designed clinical trials have control and active therapy arms with patients randomized to therapy ON or OFF. The patient and treating physicians are blinded to this information in order to limit bias.

To determine the efficacy of a particular brain stimulation paradigm (target of stimulation, timing of stimulation, stimulation parameters, etc.) for the treatment of epilepsy requires an appropriate study design. Pilot studies in a small number of patients are often used to initially investigate the safety, feasibility, and evidence of possible efficacy. Pilot and feasibility studies are not adequately powered to prove efficacy but should also use an appropriate design with controls and blinding. Figure 91.1 is a schematic for a double-blind, placebo-controlled trial that has been adopted for two recent multicenter brain stimulation trials (Medtronic stimulation of the anterior nucleus of the thalamus [SANTE] trial and NeuroPace responsive neurostimulator system [RNS] trial; see Figs. 91.2–91.4). As discussed in the following sections, a number of studies that reported positive results have not held up in better designed, more rigorous studies with a placebo-controlled arm.


Leads
Lead/Extension Connections
Extensions
Extension/ Neurostimulator Connections

A



B

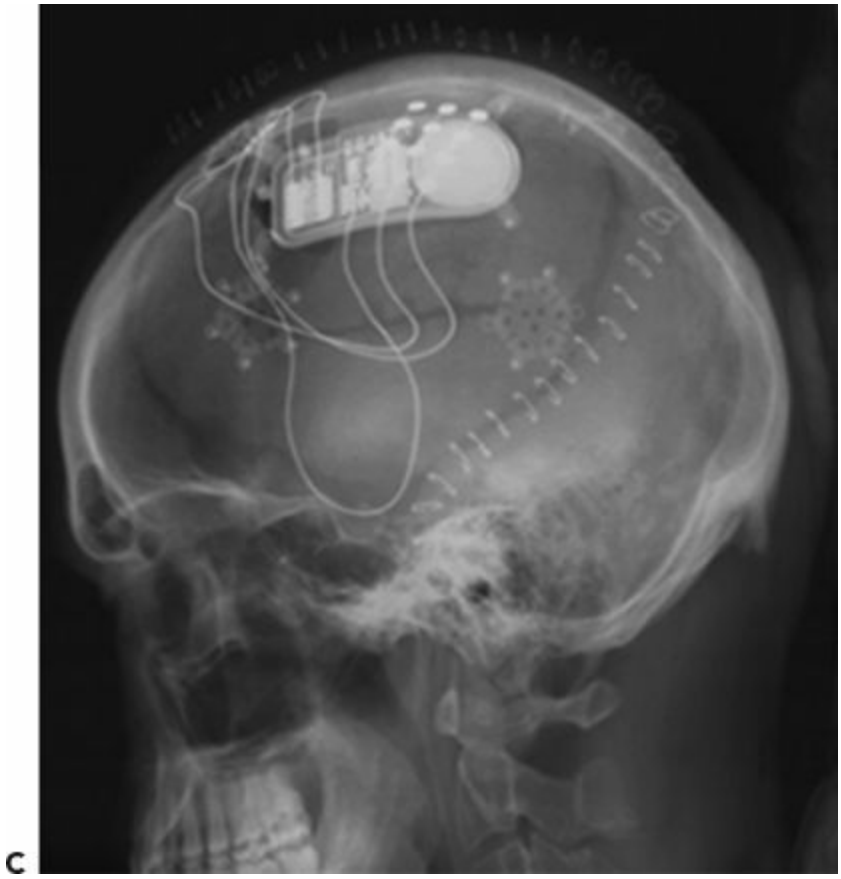


Figure 91.2. Epilepsy device trials. **A:** Stimulation of the anterior nucleus of the thalamus (SANTE). Schematic showing implanted anterior nucleus of thalamus (ANTS) electrodes and subclavicular generator; **B:** MRI showing bilateral ANTS electrodes (courtesy of Gordon Baltuch); **C:** Responsive neurostimulator system (RNS) consists of a neurostimulator implanted into the cranium and subdural electrodes; **D:** Seizure advisory system (SAS) schematic showing implanted subdural electrodes, subclavicular EEG telemetry unit, and external personal advisory device.

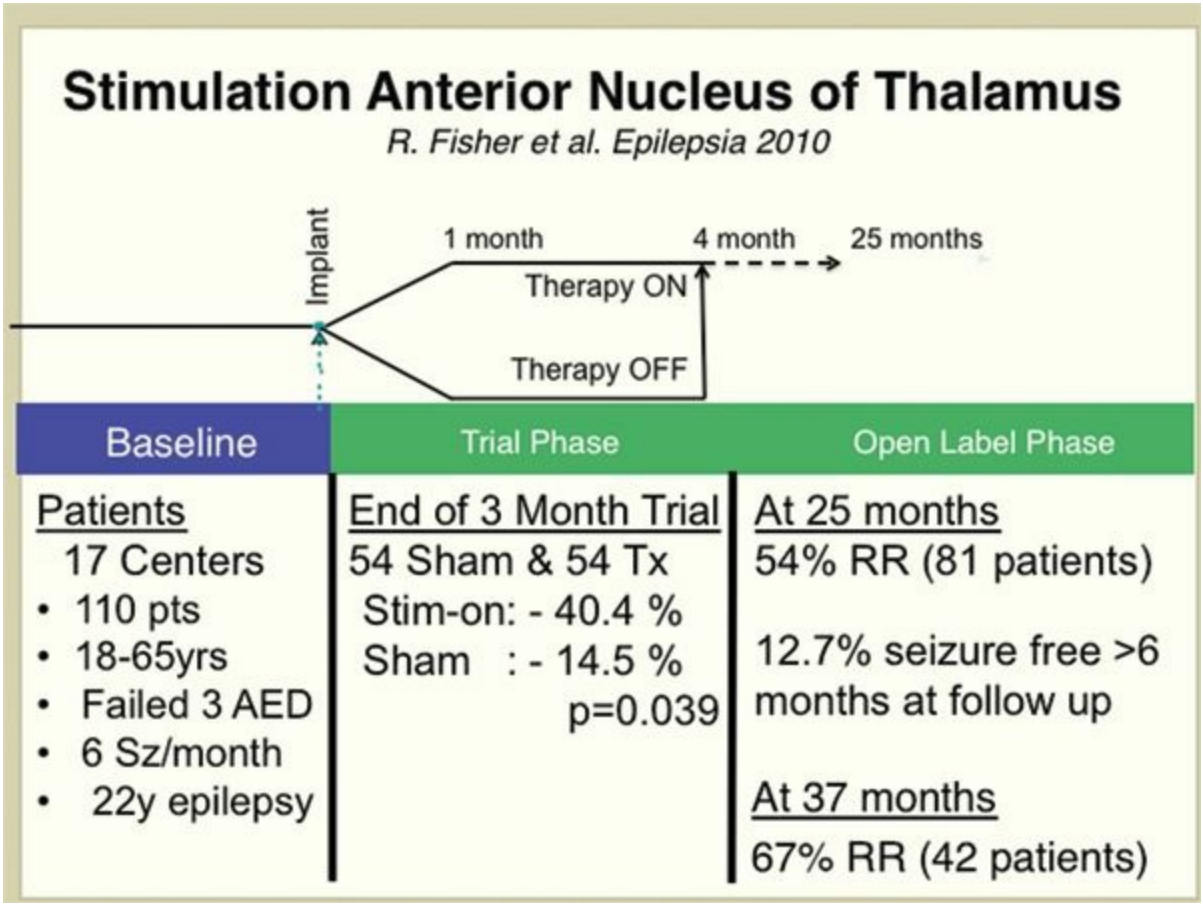


Figure 91.3. The results from a large multicenter, randomized, controlled trial of stimulation of the anterior nuclei of thalamus for epilepsy (SANTE) using the Medtronic DBS device (15).

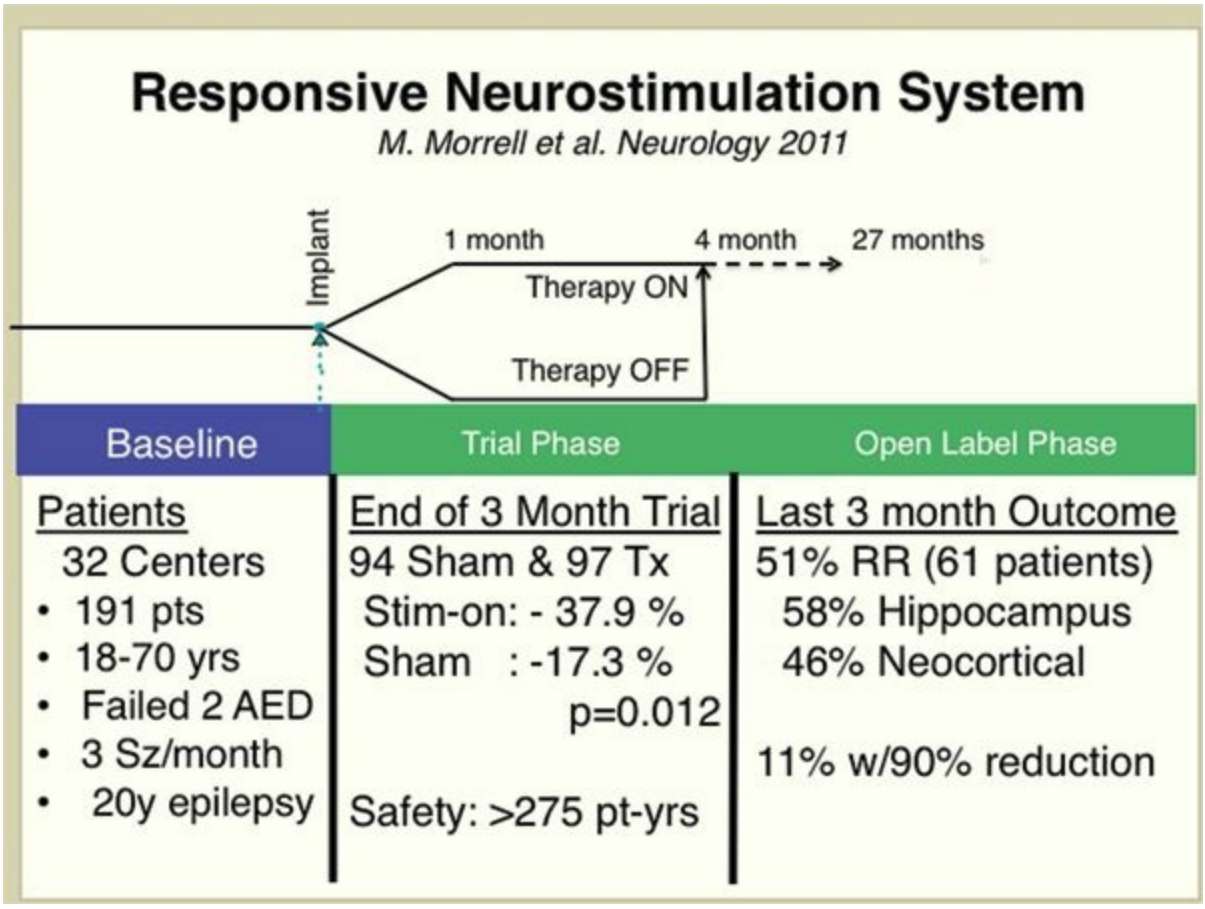


Figure 91.4. The results from a large multicenter, randomized, controlled trial for hippocampal and neocortical responsive stimulation using the NeuroPace RNS device (16).

Baseline

The baseline seizure frequency is determined from the patient diary in a defined period prior to the intervention under investigation. Studies of epilepsy, whether they are drug studies or brain stimulation, typically rely on the patient diary for determining seizure frequency. The reliability of patient reporting is a recognized weakness. Although there are currently no tools for reliably counting seizures in the outpatient setting, a recent study presented data from an implanted seizure advisory system (SAS), which could potentially be used for seizure counting (14).

Implantation

The device is implanted in patients who have met the enrollment criteria of the study. For example, only patients who had the required number of seizures in the 3-month baseline seizure frequency phase are implanted. In order to minimize the acute effect of implantation, there is typically a period of time (approximately 1 month) prior to randomization to stimulation ON/OFF and commencing the blinded treatment phase.

Randomization and Placebo Control

In order to rigorously differentiate the effect of electrode implantation, placebo, and stimulation, a sham surgery arm would be required. In most cases, it is not ethically possible to include sham implantation surgery. The placebo response and efficacy of stimulation are determined by randomization of patients to therapy ON or OFF. In effect, a coin toss (heads/tails) determines whether stimulation is activated or remains inactivated after surgery. In this way, approximately half the patients in the trial are randomized to therapy ON or OFF.

Double-Blind Design

The placebo response is well established in clinical trials and can have a powerful impact on the patient and physician's perception of treatment efficacy. By blinding the patient and physician to the treatment information, that is, stimulation ON or OFF, the placebo response can be determined. The efficacy of stimulation can be evaluated by directly comparing seizure frequency with stimulation ON versus OFF. A statistically significant reduction in seizures in the stimulation arm versus placebo (i.e., control) can be attributed to the stimulation therapy. Any seizure reduction occurring in the control arm is attributed to placebo response, chance, or possibly implantation effect. As mentioned in the two completed device trials (Medtronic SANTE and NeuroPace RNS), the implantation of the electrodes could conceivably create a therapeutic lesion. Yet, the acute therapeutic effect of electrode implantation appears to wear off with time.

Crossover

A crossover design allows patients who were initially randomized to therapy OFF to receive stimulation after completion of the double-blind study phase. The multicenter trials discussed in the following sections have utilized this single crossover design. In a double crossover study design, patients receiving therapy (ON) are crossed over to no therapy (OFF). In this study design, the

possible carryover effects of brain stimulation could confound the interpretation of the results. The "wash-out" period for anticonvulsant medications can be easily obtained, but the time required for "wash-out" of the effect of months of brain stimulation is not known.

Open-Label Extension

In the open-label portion of the trial, all patients receive stimulation without blinding. Often in the open-label phase, medications are adjusted or added, so interpretation of results requires caution. In addition, the patients and physician are no longer blinded to the therapy. Interestingly, the two large-scale multicenter clinical trials (see SANTE and RNS studies discussed below) have all shown evidence for increasing efficacy of brain stimulation with duration of time of receiving stimulation. These results must be interpreted with caution since they come from the open-label portion of the trial, but raise the possibility that brain stimulation has a cumulative therapeutic benefit.

Measures of Efficacy

Commonly reported outcome measures are (i) responder rate (RR), defined as the percentage of patients with a 50% or greater reduction in seizures, (ii) mean reduction in seizures from all patients, and (iii) number of seizure-free patients (defined over a specific duration of the trial, e.g., the most recent 3 months of the open-label phase of the trial). In addition, quality-of-life measures are often assessed, for example, Quality of Life in Epilepsy (QOLIE)-89 scale (17).

Measures of Safety

Side effects are categorized as serious or minor and anticipated or unanticipated. For example, an intracranial hemorrhage associated with electrode placement would be a serious, but anticipated, complication.

Electrical Stimulation Paradigms

The parameter space defining the range of stimulation variables is large and includes the type of stimulation (constant current vs. constant voltage), amplitude, stimulation waveform, frequency, duration, etc. The paradigms of stimulation can be broadly categorized as follows.

Open-Loop Stimulation (Duty Cycle Stimulation)

To date, the majority of stimulation systems utilize duty cycle stimulation. The stimulation is given regardless of the occurrence of seizures or brain activity. For example, deep brain stimulation (DBS) for tremor and open-loop stimulation protocols for the SANTE trial.

Closed-Loop Stimulation (Automated or Responsive Stimulation)

Recently developed systems utilizing implantable microprocessors make it possible for programmable stimulation to be delivered in response to recorded electrophysiologic signals. The NeuroPace RNS system is a closed-loop device capable of recording continuous iEEG and delivering therapeutic stimulation based on automated detection of pathologic activity and seizures.

Control Law Stimulation (Feedback Control Stimulation)

Based on the hypothesis that seizures occur out of a particular brain state that can be characterized by some observable (e.g., features of iEEG), it may be possible to actually prevent seizures by continuously adjusting a therapy (such as stimulation) that is determined by the measured observable. This approach is commonly used in a wide range of engineering applications and has been applied to animal models of epilepsy (18–20).

STIMULATION TARGETS IN THE HUMAN NERVOUS SYSTEM

Intracranial Stimulation

The idea of using electrical stimulation to treat epilepsy has a long history (1,2,21). The following is a discussion of earlier studies with a focus given to studies with good clinical design. The ability to accurately and safely implant electrodes into human brain has led to dramatically successful therapies for some neurologic disorders such as tremor (1). Less successful has been the application of DBS, hippocampus stimulation, and neocortical stimulation for the treatment of epilepsy. Nonetheless, the field has advanced. Two well-designed multicenter clinical trials (Medtronic SANTE and NeuroPace RNS) investigating the feasibility, safety, and efficacy of brain stimulation for treatment of medically resistant focal epilepsy have recently been reported and will be discussed in the following sections.

Cerebellar Stimulation

The cerebellum provides inhibitory outflow and for this reason was an early candidate target for electrical stimulation to treat epilepsy (7,22). In early uncontrolled studies, cerebellar stimulation was reported to yield significant reductions in seizures. An early uncontrolled trial of 115 patients reported 31 patients became seizure free and 56 improved significantly (23). This was a remarkable result and generated considerable interest. However, in a later controlled, double-blinded study of 12 patients, only 2 patients showed improvement (10). The small number of patients studied in the trial limits the ability to draw conclusions.

Caudate Nucleus Stimulation

Chkhenkeli and Chkhenkeli (24) reported a decrease in “interparoxysmal activity” in neocortical and mesial temporal epileptic foci in patients with stimulation of caudate nucleus, but clinical seizures were not investigated.

Mammillary Nuclei

Mirski and Fisher (25) reported an increase in the seizure threshold for pentylenetetrazol-treated rats. However, trials have not been performed in humans.

Centromedian Nucleus of the Thalamus

The CMN is implicated as part of the circuit involved in the generation of spike-and-wave discharges in generalized epilepsy (26). Early studies from Velasco et al. reported significant reductions in seizures for patients with generalized convulsive seizures and atypical absence seizures, but no benefit in patients with complex partial seizures (27,28). Fisher et al. (11) reported the first randomized, controlled trial of CMN stimulation in seven patients. The trial did not show a statistically significant difference between the stimulation ON versus OFF (although one patient showed marked improvement). The trial was a rigorous double-blind, placebo-controlled, crossover design. One patient experienced dramatic benefit, which prevented his crossover to the OFF arm. In addition, in this double crossover design, the possible "carryover" benefit from 3 months of stimulation may have confounded the results. Unfortunately, it is not known if there is a carryover effect from stimulation and if there is the "wash-out" time required for its elimination.

Subthalamic Nucleus

Stimulation of the subthalamic nucleus (STN) for the treatment of essential tremor and Parkinson disease is safe and effective (29). The use of stimulation of STN for epilepsy is based on evidence for a subcortical control network that influences cortical excitability (29). Loddenkemper et al. (30) reviewed the studies supporting the existence of the nigral control of epilepsy system and preliminary results of STN stimulation in animals and humans. There are no controlled trials.

Anterior Nucleus of the Thalamus Stimulation

The antiepileptic effect of stimulation of the anterior nucleus of the thalamus is thought to be mediated by its integral role in the circuit of Papez (2). Sectioning the connection between the mammillary bodies and the anterior thalamus markedly increased the threshold for pentylenetetrazol-induced seizures in guinea pigs (31). Later studies showed that high-frequency electrical stimulation of the anterior thalamus in rats also significantly increased the threshold for pentylenetetrazol-induced seizures (25).

Upton et al. (32) reported an antiepileptic effect associated with stimulation of the anterior nucleus of thalamus. Hodaie et al. (33) reported on five patients who underwent bilateral anterior thalamus stimulation. The patients experienced a 54% mean reduction in seizure frequency, with two patients having approximately 75% reduction. Interestingly, however, there was not a significant difference between the stimulation ON and OFF arms of the trial, perhaps indicating a strong placebo component, carryover confound, or therapeutic lesion from implantation.

Medtronic SANTE Trial

The results from a large multicenter, randomized, controlled trial for SANTE using the Medtronic deep stimulator were reported in 2010 (Figs. 91.2 and 91.3) (15). The SANTE trial investigated the safety, feasibility, and efficacy of duty cycle stimulation of the anterior nucleus of the thalamus. In this well-designed, industry-funded (Medtronic, Inc.) trial, 110 patients were enrolled from 17 centers. Baseline diaries were kept for 3 months, and patients with 6 or greater partial, complex partial, or secondary generalized seizures per month were implanted with bilateral thalamic DBS electrodes and a subclavicular generator. One month after implantation, the patients were randomized to stimulation

ON or OFF. Patients and treating physicians were blinded to whether stimulation was ON or OFF. After 3 months of the blinded trial, all patients entered an open-label trial with stimulation ON. The results showed a 40.5% mean reduction in seizures for the stimulation ON arm compared to 14.5% reduction with stimulation OFF. Significantly, by 2 years, a greater reduction in seizures was seen in the open-label phase of the trial with a 54% responder rate (50% or greater reduction in seizures); 14% of patients were seizure free for at least 6 months (15). Importantly, patients refractory to vagal nerve stimulation (VNS) or epilepsy surgery had the same favorable response to DBS as did the overall group (34). There were no unanticipated side effects, but 5 patients had asymptomatic brain hemorrhage as revealed by neuroimaging. Neuropsychological tests showed no difference in cognition and mood tests, although patients in the stimulated group were more likely to complain of depression or memory impairment. These rates of complication are consistent with other studies that DBS has been used for movement disorders (34). Taken together, this study demonstrated that DBS of the anterior thalamus is useful for some people with medically refractory partial and secondarily generalized seizures.

Hippocampus Stimulation

Velasco et al. (35) reported on 9 patients with a 3-month-baseline seizure count, after which they underwent bilateral hippocampal diagnostic electrode implantation to establish epileptogenic focus laterality and location. Three patients had bilateral, and six patients had unilateral foci. Electrodes were implanted directly into the hippocampal epileptogenic foci. Duty cycle stimulation was delivered using the Medtronic DBS system. Follow-up ranged from 18 months to 7 years. Patients were divided in two groups with normal MRI and MRI consistent with mesial hippocampal sclerosis. Patients with normal MRIs had seizure reductions of >95%, while the four patients with hippocampal sclerosis had seizure reductions of 50% to 70%. Vonck et al. (36) reported on 10 patients with temporal lobe epilepsy and normal MRIs who received duty cycle stimulation to unilateral amygdalohippocampal stimulation. All patients had a >50% reduction in seizures at 5 months.

Tellez-Zenteno et al. (37) reported on a well-designed controlled trial of four patients who had hippocampal stimulation with the Medtronic DBS device and only achieved a 15% median reduction in seizures. All but one patient's seizures improved; however, the results did not reach significance. The authors concluded that there are beneficial trends, some long-term benefits, and absence of adverse effects of hippocampal electrical stimulation in mesial temporal lobe epilepsy. However, the effect sizes observed were much smaller than those reported in nonrandomized, uncontrolled, nonblinded studies. Again, the above results were from small groups of patients. More recently, the results of hippocampal stimulation in the RNS trial were reported to show benefit (see below).

Neocortical Stimulation

The responsive neurostimulator system (RNS NeuroPace) was approved on November 2013 by the FDA for adults with medically resistant focal epilepsy. The RNS includes a cranially implanted programmable device, depth or subdural electrodes, physician programmer, patient data transmitter, and a web-based interactive data repository. A multicenter, double-blind, randomized, controlled trial provided class I level of evidence for safety and efficacy (16). One hundred and ninety-one patients with medication-resistant focal epilepsy were implanted with an RNS. Patients were randomized to receive active or sham stimulation. Specifically, efficacy and safety were assessed

over a 3-month blinded period and a subsequent open-label period during which all subjects received responsive stimulation. Similar to the SANTE study, the RNS device significantly reduced seizure frequency relative to baseline for the actively stimulated group versus sham group (see Figs. 91.2 and 91.4). Moreover, the implant-associated seizure reduction in the stimulated group was sustained in subsequent months and improved over time. The median reduction in seizures at 1 year was 44% and at 2 years was 53%, respectively. The authors also reported that the overall quality of life was significantly improved, and there was no deterioration in any mood or neuropsychological measurement. Importantly, stimulation was well tolerated and also beneficial for the patients who were even intractable to VNS or epilepsy surgery (16).

Seizure Forecasting

Seizure forecasting may prove useful in improving patient safety and guiding acute treatments. Recently, a multicenter clinical study in Australia evaluated safety and feasibility of a long-term implanted SAS designed to predict seizure likelihood and quantify seizures in patients with medically resistant focal epilepsy (Fig. 91.2). Fifteen patients were implanted with the SAS, and a seizure forecasting algorithm was trained on each patient's EEG during a training phase that included at least four seizures and lasted several months. In 11 patients, the device met enabling criteria, that is, the algorithm demonstrated prediction that was better than expected by chance. These patients advanced to an advisory phase, during which the warning device prospectively indicated the likelihood of seizure occurrence. No serious system-related adverse effects were reported in these patients. This small proof-of-concept study demonstrated that seizure prediction is possible and could eventually lead to new therapeutic strategies for epilepsy (14,38).

CONCLUSIONS

Despite the development of numerous new anticonvulsant medications, the number of patients that continue to have seizures with the optimized medical therapy is significant. Devices can provide clinically meaningful benefits in people who have failed medications and less invasive therapies. The potential for therapeutic brain stimulation has attracted considerable attention over the past decades, and the technology is now matured to the point that devices have been studied in clinical trials. There are two well-designed multicenter trials investigating electrical stimulation for the treatment of epilepsy. The results from both trials, SANTE (Medtronic) and RNS (NeuroPace), showed promise as viable therapies for medically resistant focal epilepsy. The safety record from both these device trials of long-term brain stimulation is also very encouraging. Currently, Medtronic device for anterior thalamic stimulation is approved in Europe and Canada, but not in the United States. The NeuroPace RNS device for closed loop stimulation was approved in the United States in late 2013. The next decade will hopefully see the emergence of FDA-approved viable therapeutic devices for patients with epilepsy.

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PART VI PSYCHOSOCIAL IMPACT, QUALITY OF CARE, COMORBIDITIES, AND ECONOMICS OF EPILEPSY

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CHAPTER 92 COGNITIVE EFFECTS OF EPILEPSY AND ITS TREATMENTS

KIMFORD J. MEADOR

COGNITIVE DEFICITS IN EPILEPSY

As a group, individuals with epilepsy have impaired cognitive performance in comparison to healthy subjects matched for age and education (1); however, considerable intersubject variability exists. Most persons with epilepsy have intelligence in the normal range, and some have superior cognitive abilities. Various factors can have a detrimental effect on cognition in epilepsy patients, including (a) etiology of seizures, (b) cerebral lesions acquired prior to onset of seizures, (c) seizure type, (d) age at onset of epilepsy, (e) seizure frequency, (f) duration and severity of seizures, (g) physiologic dysfunction (intraictal, interictal, or postictal) resulting from seizures, (h) structural cerebral damage as a consequence of repetitive or prolonged seizures, (i) hereditary factors, (j) psychosocial factors, (k) sequelae of epilepsy surgery, and (l) untoward effects of antiepileptic drugs (AEDs).

Patients with new-onset epilepsy may have impaired cognition (1). The etiology of seizures may be one of the strongest factors influencing cognitive abilities (2). Patients with seizures attributable to progressive cerebral degeneration usually exhibit dementia, those with mental retardation have an increased incidence of epilepsy, and those with seizures caused by a focal brain lesion may exhibit a specific neuropsychological pattern of deficits. In contrast, patients with idiopathic epilepsy are more likely to have normal intelligence (2). Seizure syndrome may be strongly associated with cognition. Patients with juvenile myoclonic epilepsy usually have normal intelligence, but children with infantile spasms have a poor prognosis. In general, the earlier the age of seizure onset, the more likely it is that a patient will have cognitive impairment. Additionally, patients with mental retardation are more likely to have refractory epilepsy.

Seizure type, frequency, duration, and severity may affect cognition in several ways. Obviously, cognition is impaired intraictally when consciousness is altered during generalized or complex partial seizures. Epileptiform discharges and postictal suppression may impair cognition interictally. Recent temporal lobe seizures impair memory consolidation, and hippocampal interictal discharges can impair memory recall (3,4). Classic postictal Todd paralysis lasts <24 hours, but postictal cognitive dysfunction, such as dysphasia, may persist for several days. Chronic physiologic dysfunction may also exist well beyond the zone of epileptogenesis. For example, positron emission tomography (PET) scans reveal interictal hypometabolism extending to the lateral temporal cortex in patients with epilepsy caused by mesial temporal lobe sclerosis. Although not true for all seizure types (e.g., absence seizures), repetitive or prolonged seizures may permanently damage the cerebral substrate via anoxia, lactic acidosis, or excessive excitatory neurotransmitters. Even temporal lobe seizures of relatively modest frequency over several decades can increase the severity of hippocampal atrophy and reduce cognitive abilities (5). Although many factors contribute, memory problems are common in patients with epilepsy. Interestingly, the molecular mechanisms of animal

models for epilepsy (i.e., kindling) and memory formation (i.e., long-term potentiation) are very similar (6).

Factors indirectly related to epilepsy may also affect cognition. Hereditary factors strongly influence intelligence; maternal intelligence quotient (IQ) is the most influential factor overall in predicting a child's intelligence. Psychosocial factors may adversely affect cognition through such mechanisms as depression or restriction of environmental influences. Finally, surgical or pharmacologic treatments of seizures may produce adverse cognitive effects.

EPILEPSY SURGERY

Patients who become seizure free from epilepsy surgery have a significant improvement in their emotional well-being and perceived quality of life (QOL), but those who fail epilepsy surgery are at risk for depression and poor QOL. Epilepsy surgery usually does not cause a general cognitive decline because dysfunctional tissue is primarily removed. Surgery may even improve cognition because of reduction in seizures and AEDs. However, clinically significant postoperative cognitive deficits may occur (7). For example, left temporal lobectomy may lead to declines in naming and in verbal memory. However, the risks are largely predictable (7). Risks are greater if the following are present: older age of epilepsy onset, absence of hippocampal gliosis/atrophy, temporal lobectomy in language-dominant hemisphere, high baseline verbal memory for resection on language-dominant side, or absence of ipsilateral dysfunction (e.g., PET, Wada, functional magnetic resonance imaging [fMRI]). Thus, a patient undergoing left temporal lobectomy is at particular risk if the patient has high baseline verbal memory with left cerebral language dominance and lack of evidence of left temporal lobe lesion or dysfunction. High memory performance with right intracarotid amobarbital injection and low with left injection on the Wada test, absence of left temporal lobe PET hypometabolism, or robust left temporal lobe activation on fMRI memory task all suggest increased risk. In contrast, a decline in visuospatial memory is inconsistent following right temporal lobectomy. Rarely, unilateral temporal lobectomy has resulted in a severe global anterograde memory disorder. Fortunately, modern advances in preoperative evaluation techniques have minimized this risk. In addition, selective resections (e.g., amygdalohippocampectomy) may reduce the risk for memory loss compared with standard anterior two-thirds temporal lobectomy, but the effect of selective approaches may be affected by collateral white matter damage (8). Recently, new deficits following anterior temporal lobectomy have been recognized, which include naming of proper nouns (left resection) and recognition of famous faces (right resection) (9). Preliminary data using a new surgical approach (i.e., stereotactic laser ablation of the amygdala and hippocampus) suggest that this technique reduces these deficits as well as classic deficits compared to standard anterior temporal lobectomy and selective amygdalohippocampectomy via craniotomy (10).

STIMULATION THERAPIES

No consistent negative or positive effects of vagal nerve stimulation (VNS) have been seen in patients with epilepsy (11). Fewer studies exist, but no adverse cognitive effects have been found for other stimulation therapies (i.e., anterior thalamic and responsive neural stimulator) (12,13).

ANTIEPILEPTIC DRUGS

AEDs reduce neuronal irritability and thus may reduce neuronal excitability and impair cognition. Because AEDs are the major therapeutic intervention in epilepsy, their cognitive effects are of particular concern to physicians, who must consider the risk–benefit ratio of any treatment. Therefore, differentiating the cognitive effects of AEDs and placing them in the proper perspective are critical to clinical decisions and informed consent.

The most typical cognitive side effects of AEDs include reductions in psychomotor speed, attention (especially sustained or complex attention), dual processing, memory, and for some AEDs naming or word finding. Although all AEDs may impair cognition, such side effects are generally modest, as assessed by neuropsychological tests in patients on monotherapy in whom anticonvulsant blood levels are within standard therapeutic ranges. Furthermore, the cognitive effects may be partially offset by the reduction in seizures. The risk of cognitive side effects rises with rapid initial titration, lack of time for habituation (especially the first several weeks of therapy), polypharmacy, and increasing AED dosages and anticonvulsant blood levels. Decreasing the number of AEDs frequently improves cognition and may reduce the number of seizures. However, the best drug regimen for an individual patient is the one that best controls seizures with the fewest side effects, and for some patients, this regimen may involve polytherapy. The cognitive effects of AEDs can be clinically pertinent, as evidenced by the highly significant inverse correlation of neurotoxicity symptoms and QOL scores (14). Despite the absence of overt toxicity on neurologic exam, patients who have more subjective symptoms of neurotoxicity exhibit lower perceived QOL. Further evidence of the clinical impact is the fact that certain AEDs can impair verbal paragraph memory by 15% to 20% (15) and withdrawal of some AEDs can produce an 11% to 28% improvement on neuropsychological tests (16).

Methodologic Issues

The literature examining the cognitive effects of AEDs must be viewed cautiously, because flaws in experimental design, analysis, and interpretation occur frequently (17). The magnitude of AED effects on standard neuropsychological measures is generally modest and may be missed if appropriate study designs are not used. Errors in experimental design include subject selection bias, nonequivalence of clinical variables, and nonequivalence of dependent variables. Selection bias is a problem when subjects are not randomly assigned to a treatment group or inadequately matched, or if the sample size is inadequate for a parallel-group design. Examples of nonequivalence of clinical variables include the failure to control for anticonvulsant blood levels or seizure frequency. Nonequivalence of dependent measures may occur when there is no assurance that treatment groups performed similarly on dependent measures prior to treatment. Additional design issues include sample size, test–retest effects, characteristics of behavioral tests, and effects of changes in seizures. Issues related to statistical analysis and interpretation include type I and II errors, use of inappropriate statistics, nonorthogonal contrasts, and comparison of studies with nonequivalent designs/statistics. Even when statistically significant findings are apparent, the magnitude and impact of the findings have to be interpreted in terms of clinical significance, taking into account the overall risk–benefit ratio of the AED and the severity of the seizure disorder in question.

Older Antiepileptic Drugs

No cognitive differences were observed between carbamazepine and phenytoin in two studies of

patients with epilepsy using a double-blind, randomized, crossover, monotherapy design, controlling for anticonvulsant blood levels (18,19), but one of these studies also examined phenobarbital and found worse performance for it compared to the other two AEDs. Using randomized, double-blind, crossover designs in healthy volunteers, which controls for the confounding effects of seizures and preexisting brain abnormalities, investigators found no overall difference between carbamazepine and phenytoin (20), but 52% of the variables were significantly worse with AEDs than with nondrug. Other studies have confirmed modest negative effects on cognition with both carbamazepine and phenytoin, but few differential effects (e.g., 21). In a healthy volunteer study (22), 32% of the variables were significantly worse with phenobarbital than with phenytoin or valproate, with the latter two agents being similar to each other, and about half of all variables significantly worse than nondrug condition. Overall, phenobarbital has greater untoward cognitive effects versus other older AEDs, while carbamazepine, phenytoin, and valproate have similar cognitive effects.

Newer Antiepileptic Drugs

Although data are incomplete, the cognitive/behavioral effects for selective studies of the newer AEDs are reviewed.

Gabapentin

Using a double-blind, placebo-controlled, dose-ranging (1200 to 2400 mg/day), add-on, crossover design in patients with partial epilepsy, Leach et al. (23) found no substantial effects of gabapentin. A double-blind, randomized, crossover study of healthy volunteers found significantly better performance with gabapentin versus carbamazepine on 26% of the variables, carbamazepine was worse than nondrug on 48% of the variables, and gabapentin was worse than nondrug on 19% (24). These results have been supported by a subsequent double-blind study in healthy volunteers comparing treatment with carbamazepine and gabapentin (25).

Lacosamide

A retrospective, nonrandomized, open-label study comparing adjunctive lacosamide to lamotrigine and topiramate in patients with epilepsy found that the cognitive effects of lacosamide were comparable to lamotrigine and better than topiramate (26).

Lamotrigine

Several studies with healthy adults demonstrated fewer cognitive side effects with lamotrigine compared with carbamazepine, diazepam, phenytoin, placebo, topiramate, and valproate (27–31). In a clinical trial, lamotrigine had less adverse cognitive effects than topiramate (32). Lamotrigine has positive psychotropic properties as evidenced in bipolar disorder patients and patients with epilepsy (33).

Levetiracetam

A double-blind, randomized, crossover healthy volunteer study found significantly less neuropsychological effects of levetiracetam versus carbamazepine on 44% of variables (34).

Levetiracetam has been noted to have more adverse behavioral side effects compared to gabapentin and lamotrigine (35,36).

Oxcarbazepine

No substantial differences in cognitive effects were found between oxcarbazepine and phenytoin in randomized, double- blind, studies in patients with new-onset epilepsy (37) and in healthy subjects (38).

Rufinamide

A double-blind, randomized, parallel, placebo-controlled, multidose study found no statistically significant cognitive changes for rufinamide (39).

Tiagabine

No significant cognitive effects were reported in a large, randomized, double-blind, add-on, placebo-controlled, parallel- group, dose–response study in patients with epilepsy (40).

Topiramate

In clinical trials, topiramate produced somnolence, psychomotor slowing, memory difficulties, and language problems (e.g., difficulty with word finding and fluency). Factors affecting these adverse effects include titration rate, maintenance time, dose, polytherapy, and individual susceptibility. In a study of patients with epilepsy tested on/off or off/on topiramate, declines in verbal fluency, attention, processing speed, and working memory, but not retention, were seen with topiramate (41). Two randomized, multicenter, double-blind studies of topiramate versus valproate as adjunctive therapy in patients with epilepsy found less-profound neuropsychological effects after slow titration and 8 weeks' maintenance; 1/17 variables (i.e., verbal memory) in one study (42) and 2/30 variables (i.e., verbal fluency and a graphomotor task) in another study (43) were significantly worse with topiramate. A double-blind, randomized, placebo-controlled, 12-week treatment, parallel- group study in healthy adults found that gabapentin had less adverse effects on 50% of the variables compared to topiramate (44). A double-blind, randomized, crossover study in healthy adults with 12-week treatment arms noted worse effects for topiramate on 88% of variables compared to lamotrigine (28). Similarly, a multicenter, double-blind, randomized, adjunctive therapy reported more adverse neuropsychological effects for topiramate versus lamotrigine (32). A double-blind, randomized, placebo-controlled, parallel- group, dose-ranging (64, 96, 192, or 384 mg/day) investigation of weight effects in obese subjects analyzed cognitive effects in a 24-week study (45); significant declines were seen in 12% (64 mg), 8% (96 mg), 15% (192 mg), and 35% (384 mg) of subjects compared to 5% in the placebo group.

Vigabatrin

In several double-blind, randomized, add-on studies of patients with epilepsy (e.g., 63,65), vigabatrin had few adverse effects on cognition or QOL compared to placebo. Abnormal behaviors, including depression and psychosis, have been reported in 3.4% of adults in controlled clinical trials (48).

Zonisamide

Zonisamide impaired cognition, but some tolerance appeared to develop over 24 weeks in a small, preliminary add-on study in patients (49). Long-term cognitive and mood effects of zonisamide were investigated in a randomized, monotherapy, multidose (100, 200, or 400 mg/day), open-label, 1-year investigation (50); after 1 year, 47% complained of cognitive deficits, and dose-related negative effects were seen on delayed word recall, Trail-Making Test, and verbal fluency.

Other Newer AEDs

The data on the cognitive effects of other newer AEDs (e.g., clobazam, ezogabine, perampanel) are inadequate at this time to draw conclusions.

Effects of Antiepileptic Drugs at Age Extremes

Fewer AED studies have been conducted at the extremes of the age spectrum.

Elderly

The increased susceptibility of the elderly to the cognitive effects of a variety of agents is attributable to both pharmacokinetic and pharmacodynamic factors. One study reported comparable cognitive effects of phenytoin and valproate in elderly patients (51). Reanalysis of the original VA Cooperative Study comparing carbamazepine, phenobarbital, phenytoin, and primidone revealed that elderly patients were easier to control but had greater cognitive side effects (52). The results from a VA Cooperative Study in elderly patients with new-onset epilepsy revealed that patients are more likely to remain on gabapentin or lamotrigine compared to carbamazepine (53); this finding was the result of greater CNS side effects with carbamazepine.

Children

Because the cognitive effects of AEDs might be additive over the long-term during neurodevelopment, children may be at higher risk. Unfortunately, investigations in children are inadequate (54). A double-blind, randomized, crossover, monotherapy study conducted in children with epilepsy found performance on phenobarbital was worse than valproate (55). Adverse cognitive effects of phenobarbital have also been found in a placebo-controlled, parallel-group study of children with febrile convulsions (56). Similar to the outcomes of adult studies, comparisons of carbamazepine, phenytoin, and valproate in children have yielded few differences (e.g., 57,58). No statistically significant differences in cognition were observed between oxcarbazepine, carbamazepine, and valproate in an open-label, randomized, parallel-group study in children and adolescents with newly diagnosed partial seizures (59). A randomized, double-blind, placebo-controlled study of adjunctive levetiracetam in children with epilepsy found no cognitive effects of levetiracetam at 12 weeks (60). Children are susceptible to adverse behavioral effects of AEDs. This is best known for phenobarbital, but can be seen with newer AEDs (e.g., gabapentin, lamotrigine, levetiracetam) (61–63).

NEURODEVELOPMENTAL EFFECTS OF IN

UTERO AED EXPOSURE

Multiple factors may contribute to neurodevelopmental deficits in children of mothers with epilepsy, but animal and human data suggest that AEDs play an important role in this regard.

Animal Studies

AED-induced cognitive/behavioral deficits (i.e., behavioral teratogenesis) have been observed in animals at dosages lower than those associated with somatic malformations (64). Phenobarbital produces neuronal deficits, reduces brain weight, and impairs development of normal behaviors and reduces brain catecholamine levels. Prenatal phenytoin produces dose-dependent, long-term, impaired coordination and learning. Significant neurobehavioral effects have been seen with trimethadione and valproate. A recent study has shown a range of behavioral deficits for phenobarbital and phenytoin, but also impaired rotarod performance for adult rats with neonatal exposure to lamotrigine (65).

AED-induced functional and anatomical defects may involve different mechanisms since anatomical risks are related to first trimester exposure, and functional deficits may be related primarily to third trimester exposure. Proposed possible mechanisms underlying functional teratogenicity of AEDs include folate, reactive intermediates (e.g., epoxides or free radicals), ischemia, apoptosis-related mechanisms, and neuronal suppression.

Similar to alcohol, exposure of the immature brain to some AEDs (i.e., clonazepam, diazepam, phenobarbital, phenytoin, vigabatrin, or valproate) can produce widespread neuronal apoptosis (66). The associated cognitive deficits are likely more related to dysfunction in the surviving neurons than the actual neuronal loss. The effect is dose dependent, occurs at therapeutically relevant blood levels, and requires only relatively brief exposure in monotherapy. Valproate's increased risk may occur because apoptosis begins below its typical therapeutic range. Many AEDs have not been tested in this model, but similar apoptotic effects were not seen at therapeutic dosages for carbamazepine, lamotrigine, levetiracetam, or topiramate in monotherapy. However, addition of these AEDs (except for levetiracetam) to an AED that produces apoptosis in monotherapy will increase the apoptotic effect, which may suggest polytherapy risk. These observations in animals raise serious concern that certain AEDs, which are commonly used in women of childbearing potential, could produce similar adverse effects in children exposed in utero or in the neonatal period. Additional studies are needed to examine effects of other AEDs in animal models and determine if a similar mechanism occurs in humans.

Human Studies

Although the risks for birth defects and neurodevelopmental deficits are increased in children of women with epilepsy, the role of AEDs and differential risks of AEDs have been unclear and remain only partially delineated (67). Disparities across studies are partly a result of differences in methodology and patient populations. Formal assessments of mental performance were made in most studies, but in many, it is unclear whether investigators were blind as to AED exposure when assessments were made. In many prospective studies, follow-up began postnatally rather than during pregnancy. In many studies, the influences of possible confounding factors have not been addressed in an empirical fashion (e.g., parental IQ and education, seizure type and frequency, AED dose/blood levels, maternal age/parity, socioeconomic status, and home environment).

The majority of investigations report an increased risk for developmental delay in children of mothers with epilepsy (67). The incidence of mental retardation is increased in children of mothers with epilepsy versus children of mothers without epilepsy, but not in children of fathers with epilepsy versus controls. Animal studies suggest that AEDs play at least a partial role. The risk for mental impairment in children of mothers with epilepsy has been related to intrauterine growth retardation, reduced head circumferences, major malformations, numerous (nine or more) minor malformations, and in utero AED exposure, although contradictory findings have been reported (67).

Two retrospective studies from Denmark (68) examined the effects of in utero phenobarbital exposure on intelligence in adult men of mothers without epilepsy. Men exposed prenatally to phenobarbital had significantly lower verbal IQ scores (about seven points) than predicted in both studies. Lower socioeconomic status and being the offspring of an "unwanted" pregnancy markedly increased the magnitude of negative effects (about 20 IQ points).

A retrospective study of school-aged children exposed in utero to AEDs found that special education was required in 30% of children exposed to valproate monotherapy, compared with 3% to 6% for other monotherapies, and 11% with no drug (69). A prospective study (70) found no effect of carbamazepine; however, the mean IQ of children exposed in utero to valproate was 83, compared to 96 for children exposed to carbamazepine, which did not differ from no drug exposure (IQ = 95), but the monotherapy valproate group was small and maternal IQ was not measured. A long-term prospective study, which controlled for multiple possible confounding factors including maternal IQ, confirmed the increased risk for impaired cognition from in utero valproate exposure (71,72); the IQ of children exposed to valproate was reduced 7 to 10 points compared to children exposed to carbamazepine, lamotrigine, or phenytoin. Valproate also exhibited dose- dependent adverse effects on IQ, language, nonverbal, memory, and executive functions (72). A recent population-based study confirmed prior reports of an increased risk for autistic spectrum disorder in children exposed to valproate (73). Although it is clear that in utero valproate exposure poses a greater risk for both anatomical and behavioral teratogeneses, the risks for other AEDs remain to be fully delineated.

CONCLUSIONS

Patients with epilepsy have increased risk for cognitive impairment. Various factors may contribute, but AEDs are of special concern as the major therapeutic modality for epilepsy. All AEDs can produce some cognitive side effects, which are increased with polypharmacy and higher dosage/blood levels. For an individual patient, the best risk–benefit ratio may be obtained with judicious use of polypharmacy or with anticonvulsant blood level above "standard therapeutic ranges," but physicians should be alert to increased risk under these circumstances. Further, they should be aware that certain AEDs have higher risk to produce adverse cognitive effects (e.g., benzodiazepines, phenobarbital, topiramate) while others have lower risk (e.g., gabapentin, lamotrigine, levetiracetam). Differential behavior effects are also seen (e.g., mood stabilization, depression, irritability/agitation, psychosis) with some AEDs having positive psychotropic effects (e.g., carbamazepine, lamotrigine, valproate) while others have higher risk of adverse effects (e.g., levetiracetam, phenobarbital, topiramate). However, age differences and individual variability occur.

When AEDs are used in monotherapy with blood levels within standard therapeutic ranges, their cognitive effects on formal neuropsychological tests of cognition are generally modest, but can still be clinically significant. Cognitive impairments induced by AEDs may be of particular concern for adults with jobs requiring speed or sustained vigilance and for children in whom the additive effects

during neurodevelopment may have long-lasting consequences. Further studies are needed to examine the relative effects of epilepsy therapies and to delineation cognitive effects for all AEDs, especially at age extremes (fetus, young children, and elderly).

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CHAPTER 93 PSYCHIATRIC COMORBIDITY OF EPILEPSY

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Epilepsy is a model for brain–behavior relationships. Seizures affect behavior, and behavior affects seizures. Psychiatric comorbidity is common among patients with epilepsy, the clinical presentation is frequently atypical, and there is often a temporal relationship with seizures. This chapter reviews four of the most commonly encountered psychiatric illnesses in patients with epilepsy: depression, anxiety, psychosis, and personality disorders.

DEPRESSION

Epidemiology

Depression is the most frequently occurring comorbid psychiatric disorder in patients with epilepsy, with a prevalence of 10% to 20% among patients with controlled seizures and 20% to 60% among those with refractory epilepsy (1,2). These rates are significantly higher than in controls, with major depressive disorder (MDD) diagnosed in 4.9% to 17% of the general population. The relationship between seizures and depression is bidirectional, in that the presence of one predicts the other (3,4). Those with depression have a 1.7- to 6-fold higher risk of developing seizures than controls (5,6).

Depression is a better predictor of quality of life in patients with epilepsy than are verbal memory, psychomotor function, cognitive processing speed, mental flexibility, seizure frequency, and seizure severity (7,8). Depression has a negative effect and is associated with more disability, greater social difficulties, more drug side effects, lower employment rates, cognitive dysfunction and subjective memory complaints, and greater use of the medical system (9,10). In patients with epilepsy, morbidity, mortality, and overall prognosis are poorer in those with comorbid depression. Those with psychiatric disease are less likely to attain seizure freedom with antiepileptic drugs (AEDs) or anterior temporal lobectomy (11,12).

Potential risk factors for depression in patients with epilepsy include frequent seizures (>1 per month), symptomatic focal epilepsy, younger age, psychosocial difficulties with learned helplessness, and polypharmacy (13). Depression ratings negatively correlate with the presence of idiopathic generalized epilepsy (IGE) as opposed to other types of seizures (13). Mesial temporal sclerosis (MTS) is a better predictor of the presence of depression compared to other forms of temporal lobe epilepsy (TLE). The effect in focal epilepsies appears to be independent of lateralization of the seizure focus, although studies are conflicting, with some indicating left predominance (14). Frontal dysfunction may have etiologic significance as well. Unlike idiopathic depression, female predominance is not a consistent finding.

Clinical Features

Depression is categorized into MDD, persistent depressive disorder (dysthymia), and other forms such as "other specified depressive disorder" and "unspecified depressive disorder." Criteria for major depression include low mood, feelings of worthlessness, guilt, loss of energy and interest, insomnia or hypersomnia, changes in appetite, psychomotor retardation or agitation, decreased concentration, and suicidal ideation (SI). Approximately 17% to 30% of depressed patients with epilepsy will meet formal criteria for MDD. In persistent depressive disorder, symptoms are more chronic but may be less severe. Other specified depressive disorder and unspecified depressive disorder are diagnosed when presentations do not meet full Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for MDD, persistent depressive disorder, or the other disorders of this diagnostic class.

The clinical presentation in 25% to 71% of depressed patients with epilepsy does not meet DSM Axis I category criteria (15) and may be considered an "other specified" or "unspecified" depressive disorder. Atypical presentations are particularly common in children. The concept of an atypical depression in epilepsy, first noted by Kraepelin and later formalized by Blumer, has been termed "interictal dysphoric disorder" (IDD) (16) or "dysthymic-like disorder of epilepsy" (17). Symptoms resemble those of dysthymia (now termed "persistent depressive disorder"), but occur intermittently, precluding the formal diagnosis of persistent depressive disorder. Patients may have intermittent irritability, depressed or euphoric moods, anergia, insomnia, atypical pains, anxiety, and fears in the setting of clear consciousness. Episodes begin and end abruptly. They may recur every few days to every few months and last from a few hours up to 2 days or more. Onset generally occurs 2 years after the diagnosis of epilepsy. Data suggest an association with mesial TLE. A similar presentation in the setting of limbic lesions, but without overt seizures, has been termed "subictal dysphoric disorder." Depression in epilepsy may represent a continuum, perhaps with persistent depressive disorder, intermittent episodes of IDD, and occasional worsening of symptoms meeting criteria for MDD (18). While IDD may be evident preictally, postictally, premenstrually, or in the setting of forced normalization, symptoms are typically independent of seizure occurrence. Many patients experience an increase in dysphoria over the 12 to 18 months following temporal lobectomy, after which symptoms resolve.

The Seizure Questionnaire (16) may be used to screen for IDD; presence of at least three of the key symptoms warrants the diagnosis. Ongoing treatment is often necessary. Patients with IDD tend to be sensitive to antidepressants, in that drugs are rapidly effective for their broad array of symptoms at low doses.

Major depressive symptoms vary according to the temporal relation to seizure activity. Symptoms may arise prior to seizure onset (preictal), as an expression of the seizure (ictal), following seizures (postictal), or, most commonly, unrelated to seizure occurrence (interictal). Preictal depression is characterized by a dysphoric mood that precedes a seizure by hours or days (19) and usually ends with the seizure. Ictal depression may manifest as a simple partial seizure (SPS) in which depression is the sole symptom or as an aura leading to a complex partial seizure (CPS). Psychiatric symptoms occur in 25% of auras, 15% of which involve affective changes (20). Ictal depression is the second most common, after ictal anxiety or fear, and consists of anhedonia, guilt, and SI. In dacrystic seizures, auras consist of unprovoked and inappropriate crying. The mood alterations with ictal depression are stereotypical and occur out of context. Postictal depression has long been recognized, but its frequency is unknown. In one series, postictal depression was evident in 43% of patients with

partial seizures. Postictal symptoms often persist for hours to several days and may be severe, including SI (21).

Major depression may also develop paradoxically as seizure control or EEG abnormalities improve through medication or surgery, a sequence of events termed "forced normalization." Although many of those with depression will have resolution of their symptoms after epilepsy surgery (22–24), depression may also worsen or occur de novo posttemporal lobectomy (24,25). Postoperative depression often begins acutely within the first month after surgery. In 80% of patients, symptoms will begin within the first year. Risk factors include fear auras. The effect of laterality is controversial, although Quigg et al. (26) suggest higher risk with right-sided resections.

Recent 5-year surgical resection outcome data, however, indicate that long-term, sustained improvement in mood may be attained in those with good seizure control (23). In addition, initial data suggest that radiosurgery and deep brain stimulation (DBS) do not have deleterious effects on mood. No overall mean change in depressive symptoms was evident 2 years after gamma knife radiosurgery for mesial TLE (27). While approximately 15% of patients, nearly all with a prior history of depression, reported depression as an adverse event with DBS of the bilateral thalamic anterior nuclei, there was no difference in mood between control and treated groups on formal testing at 3 months (28). In general, preexisting depression should not be a contraindication for surgical management or device implantation (i.e., vagal nerve stimulation).

Treatment

Depression is both underrecognized and undertreated in patients with epilepsy. An estimated 80% of neurologists (29) do not screen for depression in patients with seizure disorders, perhaps due to unease with its management. Difficulty in recognition of symptoms may also play a role, as many patients present atypically or have confounding side effects of medications. A further limiting factor is the lack of controlled trials for depression in patients with epilepsy. Wiegartz et al. (30) found that 38% of patients with a lifetime history of MDD had never received treatment, and Kanner and Palac (15) observed that treatment was delayed by more than 6 months in 66% of patients with epilepsy and concomitant mood disorders of >1-year duration.

When screening for depression, an initial, simple step is to inquire about anhedonia, which is the inability to experience pleasure. This is an excellent indicator of depression and generally unaffected by drug side effects or underlying medical issues. Consensus guidelines established by the International League Against Epilepsy (ILAE) recommend screening for depression using the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), Patient Health Questionnaire (PHQ-2), or equivalent measure at the time of diagnosis and yearly thereafter (31). Referral to a psychiatrist, especially one who is knowledgeable about epilepsy, is advisable for diagnosis and treatment, particularly in the setting of bipolar disorder, psychotic features, SI, or symptoms refractory to two antidepressant trials (32).

Before initiating treatment, iatrogenic factors should be considered, such as the recent discontinuation of an AED with mood-stabilizing properties (e.g., carbamazepine [CBZ], lamotrigine [LTG], valproate [VPA], and vagus nerve stimulation [VNS]). Many of the recently approved anticonvulsants also have positive effects on mood. Rufinamide was reported to have mood-stabilizing properties in isolated cases (33), and lacosamide, ezogabine, and perampanel have produced euphoria, particularly at high doses. While clobazam has been associated with depression in some patients, others have reported a "feeling of well-being" with use of this agent (34,35). The

recent introduction or dosage increase of an AED with potential negative psychotropic properties must also be considered (e.g., primidone, phenobarbital [PB], topiramate [TPM], vigabatrin, tiagabine, felbamate, gabapentin, levetiracetam [LEV], or zonisamide [ZNS]), as well as the recent remission of seizures (i.e., "forced normalization"). Phenobarbital exerts particularly negative effects on mood, with 40% of those treated developing depression (36). Risk factors for AED-induced depressive episodes include a personal or family history of mood disorders, anxiety, or alcoholism; severe epilepsy; febrile seizures; polytherapy; rapid titration; and high doses. Addition of an enzyme-inducing AED may also increase clearance of concurrently administered antidepressants, leading to breakthrough depressive symptoms (Table 93.1). If iatrogenic issues are a factor, their correction should be the first step in management. If it is not possible to alter the AED regimen, an antidepressant may be added. In addition, prior to initiation of therapy, patients should be screened for evidence of bipolar disorder to avoid precipitating a manic episode.

Table 93.1 Antidepressants Commonly Used in Patients with Epilepsy

Medication	Initial monotherapy	Hepatic enzyme effects	Interactions with AEDs/ antidepressants	Seizure risk (percent incidence in general population)	Notes
SSRI					
Citalopram	Depression Adults Children	Little effect	↑ TCA levels Levels decreased by CBZ	0.1–0.3 18.0 at 600–1900 mg	Toxicity increased by concurrent LMT Increased risk of prolonged QT with concomitant ezogabine
Escitalopram	Depression Adults Children[a]	Little effect	Levels increased by oxcarbazepine Levels decreased by phenobarbital, primidone	0–0.04	Myoclonus reported with concurrent LMT Increased risk of prolonged QT with concomitant ezogabine
Fluoxetine	Depression—children[b,c]	Inhibitor	↑ DPH levels ↑ Ethotoin levels ↑ CBZ levels ↑ Lacosamide levels ↑ TCA levels ↑ VPA levels (rare) Levels increased by clobazam	0–0.3	Possible anticonvulsant effects Serotonin syndrome; isolated case of Parkinsonian syndrome with concurrent CBZ Long half-life, less withdrawal Toxicity increased by concurrent LMT Increased risk of prolonged QT with concomitant ezogabine
Fluvoxamine	Depression—children[c]	Inhibitor	↑ DPH levels ↑ CBZ levels ↑ Clobazam levels ↑ Ethotoin levels ↑ Lacosamide levels ↑ ZNS levels ↑ TCA levels Levels increased by clobazam	0.05–0.2	Toxicity increased by concurrent LMT
Paroxetine		Little effect	↑ TCA levels Levels increased by clobazam	0.07–0.1	Increased risk of weight gain Short half-life, withdrawal syndrome Toxicity increased by concurrent LMT Not recommended for children
Sertraline	Depression—children[c]	Little effect	↑ CBZ levels ↑ DPH levels (rare) ↑ TCA levels	0–0.3	Increased risk of weight gain Toxicity increased by concurrent LMT
SNRI					
Venlafaxine	Depression—adults		↑ TCA levels Levels increased by clobazam	0.1–0.3 0 with XR formulation 5.0 with overdose	Not for use in young children; may use in older adolescents and those with resistant depression Higher remission rates than SSRI Faster onset of action For somatic symptoms; wide spectrum of action More complicated titration Significant withdrawal Use extended release May cause lethargy, irritability, hypertension Use at half starting dose in elderly
Tetracyclic					
Mirtazapine	Depression—adults		Levels increased by clobazam	0.04	Not for use in young children; may use in older adolescents and those with resistant depression For melancholic features May cause sedation, weight gain Lacks SE of nausea, sexual dysfunction May cause agranulocytosis; do not use with CBZ

[a]FDA approved for age ≥12 y.
[b]FDA approved for age ≥8 y.
[c]FDA approved in children for OCD.
TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; SNRI, selective serotonin norepinephrine reuptake inhibitor; DPH, phenytoin; CBZ, carbamazepine; PB, phenobarbital; OXC, oxcarbazepine; TPM, topiramate; VPA, valproic acid; LMT, lamotrigine; SE, side effects; AED, antiepileptic drug; XR, extended release.

For those with peri-ictal depression, improved seizure control may be a sufficient treatment. For patients with resistant peri-ictal depression, interictal MDD, persistent depressive disorder, or IDD, antidepressant treatment is indicated. Antidepressant medications tend to be less effective, however, for peri-ictal episodes. In the absence of controlled trials, the choice of antidepressant should be based upon safety, tolerability, and ease of use (e.g., frequency of dosage, likelihood of drug–drug interactions). If a particular antidepressant was successful in the past for the patient or a family member, another trial of this agent should be considered.

A common misconception is that all antidepressants significantly lower seizure threshold and should be avoided. These fears are largely based upon seizures associated with overdoses, which have little predictive value when levels are within therapeutic range (37,38). Lower doses of antidepressants may in fact have anticonvulsant properties (39). Rate of escalation and duration of treatment may also play a role. Patients with primary generalized epilepsy may have a greater propensity for seizure exacerbation secondary to antidepressants; depression in such patients appears to respond well to low doses of these agents (16).

The medications with substantial risk are few; however, it is prudent to avoid bupropion, maprotiline, clomipramine, and amoxapine because of their potential for exacerbating seizures (39). Seizures due to bupropion are classically generalized tonic–clonic convulsions (GTC), as may be seen particularly in patients with bulimia. The immediate-release preparation presents the greatest concern, with a seizure incidence of 0.36% to 5.8%. The seizure-inducing potential is dose related, and the therapeutic index is low. Maprotiline induces seizures in 12.2% to 15.6% of patients; higher serum levels and longer durations of treatment are the risk factors. The epileptogenicity of clomipramine varies by dose, with seizures in up to 3% of patients taking >250 mg/day. Risk also increases with concomitant VPA, with status epilepticus occurring in some cases. Although the propensity for seizures is lower (0.5%) with doses <250 mg/day, clomipramine is best avoided. Likewise, seizure risk with amoxapine is 36.4%, with reports of status epilepticus.

In contrast, selective serotonin reuptake inhibitors (SSRIs; citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) are unlikely to worsen seizure frequency or severity and are generally effective for dysthymic disorders, symptoms of irritability, and poor frustration tolerance. Furthermore, an overdose of an SSRI is unlikely to be fatal, interactions with AEDs are minimal, and side effects are manageable. For these reasons, SSRIs are first-line treatments in adults and children with depressive disorders. Women tend to be more responsive than men, however, and sexual dysfunction and weight gain are common adverse reactions. Sexual dysfunction may occur in 70% of those treated with SSRIs. Weight gain is of particular concern when SSRIs are used in combination with AEDs that cause the same effect, including gabapentin, VPA, CBZ, and pregabalin.

Among the SSRIs, sertraline has been best studied. Kanner et al. (17) used sertraline to treat depression in 100 patients with epilepsy. Depressive symptoms improved in the majority of subjects, with seizures definitely worsening in only one patient. Clinicians favor the use of the newer SSRIs, citalopram and escitalopram, due to their lack of hepatic enzyme effects. Fluoxetine and fluvoxamine, in contrast, have enzyme-inhibiting effects that may elevate AED levels. Starting with the lowest dose of an SSRI is recommended, with a gradual dose increase at 1- to 2-week intervals. If a more rapid increase is necessary due to severe symptoms, closer observation is required.

Vortioxetine, approved in 2013, acts as an SSRI, but with additional serotonergic effects, including 5-HT_3 receptor antagonism and 5-HT_{1A} receptor agonism. Seizure induction rates have not yet been published, and data in epilepsy populations are lacking. Vortioxetine levels are decreased

by CYP inducers, including CBZ and phenytoin (DPH). Vilazodone, a newly approved SSRI and partial serotonin 5-HT_{1A} receptor agonist, has not yet been studied in patients with epilepsy. Prescribing information notes that "seizures can occur with treatment," although induction rates were not specified. An isolated case of generalized tonic–clonic status epilepticus was reported in a young child with a toxic ingestion (40). Given such limited seizure-related data and overall experience, vortioxetine and vilazodone are unlikely to be prescribed for epilepsy patients at present.

The tricyclic antidepressants (TCAs; amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine) are not recommended as first-line agents in patients with epilepsy because of a greater likelihood of side effects and drug–drug interactions. Weight gain and sexual dysfunction are common. Also of concern are the potential for cardiac conduction abnormalities and the greater tendency to induce mania. The anticholinergic effects may exacerbate memory dysfunction in patients with Alzheimer disease as well. Finally, these medications have been shown to increase the risk of seizures in the general population in up to 0.1% to 4% at therapeutic levels and 8.4% to 22% in the setting of overdose (levels >1000 mg/mL). This class of medications is contraindicated in children with epilepsy due to the seizure risk. Imipramine and amitriptyline at dosages ≤200 mg/day, however, do not generally provoke seizures in adults. Imipramine, amitriptyline, and trimipramine may cause epileptiform EEG changes at high doses, although this is not generally accompanied by clinical seizures.

For these reasons, monitoring TCA levels may be helpful, particularly in the setting of polypharmacy or to identify slow metabolizers. Enzyme-inducing AEDs (e.g., phenytoin [DPH], PB, primidone, CBZ) may cause low TCA levels, while enzyme inhibitors (i.e., VPA) may increase TCA levels. Conversely, imipramine and nortriptyline may increase concentrations of DPH, CBZ, and PB, and amitriptyline may increase the volume of distribution of VPA. Drug–drug interactions may be quite complex, at times with increased formation of toxic metabolites but decreased activity of parent compounds. The common recommendation to start at a low dose and increase slowly applies.

The monoamine oxidase inhibitors (MAOIs; rasagiline, selegiline, isocarboxazid, phenelzine, tranylcypromine) are generally safe in patients with epilepsy. They are not often prescribed due to their side effect profile, however, which includes hypertensive crises due to interactions with tyramine-containing foods. The potentially fatal serotonin syndrome may also occur when an MAOI is combined with an SSRI or a TCA, with symptoms including restlessness, myoclonus, diaphoresis, tremor, hyperthermia, and seizures. Although useful for atypical features of depression, these are third-line agents and should be prescribed only by psychiatrists.

Of the selective norepinephrine reuptake inhibitors (SNRIs; duloxetine, venlafaxine), venlafaxine is a first-line agent in adults with depression, particularly for those with melancholic features. Dosages as high as 225 mg/day have been demonstrated to be safe in depressed patients with epilepsy. Lethargy, irritability, and hypertension are the main side effects. Blood pressure elevations are typically seen at higher doses, above 300 mg/day.

Levomilnacipran is a new serotonin and norepinephrine reuptake inhibitor, FDA approved in 2013. An isolated case of seizure activity was reported in premarketing clinical studies, but data regarding use in epilepsy patient populations are not yet available. As with many new psychiatric medications, the drug is not commonly used in epilepsy patients, pending further experience and less expensive generic formulations.

The goal of treatment for depression is symptom remission; those with any residual symptoms have a greater likelihood for relapse. A full response should be evident in 6 to 12 weeks. Continuation of medication is generally indicated for 4 to 9 months. The ILAE consensus guidelines

recommend continuation of treatment for 6 months after recovery from the initial episode and for at least 2 years after recovery from any subsequent episodes (31). If a patient has three or more episodes of depression, residual symptoms, suicidality, psychosis, or an otherwise severe episode, long-term prophylaxis is indicated. Children tend to have high relapse rates, with continuation of symptoms into adulthood (41).

In the elderly, SSRIs and venlafaxine may be used, but dosages should begin at one-half the usual starting dose, and treatment should be continued for at least 2 years in those with frequent or severe episodes (20).

In addition to pharmacotherapy, evidence supports use of cognitive–behavioral therapy (CBT) and interpersonal therapy in those with mild to moderate symptoms, and additional benefit may be attained from combined approaches with therapy plus medication. Psychotherapy can help patients cope with limitations imposed by epilepsy and may result in significant improvements in rating scales of depression and anxiety, as well as seizure frequency (42). Psychoeducation and therapy (e.g., CBT, interpersonal psychotherapy, or supportive therapy) are strongly recommended for children (43).

For refractory depression, alternative regimens may include dopamine agonists and electroconvulsive therapy (ECT), which is particularly useful for refractory depression or acute, severe episodes (e.g., including suicidality, psychosis). ECT is not contraindicated in epilepsy. Dose reduction of AEDs may be required during a course of ECT, and AEDs should be withheld the morning of a treatment unless there is concern for status epilepticus.

The Epilepsy Foundation's Mood Disorders Initiative has made the following recommendations regarding treatment of depression in adults with epilepsy (20):

Stage 1: Monotherapy with an SSRI (citalopram, escitalopram), venlafaxine or mirtazapine, and/or CBT is first-line treatment. If there is an incomplete response, proceed to stage 2.

Stage 2: Monotherapy with a different agent is recommended (another SSRI, a TCA, venlafaxine, or mirtazapine). If there is an incomplete response, proceed to stage 3.

Stage 3: Monotherapy with an SSRI, a TCA, venlafaxine, mirtazapine, or an MAOI is recommended. A medication from a different class than that used in stages 1 or 2 should be administered. Alternatively, combination therapy may be used (TCA with SSRI, TCA with venlafaxine, TCA with mirtazapine, venlafaxine with mirtazapine). If there is an incomplete response, proceed to stage 4.

Stage 4: Combination therapy is recommended (TCA with SSRI, TCA with venlafaxine, TCA with mirtazapine, venlafaxine with mirtazapine). If there is an incomplete response, proceed to stage 5.

Stage 5: ECT.

When transitioning between drugs, an overlap and taper strategy should be used to avoid withdrawal symptoms.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) recently issued general recommendations for the treatment of mood disorders in epilepsy (44), which vary somewhat from the Epilepsy Foundation's guidelines. CANMAT recommendations, for example, suggest lamotrigine as a second-line treatment for depression in epilepsy patients. They also consider the use of folate supplementation, given the concern that AED-associated folate deficiency may contribute to depression. Furthermore, in refractory depression, the authors propose possible VNS implantation.

Suicidality

Though estimates vary, the lifetime prevalence of SI in patients with epilepsy is approximately twice that of the general population, occurring at a rate of about 12%. Suicide attempts occur in 4.6% to 30% of patients with epilepsy, compared to 1.1% to 7% of controls. Patients with seizures are also at greater risk of completing suicide compared to controls: 2.32% to 14% and 0.74% to 1.4%, respectively (45). Elevated risk occurs in children and adolescents with epilepsy as well, with 20% of such children experiencing SI (46).

The prevalence of suicide in epilepsy increases with comorbid psychiatric diagnoses, including depression, psychosis, anxiety, personality disorders, and bipolar disorder (45). Ictal and postictal depression, mania, postictal psychosis (PIP), and command hallucinations present particular risks. In 90% to 95% of patients who commit suicide, prior psychiatric diagnoses were present (45).

Other risk factors include psychosocial stressors, poor physical health, young age in men (25 to 49 years), early age of seizure onset (<18 years, particularly during adolescence), presence of brain lesions, inadequate follow-up or treatment of seizures, access to firearms or other methods of self-harm, and interictal behavioral disorders (i.e., viscosity) (45,47). In TLE, the suicide rate is 25 times higher than in the general population, and a history of epilepsy surgery presents a risk five times of that presented by medical management. Furthermore, cognitive impairment carries a 10 to 25 times greater risk than normal cognition. The degree to which these factors are predictive, however, may differ between men and women (48).

Time periods for particular concern are in the first 6 months after the diagnosis of seizures (49) and within a few months to years of attaining good seizure control after a long history of refractory epilepsy (50). SI may also occur with a temporal relationship to seizure activity. Among patients with refractory seizures, 13% experience postictal SI, lasting 24 hours on average.

Of concern is suicidality associated with AEDs, especially PB (36,48). The risk of SI is 47% in those treated with PB compared to 4% in those treated with CBZ (36). The relationship may be related to dose (48). Patients taking PB should be specifically monitored for the development of SI, and use of the drug should be avoided in those with depression or cognitive dysfunction.

In early 2008, the FDA issued an alert regarding suicidality and use of AEDs (51). Based upon a meta-analysis of 199 placebo-controlled trials including 11 AEDs, they found approximately twice the risk of suicidal thoughts or behavior in those taking AEDs compared to placebo (0.43% vs. 0.22%, respectively). The FDA interpreted the findings as likely representing a class effect, generally consistent across medications. Rates differed, however, between the studied AEDs, and older AEDs were not included in the analysis. The risk began as early as 1 week, and continued to at least 24 weeks, at which time most trials ended. Demographic factors (i.e., age) did not clearly influence risk, although those using the drugs for seizure control had the highest relative risk of suicidality (3.6) when compared to groups taking these agents for other indications. These findings prompted labeling changes. Physicians are encouraged to discuss this issue with their patients and closely monitor those receiving AEDs for onset or worsening of depression.

Assessment should include direct questioning regarding risk factors. Risk for suicide may also be assessed by the suicidality modules of the Mini International Neuropsychiatric Interview (MINI), the Beck Depression Inventory-II (BDI-II), and the Children's Depression Inventory (CDI) (20,45). Physicians need to document the level of risk, interventions, and plans for monitoring. The patient must be kept safe, including the removal of firearms from the home, and may be provided hospitalization until the SI resolves. The clinician should also consider the patient's access to AEDs

and the potential for overdose. The availability of PB, for example, poses great safety concerns. Antidepressants and psychotherapy are helpful, and referral to a psychiatrist is indicated.

ANXIETY DISORDERS

Anxiety disorders include generalized anxiety disorder (GAD), panic disorder (PD), obsessive–compulsive disorder (OCD), phobias, and posttraumatic stress disorder (PTSD). Studies suggest an increased prevalence of GAD, PD, OCD, and phobias in patients with either partial or primary generalized epilepsy, with prevalence estimates of 3% to 66% in patients with seizures and up to 29% in the general population (2). Symptoms of anxiety may be more severe in patients with localization-related epilepsy (52,53), and recent data suggest a particularly high frequency of anxiety disorders in patients with left MTS (66.7%) (32). The association between anxiety and epilepsy is bidirectional, with the incidence of anxiety increased in the years pre- and postepilepsy diagnosis (4). Patients may also have symptom complexes that overlap defined categories. Anxiety may lead to significant distress, and the presence of anxiety in a depressed patient with epilepsy increases the risk of suicide (45).

Generalized Anxiety Disorder

GAD is characterized by excessive anxiety and worry about many issues, occurring almost daily. Patients with GAD may also experience restlessness, fatigue, poor concentration, irritability, muscle tension, and sleep dysfunction. Anxiety in epilepsy most commonly presents as GAD, seen in an estimated 21% of patients with refractory TLE (54).

Anxiety may occur prior to (preictal), during (ictal), or after (postictal) seizure onset. Preictal anxiety may precede the seizure by hours to days. Ictal anxiety is often described as “fear,” occurring as part of the aura in approximately 15% of patients with partial seizures and 33% of patients with TLE. Ictal fear is more common with medial foci than with lateral regions of onset. It has been suggested that ictal fear may signify well-localized anterior TLE and predict a favorable surgical outcome compared to those without ictal fear. Ictal anxiety may also be present, however, with frontal, cingulate, or other limbic-onset seizures. While some authors suggest that fear lateralizes to the nondominant hemisphere (55), this is not entirely clear. Postictal anxiety occurs in an estimated 45% of those with refractory partial seizures. Symptoms last an average of 24 hours and have been likened to a “psychiatric Todd phenomenon.” Those at greatest risk for postictal anxiety include patients with a psychiatric history (21).

Up to 66% of patients with epilepsy report interictal anxiety. While data are conflicting, interictal anxiety does not necessarily correlate with seizure frequency (56,57), and symptoms may develop paradoxically with seizure freedom or reduction (i.e., postoperatively). A shorter duration (<2 years) of epilepsy may correlate with increased anxiety.

Contributing factors include the unpredictability of seizures, psychosocial difficulties, and iatrogenic effects. More specifically, the use of felbamate, vigabatrin, LTG, or TPM may predispose to anxiety, particularly with rapid titration. The withdrawal of AEDs, such as benzodiazepines or PB, may also precipitate GAD, particularly in those with ictal anxiety. Increased anxiety can occur as a paradoxical reaction to SSRIs as well.

GAD may affect quality of life even more than seizure frequency. Anxiety prior to epilepsy surgery is a marker of poorer postresection psychosocial adjustment, perceived memory function, and

health-related quality of life. Hence, the importance of screening should be emphasized to aid in appropriate treatment and presurgical counseling. A number of assessment tools are available, including the State–Trait Anxiety Scale (STAI, revised scale Form Y), Goldberg Depression and Anxiety Scales, the Beck Anxiety Inventory (BAI), the Symptoms Checklist (SCL-90-R), the Hospital Anxiety and Depression Scale, and the Hamilton Anxiety Rating Scale (HAM-A or HARS) (58).

Treatment in patients with epilepsy currently varies little from that of the general population, although no controlled studies have been conducted to date. SSRIs, specifically paroxetine and escitalopram, are first-line agents (Table 93.2). Data also demonstrate efficacy of venlafaxine. Benzodiazepines may be used for insomnia and acute, severe distress, although continuous use should probably be limited due to their addictive properties. Pharmacologic treatments used empirically also include TCAs (i.e., imipramine), trazodone, propranolol, and AEDs. AEDs with anxiolytic effects include VPA, tiagabine, benzodiazepines, barbiturates, gabapentin, pregabalin, phenytoin, oxcarbazepine (OXC), and possibly rufinamide. Mula (59) suggested pregabalin as a first-line agent for acute and long-term maintenance therapy, with paroxetine, imipramine, and venlafaxine as second choices. While buspirone is effective in the general population, this agent should be avoided in patients with epilepsy due to the risk of exacerbating seizures.

Table 93.2 Preferred Agents for the Treatment of Anxiety Disorders

	GAD	PD	OCD	PTSD	Social anxiety
Antidepressants	SSRI Paroxetine Escitalopram	SSRI Sertraline Paroxetine Fluoxetine	SSRI Sertraline Paroxetine Fluoxetine Fluvoxamine	SSRI Sertraline Paroxetine	SSRI Sertraline Paroxetine
	Venlafaxine	Venlafaxine			Venlafaxine
Benzodiazepines	Clonazepam Alprazolam	Clonazepam Alprazolam			
Other anticonvulsants		Valproic acid Gabapentin Oxcarbazepine	Carbamazepine		
Additional agents	Propranolol				

Medications in bold are FDA approved for that indication.

Nonpharmacologic treatment may be helpful in individual cases, including family counseling, supportive psychotherapy, psychoeducational programs, and self-help groups. Although data regarding efficacy are conflicting, CBT may be useful, either adjunctive to anxiolytics or alone, in patients with mild to moderate symptoms. CBT addresses the negative thought patterns that lead to anxiety, followed by desensitization to anxiety-provoking stimuli. In severe cases, anxiety may also be treated by ECT.

Panic Disorder

Panic attacks consist of episodic symptoms including light-headedness, tremor, fear of loss of control or death, paresthesias, shortness of breath, chest pain, palpitations, perspiration, chills, abdominal upset, sensation of choking, derealization, and persistent worry about future attacks. Clinicians must distinguish between seizures manifesting as panic ("ictal panic"), a primary panic disorder (PD), and comorbid epilepsy and PD. Factors favoring the diagnosis of PD include a gradual onset of

symptoms, duration from minutes to hours, and lack of postepisode confusion (Table 93.3). Making the distinction, however, may be difficult. Sazgar et al. (60) identified 4.5% of patients with intractable TLE as having been initially misdiagnosed as PD. Mintzer et al. (61) have adapted the MINI with an "Epilepsy Addendum" that attempts to aid in the distinction between PD and ictal fear. Anecdotally, patients often report that they sense the difference between the two types of spells. Still, seizures may be diagnosed only after a long delay, when progression to more clear complex partial events occurs.

Table 93.3 Differentiation of Panic Attacks and Partial Seizures

	Panic attacks	Partial seizures
Duration of episode	Longer duration, last at least 5–15 min up to several hours	Brief, typically lasting 30 s–2 min
Variability of symptoms	Variable symptoms and sequence	More stereotyped
Consciousness	Preserved	May progress to alteration/loss of awareness
Postevent symptoms	No confusion/amnesia	May have confusion/amnesia
Symptom onset	Slow building of symptoms	Rapid shifts of symptoms
Déjà vu, olfactory or gustatory hallucinations	Rare Hallucinations in psychiatric disease perceived as internal to self, often with associated paranoia	>5% Hallucinations perceived as external to self, without paranoia
Smothering or choking sensation, tachypnea	Common	Rare
Anticipatory anxiety	Common	Uncommon
Associated symptoms (aphasia, gustatory hallucinations, behavioral arrest, automatisms)	Uncommon	May be associated as progress to CPS
Treatment	Response to benzodiazepines, antidepressants; other AEDs occasionally helpful	Response to AEDs, resection May rarely worsen with certain antidepressants (i.e., tricyclics)
Recurrence	More associated with periods of emotional upset; occur in wakefulness	Sporadic; may occur during sleep
Agoraphobia	50%	No association
Family history	25.1% first-degree relatives with panic disorder	Uncommon
Palpitations	Tachycardia	Brady- or tachycardia
Paresthesias	Perioral, distal extremities associated with hyperventilation	May be generalized although bilaterality rare; often focal, unilateral
EEG	Usually normal	Often abnormal
MRI	Usually normal	Lesions common
Age of onset	Most often 20–30 y	Any age

An estimated 21% of patients with epilepsy have comorbid PD (62), in contrast to a prevalence of PD in 1% to 3.5% of the US general population. The comorbidity may occur in up to 33% of patients with ictal fear (61). PD may emerge or worsen after epilepsy surgery, particularly in those with ictal fear. The incidence of PD in epilepsy appears to increase with age.

Seizures manifesting as panic are uncommon. When present, ictal panic is most often associated with right midanterior temporal lobe onset. One study suggested that ictal panic is particularly rare in patients with extratemporal lobe seizures, with no cases observed in a series of 72 such patients (60). Isolated case reports, however, suggest that ictal panic may occur with left parietooccipital lobe– (63), right parietal lobe– (55), and left temporal lobe–onset seizures (64).

Panic attacks may also present as a postictal phenomenon. Like other forms of postictal anxiety, symptoms last 24 hours on average and are predicted by psychiatric history and relatively low

seizure frequency.

PD can cause significant distress, and proper treatment should be initiated upon diagnosis. Serotonergic medications and benzodiazepines are the agents of choice (65). FDA-approved medications for the treatment of panic include sertraline, paroxetine, fluoxetine, venlafaxine, clonazepam, and alprazolam. The role for other anticonvulsants in the treatment of PD is unclear, although VPA, gabapentin, and OXC may be helpful. In a recent review, Mula (59) recommended an SSRI and CBT in combination during the acute phase, with a TCA and CBT as a second choice. For long-term maintenance, either SSRI–CBT combination therapy or CBT alone was suggested. Of note, hyperventilation/deep breathing during CBT is contraindicated in patients with PD and epilepsy, per ILAE guidelines (31).

Obsessive–Compulsive Disorder

OCD manifests as obsessive thoughts or repetitive, ritualistic behaviors, typically carried out in order to neutralize anxieties or prevent imagined negative events. The prevalence of OCD in the general population is estimated at 1% to 3%. Limited data suggest an increased frequency of OCD in patients with seizures, with studies demonstrating prevalence between 10% and 22% in patients with TLE (32,66,67). Several case reports also document the co-occurrence of OCD and epilepsy in patients with temporal lobe (68,69), anterior cingulate (70), frontorolandic (71), and primary generalized (72) seizures. Data regarding an association with lateralization of the seizure focus, however, are conflicting. In a study of patients with TLE and IGE, common obsessions included those related to symmetry or exactness, contamination, and aggressiveness, while common compulsions included ordering, washing, and checking (67). Interictal personality characteristics associated with TLE, such as attention to detail or hyperreligiosity, may also be viewed as a mild form of obsessions or compulsions.

OCD in the setting of epilepsy, however, remains underrecognized. In a series of nine patients with TLE meeting criteria for OCD, only one had been previously diagnosed (66). Barbieri et al. (68) described a patient who experienced symptoms of OCD for 17 years and never informed her physicians. These cases underscore the importance of screening and the involvement of neuropsychiatrists in epilepsy clinics. Depression and anxiety are common in patients with epilepsy and obsessive–compulsive symptoms (73), and it is important that these comorbid conditions do not obscure the diagnosis of OCD.

Male sex, older age, earlier age of seizure onset, longer duration of epilepsy, focal-onset seizures, and poor seizure control have been associated with more severe symptoms (73), although the effect of epilepsy duration is controversial. Surgical resection may either ameliorate or worsen symptoms of OCD. Rare cases of postsurgical de novo OCD have also been reported (74).

No controlled trials have evaluated the treatment of OCD in patients with epilepsy, and no consensus regarding management exists. Patients are best managed by an experienced psychiatrist. Idiopathic OCD may be treated with psychotherapy and antidepressants, with SSRIs as first-line medications. When using antidepressants, high doses are often required, with monitoring for seizure exacerbation, side effects, and drug interactions. Although one case report documented a 50% improvement in symptoms, many attempts at nonpharmacologic, behavioral treatments have met with limited success in patients with comorbid seizures (69). Nevertheless, Mula (59) recently recommended CBT as the first choice for acute and long-term treatment in epilepsy patients, with the second choice being CBT with sertraline, followed by CBT with clomipramine, when drug treatment

is needed in severe or refractory cases. Successful treatment with CBZ or OXC has also been reported (72). Koopowitz and Berk (72) suggested that comorbid epilepsy may predict better response of OCD symptoms to AEDs than antidepressants, although many other case reports document a lack of effect.

Phobias

Phobias occur in 20% of patients with epilepsy. An estimated 8% to 9% of patients with refractory TLE have agoraphobia and 29% have social phobia (54). Underlying cognitive deficits, low self-esteem, depression, family psychiatric history, and lack of social support may predispose to phobias.

Rare, and perhaps unique to epilepsy, is a "seizure phobia" in which patients fear future seizures. Patients may specifically fear resultant death or brain damage and relive prior seizures. Patients may develop agoraphobia or social phobia, stemming from fear that others would observe their seizures if they were to occur in public. While phobias are typically an interictal phenomenon, some patients experience postictal agoraphobia. The degree of anxiety may parallel the perceived severity of seizures.

Such phobias may be successfully treated by CBT in addition to other forms of counseling and seizure education (75). Caution should be used in the prescription of benzodiazepines, given concerns that they may lead to dependence and avoidance of the deeper cognitive–behavioral issues.

PSYCHOSIS

Epidemiology

The risk of psychosis varies with epilepsy syndrome, seizure severity, and seizure frequency. Incidence rates of psychosis are increased in patients with epilepsy, both before and after the onset of seizures, suggesting a bidirectional relationship (4). Psychosis is reported in 0.6% to 7% of patients with epilepsy in the community and in 19% to 27% of hospital-derived populations (76). The overall frequency of psychosis among patients with epilepsy is approximately 7% to 14%. Most studies indicate a predilection for those with TLE (15.8%), particularly those with left MTS (77,78). Reports of an association with other localization-related epilepsies indicate, less commonly, a relationship with left frontal lobe–onset seizures (79). In addition, a prevalence of 3% to 5% has been documented in patients with IGE.

Diagnosis

Preictal or ictal psychosis is rare. Shukla et al. (80) described a series of patients with intractable right temporal or frontotemporal seizures and preictal psychosis. Symptoms consisted of hallucinations, delusions, affective changes, heightened religiosity, and abusive behavior lasting from 12 hours to 15 days prior to habitual seizures. The psychotic features resolved after each seizure.

During seizures, patients may experience visual or auditory illusions and hallucinations, paranoia, depersonalization, derealization, autoscopy, or a sense of someone lurking behind them. As with most partial seizures, symptoms typically last <3 minutes duration. Prolonged ictal psychosis is rare but may be evident in the setting of nonconvulsive partial or absence status. Often, such patients have a corresponding central nervous system (CNS) lesion (i.e., tumor) (81). Prolonged psychosis and

seizures in the setting of unresponsiveness, dyskinesias, autonomic instability, and hypoventilation, particularly in women, should prompt consideration of an anti–NMDA receptor antibody encephalitis.

The most common form of psychosis occurs between seizures (interictal) (82). Interictal psychosis is present in up to 9.4% of patients with MTS. Average age of onset is approximately 25 to 30 years (83,84), at a mean of nearly 15 years after the first unprovoked seizure (83). Earlier onset of psychosis is associated with generalized epilepsy and a positive family history of psychosis (83). Symptomatology appears to be similar across epilepsy syndromes (78). Features resemble that of schizophrenia, with persistent or recurrent positive symptoms, such as delusions and visual or auditory hallucinations, in the setting of otherwise clear consciousness (85,86). Themes are often persecutory or religious and may have strong affective components. Common associated affective changes include irritability, depression, and aggressive behavior. As in schizophrenia, symptoms may be insidious in onset. Episodes tend to be long-lasting, but may vary in duration, from minutes to years. The mean duration in a study of 155 patients was approximately 80 weeks, with half of the episodes lasting 4 months or longer. The duration tends to be shorter with advancing age (84).

Many key differences to schizophrenia, however, have prompted the term "schizophrenia-like psychosis" of epilepsy (86). Compared with the psychosis of schizophrenia, patients with interictal psychosis often have an absence of negative symptoms or formal thought disorder, better premorbid states, and less deterioration of personality (87), although more recent data suggest that most patients with epilepsy and psychosis will have at least one negative symptom (78). Patients with psychosis related to epilepsy also have a slightly older age of onset compared to those with schizophrenia, with symptoms beginning in the mid-20s to mid-30s (83,84,87,88). Those with epilepsy-related psychosis are more likely to be male, as opposed to patients with schizophrenia (87). Patients with interictal psychosis may also have a better prognosis, with a tendency for remissions and positive responses to treatment (87).

In some patients, a positive correlation exists between overall seizure frequency and psychotic symptoms. A notable exception to this pattern, however, is the concept of "forced normalization" or "alternative psychosis" introduced by Landolt in 1953 (85). Although evident with other psychiatric disorders as noted above, forced normalization is classically associated with psychotic behavior. The patient may have periods of psychosis coinciding with improved seizure control or reduced epileptiform discharges on EEG, often seen with the addition of a new AED. Such periods may alternate with epochs of improved psychiatric function in the setting of a paradoxical increase in seizure frequency or abnormalities on EEG. The underlying pathophysiology is unclear. As Nadkarni et al. (81) note, the psychosis may also be a reaction to the new drug, with improved EEG patterns representing an epiphenomenon. AEDs associated with psychosis include DPH, LEV, TPM, ZNS, tiagabine, ezogabine, perampanel, and vigabatrin (82,89–93). Although generally well tolerated, a case of lacosamide-induced psychosis was also recently reported (94). Forced normalization has been documented with other treatments as well, including VNS (95).

De novo psychosis after epilepsy surgery has also been reported, with rates varying from <1% to 28.5%. Symptoms most often occur transiently after surgery, and the diagnosis may be easily missed. The time period of greatest concern is the first 6 months after resection. Risk factors include a family history of psychosis and surgery after 30 years of age. Some authors suggest an increased incidence in those undergoing nondominant temporal resections, although this is not a consistent finding. Etiology of epilepsy does not appear to affect risk assessment (81). While preoperative psychosis is a risk factor for postoperative psychosis, it should not pose a contraindication for surgery, as long as the

patient has appropriate psychiatric care, can cooperate with evaluation and treatment, and understands associated risks and benefits (31).

PIP is less common, occurring in 6.4% of patients with MTS (77). It typically presents after a cluster of seizures or status epilepticus, oftentimes in someone whose seizures were otherwise well controlled. PIP after a single seizure is rare. Symptoms often begin after 24 to 48 hours of normal baseline behavior, a period termed the "lucid interval." Episodes may last a few days to several weeks, terminating within 1 to 2 weeks on average. Approximately 95% of episodes will resolve within 1 month. A history of interictal psychosis, a family history of psychosis, and low intellectual functioning predict a longer duration of symptoms (96). Symptoms may include visual or auditory hallucinations, paranoia, delusions, confusion, affective changes, violence (i.e., suicidal acts), and amnesia (76,97,98). Religious or grandiose themes among hallucinations and delusions are common, while thought insertion, commenting/command hallucinations, and negative symptoms are rare. Most religious conversions occur during this period.

It is important to distinguish between PIP and postictal mania, as treatment options differ (Table 93.4). The two entities may be easily confused, as both may involve manic features and exhibit a similar lucid period. Logsdail and Toone (97) suggested the following diagnostic criteria for PIP:

Table 93.4 Comparison of Postictal Mania and Psychosis

	Postictal mania	Postictal psychosis
Duration of episode	Longer; mean 16.1 d	Shorter; mean 6 d
Recurrence	More likely	Less likely
Age at onset of epilepsy	Older; mean onset 18.4 y	Younger; mean onset 9.1 y
Localization	Frontal, temporal	Temporal
Lateralization	Dominant hemisphere	Less well lateralized
Symptoms	Elated/expansive/euphoric mood Distractibility Hyperactivity Pressured speech Decreased need for sleep Flight of ideas Grandiosity Hyperreligiosity	Delusions (often persecutory, delusions of reference) Hallucinations (often auditory) Insomnia Emotional lability (transient) Elated/euphoric mood (transient)
Congruency	Mood congruent symptoms	Mood incongruent symptoms
Psychotic features	Rarely	Always

From Nishida T, Kudo T, Inoue Y, et al. Postictal mania versus postictal psychosis: differences in clinical features, epileptogenic zone, and brain functional changes during postictal period. *Epilepsia.* 2006;47(12):2104–2114.

1. An episode of psychosis developing within 1 week of a seizure or cluster of seizures
2. Lasting ≥24 hours and ≤3 months
3. Characterized by disorientation, delirium, delusions, or hallucinations in clear or clouded consciousness

4. Without AED toxicity, nonconvulsive status on EEG, prior interictal psychosis, recent head trauma, or alcohol/drug intoxication

Possible risk factors for PIP include age >30 years; male gender; focal-onset seizures; bilateral onset (often bitemporal) or spread of seizures (i.e., secondary generalization); a history of status epilepticus; prior encephalitis or other widespread CNS injury, borderline intelligence; EEG slowing; psychiatric illness; clusters of seizure activity; presence of ictal fear; and a family history of mood disorders, alcohol use, or epilepsy (98–101). Age at seizure onset and seizure frequency may not be predictive, although data are conflicting. These patients tend to have complex presentations, in that bitemporal dysfunction on neuropsychological testing may be greater than expected based upon structural imaging, and seizure onsets on video–EEG monitoring are often nonlateralizing (101). Postictal psychoses typically develop after at least 10 years of epilepsy and occur almost exclusively in adults, with the mean age of onset 32 to 35 years. Recurrent episodes have been documented in 12% to 50% of cases. As the frequency of psychotic episodes increases, the risk for developing chronic interictal psychosis becomes greater (81). In a series of 18 patients with PIP, 39% also experienced interictal psychosis (102).

Treatment

The first step in treatment is identification of the problem. Patients may not report their symptoms; hence, direct questioning is necessary. As "psychotic episodes may beget psychotic episodes," once identified, symptoms should be treated immediately (81). On average, earlier antipsychotic administration significantly shortens episode duration (84).

For those with peri-ictal psychosis, optimal seizure control is advised. Symptoms may resolve with treatment of the seizures (i.e., with resection) (79). Antipsychotic medications are the mainstay of management for both acute episodes and prevention, as long-term treatment may be necessary for patients with interictal or frequent peri-ictal episodes (Table 93.5). The ILAE guidelines make specific recommendations regarding the duration of treatment, suggesting a taper after 5 days for brief postictal psychotic episodes, a taper after 1 to 2 months when PIP lasts more than a few days, and long-term continuation for interictal psychosis (31). Some patients require psychotherapy, day treatment programs, case managers, or assisted living facilities, as well (81). ECT may be helpful in refractory cases. Patients with psychosis are best referred to epilepsy centers with teams that include psychiatrists and social workers.

Table 93.5 Atypical Antipsychotics

Drug	Levels decreased by	Levels increased by	Seizure risk (%)	Notes
Clozapine	DPH CBZ PB Primidone OXC[a] TPM[a] Rufinamide	VPA[b]	Avoid use; black box warning for higher seizure risk 4.4% at >600 mg/d[c] <1% at <300 mg/d[c] Patients with epilepsy had increased seizure frequency on <300 mg/d	Concomitant CBZ increases risk of leukopenia and neuroleptic malignant syndrome
Olanzapine	CBZ PB Primidone VPA		Higher seizure risk 0.9	Also used for bipolar mania, depression, and agitation
Ziprasidone	DPH[b] CBZ PB[b] Primidone[b] OXC[a] TPM[a] Rufinamide[b]		0.4–0.5	Also used in bipolar disorder; affective and anxiolytic properties May cause akathisia Increased risk of prolonged QT with concomitant ezogabine
Risperidone	DPH CBZ PB	Clobazam	0.3	More likely to cause extrapyramidal side effects Increased risk of prolonged QT with concomitant ezogabine
Quetiapine	DPH CBZ PB Primidone OXC[a] TPM[a] Rufinamide		0.8	Affective and anxiolytic properties Does not cause EEG changes Increased risk of prolonged QT with concomitant ezogabine
Aripiprazole	CBZ DPH OXC PB Primidone Rufinamide TPM	Clobazam	0.4	May cause akathisia
Lurasidone	CBZ[d] DPH[d] OXC[d] PB[d] Primidone[d]		0–0.1[c]	Also for bipolar depression Contraindicated with potent CYP3A4 inducers and inhibitors Increases effect of acetazolamide May cause akathisia
Iloperidone	CBZ DPH OXC PB Primidone Rufinamide TPM		0.1[c]	Not recommended with hepatic impairment Inhibits CYP3A; increases levels of CBZ, ethosuximide, felbamate, perampanel, tiagabine, ZNS Increased risk of prolonged QT with concomitant ezogabine
Asenapine	Carbamazepine[b] PB[b] Primidone[b]		0–0.3	Also for manic or mixed episodes of bipolar disorder Weakly inhibits CYP2D6 Increased risk of prolonged QT with concomitant ezogabine Not recommended with severe hepatic impairment May cause akathisia No reports of EEG changes

[a]Moderate, dose-dependent effects.
[b]May be minimal effects.
[c]Studies in patients without epilepsy.
[d]Contraindicated.
DPH, phenytoin; CBZ, carbamazepine; PB, phenobarbital; OXC, oxcarbazepine; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.

The "positive symptoms," such as delusions, hallucinations, and disordered thinking, respond best to medications. The "negative symptoms," such as apathy, social withdrawal, and catatonia, are notoriously difficult to treat but may respond to the newer, atypical antipsychotics. In general, patients with psychosis associated with epilepsy have better response rates than patients with schizophrenia, with lower initial and maximum doses. These findings were likely due in large part, however, to better compliance (87).

The older, typical antipsychotics carry a greater risk of seizure exacerbation, with seizure induction rates of 0.5% to 1.2% in the general population. Risk is increased by a history of seizures or abnormal EEGs, CNS disorders, rapid titration, high doses, and the concomitant use of other drugs that lower the seizure threshold (103). Hence, the atypical antipsychotics, with lower epileptogenic potential, are preferred. Due in part to a lack of controlled studies, specific treatment decisions are individualized and based upon side effect profiles. Of note, all of the atypical antipsychotics carry some risk of weight gain, hyperlipidemia, and type 2 diabetes mellitus. New data also suggest an increased risk of sudden cardiac death (104). Blood glucose and lipid profiles must be followed, particularly in those taking AEDs that are associated with weight gain (e.g., VPA, gabapentin, pregabalin, and CBZ). One may also consider checking pre- and posttreatment EKGs for evidence of prolonged QT intervals (105).

Ziprasidone is the most common agent used to treat postictal and interictal psychosis, followed by quetiapine and aripiprazole (81). Although an isolated case of frequent GTC seizures associated with aripiprazole was recently reported (106), the drug has an overall low seizure-inducing potential. Other options with relatively low rates of seizure induction include risperidone (107) and olanzapine. The new atypical antipsychotics, lurasidone, iloperidone, and asenapine, have low rates of associated seizures but are not often prescribed. Older agents are generally preferred as they have equal efficacy, but are more familiar, available as low-cost generics, and included on hospital formularies. In addition, lurasidone is contraindicated in the setting of many AEDs due to drug–drug interactions, which may limit its use. Among the typical antipsychotics, haloperidol appears to be the safest. Other typical agents with lower seizure-inducing potential include molindone, fluphenazine, perphenazine, and trifluoperazine (103). Lorazepam may also be used in conjunction with an antipsychotic for acute exacerbations and reinforcement of sleep schedules.

Clearly, psychotropic agents that are associated with a high incidence of seizures in nonepileptic patients should be avoided. These include the antipsychotics clozapine, chlorpromazine, and loxapine. Many antipsychotics can cause slowing of the EEG waveforms, particularly at higher doses. Clozapine, however, can cause frank epileptiform discharges. While these spikes and sharp waves are not predictive of seizure occurrence, severe disorganization of the EEG background may be a harbinger of seizures. Whether concurrent use of AEDs will protect against seizure-inducing potential is unknown. The adage "start low, go slow" applies to all antipsychotics.

Forced normalization is a unique entity, in that a breakthrough seizure may resolve the psychotic symptoms. In such patients, the goal of seizure freedom must be balanced by the risk of potentially disabling psychiatric disease. Seizure freedom may not be ideal for such patients. As Landolt stated, "there would seem to be epileptics who must have a pathological EEG in order to be mentally sane." For those with forced normalization due to VNS, decreasing the pulse intensity can improve symptoms (95). In the setting of forced normalization or drug-induced psychosis, gradual withdrawal of medications may be necessary, and antipsychotics, antidepressants, and anxiolytics may be used.

PERSONALITY DISORDERS

The association between epilepsy and certain personality characteristics dates back to Hippocrates in 400 BC. Reports suggest that up to 69% of patients with TLE and 72% of patients with generalized epilepsy suffer from personality disorders (PSD) (108). DSM-5 cluster B and C disorders, particularly borderline, dependent, and avoidant PSD, are typically cited as the most common. In a series of patients with juvenile myoclonic epilepsy (JME) (109), 14% had PSD, including borderline (6%), dependent (3%), histrionic (1%), and obsessive–compulsive (0.6%) PSD, as well as 3% with PSD not otherwise specified.

Perhaps more controversial is the notion of a specific personality type in the setting of TLE, thought to occur in 7% of TLE patients (110,111). In 1975, Waxman and Geschwind formalized the concept of an "interictal behavioral syndrome," alternatively termed "Geschwind syndrome" or "Gastaut–Geschwind syndrome," which consisted of deepened emotions, circumstantiality, hyperreligiosity, hyposexuality, and hypergraphia. Gastaut suggested that this cluster of personality traits was the opposite of that exhibited by patients with Kluver–Bucy syndrome. Bear and Fedio later expanded the cluster of traits to include the 18 items listed in Table 93.6. The most significant differences in patients with TLE compared to nonneurologic controls were in humorlessness, circumstantiality, dependence, and sense of personal destiny. These are not necessarily negative, pathologic, or maladaptive traits, but rather a constellation of often subtle behavioral changes. The alterations in personality tend to develop gradually, after at least 2 years of seizures (111).

Table 93.6 Characteristics of the "Interictal Behavioral Syndrome"

Characteristics of the interictal personality in temporal lobe epilepsy
Emotionality
Elation/euphoria
Sadness
Anger
Aggression
Altered sexual interest
Guilt
Hypermoralism
Obsessionalism
Circumstantiality
Viscosity
Sense of personal destiny
Hypergraphia
Religiosity
Philosophical interest
Dependence/passivity
Humorlessness/sobriety
Paranoia

From Bear DM, Fedio P. Quantitative analysis of interictal behavior in temporal lobe epilepsy. *Arch Neurol.* 1977;34(8):454–467.

These behavioral characteristics may correlate with mild intellectual impairment and AED

levels. The effect of laterality in TLE is likely minor, with mixed results (112,113). An observed trend is for those with right temporal foci to report more emotional traits and minimize their difficulties, while those with left temporal foci endorse more aberrant behaviors thereby "tarnishing their image" (110).

While much of this discussion focuses on patients with TLE, those with other localization-related epilepsies or IGE may have personality changes as well (110). Patients with anterior cingulate seizures can demonstrate aggressive, sociopathic, irritable, obsessive–compulsive, or impulsive traits (110). Orbitofrontal epilepsy may be characterized by abnormal emotionality, aggression, disinhibition, and confabulation. Patients with typical absence epilepsy may have poor social relationships, particularly in the setting of ongoing seizures. Patients with JME may exhibit irresponsibility, poor impulse control, self-interest, emotional instability, exaggeration, denial, inconsiderate behaviors, and distractibility (110,114,115). These characteristics in a patient with JME may lead to indifference toward illness, poor lifestyle choices, and a failure to learn from past mistakes, leading to perpetuation of the seizure disorder.

Not all studies, however, have found specific personality traits or disorders related to seizure localization. Although scores on PSD inventories are often higher in TLE than in generalized epilepsy, this is not a consistent finding. Nor are there consistent differences in personality measures between patients with temporal and extratemporal lobe seizures (113). The development of specific personality traits and disorders is clearly multifactorial, and while data are often conflicting, factors including prior psychiatric diagnoses, family psychiatric history, female sex, lower educational level, greater seizure frequency, occurrence of CPS and auras, longer duration of epilepsy, earlier age of seizure onset, and AED polytherapy likely play roles as well (112,116–118).

Symptoms of presurgical PSDs typically fail to improve postoperatively, and PSDs may also develop de novo after epilepsy surgery (116). In addition, preoperative PSD may herald the development of other postoperative psychiatric complications, that is, de novo affective disorders. Identification of preoperative PSD may also be important with respect to prediction of seizure outcomes, as their presence in patients with MTS correlates with the persistence of auras (Engel class 1B) and initial disabling seizures followed by seizure freedom (Engel class 1C) after temporal lobectomy (119).

A number of instruments are available for the evaluation of PSD. Administered most commonly is the Minnesota Multiphasic Personality Inventory-2 (MMPI-2). The Bear–Fedio Inventory (BFI), evaluating the characteristics outlined in Table 93.6, has been used less often in recent years. Other self- report batteries include the Questionnaire on Personality Traits, Neurobehavioral Inventory (NBI, a revised version of the BFI), Neurobehavioral Rating Scale (NBHRS), Overt Aggression Scale, Freiburg Personality Inventory/Form A (FPI-A), Index of Personality Characteristics (IPC), and Millon Behavioral Health Inventory (MBHI) (110).

When personality traits impair function and quality of life, treatment should be considered. Unfortunately, treatment options for PSD are limited. Patients may be referred for long-term psychotherapy, although little data formally support its use in epilepsy patients (110). Therapy is often challenging, and complicated by a lack of patient insight. Empathy and reassurance during clinic visits will aid in developing rapport and ensuring adherence to treatment regimens. In patients with JME, the need for self-control, treatment compliance, and healthy lifestyle choices should be stressed (120).

It is important, though difficult, to distinguish those behavioral components due to psychological comorbidities of the epileptic disorder from effects of underlying lesions, medications, or other

behavioral issues. It may also be challenging to differentiate between the ictal, preictal, interictal, and postictal states, as boundaries may be indistinct. Studies are further confounded by difficulties in identifying the focus of onset and degree of spread of abnormal activity, particularly when using routine scalp recordings. Differing criteria for the diagnosis of a behavioral disorder, varying definitions of the epilepsy or control populations, and small sample sizes make studies complicated to interpret or compare. Furthermore, none of the symptoms above are pathognomonic for any one seizure subtype or even to epilepsy as a whole. For these reasons, identification of a personality syndrome specific to TLE has met with criticism (121).

Aggression

Aggression and hostility have been documented in approximately 5% of patients with epilepsy (110,122). In more selected groups and prisoners with TLE, interictal aggressive behavior is present in up to 56% of patients. Nevertheless, aggressive behavior is likely underdiagnosed due to underreporting and a lack of appreciation that the behavior may constitute a treatable disorder.

Although classically associated with TLE and lesions of the amygdala, patients with JME, Lennox–Gastaut syndrome, anterior cingulate seizures, and orbitofrontal epilepsy may also demonstrate interictal aggression. Such behavior is more likely in men and children. Onset of epilepsy before 10 years of age, disability, traumatic brain injury, psychosis, cognitive deficits, fewer years of formal education, lower IQ, and lower socioeconomic status are possible risk factors (123–125).

The association between aggression and epilepsy may relate to common limbic pathways or psychosocial factors. Seizure treatments are also important contributors. Because AEDs may indirectly cause aggressive behavior as a consequence of forced normalization (126) or disinhibiting, anxiogenic side effects, iatrogenic causes should first be considered. Agents causing irritability or aggression include PB, LEV, perampanel, clobazam, and gabapentin, particularly in children and patients with learning disabilities. Effects of LTG, vigabatrin, and TPM are variable, with reports indicating either increased or decreased aggression with use of these agents. Aggressive behavior has also been noted after resection for refractory TLE (127).

Interictal aggression may be evident as a symptom of depression, psychosis, or the more controversial IDD in which patients have “paroxysmal affects” ranging from mild irritability to rage. When in association with interictal psychosis, the aggression is often directed toward imaginary enemies resulting from hallucinations and delusions, rather than surrounding bystanders.

Aggressive behavior may also occur with a temporal relationship to seizures. Some patients exhibit irritability and aggression in the minutes, hours, or days leading up to a seizure (preictal) (19). Ictal automatisms may include stereotyped kicking, boxing, biting, scratching, or other forceful movements. Directed, purposeful, violent behavior during seizures (ictal), however, is rare (122,128,129). Violent crimes are typically too complex to result from the simple, brief automatisms associated with ictal activity. In 1981, an international panel established five criteria to determine whether a crime may result from seizure activity, which are still referenced today (128). These include the following:

1. The diagnosis of epilepsy, established by at least one neurologist with competence in epilepsy
2. Epileptic automatisms documented by history and video–EEG monitoring

3. Aggressive behavior during the epileptic automatisms, confirmed by a video–EEG recording demonstrating ictal discharges
4. Aggressive behavior characteristic of the patient's typical seizures during the ictal EEG
5. Determination by a neurologist that it was possible for the crime to result from a seizure

Postictal aggression is the best recognized entity. Postictal violent behavior may result from attempts at physical restraint, termed "resistive violence" (130). The behavior is typically associated with impaired consciousness or confusion and is most frequently seen in those with CNS pathology (e.g., prior head injury or CNS infection), mental retardation (MR), and psychiatric illness. Self-injury is more often evident in patients with developmental disabilities. Violent behavior may also occur in association with PIP (131,132), during which aggression may be more purposeful and directed toward those nearby in response to hallucinations or delusions.

Subacute postictal aggression (SPA) consists of stereotyped, directed violent or verbally abusive behavior beginning several minutes to hours after a seizure (133). Episodes may occur after waking from postictal sleep and are unrelated to ictal discharges or postictal confusion. The episodes are brief, lasting 5 to 30 minutes. Curious features include at least partially retained awareness and remorse after the episode. SPA tends to occur many years after the onset of epilepsy, in patients with long-standing refractory partial seizures and extensive neural dysfunction. These episodes are more common in men and in patients with TLE and secondary generalized seizures. SPA is not a well-recognized clinical entity and must be differentiated from the more common PIP.

Treatment depends upon the severity of the behavior and the temporal relationship to seizures. Ictal aggression should respond to AEDs. Postictal resistive violence is best treated by avoiding or limiting physical restraint during the postictal period (130). The treatment of interictal aggression is less certain, as it does not necessarily improve with seizure freedom and controlled studies are lacking. AEDs (particularly CBZ, LTG, and VPA), antidepressants (i.e., SSRIs), and atypical neuroleptics (e.g., olanzapine, risperidone, quetiapine, and ziprasidone) have been used empirically. Valproic acid, however, may also cause paradoxical irritability. Beta-adrenergic receptor blockers, including propranolol, nadolol, and pindolol, provide alternative treatment options. Drug interactions are of concern, however, as beta blockade may be increased by SSRIs and decreased by CBZ. Amphetamines may be effective for the treatment of impulsivity and aggression, and are generally safe for use in epilepsy, although methylphenidate has been reported to increase seizure frequency in isolated cases. Lithium may be used for treatment of aggression and agitation, although patients with brain injuries are particularly sensitive to its neurotoxic side effects. Encephalopathy has also been noted with concomitant use of CBZ. While lithium has been used safely in patients with epilepsy and bipolar disorder, it is not generally recommended as initial therapy because of its potential for seizure exacerbation and induction. Similarly, while buspirone is effective for aggression in the general population, its use is discouraged in patients with epilepsy. Removal of anxiogenic agents and treatment of coexisting mood disorders should be pursued. Behavioral therapy may also be helpful, and psychiatric hospitalization should be considered for patients at risk for impulsive, potentially self-injurious behavior (130). For acute episodes, benzodiazepines and antipsychotics are recommended.

SUMMARY

Psychiatric disease is common and significantly impacts quality of life in patients with seizures.

Physicians must actively screen for these disorders, and proper treatment is essential.

Depression, the most common comorbid psychiatric disorder in epilepsy, negatively affects quality of life and increases the risk for suicide. Unfortunately, depression in epilepsy remains underrecognized and undertreated. Many patients present with atypical symptoms, and establishing a diagnosis may be challenging. The importance of screening and treatment for depression in this population, however, should be emphasized. The myth that all antidepressants significantly lower seizure threshold and should be avoided must be dispelled.

Anxiety disorders also occur more commonly in patients with seizures than in the general population. Symptoms typically manifest as GAD and may occur inter- or peri-ictally. Comorbid PD may be present in the setting of epilepsy and must be distinguished from seizures manifesting as panic attacks. Anxiety may also present as OCD or phobias. Common phobias in patients with epilepsy include agoraphobia, social phobia, and a fear of having seizures. Anxiety disorders can be a source of significant distress, and proper treatment is essential.

Patients with epilepsy may also experience comorbid psychosis. Psychotic symptoms generally occur during the interictal state with features similar to that of schizophrenia (e.g., delusions and hallucinations). In contrast to schizophrenia, however, patients with epilepsy and psychosis often have fewer negative symptoms and lack deterioration of personality. Psychosis may also occur as a peri-ictal phenomenon. As an increased frequency of postictal psychotic episodes may evolve to chronic interictal psychosis, immediate treatment is indicated. Atypical antipsychotics and psychiatric consultation are the cornerstones of management.

Finally, clinicians should note the frequent presence of comorbid PSD in this patient population. Perhaps more controversial is the notion of a specific “interictal behavioral syndrome” in patients with TLE, including such traits as viscosity, hyperreligiosity, and hyposexuality. Aggression may also be evident in patients with seizures and should be recognized as a treatable disorder.

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CHAPTER 94 DRIVING AND SOCIAL ISSUES IN EPILEPSY

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A person with epilepsy faces many social concerns that are taken for granted by those without the disorder (1,2). The 2012 Institute of Medicine Report on epilepsy "Epilepsy Across the Spectrum" utilized published data and patient testimonies to assert that everyday limitations placed upon persons with epilepsy can have as significant an impact on quality of life as seizures. The report identified a list of needs, ranging from education regarding the disease to local resources, employment, and transportation needs (3). Quality-of-life (QOL) surveys have identified driving a motor vehicle as the number one concern for a person with epilepsy (1). In addition, other important social issues repeatedly identified by persons with epilepsy include obtaining and maintaining employment and participating in athletic and recreational activities (2,4). This chapter explores important social issues that can influence the QOL of a person with epilepsy.

EVALUATION OF THE RISK OF ENGAGING IN A DESIRED ACTIVITY

Engagement in any activity requires some analysis of the risks of desired activity against the potential benefits of that activity. For a person with epilepsy, there is additional significance to considering this cost-to-benefit analysis. A person with epilepsy must conduct the analysis in the context of a specific situation, with the consideration that a seizure-related injury might occur during the specific activity. To determine potential risk, a person with epilepsy needs to understand all aspects of the activity and try to anticipate the potential exposure to injury should a seizure occur during participation. The risk of seizure recurrence will determine, at least in part, how safe it is to participate in a desired activity. Factors that influence seizure recurrence have been reported (5) and may provide important insight into determining the risks associated with a desired activity. These factors include the presence of an abnormal electroencephalogram (EEG), initial seizure type, and etiology of the seizure. Seizures due to structural etiologies are twice as likely as seizures related to unknown causes to recur (6–8). Focal seizures are also more likely to recur compared with an initial major motor seizure (6,9). If the etiology of a seizure disorder is head injury, the risk for recurrence may be higher. In patients with severe head injury, the recurrence rates for seizures are 7.1% and 11.5% at 1 and 5 years, respectively (10), with severe head injury defined as amnesia and/or loss of consciousness for more than 24 hours, or the presence of an intracranial hematoma. Structural lesions, such as brain tumors, stroke, abscesses, and penetrating head wounds, all carry an increased risk for recurrent seizures. After a new-onset major motor seizure in a patient with a normal examination and workup, including magnetic resonance imaging, electroencephalography, and blood tests, seizure recurrence is estimated to range between 25% (7) and approximately 70% (11) at 3 years. The period

of seizure freedom can predict future risk of seizure recurrence. After a single seizure and a 6-month seizure-free interval, the risk of seizure recurrence in those treated with antiepileptics is 14% and 18% in those not treated (12). If one remains in remission (i.e., seizure free) for 2 years or longer, a good prognosis is possible (13).

The danger period for a particular activity should also be considered when evaluating potential risk. The person with epilepsy is exposed to less risk when the danger period for an activity is brief. Activities with inherent danger must also be factored into the decision of whether to participate. Finally, other factors, such as medication compliance, medication side effects, age, concomitant medical problems, use of safety equipment, seizure triggers, and a prolonged and consistent aura, can all influence the risks faced by a person with epilepsy when engaging in a specific activity.

DRIVING AND THE PERSON WITH EPILEPSY

Driving is a privilege that many adults take for granted yet rely upon in order to go to work, complete errands, and travel. For many individuals with first-time seizures, loss of driving privileges is the most burdensome consequence of the seizure. In a survey of persons with epilepsy, sadness was the most common reaction to driving restrictions, while those who drove despite restrictions most commonly reported anger (14). Governing bodies have increasingly attempted to critically assess risk to make the most reasonable driving regulations for persons with epilepsy.

The Risks

A person with epilepsy faces a risk of injury and a risk of causing injury if a seizure should occur while operating a motor vehicle. Individual country, state, or territorial governments govern this privilege (15). There are approximately 225 million registered vehicles in the United States. In 2011, an estimated 5.3 million motor vehicle crashes occurred in the United States. These crashes resulted in approximately 1.5 million injuries and nearly 30,000 deaths (16). It is estimated that approximately 0.5% to 1.0% of the US population has epilepsy (5), potentially placing up to than 3 million drivers with epilepsy on the roads of the United States. However, the actual number of persons with epilepsy who drive with or without a valid license is unknown. Applicants for a motor vehicle license must answer questions about their medical status and affirm that they are healthy and fit to drive before they are allowed to operate a motor vehicle. One study suggested that only 14% of individuals had answered truthfully on their driving application when asked about the presence of epilepsy (17). In a prospective survey of 367 patients with focal epilepsy pooled from a consortium of comprehensive epilepsy programs, approximately 30% of the respondents had operated a motor vehicle in the previous 12 months (18). A recent Brazilian study identified male sex, occurrence of focal seizures without dyscognitive features, epilepsy onset over 18 years of age, and monotherapy treatment as being associated with driving after the diagnosis of epilepsy, despite local laws (19). In a Korean study of patients with uncontrolled epilepsy, being male, married, employed, and on fewer antiepileptic drugs (AEDs) were risk factors for continuing to drive despite being instructed not to (20). The paucity of available data makes it difficult to definitively establish the number of automobile crashes caused by persons with epilepsy who have a seizure while driving. Reports suggest that persons with epilepsy account for approximately 0.02% to 0.04% of all reported automobile car crashes (21,22). In comparison to healthy controls, an evidence-based review found that epilepsy is probably not predictive of motor vehicle accidents. In addition, epilepsy surgery, few

non-seizure–related crashes, regular medication adjustments, and longer seizure-free intervals are probably protective against crashes (23). However, these data were largely based upon patient surveys, which may underestimate risk.

Seizures are unpredictable, and the presumption is that longer seizure-free intervals translate into a decreased likelihood of seizure-related crashes. However, verifying this fact is difficult, as individual driving records are generally not available for review. A retrospective survey of patients in several Maryland outpatient epilepsy clinics suggested that the risk of motor vehicle crashes was reduced by 85% and 93% if the patient did not have a seizure at 6 and 12 months, respectively (24). This survey relied on self-reported crashes.

It is challenging to determine what factors are likely to predict seizure freedom in an individual. In those patients who report being seizure free, there is concern they may be unaware of brief seizures they experience, placing them at risk while driving. It has been suggested that using medium- or long-term video EEG or ambulatory EEG may assist in estimating risk of seizure relapse (25,26).

Moreover, self-reporting of crashes by respondents in surveys is often considered unreliable (27,28). Drazkowski et al. (22) reviewed actual accident reports in Arizona from crashes caused by seizures before and after the seizure-free interval was reduced from 12 to 3 months (Table 94.1). Although no significant increases in seizure-related crashes were reported, the retrospective study provided some objective data on these crashes. To date, no controlled prospective data are available to guide regulating authorities as to the optimum seizure-free interval for the protection of both the person with epilepsy and the public.

Table 94.1 Changes in the Incidence Rates of Crashes (/10^9 Miles Driven) After Reducing the Restriction on Drivers with Epilepsy from 12 to 3 Months, 3 Years Before and After Law Change

	Before	After				
Type/Cause	95% CI		Incidence[a] rate	95% CI		RR[b]
Total						
Seizure	1.1	1.1	−0.028	−0.30 to 0.24	0.98	0.77–1.24
Other medical	2.6	2.6	−0.092	−0.51 to 0.33	0.97	0.82–1.13
Not seizure (103)	2.6	2.8	0.20	0.19–0.22	1.08	1.07–1.08
Injury						
Seizure	0.58	0.76	0.18	−0.03 to 0.39	1.31	0.95–1.80
Other medical	1.6	1.3	−0.21	−0.52 to 0.10	0.87	0.70–1.07
Not seizure (103)	1.0	1.1	0.045	0.037–0.053	1.04	1.04–1.05
Fatal[c]						
Seizure	0.046	0.016	−0.029	−0.076 to 0.017	0.36	0.07–1.85
Other medical	0.055	0.099	0.043	−0.027 to 0.11	1.79	0.67–4.8
Not seizure	20	21	1.6	0.39–2.7	1.08	1.02–1.14

[a]Incidence rate difference (before vs. after).
[b]Relative risk (before vs. after).
[c]Fatal crashes are a subset of the injury category and are segregated for separate analysis.
CI, confidence interval; RR, relative risk.
Modified from Drazkowski JF, Fisher RS, Sirven JI, et al. Seizure-related motor vehicle crashes in Arizona before and after reducing the driving restriction from 12 to 3 months. *Mayo Clin Proc.* 2003;78:819–825.

The Regulatory Requirements

The first seizure-related car crash was reported near the turn of the 19th century. Since then, regulatory authorities have placed restrictions on driving for a person with epilepsy. In the early

1990s, the American Academy of Neurology, the American Epilepsy Society, and the Epilepsy Foundation of America convened a conference of thought leaders to issue guidelines on the topic of driving and the person with epilepsy (29). Recommendations from the conference included (i) a seizure-free interval of 3 months, (ii) allowances for purely nocturnal seizures, and (iii) a provision allowing driving when there is an established pattern of a prolonged and consistent aura (29).

It is challenging to determine the duration of seizure freedom that should be required to appropriately balance public safety and overly arduous restrictions on a person with epilepsy. Seizure-free intervals adopted by jurisdictions vary widely and have many unique exceptions (31). State regulatory agencies and the Epilepsy Foundation of America Web site (www.epilepsy.com) can be contacted for current laws governing driving and epilepsy, which has been recently updated (32). Though there is a range of restrictions among states, it has yet to be shown whether tighter restrictions are associated with decreased driving and accidents by persons with epilepsy.

In an editorial, Krumholz suggested that it is time to consider uniform laws governing epilepsy and driving throughout the United States (33). International rules on driving have been reviewed, and because of the high variability among individual countries, the appropriate national authority should be consulted to determine current local laws regarding driving before traveling to these nations (34).

Six states currently have laws that require health care providers to report persons with epilepsy to the appropriate state driving authorities. The rationale behind physician reporting is the concern that a person with epilepsy will not reliably self- report the presence of active or recurrent seizures to the proper authority. Laws that require a health care provider to report a person with epilepsy to authorities are criticized as impairing the physician–patient relationship and thus compromising optimal medical care. The premise is that when physicians are required to report epilepsy to driving authorities, persons with epilepsy may conceal information about their seizures to avoid being reported and potentially losing their license (27). Of persons with epilepsy who had been counseled about driving laws, only 27% reported their condition to the appropriate authorities (28). The low percentage of self-reporting may partially be attributed to lack of counseling on behalf of the health care professional. In a recent review of ER visits requiring self-reporting to the driving authorities, <10% were counseled in a major metropolitan city in the southwest (35); in another survey, only 13% of providers knew the appropriate requirements in any event (36). In California, which is the most populous state requiring physician reporting, a survey again suggested that the physician reporting requirement impaired medical care and the doctor–patient relationship (37). There are no available studies showing that physician reporting reduces seizure-related automobile crashes. In Canada, a conference of invited experts concluded that the laws requiring health care professionals to report persons with epilepsy to authorities should be abolished and suggested that driving laws be uniform across Canada (38). McLachlan et al. reported on the impact of mandatory reporting to driving authorities in one province requiring reporting compared to a province that does not. Their conclusion was that mandatory reporting of the person with epilepsy to the driving authorities by physicians did not reduce accident risk. They go on to suggest that the reporting requirements may be excessive compared to other medical conditions or nonmedical risk factors (39). In a comparison between one state with mandatory reporting and one without, there was no difference found in rate of physician counseling regarding driving, driving despite between told not to, or automobile accidents (40). An editorial by emergency department physicians suggested that mandatory reporting of seizures be abolished in the United States (41). This editorial highlighted several other medical conditions and situations that are associated with a similar or higher relative risk of a car crash compared with epilepsy, such as sleep, apnea, diabetes, dementia, and cell phone use (38).

EMPLOYMENT AND THE PERSON WITH EPILEPSY

QOL surveys have identified employment issues and concerns of persons with epilepsy as significant (1,2). The economic impact that epilepsy has on society is huge (more than $10.8 billion/year) and is largely attributable to indirect employment- related costs, which account for 85% of all epilepsy costs (42). Persons with epilepsy have a lower prevalence of employment (43). They are also reported to have lower household incomes, which are estimated to be 93% of the US median income (44), compared with the general population.

In the United States, the rate of unemployment for persons with epilepsy is reported to be between 25% and 69% (44,45). Although many factors are likely to contribute to the high rate of unemployment among persons with epilepsy, poorly controlled epilepsy is associated with a high level of unemployment (45). Age of epilepsy onset also impacts employment status, with an earlier age of onset correlating with work difficulties later in life (46). In patients with adult-onset epilepsy, initial seizure control or lack of control does affect work status. Newly diagnosed, unprovoked seizures in adults do not seem to negatively impact employment rates. The same study associated the development of refractory seizures in adults with reduced income (47).

Many persons with epilepsy have to deal with the reality of employment discrimination. A survey of young persons with epilepsy enrolled in a job training program in Ireland indicated that 50% of the participants believed they were being actively discriminated against when seeking employment (48). A similar percentage of employed persons with epilepsy in Australia felt they were discriminated against (30). Widely available public education regarding epilepsy has the potential of reducing stigma within the community and, hopefully, within workplaces (49,50).

The Americans with Disabilities Act (ADA) (51) was enacted in 1990 to combat job discrimination against individuals with illnesses. The law was intended to help persons with epilepsy and persons with other disabilities obtain and retain employment. A prominent feature of the ADA is that a person with a covered malady cannot be discriminated against if "reasonable accommodations" can be made that would allow the covered individual to obtain or remain in a specific job. But the ADA exempts employers with 15 or fewer employees, thereby eliminating many small businesses. Furthermore, what constitutes a reasonable accommodation was left open to interpretation. The standard may be based on the actual cost of any modifications required that allow a person to keep a specific job. Finally, the employee must be able to perform the "essential" tasks of the job. Administrative and court rulings have made it clear that the protection sought has not been achieved (52). In a unanimous U.S. Supreme Court opinion, Justice O'Connor wrote that for an individual to be considered disabled, the person's disability must be "permanent or long-term," and the impairment must "prevent or severely restrict the individual from doing activities that are of central importance to most people's daily lives" (53). The following statement summarizes the court's opinion: "Merely having an impairment does not make one disabled for the purposes of the ADA." This ruling and others like it have changed the thinking on what defines disability for many patients. These uncertainties and restrictive rulings by the court have prompted a reevaluation of the issue by the US Legislature, which resulted in the passage of the "ADA Restoration Act of 2008." The law took effect on January 1, 2009. The law was passed in an effort to clarify and be more inclusive on what constitutes disability under the law. It still covers business and governmental agencies of 15 or more employees. The U.S. Equal Employment Opportunity Commission has reviewed and published

guidelines for person with epilepsy and employers regarding employment and epilepsy issues (http://www.eeoc.gov/facts/epilepsy.html). Major life activities specifically covered in the law are highlighted in Table 94.2. The major life limitations due to epilepsy can result from seizures or the complications and side effects of medications used to treat the seizures. Specific examples of hiring practices' do's and don'ts for the person with epilepsy determinations about disability are fraught with complexities and should be considered on a case-by-case basis, taking into account the unique facts involved. Individual cases may require specialized legal advice. All the possible accommodations that may affect the person with epilepsy would be lengthy. A potentially helpful website, the Job accommodation network (3), with common examples of accommodation is http://www.jan.wvu.edu/media/epilepsy.html. Readily accessible social service resources can assist patients in navigating employment accommodations and disability eligibility in regard to their epilepsy (54).

Table 94.2 Life Activities that Must be Impaired to be Considered Disabled by Seizure as Defined by the Americans with Disabilities Act Amendments Act of 2008

Walking
Seeing
Speaking
Breathing
Thinking
Performing manual tasks
Concentrating
Learning
Social interaction
Reproduction
Sleeping

Limitations on one or more of the above life activities due to seizures or side effects of medications used to treat epilepsy must be present to be considered disabled.

Certain jobs may be perfectly safe for many persons with epilepsy but other jobs may impose unacceptable risk. A person with epilepsy must carefully evaluate jobs involving dangerous machinery, or equipment heights, or situations in which there is a possibility for injury or death because of potentially dangerous conditions in the event of a seizure. Persons with epilepsy also face regulatory-imposed restrictions for some jobs. For example, a person with epilepsy's pursuit of a commercial pilot's license is severely limited by the Federal Aviation Administration (FAA) (55). Similarly, a person with epilepsy wishing to obtain a commercial driver's license (CDL) to operate a truck in interstate commerce must overcome significant hurdles imposed by the Federal Department of Transportation. The diagnosis of epilepsy and the use of AEDs generally disqualify an applicant or current driver from obtaining a CDL. A CDL is required to operate a truck with a gross weight >24,000 pounds. Although many states have mirrored the federal regulations with regard to state commercial driving laws, individual state regulations should be reviewed for accuracy. Internationally, laws vary regarding CDLs. For example, in Norway, bus and taxi drivers may not have had a seizure after age 18 (56). Tailoring the specific job to the person with epilepsy, based on the person's unique, individual situation, should be emphasized.

Under Social Security Administration (15) regulations, epilepsy is covered by specific listings (57). These listings, which define what constitutes a disability for the person with epilepsy, are used in determining who is eligible to receive disability payments. Persons with epilepsy are required to provide specific evidence, through medical records documenting that they "meet the listing," as featured in Table 94.3. Other factors, such as postictal effects of seizures and side effects of prescribed medications, may be considered in determining disability, especially during a hearing or an appeals process for a denied claim. The specific listings for epilepsy are sections 11.03 and 11.02 for minor motor and major motor seizures, respectively (57). Decisions regarding SSA for epilepsy based upon the listings have been shown to be inconsistent and without evidence-based guidelines, potentially requiring further guidelines in the future (4,58).

Table 94.3 Factors Required for Consideration of Social Security Administration Disability Benefits

- Four partial seizures per month
- One major motor seizure per month
- Continued seizures despite adequate use of medication for 3 mo
- Electroencephalogram results
- Detailed description of the events documented in the medical record

SPORTS AND RECREATIONAL ACTIVITIES

Persons with epilepsy are often excluded or discouraged from participation in sports and recreational activities because of fear of what might occur during the activity. Since the 1960s, official recommendations regarding limitations in the participation of physical activity have been significantly liberated, and at this point, physical activity is recognized as being beneficial for persons with epilepsy. In addition, lack of leisure time and physical activity may be a detriment to persons with epilepsy. It has been shown that a low level of physical activity is a risk factor for depression in epilepsy (59) and that greater physical activity is associated with fewer days where their health limited their routine (60). However, engagement in leisure and physical activity require certain considerations.

Epilepsy and Recreational Vehicles

Motorized vehicles can potentially cause serious injury or death even in persons without epilepsy. The unpredictability of uncontrolled seizures might pose a serious threat should a seizure occur at the wrong time. Operating motorized vehicles is associated with a prolonged danger period.

A seizure that occurs while a person is piloting a private plane is likely to have disastrous consequences. Noncommercial aviation is at least partially regulated by the FAA. A third-class pilot's license is required for all general noncommercial aviation (55). If an individual has experienced a single unprovoked seizure with no EEG abnormalities, normal brain imaging, and no additional risk factors, that person can be considered for a third-class license if he or she has not taken an AED for 4 consecutive years. The FAA uses certified examiners to assist in the decision-

making process for granting licenses when there is a potential medical problem. Piloting ultralight aircraft, hang gliders, and other small aircraft may not require a license, but these are unlikely to be any safer than a private plane should a mishap occur.

Other motorized vehicles, such as motorcycles, personal watercraft, all terrain vehicle (four wheel), and boats, may pose less of a threat to a person with epilepsy than does flying. If the person with epilepsy operating the vehicle has a prolonged and consistent aura, it may allow that person the opportunity to stop and protect ones self. However, a person with epilepsy when contemplating sports activities should consider other factors. For example, drowning is a common accident among persons with epilepsy (61). The use of a personal flotation device at all times when operating or riding in any watercraft should be considered. When operating off-road vehicles, safety equipment should also be considered, especially the use of boots, shoulder pads, protective clothing, and helmets. Although a person operating such a vehicle does not require a license, specific training courses are available and are highly recommended.

In contrast, organized motor sports generally require some form of medical clearance before participation (53). The different motor sport sanctioning bodies, such as the Sports Car Club of America, the National Association of Stock Car Racers, and the Indy Car Series, all have specific requirements for a person to be allowed to drive in sanctioned events. Each series requires approval from a qualified health care professional before driving, and therefore, specific rules should be reviewed.

The Person with Epilepsy and Athletics

The decision to participate in individual (i.e., one-on-one) and team sports should follow those principles outlined above in order to ensure maximum benefits (and thus satisfaction) and safety. The extent to which a person with epilepsy wishes to pursue athletics is an individual decision that should be based on individual circumstances. Table 94.4 classifies risks to the person with epilepsy according to the sport.

Table 94.4 Sporting Activities Classified According to Possible Risk for the Person with Epilepsy

Low risk Track
Cross-country skiing
Golf
Bowling
Ping-Pong
Baseball
Weight training (machines)
Moderate risk football
Biking
Soccer
Gymnastics
Horseback riding
Basketball
Boating/sailing
High risk
Scuba diving
Hang gliding
Motor sports
Boxing
Downhill skiing/ski flying
Long-distance swimming
Hockey
Boxing

Modified from Mesad SM, Devinsky O. Epilepsy and the athlete. In: Jordan BD, Tsairis P, Warren PF, eds. *Sport Neurology*. 2nd. Philadelphia, PA: Lippincott-Raven Publishers; 1998:285.

Participation in team sports should also be determined on an individual basis. Football could be dangerous if a player is unable to protect him or her during a play, whereas basketball is less likely to be dangerous. Noncommercial scuba diving is also not regulated from a medical standpoint, but good judgment is required on the part of the participant. Hyperventilation techniques and the high concentration of inspired oxygen used during scuba diving have the potential to provoke seizures, and seizures that occur during a dive can have a fatal outcome. Scuba diving organizations vary in their recommendations. These recommendations range from considering seizures to be an absolute contraindication to requesting an individual be seizure free for several years before diving (62). If a person with epilepsy does engage in scuba diving, it is crucial that person notifies the diving group and has a strong diving partner that is ready to assist in the instance of an underwater seizure. Water sports and drowning pose a likely threat to the person with epilepsy. A review of drowning deaths found that 40% of seizure-related drownings occurred during recreational activities (61). A study by Gotze (63) found no increase in seizure occurrence during strenuous swimming.

Evidence suggests that regular exercise has a beneficial effect in the control of epilepsy and regular physical activity may reduce seizure occurrence (63,64). Recent opinion has encouraged sports participation for the person with epilepsy despite the potential risks (65,66) and it has even been suggested that exercise may be a non-pharmacologic intervention in epilepsy (67). Engagement in physical activity and sporting activities have benefit in persons with epilepsy, but individual considerations need to be made to ensure safety.

Often overlooked are the possible AED-associated side effects that may interfere with participation in sports. For example, zonisamide reduces sweating in children and could potentially

lead to heat-related injury in hot climates. Tremor associated with the use of valproic acid could be dangerous when shooting target pistols. Phenytoin-induced ataxia could potentially be deadly while riding a motorbike (68). Many more potential examples could be conceived and listing all the potential combinations is beyond the scope of this chapter; thus, the health care professional should be knowledgeable of the person with epilepsy's history, desires, and a basic understanding of the recreational activity considered. Individualizing the specific drug side effect profile, patient characteristics, and particular recreational activity generally should all be considered when advising the person with epilepsy about participation in recreational and sporting activities.

CONCLUSIONS

The patient with epilepsy faces many challenges beyond seizures. Seizures have the potential to impact aspects of daily life, which are otherwise taken for granted, including transportation, employment, and leisurely activities. These issues, among others, have a significant impact on quality of life, but also need to be balanced with safety. It must be emphasized that each patient has individual characteristics requiring knowledge of the specific activity in which the person with epilepsy wishes to participate. Recent changes to the U.S. laws governing disability and employment may prove helpful for the person with epilepsy.

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CHAPTER 95 QUALITY OF LIFE WITH EPILEPSY

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According to the World Health Organization Quality of Life Group, quality of life (QoL) is defined as the individual perception of position in life in the context of value system, goals, expectations, standards, and concerns (1). As for any chronic disease, there is a component of psychosocial adjustment when living with epilepsy. The stigma and misconceptions that surround epilepsy come from the general public's lack of understanding about the condition. This includes response to seizures and to individuals who have them. People with epilepsy have limitations that affect how they think of themselves as individuals. This stigma badly affects the health and well-being of these individuals as a whole. In addition, comorbidities, seizure frequency, and antiepileptic drugs (AEDs) affect QoL in epilepsy.

HISTORICAL OVERVIEW

QoL is not a new concept and can be traced back to the days of Greek philosopher Aristotle (2). According to the Center for Disease Control "health" includes physical, mental, and social dimensions (2,3). In much the same way, epilepsy is a multidimensional disease affecting individuals physically, mentally, and socially (4). QoL is subjective and is thereby defined differently by a number of groups and populations (5). For this reason, it is hard to measure. The U.S. Department of Health and Human Services states that QoL is synonymous with well-being and can be defined by both positive and negative emotions in one's life (6). QoL is influenced not only by a person's health but also by his or her day-to-day functioning. Health-related quality of life (HRQOL) is a disease-related measure that explores how one's health status affects one's QoL (3). It is important in epilepsy to be cognitive of how the condition is interfering with daily tasks (3).

QUALITY OF LIFE IN EPILEPSY

In children with epilepsy (CWE), lack of accurate knowledge about the condition has been associated with social anxiety and poor self-esteem (7). Disruption of normal tasks required to be attained by different developmental stages impacts the social functioning of the individual with epilepsy (7).

In Early and Middle Childhood

In this stage, children are learning tasks to become independent. They need a family environment that facilitates their development and is conducive to exploration of the world around them. Parents of CWE are distressed about seizure probability, hence restricting child social interactions and potentially hindering their development both socially and emotionally. Studies looking at level of

parental anxiety and socialization in CWE describe that anxious parents are more likely to have children with poor socialization skills. Parental skills are another important issue in CWE; because the child has a chronic illness, parents feel guilty enforcing family rules, which consequently impacts negative behaviors (7).

In Adolescence

One of the most important developmental tasks of adolescence is the formation of identity. In this stage, adolescents build a sense of emotional and physical competence. Epilepsy impacts the ability to feel confident about emotional and physical well-being, and feeling unable to perform some tasks impacts self-esteem. Bullying is frequent in this stage and impacts the way adolescents perceive themselves and their world. In a study examining adolescents' attitudes toward peers with epilepsy, three-quarters of the adolescents in the general population believed that peers with epilepsy were more likely to be bullied. Also, less than one-third of adolescents reported that they would date someone with epilepsy (8). A separate study found that adolescents with epilepsy felt that the stigma of having a chronic debilitating condition set them apart from their peers. They also felt that the uncontrollability of the seizures made it hard to become independent (9). In addition, driving is an important developmental task in late adolescence, and people with epilepsy feel that the inability to drive limits opportunity for participation in social activities (7).

In Adulthood

Most of the studies on psychosocial function on adults with epilepsy were conducted in clinical population samples, limiting their generalization. Employment is key in the personal development of adults and is a predictor of QoL in patients with epilepsy (10). Many studies have reported on the struggles that patients with epilepsy face gaining and maintaining employment. The unemployment rates for people with epilepsy are reported to be around 42% to 50% and are higher than in the general population. Patients feel the epilepsy is an important barrier to gaining employment (11).

Important cultural differences have been reported on rates of marriage in people with epilepsy. In developed countries, rates of marriage are around 66.2% overall (10), 32% for men and 58% for women (11). In a British study, 50% of people with epilepsy were married. In India, laws that prohibited people with epilepsy from getting married were only recently repealed (12). Other developing countries still have negative connotations associated with epilepsy, which limits the potential for people with epilepsy to get married.

Woman with epilepsy are affected differently than men with epilepsy. It is vital that this be addressed early on in the diagnosis of epilepsy in females. Health needs unique to the female and her sexuality extend beyond pregnancy, and it is never too early to start counseling (13). In the prepubescent and pubescent female and throughout the rest of female adult life (including menstruation years, pregnancy, and menopause), seizure frequency, severity, and duration are affected. Seizure frequency may be directly related to the menstrual cycle in the pattern known as catamenial epilepsy (13). Folic acid supplementation should be discussed at the start of AEDs in the menstruating woman of any age (13). In addition to other potential side effects of AEDs, their cosmetic side effects need be considered when starting treatment in the female. Cosmetic effects of AEDs, such as acne, weight gain/loss, and hirsutism, affect a woman's self-image and thereby affect her QoL. It is important to know that what is acceptable to the clinician is not always acceptable to

the patient (14,15). Communication between the patient and the provider is very important, as sometimes the deleterious side effects of higher doses of AEDs could worsen the QoL more than the lesser seizure control previously attained with the lower dose of the medication. Patients might also neglect to share with the provider the dose of the AED that they are actually taking.

The Role of Stigma and Quality of Life

The negative social perception of epilepsy dates back to the Biblical New Testament where epilepsy is mentioned as "a madness." Early primitive societies attributed the cause of epilepsy to demonic possession or as a consequence of negative karma by the individual or family (8). In some ancient cultures, people with epilepsy were segregated in a remote location to prevent "contagion" of the illness. The evolution of the concept of epilepsy from "badness to sickness" has potential important correlations with the role of stigma (16). Early studies reporting increase of aggressive behavior, criminal behavior, sexual misconduct, and negative personality characteristics have certainly perpetuated the stigma that patients with epilepsy face. Scambler (17) describes how people with epilepsy exposed to negative perceptions about the disease develop a "special identity" that is certainly related to the exposure to stigma.

Cultural beliefs have an important role in societal stigma against epilepsy. In the highly educated population, the lack of understanding about the disease impacts societal views about epilepsy. In the United States, Austin et al. (8) stated 22% of adolescents reported uncertainty about epilepsy being contagious. Westbrook et al. (18) remarked how up to 50% of the families studied decided to keep the condition secret from others. Falcone et al. (19) identified that 50% of families decided not to disclose the epilepsy diagnosis to the school. Bauman et al. (20) reported that one out of four of the families surveyed believe that having a child with epilepsy in the classroom deteriorates the learning environment.

PSYCHOSOCIAL ADJUSTMENT OF PEOPLE WITH EPILEPSY

McQueen et al. (21) described two different models to understand the psychosocial adjustment in people with epilepsy. The medical model focuses on severity of epilepsy and is the driver of the psychosocial adjustment. The sociologic model attributes the adjustment to the perception of the individual's condition or social stigma.

Seizure frequency has been reported by many studies as the most important predictor of psychosocial functioning. The better seizure control, the better the QoL. QoL directly relates to seizure frequency and severity. What may be a medically safe frequency to the provider may not be defined the same by the patient who is having the seizures, and the same goes for seizure severity (14). In addition, frequency and severity and how both affect QoL may vary from the caretaker's opinion to the epilepsy patient's opinion.

Chronicity is another important factor; newly diagnosed people usually adjust better than do patients with chronic epilepsy. The age of onset of epilepsy may also have a key role in psychosocial adjustment (19). For example, the first 8 years of life are key in the development of social skills; when epilepsy starts in this important developmental period, it might also have important repercussions in the development of social skills. Parents also play a very important role in the development of social skills, and overprotective parents or social isolation might also have an

important role in the inability of youth with epilepsy to develop appropriate social interaction with peers (19). A patients' perception of his or her own ability has an important key role in QoL, and good self-perception was correlated with better QoL in epilepsy. Some have suggested that the patient's own perception of disability was a stronger predictor than was seizure frequency in affecting different domains of QoL such as employment or social interaction (19).

In a study attempting to elucidate the effect of the different factors on QoL, Suurmeijer et al. (10) reported that <5% of QoL was related to the clinical aspects of epilepsy (onset, seizure frequency, and side effects of the medication) and only 15% to clinically related aspects such as perception of epilepsy and health perception. Social functioning, self-efficacy, and psychological functioning contributed twice as much to the QoL compared to the clinical aspects of epilepsy. Social support was reported as a key factor in the emotional adjustment to having a chronic illness such as epilepsy.

THE ROLE OF PSYCHIATRIC COMORBIDITIES IN QUALITY OF LIFE IN PATIENTS WITH EPILEPSY

Psychiatric comorbidities are frequent in patients with epilepsy. Among psychiatric comorbidities in patients with epilepsy, depression is one the most frequent. In fact, the prevalence of depression in epilepsy appears to be higher than in other chronic illnesses. In a population-based study involving 18,000 individuals, the prevalence of depression for patients with epilepsy was 29% compared to 17% in those with diabetes and 16% in those with asthma (22). Epidemiologic studies indicate that 10% to 20% of patients with epilepsy and 20% to 60% of patients with recurrent seizures have depression (23). Likewise, rates of psychopathology are very high, ranging from 37% to 77% in children and adolescents with epilepsy (23–25). A meta-analysis of 29 cohorts of epileptic patients demonstrated increased suicidality as compared with the general population (26). Despite continued progress in the treatment of epilepsy, the psychosocial outcome in adults is reported as poor, even in patients who reach seizure freedom (23). Patients with epilepsy and depression have some of the lowest scores on QoL, even when seizures are under control (23).

In addition, psychosocial adaptation has not been investigated extensively in this population. Some studies suggest that psychosocial adaptation in CWE might be lower than in healthy children, which may be due to the stigma of having a chronic disorder that subsequently lowers their self-esteem. CWE have been reported to have poorer self-concepts than children with other chronic medical conditions and to frequently struggle in school and other social settings. These experiences may lead to poor self-esteem and symptoms of depression. Studies have reported that female CWE with low IQ are especially at risk for poor self-concept and the development of depression (25).

Some stressors, such as stigma, language and cultural barriers, financial difficulties, stressful life events, decreased expressed emotions, and poor family coping skills, have been reported in depressed epileptic patients. A positive attitude toward epilepsy has been correlated with less depression (25,27,28). Population surveys of mental health problems in CWE in the United Kingdom reported the rate of psychiatric comorbidities to be 37%, compared to 11% in diabetes and 9% in healthy children. This is comparable to the landmark study from the Isle of Wight, where Rutter (29) reported psychiatric comorbidities as high as 29% in CWE compared with 12% in those with other chronic clinical conditions and 7% in the general population. The associations between these two disorders point to the importance of early recognition and treatment (29).

In a meta-analysis involving 29 selected studies comprising 50,814 patients and 187 who

committed suicide, Pompili et al. (26) calculated the mean number of suicides per 100,000 individuals with epilepsy and showed that suicide is more frequent in patients with epilepsy than in the general population. Likewise, in a population-based case–control study in Denmark from 1987 to 1997, a threefold higher risk of suicide was found among people with the diagnosis of epilepsy (26). However, there are studies that did not find any difference in the suicide rate between patients with or without epilepsy (26).

Patients, and sometimes care providers, decide to wait to access mental health treatment for patients with epilepsy. The common belief is that when the epilepsy will improve, all the other issues will also improve. However, evidence has demonstrated the contrary. The longer that the mental health symptoms persist, the more difficult they are to treat and the greater the risk of suicide. There is an important correlation between depression and anxiety with QoL, independent from seizure rates. In patients with epilepsy, depression has been related to poor seizure control, poor health care utilization, lower scores on the QoL scales, and increased cost in patients with epilepsy.

OTHER COMORBIDITIES

Tellez-Zenteno et al. (30) reported that people with epilepsy had two to five times higher rates of somatic comorbidities such as stroke, headache, and gastrointestinal problems among others. More evidence is needed to further understand the role of epilepsy in these comorbidities.

Sleep

Sleep disorders and epilepsy have a bidirectional relationship. Having sleep problems can certainly impact epilepsy, but also having epilepsy will worsen sleep problems. Many of the medications used to treat seizure disorders have deleterious impact on sleep efficiency. Some studies have reported sleep apnea in up to 30% in patients with epilepsy (31).

In a study comparing sleep disorders in epilepsy with controls, the patients with epilepsy had double the probability to have any sleep disorder. In addition, having a comorbid sleep disorder was associated with an important decrease on QoL in the previous 6 months in patients with epilepsy (31). In a study of patients with epilepsy in Mexico, one of the most important negative predictors of QoL was sleep disturbance, and this was unrelated to any of the other predictors of QoL in adults with epilepsy (32). The authors concluded that insomnia was an independent negative factor in QoL. Insomnia impacted emotional well-being including energy, cognitive function, and social functioning (33). In a group of 130 CWE and 161 matched controls, the group of CWE had worse sleep than did children with no epilepsy. Sleeplessness also impacts cognition and behavior (34).

Migraine

The relationship between epilepsy and migraine has been extensively reported. Patients with history of one of the illnesses double the risk of the other. In a population-based study, Ottman and Lipton (37) reported that migraines were frequent in patients with epilepsy, seen in up to 24%. Depression has also been reported as increased in patients with migraines, with an associated deleterious impact on the HRQOL scores. In a study evaluating the impact of migraines on seizure variables, Veliogu et al. (36) reported that patients with migraines have poorer seizure control, higher proportion of intractable seizures, longer duration of illness, and poorer treatment response (37).

Studies continue to report the importance of recognizing, diagnosing, and addressing all the other issues that impact the QoL in epilepsy. Becoming seizure free is an important goal, but if the comorbidities are not addressed, even after seizure freedom is reached, the QoL may not improve (38).

QUALITY OF LIFE AND ANTIEPILEPTIC DRUGS

A goal of epilepsy treatment with AEDs is the best seizure control with the least amount of side effects and the best QoL. Although this is often said to the patients, it is more difficult to implement than providers realize, mainly because of the effect both have on QoL (14,15). Lifestyle, compliance, income level, and AED side effects also play a role in the mainstream goal of epilepsy treatment (14). Elliot et al. (39) reported that compliance is a serious problem among epilepsy patients who live in poverty. Pharmaceutical companies do offer patient assistance programs; however, extensive time and effort on the part of the provider and the patient are involved to set up the assistance (39).

Just as there are misconceptions about epilepsy, there are also misconceptions about its treatment. Patients may or may not ask questions that reveal their lack of understanding. Many fear what the medications can do to the organs in the body and what the long-term effects of use may be (14). This misinformation or lack of information may also contribute to compliance and negatively impact QoL.

The number of medications and their dosages is important to how an epilepsy patient rates his or her QoL. Some patients are on polytherapy with subtherapeutic dosing, side effects, and inadequate seizure control. AEDs affect each individual; one patient may be on a low dose of AEDs with side effects at subtherapeutic serum levels, while another patient may be on a high dose of AEDs with a high serum level and no side effects (15).

QUALITY-OF-LIFE INSTRUMENTS IN EPILEPSY

The best definition for QoL is defined by the tool you are using to measure it (15). The National Institutes of Neurological Disorders and Strokes (NINDS) lists QoL tools in the Epilepsy Common Data Elements such as the Quality of Life in Epilepsy (QOLIE). It is used to measure QOL in epilepsy and has both research and clinical versions in addition to an adult and adolescent version (15,40). This tool was designed to explore how epilepsy and its treatment affect activities of daily living (15).

The original version is the QOLIE-89, which was designed in 1995 for research purposes (15). From it, the QOLIE-10 was derived (15). It is a shorter version containing a 10-item evaluation that takes only minutes to complete, thus ideal for the clinical setting (40). One item was selected from the scales of seizure worry, emotional worry, energy/fatigue, cognition, and overall QoL (15). In addition, two items were selected from AED side effects and three items from the social function scale (15). It is easy to complete and simple to score. According to the NINDS Common Data Elements report, the test-retest reliability ranged from 0.48 to 0.58 for different items and from 0.55 to 0.77 for different subscales, and the validity score was established for seizure frequency, AED polytherapy, and sleep disturbance (40). It is available in Spanish, English, and Dutch (40).

The QOLIE-AD-48 was developed in 1999 by the QOLIE Development Group for adolescents (11 to 17 years old) (15). Items address epilepsy impact, memory/concentration, attitudes toward epilepsy, physical functioning, stigma, social support, school behavior, and health perceptions and have a total summary score (15). The 15-minute self-administered questionnaire has no parent version (14,40). According to the NINDS Common Data Elements report, validity is statistically

significant at the $P < 0.05$ level and test–retest reliability is good at 0.83 (40). It is available in Chinese, English, Serbian, Portuguese, and Spanish (40).

For children, the NINDS recommends the Quality of Life in Childhood Epilepsy that covers physical function, emotional well-being, cognitive function, social function, and behavior (40). It is done by the parent and takes approximately 30 minutes to complete (40). The length of time for completion is not ideal, but it is an epilepsy-specific quality-of-life tool. According to the NINDS Common Data Elements report, reliability is ranged from 0.72 to 0.93 (40). Its weakness is that the validation was done with caretakers of children with refractory epilepsy, and it is only available in English (40).

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FINAL NOTE A MOTHER'S PERSPECTIVE

SUSAN AXELROD

It had to be one of the coldest Januarys on record in Chicago. The year was 1982, and my daughter Lauren was just 7 months old.

She was a remarkably beautiful baby. She was sick for the first time in her short life. A cold. No fever. Because of her nasal congestion, she had not slept well in 3 nights, and so her pediatrician advised me to give her a small dose of Triaminic. I did so, put her to bed, and we each slept well.

Or, at least, I did. I thought she was sleeping well too. But, when I entered her room in the morning, I found her lying limp and grayish blue in her crib. I thought she had died. I whisked her out of bed, and her body then stiffened, her beautiful blue eyes rolled back in her head, and bubbles of saliva collected around her lips.

It was the first of thousands of seizures I would come to witness. But, at that point, I had never seen a single seizure. I hadn't the slightest idea what was happening.

The emergency room nurse grabbed her from me when she witnessed her displaying another of these strange behaviors, identified it as a seizure, and I'm not even sure what happened next. Needle sticks. IVs. Spinal taps. Medications we had never even heard of poured into her tiny body.

A month later, we brought her home from the hospital on megadoses of phenobarbital and phenytoin. She had lost many of her developmental milestones. She was still having at least six seizures a day. She was alternately groggy, hyperactive, irritable, and moody. We couldn't recognize our child—she bore very little resemblance to the Lauren we knew before.

With no warning, no preparation, and certainly without our consent, epilepsy blasted into our lives with a vengeance. Over the next 18 years, Lauren had clusters of seizures that could last for days on end. Uncountable visits to the ER and hospitalizations that could each last for weeks. Over 20 anticonvulsants, in combinations of up to 5 at a time, failed to control her seizures. The ketogenic diet was ineffective, as was vagal nerve stimulation and surgery. We saw numerous specialists, none of whom could offer us answers or relief.

Sadly, Lauren's story is not unique. Certainly, many children with epilepsy are not nearly as refractory to treatment and don't experience the same degree of psychosocial and cognitive impact that she has. And too many more, sadly, have a much rougher, tougher ride, including those who succumb to the very worst consequence of epilepsy—loss of life.

Our federal agencies now recognize the spectrum of syndromes, forms, and severity of recurrent, unprovoked seizures as “the epilepsies.” It would behoove us all—physicians, caregivers, and patients alike—to also acknowledge that there is not one epilepsy. The epilepsies are a significant public health problem with a myriad of complex causes, effects, and outcomes that are yet to be well understood.

And so, treating children is far from a “one size fits all” proposition. And interacting with and supporting parents and caregivers are perhaps as complicated and multifaceted as the epilepsies

themselves.

Simplistic as it may sound, it comes down to building and nurturing a mutually respectful relationship, one that can only be built on a foundation of trust. It has to go both ways—the family needs to be as fully honest and respectful as the physician and his/her team.

No parent or caregiver should be denied the complete truth about their child's diagnosis and prognosis. Parents—particularly those just entering the world of epilepsy—rely on their child's doctors to steer them to the best information available. Even if physicians feel that the answers may not be what a parent wants (or is ready) to hear. Or, even if the best that can be done is to admit that the answers do not yet exist.

This doesn't require that all of the harshest potential outcomes be addressed immediately—particularly if the patient is not at high risk. But it is the responsibility of the physician's team to steer families toward reliable information and resources—hopefully as soon as possible, with as much encouragement as possible.

In 1982, the Internet did not exist. We were sent home from that first hospitalization with an incredibly sick child, powerful cocktails of daily medications, no answers to our questions, and no resources for either support or information. We were desperately alone.

Although information from the Internet may often not be optimal, health care professionals need to help families find the best resources and filter out what is not helpful. This needs to be done in a manner that acknowledges that people seek information because they are desperate to know. They should not be discouraged from doing so, because to do so is both empowering and inevitable.

In addition, just as parents are more likely to witness their child's seizures than their physicians, they—along with other professionals in their child's life—are the ones in the best position to notice changes in mood, behavior, cognition, and social skills.

When we began this journey, we were never once asked to monitor and record seizures or medication side effects. We contacted Lauren's doctor only when things reached what seemed to us like an emergency. But, equally disturbing, there was absolutely no conversation around how this barrage of electrical storms in her developing brain—not to mention the high-powered medications she was taking—were impacting her life.

Consequently, we soon felt that everything we witnessed in her—apart from the seizures—was somehow irrelevant. This caused a significant breakdown in our working relationship with her doctors. Later, I came to believe that this dismissal of our concerns was due to the fact that answers did not exist. Because we weren't told that, we sought other opinions and became increasingly frustrated and mistrustful.

Sadly, many of the answers we need are still unavailable to us. We have a long way to go in our understanding of causes, prevention, optimal treatments, sequelae, and long-term outcomes. This is what drove me, along with other desperate and frustrated mothers, to found CURE, Citizens United for Research in Epilepsy, in 1998.

One of the most significant results of our advocacy efforts was to open up a long overdue conversation about what had become, along with the diagnosis of epilepsy, an acceptance of both repeated seizures and intolerable treatment side effects, particularly in the 30% or more of patients whose seizures are not controlled on the first few medications.

Our work has been with the epilepsy research community—shifting their focus from simply seizure control to improving our understanding of causes and underlying mechanisms, so that antiepileptogenic therapies may one day be the standard course of treatment, in lieu of the arsenal of anticonvulsant treatments available today.

I hope that this shift has also been reflected in clinical care and that physicians who treat patients with epilepsy—along with patients and their loved ones—are no longer willing to accept the status quo. We all need to be as vigilant as possible at preventing and stopping all seizures. The inherent danger of each and every seizure means that they are not something we can continue to accept as a "given" of this diagnosis. The often-debilitating side effects of current treatments are unacceptable.

Amazingly, it wasn't until Lauren was almost 3 years old that I learned she had epilepsy. I read the dreaded "E" word on an EEG report and panicked. No doctor had ever used the word before in reference to Lauren.

She had been sent home from that first hospitalization with the diagnosis of "idiopathic seizure disorder." We were told that she was likely to outgrow the seizures by the time she was the magical age of 5. We were told that her seizures—during which her lips often turned a disturbing bluish gray color—were not damaging her developing brain. We were told that the cocktail of medications, we had no choice but to give her, would have no lasting negative effect. We were never told she had epilepsy.

I hope that no physician avoids using that word again. To call it anything else can delay a family from finding the information and resources they need. And, rather than destigmatizing, it continues the secrecy and shame that increase—not decrease—society's misperceptions about what epilepsy is.

I hope that doctors will no longer sugarcoat what we know or pretend we know something we don't. This is not the foundation on which trust and partnership are built.

I hope that physicians will encourage their patients to seek support and knowledge. And, that they will respect and honor them for those pursuits. They want and need knowledge. They want an end to epilepsy and all that it entails for their loved ones.

I hope that physicians will refer families to specialists whenever indicated and available. This includes epileptologists as well as specialists who may be in the best position to address the comorbidities that are increasingly recognized as accompanying epilepsy in so many children. Particularly in children diagnosed with epilepsy, a whole-patient perspective is essential to ensuring as promising a future for the child as possible.

I hope that patients will recognize—and that physicians will help them do so—that they are equal partners in this journey.

I also hope, for the sake of future generations, that physicians will help their patients understand the value of biomedical research and that stakeholders have an invaluable role to play in advancing research toward better therapies and cures.

Epilepsy—by its very nature—causes an enormous loss of control. Children and their families are dealing with this on a day-to-day, moment-to-moment basis. They need the stability of a relationship with their physician, which includes honest discourse, mutual respect, and trust.

Finally, we must ensure that nobody in this community—stakeholders or professionals—continues to be tolerant of continued seizures and debilitating, ineffective side effects from treatments. If we continue to be complacent and accepting of the status quo, then the rest of society—who may know nothing about epilepsy—will certainly not expect anything more. If we aren't our own self-advocates—beginning in the setting of a doctor's office and expanding beyond to schools, workplaces, and community—epilepsy will continue to be a major public health problem that has plagued mankind for far too long.

Susan Axelrod
Chair and Founding Member

APPENDIX

ASSOCIATE EDITOR: BARRY E. GIDAL

Indications for Antiepileptic Drugs Sanctioned by the United States Food and Drug Administration

KAY C. KYLLONEN

Authors in this text have described uses of antiepileptic drugs based on clinical experience and results of clinical trials. In some cases, these clinical indications are broader than those sanctioned by the U.S. Food and Drug Administration (FDA) for product labeling.

To obtain specific FDA-approved indications, pharmaceutical companies present efficacy data from controlled clinical trials. If the data are judged scientifically sound, then the FDA may approve use of the drug for the specific types of patients and seizures studied in the trials. The approved indications are based only on the data presented by the pharmaceutical manufacturer and may not reflect all of the available research information. Once the indications are authorized by the FDA, the pharmaceutical manufacturers may not promote use of the drug for indications other than those specifically delineated in the labeling. However, this does not preclude the "off-label" use of these medications for other indications, including those discussed in this clinical text. By necessity, certain patient populations—most notably, children—are often treated outside of the labeled indications, because prior to recent FDA regulations, they were infrequently included in controlled clinical trials.

Antiepileptic medications mentioned in this text are listed in the following table with their FDA-approved epilepsy- related indications from the 2013 online editions of the Pediatric Lexi-Drugs Online (1), DailyMed (2), or Drug Facts and Comparisons (3), standard references for pharmacists. Some of the listed indications use outdated terminology because they were designated prior to the adoption of international standards for seizure and epilepsy classification. Drugs not yet in any part of the U.S. federal approval process have been marked as "not listed" in the table.

Only four antiepileptics had specific FDA-approved pediatric indications listed in the 1999 Physicians' Desk Reference (4) or Drug Facts and Comparisons (5). At this writing, over 20 medications carry specific FDA approval for pediatric indications. For many other antiepileptic drugs, use in children is implied in the approved product information by mentioning use in specific pediatric syndromes (e.g., infantile spasms or febrile seizures), by listing pediatric formulations (chewable tablets or elixirs), or by describing dosage schedules based on pediatric ages or body weights. The table also notes whether pediatric doses are listed in the any of the following—The

Pediatric Lexi-Drugs Online, DailyMed, or Drug Facts and Comparisons—regardless of whether or not the drug carries a specific FDA-approved pediatric indication. Dosing schedules are further discussed in "Part IV: Antiepileptic Medications" of this textbook; however, it is advisable to consult full prescribing information before clinical use.

Drug	Listed indications: seizure or epilepsy type	Pediatric dose	Pediatric labeling indication
Acetazolamide	Centrencephalic epilepsies (petit mal, unlocalized seizures)	Yes	
Carbamazepine	Epilepsy—partial seizures with complex symptomatology (psychomotor, temporal lobe), generalized tonic–clonic seizures (grand mal), mixed seizures	Yes	Yes
Clobazam	Lennox–Gastaut syndrome	Yes	>2 y
Clonazepam	Lennox–Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures	Yes	
Clorazepate	Adjunctive therapy; management of partial seizures	Yes	>9 y
Corticotropin	Infantile spasms	Yes	Yes
Diazepam	Status epilepticus, severe recurrent convulsive disorders	Yes	Yes
Eslicarbazepine	Not available in the United States		
Ethosuximide	Absence (petit mal) epilepsy	Yes	Yes
Ethotoin	Tonic–clonic (grand mal) and complex partial seizures	Yes	Yes
Felbamate	Adjunctive therapy in Lennox–Gastaut syndrome, monotherapy for partial seizures in adults with epilepsy	Yes	Yes (age >2 y)
Fosphenytoin	Short-term treatment of acute seizures, including status epilepticus; prevention of seizures during and after neurosurgery; substitute for oral phenytoin	Yes	
Gabapentin	Adjunctive treatment of partial seizures with or without generalization	Yes	Yes (age >3 y)
IVIG—intravenous	Intractable epilepsy (possible due to IgG2 subclass deficiency) immunoglobulin, infantile spasms	Yes	
Lamotrigine	Adjunctive treatment of partial seizures and Lennox–Gastaut syndrome	Yes	Yes (≥2 y)
Lacosamide	Partial-onset seizures		
Levetiracetam	Neonatal seizures, partial seizures, and primary generalized epilepsy	Yes	Yes (≥4 y)
Lorazepam	Status epilepticus	Yes	
Mephenytoin	Not available in the United States		
Methsuximide	Absence seizures refractory to other drugs	Yes	Yes
Midazolam	Refractory seizure; status epilepticus	Yes	
Nitrazepam	Not available in the United States		
Oxcarbazepine	Adjunctive therapy partial seizures	Yes	Yes (≥2 y)
Paraldehyde	Not available in the United States		
Paramethadione	Not available in the United States	Yes	
Perampanel	Refractory seizures; partial-onset seizure		Yes (>12 y)
Phenobarbital	Generalized and partial seizures, febrile seizures, status epilepticus	Yes	Yes
Phenytoin	Generalized tonic–clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures; prevention and treatment of seizures occurring during or following neurosurgery; status epilepticus	Yes	Yes
Pregabalin	Partial-onset seizures in adults		
Primidone	Grand mal, psychomotor, and focal epileptic seizures	Yes	Yes (age > 8 y)
Pyridoxine	Pyridoxine-dependent seizures	Yes	
Remacemide	Not available in the United States		
Rufinamide	Lennox–Gastaut, complex partial-onset seizures	Yes	Yes (>4 y)
Stiripentol	Not available in the United States		
Tiagabine	Adjunctive therapy for partial seizures	Yes	Yes (age ≥12 y)
Topiramate	Adjunctive therapy for partial seizures	Yes	Yes (age > 2 y)
Trimethadione	Withdrawn from US market		
Valproate	Simple and complex absence seizures; adjunctive therapy in multiple seizure types, including absence and complex partial seizures	Yes	Yes (age > 2 y)
Vigabatrin	Adjunctive therapy for complex partial seizures	Yes	Yes (age > 1 mo)
Zonisamide	Adjunctive therapy for partial seizures	Yes	

References

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