EPILEPSY AND BRAIN TUMORS

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Dedication

I would like to thank my wife, Cindy, and my children, Alex and Ashley, for their love and support. I would also like to thank my Neuro-Oncology patients and their families for their constant inspiration, as we continue the fight against brain tumors.

Herbert B. Newton

Knowledge and understanding allow our dreams to take flight.
Though at times arduous, especially against the wind, flying is always beautiful..

Don't ever stop.

To my daughter

Italian version:

La conoscenza e il sapere sono le ali dei nostri sogni.
A volte è faticoso volare, specie controvento.
Eppure è sempre bellissimo.

Non smettere mai.

A mia figlia

Marta Maschio

Foreword

Epilepsy caused by brain tumors is a growing problem for both patients and the doctors who treat them, but it has not yet received the attention that it deserves from the research community. The numbers alone are impressive. The annual incidence of primary brain tumors is estimated to be 5 to 15 per 100,000 people, and the incidence of metastatic brain tumors is within the same range. Between 30 and 70% of people with brain tumors develop epilepsy, and in approximately 20–40% of cases, seizures are the initial presenting symptom. The diagnosis and management of epilepsy secondary to brain tumors require the clinician to confront unique challenges, including the complications associated with each of the two conditions, each with its given treatment approach and possible interactions. In light of these challenges, Marta Maschio and Herbert Newton should be commended for assembling a panel of top international experts to create a book that comprehensively addresses the relationship between brain tumors and epilepsy, as viewed by both the neuro-oncologist and the epileptologist. *Epilepsy and Brain Tumors* provides up-to-date information on several key aspects of the disorders and their treatment, including epidemiology, diagnostic approaches, pathology, and pathophysiology, as well as mechanisms of focal epileptogenesis, surgical, radiation and pharmacological treatments, neuropsychology, and rehabilitation programs. The book correctly emphasizes that managing people with epilepsy and brain tumors requires more than managing two separate conditions; it must involve a holistic approach with contributions from many disciplines. *Epilepsy and Brain Tumors* fills an important gap in the medical literature, and I am confident that it will be well received by neurologists, neuropediatricians, oncologists, palliative care specialists, and all scientists with an interest in epileptogenesis, epileptic seizures, and the specificities of brain tumors.

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Preface

It is not by chance that we, the editors of this book, come from two different areas of expertise, epileptology and neuro-oncology, and from two different continents. After many stimulating discussions about our different approaches to taking care of patients with brain tumor-related epilepsy, we concluded that our different visions could be the key to creating a unique and more complete approach to this complex disease.

Hence, we decided to embark on this endeavor, bringing with us many friends and colleagues whose work has contributed greatly to this field. Our intention was to strike the proper balance between advances in basic science and clinical practice, with patient quality of life as an integral part of each chapter. Reading this special volume will provide a more comprehensive understanding of brain tumor-related epilepsy mechanisms and care, with a special focus on the next steps toward individualized targeted therapies, which will be the primary research and clinical objective for all medical practitioners in the next decade.

We hope that we have successfully communicated to you, the readers, our firm belief that brain tumor-related epilepsy is the disease that best represents the need for specialists from different disciplines to work together, always and above all, with the patient and his/her caregivers in mind.

Marta Maschio
Herbert B. Newton

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CHAPTER

1

Brain Tumor-Related Epilepsy: Introduction and Overview

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CHAPTER CONTENTS

INTRODUCTION

In recent years, we have been fortunate to witness remarkable progress in the research of brain tumor-related epilepsy (BTRE), as evidenced by the increasing number of articles and reviews published on the pathophysiological mechanisms, treatment approaches, and quality of life (QoL) concerns related to this challenging clinical problem. There is still much to be done, however, because many questions still remain, for which there are no easy answers. Indeed, BTRE represents an ongoing challenge for clinicians and continues to stimulate much debate and a fair share of controversy in the scientific community.

Patients with BTRE suffer from two serious pathologies simultaneously: brain tumor (BT) (e.g., glioma, meningioma) and a secondary form of epilepsy. This presents many challenges for medical professionals, patients, their families, and their caregivers. With this book, which we believe to be the first volume completely dedicated to BTRE, we hope to present with clarity some of the issues that the health-care team must face as well as some of the novel and promising directions that future research might take.

Epilepsy and BTs is not only meant to be an up-to-date textbook of BTRE, but also a practical guide based on clinical experiences, with a comprehensive collection of presentations from international experts who will share some of the latest discoveries and their approaches to tackling a wide range of difficult and complex issues related to BTRE.

Patients with BTRE present a complicated therapeutic profile and require a unique and multidisciplinary approach. There are several factors to take into consideration. First, there is the management of pharmacological therapies: the concurrent use of antiepileptic drugs (AEDs), chemotherapy (CT), and supportive therapies can present problems with drug interactions and side effects.[1] Secondly, maintaining a good QoL for these patients is always an ongoing concern. In addition, we must recognize the fact that epilepsy still brings with it a societal stigma and can cause the individual who is diagnosed with the disease to feel socially outcast and severely invalided.

Considering the burden of all of these factors, it is understandable that freedom from seizures, or at least a reasonable degree of seizure control, is of utmost importance for the patient if he or she is to function successfully in a professional and social context and conduct a satisfying family life. To accomplish this, it is fundamental that health-care professionals see the patient as a unique individual with his or her particular needs. This requires an approach to patient management that is not only concerned with medical therapies (pharmacological, surgical, radiological, etc.) but also with emotional and psychological support for the individual as well as for his or her family throughout all stages of the illness.

All of these issues are key to understanding the nature of this disease, of which we still know very little. The new insights gained from recent experimental studies, while leading to more questions than answers, continue to make this unique pathology a stimulating and dynamic area of research. There is a certain sense of discovery that unites us—the editors and authors of the chapters in this volume—and it is with this spirit that we introduce the following topics, all of which will be explored in more detail in later chapters of this book:

1. Epilepsy in the context of BTs: epidemiology and incidence
2. Detection, classification, and documentation of seizures
3. The unique role of epileptogenesis and drug resistance in BTRE
4. QoL in BTRE patients
5. Impact of AEDs in BTRE patients
6. Neurocognitive evaluation and possible rehabilitative programs
7. Health economics and BTRE

EPILEPSY: DEFINITION, INCIDENCE, SOCIAL CONTEXT AND TREATMENT OPTIONS

The word epilepsy derives from the Greek "epilambanein," meaning to be seized, to be overwhelmed by surprise.[2] Epilepsy is one of the most common serious disorders of the brain, affecting at least 50 million people worldwide. It is indifferent to geography, race, or social boundaries and accounts for 1% of the global burden of disease, determined by the number of productive life years lost as a result of disability or premature death.[3,4] Epilepsy joins depression and other affective disorders, Alzheimer's disease and other dementias, and substance abuse as one of the primary disorders of the brain. Among all medical conditions, its burden ranks with breast cancer in women and lung cancer in men. Epilepsy leads to multiple interacting medical, psychological, economic, and social repercussions, all of which need to be considered. Therefore, the illness must be viewed as more than just seizures for the affected individual; the many serious challenges for the family must also be taken into consideration. Fear, misunderstanding, and the resulting social stigma and discrimination surrounding epilepsy often force people with this disorder "into the shadows".[5] While the social responses and challenges may differ among countries and cultures, it is clear that throughout the world, social consequences of epilepsy are often more difficult to overcome than the seizures themselves; problems with personal relationships as well as legislative issues are among the difficulties that individuals with epilepsy must face. Most importantly, health-care professionals must be aware of all of these issues, because in many cases, they could undermine the treatment of the disease.

Epilepsy is the propensity for an individual to have recurrent, unprovoked epileptic seizures. These seizures are produced by abnormal discharges of neurons and may be a manifestation of many different conditions, which modify neuronal function or cause pathological changes in the brain. Many environmental, genetic, pathological, and physiological factors may be involved in the development of seizures and epilepsy. Etiologically, the epilepsies are classified into four groups: idiopathic (or primary), symptomatic (or secondary), cryptogenic, and progressive.[6,7] Symptomatic or secondary epilepsies are acquired conditions and are usually associated with a structural abnormality of the brain. BTRE is, therefore, a symptomatic or secondary form of epilepsy.

A multidisciplinary approach is the optimal care model for epilepsy patients, with specialists from different areas addressing all aspects of the patient's life: health, education, social, professional, and psychological. Health, educational training in epileptology is needed on multiple levels among health care providers to offer optimal epilepsy management.[5] These medical specialists—devoted predominantly to providing epilepsy care—and allied health-care professionals, especially at the tertiary level, such as neurological nurses, psychologists, and social workers, are all important members of the team providing comprehensive care to epilepsy patients. They are essential for training and providing support and supervision to primary health-care providers of epilepsy care. They play an important role in the diagnosis, treatment, and rehabilitation of epilepsy patients and play an essential part in raising awareness, advocacy, and education of professionals, people with epilepsy, and the general public. A team effort is of utmost importance for this disorder where sociocultural issues are still a major barrier to adequate treatment and rehabilitation.

Epilepsy in the Context of BTs: Epidemiology and Incidence

For most patients, the diagnosis of a BT, as well as the diagnosis of cancer in general, is enough to cause grave difficulties: behavioral, emotional, and intellectual. These problems can lead to a compromise in daily life and a limited ability to live independently. Epilepsy is a common symptom of BTs that can occur as a presenting symptom or during the progression of the disease. Although these tumors are rare, they represent a tremendous burden for patients, their families, and society at large.[8] The overall incidence of BTs is 18.71 cases per 100,000 inhabitants/year.[9,10] Benign tumors arise in 11.52 cases per 100,000 inhabitants/year, while malignant tumors affect 7.19 cases per 100,000 inhabitants/year. Overall, primary BTs represent 1.5-2% of all adult tumors and are considered rare, especially in comparison to the more common tumors such as lung cancer and breast carcinoma.[9,10] Brain metastases (MBT) are one of the most common neurologic complications of cancer; most frequent in lung cancer, breast cancer, and melanoma.[11] The incidence is 9-17% based on various studies, although the exact incidence is thought to be higher. The incidence of MBT is increasing due to improved imaging techniques that aid early diagnosis and effective systemic treatment regimens, which in turn prolong life, thus, allowing cancer to disseminate to the brain.

In patients with BTs, seizures are one of the presenting symptoms in 20-40% of patients, while a further 20-45% of patients will develop seizure activity during the course of their disease. Overall, the incidence of epilepsy in BT patients, regardless of histological type and anatomical site of the lesion, varies from 35% to 70%.[12–20] Epilepsy due to BTs constitutes 6-10% of all cases of epilepsy as a whole, and 12% of acquired epilepsy.[21,22]

Seizures arise in 20-40% of patients with MBT, especially when the tumors are multifocal. Of this total group, approximately 10% will have the seizures develop during the course of the disease, instead of at presentation. In particular, patients with MBT who have seizures can have melanoma (67%); lung cancer (48%); breast cancer (33%) and unknown cancer (55%).[1,23–30]

In primary BTs, the incidence of epilepsy onset is inversely correlated to the histological grade of the tumor and degree of malignancy, with the highest incidence (from 65% to 95%) occurring in low-grade tumors (WHO grades I and II astrocytoma, oligodendroglioma, and mixed gliomas, as well as meningiomas), and the lowest incidence (from 15% to 25%) occurring in malignant gliomas.[14,17] In general, the onset of seizures as the presenting symptom of a BT confers a more favorable prognosis.[31] This more favorable prognosis could be due to several factors, including an earlier diagnosis resulting from neurological exams requested because of seizure occurrence, a better tumor location that is often more amenable to surgical intervention (i.e., more superficial and near the cortex), and the presence of a more favorable histology (i.e., slower growing, less aggressive tumors). Another factor that determines whether there will be seizure activity is the intracranial location of the tumor, with a higher seizure frequency being associated with supratentorial tumors, especially those involving the temporal and frontal lobes, in comparison to infratentorial tumors, which are more likely to involve the brainstem and cerebellum.[15]

The incidence of primary BTs of the central nervous system in Europe is 5 cases per 100,000 inhabitants/year (3.7 per 100,000 persons/year for men and 2.6 per 100,000 persons/year for women), without significant differences among single European nations, resulting in 2% of all cancer-related deaths.[9,10] Over the last three decades, there has been a progressive increase in the incidence of these tumors; this increase is not attributed to the mere development of more accurate diagnostic methods (e.g., magnetic resonance imaging; MRI) that facilitate earlier diagnosis, but is probably due to other causes not yet clearly understood (e.g., environmental exposures). The most significant increase has been seen among individuals over the age of 65, where the incidence has more than doubled.[14,16,19,32]

Glioma tumors represent 67.6% of all primary BTs and are responsible for more than 26,000 deaths per year in the United States.[14,33] They derive from three types of glial cells: astrocytes (astrocytomas), oligodendrocytes (oligodendrogliomas), and ependymal cells (ependymomas). They have the following characteristics: the impossibility of a complete surgical resection, incurability, genetic instability, progressive worsening over time, and a tendency toward local reccurrence after the initial therapy. Glioblastoma multiforme (GBM) is the most aggressive form of primary BT, as well as the most frequent, with an incidence of 7-8 cases for every 100,000 inhabitants. GBM usually arises in the sixth and seventh decades, with one-third of patients diagnosed at age 60 or older.[12,16] It represents over 50% of all gliomas, with a male-female ratio of 1.5:1. The median survival is 12-18 months for newly diagnosed GBM. Anaplastic astrocytomas are more frequent in younger patients and represent 10-35% of all gliomas. The age of onset is 35-50 years, with a male-female ratio of 1.2:1 and a median survival of 30-36 months in most studies.[14] Low-grade gliomas (e.g., WHO grade I and II) are more frequent among individuals between 20 and 40 years of age, and have median survivals ranging from 5 to 10 years. Age, performance status (i.e., degree of personal autonomy and function), and histological grade are the most significant prognostic factors with regard to gliomas. Epilepsy is of particular significance in the management of

young patients with low-grade tumors, since they have a more favorable prognosis and are more active in their social and professional lives, and where a lack of seizure control and possible side effects (SE) of AEDs could seriously compromise daily QoL.[34]

The histological type of tumor, type of antineoplastic treatment (radiation, CT), type of support therapy (corticosteroids, antacids, neuroleptics, etc.), AED, and other possible medical complications can affect the patient's neurocognitive functioning, psychological well-being, and the ability to perform daily tasks. However, much can be done to improve the patient's QoL and his/her care.

Seeing the BT and resultant epilepsy as two distinct illnesses coexisting in the same patient has been the traditional concept for many years. In our opinion, this approach does not permit a complete vision of BTRE, which, in this volume, is conceived of as a single illness, albeit complex and multifaceted.

Detection, Classification, and Documentation of Seizures

The following classification system refers to nononcological epileptic seizures, but it is important to take into consideration that seizures related to BTRE can be more difficult to classify. Regarding the classification of seizures in epilepsy, *generalized seizures* are considered as originating at some point within, and rapidly engaging, bilaterally distributed neural networks. Such bilateral networks can include cortical and subcortical structures, but do not necessarily include the entire cortex. On an individual basis, the onset of seizures can appear localized, but the location and lateralization can vary from one seizure to another. *Focal seizures* are considered as originating within networks limited to one hemisphere. They may be clearly localized or have a wide distribution. Focal seizures may also originate in subcortical structures. For each seizure type, ictal onset is consistent from one seizure to another, with preferential propagation patterns that can involve the contralateral hemisphere. In some cases, however, there is more than one network, and more than one seizure type, but each individual seizure type has a consistent site of onset. It is important, however, to recognize that impairment of consciousness/awareness or other dyscognitive features, localization, and progression of ictal events can be of primary importance in the evaluation of individual patients and for specific purposes (e.g., differential diagnosis of nonepileptic events from epileptic seizures, randomized trials, surgery). Therefore focal seizures should be described according to their manifestations (e.g., dyscognitive, focal motor).[35,36]

Seizures can be extremely difficult for physicians and patients to recognize. Focal seizures, most often encountered by BTRE patients, can be manifested as any of the following: epigastric aura described as pain, ictal fear-like panic attacks, dreamy states, experiential phenomena, mental or psychic symptoms, and hallucinations. Focal seizures with secondary generalization are also frequent, but they are difficult to recognize clinically.[9,17] Occasionally, repeated focal activity (often originating in the temporal lobe) can cause a nonconvulsive epileptic state with variable duration that can last up to several hours. The clinical manifestations of these types of seizures can take the form of a confusional state, automatisms, or behavioral alterations, which from a clinical standpoint, can be confused with psychiatric disorders or other causes. Primary generalized seizures rarely occur in these patients.[1] Given this range of clinical manifestations, it becomes clear that even if a seizure diary (i.e., used for documentation of seizure number, type, and frequency to aid in planning therapeutic strategies) is given to patients and family members, it is not guaranteed to be an effective tool.[5] If medical professionals, family members, and the entire nonmedical support team that interacts with the patient do not receive proper training for verifying and quantifying seizures, the number of seizures can be underestimated or missed altogether; this makes finding the right drug therapy enormously difficult. Also, it is entirely possible that many oncological centers that treat BTRE do not have the resources to properly train staff, patients, and family members.

In 73% of patients with BTs, epilepsy can either be the presenting symptom or can occur during the course of the oncological disease due to a number of factors: (1) reoccurrence of brain cancer or disease progression; (2) affect of various therapies (CT, support therapies, and radionecrosis) on the brain, or (3) other causes such as vascular, infective, metabolic, and limbic encephalopathy.[18]

Evaluation of the efficacy of a therapeutic treatment in epileptic patients (i.e., nononcological therapy) is based on the seizure frequency; therefore, an accurate quantification of seizure activity is fundamental. For this reason, it is essential that a seizure diary be considered routine for each BTRE patient, along with sufficient enough instruction to allow him/her (or the caregivers) to correctly document seizure frequency and communicate the numbers during check-ups.

The Unique Role of Epileptogenesis and Drug Resistance in BTRE

The epileptogenic mechanisms of BTRE are still poorly understood; they are complex and likely multifactorial[37–39] and include such factors as tumor-related alteration of inhibitory pathways (e.g., GABA), genetic

alterations of proteins, ion channels, and receptors as well as tumor cell type and localization.[40]

The mechanism by which seizures occur may differ from epileptogenic mechanisms: seizure generation, or *ictogenesis*, may depend on peritumoral changes, because the core tumor rarely represents the seizure onset zone. The onset zone is more frequently located at the tumor-to-brain interface. Receptor changes (e.g., GABA, glutamate, among others), disruption of intercellular communication and integrity (such as a disturbed blood-brain barrier (BBB), or altered expression of connexins), and chemical alterations (like pH, ionic imbalance, amino acid changes) may promote ictogenesis.[41] It remains unclear how various types of BTs induce epileptogenesis, and several hypotheses have been proposed.[40–42] Identifying factors in the pathway that leads to epilepsy may help find preventive therapies.[43] The peritumoral region has been shown to be relevant for the generation and propagation of seizure activity.[39] The epileptogenicity of the peritumoral zone is supported by both functional and immunocytochemical studies that show network alterations and revealing cytoarchitectural and neurochemical changes in the cortex resected from patients with intractable epilepsy associated with different types of glial tumors.[39,41] Understanding the mechanisms that underlie epileptogenesis in BTs is essential to the identification of new therapeutic targets and to the development of effective treatment.[44]

Pharmacoresistance

One of the primary characteristics of BTRE is that it is often drug resistant. The International League Against Epilepsy Commission on Therapeutic Strategies defines refractory epilepsy as an epilepsy that is not controlled by two tolerated and appropriately chosen and used AED schedules (whether used as monotherapies or in combination).[45] However, this definition is currently a matter of debate.[46] Drug resistant epilepsy can be also classified as: primary (related to intrinsic components of the illness) or secondary (e.g., undesired consequences of the illness itself), specific (e.g., due to a response to a specific drug) or nonspecific (e.g., due to a response to a variety of drugs).

Pharmacoresistance or medically refractory epilepsy is common in patients with primary BTs, especially with low-grade tumors and, based on these classifications, BTRE can be considered a pharmacoresistant epilepsy with mixed characteristics: primary (presumed to be related to the tumor itself), secondary (with limited efficacy of pharmacological therapies due to drug interactions), and often not due to only one specific drug.

Several hypotheses have been explored to explain the pharmacoresistance noted in BTs. One hypothesis, the *target hypothesis*,[47] presumes alterations in drug targets; targets to which AEDs normally bind are possibly altered in the tumor and peritumoral tissue. Another hypothesis is the *transporter hypothesis*[48,49]: drugs can enter and leave the brain through carrier-mediated transport. Multidrug transporters such as P-glycoprotein, multidrug resistant protein, and breast cancer resistance protein, as well as detoxifying enzymes such as glutathione-*S*-transferase, actively remove lipophilic molecules out of the brain parenchyma. This mechanism contributes to the function of the BBB, which is to protect the brain from toxic substances. However, upregulation of multidrug transporters, as may be found in epileptogenic brain tissue, may restrain access of AEDs to the epileptogenic tissue.[50] Overexpression of multidrug transporters, such as P-glycoprotein, multidrug resistance protein, and breast cancer resistance protein has been reported in BTs and may underlie the drug refractoriness observed in this group of patients.[51,52] For the transporter hypothesis to be applicable to BTRE, the AEDs must be substrates for the transporter proteins.[44] Several major AEDs (phenytoin [PHT], phenobarbital, lamotrigine and levetiracetam, but not carbamazepine [CBZ]) are transported by P-glycoprotein.[53] The upregulation of multidrug transporters in the vasculature of primary BTs, and the fact that the majority of AEDs are substrates for multidrug transporters, suggests that multidrug transporters have a role in pharmacoresistant epilepsy in patients with BTs.[44] For all of these reasons, the integration of basic scientific knowledge about the pathophysiological mechanisms of BTRE with innovative clinical treatments, based on individual genetic and proteomic profiling, will lead to more effective and less costly therapies and, most importantly, to a significant improvement in the QoL of our BT patients.

QoL in BTRE Patients

The diagnosis of epilepsy in a patient without a BT already implicates an important change in his/her concept of QoL that involves three main factors:

1. Possible side effects from anticonvulsant drug therapy.
2. The negative psychological impact caused by losing control of one's body and the surrounding environment during seizure activity.
3. The rejection and marginalization that is still prevalent today—due to a societal view of individuals with epilepsy.

These three factors become even heavier to bear in patients who must confront both pathologies: epilepsy

and the presence of a BT. These patients are subjected to systemic treatments for the neoplastic disease as well as antiepileptic therapies and are therefore at even greater risk for SE and drug interactions. The loss of control of one's body during a seizure and the worry that accompanies such an experience represent for the patient a total lack of autonomy. The unpredictability of adverse events leads to an enormous sense of insecurity. In addition, seizures are a constant reminder to the patient of his or her illness and of being considered "different." Marginalization and rejection are especially felt by individuals who have a visible physical disability like hemiparesis or problems with speech, and also by those whose physical aspect has been altered due to systemic therapies (e.g., hair loss from radiation, fluid retention or noticeable weight gain due to the prolonged use of steroids). All of these factors together with the label "epileptic" can cause the patient to feel extremely frustrated when attempting any type of social and/or interpersonal interaction. Taking into consideration all of these factors, it is understandable why total seizure freedom or at least good control of seizures is so essential to the patient's ability to resume work and normal family and social relationships.

The QoL for patients with a BT is affected by many factors, the most significant being the various therapies they have to undergo (e.g., CT, radiation, surgery, supportive therapies, and AEDs), possible physical disability due to neural injury secondary to the tumor, and possible neurocognitive disturbances induced by the tumor and treatment. With the knowledge that epilepsy can affect the long-term disability of the patient, the choice of AED must take into consideration the fact that in addition to controlling seizures, the drug could have an effect on cognitive functioning, efficacy of systemic therapies, and the frequency of adverse events.

Impact of AEDs in BTRE Patients

The presence of epilepsy is considered the most important risk factor for long-term disability in BT patients.[54,55] For this reason, the problem of the proper administration of medications and their potential SE is of great importance. Good seizure control can significantly improve the patient's psychological and relational sphere (i.e., social, personal, and professional). Many studies (i.e., meta-analyses) pertaining to nononcological epileptic patients have been done, but it is difficult to transfer these results to the clinical care of BTRE patients.[34]

Prior to determining whether or not a given therapy is efficacious, it is critical to have documentation concerning whether the drug in question has been administered at the maximum possible dose for the patient and which type of add-on has been used. Often, these kinds of records have not been kept. It must also be taken into consideration that AEDs can induce many potentially serious SE. In addition to these types of intrinsic toxicities, there can also be drug interactions with the oncological therapies. Therefore, the evaluation of the efficacy of a therapeutic treatment must be based on the number and types of seizures, as well as on significant drug-related information that, as we have stated, is often not available. Elimination of seizures is the long-term goal, while improvement in seizure frequency is, of course, the initial objective at hand. However, as in the case with recent reports on the possible positive effects of some radiation and chemotherapies on seizures, the difficulty in standardizing methods of defining and measuring improvement needs to be considered.

Adverse effects of AEDs are more frequent in patients with tumor-related epilepsy than in the rest of the epileptic population.[16,18] Each AED can be associated with adverse effects, in both oncological and nononcological patients. However, in cancer patients, the evaluation of AED SE is crucial due to the fact that SE can affect the patient's perception of QoL more than seizure frequency.[34] Patients' priorities often have less to do with seizure freedom than with the desire to have the least amount of SE induced by drugs; they perceive serious SE as being extremely limiting on their daily lives. With the older AEDs (i.e., first generation), there is a high incidence of serious SE (23.8%) and mean incidence of SE (20-40%), higher than in the nononcological epileptic population.[16] Only recently, studies have been published that have evaluated the percentage of SE that appeared in BTRE patients; regarding new AEDs (i.e., second generation), these data indicated a lower percentage of SE in comparison to the older drugs.[56,57] Other SE that must be taken into consideration regarding QoL of patients with BTRE are the potential deleterious effects on cognitive function and on sexual activity.

There have been no studies dedicated specifically to studying the impact of the older AEDs on cognitive function in patients with BTs. However, there have been studies on cognitive function in oncological patients in general.[34,58,59] While not examining the impact of AEDs in this specific area, these studies demonstrated that the older AEDs, such as PHT, CBZ, valproic acid, and phenobarbitol, had the highest incidence of adverse effects on cognitive function.

There is literature to support the contention that some AEDs can induce negative effects on the sexual sphere,[60] a fundamental aspect of emotional well-being and a significant contribution to a good QoL. For this reason, in patients with BTRE who may have a short life expectancy, and as a result, and a possible fear of dying and/or a sense of uncertainty due to the duplicity of their disease, the choice of the AED should take into account the possible effects on sexuality.[61]

Another key area that needs to be addressed is the possibility of pharmacological interactions between all of the different therapies. In BTRE, pharmacological interactions may take place between an AED and CT. In the event that this occurs, it can have one of two contrasting results: in the first scenario, a rapid elimination of one or the other of the drugs (i.e., either the AED or the CT), would result in either a lesser degree of seizure control or a reduction of CT-related survival benefits. In the second scenario, a reduced elimination of one or the other of the drugs would result in an increase in toxicity.[62,63]

The knowledge that epilepsy in BTRE patients might provoke long-term disability necessitates careful consideration of the following when choosing an AED therapy: the frequency/seriousness of SE, the drug's impact on cognition, and the fact that possible interactions with other therapies may modify the effectiveness of systemic therapy. The optimal approach would be the development of a customized treatment plan for each individual patient with BTRE, the goals of which should be: complete seizure control, minimal or no SE, and elimination of cognitive impairment and/or psychosocial problems.

Another important issue concerns AED use in BTRE as prophylactic therapy (i.e., before a verified seizure event has been documented). This topic has been the subject of much debate, given that despite the American Academy of Neurology Practice Parameters published in 2000,[16] which affirmed that AEDs used prophylactically were unable to prevent the onset of seizures, this practice is still in widespread use (often by neurosurgeons).

Neurocognitive Evaluation and Possible Rehabilitative Programs

In recent years, interest has grown in the area of cognitive rehabilitation for BT patients. Although there have been few studies regarding possible interventional strategies to improve cognitive dysfunctions in these patients, limited data have demonstrated that BT patients with cognitive impairment can participate meaningfully in a structured intervention of cognitive rehabilitation, ultimately gaining increased independence, productivity, and an improvement in QoL. Future research is needed to explore variables that will help us identify which BTRE patients might be most likely to benefit from cognitive rehabilitation strategies; however, we think that this is a promising area for improving the overall QoL of BT patients. Recent reports in the literature have indicated that brain cancer, which is characterized by progressive impairment of mental function, may benefit from treatment that stabilizes or slows the progression of worsening symptoms, regardless of whether overall survival is extended.[64]

In patients with BT, especially those with BTRE, periodic neurological and neuropsychological check-ups are an important part of the ongoing patient evaluation and of the patient-doctor feedback. They allow the monitoring of neurocognitive performance and possible collateral effects over time and thus enable the team of medical professionals to plan any necessary cognitive rehabilitation interventions.[20,54] Ideally, they would be included in routine patient care. For this reason, despite the extremely limited body of literature on this topic in BTRE, we included a chapter on neurocognitive impairment. The majority of the data presented regards neurocognitive assessment, evaluation of neurocognitive performances for patients with either epilepsy or BT. We are optimistic that this data can have significant implications for patients with BTRE as well.

Health Economics and BTRE

The necessity of placing illness and treatment alternatives (i.e., without distinction of which ones in particular), and most importantly patients' well-being, in a political, economic, and social context is inescapable; governments across the globe with different national market conditions, environments, and types of health systems, all have in common the fact that their policy makers must reach compromises and deal with powerful interest groups and strong political constituencies.[65] A range of formats for health economic studies have been developed in an attempt to inform policy makers, who are urgently looking for reliable data upon which to base critical decisions regarding the allocation of precious, ever-diminishing resources; demonstrating, however, many methodological and conceptual challenges in evaluating the economic factors related to health care and to specific illnesses (i.e., cost of illness studies, known as COI). This chapter was included here for many reasons, the most important being that there are few studies, if any, that evaluate the economic issues related to a pathology that involves two serious illnesses simultaneously, as is the case with BTRE. Well-tested, accurate models with which to do this type of analysis have yet to be created. The COI studies that have been published, while representing important steps forward in certain areas of brain-related diseases, exist either for BT or for epilepsy (the most significant of which will be presented at the end of this chapter). However, there is not one health economic study to date (to our knowledge) that takes into consideration BTRE as the sole focus.

The data in the literature on nononcological epilepsy demonstrate that epilepsy is a relevant socioeconomic burden at the individual, family, health services, and social level in Europe. The greater proportion of such

burden is outside the formal health-care sector, and AEDs represent a small proportion.[38]

The costs described above refer only to nononcological epilepsy. Therefore, when speaking of costs related to BTRE, it is necessary to take into consideration that there are two serious pathologies involved. This makes patient care for these individuals extremely complex and costly. Nevertheless, there have been no studies in the literature that examine the direct and indirect costs involved with treating both pathologies, which could probably influence patient management significantly, if handled appropriately.

The disability caused by BTRE has a particular relevance to social and individual costs. These costs could be avoided, reduced, or at the very least, kept under better control by applying preventive measures through the utilization of correct therapies for seizure control, educating caregivers and those in the patient's immediate environment (family members, in-home caregivers, coworkers) about the management of seizures.

A general overview of the kinds of economic studies that exist will be presented within the framework of the issues that influence which diseases or research areas receive funding, together with a discussion of the principle drivers of health-care costs everywhere: aging populations, chronic illnesses, and technology costs.

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CHAPTER

2

Overview of Epidemiology, Pathology, and Treatment of Primary Brain Tumors

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CHAPTER CONTENTS

In this chapter, we will provide an overview of the epidemiology, classification, pathology, and treatment of common primary brain tumors (PBT). PBT remain a significant health problem in the United States and worldwide. Overall, they account for some of the most malignant tumors known to affect human beings and are often refractory to all modalities of treatment. PBT will be diagnosed in approximately 30,000-35,000 patients in the United States this year and are associated with significant morbidity and mortality.[1–7] Of the estimated 14 patients per 100,000 population that will develop a PBT this year, 6-8 per 100,000 will have a high-grade neoplasm, usually some form of glioma such as glioblastoma multiforme (GBM) or anaplastic astrocytoma (AA).

EPIDEMIOLOGY OF PBT

As mentioned above, approximately 14 per 100,000 people in the United States will be diagnosed with a PBT each year, and the majority of those will have a high-grade neoplasm (typically AA or GBM).[2–7] Contemporary epidemiological studies suggest an increasing incidence rate for the development of PBT in children less than 14 years of age and in patients 70 years or older.[8] For people in the 15- to 44-year-old age group, the overall incidence rates have remained fairly stable in recent years. The cause of the increased incidence of PBT in some age groups remains unclear, but may be due to improvements in diagnostic neuro-imaging such as magnetic resonance imaging (MRI), greater availability

of specially qualified neurosurgeons and neuropathologists, improved access to medical care for children and elderly patients, and more aggressive approaches to health care for elderly patients.[5,8] In other words, the increase in PBT incidence may be more apparent than real due to ascertainment bias.

The prognosis and survival of patients with PBT remains poor.[1–7] Although uncommon neoplasms, they rank among the top 10 causes of cancer-related deaths in the United States and account for a disproportionate 2.4% of all yearly cancer-related deaths.[9] The median survival for a patient with GBM is approximately 12-16 months, a figure that hasn't improved substantially over the past 30 years. For patients with a low-grade astrocytoma or oligodendroglioma, the median survival is still significantly curtailed and is about 6-10 years. For PBT patients in the United States as a whole, across all age groups and tumor types, the 5-year survival rate is 20%.[3] If a patient with a PBT survives for an initial 2 years, the probability of surviving another 3 years is 76.2%. In general, for any given tumor type, survival is better for younger patients than for older patients. The only exception to this generalization is for children with medulloblastoma and embryonal tumors, in which patients under 3 years of age have poorer survival rates than children between 3 and 14 years of age.[10] The 5-year survival rate for all children less than 14 years of age with a malignant PBT is 72%.

The median age at diagnosis for PBT is between 54 and 58 years.[1–7] Among different histological varieties of PBT, there is significant variability in the age of onset. A small secondary peak is also present in the pediatric age group, in children between the ages of 4 and 9. Overall, PBT are more common in males than females, with the exception of meningiomas, which are almost twice as common in females. Tumors of the sellar region, and of the cranial and spinal nerves, are almost equally represented among males and females. In the United States, gliomas are more commonly diagnosed in whites than blacks, while the incidence of meningiomas is relatively equal between the two groups.

Numerous epidemiological studies have been performed in an attempt to define risk factors involved in the development of brain tumors (see Table 2.1).[2–7] The vast majority of these potential risk factors have not been associated with any significant predisposition to brain tumors. One risk factor that has proven to be important is the presence of a hereditary syndrome with a genetic predisposition for developing tumors, some of which can affect the nervous system.[4,5,11] Several hereditary syndromes are associated with PBT, including tuberous sclerosis, neurofibromatosis types 1 and 2, nevoid basal cell carcinoma syndrome, Li-Fraumeni syndrome, and Turcot's syndrome. However, it is estimated that hereditary genetic predisposition may be involved in only 2-8% of all cases of PBT. Familial aggregation of brain tumors has also been studied, with conflicting results.[5,11] The relative risk for developing a tumor among family members of a patient with a PBT is quite variable, ranging from 1 to 10. One study that performed a segregation analysis of families of more than 600 adult glioma patients showed that a polygenic model most accurately explained the inheritance pattern.[12] A similar analysis of 2141 first-degree relatives of 297 glioma families did not reject a multifactorial model, but concluded that an autosomal recessive model fit the inheritance pattern more accurately.[13] Critics of these studies suggest that the common exposure of a family to a similar pattern of environmental agents could lead to a similar clustering of tumors. Other investigators have focused on genetic polymorphisms that might influence genetic and environmental factors to increase the risk for a brain tumor.[4,5] Alterations in genes involved in oxidative metabolism, detoxification of carcinogens, DNA stability and repair, and immune responses might confer a genetic

TABLE 2.1 Risk Factors That Have Been Investigated in Epidemiological Studies of Primary Brain Tumors

Hereditary syndromes (proven): tuberous sclerosis, neurofibromatosis types 1 and 2, nevoid basal cell carcinoma syndrome, Turcot's syndrome, and Li-Fraumeni syndrome
Family history of brain tumors
Constitutive polymorphisms: glutathione transferases, cytochrome P-450 2D6 and 1A1, *N*-acetyltransferase, and other carcinogen metabolizing, DNA repair, and immune function genes
History of prior cancer
Exposure to infectious agents
Allergies (possible reduced risk)
Head trauma
Drugs and medications
Dietary history: N-nitroso compounds, oxidants, antioxidants
Tobacco usage
Alcohol consumption
Ionizing radiation exposure (proven)
Occupational and industrial chemical exposures: pesticides, vinyl chloride, synthetic rubber manufacturing, petroleum refining and production, agricultural workers, lubricating oils, organic solvents, formaldehyde, acrylonitrile, phenols, polycyclic aromatic hydrocarbons
Cellular telephones
Power frequency electromagnetic field exposure

Data adapted from Refs. 2–7.

predisposition to tumors. For example, Elexpuru-Camiruaga and colleagues demonstrated that cytochrome P-4502D6 and glutathione transferase theta were associated with an increased risk for brain tumors.[14] Other studies have not supported these results, but have found an increased risk for rapid *N*-acetyltransferase acetylation and intermediate acetylation.[15] In general, further studies with larger cohorts of patients will be necessary to determine if genetic polymorphisms of key metabolic enzyme systems play a significant role in the risk for developing a brain tumor.

Cranial exposure to therapeutic ionizing radiation is a potent risk factor for subsequent development of a brain tumor, and is known to occur after a wide range of exposures.[1–7] Application of low doses of irradiation (1000-2000 cGy), such as were prescribed in the past for children with tinea capitis or skin hemangiomas, have been associated with relative risks of 18 for nerve sheath tumors, 10 for meningiomas, and 3 for gliomas.[5,16] Gliomas and other PBT are also known to occur after radiotherapy for diseases such as leukemia, lymphoma, and head and neck cancers.[5,17,18] In addition, alternative methods of radiation exposure, such as nuclear bomb blasts and employment at nuclear production facilities, have also been implicated as significant risk factors for the development of brain tumors.[19,20]

Many other risk factors have been evaluated for their potential role in the genesis of brain tumors.[1–7] The majority of these factors have been proven to have little, if any, relationship to brain tumor development, or to have an indeterminate association due to a mixture of positive and negative studies. Factors in this category include the history of a prior primary systemic malignancy, head injury, prenatal or premorbid ingestion of various types of medications, exposure to viruses and other types of infection (except for the human immunodeficiency virus, which is known to be associated with brain lymphoma), dietary history (i.e., ingestion of *N*-nitroso compounds, oxidants, and antioxidants), alcohol ingestion, smoking tobacco, residential chemical exposures, and proximity to electromagnetic fields. The relationship between industrial and occupational chemical exposures and brain tumors is very complex and remains unclear.[2,4,5] Workers are exposed to chemicals that are potentially carcinogenic or neurotoxic, or both, including lubricating oils, organic solvents, formaldehyde, acrylonitrile, phenols and phenolic-based compounds, vinyl chloride, and polycyclic aromatic hydrocarbons. Preclinical studies have proven the ability of vinyl chloride to induce brain tumors in rat models and some studies suggest an increased risk for chemical workers that handle this compound.[21] However, more recent and extensive analyses suggest that the relationship between vinyl chloride exposure and brain tumors remains inconclusive.[22] Similar inconclusive results for other chemicals are common in the epidemiology literature and demonstrate the difficulty of proving an association between workplace exposures and an uncommon form of cancer. At this time, no definitive associations have been proven between brain tumors and any specific chemicals found in the occupational or industrial setting, including those that are known to be definite or putative carcinogens.

Several large studies have evaluated the possibility of a link between the use of handheld cellular telephones and brain cancer as well as other tumors of the head and neck region. Researchers from Denmark performed a nationwide review of 420,095 cell phone users and determined that the overall incidence of cancer was not elevated (OR = 0.89) in comparison to controls including brain tumors, salivary gland tumors, and leukemias.[23] Other studies focusing on the incidence of high-grade gliomas in cellular telephone users have not been able to substantiate an increased incidence.[24–26] Several reports have focused on the use of cellular telephones and the incidence of acoustic schwannomas.[27,28] Neither study was able to discern a relationship between the duration of use, lifetime cumulative hours of use, or frequency of use of a cellular telephone and the risk of developing an acoustic schwannoma. The only positive report to date was a population-based case-control study from Germany that evaluated 366 glioma, 381 meningioma, and 1494 control patients.[29] In this study, the overall risk for a brain tumor was not associated with the use of a cellular telephone. However, there was a small increased risk of glioma (OR = 2.20), but not meningioma (OR = 1.09), in patients that had used a cellular telephone for 10 years or more.

More recent molecular epidemiological studies in adult patients with high-grade glioma are beginning to show promise for further research efforts.[30] In a study of the association between human leukocyte antigens (HLA) and related polymorphisms (HLA-A, -B, -C, -DRB1), and the onset and prognosis of GBM, 155 GBM patients and 157 controls were studied in the San Francisco area.[31] During multivariate logistical regression analysis, the HLA-B*13 and the HLA-B*07-Cw*07 haplotype were positively associated with the occurrence of GBM ($p = 0.01$, $p < 0.001$, respectively). The Cw*01 variant had a negative association with the occurrence of GBM ($p = 0.05$). In addition, progression to death among GBM patients was slower in patients with HLA-A*32 (HR = 0.45, $p < 0.01$) and faster in those with HLA-B*55 (HR = 2.27, $p < 0.01$). In a study of polymorphisms of ERCC1 and ERCC2, genes that are important for DNA nucleotide excision repair, 450 adult glioma patients and 500 controls were analyzed.[32] Overall, the

presence of ERCC1 and ERCC2 was not associated with an increased risk for GBM. However, among whites, glioma patients were significantly more likely than controls to be homozygous for variants in ERCC1 C8092A and ERCC2 K751Q (OR = 3.2). In a similar study, 556 astrocytic tumors were analyzed for the expression of p53, epidermal growth factor receptor (EGFR), MDM2, and O^6-methylguanine-DNA-methyl-transferase (MGMT), and then correlated with clinical parameters and risk factors.[33] The data confirmed the previously noted inverse relationship between p53 mutation and MDM2 ($p = 0.04$) or EGFR ($p = 0.004$) amplification. In addition, the presence of p53 mutations were more likely to occur in younger patients ($p < 0.001$). EGFR gene amplification was more likely to occur in older patients (mean 63 years old amplified vs. mean 48 years old nonamplified; $p = 0.005$). p53 mutations were more likely to occur in GBM among nonwhite patients than white patients ($p = 0.004$). Patient carriers of the MGMT variant 84Phe allele were significantly less likely to have tumors with p53 overexpression (OR = 0.30) and somewhat less likely to have tumors with p53 mutations (OR = 0.47). The authors concluded that these molecular data demonstrated ethnic variation in the pathogenesis of glioma.

Of all the potential risk factors studied, the only one that might be associated with a protective effect for developing a brain tumor is the presence of an allergy.[34] The presence of any form of allergy was inversely associated with the development of a glioma (OR = 0.7), but not with meningiomas or acoustic neuromas. Similar inverse associations were noted for the presence of autoimmune diseases and the presence of both gliomas and meningiomas. The authors suggested that allergy-related immunological factors might play a protective role in the genesis of certain brain tumors. As a follow-up to this initial study, Schwartzbaum and colleagues performed a population-based case-control evaluation of 111 GBM patients and 422 controls, using germ line polymorphisms associated with asthma and inflammation as biomarkers.[35] Self-reported asthma and eczema were inversely related to the incidence of GBM (OR = 0.64). In addition, IL-4RA Ser478Pro TC, CC and IL-4RA Gln551ArgAG, AA were positively associated with GBM (OR = 1.64), while IL-13-1, 112CT, TT was negatively associated with GBM (OR = 0.56). The authors suggested that associations existed between IL-4RA, IL-13, and GBM that were independent of their role in allergic conditions.

PATHOLOGY OF SELECTED PBT

The application of appropriate therapeutic strategies is dependent upon knowing the type of tumor affecting a given patient. In addition to assisting with treatment decisions, the tumor classification and grade provide important information regarding prognosis. This chapter will follow the World Health Organization (WHO) classification that separates nervous system tumors into different nosological entities and assigns a grade of I-IV to each lesion (see Table 2.2), with grade I being biologically indolent and grade IV being biologically most malignant and having the worst prognosis.[36,37] Within the WHO classification, tumors of neuroepithelial and meningeal origin contain the two largest and most clinically relevant groups of neoplasms.

TABLE 2.2 WHO Classification: Tumors of the Central Nervous System

Tumors of neuroepithelial tissue
Tumors of cranial nerves and spinal nerves
Tumors of the meninges
Lymphomas and hemopoietic neoplasms
Germ cell tumors
Tumors of the sellar region
Cysts and tumor-like lesions
Metastatic tumors

Tumors of neuroepithelial origin comprise a large and diverse group of neoplasms, with a mixture of slowly growing and malignant tumor types (see Table 2.3).[36–38] Gliomas (e.g., GBM, AA, oligodendrogliomas, medulloblastoma) are the largest subgroup within the neuroepithelial class of neoplasms and are also the most common type of PBT. Tumors of neuroepithelial origin, and gliomas in particular, can grow diffusely within the brain or be more circumscribed. Diffusely growing tumors are most common and include the astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas. Any of these subtypes can undergo malignant transformation and degenerate into the most aggressive form of glioma, the GBM.

TABLE 2.3 WHO Classification: Tumors of Neuroepithelial Tissue

Astrocytic tumors
Oligodendroglial tumors
Ependymal tumors
Mixed gliomas
Choroid plexus tumors
Neuronal and mixed neuronal-glial tumors
Pineal parenchymal tumors
Neuroepithelial tumors of uncertain origin
Embryonal tumors

TABLE 2.4 WHO Classification: Astrocytic Tumors

Diffuse astrocytomas
Astrocytoma (WHO grade II)
Fibrillary
Protoplasmic
Gemistocytic
Anaplastic astrocytoma (WHO grade III)
Glioblastoma multiforme (WHO grade IV)
Giant cell glioblastoma
Gliosarcoma
Localized astrocytomas (WHO grade I)
Pilocytic astrocytoma
Pleomorphic xanthoastrocytoma
Subependymal giant cell astrocytoma

Diffuse Astrocytomas

The current WHO classification divides astrocytomas into diffuse and localized varieties (see Table 2.4).[36–38] The diffuse astrocytomas are intrinsically invasive and often travel along white matter tracts deep into normal brain. There are three groups of diffuse astrocytic neoplasms: astrocytoma (WHO grade II; peak age of 30-39 years), AA (WHO grade III; peak age of 40-49 years), and GBM (WHO grade IV; peak age of 50-69 years). Diffuse astrocytic tumors can be divided into fibrillary, protoplasmic, and gemistocytic forms, with the fibrillary form being most common. The presence of gemistocytic and protoplasmic cellular variations are most often seen in WHO grade II tumors. WHO grade II astrocytomas are considered low-grade tumors and usually occur in the cerebral white matter. These tumors are characterized by a relatively uniform population of proliferating neoplastic astrocytes in a fibrillary matrix, with minimal cellular and nuclear pleomorphism or atypia (see Figure 2.1). Tumor margins are poorly delineated and suggest significant infiltration into surrounding brain. Mitotic figures are absent and there is no evidence for vascular hyperplasia. Microcystic change is commonly noted in all variants of grade II astrocytoma. The Ki-67 labeling index of WHO grade II astrocytomas is typically less than 4%, with a mean of approximately 2.0-2.5%.

Higher-grade diffuse astrocytomas include AA (WHO grade III) and GBM (WHO grade IV), as well as the GBM variants giant cell glioblastoma and gliosarcoma (WHO grade IV) (see Table 2.4).[36–39] AAs are similar to grade II tumors, except for the presence of more prominent cellular and nuclear pleomorphism and atypia, and mitotic activity (see Figure 2.2). In addition, grade III and IV tumors usually do not stain as intensely or as homogeneously with glial fibrillary acidic protein (GFAP). According to WHO criteria, the critical feature that upgrades a grade II tumor to an AA is the presence of mitotic activity, with anaplastic tumors having Ki-67 indices in the range of 5-10% in most cases. Other features of anaplasia can be present, such as multinucleated tumor cells, abnormal mitotic figures, and regions of vascular proliferation. Necrosis is absent in grade III astrocytomas.

GBM is classified as a WHO grade IV tumor and has similar histological features to AA, but with more pronounced anaplasia (see Figure 2.3a).[36–39] The presence of microvascular proliferation and/or necrosis in an otherwise malignant astrocytoma upgrades the tumor to a GBM. Vascular proliferation is defined as blood vessels with "piling up" of endothelial cells, including the formation of glomeruloid vessels (see Figure 2.3b). The

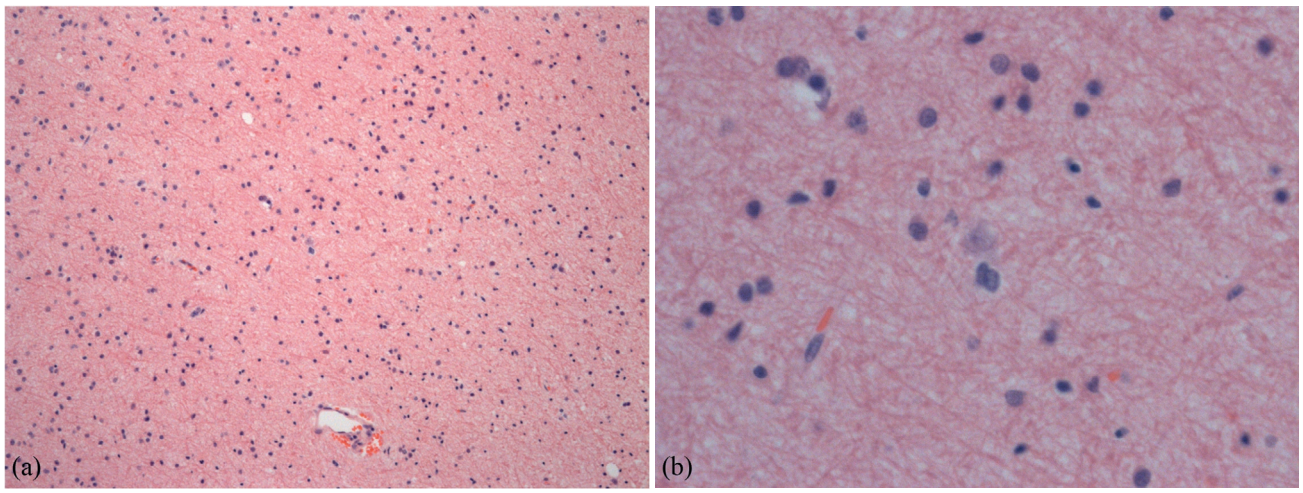

FIGURE 2.1 WHO grade II fibrillary astrocytoma. (a, b) Note the neoplastic astrocytes in a fibrillary matrix, with mildly increased cellularity and pleomorphism. No mitoses or hypervascularity are present. H&E @ 10× and 40×.

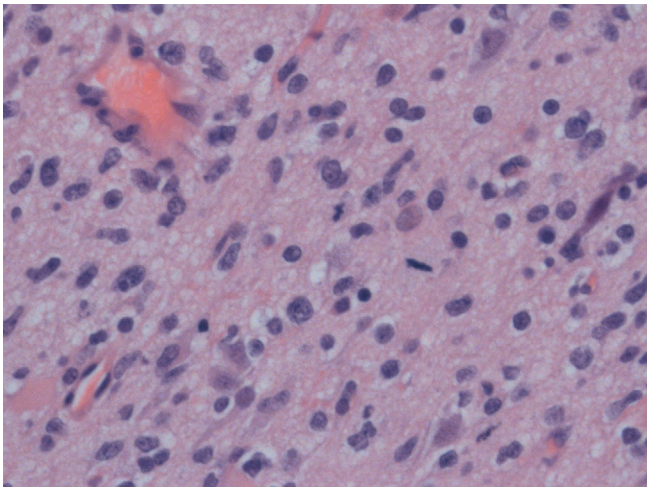

FIGURE 2.2 WHO grade III fibrillary astrocytoma (AA). The tumor is more densely cellular than grade II, with significant cellular and nuclear pleomorphism and atypia. Mitotic figures are evident. H&E @ 40×.

glomeruloid vessels can form undulating garlands that surround necrotic zones in some cases. Necrosis can be noted in large amorphous areas, which appear ischemic in nature, or can appear as more serpiginous regions with surrounding palisading tumor cells (i.e., perinecrotic pseudopalisading; see Figure 2.3c). Necrosis with nuclear pseudopalisading is essentially pathognomonic for GBM. Other features of GBM that are typically prominent include marked cellular and nuclear pleomorphism and atypia, mitotic figures and multinucleated giant cells, and pronounced infiltrative capacity into surrounding brain. Labeling indices with Ki-67 are usually in the range of 15-20%, but can be much higher in some tumors.

Localized Astrocytomas

In the WHO classification, the localized astrocytomas include the pilocytic astrocytoma (WHO grade I), pleomorphic xanthoastrocytoma (PXA; WHO grade II),

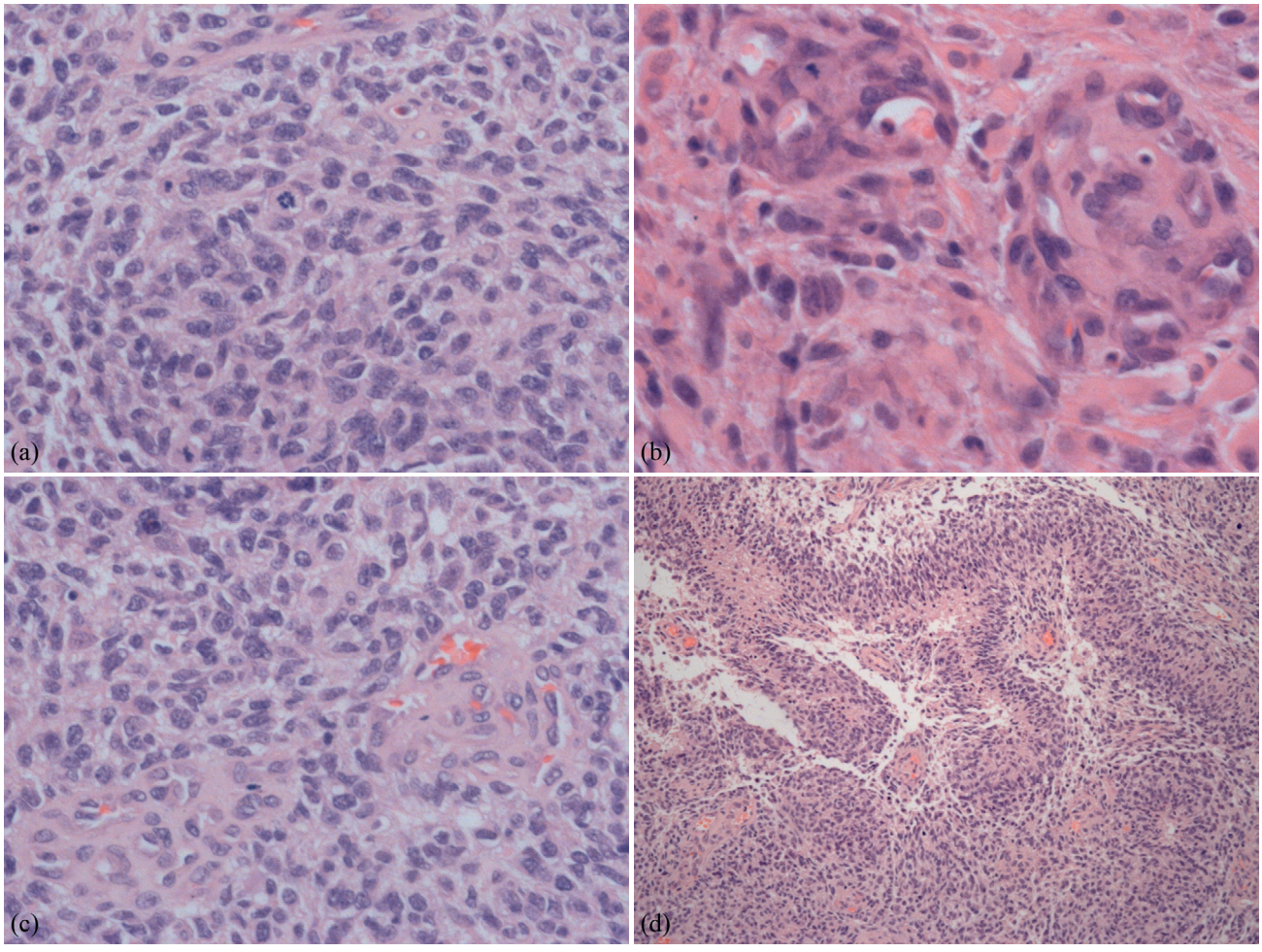

FIGURE 2.3 WHO grade IV fibrillary astrocytoma (GBM). A highly cellular tumor with marked cellular and nuclear pleomorphism, numerous mitoses, giant cells (a, b; H&E @ 400×); dense vascular proliferation (c; H&E @ 40×), and regions of necrosis with pseudopallisading tumor nuclei (d; H&E @ 10×).

and the subependymal giant cell astrocytoma (WHO grade I).[36–39] Pilocytic astrocytomas are slow growing, relatively circumscribed tumors that usually occur in children (peak age 10-12 years) and young adults. These tumors have a predilection for the cerebellum, optic nerves and optic pathways, and hypothalamus. The distinctive histological feature is the presence of cells with slender, elongated nuclei and thin, hair-like (i.e., piloid), GFAP-positive, bipolar processes. These cells are found in a biphasic background, which consists of dense fibrillary regions alternating with loose, microcystic areas. Labeling index studies with Ki-67 report values of 0.5-1.5% in most tumors. The PXA is a supratentorial tumor with a predilection for the superficial temporal lobes that usually occurs in younger patients (mean age 15-18 years) with a longstanding history of seizure activity.[36–39] On histological examination, PXA demonstrates significant pleomorphism, with numerous atypical giant cells and astrocytes with prominent nucleoli.[40] Also present are large foamy (xanthomatous) cells with lipidized cytoplasm that express GFAP. Subependymal giant cell astrocytoma is an indolent, slowly growing tumor that typically arises in the walls of the lateral ventricles and is almost invariably associated with tuberous sclerosis.[36–39]

Oligodendrogliomas and Oligoastrocytomas

Oligodendrogliomas are a form of diffuse glioma that can be of pure or mixed histology and are classified as WHO grade II or III.[36–39] They typically occur in young to middle aged adults (peak age 35-45 years) with a history of seizures, within the white matter of the frontal and temporal lobes. Pure low-grade oligodendroglial tumors (WHO grade II) are characterized histologically by a moderately cellular, monotonous pattern of cells with round nuclei and perinuclear halos (the classic "fried egg" appearance; see Figure 2.4).[41] The perinuclear halos are an artifact of the formalin fixation process of the tumor tissue. Foci of calcification are frequent and can be quite dense in some cases. Delicately branching blood vessels are prominent (i.e., "chicken-wire" vasculature), but do not display endothelial proliferation. Oligodendrogliomas have a pronounced invasive capacity and are known to invade the gray and white matter diffusely, with a strong tendency to form secondary structures of Scherer, in particular perineuronal satellitosis. Mitoses are absent or rare and necrosis is not present. Labeling studies with Ki-67 usually demonstrate indices less than 5%, with a mean of approximately 2%. The diagnosis of an anaplastic oligodendroglioma (WHO grade III) requires the presence of additional histologic features, including a higher degree of cellularity and mitotic activity, vascular endothelial hyperplasia, nuclear pleomorphism, and regions of necrosis (see Figure 2.5a and b). These tumors behave in a more aggressive fashion, with a higher proliferative rate (Ki-67 labeling index > 5%) and capacity for invasion of surrounding brain. Mixed oligoastrocytomas can be classified as WHO grade II or III tumors.[36–39] Distinct populations of neoplastic oligodendroglial cells and astrocytes can be identified within the mass that have similar features to pure versions of the tumor. The percentage of each cell population can be quite variable, with an even mixture of cell types or with one cell type predominating.

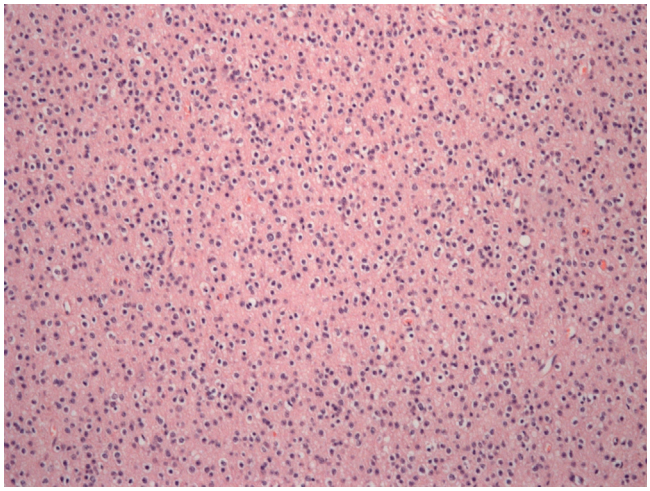

FIGURE 2.4 WHO grade II oligodendroglioma. Demonstrates the classic features of typical oligodendroglioma, with moderate cellularity and numerous round cells with the "fried egg" pattern of perinuclear halos, and delicate "chicken-wire" vasculature. H&E @ 10×.

Advances in molecular neuropathology have begun to clarify the biological underpinnings of variability in response to treatment of oligodendrogliomas.[41–43] The majority of tumors demonstrate genetic losses on chromosome 1p (40-92%) and/or 19q (50-80%). There is a strong predilection for deletions of 1p and 19q to occur together, but in some tumors they can be singular events. Patients with oligodendrogliomas that contain deletions of 1p and 19q are consistently more responsive to irradiation and chemotherapy, and they have an overall median survival of 8-10 years. In contrast, patients with tumors that do not have deletion of 1p and 19q are more resistant to all forms of therapy, and have an overall median survival of only 3-4 years.

Medulloblastoma and Other Embryonal Tumors

Embryonal tumors are a group of aggressive, malignant neoplasms that usually affect children. They are classified by the WHO as grade IV in all cases (see Table 2.5).[36–39] All embryonal tumors share the common features of high cellularity, frequent mitoses, regions of necrosis, and a propensity for metastases along cerebrospinal fluid (CSF) pathways. Medulloblastoma is the most common of the embryonal tumors and is considered a

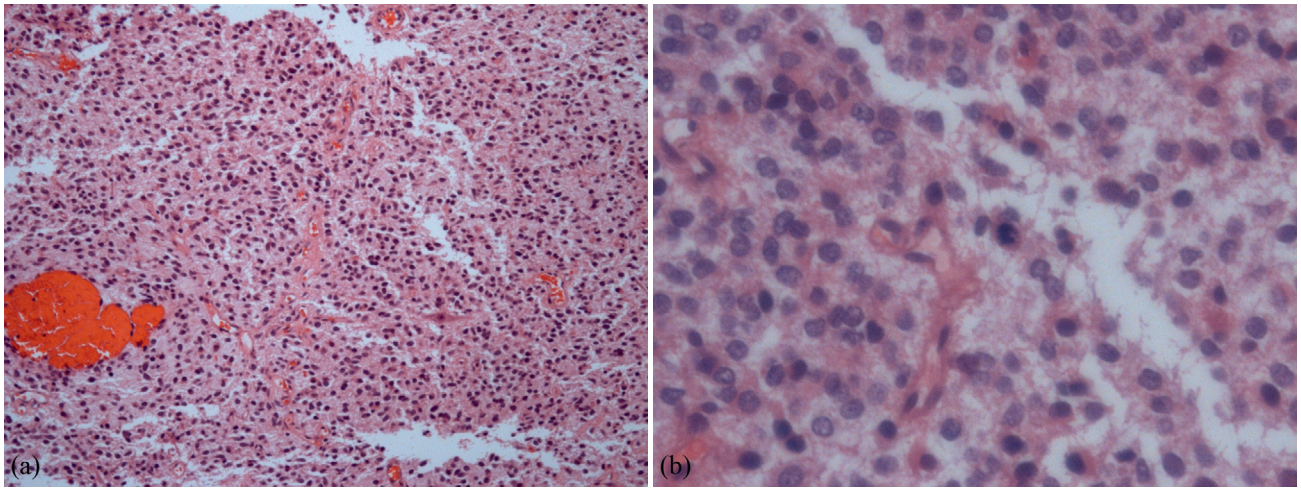

FIGURE 2.5 WHO grade III oligodendroglioma. A more densely cellular tumor with prominent cellular and nuclear pleomorphism, mitotic activity (a), and increased vascularity (b). H&E @ 10× and 40×.

TABLE 2.5 WHO Classification: Embryonal Tumors

Medulloepithelioma
Ependymoblastoma
Medulloblastoma
Desmoplastic medulloblastoma
Large-cell medulloblastoma
Medullomyoblastoma
Melanotic medulloblastoma
Supratentorial primitive neuroectodermal tumor
Neuroblastoma
Ganglioneuroblastoma
Atypical teratoid/rhabdoid tumor

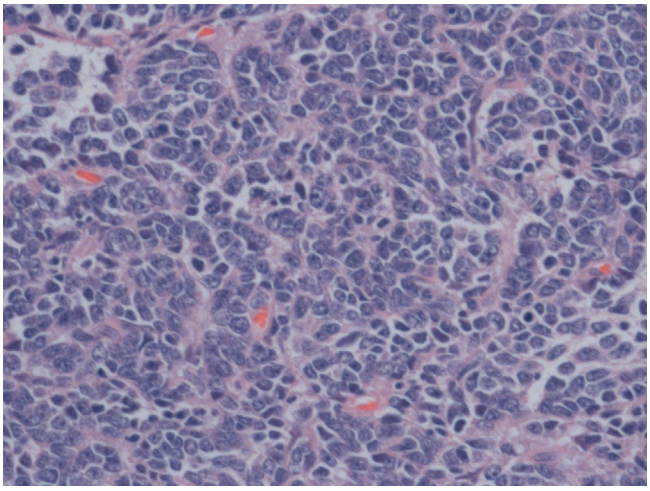

FIGURE 2.6 WHO grade IV medulloblastoma. Note the dense cellularity and presence of undifferentiated cells with hyperchromatic, oval to carrot-shaped nuclei with scant cytoplasm. The nuclei have a tendency to mold against one another. H&E @ 40×.

primitive neuroectodermal tumor of the cerebellum. It usually arises in the midline in children, within the cerebellar vermis, while in adults it is more likely to have an off-center location within the cerebellar hemispheres. The typical medulloblastoma is densely cellular and composed of undifferentiated cells with hyperchromatic, oval to carrot-shaped nuclei with scant cytoplasm (see Figure 2.6).[38,44] The nuclei have a tendency to mold against one another. Mitoses and single cell necrosis are frequently present. Evidence of anaplasia is variable and may include increased nuclear size, abundant mitoses, and the presence of large-cell or similar aggressive cellular morphology. Some tumors may display immunohistochemical and morphological evidence for differentiation along neuronal, glial, or mesenchymal lines. Medulloblastomas are highly proliferative tumors, with Ki-67 labeling indices ranging from 15% to 50%.

Meningioma and Other Tumors of the Meninges

Tumors of the meninges comprise a large and diverse group of neoplasms that mostly have meningothelial or mesenchymal, nonmeningothelial origins (see Table 2.6).[36,37] The most common primary tumor of this group is the meningioma (18-20% of intracranial tumors), which has meningothelial cell origins and is composed of neoplastic arachnoidal cap cells of the arachnoidal villi and granulations. Meningiomas can occur anywhere within the intracranial cavity, but favor the sagittal area along the superior longitudinal sinus, over the lateral cerebral convexities, at the tuberculum sellae and parasellar region, the sphenoidal ridge, and along the olfactory grooves. Numerous histologic variants of meningioma are described and recognized by the WHO (see Table 2.6). However, the histopathological description of most of these variants has no bearing upon the clinical behavior of the tumor. Meningioma subtypes

TABLE 2.6 WHO Classification: Tumors of the Meninges

Tumors of meningothelial cells	
Meningioma	Solitary fibrous tumor
Meningothelial	Fibrosarcoma
Fibrous (fibroblastic)	Malignant fibrous histiocytoma
Transitional (mixed)	Leiomyoma
Psammomatous	Leiomyosarcoma
Angiomatous	Rhabdomyoma
Microcystic	Rhabdomyosarcoma
Secretory	Chondroma
Lymphoplasmocyte-rich	Chondrosarcoma
Metaplastic	Osteoma
Clear cell	Osteosarcoma
Chordoid	Osteochondroma
Atypical	Hemangioma
Papillary	Epithelioid hemangioendothelioma
Rhabdoid	Hemangiopericytoma
Anaplastic meningioma	Angiosarcoma
Mesenchymal, nonmeningothelial tumors	Kaposi sarcoma
Lipoma	*Primary melanocytic lesions*
Angiolipoma	Diffuse melanocytosis
Hibernoma	Melanocytoma
Liposarcoma (intracranial)	Malignant melanoma
	Meningeal melanomatosis

that have a more indolent nature and low risk for aggressive growth or recurrence are classified as WHO grade I, and include the meningothelial, fibrous/fibroblastic, transitional (mixed), secretory, psammomatous, angiomatous, microcystic, lymphoplasmocyte-rich, and metaplastic variants.[45,46] Of this group, the meningothelial, fibrous, and transitional variants are most frequently diagnosed. The histological features common to most low-grade meningiomas are the presence of whorls (tightly wound, rounded collections of cells), psammoma bodies (concentrically laminated mineral deposits that often begin in the center of whorls), intranuclear pseudoinclusions (areas in which pink cytoplasm protrudes into a nucleus to produce a hollowed-out appearance), and occasional pleomorphic nuclei and mitoses (see Figure 2.7).[45,46] Meningothelial meningiomas are composed of lobules of typical meningioma cells, with minimal whorl formation. The tumor cells are uniform in shape, with oval nuclei that may show central clearing. Fibrous variants have spindle-shaped cells resembling fibroblasts that form parallel and interlacing bundles within a matrix of collagen and reticulin.

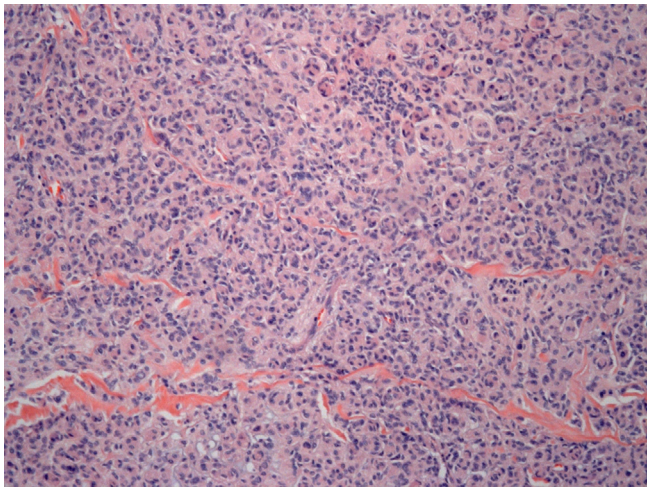

FIGURE 2.7 WHO grade II meningioma. The tumor demonstrates a moderately dense, uniform pattern of cells with oval shaped nuclei and the presence of many cellular whorl patterns. H&E @ 10×.

Meningioma subtypes that are more likely to display aggressive clinical behavior and to recur are classified by the WHO as grade II (atypical, clear cell, chordoid) and grade III (rhabdoid, papillary, anaplastic).[36,37,45,46] On histological examination, all of the grade II tumors are likely to demonstrate increased cellularity, more frequent mitoses, diffuse or sheet-like growth, nuclear pleomorphism and atypia, and evidence for micronecrosis. Grade III tumors, such as anaplastic meningioma, show features consistent with frank malignancy, including a high mitotic rate, advanced cytological atypia, nuclear pleomorphism, and necrosis (see Figure 2.8). Invasion of underlying brain is frequently noted in grade III meningiomas, but can also occur in lower grade variants. Proliferation studies using Ki-67 demonstrate labeling indices ranging from 8% to 15%.

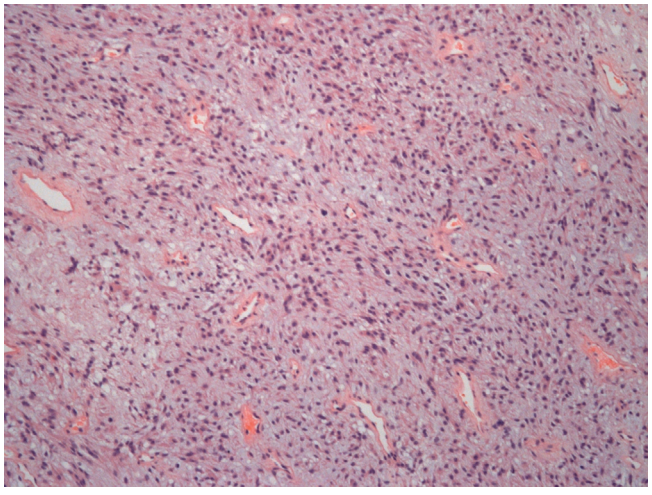

FIGURE 2.8 WHO grade III anaplastic meningioma. This view demonstrates increased nuclear pleomorphism and scattered mitoses. H&E @ 10×.

Primary Central Nervous System Lymphoma

Primary CNS lymphomas (PCNSLs) are malignant tumors classified as WHO grade IV, that affect adults in the sixth and seventh decade of life.[36,37] They are often multifocal and usually arise in the deep supratentorial white matter, with a predilection for the periventricular region and basal ganglia. PCNSL are composed of a clonal expansion of neoplastic lymphocytes, typically of the diffuse, large cell or immunoblastic variety. In 95% of the tumors, the cells have a B-cell lineage, often with monoclonal IgM kappa production. On histological examination, PCNSL display a perivascular cellular orientation, with expansion of vessel walls and reticulin deposition (see Figure 2.9).[47] Regions of necrosis are common, especially if steroids have been administered prior to the biopsy. The lymphomatous cells are noncohesive and usually have large, irregular nuclei, prominent nucleoli, and scant cytoplasm. From the perivascular region, tumor cells are noted to invade the surrounding brain parenchyma, either in compact cellular aggregates or as singly infiltrating tumor cells. PCNSL are highly proliferative tumors, with Ki-67 labeling indices ranging from 20% to 50% in most studies. The diagnosis can be confirmed by immunohistochemical positivity for leukocyte common antigen (CD45) and specific B-cell markers (CD19, CD20, and CD79a).

SURGICAL THERAPY OF PBT

Surgical intervention is the most common form of treatment for PBT and is an important aspect of initial therapy in most patients. Indications for surgery include reduction of tumor burden, alleviation of mass effect, control of seizures and reversal of neurological deficit, confirmation of the histological diagnosis, diversion of CSF by shunting procedures in selected cases, and the introduction of local antineoplastic agents.[1,48,49] Recent advances in neurosurgical technology offer new approaches to tumor removal, such as frame-based and frameless stereotactic biopsy, preoperative functional MRI and intraoperative cortical mapping, neuronavigation and tumor resection in the awake patient, and the use of intraoperative MRI.[50–52] These techniques allow the surgeon to more carefully delineate tumor margins and to preserve surrounding regions of eloquent brain (e.g., Broca's area, primary motor cortex) and delicate vascular structures, while performing a more aggressive and thorough tumor resection. Complete removal of benign tumors such as meningioma, pilocytic astrocytoma, and schwannomas can be curative. For malignant tumors (i.e., GBM, AA), although the lack of a prospective, controlled randomized clinical trial still fosters debate in the literature, most neurosurgeons recommend a near-total or gross-total resection, whenever possible, of all enhancing tumor volume and regionally infiltrated brain as defined on T2-weighted or FLAIR MRI sequences. Gross-total tumor resection is not curative for these tumor types, but has been associated with longer overall and progression-free survival in several studies, as well as improved neurological quality of life.[53,54] For tumors that are diffusely infiltrative or multifocal, a stereotactic biopsy is more likely to preserve neurological function than an attempt at resection and, in most cases, will be able to provide a histological diagnosis to guide further treatment. The accuracy of stereotactic biopsy is further improved when the region of interest is defined by contrast enhancement on MRI or abnormal signal on MRI spectroscopy or positron emission tomography.

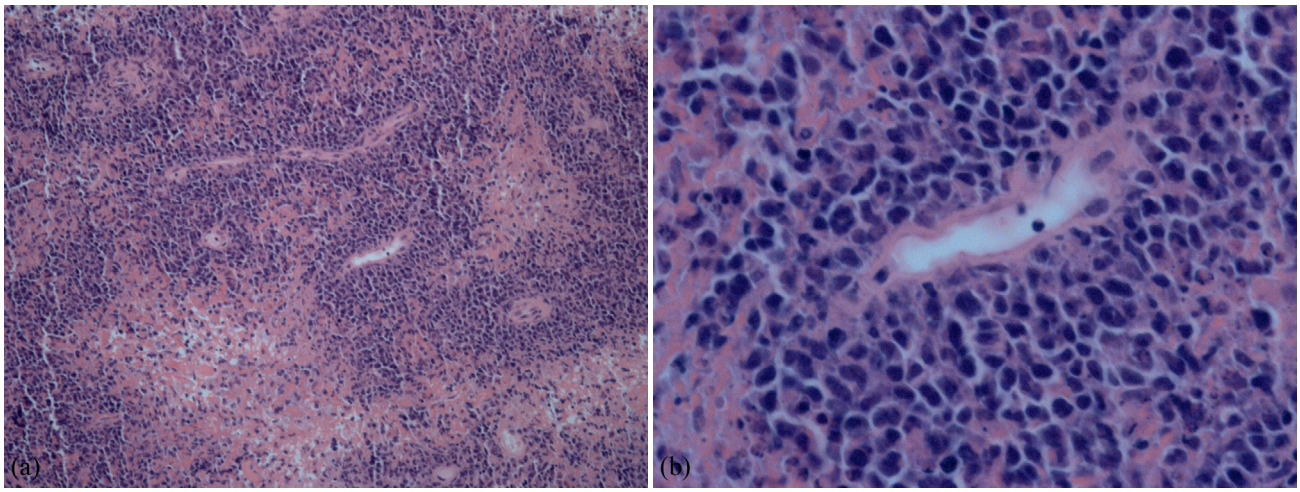

FIGURE 2.9 WHO grade IV primary CNS lymphoma (PCNSL). Note the presence of neoplastic lymphocytes in an angiocentric growth pattern, with nuclear pleomorphism and mitoses (a, b). H&E @ 10× and 40×.

RADIATION THERAPY OF PBT

External beam fractionated radiation therapy is an appropriate form of treatment for virtually all patients with high-grade gliomas (i.e., GBM, AA, AO, medulloblastoma) as well as for selected low-grade PBT that are surgically inaccessible or have progressed following initial resection.[1,55–58] Numerous randomized controlled trials have demonstrated a survival benefit for high-grade glioma patients receiving surgical resection and irradiation in comparison to resection alone (approximately 34-38 weeks vs. 14-18 weeks, respectively). The mechanism of cell death appears to be the production of DNA strand damage by ionizing radiation and the generation of highly reactive oxygen radicals that induce further DNA damage and disrupt cellular processes. Sublethal or mortal damage to endothelial cells in tumor vessels may also be of importance. The standard approach is administered in the early postoperative phase and initially uses conformal radiation ports that encompass the T2-weighted target with a margin of 1-3 cm, using a dose of approximately 4500-4700 cGy in 180-200 cGy daily fractions. After this portion has been completed, a "cone down" is performed, targeting the T1-weighted contrast-enhancing volume of the tumor with a 1-3 cm margin, bringing the total dose to approximately 6000 cGy. Irradiation is performed over the course of 6-7 weeks, with the patient receiving treatment 5 days per week. Radiation therapy schedules can sometimes be modified with hypofractionation and/or an abbreviated treatment course for elderly patients or for those with a low performance status, while maintaining a similar level of toxicity and overall survival.[59,60] More aggressive approaches to irradiation using hyperfractionation schemes have not been shown to improve tumor control and, in some reports, have been associated with worse outcomes.[56,57] Other techniques to increase localized radiation doses to the tumor resection cavity, such as brachytherapy with permanent or temporary radioactive seeds, have also had disappointing results in controlled trials.[61] In addition to the cranial dosage, spinal-axis RT is necessary for tumors that often seed the meninges, such as medulloblastoma, pineoblastoma, and anaplastic ependymoma.

Stereotactic radiosurgery (SRS), using a linear accelerator-based system (e.g., Cyberknife®) or a Co^{60}-based system (e.g., Gamma Knife®) to deliver a single (or a few) high-dose radiation fraction(s) to a defined volume using stereotactic localization, is another method to boost radiation doses in the tumor bed of a newly diagnosed or recurrent glioma, while sparing normal surrounding tissues.[62–64] Because of the diffuse, infiltrative nature of the growth pattern of these tumors, the application of focal treatment modalities such as radiosurgery remains controversial. Retrospective and single-armed, uncontrolled prospective trials suggest an improvement in local tumor control rates and survival when using either radiosurgical system. However, these results were not confirmed in the randomized, controlled trial of radiosurgery for GBM reported by the Radiation Therapy Oncology Group (RTOG 93-05).[64,65] In this study, 203 GBM patients were randomized to receive radiosurgery followed by conventional irradiation (60 Gy) and intravenous carmustine chemotherapy ($80\ mg/m^2/day \times 3$ days every 8 weeks) or irradiation plus chemotherapy alone. The median survival for the radiosurgical and conventional treatment groups were 13.5 months and 13.6 months, respectively ($p = 0.5711$). In addition, the 2- and 3-year survival rates and patterns of failure were similar between groups. There was no difference in general quality of life or retention of cognitive function between groups.

CHEMOTHERAPY OF PBT

Chemotherapy is used as an adjunctive treatment for malignant PBT (i.e., mostly high-grade gliomas—GBM, AA) and for selected low-grade gliomas that progress through initial surgical resection and irradiation.[1,66–69] The addition of chemotherapy has resulted in modest improvements in survival of patients with malignant glioma, as demonstrated by two detailed meta-analyses.[70,71] Over the past two decades and until recently, nitrosourea alkylating drugs such as carmustine and lomustine (BCNU and CCNU, respectively), were considered the most effective chemotherapeutic agents for these tumors.[66,67] Other agents with mild activity included procarbazine (administered alone or in combination with CCNU and vincristine; i.e., PCV), cisplatin, etoposide, carboplatin, and cyclophosphamide. For the treatment of PCNSL, methotrexate has been shown to be the most active agent, either alone or in combination with other drugs (e.g., cytarabine, rituximab).[72]

Over the past decade, the focus has been on the second-generation alkylating agent, temozolomide (TZM), which has an activity profile superior to nitrosoureas and other agents. TZM is an imidazotetrazine derivative of the alkylating agent dacarbazine, with activity against systemic and CNS malignancies.[66,67,73–76] The drug undergoes chemical conversion at physiological pH to the active species 5-(3-methyl-1-triazeno)imidazole-4-carboxamide (MTIC). TZM exhibits schedule dependent antineoplastic activity by interfering with DNA replication through the process of methylation. The methylation of DNA is dependent upon formation of a reactive methyldiazonium cation, which interacts with DNA at the following sites: N^7-guanine (70%), N^3-adenine (9.2%), and O^6-guanine (5%). Because TZM

is stable at acid pH, it can be taken orally in capsules. Oral bioavailability is approximately 100%, with rapid absorption of the drug. In addition, TZM has excellent penetration of the blood-brain barrier and brain tumor tissue.

Initial studies of TZM were in patients with recurrent AA and GBM, and suggested significant activity.[66,67,73–76] Subsequent larger studies demonstrated unequivocal efficacy in the recurrent setting. The first study evaluated the use of TZM (150-200 mg/m^2/day × 5 days every 28 days) in a series of 162 patients with recurrent malignant gliomas, including 97 patients with AA.[77] In the AA cohort, there were 6 patients with CR, 27 with PR, and another 31 with stable disease (CR + PR + SD = 66%). The response rate was similar in patients that had failed prior chemotherapy or were chemotherapy-naïve. Median overall PFS was 5.4 months, with 6- and 12-month PFS rates of 46% and 24%, respectively. The median overall survival was 13.6 months, with 6- and 12-months survival rates of 75% and 56%, respectively. A similar comparative Phase II trial evaluated the activity of TZM versus procarbazine (125-150 mg/m^2/day × 28 days every 8 weeks) in a cohort of 225 patients with GBM at first relapse.[78] Overall response rates (PR + SD) were significantly higher for patients in the TZM cohort (45.6% vs. 32.7%; $p = 0.049$). Treatment with TZM resulted in a significant improvement in median PFS (12.4 weeks vs. 8.32 weeks; $p = 0.0063$) and 6-month PFS (21% vs. 8%; $p = 0.008$) in comparison to procarbazine. In addition, the 6-month overall survival rate was significantly higher for patients in the TZM arm of the study (60% vs. 44%; $p = 0.019$).

TZM has also been applied to GBM patients in the "up-front" setting by Stupp and colleagues in a set of Phase II and III studies, in combination with standard external beam irradiation and monthly adjuvant chemotherapy.[66,67,79,80] For the Phase III study, a total of 573 patients were randomly assigned to receive radiation alone (6000 cGy; 200 cGy/day × 5 days/week for 6 weeks) or radiotherapy in combination with daily TZM (75 mg/m^2/day × 7 days/week for 6 weeks).[50] After the completion of irradiation, each patient in the chemotherapy arm went on to receive six cycles of adjuvant single-agent TZM (150-200 mg/m^2/day × 5 days, every 28 days). The overall median survival was 14.6 months for the radiotherapy plus TZM cohort and 12.1 months for the cohort that received irradiation alone, for an overall median survival benefit of 2.5 months. The unadjusted hazard ratio for death due to the GBM for the radiotherapy plus TZM cohort was 0.63 ($p < 0.001$, log-rank test). The 2-year survival rate was 26.5% for the chemoradiation cohort and 10.4% for the cohort receiving radiotherapy alone. Responsiveness to chemoradiation and overall survival were found to correlate strongly with the presence of promoter methylation of the methyl-guanine-methyl-transferase (MGMT) gene, which is important for tumor cell resistance to radiotherapy and chemotherapy. Since the publication of this report, chemoradiation using low-dose TZM, followed by adjuvant monthly TZM, has become FDA approved and is now the "standard of care" for newly diagnosed GBM patients in the United States and around the world. In a 5-year follow-up of this cohort of patients, Stupp and colleagues report a persistent and significant difference in survival between the group of patients that received radiotherapy and TZM versus the group that received radiotherapy alone.[81] For the chemoradiation group, overall survival at 4 and 5 years was 12.1% and 9.8%, respectively. In contrast, the radiotherapy alone group had 4 and 5 year overall survivals of 3.0% and 1.9%, respectively. The differences in overall survival were highly significant, with a hazard ratio of 0.60 ($p < 0.0001$). Methylation of the MGMT promoter region was still a very strong predictor of response to TZM chemotherapy.

Dose intensive or dose dense schedules of TZM (e.g., 7 days on/7 days off, 3 weeks on/1 week off) have also been under investigation, since laboratory studies suggest that the higher cumulative dose may result in improved efficacy through augmented depletion of MGMT in tumor cells.[82] This premise was tested by the Radiation Therapy Oncology Group (RTOG), in the RTOG-0525 Phase III trial, in a cohort of 833 patients with newly diagnosed GBM.[83] Patients were treated with standard surgical resection and chemoradiation, and then randomized to receive either conventional TZM (5 days per month; 150-200 mg/m^2/day) or dose dense TZM (21 days on/7 days off; 75-100 mg/m^2/day), for a total of 6-12 cycles. The two treatment groups were not statistically different at final analysis in terms of median overall survival (16.6 vs. 14.9 months; HR = 1.03) or median progression-free survival (5.5 vs. 6.7 months; HR = 0.87). MGMT promoter methylation was associated with improved overall survival (21.2 vs. 14 months; HR = 1.74), progression-free survival (8.7 vs. 5.7 months; HR = 1.63), and response rate.

Angiogenesis is a tightly controlled process that involves growth and maintenance of blood vessels within tissues and organs.[84–87] A delicate equilibrium exists between positive angiogenic factors (e.g., vascular endothelial growth factor [VEGF], transforming growth factor-β [TGF-β]), and inhibitory factors (e.g., thrombospondin-1 [TSP-1], angiostatin, endostatin).[84–87] These factors interact with specific receptors on endothelial cells and the extracellular matrix, such as VEGF receptor-1 (VEGFR-1), VEGFR-2, VEGFR-3, TIE1, and TIE2.[86] There are several important stimuli for conversion to the angiogenic phenotype in GBM. The presence of hypoxia induces upregulation of secretion of VEGF and expression of VEGFR's in tumor endothelial cells

and surrounding regional vasculature.[86] Another critical element for the switch to the angiogenic phenotype is overactivity of the major growth factor signaling pathways and loss of certain tumor suppressor genes.[88] Overexpression and excessive activity of platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor, Ras, TGF-α, and TGF-β are critical to the development of the angiogenic phenotype.[89–91] In addition to growth factor activity, internal signal transduction mediators also appear to play a role in the angiogenic phenotype. The PI3K/Akt/PTEN signaling pathway is involved in the regulation of angiogenesis through the control of expression of VEGF, hypoxia-inducible factor-1, and TSP-1.[92–94]

Numerous investigators have begun to focus on treatment approaches that capitalize on the prominence of VEGF signaling in solid tumor angiogenesis.[95] The most promising approaches include monoclonal antibodies against VEGF (e.g., bevacizumab) and VEGFR (e.g., IMC-1C11, DC101).[88,95–97] Bevacizumab (Avastin™) has advanced the furthest in terms of preclinical evaluation and clinical trials.[98,99] Bevacizumab is a humanized IgG_1 monoclonal antibody that is specific for all isoforms of VEGF, preventing their binding to VEGFR. It has demonstrated significant activity in preclinical studies against a wide variety of solid tumors, including gliomas, as a single agent and in combination with conventional chemotherapy.[100–102]

The first report of the use of bevacizumab for brain tumor patients was by Stark-Vance in 2005, who treated 21 patients with malignant gliomas, in combination with irinotecan.[103] The response rate was an impressive 43%, although there were two treatment-related deaths (intracranial hemorrhage, intestinal perforation). Based on this promising preliminary work, Vredenburgh and colleagues organized a prospective Phase II trial of bevacizumab and irinotecan for patients with recurrent malignant gliomas.[104] Thirty-two patients were enrolled (GBM 23; anaplastic tumors 9) and received intravenous bevacizumab (10 mg/kg) and irinotecan (340 mg/m^2 on EIAED, 125 mg/m^2 not on EIAED) every 2 weeks. Radiographic responses were noted in 20 of 32 patients (63%; CR 1, PR 19), including 14 of 23 in the GBM cohort and 6 of 9 in the anaplastic glioma subgroup. The median overall PFS was 23 weeks; 20 weeks in GBM patients and 30 weeks in patients with anaplastic tumors. The 6-month PFS and overall survival rates were 38% and 72%, respectively. In updated reports from 68 patients (GBM 35; anaplastic tumors 33) the MRI response rate was similar (59%).[105,106] For the GB cohort, the 6-month PFS was 46%, with a 6-month overall survival of 77%. For the anaplastic glioma subgroup, the 6-month PFS rate was 61%, with a median PFS of 42 weeks. Eight patients were taken off study for thrombotic complications, including pulmonary emboli (4), deep venous thrombosis (2), thrombotic thrombocytopenic purpura (1), and thrombotic stroke (1). The preliminary use of bevacizumab and irinotecan at other institutions resulted in similar results in terms of MRI response rates, time to progression, and overall survival.[102,107–111] The Duke group has also performed a Phase II study of bevacizumab and irinotecan that was restricted to only patients with recurrent grade III gliomas (25 AA, 8 AO).[112] There were two cohorts of patients: the first group of nine patients received the standard combination regimen every 2 weeks, while the second group received bevacizumab (15 mg/kg every 3 weeks) and irinotecan (days 1, 8, 22, 29 of each cycle; 340 mg/m^2 on EIAED, 125 mg/m^2 on NEIAED) on a 6-week cycle. Objective responses were noted in 29 patients (61% with at least a PR). The 6-month PFS and overall survival rates were 55% and 79%, respectively. There was no difference in PFS or survival rates between the two treatment cohorts. Although bevacizumab has been well tolerated by the majority of patients, severe toxicity can occur, including hypertension, proteinuria, arterial and venous thromboembolic events, hemorrhage, gastrointestinal perforation, and impaired wound healing.[113]

The results of the BRAIN trial were reported by Friedman and colleagues in 2009.[102,114] This study was a Phase II, multicenter, open-label, noncomparative trial evaluating the efficacy of bevacizumab, alone or in combination with irinotecan, in a group of 167 patients with GBM in first or second relapse. Patients were randomly assigned to receive bevacizumab (10 mg/kg) as a single agent, or in combination with irinotecan (340 mg/m^2 or 125 mg/m^2, depending on EIAED or NEIAED), on a schedule of every 2 weeks. The primary endpoints for the study were 6-month PFS and objective response rate on follow-up MRI, with secondary endpoints of safety and overall survival. The 6-month PFS rates in the bevacizumab alone and bevacizumab plus irinotecan groups were 42.6% and 50.3%, respectively. Objective response rates on follow-up MR imaging were 28.2% for the bevacizumab alone cohort and 37.8% for the bevacizumab plus irinotecan group. Median PFS times for the bevacizumab alone and bevacizumab plus irinotecan cohorts were 4.2 months and 5.6 months, respectively. The overall survival times were also similar between the single-agent bevacizumab and bevacizumab plus irinotecan groups (9.2 months vs. 8.7 months). There was a trend for patients on corticosteroids at the beginning of the trial to remain on stable or decreasing doses over time.[115] Grade 3 or 4 toxicity was more frequent in the bevacizumab plus irinotecan group (65.8%) in comparison to those receiving bevacizumab alone (46.4%). The most common adverse events were hypertension, fatigue, neutropenia, and seizures. Intracranial hemorrhage was uncommon in both groups (2.4% bevacizumab

alone, 3.8% bevacizumab plus irinotecan; five total patients, only one was grade 4). The authors concluded that bevacizumab, alone or in combination with irinotecan, was active against recurrent GBM, with 6-month PFS rates that were far superior to the expected 15% rate for salvage chemotherapy and irinotecan alone.

Clinicians have begun to evaluate the safety and feasibility of using bevacizumab in combination with TZM during chemoradiation in newly diagnosed patients with high-grade gliomas.[102,116,117] An early pilot study of bevacizumab (10 mg/kg every 2 weeks) in combination with TZM (75 mg/m^2 during irradiation, followed by 150-200 mg/m^2 × 5 days every 4 weeks) was performed by Lai and colleagues in 10 patients with newly diagnosed GBM.[116] The toxicity was considered to be acceptable, and consisted of fatigue, myelotoxicity, wound breakdown, DVT/PE (deep venous thrombosis/pulmonary embolus), and one case of radiation-induced optic neuropathy. Preliminary efficacy analysis suggested an encouraging mean PFS (range 15-45 weeks). A similar feasibility study from Narayana *et al.* evaluated 15 patients with high-grade glioma, with the adjuvant therapy phase planned over 1 year (TZM 150 mg/m^2/day).[117] Thirteen patients (86.6%) completed the entire year of adjuvant treatment; radiographic responses were noted in 13 of 14 assessable patients (92.8%). The 1-year PFS and overall survival rates were 59.3% and 86.7%, respectively. Using a more aggressive approach, Vredenburgh *et al.* treated 75 patients with newly diagnosed GBM with standard chemoradiation plus bevacizumab (10 mg/kg every 2 weeks), followed by adjuvant TZM (200 mg/m^2 × 5 days every month) in combination with bevacizumab and irinotecan (340 mg/m^2 on EIAED, 125 mg/m^2 on NEIAED) every 2 weeks.[118] The median PFS for the entire cohort was 14.2 months, with a median overall survival of 21.2 months. At 16-month follow-up, the overall survival rate was 65%. Another recent update by the Duke group reports the results from 125 newly diagnosed GBM patients who were treated with standard chemoradiation and TZM, in addition to bevacizumab (10 mg/kg IV every 2 weeks).[119] Overall, the combination of TZM and bevacizumab was tolerated well in the majority of patients, with 96% completing the full course of chemoradiation, and 90% able to continue on with treatment into the adjuvant chemotherapy phase. Toxicities associated with treatment discontinuation included pulmonary emboli, CNS hemorrhage, pancytopenia, wound dehiscence, and colonic perforation.

Based on these intriguing preliminary studies, two large Phase III clinical trials were performed to determine the impact of adding bevacizumab to standard chemoradiation with TZM in newly diagnosed GBM patients. The first study was the Avastin in Glioblastoma trial (AVAglio), an international effort based mainly in Europe, which enrolled 921 patients and randomly assigned them to receive either bevacizumab (10 mg/kg every 2 weeks) or placebo, plus standard radiotherapy and concomitant TZM.[120] The coprimary end points of the study were progression-free survival and overall survival. After chemoradiation was completed, patients then received either bevacizumab or placebo every 2 weeks, along with adjuvant TZM (150-200 mg/m^2/day) for up to six cycles. After the completion of adjuvant TZM, patients would then continue with single-agent bevacizumab (15 mg/kg every 3 weeks) or placebo until disease progression or unacceptable toxicity. The median progression-free survival was longer in the bevacizumab group than in the placebo group (median 10.6 months vs. 6.2 months; HR = 064; $p < 0.001$). Overall survival was not significantly different between the groups (median 16.8 months vs. 16.7 months; HR = 0.88; $p = 0.10$). The overall survival rates of the bevacizumab and placebo groups were 72.4% and 66.3% at 1 year ($p = 0.049$) and 33.9% and 30.1% at 2 years ($p = 0.24$), respectively. Health-related QoL and performance status were maintained longer in the bevacizumab group; in addition, patients required a lower dose of corticosteroids. The other Phase III trial was the RTOG 0825 study, which enrolled and randomized 637 patients with newly diagnosed GBM; it had a similar design and treatment groups to the AVAglio study, except that during the adjuvant treatment phase, patients could continue TZM for up to 12 cycles.[121] There was no difference between the bevacizumab and placebo groups in terms of overall survival (median 15.7 months vs. 16.1 months; HR = 1.13). The progression-free survival was longer for the bevacizumab cohort (median 10.7 months vs. 7.3 months; HR = 0.79), but was not considered significant because it did not reach the prespecified improvement target. During the course of the study, the bevacizumab group showed an increased symptom burden, worse QoL, and a decline in neurocognitive function in comparison to the placebo group.

MOLECULAR OR "TARGETED" TREATMENT

As noted above, conventional chemotherapeutic approaches to treatment for malignant glioma are not predicated on the biology of the malignant phenotype. It has become apparent that the transformed phenotype of brain tumor cells is highly complex and results from the dysfunction of a variety of inter-related regulatory pathways.[122,39,124] The transformation process involves amplification or overexpression of oncogenes in combination with loss or lack of expression of tumor suppressor genes. Oncogenes and signal transduction molecules

that have been demonstrated to be important for gliomagenesis include PDGF and its receptor (PDGFR), EGF and EGFR, CDK4, mdm-2, Ras, phosphoinositol-3 kinase (PI3K), Akt, and mTOR (mammalian target of rapamycin). Tumor suppressor genes of importance in glial transformation include p53, retinoblastoma, p16 and p15 (i.e., INK4a, INK4b), DMBT1, and PTEN. Most of these tumor suppressor genes function as negative regulators of the cell cycle, while others are inhibitors of important internal signal transduction pathways. The net effect of these acquired abnormalities is dysregulation of, and an imbalance between, the activity of the cell cycle and apoptotic pathways.

Because the survival of patients with high-grade gliomas has remained so poor using conventional chemotherapeutic approaches, new treatment modalities are being investigated that have a more molecular, "targeted" mechanism of action, with the ability to overcome the transformed phenotype.[88,89,125–127] Recent advances in growth factor and signal transduction biology are now providing the background for the development of "molecular therapeutics," a new class of drugs that manipulate and exploit these pathways. Molecular drugs targeting critical signal transduction pathway effectors, such as PDGFR, EGFR, Ras, PI3K, and mTOR, have entered clinical trials in brain tumor patients.[88,89,125–127] To date, numerous drugs have been tested in Phase I, II, and III trials, designed to target various key receptors, signal transduction proteins, and cell membrane-related proteins such as EGFR (gefitinib, erlotinib, cetuximab), PDGFR (imatinib), Ras (tipifarnib, lonafarnib), mTOR (temsirolimus), integrins (cilengitide), and protein kinase C (enzastaurin) as well as multi-kinase drugs (e.g., lapatinib) that can target combinations of the above. Preliminary results suggest only modest activity against recurrent high-grade gliomas when used as single agents. Current and subsequent clinical trials will investigate using molecular drugs in combination with conventional chemotherapeutic agents (e.g., TZM, hydroxyurea), with other molecular drugs that target different signal transduction pathways, and with irradiation.

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CHAPTER

3

Overview of Epidemiology, Pathology, and Treatment of Metastatic Brain Tumors

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CHAPTER CONTENTS

In this chapter, we will provide an overview of the epidemiology, classification, pathology, and treatment of the common metastatic brain tumors (MBTs). MBTs arise in 20-40% of all adult cancer patients and are the most common complication of systemic neoplastic disease.[1–5] They will be diagnosed in approximately 150,000-170,000 patients this year in the United States and are associated with significant morbidity and mortality. Of the estimated 8.3-11 patients per 100,000 population that will develop a MBT this year, more than 75% will have underlying primary tumors of the lung, breast, and skin (i.e., melanoma) (see Table 3.1). However, virtually any primary tumor has the potential to metastasize to the brain.

EPIDEMIOLOGY OF MBTs

Brain metastases are the most common complication of systemic cancer, with estimated incidence rates of 8.3-11 cases per 100,000 population.[1–6] Hospital and autopsy-based studies estimate that these tumors develop in 20-40% of all adult cancer patients, which corresponds to approximately 150,000-170,000 new cases per year in the United States. However, other reports using population-based estimates would suggest a lower incidence of MBT, in the range of 10%.[7] The presence of a MBT does not always correlate with clinical sequelae; it is estimated that only 60-75% of patients with a MBT will become symptomatic. The frequency of MBT

TABLE 3.1 Primary Sites of Metastatic Brain Tumors (MBTs)

Primary Tumor	Percentage (%)
Lung	50-60
Squamous cell	25-30
Adenocarcinoma	12-15
Small cell	10-13
Large cell	2
Breast	15-20
Melanoma	5-10
Gastrointestinal	4-6
Genitourinary	3-5
Unknown	4-8
Other	3-5

Data compiled from Refs. 1–6.

appears to be rising due to more successful systemic treatment and longer patient survival, earlier detection and implementation of therapy, and improved imaging techniques. MBT most often arise from primary tumors of the lung (50-60%), breast (15-20%), melanoma (5-10%), and gastrointestinal tract (4-6%).[1–6] Empiric screening of patients with newly diagnosed non-small lung cancer identify MBT in 3-10% of cases.[6] However, MBT can develop from virtually any systemic malignancy, including primary tumors of the prostate, ovary and female reproductive system, kidney, esophagus, soft tissue sarcoma, bladder, and thyroid.[8–17] In addition, between 10% and 15% of patients will develop MBT from an unknown primary.[5,6,18] Autopsy studies in adults would suggest that melanoma (20-45% of patients) has the most neurotropism of all primary tumors; however, small-cell lung carcinoma, renal carcinoma, breast, and testicular carcinoma also have a strong propensity for spread to the brain.[5,6] Tumors with a low degree of neurotropism include prostate, gastrointestinal tract, ovarian, and thyroid malignancies. In children and young adults, MBT arise most often from sarcomas (e.g., osteogenic, Ewing's), germ cell tumors, and neuroblastomas.[5,6,19] In 65-75% of patients, two or more metastatic tumors will develop simultaneously and be present at the time of cancer diagnosis. Single brain metastases are less common, and are most often noted in patients with breast, colon, and renal cell carcinoma. Patients with malignant melanoma and lung carcinoma are more likely to have multiple metastatic lesions.

The prognosis for patients with MBT is quite poor and is dependent on the histological tumor type, number and size of the metastatic lesions, neurological status, and degree of systemic involvement. Overall, the presence of a MBT is associated with high morbidity and mortality, with approximately one-third of all patients dying from the brain tumor.[1,5,6] The natural history is such that, left untreated, patients with MBT will usually die of neurological deterioration within 4 weeks. The addition of steroids will typically extend survival to 8 weeks. External beam radiotherapy, the most common modality of treatment, can further extend survival to 12-20 weeks in many patients.[1,2,5,6] However, survival is also dependent on the type of primary malignancy, as shown in the report by Hall and colleagues.[20] In their study, the overall 2-year survival rate for patients with MBT was 8.1%, with a range from 1.7% in patients with small-cell lung carcinoma, up to 23.9% for those with ovarian cancer. Several studies have assessed how various prognostic factors relate to MBT patients at the time of diagnosis. A recursive partitioning analysis (RPA) of three Radiation Therapy Oncology Group (RTOG) trials by Gaspar and coworkers evaluated a wide range of prognostic factors and their impact on patient survival.[21] The most important favorable factors were younger age (younger vs. older than 65 years; $p < 0.0001$), higher Karnofsky Performance Status (KPS) score (greater or less than 70; $p < 0.0001$), and limited extent of systemic disease (controlled vs. widespread disease; $p < 0.0001$). Using these criteria, patients could be grouped into three distinct classes. Class 1 included patients who were less than 65 years of age, had KPS scores greater than 70, and had well-controlled systemic disease; Class 3 consisted of all patients with KPS scores less than 70; while Class 2 included all other patients who did not fit into Class 1 or Class 3. The median overall survival varied significantly between groups: 28.4 weeks for patients in Class 1, 16.8 weeks for those in Class 2, and 9.2 weeks for Class 3 patients. In addition, by univariate analysis, patients with multiple MBT had a significantly reduced survival compared to that of those with solitary lesions ($p = 0.021$).

In a similar study by Nussbaum and colleagues, the number of metastatic lesions present at diagnosis was found to correlate with overall survival.[22] They noted a significant difference ($p = 0.0001$) in median survival between patients with solitary brain metastases and those with multifocal disease: 5 months versus 3 months, respectively.

The molecular events that lead to the metastatic phenotype in a given primary tumor, with subsequent metastases to systemic organs and to the brain, remain unclear. Over the past few decades, the predominant theory postulated that somatic mutations in rare cells of the primary tumor (i.e., less than 1 in 10 million) would lead to an acquired increase in metastatic capacity, with the ability to migrate through tissues, survive in blood and lymphatic fluid, invade distant organs, and establish metastatic nodules.[23] Although this theory was supported somewhat by animal models, there was no data to verify

this process in human tumors. More recent evidence, based on expression micro-array analyses of primary and metastatic tumors, support the concept that metastatic potential is related to the intrinsic molecular biological state of the primary tumor as a whole, rather than to the emergence of a few rare cells.[24,25] The metastatic gene-expression signature consisted of a subset of eight genes that were upregulated (e.g., SNRPF, EIF4EL3, PTTG1) and a subset of nine genes that were downregulated (e.g., MHC Class II DP-β1, RUNX1) in the primary cancer.[24] None of the genes were individual markers of the metastatic phenotype; they were only predictive when analyzed as a whole group. Patients with primary cancers that expressed the metastatic phenotypic signature had significantly shorter survival times in comparison to patients whose tumors did not express it ($p = 0.009$).

In a related study, Milas and colleagues attempted to identify biological markers that could predict brain MBT and treatment outcome in patients with non-small cell lung cancer (NSCLC).[26] Twenty-nine patients with MBT, and matched controls without MBT, were analyzed using immunohistochemical techniques. Primary cancer and brain tumor tissue samples were analyzed for the expression of epidermal growth factor receptor (EGFR), cyclooxygenase-2 (COX-2), and BAX. Expression of COX-2 in brain lesions correlated with expression in primary cancers ($p = 0.023$), while the expression of BAX was lower in the MBT in comparison to the primary cancer ($p = 0.045$). However, the overall expression of EGFR, COX-2, and BAX in primary NCSLC tumors did not differ between patients with MBT and those without MBT. Therefore, this set of molecular markers cannot be used to predict the likelihood of MBT in patients with NSCLC.

PATHOLOGY OF MBTs

Systemic tumor cells usually travel to the brain by hematogenous spread through the arterial circulation, often after genetic alterations that produce a more motile and aggressive phenotype.[27–32] The metastasis most often originates from the lung, either from a primary lung tumor or from a pulmonary metastasis. Occasionally, cells reach the brain through Batson's paravertebral venous plexus or by direct extension from adjacent structures (e.g., sinuses, skull). The distribution of brain metastases follows the relative volume of blood flow to each area, so that 80% of tumors arise in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brain stem. Tumor cells typically lodge in small vessels at the gray-white junction and then spread into the brain parenchyma, where they proliferate and induce their own blood supply by neoplastic angiogenesis.[30] Expansion of the MBT disrupts the function of adjacent neural tissue through several mechanisms, including direct displacement of brain structures, perilesional edema, irritation of overlying gray matter, and compression of arterial and venous vasculature.

The metastatic phenotype is the result of a complex alteration of gene expression that affects tumor cell adhesion, motility, protease activity, and internal signaling pathways.[29–31] Initial changes involve downregulation of surface adhesion molecules, such as integrins and cadherins, which reduces cell-to-cell interactions and allows easier mobility through the surrounding extracellular matrix (ECM). Cell motility is also accelerated in response to specific ligands, such as scatter factor and autocrine motility factor.[28–31] Several oncogenes and signal transduction pathways are also commonly activated in these aggressive cells, including members of the *Ras* family, *Src*, *Met*, and downstream molecules such as Raf, MAPK 1/2, Rac/Rho, PI3-kinase, and focal adhesion kinase. Cellular invasive capacity is augmented in the metastatic phenotype by increased tumor cell secretion of matrix metalloproteinases (e.g., collagenases, gelatinases) and other enzymes that degrade the ECM.[30,31] In addition, metastatic cells often have downregulated secretion of tissue inhibitors of metalloproteinases (i.e., TIMP-1, TIMP-2), which further enhances their invasive potential and access to the vasculature. Loss of certain metastasis-suppressor genes has also been implicated in the metastatic phenotype, including *nm23*, *KA11*, *KiSS1*, *PTEN*, *Maspin*, and others.[29–32] Reduced expression of these genes removes inhibitory control over the formation of macroscopic metastases. A recent case control study of non-small cell lung cancer patients, with and without MBT, attempted to correlate the expression of EGFR, COX-2, and BAX with the risk of developing brain metastases.[26] It was found that expression of the biomarkers was similar for patients with and without MBT, and could not be used to predict the potential for developing a MBT. In addition, expression levels of EGFR, COX-2, and BAX did not correlate with patient survival in multivariate analysis.

Once the metastatic bolus of cells has traveled to the nervous system and has lodged within the brain, neoplastic angiogenesis is required for the tumor to grow to a clinically relevant size.[30,31,33,34] The angiogenic phenotype requires upregulation of angiogenic promoters such as vascular endothelial growth factor (VEGF), fibroblast growth factors (basic FGF, acidic FGF), angiopoietins (Ang-1, Ang-2), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factors (TGFα and TGFβ), interleukins (IL-6, IL-8), and the various growth factor receptors (e.g., VEGFR, PDGFR, EGFR).[33,34] During the "angiogenic switch" to the metastatic phenotype, tumor cells also reduce secretion of angiogenesis inhibitors, such as thrombospondin-1, platelet factor-4, and interferons α and β.[33] This

reduced concentration of inhibitory factors further "tips the balance" in the local environment to permit angiogenic activity within and around the tumor mass.

On macroscopic evaluation, MBT usually form rounded, discrete deposits in the brain parenchyma that are well circumscribed and demarcated from surrounding neural tissues (see Figures 3.1 and 3.2).[35,36] The most common locations for metastases are the frontal and temporal lobes, other lobes of the cerebrum, the cerebellum, and diencephalic region. The lesions can be single (25-35% of cases) or multiple (65-75% of cases), and may even present as a miliary pattern of numerous tiny masses. Primary tumors most likely to cause multifocal MBT include small-cell and adenocarcinoma of the lung, melanoma, and choriocarcinoma. Single metastatic deposits are more likely to arise from renal cell, gastrointestinal, breast, prostatic, and uterine carcinomas. The tumor deposits may have areas of hemorrhage or necrosis, particularly in the center of large lesions. Primary tumors most likely to cause hemorrhagic brain metastases include melanoma, choriocarcinoma, lung carcinoma, and renal cell carcinoma. With or without hemorrhage, the tumor is usually surrounded by an extensive amount of vasogenic edema, which often seems out of proportion to the size of the mass, and contributes to regional mass effect.

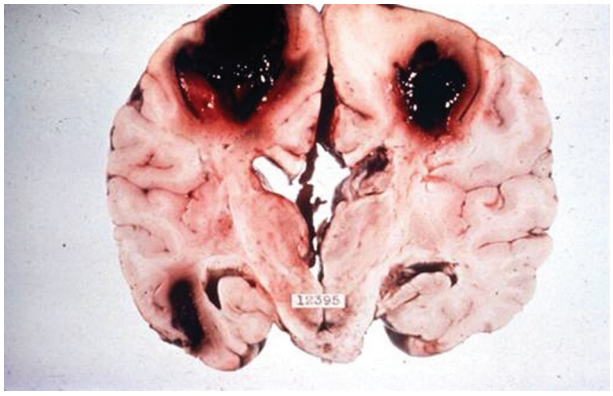

FIGURE 3.1 Gross specimen of brain demonstrating several MBTs from malignant melanoma. Note the hemorrhagic nature of the lesions, along with significant surrounding edema and mass effect.

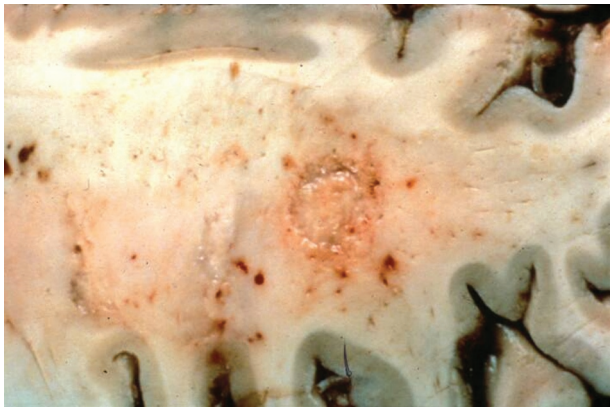

FIGURE 3.2 Gross specimen of brain demonstrating a MBT from a primary lung carcinoma, located at the gray-white junction. Note the well-circumscribed nature of the lesion, with little infiltration into surrounding brain.

On microscopic examination, the histological features of the MBT are usually similar, if not identical, to those of the primary neoplasm (see Figures 3.3–3.5).[35,36] In some cases, there may be a vigorous angiogenic response, with more prominent vascular proliferation and the formation of glomeruloid structures. In other tumors, there may be extensive necrosis, with only small regions of recognizable neoplastic tissue at the periphery of the lesion or adjacent to blood vessels. However, unlike glioblastoma multiforme, pseudopalisading of tumor nuclei around necrotic foci is very uncommon. The tumor mass will usually have well defined borders, tending to displace adjacent brain parenchyma without significant infiltration. Areas of hemorrhage and gliosis are often noted. Initial review of the tissue morphology can often identify a major tumor category, such as metastatic carcinoma, melanoma, or lymphoma. For a more detailed determination of cellular differentiation and assignment to a specific histological category, immunocytochemical analysis is required.[35–37] The tissue is usually screened with a detailed antibody panel, which includes numerous cell- and tumor-specific markers (see Table 3.2). In some cases, further investigation with electron microscopy or molecular genetic techniques may be necessary to finalize the diagnosis.

SURGICAL THERAPY OF MBTs

In the modern era of neurosurgery, there is now an important role for surgical resection of MBT, in carefully selected patients.[38–41] Surgical removal should be considered in all patients with a magnetic resonance imaging (MRI)-documented solitary metastasis. Unfortunately, this constitutes only 25-35% of all patients. Among those patients with solitary lesions, only half will be appropriate for surgery because of factors such as inaccessibility of the tumor (e.g., brainstem, eloquent cortex), extensive systemic tumor burden, or other medical problems (e.g., cardiac ischemia, pulmonary insufficiency). Using second generation image-guided, neuronavigation systems with frameless stereotaxy, patients with MBT can undergo aggressive surgical resection with significantly less risk for neurological injury.[42] In a review of 49 patients by Tan and Black, the use of image-guided craniotomy allowed for a gross total resection of the tumor and complete resolution of symptoms in 96% and 70% of the cohort, respectively. Neurological deterioration was only noted in two

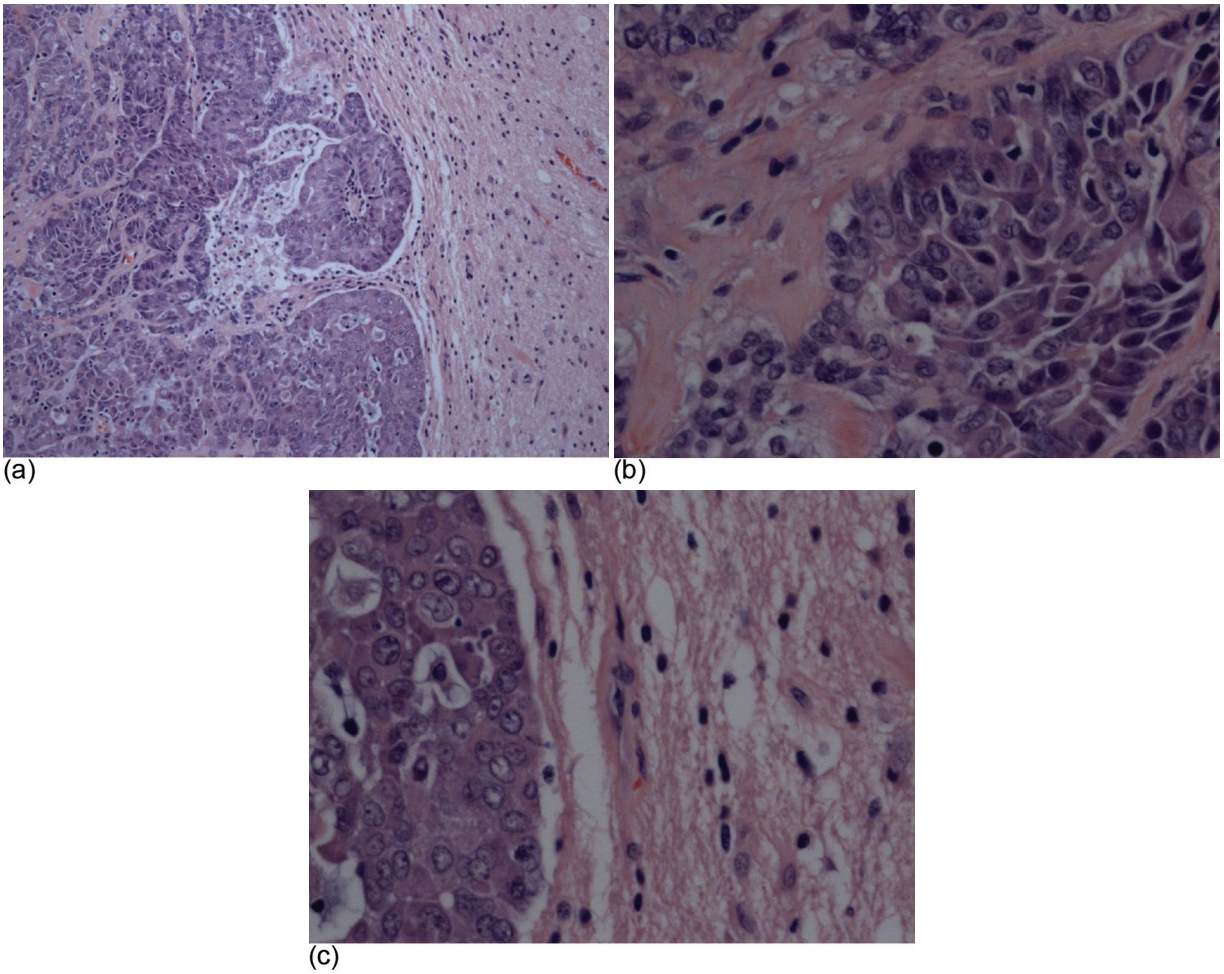

FIGURE 3.3 Microscopic preparation of tissue from a metastatic adenocarcinoma of the lung (a–c). Note that the metastatic tissue in the brain maintains the ability to form complete glandular structures and has a sharp demarcation to surrounding brain tissue. H&E @ 10× and 40×.

patients (3.6%), in whom significant deficits were present prior to surgery. The median survival for the entire group was 16.2 months, with a local recurrence rate of 16%. When neuronavigation and image-guidance is integrated with intraoperative MRI, the extent of surgical resection can be monitored and maximized in the operating room.[43,44] This often allows for a more complete resection of tumor and the potential for improved local control.

Class I evidence from two phase III trials is available to support the use of surgical resection in MBT patients.[38–41,45,46] In the seminal study by Patchell and colleagues, 48 patients with solitary MBT were randomly assigned to receive surgical resection plus irradiation versus irradiation alone.[45] Local recurrence at the site of the original metastasis was significantly less frequent in the surgical cohort in comparison to the irradiation alone cohort (20% vs. 52%; $p < 0.02$). Overall survival was significantly longer in the surgical group (median 40 weeks vs. 15 weeks; $p < 0.01$). In addition, functional independence was maintained longer in the surgical cohort (median 38 weeks vs. 8 weeks; $p < 0.005$). In a similar European phase III trial, 63 evaluable patients with solitary MBT were randomized to receive hyperfractionated irradiation (200 cGy × 2 per day; total of 4000 cGy) with or without surgical resection.[46] The overall survival was significantly longer in the surgical cohort (median 10 months vs. 6 months; $p = 0.04$). A survival advantage was also noted for the surgical group in the 12-month (41% vs. 23%) and 24-month (19% vs. 10%) overall survival rates. The effect of the surgical procedure on survival was most pronounced in the patient cohort with stable systemic disease, with significant differences in overall survival (median 12 months vs. 7 months; $p = 0.02$), 12-month survival rate (50% vs. 24%), and 24-month survival rate (27% vs. 10%). For patients with active systemic disease, the surgical resection and irradiation alone cohorts had the same median overall survival (5 months). One negative phase III trial has been reported by Mintz and coworkers, in their

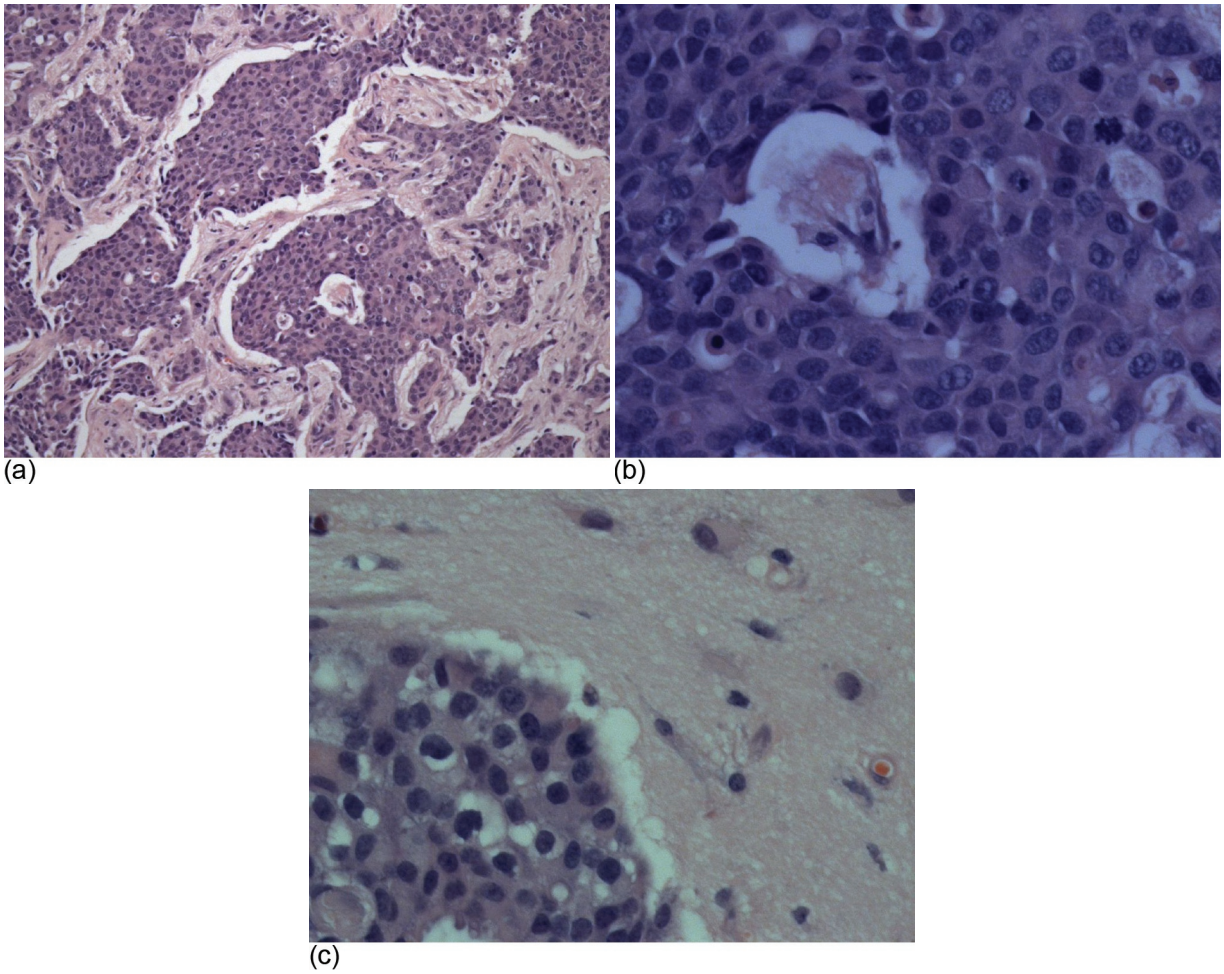

FIGURE 3.4 Microscopic preparation of tissue from a metastatic carcinoma of the breast (a–c). Note the presence of fairly uniform nuclei and the presence of mitotic figures and that the tumor nodules are sharply demarcated from surrounding brain parenchyma, with no infiltration. H&E @ 10× and 40×.

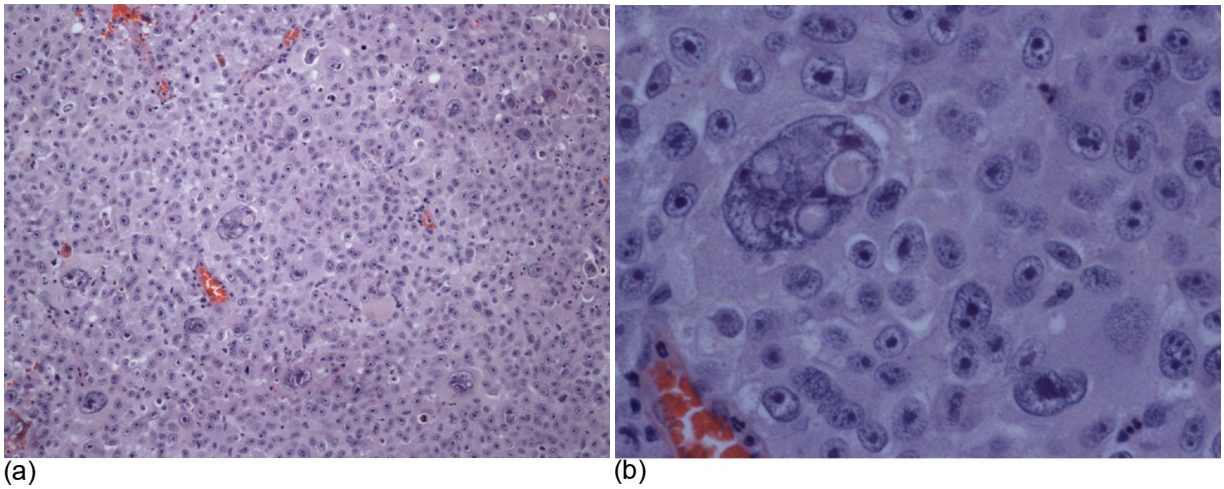

FIGURE 3.5 Microscopic preparation of tissue from a metastatic malignant melanoma (a and b). Note the histological features with dense cellularity, cellular and nuclear pleomorphism, prominent nucleoli, and varying quantities of melanin pigment. H&E @ 10× and 40×.

TABLE 3.2 Immunocytochemical Staining Techniques Used in the Diagnosis of MBTs

Initial screening panel
Epithelial membrane antigen
Cytokeratins
Glial fibrillary acidic protein
Cell-specific markers
Lung cancer: cytokeratin 7, surfactant
Breast cancer: cytokeratin 7, estrogen and progesterone receptors
Gastrointestinal cancer: cytokeratin 20
Ovarian cancer: CA 125
Neuroendocrine: chromogranins, peptides
Thyroid cancer: thyroglobulin
Prostate cancer: prostate specific antigen, prostatic acid phosphatase
Germ cell tumors
Placental alkaline phosphatase
Sarcomas
Desmin
Smooth-muscle actin
S-100
Malignant melanoma
S-100
HMB45
MART-1
Lymphoma
CD45
CD3
CD20

Data derived from Refs. 35–37.

review of 84 patients randomized to receive irradiation with or without surgical resection.[47] The overall survival was similar between the surgical and irradiation alone groups (median 5.6 months vs. 6.3 months; $p = 0.24$). There was also no difference between treatment cohorts in the ability of patients to maintain KPS equal to or above 70%. However, it should be mentioned that this study had several methodological shortcomings, including the fact that 73% of all patients had poorly controlled systemic disease, there was an unequal distribution of primary pathologies between treatment cohorts (i.e., more radioresistant colorectal cancer in the surgical group and more radiosensitive breast cancer in the irradiation alone group), and non-uniform calculation of survival times.[41]

There is also Class II and III evidence to support the use of surgical resection for selected patients with a solitary MBT, mainly reflecting individual institutional experience.[38–42,48–52] This has been demonstrated in patients with solitary MBT from various types of primary tumors, including those from lung, breast, colon and rectum, melanoma, renal cell, and others. In general, these studies also demonstrate improved local control rates and longer survival in patients with solitary, accessible MBT that receive surgical resection followed by external beam irradiation.

For patients with multiple MBT, the use of surgical treatment is more controversial and remains unclear.[38–41] Some authors advocate the removal of all metastatic tumors, if the lesions are accessible and not located in eloquent regions of brain.[53] Using this approach with carefully selected patients, the survival can be similar to that of patients undergoing surgery for solitary metastases. Other authors suggest limiting the use of surgical resection for the "dominant or symptomatic" lesion, if it is accessible.[40,52] The smaller and less symptomatic tumors can then be controlled by postoperative irradiation.

RADIATION THERAPY OF MBTs

Whole-brain external beam irradiation (WBRT) remains the primary form of therapy for the majority of patients with brain metastases.[1–6,54–56] It is still the treatment of choice for tumors that are located in eloquent cortex or are too large or too numerous for surgical resection or radiosurgical approaches. Early randomized trials in the 1970s and 1980s by the RTOG and others evaluated variable dosing (10-54.4 Gy) and fractionation (1-34 fractions) schemes, in an attempt to determine the optimal therapeutic regimen.[55,56] The median survival across all studies ranged from 2.4 to 4.8 months, thereby proving that differences in dosing, timing, and fractionation schedules did not significantly influence the results in MBT patients. Objective tumor responses (i.e., complete response [CR], partial response [PR], MR) were noted in approximately 60% of patients in the randomized RTOG trials. The most widely used WBRT regimen delivers a total of 30 Gy in 10 3 Gy fractions over 2 weeks. Although this dose has limited potential for long-term tumor control, it is well tolerated and designed to minimize the neurotoxicity associated with WBRT. An analysis of RTOG clinical trial data suggests that this regimen can provide control of disease in roughly 50% of patients at 6 months. After receiving WBRT, most MBT patients note an improvement or stabilization of neurologic symptoms, including headache, seizures, impaired mentation, cerebellar dysfunction, and motor deficits.[55]

A randomized trial has also evaluated the utility of WBRT in the context of patients with a solitary MBT that have undergone surgical resection.[57] In this study, 95 patients with solitary MBT were treated with complete surgical resection and then randomized into a postoperative radiotherapy group or an observation group. The overall recurrence rate of MBT anywhere in the brain was significantly reduced in the radiotherapy group (18% vs. 70%; $p < 0.001$). Postoperative WBRT was able to reduce the rate of MBT recurrence at the site of the original metastasis (10% vs. 46%; $p < 0.001$) and at distant sites in the brain (14% vs. 37%; $p < 0.01$). In addition, patients in the radiotherapy cohort were less likely to die of neurological causes than patients in the observation group (14% vs. 44%; $p = 0.003$). However, there was no significant difference between groups in terms of the overall length of survival or the length of time that patients were able to maintain functional independence. This is not surprising because one would not expect WBRT to have any effect on the course of the systemic cancer.

Prophylactic cranial irradiation (PCI) is an "up-front" application of WBRT that is only appropriate for consideration in selected patients with lung cancer. The efficacy of PCI was first demonstrated in patients with small-cell lung cancer (SCLCA), especially those with well-controlled systemic disease.[58,59] Initial reports demonstrated a survival benefit of 5.4% at 3 years, with a 25.3% reduction in the cumulative incidence of MBT in the cohort of patients achieving a complete systemic remission with chemotherapy.[58] A subsequent analysis of 505 patients that had participated in randomized trials has further characterized the benefit of PCI in SCLCA patients.[59] The 5-year cumulative incidence of MBT as an isolated first site of relapse was 20% in the PCI cohort and 37% in control patients ($p < 0.001$). The overall 5-year incidence of MBT for the PCI and control groups were 43% and 59%, respectively (relative risk [RR] 0.50; $p < 0.001$). However, the effect on overall survival was modest, with 5-year rates for the PCI and control groups of 18% and 15%, respectively (RR 0.84; $p = 0.06$). Presumably, this is because the majority of SCLCA patients ultimately die of systemic metastases, an issue not addressed by PCI. PCI has also been investigated in patients with non-small cell lung cancer (NSCLC), but with less compelling evidence of benefit.[60,61] Although there does appear to be a reduction in the incidence of MBT in the PCI cohorts, no survival benefit has been observed. This view is consistent with a recent Cochrane Review of the use of PCI in NSCLC patients.[62] The authors concluded that there was insufficient evidence at this time to recommend the use of PCI in clinical practice, and that it should only be offered in the context of a clinical trial.

Stereotactic radiosurgery (SRS) is a method of delivering focused irradiation to the boundaries of a tumor (i.e., conformal dosing), in a single or few fractions, using great precision.[2,3,5,63–67] SRS has become an important therapeutic option for brain metastases for several reasons, including the fact that most MBT are spherical and small at the time of diagnosis, the degree of infiltration into surrounding brain is usually quite limited, the gray-white matter junction is considered a relatively "non-eloquent" area of the brain, and improved local control in the brain may extend patient survival. The treatment is most often administered using a Gamma Knife® (i.e., Co^{60} sources); however, linear accelerator (e.g. Cyberknife®) and proton beam units are also used and demonstrate comparable local control and complication rates. SRS is most effective for tumors less than or equal to 3 cm in diameter. However, some authors recommend treatment of tumors up to 4 cm in diameter. Typical doses are in the range of 15-20 Gy to the margins of the tumor, with higher doses administered at the center of the mass. Optimal dosing will depend on the size of the tumor, previous exposure to irradiation, and proximity to delicate neural structures (e.g., optic chiasm).

There are two reports that provide Class I evidence for the efficacy of SRS in the context of a boost to WBRT.[68,69] In the first study from the University of Pittsburgh, 27 patients with 2-4 MBT were randomized to receive WBRT (30 Gy over 12 fractions) plus SRS (tumor margin dose of 16 Gy) or WBRT alone.[68] Local control was improved by the use of the SRS boost, with local failure rates at 1 year of 8% for the combined treatment group and 100% for the WBRT alone group. The median time to local failure was 36 months for the WBRT plus SRS cohort and 6 months for the WBRT alone group ($p = 0.0005$). In addition, median time to overall brain failure (local or distant) was longer for the combined treatment cohort in comparison to the WBRT alone group (34 months vs. 5 months; $p = 0.002$). However, the addition of the SRS boost did not significantly influence overall survival between the two groups (11 months vs. 7.5 months, respectively; $p = 0.22$). Again, this lack of effect on overall survival could simply reflect the effect of systemic metastases in these patients. In a similar study by the RTOG (RTOG 9508), 333 patients with one to three MBT were randomized to receive either WBRT (37.5 Gy over 15 fractions) or WBRT plus a SRS boost of 15-24 Gy, depending on tumor size.[69] Local control at 1 year was significantly better for the SRS group in comparison to the WBRT alone group (82% vs. 71%; $p = 0.01$). In addition, time to local progression was extended in the combined treatment cohort ($p = 0.0132$). Overall median survival was similar between groups; however, for patients with a single MBT, median survival was longer in the WBRT plus SRS cohort (6.5 months vs. 4.9 months; $p = 0.0393$). The

KPS was more likely to be stable or improved at 6 months follow-up in the WBRT plus SRS group (43% vs. 27%; $p = 0.03$). This is consistent with the multivariate analysis, which demonstrated improved survival in patients with RPA Class 1 disease ($p < 0.0001$).

There are numerous reports in the literature describing Class II and III evidence supporting the use of SRS for treatment of MBT.[2,3,5,63–67] A review of the larger trials (i.e., 100 or more patients) would suggest that SRS is as effective as, if not more effective than, WBRT.[70–81] In most of the studies, the median survival ranged between 5.5 and 13.5 months, with overall local control rates of 85-95%. The increase in local control rates did not translate into an improvement in survival, with most patients dying of systemic-disease progression. Several factors have been found to influence the degree of local control, including primary tumor histology (e.g., melanoma vs. lung carcinoma), tumor volume, tumor location, presentation (e.g., new vs. recurrent), and pattern of MRI enhancement (e.g., homogeneous vs. heterogeneous vs. ring). Some authors are recommending the use of SRS as the primary, "up-front" mode of irradiation in high performance patients with well-controlled systemic disease, instead of WBRT.[70–81] However, this view is not supported by the conclusions of a recent ASTRO meta-analysis of SRS treatment of MBT.[82] The ASTRO recommendations are to advise an SRS boost to WBRT in selected patients with one to four newly diagnosed MBT. The omission of WBRT results in significantly lower rates of local and distant brain control.

CHEMOTHERAPY OF MBTs

Chemotherapy has become a more viable option for the treatment of MBT in recent years, especially for recurrent disease.[83–89] The prior reluctance to use chemotherapy stemmed from concerns about the ability of chemotherapy drugs to cross the blood-brain barrier (BBB) and penetrate tumor cells, intrinsic chemoresistance of metastatic disease, and the high probability of early death from systemic progression. However, recent animal data suggests that metastatic tumors that strongly enhance on CT or MRI have an impaired BBB and will allow entry of chemotherapeutic drugs.[83,84] In addition, systemic resistance to a given drug does not always preclude sensitivity of the metastasis within the brain.[83] Several types of MBTs are relatively chemosensitive and may respond, including breast cancer, SCLCA, non-small cell lung cancer, germ cell tumors, and ovarian carcinoma.

The most common approach to chemotherapy for brain metastases is to administer it "up-front," before or during conventional WBRT or SRS.[90–99] Several authors have demonstrated that combination regimens given intravenously can be active in this context. The most frequently used agents included cisplatin (CDDP), etoposide (VP16), and cyclophosphamide (CTX). In a series of 19 patients with SCLCA and brain metastases, Twelves and coworkers used intravenous (IV) CTX, vincristine, and VP16 every 3 weeks before any form of irradiation.[90] Ten of the 19 patients (53%) had a radiological or clinical response. In nine patients, there was CT evidence of tumor shrinkage; while in one patient there was neurological improvement, without neuro-imaging follow-up. The mean time to progression (TTP) was 22 weeks, with a median overall survival of 28 weeks. Cocconi and colleagues used up-front IV cisplatin and etoposide every 3 weeks for 22 evaluable patients with MBT from breast carcinoma.[91] There were 12 objective responses, for an overall objective response rate of 55%. The median TTP was 25 weeks overall and 40 weeks in the objective response cohort. Overall median survival was 58 weeks. The same authors have expanded their series to include 89 patients with MBT from breast, non-small lung carcinoma, and malignant melanoma.[92] Objective responses were noted in the breast and lung cohorts. None of the patients with melanoma had objective responses. The overall objective response rate was 30% (34/89). Median TTP was 15 weeks, with a median survival for the cohort of 27 weeks. Similar responses have been noted in series of patients with MBT from lung and breast carcinoma.[93–99] However, although objective responses were noted in many of these studies, they did not translate into improvements in patient survival.

Topotecan is a semisynthetic camptothecan derivative that selectively inhibits topoisomerase I in the S phase of the cell cycle.[100] It demonstrates excellent penetration of the BBB in primate animal models and humans. Summating the data of more than 60 patients in several European studies of single agent topotecan, the objective response rates have been encouraging, with 30-60% of patients demonstrating a CR or PR.[101–104] Topotecan is also being investigated in combination with radiotherapy and other cytotoxic chemotherapy agents, such as temozolomide. A recent phase I trial has evaluated the tolerability of temozolomide (50-200 mg/m^2) and topotecan (1-1.5 mg/m^2), given daily for 5 days every 28 days.[105] Twenty-five patients with systemic solid tumors were treated. Toxicity was mainly hematological, with frequent neutropenia and thrombocytopenia. Three patients were noted to have a PR.

Temozolomide is an imidazotetrazine derivative of the alkylating agent dacarbazine with activity against systemic and CNS malignancies.[83,84,106–108] The drug undergoes chemical conversion at physiological pH to the active species 5-(3-methyl-1-triazeno)imidazole-4-carboxamide. Temozolomide exhibits schedule dependent antineoplastic activity by interfering with DNA replication through the methylation of DNA at the

following sites: N^7-guanine (70%), N^3-adenine (9.2%), and O^6-guanine (5%). Several reports have suggested activity of single agent temozolomide against MBT, with occasional objective responses.[109,110] Temozolomide is also under investigation as a radiation sensitizer, including a randomized phase II trial by Antonadou and associates.[111] In this study, 52 newly diagnosed MBT patients (lung and breast) were treated with either WBRT alone (40 Gy) or WBRT plus conventional temozolomide. The addition of temozolomide improved the objective response rate when compared to WBRT alone (CR 38%, PR 58% vs. CR 33%, PR 33%). In addition, neurologic improvement during treatment was more pronounced in the cohort of patients receiving chemotherapy. A similar randomized phase II trial by Verger and colleagues treated 82 patients with MBT (mostly lung and breast) using combined WBRT (30 Gy) and temozolomide (75 mg/m^2/day during irradiation, plus two cycles of conventional adjuvant dosing) versus WBRT alone.[112] The objective response rate and overall survival were similar between treatment groups. However, there was a significantly higher rate of progression-free survival at 90 days in the combined treatment cohort (72% vs. 54%, $p = 0.03$). In addition, the percentage of patients dying from the MBT was lower in the chemotherapy arm (41% vs. 69%; $p = 0.03$). Temozolomide has also been shown to have activity, as a single agent and in combination with other drugs (e.g., cisplatin, doxetaxel, thalidomide), against MBT from malignant melanoma.[113–116] A recent review of 21 published clinical trials using temozolomide for the treatment of progressive brain metastases from solid tumors concluded that the drug had modest activity as a single agent, as well as in combination with RT and other anticancer drugs.[117]

Interstitial or localized delivery of chemotherapy drugs (i.e., BCNU) into the resection cavity of resected tumors has been well established for high-grade gliomas, and is also under investigation for brain metastases.[118–120] Animal studies by Ewend and coworkers suggested that BCNU was more effective in this setting than carboplatin or camptothecin, and that local control of tumors and prolonged survival was better in the setting of RT + BCNU wafer implantation, versus RT alone or BCNU wafers alone.[119] Early phase I and II trials using BCNU wafers in MBT patients were promising, with 100% local control of newly diagnosed and resected tumors, with or without adjuvant RT.[119] A recent study by Brem and colleagues reported the use of BCNU wafer placement in a series of 59 patients with up to 3 brain metastases, with detailed neuro-cognitive follow-up.[121] All of the patients underwent resection of a solitary or "dominant" lesion (oligometastatic, two to three lesions), followed by wafer placement in the resection cavities, with radiosurgical treatment of any small non-resected tumors. In all but one patient, neuro-cognitive function improved in the domains of memory, executive function, and fine motor skills. The wafers were well tolerated, without any irreversible serious adverse reactions. The local recurrence rate was 28% at 1-year follow-up.

In an effort to improve dose intensity to MBT, some authors have given some or all of the chemotherapy drugs by the intra-arterial (IA) route.[83,122–127] There are several advantages to administering chemotherapy IA instead of by the conventional IV route, including augmentation of the peak concentration of drug in the region of the tumor and an increase in the local area under the concentration-time curve.[83,122,127] Pathologically, MBTs are excellent candidates for IA approaches, because they tend to be well circumscribed and non-infiltrative.[5,36] In addition, MBT almost always enhance on MRI imaging, indicating excellent arterial vascularization and impairment of the blood-tumor barrier. Pharmacologic studies using animal models of IA and IV drug infusion have shown that the IA route can increase the intra-tumoral concentration of a given agent by at least a factor of threefold to fivefold.[128,129] For chemosensitive tumors, improving the intra-tumoral concentrations of drug should augment tumor cell kill and the ability to achieve objective responses.[122,127] Initial applications of IA chemotherapy to MBT involved the use of BCNU and cisplatin.[123–126] Although objective responses were noted in patients with lung and breast tumors, significant neurotoxicity occurred (e.g., seizures, confusion). More recent reports have used carboplatin as the primary IA agent, and have resulted in similar objective response rates, with significantly less neurotoxicity.[130–132]

The recent expansion of knowledge regarding the molecular biology of neoplasia and the metastatic phenotype has led to intense development of therapeutic strategies designed to exploit this new information.[133] Several targets of therapeutic intervention have been developed, including growth factor receptors and their tyrosine kinase activity, disruption of aberrant internal signal transduction pathways, inhibition of excessive matrix metalloproteinase activity, downregulation of cell cycle pathways, and manipulation of the apoptosis pathways. The most promising approach thus far has been the development of small-molecule drugs or monoclonal antibodies to the major growth factor receptors (e.g., PDGFR, EGFR, Her2, C-Met, VEGF).[134–138] Monoclonal antibody agents such as rituximab (i.e., Rituxan) and trastuzumab (i.e., Herceptin) have proven to be clinically active against non-Hodgkin's lymphoma and breast cancer, respectively. Several small-molecule inhibitors of the tyrosine kinase activity of the EGFR (e.g., geftinib, erlotinib) continue to be evaluated in clinical trials of patients with solid tumors.[134,135,137] Similar efforts are underway to develop agents that can target the tyrosine kinase activity of PDGFR and the ras

signaling pathway.[137,138] Other agents under development are being designed to target downstream effectors, such as Raf, MAPK, Rac/Rho, and angiogenesis. Targeted approaches to treatment of brain metastases have now begun to appear in the literature, with some evidence of activity.[139,140] An early report using imatinib, a tyrosine kinase inhibitor with activity against C-KIT and PDGFR, describes a 75-year-old male with a C-KIT positive GI stromal tumor that developed neurological deterioration and gait difficulty.[141] An MRI demonstrated leptomeningeal disease with brain infiltration and edema. After treatment with imatinib mesylate (400 mg bid) for 2 months, his neurological function and gait improved. A follow-up MRI scan revealed complete resolution of the meningeal and intra-parenchymal abnormalities. Several authors have described case reports of the use of gefitinib, an oral tyrosine kinase inhibitor of EGFR, in patients with MBT from NSCLC.[142–146] A few of these initial patients had objective responses, including CR, that were quite durable. These early reports lead Ceresoli and colleagues to perform a prospective phase II trial of gefitinib in patients with MBT from NSCLC.[147] Forty-one consecutive patients were treated with gefitinib (250 mg/day); 37 had received prior chemotherapy and 18 had undergone WBRT. There were four patients with a PR and seven with SD. The overall progression-free survival was only 3 months. However, the median duration of responses in the patients with a PR was an encouraging 13.5 months.

Bevacizumab (BEV), a humanized monoclonal antibody against VEGF, has been shown to have a potent anti-angiogenesis effect in many systemic solid tumors, as well as in GBM.[139,140] There has been concern about using BEV in patients with MBT, due to the overall increased risk of hemorrhagic events. However, recent reports suggest that the risk of intra-tumoral hemorrhage is similar for MBT that have received BEV in comparison to those that have not received BEV.[148] In addition, a report by Zustovich and coworkers shows that BEV has efficacy as a primary treatment modality against MBT.[149] In a series of 18 patients with mostly lung and renal adenocarcinoma and MBT, BEV was used as part of the primary chemotherapy regimen. There was a 60% PR rate of the MBT, with another 40% with tumor stabilization. The progression-free survival of the cohort was 14 months, with an overall survival of 15 months. Clinical trials are underway to investigate the efficacy and safety of using BEV for patients with MBT from non-small lung cancer, breast cancer, and melanoma.

Patients with HER2-positive breast cancer and MBT are also being evaluated for molecular therapeutic approaches.[139,140] Several agents have been under investigation due to their potent anti-HER2 activity, including trastuzumab and lapatinib. Thus far, lapatinib seems to be the most promising approach, especially in combination with capecitabine.[150,151] However, even when used as a single agent, lapatinib can lead to objective tumor shrinkage, as shown in a recent Japanese report.[152]

Molecular therapeutic approaches have also been applied to patients with MBT from malignant melanoma, with some success.[139,140,153,154] BRAF inhibitors have proven active against melanoma tumors harboring the V600 mutation, including vemurafenib, which is now FDA approved.[153–156] In a pilot study of vemurafenib in patients with symptomatic MBT, there was a 42% overall PR rate for systemic and CNS disease, with another 38% with stable disease. Of 19 patients with measurable MBT, 3 (16%) achieved a PR, while 7 (37%) showed greater than a 30% reduction in tumor size.[155] A similar study evaluated the efficacy of dabrafenib, another BRAF inhibitor, in a series of 172 patients with melanoma and MBT, harboring either Val600Glu or Val600Lys BRAF mutations.[156] In patients with MBT that were newly diagnosed or had received prior therapy, dabrafenib was able to achieve objective responses of intracranial disease in 31-39% of the cases. Another approach has been to target the interaction between cytotoxic T-lymphocyte-associated antigen (CTLA-4) and its ligands B7.1 and B7.2, thereby enhancing antitumor cellular immunity and reducing tolerance to tumor-associated antigens.[153,154] The FDA approved monoclonal antibody, ipilimumab, targets CTLA-4 and has been shown to be clinically active against primary and metastatic melanoma.[153,154,157] In addition, ipilimumab has been able to induce durable responses in melanoma metastatic to the brain.

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CHAPTER

4

Supportive Care of Brain Tumor Patients

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CHAPTER CONTENTS

INTRODUCTION

The modern treatment of brain tumor patients usually involves a team approach from a dedicated group of physicians, nurses, and support staff that specialize in various aspects of neuro-oncology.[1] Although the focus of the treatment team will be on therapeutic strategies to control tumor growth (e.g., surgical resection, radiotherapy, chemotherapy), many other facets of care are necessary and will involve patient support and symptom management in an effort to maintain quality of life (QoL). The challenge for the treatment team begins at the moment of diagnosis, when the bad news must be communicated to the patient and family. Recent research suggests that there are several important factors that should be considered when imparting a new cancer diagnosis.[2] It is critical that the physician use simple, nontechnical language in a nonpatronizing manner, with a warm and caring tone. Every effort should be made to empathize with the emotions the patient is experiencing. The physician should sit close to the patient and maintain good eye contact. It is also permissible to initiate physical contact, in an effort to provide comfort. A quiet, private, and comfortable room should be used for the meeting, where interruptions and distractions can be minimized. Many patients also find it helpful when the physician gives some kind of warning that bad news is forthcoming and does not rush through the ensuing discussion.

The role of support is crucial for brain tumor patients and their families and continues until the patient is cured or, more often, succumbs to his or her disease.[3] The most important initial form of support is information and education about the diagnosis. At the moment the patient and family hear the words "brain tumor," they enter into a crisis mode and often feel a loss of control, fear of the

unknown, and sense of helplessness. To regain some aspect of control of their lives, they need to learn as much as possible about the disease and form a partnership with their physician, taking an aggressive and active role in the plan for treatment and recovery. Informational brochures and other written materials are helpful, as are the websites of organizations that provide services and resources for brain tumor patients and families, such as the North American Brain Tumor Coalition.[3] The coalition is a network of charitable organizations dedicated to the cure of brain tumors, and includes the American Brain Tumor Association, the Brain Tumor Foundation for Children, the Brain Tumor Foundation of Canada, the Brain Tumor Society, The Children's Brain Tumor Foundation, the National Brain Tumor Foundation, the Pediatric Brain Tumor Foundation of the United States, and the Preuss Foundation. During the course of a devastating illness such as a brain tumor, the patient's family will usually be the greatest source of support and comfort, as will active caregivers in the home setting.[3,4] In this context, family members often take on the role of information seekers and patient advocates. It is important to note that family caregivers are also at risk for depression and other signs of stress and require a strong support network to function effectively in this role.[5] Other sources of support for the patient and caregivers include the nurses of the treatment team, oncological social workers, chaplains affiliated with the hospital or from the private sector, and hospital-based support groups (brain tumor specific or general).

The remaining sections of this chapter will review the various aspects of supportive care that may be necessary in the management of brain tumor patients.

SEIZURES AND ANTICONVULSANT THERAPY

Seizure activity is a frequent complication in neuro-oncology patients and often compromises QoL by the restriction of driving privileges, seizure-related injuries, loss of time at work, and anxiety related to subsequent ictal events.[1,6–8] In addition, QoL can be further affected by the side effects, drug interactions, and expenses incurred by the use of antiepileptic drugs (AED). Seizures occur at presentation in 20-50% of patients with primary (PBT) and metastatic (MBT) brain tumors.[1,6–9] It is important to note that more than 25% of adults between 25 and 64 years of age with newly diagnosed seizures will have an underlying brain tumor.[6] At the time of tumor progression, seizure activity often becomes more frequent and severe, affecting another 10-20% of patients. The overall incidence of seizures is highest in patients with PBT of low histological grade and slow growth potential and becomes less frequent in those with high-grade PBT and MBT. For example, approximately 80-90% of patients with oligodendroglioma and ganglioglioma will have seizures, while patients with more malignant PBT, such as anaplastic astrocytoma and glioblastoma multiforme, carry a risk for seizure activity of 68% and 33%, respectively.[8] Multiple factors affect the incidence of seizures in brain tumor patients, including age, location, histology, and grade of the tumor. Younger patients (e.g., children and young adults) and those over age 65 years tend to have a higher incidence of seizure activity. In general, supratentorial tumors are most likely to cause seizures, especially when located within or near the cortex. Multifocal or bihemispheric tumors are also known to cause frequent ictal events. Seizures are much less common with tumors that are deep-seated or confined to the white matter.

Patients with low-grade tumors typically manifest seizures that are equally divided between partial motor, partial complex, and secondarily generalized varieties.[6–8] For patients with high-grade gliomas (HGGs) or brain metastases, focal motor seizures are the predominant variety, with less common secondarily generalized and complex partial seizures. The neurological examination tends to be relatively normal and non-focal in patients with seizures from low-grade tumors. In contrast, patients with high-grade PBT and MBT are more likely to have seizure activity associated with focal neurological deficits on examination.[6,7]

The pathophysiological mechanisms underlying tumor-associated seizures (TAS) remain unclear.[8,10,11] Recent evidence using direct brain recordings of electrical activity suggest that TAS originate from intact, non-infiltrated, neural tissue adjacent to tumors, and not from within the tumor mass itself.[10] Histologically, epileptogenic regions of brain demonstrate gliosis and mild reactive astrocytosis, without evidence for tumor cells. It is now theorized that these peritumoral epileptogenic foci develop an imbalance between excitatory and inhibitory inputs, due to multifactorial alterations in the local milieu from the tumor. The intra- and extracellular pH is slightly alkaline in peritumoral tissues, which enhances excitatory neuronal pathways and induces a 30% reduction of activity in GABAergic inhibitory pathways.[10] In biopsy samples from peritumoral epileptic foci, the number of GABA- and somatostatin-containing neurons are decreased.[12] Similar biopsy studies have noted an elevated concentration of glutamine, the direct precursor of glutamate, in peritumoral epileptogenic foci.[13] Glutamine is taken up and secreted by normal glia and glioma cells, thus providing a large reservoir of precursor for peritumoral neurons to convert to glutamate. In addition, recent evidence suggests that glioma cells directly secrete glutamate, causing significantly increased, excitotoxic concentrations in peritumoral tissues.[14,15] *In vitro*

experiments have demonstrated extensive NMDA and AMPA receptor stimulation and delayed Ca^{2+}-dependent cell death in exposed neurons. These reports suggest that exposure of peritumoral neurons to chronically elevated concentrations of glutamate could contribute to neuronal injury, abnormalities of neuronal circuitry, and the development of epileptiform activity. Other peritumoral alterations that may contribute to epileptogenic potential include increased extracellular Fe^{3+}, dysfunction of astrocytic syncytial gap junctions due to the infiltration of tumor cells, and the presence of pro-inflammatory cytokines (e.g., TNF-α), which can increase membrane excitability.[8]

The diagnosis of a seizure in a brain tumor patient is usually a clinical diagnosis, based on the history and description of the symptom complex from the patient and family members.[1,6–8] Testing with routine electroencephalography (EEG) is not helpful in most patients, since only 25-33% will demonstrate any focal interictal epileptiform activity. Prolonged EEG monitoring (with or without a video component) may be more helpful in diagnosing seizures in confusing or subtle cases. Once a patient with a malignant PBT has had a seizure, 50-75% will continue to have seizures.[7] In one half of the active seizure group, ictal events will occur more than once per month, while another 25% will have events more than once per week, despite the use of AED. The presence of seizure activity does not impact on the overall survival of brain tumor patients.[6] However, patients who present with a seizure or have long-standing seizures do have a more favorable prognosis. There are several explanations for this phenomenon, including the increased likelihood that the tumor will be an oligodendroglioma, which typically have longer survival times, and that seizures will often lead to a more prompt work-up and earlier diagnosis, when the tumor is smaller and more amenable to surgical resection. Patients with chronic seizures who develop a new pattern, with frequent "breakthrough" activity, may relate to a change in the tumor, such as bleeding or dedifferentiation into a more rapidly growing and more malignant lesion. It is also possible to have a "flare-up" of seizure activity, in otherwise well-controlled patients, at the onset of certain therapies that may cause irritation to surrounding brain, such as at the initiation of external beam radiotherapy and with certain forms of chemotherapy (e.g., gliadel wafers, intra-arterial cisplatin).

Implementation of AED in newly diagnosed patients should be held until a seizure has been documented. This approach is supported by a meta-analysis by Glantz and associates for the American Academy of Neurology.[16] Data establishing this practice are from studies using older AEDs including phenytoin, valproate, carbamazepine, and phenobarbital. It is unclear whether the newer-generation AEDs (e.g., levetiracetam, topiramate) may have any benefit in preventing late seizures. In addition, for patients who have not had a seizure and have received AED for craniotomy, tapering and discontinuing the AED after the first postoperative week is recommended.[16]

There is general consensus that any brain tumor patient with a well-documented, unequivocal seizure (generalized or focal) should be placed on an AED (see Table 4.1).[1,6–10] The choice of anticonvulsant medication is based on the type of seizure, which for most patients will be partial in onset with or without secondary generalization. Large, randomized studies of AEDs in patients with brain tumors are lacking. In the general population of adult patients with generalized seizures, phenytoin, carbamazepine, and valproate have relatively equivalent efficacy for reducing seizure activity.[17,18] Similarly, all three drugs are effective for partial motor, partial sensory, and partial complex seizures. However, a comparative trial of carbamazepine and valproate has demonstrated better control of complex partial seizure activity with carbamazepine.[22] Monotherapy with phenytoin, carbamazepine, or valproate should be the initial management approach in most patients.[1,17,18] In some patients, a second drug must be added if high therapeutic concentrations of several of the first line drugs are unable to control seizure activity.

Phenytoin or carbamazepine in combination with valproate is a common strategy. Alternatively, one of the new anticonvulsants (e.g., levetiracetam, gabapentin, topiramate, zonisamide) could be added to one of the first line agents.[19–21] Levetiracetam may be an excellent choice, since initial experience suggests it is effective and well tolerated in brain tumor patients, and has minimal potential to interact with other drugs such as corticosteroids or chemotherapy agents.[21] Ongoing studies will determine if levetiracetam and other new agents might be appropriate for first line use or as secondary, stand-alone agents. Serum drug concentrations must be monitored and optimized in all patients whenever possible (e.g., phenytoin, carbamazepine, valproate). Newer anticonvulsants have been particularly appealing for the management of seizures in patients with cancer for multiple reasons. These reasons, as well as data specific to patients with brain tumors, will be discussed further in Chapter 13.

In the brain tumor population, seizures remain difficult to control despite the use of AED. Patients who present with seizures tend to be more refractory to therapy than those that develop seizures later in the course of their disease.[6,7] In general, recurrent seizure activity is common, despite aggressive anticonvulsant therapy. Patient compliance can contribute to this problem and is frequently suboptimal. In many patients with a recent seizure, anticonvulsant levels are subtherapeutic.

TABLE 4.1 Antiepileptic Drugs Commonly Used for Treatment of Seizures in Brain Tumor Patients

Drug	Dose (mg/d)	Metabolism	Enzyme Inducing?	Mechanism	Bound Fraction (%)
Traditional AEDS					
Phenytoin	300-400	Hepatic +++	+++	Sodium channel	90-95
Carbamazepine	800-1600	Hepatic +++	+++	Sodium channel	75
Valproic acid	1000-3000	Hepatic +++	No Inhibitory	Sodium channel; enhanced GABA	80-90
Phenobarbital	90-180	Hepatic +++	+++	EAA antagonist; enhanced GABA	45
Newer AEDS					
Felbamate	2400-3600	Hepatic ++	+	EAA antagonist; enhanced GABA	25
Lamotrigine	100-500	Hepatic +++	None	Sodium channel	55
Gabapentin	1800-3600	Renal +++	None	Enhanced GABA	<5
Topiramate	200-400	Hepatic +	None	Sodium channel; EAA antagonist; enhanced GABA	9-17
Tiagabine	32-56	Hepatic +++	None	Enhanced GABA	95
Oxcarbazine	600-1800	Hepatic +++	+	Sodium channel	40
Levetiracetam	1000-3000	Renal ++	None	Binds to synaptic vesicle protein SV2A; N-type calcium channels	<10
Zonisamide	100-400	Hepatic ++	None	Sodium and calcium channels; enhanced GABA	40

Abbreviations: mg/d, mg/day; AED, antiepileptic drug; +, mild; ++, moderate; +++, severe; EAA, excitatory amino acids; GABA, gamma amino butyric acid.
Data derived from Refs. 17–21.

Further complicating the situation is that brain tumor patients are more susceptible to AED toxicity and side effects, including cognitive impairment, hepatotoxicity, myelosuppression, skin rashes (including Stevens-Johnson syndrome), and interactions with concomitant medications.[6] Management of seizures in a cancer patient should not only consist of controlling seizure activity with AEDs. Consideration should also be given to the control of systemic and intracranial neoplastic disease. For patients with systemic cancer, AEDs will likely be the only treatment. However, for those with intracranial primary or metastatic neoplasms, a combination of chemotherapy, surgery, radiation therapy, and AEDs may be appropriate.[23]

CORTICOSTEROIDS

The use of corticosteroids is often necessary in PBT and MBT patients to control symptoms caused by increased intracranial pressure (e.g., headache, nausea and emesis, confusion, weakness).[1,9,24] Peritumoral edema is the principal cause of elevated intracranial pressure and is mediated through numerous mechanisms, including the leaky neovasculature associated with tumor angiogenesis as well as increased permeability induced by factors secreted by the tumor and surrounding tissues, such as oxygen free radicals, arachidonic acid, glutamate, histamine, bradykinin, atrial natriuretic peptide, and vascular endothelial growth factor (VEGF).[25–27] Dexamethasone is the high-potency steroid used most often to treat the edema associated with brain tumors.[1,24] It has several advantages over other synthetic glucocorticoids, including a longer half-life, reduced mineralocorticoid effect, lower incidence of cognitive and behavioral complications, and diminished inhibition of leukocyte migration.[28] The mechanisms by which dexamethasone and other glucocorticoids reduce peritumoral edema remain unclear. It is known that both PBT and MBT have high concentrations of glucocorticoid receptors. The effects of these

drugs on tumor-induced edema are most likely mediated through binding to these receptors, with subsequent transfer to the nucleus and the expression of novel genes.[27] In a recent MRI study, dexamethasone was able to induce a dramatic reduction in blood-tumor barrier permeability and regional cerebral blood volume, without significant alteration of cerebral blood flow or the degree of edema.[29] The inhibition of production and/or release of vasoactive factors secreted by tumor cells and endothelial cells, such as VEGF and prostacyclin, appears to be involved in this process.[26,27] In addition, glucocorticoids appear to inhibit the reactivity of endothelial cells to several substances that induce capillary permeability.

The exact dose of steroids necessary for each patient will vary depending on the histology (i.e., benign or malignant), size and location of the tumor, and amount of peritumoral edema. In general, most patients with malignant tumors will require between 8 and 16 mg of dexamethasone per day to remain clinically stable. The lowest dose of steroid that can control the patient's pressure-related symptoms should be used.[1,24] This approach will minimize some of the toxicity and complications that can arise from long-term corticosteroid usage, which includes hyperglycemia, peripheral edema, proximal myopathy, gastritis, infection, osteopenia, weight gain, bowel perforation, and psychiatric or behavioral changes (e.g., euphoria, hypomania, depression, psychosis, sleep disturbance).[1,24,30–35] Patients with dexamethasone-induced proximal myopathy will often improve when the dosage is reduced.[34,35] In addition, the proximal leg muscles can usually be strengthened if the patient is placed on a lower extremity exercise regimen. Some authors have also reported an improvement in the myopathy when dexamethasone is replaced by an equivalent dosage of prednisone or hydrocortisone.[34,35] The neuropsychiatric complications of steroids can often be improved by dosage reduction or discontinuation of the drug.[33] For those patients in whom continued steroid usage is necessary, symptomatic pharmacological intervention is appropriate. For example, patients experiencing steroid-induced delerium or psychosis will often improve with low-dose haloperidol (0.5-1.0 mg PO, IM, or IV), titrated to control symptoms. Steroid-induced sleep disturbances often respond to dosage reduction or by eliminating any doses after dinner. In refractory cases, the use of a hypnotic medication at bedtime (e.g., triazolam, 0.25 mg) will often be of benefit. Corticosteroid-induced osteoporosis is a common problem, affecting 30-50% of patients receiving treatment for a year or more.[30,36,37] Patients on long-term dexamethasone require a preventive program to minimize osteoporosis, including calcium and vitamin D supplements, and weight-bearing exercises. The osteoporosis guidelines of the American College of Rheumatology Task Force suggest that any patient taking glucocorticoids (at any dose with anticipated duration >3 months) maintain total elemental calcium intake of 1200 mg per day with vitamin D intake of 800 international units per day either through diet or supplementation.[38] These measures should be started early, since bone loss is greatest in the first 2-4 months of chronic steroid treatment. For patients on long-term steroid therapy (i.e., ≥3 months), or in those with established osteoporosis or evidence of an osteoporotic fracture, bisphosphonate therapy (e.g., risedronate, 2.5-5.0 mg/day; alendronate, 5-10 mg/day) should be added to the regimen of calcium and vitamin D supplements.[39]

Brain tumor patients can be immunosuppressed for a variety of reasons, including long-term steroid use, immunomodulatory factors secreted by the tumor, and the effects of chemotherapy.[35,37] Chronic steroid usage can lead to lymphopenia, mainly through a reduction in the concentration of CD4+ T cells and an associated increased risk of systemic infection. Recent studies suggest that brain tumor patients on chronic steroids are at substantial risk for pneumocystis carinii pneumonia (PCP), a serious fungal infection with a 50-55% case fatality rate. In a recent pair of reports reviewing the Johns Hopkins experience over the past 20 years, Grossman and colleagues noted that the rate of PCP in PBT patients was less than 1.0%.[40,41] However, of all HIV negative patients with PCP over the past 5 years, the percentage with PBTs had increased from 22% to 40% (half of which were primary CNS lymphoma; PCNSL). In fact, it appears that patients with PCNSL are at particular risk for developing PCP, possibly due to the recent widespread use of methotrexate-based chemotherapy regimens, which can significantly reduce CD4+ T cell counts.[41] The authors did not recommend PCP prophylaxis for every brain tumor patient on long-term steroids or chemotherapy. Rather, they suggested careful monitoring of all patients for the onset of lymphopenia, including an assessment in high-risk cases of the concentration of CD4+ T cells. For those high-risk patients with lymphopenia and CD4 counts below 200 cells/mL, a prophylactic anti-PCP regimen should be instituted.[42] The most commonly used prophylactic antibiotic is trimethoprim-sulfamethoxazole (TMP-SMX, 160+800 mg), at a dose of one double-strength tablet per day. For patients with a sulfa allergy or deleterious interactions between TMP-SMX and other drugs (e.g., methotrexate), alternative prophylactic medications include pentamidine (300 mg/month by nebulizer), atovaquone (750 mg B), and dapsone (100 mg/day by mouth). Patients should be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency before taking dapsone. Patients with G6PD deficiency are at an increased risk of hemolytic anemia from dapsone.

GASTRIC ACID INHIBITORS

Brain tumor patients on long-term dexamethasone are at increased risk for gastrointestinal complications (i.e., gastritis, ulceration, bowel perforation), although there remains some debate in the literature regarding ulcer formation.[24,30,32] Risk of peptic ulcer disease due to glucocorticoids alone is low; however, a comprehensive review of the topic would suggest that ulcer prophylaxis is appropriate in this patient population, since the incidence of ulcer formation is increased in patients with advanced malignant disease.[43] Patients at risk should be treated prophylactically with an acid suppressing medication such as a proton pump inhibitor (PPI) or H2-blocker (see Table 4.2). Most of these medications are available over the counter, without a prescription. H2-blockers include ranitidine hydrochloride (150 mg po twice daily), famotidine (20 mg po twice daily), and cimetidine (400 mg hs). Cimetidine inhibits multiple cytochrome P450 enzymes and should be used with caution due to the risk of drug-drug interactions. H2 blockers tend to be less expensive and have a faster onset of action when compared with PPIs. However, PPIs tend to have greater acid suppression and may be more effective long term. PPIs include omeprazole (20-40 mg po once daily), lansoprazole (15-30 mg po daily), esomeprazole (20-40 mg po daily), and pantoprazole (20-40 mg po daily).[44,45] These medications can be discontinued after the patient has been completely tapered off dexamethasone.

THROMBOEMBOLIC COMPLICATIONS AND ANTICOAGULATION

The risk of venous thromboembolism (VTE) (i.e., deep venous thrombosis [DVT], pulmonary embolism [PE]) is high in cancer patients, with an antemortem incidence of symptomatic events approaching 15%.[39,46] However, at autopsy the incidence rates are much higher, between 45% and 50% in some series. For patients with brain tumors, the risk for VTE appears to be even higher than the general cancer population.[42,46] In the perioperative period, the overall incidence of thrombosis after brain tumor resection was 45%, as detected by ^{125}I-labeled fibrinogen scans.[47] The incidence varied depending on the tumor type and was 72%, 60%, and 20% for meningioma, GBM (glioblastoma multiforme), and MBT patients, respectively. The high incidence of thromboembolism in meningioma patients was unexpected, considering their generally benign natural history, and suggested that tumor biology may play a predominant role in risk for perioperative DVT and PE. Thromboembolic risk continues to remain high in brain tumor patients after the perioperative period (i.e., beyond 6 weeks). A meta-analysis of malignant glioma patients by Marras and colleagues noted a DVT incidence rate that ranged from 0.013 to 0.023 per patient-month of follow-up, corresponding to overall rates of 7-24%.[48] The only prospective study included in the analysis followed 75 patients until death and had a DVT incidence rate of 24% (0.015 DVT/patient-month).[49] In addition to biological factors related to individual tumor histology, several clinical factors are also associated with increased risk of DVT and PE, including arm paresis, leg paresis, history of prior DVT or PE before tumor diagnosis, longer operative time, and presence of GBM.[42,48,50] Other less important factors that may also be relevant are older age, larger tumor size, and the use of chemotherapy.

Treatment of VTE in patients with PBT or MBT involves balancing benefits and risks of anticoagulation or placement of an inferior vena cava (IVC) filter. The important question at the core of this dilemma is the risk of intra-tumoral hemorrhage while receiving anticoagulant therapy. This is a common problem for the Neuro-Oncology treatment team and continues to be studied in the literature. In general, the risk for symptomatic hemorrhage into a primary or MBT is quite low during

TABLE 4.2 Drugs Used for Gastric Acid Suppression

Drug	Dose	CYP Enzyme Effects	Available OTC?
Histamine H2 blockers			
Ranitidine	150 mg BID	No	Yes
Famotidine	20 mg BID	No	Yes
Cimetidine	400 mg HS	Moderately inhibits CYP 1A2, 2C19, 2D6, and 3A4	Yes
Proton pump inhibitors (PPI)			
Omeprazole	20-40 mg	Moderately inhibits 2C19, 2C9	Yes
Esomeprazole	20-40 mg	Moderately inhibits 2C19	No
Lansoprazole	15-30 mg	No	Yes
Pantoprazole	20-40 mg	No	No

conservative anticoagulation with heparin and coumadin.[42,49–54] Most authors report a hemorrhage rate of 2-3% for PBT and 5-7% for MBT.

The American Society of Clinical Oncology (ASCO) Practice Guideline on VTE prophylaxis and treatment in patients with cancer recommend that for patients with primary CNS malignancies, anticoagulation be given for established VTE as described for other patients with cancer. These patients do require care monitoring to limit the risk of hemorrhagic complications.[55] The preferred treatment of VTE in patients with cancer is a low-molecular weight heparin (LMWH) for at least 6 months. The LMWHs (e.g., enoxaparin, dalteparin) are composed of fragments of unfractionated heparin produced by controlled enzymatic or chemical depolymerization, yielding chains with an average molecular weight of 5000 Da. In comparison to unfractionated heparin, LMWHs have a more predictable anticoagulant response due to better bioavailability, a longer half-life, and more dose-dependent clearance.[56] In addition, the LMWHs can be administered subcutaneously in the outpatient setting and do not require monitoring of coagulation status. When used in clinical trials of patients with DVT, LMWHs (e.g., enoxaparin, 100 U/kg twice daily) have proved as effective or more effective than unfractionated heparin, with a lower hemorrhage rate.[56] Meta-analyses of the clinical trial data conclude, in general, that LMWHs are more effective and safer than unfractionated heparin. Lee and colleagues published the Comparison of LMWH versus Oral Anticoagulant Therapy for Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) in 2003.[57] In this trial, adult patients with active cancer and newly diagnosed proximal DVT, PE, or both were randomized to receive subcutaneous dalteparin or an oral anticoagulant (i.e., warfarin or acenocoumarol, after dalteparin bridge). There was a statistically significant decrease in recurrent VTE among cancer patients treated with dalteparin over oral anticoagulants. Bleeding rates were similar between the two groups. Furthermore, there were only 27 patients with brain tumors included in the CLOT trial, 14 that received dalteparin and 13 that received oral anticoagulants. Clinical trials to more specifically evaluate the safety and efficacy of LMWH in brain tumor patients have not been completed.

The utility of VCF in brain tumor and other cancer patients remains controversial.[58] Several studies have demonstrated a significant complication rate for VCF in PBT and MBT patients (in the range of 40-62%) and suggest that biological factors related to the tumor may be involved.[53,54] Complications after VCF placement include filter thrombosis, recurrent DVT, recurrent PE, and thrombosis of the IVC. Patients receiving anticoagulation had a lower recurrence rate of PE and DVT. Due to the high failure rate associated with IVC filters and the lack of improved overall survival or reduced intracranial hemorrhage in small retrospective series, the ASCO recommends the insertion of a vena cava filter only for patients with contraindications to anticoagulation.[53,55] Absolute contraindications to anticoagulation include active major bleeding (i.e., intracranial, retroperitoneal, intraspinal). Active but non-life-threatening bleeding (e.g., trace hematuria) or intracranial/CNS bleeding within the past 2 weeks would be considered a relative contraindication to anticoagulation.[55]

Within the last 5 years, multiple new oral anticoagulants have been introduced to the market for the prevention and treatment of VTE. These agents offer novel mechanisms of action, including oral direct thrombin inhibitions (dabigatran) and inhibition of activated factor Xa (rivaroxaban and apixaban). In addition to the benefit of oral administration, these agents do not require the intense monitoring associated with older oral anticoagulants (i.e., INR monitoring with warfarin). However, randomized clinical trials with these drugs included very few patients with malignant disease. Additional concerns regarding the use of new oral anticoagulant in patients with cancer include unpredictable absorption and higher risk of GI bleeding in those with mucositis or other GI complications, altered metabolism in those with liver or renal impairment, drug interactions with hormonal and chemotherapeutic agents, inability to measure the anticoagulant activity using standard assays, and lack of an antidote. Not all of these concerns apply to patients with brain tumors, but certainly the lack of an antidote is especially concerning in this patient population, which is at high risk for intracranial bleeding. For all of these reasons, the use of novel oral anticoagulants is not recommended for treatment of VTE in patients with cancer.[55]

DYSPHAGIA AND SWALLOWING DISORDERS

Dysphagia and disorders of swallowing are common in patients with neurological disease and can be associated with stroke, multiple sclerosis, motor neuron disease, neurodegenerative disorders, and structural lesions such as a brain tumor.[59–65] Swallowing dysfunction can lead to serious morbidity from malnutrition, dehydration, and aspiration pneumonia. There remains a paucity of literature regarding the incidence and presentation of dysphagia in the brain tumor population. The most well-described presentation involves dysfunction of the brainstem, either from compression to, or growth within, this region.[59,66,67] Tumors that can induce dysphagia in this manner include brainstem glioma, brainstem metastases, ependymoma, choroid plexus

papilloma, large pineal region tumors (i.e., pinealoma, astrocytoma), and neoplasms of the cerebellopontine angle, such as acoustic schwannoma and meningioma. Direct tumor compression causes impairment of the brainstem circuitry that underlies swallowing, including the nucleus tractus solitarius, ventromedial reticular formation, and cranial nerve motor efferents (V_3, VII, IX, X, XII, and ansa cervicalis).[68–70] Other reports contend that unilateral, supratentorial tumors can also cause dysphagia.[71,72] In a prospective analysis of dysphagia in PBT patients and a set of non-brain-tumor neurological controls, Newton and colleagues noted that 17 of 117 (14.5%) tumor patients complained of swallowing problems.[72] Formal swallowing assessment of the symptomatic cohort revealed that most patients significantly underestimated their degree of dysfunction. It was also noted that symptomatic patients with decreased level of alertness (LOA) were more likely to have abnormalities during bedside and videofluoroscopic testing. Twelve of the 17 symptomatic patients (70.5%; GBM-7) had large and diffuse, unilateral, supratentorial lesions with surrounding edema and mass effect, often associated with decreased LOA. The neuroanatomical basis for dysphagia from a unilateral lesion remains unclear. However, it is probably due to a combination of several factors, including reduced awareness of oral sensory feedback cues during mastication in patients with reduced LOA, contralateral weakness of the face and tongue, and oral apraxia with impaired motor programming ability for oral-lingual feeding behavior.

Based on the available literature, it would seem prudent to routinely screen all brain tumor patients for dysphagic symptoms, especially in the latter stages of their disease, with or without reduced LOA. All symptomatic patients should undergo a formal swallowing evaluation, even when the complaint seems trivial.[72] The initial bedside screening examination can assess oral and laryngeal function and identify patients at risk for aspiration.[73] In addition, bedside testing can allow modification of eating behavior to diminish the risk of aspiration. Further examination is often needed after the initial bedside evaluation to allow more detailed assessment of the swallowing mechanism, such as delays during the pharyngeal swallow, the degree of laryngeal elevation, pharyngeal symmetry, pooling or coating of pharyngeal recesses, and silent aspiration. The modified barium swallow is used for this assessment and can accurately reveal the abnormalities of the swallowing mechanism, the degree of aspiration, and how best to modify the diet.[72–75]

Management of dysphagic brain tumor patients can often be a complex issue. Patients must be able to demonstrate the necessary cognitive and communication skills to actively participate in a swallowing management program.[73,75] Tumor patients with diminished LOA or significant cognitive alterations may be unable to pursue complex rehabilitation strategies similar to those used for patients with other neurologic disorders (e.g., stroke). In those patients with adequate LOA, swallowing rehabilitation should be pursued. If compensatory techniques do not improve oral efficiency, an alternate route of nutrition may be required, such as a gastric feeding tube.

PSYCHIATRIC ISSUES

There are several important psychiatric issues that must be assiduously screened for during the care of brain tumor patients and family members. These issues include depression, associated problems with sleep, and anxiety.[76–81] All cancer patients face numerous stressors during their illness, including fears of a painful death, disability, disfigurement, dependency, and separation from loved ones. The psychological impact of these stressors is quite variable, however, depending on differences in personality, coping mechanisms, social support structure, and medical factors. The National Comprehensive Cancer Network (NCCN) Panel on Distress Management defines distress as "a multifactorial, unpleasant emotional experience of a psychological (i.e., cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment."[82] Distress extends along a continuum and can range from common normal feelings of vulnerability, sadness, and fear to problems that become disabling, such as depression, anxiety, panic, and social isolation.

Depression is the most common psychological symptom in patients with cancer and can range in severity. Major depression has been found to occur in approximately 16% of patients with cancer, while minor depression (dysthymia) is reported in almost 22% of cancer patients. This is approximately three times as common as in the general population.[83] More severe symptoms of depression are of clinical concern because of their association with more prolonged hospital stays, physical distress, poorer treatment compliance, lower QoL, increased desire for hastened death, and completed suicide.[83] Patients at more advanced stages of disease, or with severe disability and/or pain, are more likely to develop depression, with rates approaching 75-80%. At the time of initial diagnosis, patients usually enter a brief phase of shocked disbelief that lasts for several days. The next phase is one of depressed mood, anxiety, anorexia, insomnia, irritability, and psychological malaise that may last 2-3 weeks. During this phase, patients note a pervasive sense of sadness and uncertainty about the future and are preoccupied with thoughts about their

illness, death, and loss of loved ones. Activities of daily living may become difficult to perform, along with generally poor concentration and information processing. These symptoms are consistent with a reactive depression and are transient. The next phase is one of adaptation to the diagnosis, with renewed hope and optimism as the patient begins to implement the treatment plan with their physicians and treatment team. Symptoms of reactive depression do not require specific antidepressant therapy. However, reactive depression may recur during critical transition points in the illness, as the patient is made aware of bad news (e.g., progressive disease on MRI scan).

When are the presence of depressive symptoms severe enough to require treatment? Many of the symptoms of major depression are similar to those of reactive depression, but differ in their severity and persistence. Using criteria as outlined in the *Diagnostic Statistical Manual of Mental Disorders IV* (DSM-IV) (see Table 4.3), a major depressive episode can be diagnosed if five or more of the listed symptoms have been present for 2 weeks or more and represent a change from the baseline level of functioning.[84] At least one of the symptoms needs to be depressed mood or loss of interest in pleasurable activities (i.e., anhedonia). The symptoms need to be severe enough to cause significant distress to the patient and to impair social, occupational, or familial functioning. Other symptoms include appetite or sleep disturbances, psychomotor agitation or retardation, decreased energy, feelings of worthlessness or guilt, difficulty concentrating, or suicidal ideation. Minor depression can be diagnosed when only two to four of these symptoms are present for at least 2 weeks. Diagnosis of depression in patients is uniquely challenging. Many of the symptoms of cancer and its treatment overlap with those of depression, such as fatigue, anorexia, insomnia, and cognitive impairment. The symptoms need to be severe enough to cause significant distress to the patient and to impair social, occupational, or familial functioning. Patients with advanced stages of disease and poorly controlled pain are usually the most severely depressed. For example, the Karnofsky Performance Status (KPS) is highly correlated with the occurrence of depression.[85] Major depression was noted in only 23% of patients with a KPS of 70 or higher, but was present in 77% of those patients with a KPS of less than 40. Many of the somatic symptoms of depression (e.g., fatigue, loss of energy, anorexia, weight loss, insomnia) overlap with the common symptoms of cancer patients, especially those undergoing treatment. Therefore, to correctly diagnose depression in brain tumor patients, it is important to focus on the psychological symptoms, including dysphoric mood, hopelessness, guilt, worthlessness, anhedonia, and suicidal ideation.

TABLE 4.3 DSM-IV Criteria for the Diagnosis of Major Depression[84]

1. Depressed mood most of the day, nearly every day. Can be subjective report or observation by others.

2. Markedly diminished interest in pleasurable activities most of the day, nearly every day.

3. Significant weight loss when not dieting or weight gain (i.e., a change of more than 5% of body weight in a month), or a decrease or increase in appetite nearly every day.

4. Insomnia or hypersomnia nearly every day.

5. Psychomotor agitation or retardation nearly every day, which is observable by others and not just a subjective feeling of restlessness or being slowed down.

6. Fatigue or loss of energy nearly every day.

7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day.

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day.

9. Recurrent thoughts of death (not just a fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Five or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms is either depressed mood or loss of interest in pleasurable activities.

Patients with suicidal ideation should be questioned in more detail to assess suicide risk.[76–78,80] Cancer patients are at increased risk of suicide compared to the general population, particularly in the advanced stages of disease. Suicidal ideation is noted in 15-20% of cancer patients with painful symptoms.[77] In half of the cohort with suicidal ideation, an adjustment disorder was present with anxious and depressive features, while in another 30-35% a major depression was noted. For most patients, suicidal ideation functions as a "steam valve" for thoughts and worries centered on issues of control of the cancer and of not being overwhelmed (i.e., "if things get too bad, I have a way out"). Patients most likely to act on thoughts of suicide have feelings of hopelessness and loss of control, in addition to depression. The physician should explore how serious the suicidal thoughts are and assess risk factors (e.g., prior suicide attempts, severe pain, poor performance status, severe depression, and hopelessness). It is important to determine if the patient has a plan in place and the means to carry it out. All patients considered at risk for a suicide attempt require a prompt psychiatric evaluation for suicide intervention. In general, most cancer patients are not at high risk for suicide. Early intervention, including treatment of depression and adequate pain control, will usually negate this option. Crisis-intervention-oriented psychotherapy is often beneficial to the suicidal patient and should include the patient's loved ones and social support system.

Treatment of depression in patients with cancer should address not only depressive symptoms but also the disease-related and psychosocial factors that contribute to the emergence of depression in this context, including pain and other distressing physical symptoms. Once the patient has been diagnosed with major depression and contributing medical problems have been resolved, several treatment approaches are available.[76–78,80] Treatment of depression involves two components: psychotherapy and pharmacologic therapy. Antidepressant medications tend to be most effective for those with severe depression, whereas psychotherapeutic approaches may be of value in both milder and more severe cases of depression.[83] Psychotherapeutic options that are often helpful alone or in combination with drug therapy include counseling, psychoeducation, relaxation training, problem-solving therapy, and cognitive-behavioral techniques.[83,86,87] Counseling either for the individual or in a group setting is effective at reducing depressive symptoms and psychological distress in cancer patients. Cognitive-behavioral interventions, such as relaxation techniques and positive imagery, have also been shown to improve depressive symptoms in patients with mild to moderate levels of depression. Optimal psychotherapy may depend on the severity of depressive symptoms, the functional status of the patient, the patient's motivation to participate in psychosocial treatment, and patient interest in self-reflection.[83] Multiple meta-analyses evaluating the effectiveness of psychosocial interventions for the treatment of severe depression in cancer patients have produced mixed results. For most cancer patients with moderate to severe depression, the mainstay of therapy will be pharmacological intervention with an antidepressant medication (see Table 4.4). There are several classes of antidepressant drugs; comparative clinical trials suggest that the efficacy of drugs within each class and between classes is similar. Clinical improvement usually takes 2-3 weeks to become evident, with a peak effect at 4-6 weeks. The first depressive symptoms to improve are mood, quality of sleep, appetite, and personal grooming. Renewed interest in activities and increased energy level occur soon afterward. In general, depressed cancer patients tend to respond to lower doses of antidepressant medication than patients without cancer. If a patient does not respond to maximal dosing of one antidepressant, a drug from a different class should be attempted next.

Since antidepressant efficacy is fairly uniform, the choice of drug will mainly depend on the toxicity profile and potential interactions of a given agent in relation to a specific patient and their medical condition.[76–78,80] Depressed patients with agitation, anxiety, and poor sleep would benefit from an antidepressant with sedating effects such as amitriptyline, doxepin, trazodone, nefazodone, or mirtazapine. Patients with depression that manifests psychomotor slowing, fatigue, or sedation from other medications might benefit from an activating antidepressant that causes minimal sedation, such as desipramine or one of the serotonin specific reuptake inhibitors (SSRIs): fluoxetine, bupropion, or citalopram. Patients with stomatitis, slowed intestinal motility, or urinary retention should receive an antidepressant with minimal anticholinergic activity, such as desipramine, nortriptyline, or one of the SSRIs. The tricyclic antidepressants as a class have the potential for cardiotoxicity and should be given with caution to cancer patients with unrelated heart disease. In particular, these drugs should not be prescribed to patients with cardiac conduction abnormalities or bundle-branch block. Tricyclic antidepressants, as well as monoamine oxidase inhibitors, carry a high risk for lethality in overdose and significant adverse effect profile. These agents are rarely used for depression and should be especially avoided in patients with suicidal ideation. For the majority of depressed cancer patients, the SSRIs (e.g., fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram) will be the antidepressant drugs of choice.[78,80] The SSRIs are well tolerated, effective, and associated with less cardiotoxicity and anticholinergic side effects than the tricyclic class of antidepressants. Among the SSRIs, sertraline, citalopram, and escitalopram have the fewest drug-drug interactions.

Anxiety is common in the cancer patient population, with an incidence of 10-30%, and often coexists with depression.[76,77,79] Rates of anxiety in populations of patients with primary malignant brain tumors specifically are reported to be 30-48%.[88] Anxiety is more likely to be a reactivation of a preexisting disorder than the development of a new disorder.[89] Factors found to be associated with anxiety among patients with PBTs include previous psychiatric illness and female sex. Anxiety was associated with uncertainly about when treatment would begin and what it would involve as well as worries about what symptoms and effects the tumor would have. Psychosocial interventions (such as psychotherapy, stress management, supportive counseling, and cognitive-behavioral therapy) have shown modest effects for preventing or reducing anxiety in adults with cancer.[89] In a recent evidence-based review by Traeger and colleagues, interventions with cognitive-behavioral and stress management components are recommended for patients with moderate to severe anxiety.[89] These interventions offer the opportunity to learn adaptive skills for coping with the diagnosis of cancer. Pharmacologic interventions for anxiety include benzodiazepines, antidepressants, and nonbenzodiazepine anxiolytics. Benzodiazepines are frequently used in oncology for anxiety, particularly panic, as well as for nausea and insomnia. For acute anxiety, available data supports

TABLE 4.4 Antidepressant Drugs Available for Treatment of Depression in Brain Tumor Patients

Drug	Anticholinergic	Sedation	Orthostatic Hypotension	Metabolism	Target Dose (mg/d)
Tricyclics					
Imipramine	++	++	+++	Liver	10-125
Amitryptyline	+++	+++	+++	Liver	10-125
Desipramine	+	+	++	Liver	25-125
Nortriptyline	++	++	+	Liver	25-125
Doxepin	++	+++	++	Liver	25-125
Amoxapine	+	++	+	Liver	100-150
Protriptyline	+++	+	++	Liver	30-60
Selective serotonin reuptake inhibitors (SSRIs)					
Fluoxetine	+	+	+	Liver	20-60
Sertraline	0	+	+	Liver	50-150
Paroxetine	+	+	+	Liver	20-50
Fluvoxamine	+	+	+	Liver	150-200
Citalopram	+	+	+	Liver	20-60
Escitalopram	+	+	+	Liver	10-20
Serotonin/norepinephrine reuptake inhibitors (SNRIs)					
Venlafaxine	+	++	+	Liver	75-375
Duloxetine	0?	+	0	Liver	60-120?
Desvenlafaxine	0′	+	+	Liver	50-400
Other agents					
Bupropion	0	0	0	Liver	200-400
Maprotiline	+	+	++	Liver	100-225
Amoxapine	+	+	0	Liver	200-500
Trazodone	++	+++	++	Liver	200-600
Mirtazapine	+	++	+	Liver	15-60
Nefazodone	+	++	+	Liver	300-600

Abbreviations: 0, negligible; +, mild; ++, moderate; +++, severe; mg/d, mg/day.
Adapted from Refs. 75–77,79.

the use of benzodiazepines. Shorter-acting benzodiazepines such as alprazolam (0.25-2.0 mg three to four times daily), oxazepam (10-15 mg three to four times daily), or lorazepam (0.5-2.0 mg three to four times daily), are preferred due to the decreased risk of accumulation. However, patients who experience breakthrough anxiety or end-of-dose failure using a short-acting benzodiazepine may benefit by switching to a longer-acting drug such as diazepam (5-10 mg twice to four times daily) or clonazepam (0.5-2.0 mg twice to four times daily). For longer-term treatment of anxiety disorders, antidepressants are often preferred. In the general population, SSRIs and SNRIs are first line in the treatment of several disorders including post-traumatic stress disorder, generalized anxiety disorder, and social anxiety disorder. Anxiety disorders may require higher doses and longer duration of treatment with antidepressants, but this has not been reported in patients with cancer.[89] An alternative drug is the nonbenzodiazepine anxiolytic buspirone, which is effective at doses of 5-10 mg three times daily. Neuroleptic drugs such as haloperidol (0.5-5 mg twice to four times daily) or thioridazine (10-25 mg three times daily) may be useful as adjunctive treatment for patients who do not respond well to benzodiazepines or have psychotic features (e.g., hallucinations, delusions) that accompany the anxiety. The evidenced based literature for the pharmacologic treatment of anxiety in cancer is limited largely to

antidepressants and benzodiazepines.[89] The most common causes of an organic anxiety disorder in cancer patients are uncontrolled pain, medication effects (i.e., narcotic analgesics, corticosteroids), infection, and metabolic derangements. Treatment of the underlying medical condition and judicious use of benzodiazepines and/or low-dose antipsychotics are appropriate. Depression and anxiety have been found to have several consequences for patients with PBTs; both negatively impact all aspects of QoL, a decreased functional status highly associated with depression, and preoperative depression has been associated with decreased survival.[88]

PAIN CONTROL ISSUES

Other than the fear of dying, pain is the most common concern of patients diagnosed with cancer.[90] Overall, pain occurs in 20-50% of cancer patients at diagnosis and in 75-90% at advanced stages of disease.[91,92] Many studies suggest that 10-30% of cancer patients with severe pain are inadequately treated.[91] It is imperative that the physician diagnose and treat pain aggressively. In the brain tumor population, the most common form of pain is headache (i.e., 60-90%) caused by elevation of intracranial pressure.[1,9] Dexamethasone, used in judicious doses, is the most effective pharmacological treatment for brain tumor headache.[24] Less common pain syndromes in PBT patients include central pain from tumors that affect the integrity of the thalamus or its regulatory pathways, leptomeningeal spread of neoplasm causing nerve root irritation or damage, and extraneural metastases.[93–95] Similar pain syndromes can develop in patients with MBTs, except that systemic involvement from the primary neoplasm (e.g., bone, lung, pleura, liver, brachial or lumbosacral plexopathy, leptomeningeal metastases, epidural spinal cord compression) is more frequent. During routine clinic visits and hospital stays, the physician should always include questions about pain control in the review of systems. Any neuro-oncology patient with an unexplained progressive pain problem (e.g., facial pain, arm pain, radiating leg pain) should immediately undergo a diagnostic investigation to ascertain the etiology.[96]

The current pharmacological management of cancer-related pain is effective in most patients (see Table 4.5).[91,92,98] In some cases, analgesics are used to augment pain relief provided by primary therapy (i.e., surgery, RT, chemotherapy). In others, analgesics form the mainstay of therapy. The three-step "analgesic ladder" provides a systematic approach to alleviating the patient's pain using analgesic pharmacotherapy.[92] In step 1, nonopioid analgesics (e.g., acetaminophen, aspirin, nonsteroidal anti-inflammatory drugs) are used, possibly in combination with an adjuvant analgesic (e.g., antidepressants, anticonvulsants, local anesthetics), to treat mild pain. If this level of analgesia proves ineffective, step 2 proceeds with the use of opioids designed for mild to moderate pain (e.g., codeine, oxycodone) in combination with nonopioid and adjuvant analgesics. In patients with moderate to severe pain, more potent opioid analgesics are selected for step 3 (e.g., morphine, fentanyl patch, oxycodone, hydromorphone), often in conjunction with nonopioid and adjuvant analgesics. The transdermal fentanyl patch is an excellent alternative to oral medication approaches, since it is available in a wide variety of doses (25, 50, 75, and 100 μg/h) and provides steady release of drug for 72 h per patch.[99] However, fentanyl patches should be reserved for chronic pain in opioid tolerant patients. Fentanyl patches take 12-24 h to begin working once placed and do not reach peak effect until up to 72 h after placement. Therefore, titration should not be more frequent than 72 h. For patients with severe pain that requires inpatient evaluation and treatment, many authors recommend a patient-controlled analgesia approach.[97] Short-acting narcotic analgesics such as morphine, hydromorphone, and fentanyl are used for this purpose and are usually administered by the intravenous, epidural, subcutaneous, or intrathecal route. In addition, short-acting narcotic analgesics are used for breakthrough pain that can occur intermittently in patients who are otherwise well controlled.[100] It is uncommon for brain tumor patients to have pain that is refractory to the stepwise application of systemic pharmacotherapy (in addition to primary treatment and dexamethasone). However, neuro-oncology patients with other types of pain syndromes, such as malignant plexopathy or spinal cord compression, may have severe pain that will only respond to step 3 analgesics. In rare cases of severe pain refractory to step 3 medications, neuro-oncology patients may require invasive analgesic techniques such as regional anesthesia, sympathetic blockade, somatic neurolysis, or cordotomy.[91,92]

Side effects of opioids are generally manageable. Despite constipation being the most commonly experienced side effect of opioids, only 27% of patients were prescribed laxatives in conjunction with their pain medication.[101] A bowel regimen should be prescribed at the time of initiation of opioids. Bowel regimens should include a stool softener, such as docusate, and a mild laxative, such as senna. These agents are available in combination products. Around the clock usage of bowel regimen should be encouraged. Sedation side effects of opioids tend to dissipate with time. For patients who experience nausea with opioids, taking the medication with food can help manage this side effects. Itching may be managed with antihistamines or by switching to a more synthetic opioid (i.e., fentanyl or hydromorphone). Often patients may worry about addiction. It is important to emphasize the difference between

TABLE 4.5 Analgesic Medications Available for Treatment of Pain in Brain Tumor and Neuro-Oncology Patients

Drug	Route	Dose (mg/d)	Peak Effect (h)	Duration (h)
Analgesics for mild pain: step 1				
Aspirin	Oral	1000-4000	0.25	4-6
Acetaminophen	Oral	1000-4000	0.25	4-6
NSAIDS (e.g., ibuprofen, ketorlac)	Oral	1200-4000	0.25	4-6
Steroids (e.g., dexamethasone)	Oral, IV, IM	4-16	2-4	6-8
Adjuvant analgesic medications				
Amitriptyline	Oral	10-100	-	qd; long term
Mexilitine	Oral	150-900	-	qd; long term
Carbamazepine	Oral	200-1200	-	qd; long term
Baclofen	Oral	10-80	-	qd; long term
Analgesics for moderate pain: step 2				
Codeine	Oral, IM	60-240	0.5	3-6
Ocycodone	Oral	30-180	0.5	3-6
Hydrocodone	Oral	15-45	0.5	4-6
Propoxyphene	Oral	130-390	1.0	4-6
Analgesics for severe pain: step 3				
Morphine	Oral, IM, IV	40-240 (oral) 10-40 (IV, IM)	1.5-2	4-6
Hydromorphone	Oral, IM, IV	10-48 (oral) 4-24 (IV, IM)	1-2	3-4
Meperidine	Oral, IM, IV	100-400	1-2	3-6
Fentanyl	TD	25-100 mcg/h q72h	72	-
Methadone	Oral	10-60	0.5-1.5	4-6

Abbreviations: mg/d, mg/day; h, hour; NSAIDS, nonsteroidal anti-inflammatory agents; IV, intravenous; IM, intramuscular; TD, transdermal; mcg, microgram.
Adapted from Refs. 90,91,96,97.

dependence and addiction. In the absence of past addictive behaviors, most patients are at a low risk for addiction to opioids, as long as they are only being taken for true pain.

Some physicians and nurses are reticent about aggressive analgesic pharmacotherapy because of fears that the patient may become addicted or could expire earlier from the treatment.[90] If one of the goals of the physician is to provide comfort and remove suffering, then it is morally and ethically proper to prescribe the amount of analgesia necessary to achieve these goals. In addition, despite the emphasis on pain management, uncontrolled pain is still a significant problem among patients with cancer. Nearly two-thirds of patients with advanced cancer experience pain and almost half of those patients are undertreated. Frequent assessment and management of pain can improve not only a patient's physical state, but also their psychological and social well-being.[101]

PALLIATIVE CARE

The hospice movement originated in England in the 1960s when Dr. Cicely Saunders founded the first multidisciplinary hospice to care for terminally ill patients.[102–104] The movement expanded and eventually spread to the United States in the 1970s. In England, most of the hospice care was administered within inpatient facilities, while in the United States the care was shifted, whenever possible, to the home setting. Recent data would suggest that the quality of hospice care is superior to the care available in the non-hospice setting for patients in the end stages of life.[105] The improved quality of care was equivalent whether the patient was in a hospital-based unit, inpatient non-hospital-based unit, or home hospice setting. Because of the success of the early hospice programs, Congress passed legislation resulting in the establishment of the Medicare Hospice

Benefit in 1982.[103,104] The Medicare Hospice Benefit subsidizes care for terminally ill patients with a life expectancy of 6 months or less, as certified by their attending physician and the hospice medical director. In addition to the life expectancy criteria, other qualifications for Medicare Hospice Benefit include eligibility for Medicare (i.e., at least 65 years of age or certified as disabled), foregoing further aggressive or "curative" therapy, being able to receive most care in the home, and having a primary caregiver present at home. The Medicare Benefit will continue to pay for patients who live longer than 6 months as long as the attending physician continues to certify the patient is terminally ill.

Palliative care in oncology mainly began as hospice and end-of-life care. During the past 20 years, increasing attention has been paid to QoL issues in oncology throughout the disease trajectory. While palliative care previously focused on end-of-life care, the idea that palliative care needs to be integrated earlier in the continuum of care is increasingly understood.[106] The ASCO panel for clinical opinion on the integration of palliative care into standard oncology care reviewed seven randomized, controlled trials and concluded that "palliative care—when combined with standard cancer care or as the main focus of care—leads to better patient and caregiver outcomes."[107] The NCCN Clinical Practice Guidelines in Oncology define palliative care as "a special kind of patient and family-centered health care that focuses on effective management of pain and other distressing symptoms, while incorporating psychosocial and spiritual care according to the patient/family needs, values, beliefs, and culture(s)."[106] The goals of palliative care are to "anticipate, prevent, and reduce suffering and to support the best possible QoL for patients and their families, regardless of the stage of disease or need for other therapies." Initially, the primary oncology team can provide most of the palliative care needed by the patient. Intractable symptoms or complex psychosocial problems can benefit from the inclusion of palliative care experts. Palliative care becomes the main focus of care when disease-directed, life-prolonging therapies are no longer effective, appropriate, or desired.[106]

Despite these recommendations and increasing evidence on the benefits of early palliative care, most patients in the United States are referred to hospice care too late or not at all for comprehensive palliative care to exert its full benefit. The 2012 edition of the *National Hospice and Palliative Care Organization Facts and Figures: Hospice Care in America* states that 43% of Medicare descendants with a cancer diagnosis accessed ≥3 days of hospice in 2007. However, the median length of hospice service was only 19 days in 2011.[106]

Despite aggressive tumor-directed treatment, the median survival for anaplastic gliomas is estimated to be between 2 and 5 years, and only 15 months for patients with GBM. For most patients with high-grade PBT or MBT, long-term survival remains elusive and therefore a comprehensive approaching focusing on maintaining QoL is required. Therefore, the most important and critical step will be to broach the subject of hospice care and palliative symptom control.[90,108–110] Similar to when the physician first tells the patient his or her diagnosis, this must be done with the utmost compassion and sensitivity. Patients with HGGs at the end of life have a consistently high symptom burden, especially during the last days, further highlighting the importance of palliative care.[111] Approximately 16% of cancer patients being discharged from a single hospital in Germany were assessed as having palliative care needs, with the greatest needs in patients with head and neck cancer, melanoma, and brain tumors.[106]

Walbert and Khan conducted a systematic literature review to identify specific symptoms and patterns of end-of-life care in HGG.[111] Patients experienced a wide range of symptoms at the end-of-life, with drowsiness or loss of consciousness being the most common. Impaired consciousness prior to death can be caused by mass effect, hydrocephalus, herniation syndromes, and seizures. Other frequently reported symptoms included poor communication, focal deficits, dysphagia, seizures, and headaches. Because decreased consciousness, poor communication, speech difficulties, and cognitive impairment are frequent at the end of life for this patient population, implementation of advanced care planning should be incorporated into standard of care earlier in the disease trajectory.

Seizures are reported in up to 56% of all brain tumor patients during the end-of-life phase, with the highest risk among patients with a prior history of seizure.[111] Optimization of seizure management is complicated by the patient's inability/difficulty in swallowing and decreased level of consciousness. Dysphagia is reported in up to 85% of patients during the end-of-life phase.[111] Different alternative routes can be used for the delivery of AEDs, including intramuscular, intravenous, subcutaneous, buccal, or intranasal application. Most AED medications can also be compounded into rectal suppositories. Proper control of seizures is important in end-of-life care, as seizures have been associated with a non-peaceful death. Dysphagia not only interferes with a patient's ability to take medication, but also nutrition and hydration. Anorexia is common at the end of life, but a lack of desire to eat is different from an inability to swallow. Continuation of hydration and initiation of tube feeding provide caregivers with a perception that it may prolong life and provide some hope and comfort. There are no formal studies on the impact of hydration and tube feeding in the brain tumor population. However, there are risks associated with the addition of hydration and tube feeding, including infection and

pulmonary edema. Care should be taken when initiating these interventions. The majority of patients reviewed in Walbert and Khan's article did receive hydration during the last days of life.[111]

In Walbert and Khan's review, between 4% and 62% of patients reported headaches at the end of life.[111] Steroids are frequently used in the care of brain tumor patients to alleviate symptoms of edema and counteract headache. Although there are no specific guidelines, several authors described the discontinuation of steroid use during the last days of life as part of end-of-life management.[111] Bausewein *et al*. reported that in their study, steroids were discontinued in 23% of patients without any change in symptoms.[112] These authors recommended that steroids be discontinued when the patient becomes unconscious to avoid artificial prolongation of the dying process. Opioids and NSAIDs are also frequently used to manage headaches as well as pain. While pain is one of the most prominent symptoms in systemic cancer, only 13-25% of brain tumor patients were reported to be affected by bodily pain.[111] Pain issues for patients with MBT may require pain control as part of the end-of-life management for their primary disease.

One barrier to palliative and hospice care is the perception by patients and/or caregivers that these services indicate "giving up" or a lack of hope. However, palliative care provides a different kind of hope than that for cure of the disease itself. Hope for cure is shifted to hope for maximizing dignity, comfort, QoL, and the process of enjoying each remaining day to its fullest. In addition, support is provided for the family members, who are also suffering and attempting to cope with the imminent loss of their loved one.[113] Palliative care should continue even after the patient's death in the form of bereavement support for the patient's survivors. One of the most common fears about advanced incurable cancer is isolation from family and loved ones. The presence of the hospice care team, especially in the home setting, alleviates this fear and ensures that isolation and loneliness are minimized.

ETHICAL ISSUES

The care of brain tumor and other neuro-oncology patients is often complicated by numerous ethical dilemmas and discussions.[114–117] In no other subspecialty of medicine are there such large numbers of seriously ill patients in which the day-to-day care involves life and death decisions. These patients are not only adversely affected by their disease, but frequently suffer deleterious side effects and complications from treatment, which is often very intense and rigorous. Physicians caring for neuro-oncologic patients should be well versed in ethical principles and theory. This foundation will better prepare the physician for the many complex ethical predicaments that inevitably develop during the course of therapy and, in many cases, subsequent palliative care.

There are several basic ethical principles that require definition. The most important ethical principles are respect for autonomy, justice, beneficence, and nonmaleficence.[114–117] *Respect for autonomy* refers to recognition by the physician of the patient's right and ability to make his own decisions. These decisions are unique, are influenced by the patient's value system, and may differ from what is advised by the physician. *Justice* relates to fairness and what people are legitimately entitled to once they enter the medical system. In this context, justice demands that patients with brain tumors have access to care (e.g., treatment, pain control, nutritional support) equal to patients with other diseases that may have a less grave prognosis. *Beneficence* refers to actions by the physician toward the patient that will maximize positive outcomes and avoid unnecessary pain, injury, and suffering. These activities can include treatment of the cancer and extension of quality survival, control of pain and other disease-related symptoms, and interpersonal support. *Nonmaleficence* means that the physician should "do no harm" while providing care to the patient. This principle has a broad scope and can refer to many issues, including withholding relevant diagnostic or prognostic information, improper treatment of pain, inappropriate undertreatment, and persistent overtreatment.

Physicians usually have an ethical position or frame of reference that incorporates these basic ethical principles. The most common ethical stance is that in which the physician makes a decision based on an assessment of the good or bad consequences of each course of action. This ethical position, called *consequentialism* or *utilitarianism*, justifies a given decision by comparing probable good or benefit with potential harm or pain.[118] The second most common ethical position, *respect for persons*, relies heavily on the ethical principles of autonomy and respect.[114] This approach emphasizes the importance of allowing patients to be involved in all decisions about their care and treatment. An alternative to *respect for persons* is *paternalism*, in which the physician assumes that all decisions should be made for the good of the patient, without regard to his or her specific wishes or needs.[114–118]

It is often difficult to be honest with a patient when discussing a new diagnosis as devastating as cancer, especially when it is a brain tumor.[103–116,119,120] In fact, a survey of ethical issues in the oncology literature determined that *truth-telling* was the most commonly debated subject.[118] Between 1961 and 1979, most physicians took the paternalistic approach and withheld information regarding diagnosis and prognosis in order to maintain hope and minimize psychological damage to their patients. Since 1979, attitudes have changed so that

many physicians now prefer to reveal accurate information about their patient's diagnosis and prognosis.[119,120] This trend away from paternalism, toward a more "patient-oriented" or "respect for persons" approach when discussing diagnosis and prognosis, is important since the vast majority of patients want to know as much as possible about their disease, treatment options, and chances of survival.[120]

The physician caring for a brain tumor patient needs to balance the ethically appropriate duty to convey accurate information about diagnosis and prognosis with the equally important responsibility to nurture and maintain hope. However, it is now clear that a more honest and accurate diagnostic interview does not remove hope and is more likely to strengthen the physician-patient relationship.[120] The physician should explore what hope means to each patient, since it can represent many different things, some of which will be separate from the hope for cure or lengthy survival.

Ethical issues arise frequently during the design and administration of clinical trials for oncology patients. The moral cornerstone of any clinical trial is the concept and practice of valid informed consent.[120] Valid consent has three features: the provision of adequate information, the absence of coercion, and the competence of the patient. Adequate information must be provided about tests, procedures, and treatments inherent in any clinical trial. Significant risks and benefits, if any, must be outlined. All serious risks that are likely to occur should be included. Any risk of death beyond a trivial risk should also be included, because death is such a serious evil that the patient must be made aware of any chance that it may occur.[121,122] Rational alternative treatment to the clinical trial in question must be presented by the physician in an open, objective, and unbiased manner. Alternative treatments should include those offered at other medical centers. One of the duties of the physician is to inform the patient of the consequences and probable outcome with no treatment at all. The patient should know that the final decision concerning any clinical trial is his or hers alone to make. Competency, in this setting, implies that the patient understands the information provided during the consent process and appreciates that it applies to him/her at that particular point in time.

The protection of the patient's best interests falls squarely and heavily on the shoulders of the physician seeking participation in the clinical trial.[117] The physician must take into account the influence of personal beliefs, biases, and academic ambitions before embarking on such endeavors. The focus of the physician who designs and performs clinical trials must always be on the need for conclusive proof of efficacy. A study designed according to rigorous scientific and ethical criteria can accrue patients with confidence and good faith.

The decision to stop therapy is often very difficult for patients, family members, and the treatment team.[114–117,123,124] It signals the "beginning of the end," when all reasonable hope for cure or prolonged stabilization is gone and the patient's death is imminent. These decisions usually arise when the patient has just progressed through the latest protocol and has often suffered further neurological deterioration. In many cases, the neurological status is quite poor, to a degree that functional ambulation, cognition, and verbal interaction are severely compromised. Although there are often other treatment options that could be offered, the physician must state clearly and honestly that further therapy will not significantly affect outcome. In this situation, it is critical to weigh the adverse effects of further therapy on QoL against the potential benefits for improvement of QoL and prolongation of survival, which would be extremely limited. The physician must reassure the patient and family that the termination of active treatment does not mean the physician will abandon them. Even though the focus of subsequent care will shift to comfort, pain relief, and symptom control, the physician will remain actively involved in the patient's care. In addition to questions about the potential for extension of survival, many patients and family members want to know if further treatment might improve neurological function. In other words, could the patient's current neurological status be reversed somewhat to enhance QoL for the time they have left? Neurological function is rarely restored or improved at these late stages of disease; it would be optimistic even to expect further therapy to stabilize the patient's condition.

Because QoL is so subjective and the behavior of brain tumors can be so variable, the proper time to stop treatment will differ from patient to patient. Some patients accustomed to a high level of function cannot tolerate living their life in a severely compromised fashion while suffering the rigors of treatment. For others, the alterations of function and lifestyle are more easily accepted, so that simple survival is adequate, with less regard for the quality of existence.

Is it ethically appropriate to terminate therapy? If the physician has explained the situation properly and is acting in accordance with the wishes of the patient or family, the decision would be consistent with the principles of respect for autonomy, beneficence, and nonmaleficence.[114–117,123–125] The physician would be acting to allow a more dignified, peaceful death without the rigors of active therapy. Active treatment is terminated to "promote the good," which is to let the patient die on their own terms. It would be ethically improper and contrary to the principle of nonmaleficence for the physician to coerce or force the patient into undergoing further therapy.

CONCLUSION

Although the focus of the treatment team is on curative or stabilizing therapy for most patients, it is still very important for the treating physician to be aware of the many aspects of supportive care outlined above. Common problems related to seizure control, toxicity of anticonvulsants and corticosteroids, depression, prophylaxis and treatment of thromboembolic complications, and pain control must be assiduously monitored in every patient. As each patient enters the final stages of his or her disease, the physician must also be aware of end-of-life issues and the appropriate utilization of hospice resources. All of these aspects of care should be performed in the context of proper ethical conduct and under the principles of respect for autonomy and beneficence.

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CHAPTER

5

Brain-Tumor-Related Epilepsy in Children

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CHAPTER CONTENTS

THE PEDIATRIC PERSPECTIVE

The occurrence of a brain tumor is a universally feared cause of seizures and epilepsy no matter what the age of a patient at presentation. At some point in their career, most clinicians reading this text will encounter a child presenting with a brain tumor. The aims of this chapter are to provide the clinician with a broad understanding of presentation, localization, natural history, and pathology of brain tumors commonly associated with seizures in children and to aid clinical diagnosis and management of seizures and epilepsy in the context of other management considerations.

EPILEPSY-ASSOCIATED BRAIN TUMORS

Just as children are not "little adults," pediatric brain tumors are different than those found in adults. Whereas higher-grade malignancies and metastases are the predominant brain tumor types in adults, low-grade, indolent tumors are much more common in children.[1,2] Even among tumors with similar histological and morphological characteristics and localization, oncogenic mechanisms and natural history in the developing brain are quite different than that seen in the adult population.[3] In addition, brain tumors are predominantly infratentorial in children.[1] The differences in biology and outcome between infratentorial and supratentorial tumors with similar histology have been the source of considerable controversy in the classification of some childhood brain tumors. Two classification schemas are currently in use: the World Health Organization classification[4] and the International Classification of Childhood Cancer.[5]

The focus of this chapter will be on primary supratentorial brain tumors that cause seizures. Descriptive studies of children with specific brain tumor pathologies are somewhat limited in applicability to this discussion because of the propensity for such series to combine adults and children as well as children with infratentorial and supratentorial tumors. The term "low-grade epilepsy-associated tumor" (LEAT) has been proposed by Luyken *et al.*[6] to denote a heterogeneous group of primary brain tumors of glial, neuronal, and mixed neuronal-glial lineage with certain typical characteristics: slow growth (WHO grade I or II), prominent involvement of the neocortex, and presentation with recurrent seizures early in the course of symptomatic disease in a young

TABLE 5.1A Common LEATs

Tumor (WHO Grade)	Peak Age Group	Supratentorial Localization	Affected Genes and Loci in Children[a]	Histopathology	Favorable Prognostic Factors in Children
Pilocytic astrocytoma (I)	Infants to young adults	Temporal	*NF1*, *BRAF*, *FGFR1*, *PTPN11*, *NTRK2*	Compact bipolar astrocytes, loosely packed areas with microcysts, eosinophilic granular bodies, rosenthal fibers	Complete resection, asymptomatic tumor in NF1 patients, *BRAF-KIAA* fusion (rare in supratentorial), ↓ mitotic index, absence of *BRAF* V600E mutation, absence of CD34 expression
Diffuse (fibrillary, pilomyxoid, gemistocytic, protoplasmic) astrocytoma (II)	Young adults	Frontal Temporal	*BRAF*, *CDKN2A*, *MYB* family, *16p*, *17p*, *19p*,*19q*, *22*	Hypercellular, merging with surrounding normal tissue, nuclear atypia, microcysts, calcification	Complete resection, older age at presentation, fibrillary pathology
Dysembryoplastic neuroepithelial tumor	Young teens	Mesial temporal	*BRAF*	Nodular pattern, nuclear atypia	Short time to surgery, complete resection, no associated dysplasia
Ganglioglioma (I)	10-20 years	Temporal	*BRAF*, chromosome 7	Nesting and clustering of neuronal and ganglion cells with large nuclei, binucleated forms, prominent nucleoli, and Nissl substance. Astrocytes in varying stages of differentiation	Complete resection

[a] *Adapted from Ref. [7].*

TABLE 5.1B Uncommon LEATs

Tumor (WHO Grade)	Peak Age Group	Supratentorial Localization	Affected Genes and Loci in Children[a]	Histopathology	Favorable Prognostic Factors in Children
Angiocentric glioma (I)	Late teens	Frontoparietal, mesial temporal	*MYB* family, *FGFR1*, *FGFR3*	Monomorphic, bipolar cells with elongated nuclei with angiocentric arrangement (ependymoma-like appearance)	None identified
Pleomorphic xanthroastrocytoma (II)	Adolescents, young adults	Temporal Parietal	*BRAF*, *CDKN2A*, *9p*	Nuclear atypia with pleomorphism and multinucleation, lipid-rich, reticulin fibers, meningeal involvement	Complete resection, ↓ mitotic index
Oligodendroglioma (II)	Adults	Frontal	*MGMT*	Diffuse infiltration of monomorphic cells with uniform round, vesicular nuclei, distinct small nucleoli, perinuclear halo, calcifications, mucoid and cystic degeneration	Loss of 1p/19q, absence of loss of deletion of 10q
Oligoastrocytoma (II)	Adults	Frontal	*TP53*, *CDKN2A/B/C*, *PTEN*, *9p*	Mixed features of oligodendroglioma and astrocytoma	Complete resection, age >3 at presentation
Gangliocytoma (I)	School age to young adult	Temporal	Not reported	Nesting and clustering of neuronal and ganglion cells with large nuclei, binucleated forms, prominent nucleoli, and Nissl substance	Complete resection
Papillary glioneuronal tumors	School age to adulthood	Frontal Temporal	*MGMT*,*PTEN*, *PMS2*, chromosome 7	Biphasic pattern—small uniform cells lining pseudopapillae with hyalinized vascular cores and neurocytes with uniform nuclei in the interpapillary zone, ganglioid and ganglion cells	Complete resection
Astroblastoma (none)	Young teen	Medial frontal/ parietal convexity	Chromosome 19, *20q*	Intermediate between astrocytoma and ependymoma	Complete resection (low grade), absence of anaplastic histology

[a] *Adapted from Ref. [7].*

TABLE 5.2 Other Low- and Intermediate-Grade Tumors Associated with Seizures

Tumor (WHO Grade)	Peak Age Group	Supratentorial Localization	Affected Genes and Loci in Children[a]	Histopathology	Favorable Prognostic Factors in Children
Choroid plexus papilloma (I)	Neonates to school age	Lateral and third ventricles	*TWIST1* (*CDKN1A*, *CFLAR*, *SERPINB2*, *FIGF*), *MGMT*, 9p, Xp22	Single layer of crowded epithelial cells with mild atypia overlying a fibrovascular core, often with vascular stalk	Complete resection
Ependymoma (II/III)	Early childhood	Frontal Temporal Parietal, 3rd ventricle	Chromosome 6, 13, 22, *1q22-31*	Moderate cellularity, monomorphic cells with round/oval nuclei and "salt and pepper" chromatin; perivascular pseudorosettes and ependymal rosettes, areas of fibrillarity and regressive changes	Complete resection, gain of chromosome 9, 15q, and/or 18, loss of chromosome 6, lack of *CDKN2A* homozygous deletion or 1q gain, absence of dissemination
Desmoplastic infantile ganglioglioma (I)	<2 years old	Frontal Parietal	*BRAF*	Massive size, prominent desmoplasia, poorly differentiated ganglion and glial cells, mitotic activity, and rare anaplasia	Complete resection

[a] *Adapted from Ref. [7].*

patient (Tables 5.1a and 5.1b). This term may not apply as well to children as it does to adults, given the higher propensity for infratentorial presentation of some of these tumor types in children; nevertheless, such tumors are overrepresented in surgical series of adults and children with pharmacoresistant tumor-related epilepsy.[8] Controlling ongoing seizures associated with LEATs is typically of primary importance, with aggressive strategies often being reserved for patients with pharmacoresistant epilepsy.[9]

The goals of management in children with other low-grade tumors (Table 5.2) and malignant primary brain tumors (Table 5.3) that cause seizures is typically improved survival, palliation, and prevention of progression or recurrence of other neurologic symptoms. Addressing these aims may directly influence seizure treatment and outcome, but seizure freedom is usually achievable and is an important determinant of quality of life.[9,10]

A broader definition of the supratentorial intracranial tumors and epilepsy may include not only the brain tumors discussed in this chapter, but also metastatic,[11–13] vascular,[14] hematologic,[15,16] meningeal,[17,18] and pineal [19–22] and sellar[23–25] region tumors as well as cortical tubers[26,27] and hypothalamic hamartoma.[28] Likewise, epilepsy and seizure-like events have rarely been associated with tumors at other sites in the brain, including the brainstem and cerebellum.[29]

PATHOPHYSIOLOGY

The pathophysiology of brain-tumor-related seizures is complex and likely different for different tumor types, but the final common pathways of epileptogenesis are similar.[7,30] Primary brain tumors arise from inherited and/or acquired genetic defects in a single cell that induce metabolic and structural changes and abnormal proliferation of one or multiple cell lines.[31] Over time, these result in blood-brain-barrier disruption and a cascade of morphological and environmental changes in the tumoral and peritumoral neural and glial tissue that lead to neuronal hyperexcitability.[32] Epileptogenesis is driven by denervation hypersensitivity (due to cortical deafferentation) and dysregulation of ions, ion channels, neurotransmitters, receptors, and inflammatory and immune mechanisms as well as hypoxia, acidosis, and other metabolic changes in the peritumoral region that, in turn, activate an epileptic network (see Chapter 7). Seizures are thought to recur even after long periods of control because of both gradual epileptogenic changes with this network and because of progressive and acute changes in the tumor microenvironment.[33]

Young children are at increased risk of developing seizures due to structural brain lesions because of increased excitation and decreased inhibition within potentially epileptogenic networks. Such networks are optimized for learning and adaption during this phase of rapid development. Several mechanisms contribute to the maladaptive epileptogenic response to structural abnormalities, including the development of excitatory synapses and processes prior to inhibitory ones, the increased presence of electrical (i.e., gap-junction-mediated) synapses, and the differential expression of neurotransmitters, ion channels and transporters. These result in poor adaptation to changes in the intracellular

TABLE 5.3 Malignant Primary Brain Tumors Associated with Seizures

Tumor (WHO Grade)	Peak Age Group	Supratentorial Localization	Affected Genes and Loci in Children[a]	Histopathology	Favorable Prognostic Factors in Children
Anaplastic astrocytoma (III)	Adults	Frontal Temporal	*PDGF/PDGFR*, *TP53* (especially >3 years old), *5q*, *6q*, *9q*, *12q*, *22q*	Similar to diffuse astrocytoma, more cellular, more nuclear atypia, and increased mitotic index	Complete resection, ↓ mitotic index
Glioblastoma (IV)	Adults	Frontal	*H3F3A*, *ATRX*, *DAXX*, *ADAM3A*, *PDGFRA*, *BRAF MDM2*, *CDKN2A*, *1q*, *3q*, *16p*, *8q*, *17p*	Anaplastic cells with cellular pleomorphism, nuclear atypia, multinucleated cells, high mitotic activity, karyorrhectic cells, secondary structures of Scherer, pseudopalisading necrosis, coagulation necrosis, microvascular proliferation	Absence of *p53* overexpression
Anaplastic oligodendroglioma (III)	Adults	Frontal	Not reported	Similar to lower grade, but with increased cellularity, nuclear atypia, increased mitotic activity, microvascular proliferation and necrosis, frequent minigemistocytes and gliofibrillary oligodendrocytes	Absence of necrosis
Anaplastic oligoastrocytoma (III)	Adults	Frontal	Not reported	Similar to lower grade, but with more cellularity, nuclear atypia, mitotic figures, and pleomorphism	
Primitive neuroectodermal tumors (e.g., CNS neuroblastoma, CNS ganglioneuroblastoma) (IV)	Children and young adults	Frontal Parietal	*IDH1*, *CDKN2A*, *PDGFRA*, 1q, 19p	Small, round blue cells with hyperchromatic nuclei, abundant mitotic figures, and desmoplasia	Age >3 at diagnosis, absence of neural subtype (gene expression profile enriched for genes associated with embryonic or neural stem cells), absence of dissemination, absence of necrosis

[a] *Adapted from Ref. [7].*

and extracellular ionic microenvironment (such as those that occur in tumors) and delayed development of networks that can modify the expression of seizures.[34] Children with brain tumors, especially those undergoing treatment, are also repetitively exposed to multiple provoking factors.

Established significant risk factors for the development of epilepsy-associated brain tumors in children include exposure to ionizing radiation (especially high-dose cranial irradiation) and monogenetic syndromes, including Li-Fraumeni syndrome, Rubenstein-Taybi syndrome, Turcot syndrome, hereditary retinoblastoma, and Neurofibromatosis type I (NF1).[35]

Outside of these syndromes, several case reports, case-control, and cohort series document the aggregation of astrocytoma in families, raising the question of the relative contributions of genetic predisposition and environmental exposures. Extensive studies of the protective or detrimental role of dietary, infectious, and other environmental exposures (including enzyme-inducing antiseizure drugs; see Chapter 11) have failed to reach definitive and reproducible conclusions in children.[36]

The field of molecular epidemiology aims to define the role of interactions between environmental exposures and relevant molecular pathway mutations and polymorphisms in the occurrence, growth, and malignant transformation of brain tumors.[37] While utilizing this methodology to establish the risk of exposure to ionizing radiation is of importance to oncologists, an example of interest to epileptologists is the interaction between environmental stimuli and the mammalian

target of rapamicin (mTOR) pathway. This pathway is thought to be central to pediatric glioma development and malignant transformation[38] as well as to the development of epilepsy in patients with several different genetic conditions and structural brain abnormalities, including tumors.[39] Evidence of human papillomavirus (HPV) 6 and 16 infections was recently found in a substantial portion of specimens of glioblastoma multiforme from adult patients. Infection status was associated with decreased survival.[40] Although similar studies have not been undertaken in childhood brain tumor specimens, evidence of human papillomavirus 16 infection was found in all pathological specimens of focal cortical dysplasia type IIB (but not in any control specimens resected from patients with tumors, including adult gangliogliomas) in a single pathology study of children and adults with intractable epilepsy. Furthermore, transfection of E6 (an HPV 16-associated protein) in fetal mice resulted in disruption of cortical lamination by a mTOR pathway-dependent mechanism (N.B. brain development of the transfected animal model beyond the first trimester was not studied).[41] Nevertheless, most brain tumors are not associated with focal cortical dysplasia II, and the converse is also true.[42] Further study needs to be done to establish if there is an interaction between exposure to specific HPV-related antigens, stage of brain development at exposure, and specific mTOR pathway polymorphisms in the development or malignant transformation of some epilepsy-associated glial tumors and, if so, whether this interaction affects oncologic or epilepsy outcome.

EPIDEMIOLOGY

Brain Tumors

The central nervous system is the most commonly affected site in children with solid tumors, accounting for about 18% of all incident childhood malignancies in the United States. Combining incidence and mortality estimates, about 26,000 children are currently living with a brain tumor in the United States. In the past 15 years, the worldwide incidence of central nervous system tumors was 2.9-5.3 cases per 100,000 person-years for children and adolescents. The highest incidence (4.2/100,000 person-years) in the United States was between age 1 and 4 and the lowest incidence (2.1/100,000 person-years) was between age 15 and 19. Incidence steadily increased with age after adolescence. Boys were slightly more commonly affected than girls. White children were more commonly diagnosed (3.2/100,000 person-years), and Asian/Pacific Islander children were less commonly diagnosed (1.8/100,000 person-years).[1,35]

Roughly one-third to one-half of all childhood central nervous system tumors are supratentorial in location, with about one-half to two-thirds of supratentorial tumors located primarily within lobar white matter or cortex.[2,43] There is a predominance of supratentorial over infratentorial tumors during the first 2 years of life and again in late adolescence. Both sexes are equally affected.

Registry data from the past 40 years suggests a modest increase in incidence of central nervous system tumors. Inconsistencies in nomenclature and advances in diagnostic practice, especially the increased utilization of magnetic resonance imaging (MRI) and tissue diagnosis, account for at least some of this growth.[2]

In 2009, central nervous system tumors and related morbidity accounted for 14% (over 12,500 per year) of all US pediatric-cancer-related hospitalizations and children accounted for 15% of all US central nervous system tumor-related admissions. Despite an overall lower rate of high-grade malignancy in children compared to adults, children with central nervous system tumors were more likely to be admitted to the hospital. The mean (US $39,000) and median (US $26,000) costs (surrogate measures of resource utilization and acuity) of a pediatric central nervous system tumor-related hospitalization were more than double those of adults with central nervous system tumors and ranked among the 15 costliest childhood hospitalization diagnosis categories.[44]

Seizures and Epilepsy

The worldwide incidence of afebrile or unprovoked seizures (regardless of the eventual diagnosis of epilepsy) in children is between 57 and 154 per 100,000 person-years and the incidence of epilepsy is between 35 and 124 per 100,000 person-years, with a cumulative incidence up until the late teens of 0.7-1.7%. Overall seizure and epilepsy incidence declines over the first two decades of life, but the incidence of focal-onset seizures peaks during the end of the first decade.[45]

The epidemiology of brain-tumor-related seizures is subject to several sources of bias and confounding factors. Reports of tumor type and location and epilepsy characteristics are almost exclusively based on retrospective surgical/pathology series, necessarily excluding those who have not undergone resection. Such series differ in referral source, tumor classification, relative proportions of children and adults, and proportions of patients with pharmacoresponsive and pharmacoresistant epilepsy. These limitations notwithstanding, there are several important differences between adults and children with brain-tumor-related seizures.

Unlike adults with epilepsy, a small minority of all children with epilepsy have a structural abnormality. Primary brain tumors are found in 1.5-2.9% of children with seizures and in about 1.1% of children with epilepsy.[45–47] Most likely, this is related to the relatively low incidence of brain tumors in children compared with adults and the relatively high incidence of genetic syndromes in children with epilepsy. Children with brain tumors also have a lower incidence of epilepsy and seizures (due to the higher proportion of infratentorial localization in children), but children with supratentorial tumors have a comparable incidence. Seizures are a presenting sign in 9-14% of all brain tumors, 22-38% of supratentorial tumors, 40% of tumors involving neocortex, and 49% of pure lobar tumors in children.[43,48,49] In a single-center surgical series, Khan and coworkers[49,50] reported the timing of presentation of children who had seizures during their clinical course. Sixty percent presented with seizures before tumor diagnosis and 40% presented afterward. This proportion was found both for children with low-grade glial and glioneuronal tumors as well as a larger group with more diverse pathology and grade. Out of seven children with primary brain tumors in a community cohort of US children with epilepsy, four were diagnosed prior to seizure onset and three were found on imaging of patients with new-onset seizures (all three of whom were developmentally normal and without abnormalities on examination).[47,51]

Gilles and coworkers[43] found that seizure presentations of primary supratentorial brain tumors were increasingly common with age: 17% in children under 1 year of age, 68% in the age 18-20 group.

In 2009, aside from hospitalization for maintenance therapy, seizures were the third most common reason for admission of children with brain tumors, accounting for 7% of all nonelective hospitalizations. Seizures were listed as a secondary diagnosis in 18% of all children admitted with a primary diagnosis of central nervous system tumor. On the basis of per-admission charges, acuity in these children was lower than that of pooled nonelective admissions in children with brain cancer, but much higher than that of children admitted because of seizures related to any other etiology.[44]

PRESENTATION

Brain Tumors

Tumor-related biological factors, especially location and aggressiveness, are the most important determinants of the tempo and type of presentation[3,48,52,53]; nevertheless, recognition of new or recurrent symptoms and signs of brain tumors, even in older children and adolescents, rests primarily on an attentive caregiver. In retrospect, caregivers often identify features that they attributed to another common childhood illness or normal behavior.[54] Subtle or nonspecific neurologic signs of supratentorial tumor are common, including increase in the rate of head circumference growth (a sign that precedes macrocephaly), early handedness, decreased use of one arm, visual inattention, headache, nausea, change in school performance, and regression or delay in achieving developmental milestones.[48] Infants may be more likely to present with macrocephaly and signs of increased intracranial pressure, including bulging fontanel, irritability, and "setting sun sign" (impaired upgaze and downward deviation of the eyes).[55]

Timely diagnosis and treatment of brain tumors in children relies on a number of other related factors. Patient and caregiver factors include age of the patient and attitudes toward the medical establishment. Provider factors include experience in childhood diagnosis and eliciting neurologic deficits on history and examination in a child who may or may not be cooperative.[56] Contextual factors, such as timely access to appropriate level of care, presentation setting (i.e., emergency room versus clinic) and availability of appropriate diagnostic modalities, play a significant role.[54,57]

Considerable literature is devoted to "lag time" (the interval between symptom onset and diagnosis) of brain tumors. Criticisms notwithstanding (e.g., recall bias, external validity among countries with wide variability in resources, necessarily right-skewed distribution of lag time), these studies are not only valuable for understanding how different types of brain tumors present, but also how they might re-present after treatment.[58] The interval from symptom onset to diagnosis of brain tumors is among the longest and most variable in childhood cancers, with reported median times ranging from 4 to 7 weeks for high-grade tumors and 4 to 60 months for lower-grade tumors.[59–62] The interval before first health-care system contact accounts for 73 (in astrocytoma of any grade) to 84% (in ependymoma) of this delay in patients with higher-grade tumors[60]; however, increased primary care utilization compared to controls has been noted up to 4 years prior to central nervous system tumor diagnosis.[63]

Seizures and Epilepsy

Seizures create additional diagnostic challenges compared to the symptoms associated with brain tumors as discussed above. They are frequently subtle and may occur as remote sequellae of treatment or residual disease or may be the only clue to occurrence, recurrence, or progression of a brain tumor in a patient with a

normal examination.[43,64] As in adults, most children (85-100%) in brain-tumor-related epilepsy series have focal seizures (with or without evolution to bilateral convulsions), but generalized seizures are more common (9-47%).[65–67] Brain tumors are a rare cause of convulsive status epilepticus (0.8% of all cases in one series),[68] but a somewhat more common cause of nonconvulsive seizures and status epilepticus in hospitalized children (8% of all cases monitored).[69] Although status epilepticus-related mortality is generally lower than that seen in adults,[70] it contributes to or signifies substantial risk for morbidity in children.[71]

Seizures are frequently misattributed to a wide range of mimics (Table 5.4), many of which do not lead clinicians to consider brain imaging in children.[73] Conversely, children with brain tumors are prone to misattribution of spells to seizure, such as opisthotonus (related to irritation of brainstem structures), sleep-related movements and parasomnias (which occur more frequently in children with frontal lobe dysfunction), breath-holding spells (in the irritated infant), psychogenic nonepileptic events (a common form of conversion disorder in adolescents with epilepsy), migraine (very common in patients with brain tumor), and syncope (common in children who are dehydrated while undergoing chemotherapy).[74] In young and intellectually disabled children, descriptions of psychological and sensory phenomena are limited. Adolescents may underreport seizure symptoms to caregivers.[75] Thus, it is important for clinicians to familiarize themselves with the unique seizure semiology seen in children.

Childhood temporal lobe seizure semiological features are subtle and change over the course of the first 10 years of life. In infants, myoclonic, tonic, or clonic motor features are common, whereas toddlers tend to present with episodes of behavioral arrest. Typical automatisms (finger rubbing, lip smacking) and subtle subjective experiences reminiscent of adult mesial temporal seizures are not appreciated until school age.[76–78] Frontal lobe seizures in children, as in adults, often occur exclusively or predominantly in sleep and consist of subtle, brief asymmetric posturing or clonic movements. Presentation with bizarre hypermotor behavior is less typical in childhood than it is in adolescents and adults. In younger children, they may only be detected by co-sleeping caregivers. Older children with frontal lobe seizures may present with new or worsening sleeping difficulties, personality changes, disinhibited and/or inattentive behavior, or even secondary nocturnal enuresis. These events are frequently misattributed to sleep disturbances.[79,80] Young children with brain tumors may present with epileptic spasms: subtle brief paroxysmal behaviors (e.g., trunk flexion, arm extension, and upward eye deviation). Reports of such children frequently mention the co-occurrence of a genetic syndrome.[81–84]

The most frequently identified cause of diagnostic delay in young children with seizures is a lack of caregiver recognition that events required medical attention, although specialist and subspecialist recognition of events, scheduling issues, and pre-existing developmental or distracting medical concerns may also contribute.[85] It is often only after an episode of bilateral convulsions or progression of other features that seizures are recognized as abnormal by the patient, caregiver, and clinician. The Childhood Brain Tumor Consortium[43] found that 89% of children presenting with seizures were not recognized to have a brain tumor until at least one other symptom or sign was present. The most common other presenting symptoms were back or abdominal discomfort; upper extremity weakness; walking difficulties; and change in personality, academic performance, or speech. The most common exam findings included lateralized motor signs, lethargy, and papilledema.

In a recent British series, the lag time in brain tumor diagnosis was a median of 2.5 months; however, when seizures were the first presenting symptom, time to diagnosis was over 12 months (longer than for any other neurologic symptom).[86] These findings have been replicated in some series,[43,87–89] but not others.[90,91] Fattal-Valevski and coworkers found that localization in the temporal lobe was associated with the greatest lag time in tumor diagnosis in those presenting with seizures.

The increased lag time in diagnosis of epilepsy-associated brain tumors may indicate a relatively indolent disease course, resulting in longer survival,[60,86,90,92,93] but increased morbidity in long-term survivors.[61] Brain tumors were most common among childhood cancers (13 out of 59 cases) reported in a database of Canadian and French malpractice claims citing diagnostic delays. Expert opinion on diagnostic delay in these cases did not apparently cite the cognitive effects found by Yule and coworkers.[94]

Contrary to most studies examining the relationship between lag time and age in children with brain tumors, Gilles and coworkers[43] found a direct relationship between age and interval to diagnosis when seizures were present prior to diagnosis. Half of children older than 15 (but only 12% of children younger than 5) at presentation were not diagnosed with brain tumor until 2 or more years after seizure onset. It is unclear what portion of the lag in brain tumor diagnosis was related to delay between first and second unprovoked seizures (i.e., delay in meeting criteria for epilepsy), unrecognized seizures, limited access to care (including current imaging technologies), or attribution to a nonstructural cause of epilepsy. In regards to the first possibility, prospective studies of children with first unprovoked seizure of any cause found that the median time to seizure recurrence was between 2 and 6 months (and was somewhat shorter among younger children with risk factors for

TABLE 5.4 Features of Seizures and Common Seizure-Like Spells in Children with Brain Tumors

Spell Feature	Infants		Toddlers		Older Children	
	Seizures	Mimics	Seizures	Mimics	Seizures	Mimics
In sleep or sleep-wake transition	ES	ALTE, sleep myoclonus, head banging	GTC, F	Hypnic jerks, arousal, parasomnia[a], SDB, head banging	GTC, F	Hypnic jerks, arousal, parasomnia[a], nocturnal enuresis, SDB, PD
On standing or exertion				RAS		RAS, PNEE, migraine
On feeding		Sandifer syndrome				
On movement		Jitteriness, DR		PD, other movement disorders, DR		PD, other movement disorders, DR
With excitation/ emotion		Shuddering attacks		PD		PD, cataplexy, panic attack, PNEE
With unpleasant/ painful stimuli		BHS		RAS, BHS		RAS
Staring/ unresponsive	F, NCS	ALTE	F, Ab, NCS		F, Ab, NCS	Daydreaming, PNEE
Pallor	F, NCS	ALTE, pallid syncope, other cardiac arrhythmia	F, NCS	Pallid syncope, other cardiac arrhythmia, RAS	F, NCS	Cardiac arrhythmia, RAS
Cyanosis	F	ALTE, BHS, structural heart disease, Sandifer syndrome	F	BHS, structural heart disease	F	Structural heart disease
Flushing	F	ALTE, SGB, DR	F	SGB, DR, migraine	F	DR, migraine
Vomiting	F	Brainstem irritation, IIP, DR	F	Brainstem irritation, IIP, cyclic vomiting syndrome, migraine, DR	F	Brainstem irritation, IIP, cyclic vomiting syndrome, migraine, DR
Headache			F,PI	Migraine, IIP, DR	F,PI	Migraine, IIP, DR
Vision change/ hallucinations			F	Migraine, DR	F	Migraine, DR
Lethargy/ confusion	F, NCS, PI	ALTE, DR, IIP, electrolyte/ metabolic disturbance	F, NCS, PI	DR, IIP, migraine, electrolyte/metabolic disturbance	F, NCS, PI	DR, IIP, migraine, electrolyte/metabolic disturbance
Repetitive stereotyped movement	F	Jitteriness, shuddering attacks, benign myoclonus of early infancy, spasmus nutans, SGB	F	SGB, stereotypies, other movement disorders	F	Tics, stereotypies, other movement disorders, PNEE
Sustained abnormal posture	F, T	Benign paroxysmal torticollis, brainstem irritation, DR	F,T	PD, brainstem irritation, DR	F,T	PD, brainstem irritation, hyperventilation/panic attack, DR, PNEE
Decreased tone	F, NCS, PI	ALTE, DR, IIP, Cardiac arrhythmia	NCS,PI	Cardiac arrhythmia	NCS,PI	Cardiac arrhythmia, cataplexy
Unsteadiness/ falls			M, At, T, PI	Benign paroxysmal vertigo, migraine, weakness	M, At, T, PI	Cataplexy, weakness, migraine
Unilateral weakness	F, PI	TIA	F, PI	TIA, migraine	F, PI	TIA, migraine
Convulsions			F, GTC	RAS	F, GTC	RAS, PNEE
Eyes closed						RAS, PNEE

GTC, generalized tonic-clonic seizure; M, myoclonic seizure; T, tonic seizure; Ab, absence seizure; At, atonic seizure; F, focal seizure; NCS, nonconvulsive seizure (i.e., focal and generalized electrographic seizures); ES, epileptic spasms (including infantile spasms); PI, postictal phenomenon; ALTE, apparent life-threatening event; SDB, sleep-disordered breathing (e.g., obstructive sleep apnea, central sleep apnea); PD, paroxysmal dyskinesia; TIA, transient ischemic attack; BHS, breath-holding spells; RAS, reflex anoxic seizure (convulsive syncope); SGB, self-gratification behavior (infantile masturbation); DR, drug reaction; IIP, increased intracranial pressure; PNEE, psychogenic nonepileptic event.

[a] *Including confusional arousals, sleepwalking, night terrors, bruxism, periodic limb movement disorder.*

Adapted from Ref. [72].

recurrence of unprovoked seizures).[95,96] Berg *et al.*[85] found that the median interval from second seizure to diagnosis of epilepsy was 0.5 months in children with a first unprovoked seizure of any cause before age 3.

Only two studies have examined the effect of delayed treatment on outcome in children with brain tumors. A higher number (>10) of pretreatment seizures in patients with low-grade tumors was associated with remaining on antiseizure drugs after resective surgery, whereas there was no such association when considering a larger group with more diverse pathology and grade.[50,97] No studies have examined the effect of untreated seizures on neuropsychological outcomes in children with brain tumors.

Number of pretreatment seizures has been found to predict seizure outcomes in one large cohort of children with epilepsy of diverse etiologies and ages,[98,99] but not others[100–102]; however, most have found that high initial seizure frequency predicts pharmacoresistance, especially in those patients with focal-onset seizures and seizures of known cause.[102–104] While the number of pretreatment seizures did not appear to be associated with clinically apparent neurological or gross intellectual deficits in the first decade after seizure onset in the Camfield and Camfield cohort, delays of more than a month in a younger cohort were associated with lower scores on cognitive and developmental testing later in life.[85]

Thus, it is unclear whether the effect of untreated seizures on outcome is related to properties of the underlying cause of epilepsy or the effect of the seizures themselves on the brain. The subject of whether "seizures beget seizures" in children with epilepsy and whether epilepsy itself is a neurodegenerative condition is beyond the scope of this chapter, but has been extensively reviewed elsewhere.[105–107]

EPILEPSY TERMINOLOGY AND CLASSIFICATION

The language of epilepsy has evolved over the last several decades. Epilepsy is defined by the International League Against Epilepsy (ILAE) as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures." An operational definition was recently published by the ILAE, as well. The relevant part of that definition is: a history of at least one unprovoked seizure and a high (>60%) probability of lifetime recurrence of unprovoked seizures. This probability is defined by the treating clinicians and, when available, epidemiologic studies considering risk factors for recurrence (including the brain tumors discussed above). According to this definition, all children with a supratentorial tumor known to cause seizures and a history compelling for at least one unprovoked seizure *have* epilepsy.[108]

The term "seizure disorder," while used interchangeably with "epilepsy" in clinical practice and possibly less stigmatizing, is ambiguous (e.g., seizure versus seizure mimic, unprovoked versus provoked) and misleading (e.g., seizures as the only symptom). Even with long-term seizure freedom, children with epilepsy and their caregivers report a lower quality of life than children without epilepsy. In those children with a brain tumor in whom long-term survival is expected, epilepsy is associated with unique psychosocial and neurodevelopmental effects. Such effects persist well beyond the effects of cancer treatments, such as resective surgery and the transient symptoms associated with seizures.[109] If the risk of recurrent seizures falls below 60% (e.g., after resective surgery) and the child has been off of medication for 5 years and free of seizures for 10 years, it can be said that the child no longer has epilepsy; however, the biological and psychosocial consequences of the underlying cause of epilepsy, the epileptogenic network, and seizures may endure.[108]

Current knowledge of brain-tumor-related epilepsy and seizure pathogenesis challenges the most recent attempt by the ILAE to classify groups of pathologic entities in order to facilitate early identification of definitive therapies.[110] Older terms used to describe the cause of epilepsy and seizures, such as "symptomatic," "cryptogenic," and "idiopathic" have recently been replaced by somewhat less ambiguous, but more rigid diagnostic categories. The first category is etiology: "genetic" (i.e., seizures as the core symptom and direct result of a known or presumed genetic defect), "structural/metabolic" (i.e., a static lesion primarily responsible for seizures, such as an infarct), or "unknown." The second is a syndrome (e.g., Lennox-Gastaut syndrome) or constellation (e.g., gelastic seizures with hypothalamic hamartoma) diagnosis that defines typical evolution of electroencephalographic features, seizure types, comorbidities, and prognosis. The third is a classification of seizures that reflects the current understanding of the interactions between the focus of seizure onset, propagation patterns, and the networks activated during seizures (see Chapter 1). Brain tumors would most easily fit into the structural/metabolic category, but the role of genetics in children with a tumor and a condition that is, itself, associated with epilepsy (e.g., NF1, Aicardi syndrome, LGI1 mutations) blurs these distinctions. Most children with brain-tumor-related seizures do not meet the criteria for an epilepsy syndrome; however, the co-occurrence of an epileptic syndrome, particularly an epileptic encephalopathy (e.g., West syndrome or Lennox-Gastaut syndrome), in children with brain tumors is well documented and the identification of such a syndrome affects prognosis and, in some cases, management strategy.[111,112]

These systems of nomenclature are expected to evolve further as pathophysiology of epilepsy and implications for treatment decision-making are further clarified.

GENERAL PRINCIPLES OF MANAGEMENT

The approach to children with brain tumors must not only account for the changes in presentation over the first two decades of life, but also the direct or indirect impact of natural history versus intervention on neurologic function, developmental trajectory, and quality of life.

Management of both epilepsy and primary brain tumors has evolved over the last several decades. In the past, the general approach to children with low-grade brain tumors was to obtain a tissue diagnosis and then either "watch and wait" (for those with a benign prognosis), or perform as complete a resection as possible (while preserving neurologic function), with additional radiotherapy in some cases of subtotal resection. The approach to growing or malignant tumors was resection and, in most cases, radiotherapy.[92]

Although resection remains a cornerstone of the management for most types of low-grade brain tumors, there is increasing recognition that achieving sustained good outcomes in children with concomitant epilepsy requires a more refined approach that considers response of seizures to medication, tumor location, physiological, and imaging characteristics, and, where appropriate, molecular pathogenesis. Electroencephalography (EEG) plays an important role in defining the margins of the seizure onset zone—these margins often extend beyond tumor borders. Newer imaging modalities and optimization of standard modalities may be sufficient to identify tumor type, grade, and prognosis and obviate the need for early and complete tumor resection or even, in some cases, obtaining tissue for diagnostic purposes. In cases where tissue should be obtained, molecular diagnostics have become central for correct histopathological identification of tumors.

Advances in pharmacotherapy for epilepsy have resulted in more than 15 new drugs over the last two decades, several with novel mechanisms and established efficacy, safety, and tolerability in children.[113] Recent developments in radiotherapy, particularly in limiting volume, conformation, and dose to optimize radiation delivery to the tumor while sparing normal tissue have resulted in improved effectiveness and treatment-related morbidity. Similarly, there is increased interest in the use of chemotherapy, especially in young children with tumors that are not amenable to resection, a group that is particularly susceptible to the late effects of radiation therapy.[114] The use of chemotherapy and/or radiation in the setting of low-grade tumors remains undefined. Ablation treatments have recently become an accepted management strategy in certain situations.

All children with brain-tumor-related seizures benefit from a collaborative multidisciplinary approach, although the specialties involved often differ depending on the primary goals and treatment approaches.[35] Depending on resources, the team may be limited to an experienced neurosurgeon and may additionally include either a neurologist or an oncologist; however, optimal management of both diagnoses requires a comprehensive approach, typically provided at a regional pediatric cancer or epilepsy center. Care at such a center facilitates participation in national and international collaborative studies and coordination among physicians and other providers with extensive subspecialty pediatric training and experience, including epileptologists, neuro-oncologists, neuroradiologists, neuropathologists, radiation oncologists, physiatrists, psychiatrists, geneticists, neuropsychologists, technologists, therapists, and social workers and other care coordinators.

HISTORY AND PHYSICAL EXAM

A thorough neurologic history (including developmental history) and physical exam are critical to the timely recognition of newly diagnosed, recurrent, or progressive brain tumors and/or seizures.[56,74]

Any provider evaluating a child for the first time should never assume that the diagnosis of tumor, seizures (see Table 5.4), or epilepsy (see Section on Presentation: Seizures and Epilepsy) is correct, even when a brain MRI has already been done and the patient is taking an antiseizure medicine. If historical description alone is inadequate for diagnosis, use of home video recording of spells and instruction in distraction techniques (e.g., touching a child on the face when they appear to be unresponsive and staring off) should be encouraged. If such evidence is compelling for seizure diagnosis, an attempt must be made to discern whether seizures have only and consistently occurred in the setting of acute provoking factors, such as drug neurotoxicity (e.g., toxic encephalopathy, posterior reversible encephalopathy syndrome), electrolyte or other metabolic disturbances, ventricular shunt malfunction, stroke, fever, or systemic infections.[115] The latter two, in particular, are very common provoking factors in children with epilepsy of any cause.[116] Children with a history of seizures that have only occurred in the setting of acute provocation do not have epilepsy (or a "seizure disorder") and most will not go on to have unprovoked seizures, thus they do not require long-term treatment with antiseizure medicine.[117,118]

Seizure semiology and frequency may change over time due to medical or surgical treatment, age, hormonal changes, or progression or relapse of the underlying tumor. For example, progression of focal seizures to bilateral convulsions is the exception, rather than the

rule in young children, but the opposite is true, especially of untreated seizures, by the time they reach school age.[119] Careful history taking in a child presenting with their first generalized tonic-clonic seizure often reveals subtle seizures that precede the convulsive event by months to years.[116] Even if a patient or caregiver declares resolution of previous episodic neurologic complaints in a child with an epilepsy-associated supratentorial tumor, the clinician should systematically ask about other seizure-like symptoms associated with the localization of their tumor.

Children with brain-tumor-related epilepsy may have additional risk factors for epilepsy that alter management and prognosis, such as any seizure during infancy, febrile seizure, global anoxic brain injury, traumatic brain injury, a family history of seizures, or a genetic condition known to be associated with seizures.[120] In general, the more severe the risk factor, the more likely that it significantly contributes to epilepsy. Following brain tumor diagnosis, a complete review of systems and targeted physical examination of other systems may reveal clues to an associated genetic diagnosis (see below Section on Genetics).

In children who are being considered for epilepsy surgery, attention should be given to the details of seizure semiology to determine whether they are congruent with the tumor localization.

DIAGNOSTIC EVALUATION

ROLE OF DIAGNOSTICS IN SURGICAL WORKUP AND MANAGEMENT

Tumor and seizure-onset zone are not synonymous (see Chapters 8 and 9). Good epilepsy and survival outcomes can be obtained by strategies that target the lesion visible on standard neuroimaging, but there is substantial evidence that use of supplementary noninvasive techniques in children with epilepsy improves the likelihood of seizure freedom.[65,121–123] Determinations must also be made of the relationship between lesion, seizure-onset zone, and structures associated with vital functions in the brain. In many cases, prognostication of seizure, neurological, and neuropsychological outcomes following resection is possible on the basis of this workup.

The minimum determination of the limits of the seizure-onset zone and lesion should include a careful objective and subjective description of the seizure from onset until the end of the postictal period, a recent high-quality MRI, and a routine interictal EEG with activation procedures (sleep deprivation, photic stimulation, captured of at least a few minutes of sleep, and, if safe, hyperventilation).[124] Ictal semiology has a higher localizing value than interictal EEG, but both have limitations.[125,126] Seizures usually originate from a single focus, but occur over a broader network. It is common for a seizure to propagate to remote network sites prior to spreading to adjacent cortex. Thus, semiology may reflect the "symptomatic zone," which often does not co-localize to the seizure-onset zone, but rather may be a distant area that produces symptoms after the seizure spreads to it. Likewise, EEG may reveal interictal epileptiform abnormalities that occur at sites of network activation (i.e., the "irritative zone"). When the seizure-onset zone is not located in an area amenable to detection by scalp EEG (i.e., cortex that is close to the scalp), the seizure-onset zone may be "silent." Because of these considerations, discordance between ictal semiology, interictal EEG (including bisynchronous discharges), and imaging does not necessarily imply a poor seizure outcome with focal resection, but, nevertheless, suggests the need for further definition of the seizure-onset zone beyond the above.[127–129]

Due to the frequency of cortical localization of epilepsy-associated brain tumors, they are often located within or adjacent to vital brain structures involved in language, memory, adaptive behavior, emotion, movement, and sensation.[130] Furthermore, low-grade epilepsy-associated tumors in children are characterized by slow growth that may begin during establishment of specific functional tracts in early brain development, causing aberrant localization of function; thus, defining the relationship between seizure-onset zone and eloquent cortex is vital to surgical planning.[131,132]

Scalp EEG

EEG is recommended in children presenting with afebrile seizures[133]; thus, a majority of children with seizures at presentation of a brain tumor will have already undergone EEG by the time the tumor diagnosis has been made. In those cases where the child has no other presenting features suspicious for brain tumor, the EEG may identify a focal abnormality that leads to imaging and subsequent tumor diagnosis.

The use of routine EEG in early management of children with known brain tumors, with or without suspected seizures, is less clear. As in adults, imaging (specifically, MRI) has supplanted EEG in diagnosis and surveillance of tumor. Although EEG can serve as a useful adjunct to careful history-taking, the latter is ultimately more important to seizure diagnosis. In children with supratentorial brain-tumor-related seizures, 8-37% of EEGs are normal and 31-68% do not reveal

epileptiform abnormalities.[49,88–90,134–136] Conversely, children without a history of seizures frequently have epileptiform abnormalities on EEG (0.8-18%).[137]

In regards to stratification of seizure recurrence risk, the presence of a relevant structural brain abnormality on imaging more strongly predicts early seizure recurrence after first seizure than EEG[138]. One trial of adults and children revealed added prognostic value of EEG in children with a known neurological disorder or deficit presenting after a single afebrile seizure.[139]

Despite these limitations and recent advances in imaging, EEG remains the only test used in routine clinical practice that can monitor the neurophysiological effects of a tumor on peritumoral cortex and the epileptic network as it passes through several stages of brain development. Thus, at least one baseline routine EEG should be obtained in all children presenting with seizures, ideally several days after their last seizure and prior to initiating treatment. Accurate use of information from this and subsequent EEGs requires interpretation by a physician with formal training in the changes in EEG patterns from the neonatal period up until adulthood. Further EEG's may be useful for aspects of medical management, including:

1. Choosing an antiseizure drug. The use of limited spectrum antiseizure drugs (e.g., oxcarbazepine, gabapentin) as first-line treatment for children with brain tumors is common practice; however, these drugs may not appropriately address (and may even exacerbate) seizures that have a tendency toward rapid progression to a bilateral convulsive seizure.[140] Bisynchronous and apparently generalized epileptiform abnormalities are frequently found on EEG of patients with epilepsy related to congenital focal lesions or those acquired at a young age.[141] They may predict patients that will respond better to broad-spectrum agents (e.g., levetiracetam). Limited spectrum agents may even activate bisynchronous discharges; thus, EEG should be repeated in children who have worsened seizures after initiation of a limited spectrum agent.

   School-age and younger children with focal brain lesions are more likely than adults to develop an epileptic encephalopathy: a chronic condition in which frequent or continuous epileptiform activity and frequent treatment-resistant seizures contribute to developmental delay, plateau, or regression. Associated EEG abnormalities, including diffuse background slowing, focal or generalized slow spike-wave discharges (associated with Lennox-Gastaut syndrome), hypsarrhythmia (associated with infantile spasms and West syndrome), and electrographic status epilepticus during slow-wave sleep, have been documented in children with brain tumors.[142–147] Recordings including a prolonged epoch of sleep will increase the chance of identifying any of these findings on EEG. Even in children who are otherwise seizure free, addition or substitution of certain medications (e.g., adrenocorticotropic hormone, valproate, high-dose diazepam) may be attempted to reduce or eliminate EEG abnormalities. Assessment of response requires serial EEGs and formal neuropsychological examinations. Limited spectrum agents may also exacerbate seizures or developmental abnormalities in these children.[148]
2. Change in spell type or frequency or differential diagnosis of suspected (e.g., recurrent nocturnal enuresis) or observed (e.g., motionless staring) seizure-like spells. As discussed above, several physiologic and nonphysiologic spells mimic seizures. While the use of mobile phones for home video recording is ubiquitous and should be used as an adjunct to history, the diagnosis may still be in question even after consultation with a subspecialist. Elective inpatient video-EEG or outpatient ambulatory EEG may be able to identify the nature of undiagnosed spells, especially those occurring at least one to two times per week, with significant added benefit over a single routine EEG. Four to forty-eight percent of children with suspected epilepsy (and up to 30% with a confident diagnosis of epilepsy) prior to video EEG monitoring have a change in diagnosis or additional diagnosis of psychogenic or physiologic nonepileptic events following monitoring, with the highest yield for patients with staring episodes.[73,75,149–155] Risk factors for psychogenic nonepileptic events in children include mood disorders, school difficulties, family discord, and interpersonal conflicts.[156,157]
3. Alteration of mental status, unexpected changes in personality or behavior, or spells concerning for seizures in the acute setting. Children with brain tumors are frequently hospitalized and undergo treatment following diagnosis. Those who have recently undergone resection, chemotherapy, or radiation are at increased risk of seizures, regardless of history of seizures or use of antiseizure medicines. Changes in neurologic exam, whether transient or not, may be related to a number of factors. A high degree of suspicion should be maintained for frequent, subtle ongoing seizures or, in the case of mental status changes, nonconvulsive status epilepticus. Continuous video-EEG recording is superior to intermittent routine recording for capturing seizures and status epilepticus in these patients. One series captured subtle seizures in two and nonconvulsive status epilepticus in an additional two out of nine hospitalized children with brain tumor who underwent continuous monitoring in

the ICU. None of those children had overt clinical seizures.[69]

4. Detection of unrecognized seizures in the apparently well-controlled patient. As mentioned above, seizures may remain subtle and some electrographic seizures are not associated with detectable behavior change, especially in children with temporal or parietal tumors. Among children with focal seizures with dyscognitive features (i.e., complex partial seizures) who are admitted for long-term video EEG monitoring, one study found that 57% have at least one seizure that goes undetected by caregivers and 10% have seizures that are not detected by caregivers at all (N.B. in an environment that is conducive to caregiver recognition of seizures).[75] No studies have addressed whether such seizures (or changes in treatment based on detection of them) influence outcome in children with brain tumors; nevertheless, following attainment of seizure freedom in children with temporal or parietal tumors, 24-48 hours of ambulatory or inpatient recording may be useful to assure that the patient does not continue to have frequent undetected seizures.
5. Surgical evaluation. Descriptions of ictal events, including even subjective phenomena, are often clarified and expanded in the setting of elective video monitoring.[75] Further activation procedures (especially reduction of medications prior to and/or during monitoring) improve the chance of capturing spells when they occur infrequently, but also increase the risk of status epilepticus and possibly seizure-related death; thus, video-EEG monitoring requires a specially designed epilepsy monitoring inpatient unit staffed by nurses and/or technicians with pediatric seizure training to improve patient safety.[158,159]

The capture of typical seizures on scalp EEG further corroborates localization in most cases.

Intracranial EEG

Because of its high spatial and temporal resolution, intracranial (invasive) EEG recording is regarded as the gold standard of functional measurements of the seizure-onset zone. The use of intracranial EEG is strongly supported in cases of discordance of localization from noninvasive data or structural or functional evidence of focal cortical dysplasia. Numerous studies show improved outcome with the use of intraoperative (electrocorticography) or extraoperative (invasive monitoring) intracranial EEG in children with epilepsy-associated brain tumors of all pathologies[65,121–123,160]; nevertheless, there is increasing awareness that EEG recording of interictal and/or ictal epileptiform abnormalities in the standard frequency band is neither sufficiently sensitive nor specific to guide resection. Recently, the measurement of high-frequency oscillations and infraslow activity on intracranial EEG[161–164] and magnetoencephalography[165,166] have been shown to improve sensitivity and specificity of localization and predict successful surgery outcome.

MRI

There is consensus that MRI is superior to computerized tomography (CT) for detection of tumors and other structural abnormalities and offers the added advantage of limiting ionizing radiation exposure to healthy tissue. When available, MRI should be obtained in children after the first or subsequent unprovoked seizures under certain circumstances: suspected focal-onset seizure, age <1 year, unexplained developmental delay, lingering neurologic deficits after a seizure, and EEG findings that are not consistent with a genetic etiology.[133] Arguably, most children with a brain tumor and first unprovoked seizure would present with several of these features, although there is little evidence that these guidelines have been routinely incorporated into practice. Nevertheless, if routine CT has identified a mass lesion, a follow-up MRI will limit the differential diagnosis and better define tumor margins.[46]

MRI of the entire central nervous system should be undertaken for tumors with a tendency toward leptomeningeal dissemination (i.e., primitive neuroectodermal tumor, choroid plexus papilloma, ependymoma). Contrast enhances the sensitivity of MRI for this purpose. In these children, seizures can be a manifestation of leptomeningeal involvement, primary tumor, or both.[167]

As in adults, contrast enhancement of the tumor may indicate a higher grade, but is not reliable. Similarly, magnetic resonance angiography done following a contrast bolus can elucidate the integrity of the blood-brain barrier. Such determinations may allow improved yield of stereotactic biopsy and predict susceptibility of the tumor to systemic tumor therapies, but do not accurately reflect tumor vascularity or grade. Other sequences, such as diffusion and dynamic perfusion imaging, may be used in lieu of biopsy to predict tumor behavior and response to tumor therapy in some children.[168]

All children with a history of seizures who are being considered for resection should undergo at least one high-resolution MRI using a predetermined epilepsy protocol. Higher resolution improves the ability to clearly demarcate tumor boundaries and may improve sensitivity of detection of subtle associated epileptogenic pathology that may have important implications for resection strategy, especially focal cortical dysplasia or mesial temporal sclerosis.[169]

The association of focal cortical dysplasia with brain tumors, especially ganglioglioma and dysembryoplastic neuroepithelial tumor, is well established. In fact, several authors refer to these entities as "developmental tumors," indicating that dysplasia and neoplasia are a continuum of pathology with indolent behavior that likely has origins in early fetal or childhood development of the limbic system and associated cortex. Classification of dysplasia has recently undergone revisions to reflect this common entity.[170] In patients with drug-resistant epilepsy, tumors associated with focal cortical dysplasia more frequently occur in males and are more often temporal in location, but are otherwise similar in clinical presentation (age at onset, seizure frequency, duration of epilepsy prior to resection) to patients with tumor alone. When considered as a part of determination of resection strategy, outcomes may be similar to tumors without associated focal cortical dysplasia.[42] There is ongoing debate about the optimal strategy for additional resection (or not) of dysplasia and/or anteriomesial temporal structures to seizure outcomes.[170]

MRI reading, acquisition, and postprocessing techniques are currently being developed in order to improve sensitivity for detecting focal cortical dysplasia. Subtle imaging features, including blurring of the gray-white matter junction, cortical thickening or focal volume loss, and cortical thinning, are increasingly recognized in patients with brain tumors.[42] Patients with dysembryoplastic neuroepithelial tumor may be classified by subtypes based on imaging, which has good concordance with histological subtype. Identification of subtypes has not been shown to improve prognostication of overall survival; nevertheless, it may have important implications for resection strategy. Complete resection of a tumor without invasive EEG monitoring may be adequate to prevent regrowth and attain seizure freedom in patients with cystic-polycystic-like, well-delineated, strongly hypointense T1 signal. Seizure outcomes may be improved by additional perilesional resection in patients with nodular-like, heterogeneous signal and by resection of the extent of focal cortical dysplasia as determined by invasive monitoring in patients dysplastic-like, isointense T1 signal, poor delineation, and gray-white matter blurring.[171] Acquisition and postprocessing techniques that define the limits of the seizure-onset zone in so-called "nonlesional" focal epilepsy (i.e., thin cuts, surface coils, curvilinear and multiplanar reconstruction, statistical parametric mapping, morphometric analysis) may also help define the boundaries of associated focal cortical dysplasia in patients with tumors.[172]

Beyond defining the type of lesion(s) present, MRI is routinely employed in surgical planning. Software programs are available that allow coregistration of structural MRI with other neuroimaging, EEG, and functional data (i.e., "multimodality imaging"). Such programs are the basis for image-guided stereotactic surgery and are currently in use in children with lesional epilepsy.[173] The availability of intraoperative MRI allows for real-time three-dimensional reconstruction of relevant data based upon changes in brain conformation that occur during surgery, which improves completeness of resection and assures integrity of the stereotactic field.[174]

Other Imaging Studies

Several noninvasive determinations of the seizure-onset zone play a complementary role to standard imaging, offering improved hypothesis-testing and spatial and temporal resolution.

Metabolic determinations of the seizure-onset zone rely on interictal hypoperfusion or ictal (or epileptiform) hyperperfusion of a well-localized area. Several tools have been successfully employed in children with brain tumors, including positron emission tomography (PET), ictal, and interictal single-photon emission CT, and EEG spike-triggered functional MRI.

Magnetic resonance spectroscopy (MRS) and PET have been increasingly used in routine clinical management to establish boundaries of tumor margins, prognosticate overall survival, and improve preoperative identification of tumor type and grade. Both techniques take advantage of specific properties of metabolic compounds in the intracellular and extracellular compartments. MRS evaluates the relative abundance of metabolic compounds (especially *N*-acetyl aspartate [NAA], creatine-phosphocreatine, choline, and lactate) within a specified portion (or "voxel") of brain and tumor tissue. Such determinations allow identification of relative proportion of neurons within a tissue, neuronal damage, cell density, cellular turnover, and regional perfusion, allowing identification of specific tumor type and grade in the appropriate clinical context. Interpretation of MRS in children requires an understanding of the normal developmental changes in relative abundance of these four compounds. Of these, the most important changes occur over the first 18 months of life, when NAA increases and choline decreases in relative abundance in both gray and white matter. (18)F-fluorodeoxyglucose PET evaluates regional glucose metabolism. It is commonly used to determine tumor margins and grade, with higher-grade tumors showing relatively higher metabolic demand than lower-grade tumors (with the exception of pilocytic astrocytoma).[175,176] (11)C-methionine PET may be able to differentiate between neoplastic and non-neoplastic lesions. These issues are discussed in further detail in Chapter 10.

Magnetic and Electrical Source Localization

Functional measurements of the seizure-onset zone may also rely on three-dimensional spatial representation of interictal and ictal discharges on neurophysiologic recordings. Magnetic and electrical source localization of interictal epileptiform activity can be derived using coregistration of MRI to magnetoencephalography and high-density EEG, respectively. The reliability of electrical source localization, but not magnetic source localization, depends upon models of the size and electrical properties of intra and extracranial tissues. The usefulness of such models in children with large structural lesions and skull defects has not been extensively studied, but recent developments in computer modeling based on an individual patient's brain structure may overcome these concerns.[177] Furthermore, high-density EEG offers an advantage over magnetoencephalography in that it is lower in cost and may be integrated into an elective EEG monitoring unit, where capture of seizures is more likely.[178,179] Both modalities have been reported to successfully predict surgical outcome in children with brain tumors, although magnetic source localization is more commonly used in clinical practice.[177,180–182]

Neuropsychological Assessment and Other Studies Used to Localize Eloquent Brain

When possible, children who are able to cooperate with neuropsychological testing should undergo a series of testing batteries to test normal neurocognitive functions. Such determinations often uncover and quantify subtle areas of dysfunction not apparent on a general neurological examination, allowing short-term prognostication of risk and postoperative determinations of loss of function with resection or transection of functional brain networks; however, such determinations are not as straightforward in the developing brain as they are in adults. Children with epilepsy more often have global cognitive deficits and behavioral issues that may limit testing of all domains.[183]

The use of other modalities to determine the limits of eloquent cortex and neural tracts is discussed in Chapter 11. The use of these studies in children requires age- and developmental stage-appropriate paradigms. Cortical mapping using intracranial grids requires different electrical stimulation parameters in children in order to adequately elicit cortical function.[184] Results of standard intracarotid barbiturate injection (Wada) testing and task-based functional MRI protocols often are nonlateralizing for specific language and memory functions in children younger than 7-10 years of age.[185,186] This is related, in part to the relative lack of lateralization in this age group, but it is also related, to lack of ability to cooperate with standard paradigms used in these tests. In uncooperative children who cannot reliably follow task-based protocols, passive range of motion and auditory stimuli has been used successfully in determining motor and receptive language cortex localization, respectively, using functional MRI and magnetoencephalography.[187–190] There is also increasing interest in the use of sedated fMRI without stimulation to measure resting state connectivity in order to lateralize and localize specific functions and determine the extent of the epileptogenic network.[191]

Genetics

All children with brain tumors should be evaluated for an underlying genetic syndrome. In the age of molecular medicine, the cornerstone of thoughtful genetic testing is still a detailed patient and family history and exam.[192] If other features of a cancer syndrome are detected, genetic testing should be sought for family planning, discussion of prognosis and surveillance planning.

NF1, Rubinstein-Taybi syndrome (*EP300*, *CREBBP*) and Turcot syndrome (*PMS2*, *MLH1*, *MSH6*, *MSH2*) are autosomal dominant disorders. Hereditary retinoblastoma (*RB1*) and Li-Fraumeni syndrome (*TP53*, *CHEK2*, *1q23*) may be sporadic or inherited in an autosomal dominant fashion. Aicardi syndrome (*Xp22*) is typically sporadic, but it is thought to be an X-linked dominant condition.

Patient and/or familial features that should alert the clinician to one of these associated conditions include infantile spasms, moderate-severe developmental delay, short stature, failure to thrive, craniospinal abnormalities (e.g., micro- or macrocephaly, asymmetric hemisphere size or sulcal pattern, nonobstructive ventriculomegaly, agenesis or dysgenesis of the corpus callosum, scoliosis, vertebral anomalies), ocular abnormalities (e.g., chorioretinal lacunae, microphthalmia, optic nerve coloboma, Lisch nodules), dysmorphic facial features, other developmental abnormalities (e.g., dental, cardiac, renal, hand), skin and soft tissue lesions (e.g., neurofibromas, axillary freckling, café-au-lait spots), and other cancers (e.g., optic nerve and visual pathway, brainstem, pineal gland, breast, bone, connective tissue, colon, blood, adrenal cortex, skin).

The most common brain tumor-associated genetic condition is NF1. Pilocytic astrocytoma (most often localized to the brainstem, optic pathways, or corpus callosum) is the most frequently identified tumor, but other central nervous system tumors (including dysembryoplastic neuroepithelial tumor) are known to occur. About 4-7% of children and adults with NF1 (and 13% with brain tumors) have epilepsy. Those with epilepsy usually have neurocognitive deficits. Pharmacoresistance is more common in children with NF1

(45-50%) than the general pediatric population with epilepsy.[48,193–195] It remains unclear whether the co-occurrence of a brain tumor predicts pharmacoresistance, but many children without tumor develop epilepsy that is often resistant to treatment; thus, the cause of epilepsy in NF1 patients with brain tumors is not always clear, and any approach that considers seizure control must take this into account.

Tissue Diagnosis and Molecular Tumor Markers

While noninvasive tumor diagnosis is possible, consistency in diagnosis of tumor type across centers undoubtedly requires molecular analysis of tissue, which will facilitate uniformity among studies of epilepsy-associated tumors. Determination of survival and epilepsy prognosis based on certain markers also has important implications for management strategy.

The relative contributions to epileptogenesis of neurons versus glia and neoplasia versus associated dysplasia within tumor and in peritumoral tissue is the subject of ongoing research. Several tumor biomarkers have been identified with various implications for seizure presentation, including: expression of CD34 glycoprotein (increased risk of seizures in gangliolioma), 19q loss of heterozygosity (improved seizure control in oligodendroglioma and, to a lesser extent, other gliomas), expression of Ki-67 (poor seizure control in low-grade glioma), mutations in IDH1 and 2 (high chance of presenting with seizures in grade II astrocytoma), and expression of aquaporin-4 (increased risk of seizures in glioblastoma).[196]

While not currently examined in routine molecular analysis of tumors in the clinical setting, altered expression patterns of several antiseizure drug targets (e.g., voltage-gated ion channels), drug resistance mechanisms (e.g., multi-drug transporters), and inflammatory mediators have been found across a variety of tumor types. Such markers may provide a mechanistic basis for choosing or avoiding certain antiseizure medications[197] (see Chapter 1). Due to the relatively poor differentiation of tumor cells, many of these mechanisms bear resemblance to the unique pathophysiology of epileptogenesis in the developing brain. They pose challenges that are not adequately addressed by currently available antiseizure drugs, in part, because of the use of non-brain-tumor adult animal models for drug development.[34]

MEDICAL MANAGEMENT

Anticipatory Guidance

Anticipatory guidance is a crucial part of pediatric care and has been shown to reduce caregiver anxiety and utilization of emergency services, improve satisfaction with care and adherence, and reduce morbidity.[198] All children and caregivers should be offered ability- and developmental stage-appropriate counseling regarding safety issues for children with epilepsy, such as bathing, injury prevention, and plan of action for each seizure type. In addition, counsel should be given regarding seizure prevention strategies, such as medication adherence, maintaining adequate sleep, and avoidance of alcohol. Young women (ages 12 and up) with epilepsy are at high risk of unplanned pregnancy due to psychosocial factors, poor adherence to hormonal contraceptive regimens, and contraceptive failure related to drug interactions. They should be counseled regarding the effect of epilepsy and antiseizure medicines on reproductive function and management.[199,200]

Maintenance Antiseizure Drugs

All children with an epilepsy-associated brain tumor and a history of one or more unprovoked seizures should start antiseizure drug treatment, ideally after undergoing an EEG (regardless of the results) (see Section on Presentation- seizures and epilepsy). As many as 80% of children with an epileptogenic structural brain lesion will go on to have further seizures, thus all of these patients meet criteria for a diagnosis of epilepsy after their first unprovoked seizure.[138] There is substantial evidence that use of antiseizure medications significantly reduces seizures in children with brain tumors. Additional potential benefits include reduction of seizure-related injury, stigma, and activity restriction, all of which contribute to quality of life. Early treatment has a positive effect on long-term seizure and cognitive outcomes (see Section above: Presentation- seizures and epilepsy).

Research that leads to approval of epilepsy therapies defines responsiveness in an individual patient as >50% reduction in seizures. In the clinical setting, achieving lifelong freedom from seizures without adverse effects is associated with the highest quality of life and long-term psychosocial outcomes. Studies in adults with brain tumors have found that newer antiseizure medications, including oxcarbazepine, zonisamide, topiramate, gabapentin, pregabalin, lacosamide and levetiracetam are safe, well tolerated, and effective against brain-tumor-related seizures. Evidence for use of specific antiseizure drugs in children with brain tumors is limited. Compared with older antiseizure drugs (i.e., phenobarbital, phenytoin, carbamazepine, and valproate), new drugs are associated with a lower rate of discontinuation due to lack of efficacy, potential for interaction with chemotherapy, or side effects in children with brain tumors.[201,202] Retrospective studies of levetiracetam and gabapentin in children with cancer-related epilepsy

(the majority of patients in both studies had brain tumors) indicate efficacy.[49,203] Regular use of phenytoin in children should be avoided, when possible, because of interaction with several common medications used in children with brain tumors and the potential for neurological, orthopedic, hematologic, and cosmetic morbidity with long-term use.

The choice of maintenance medication depends on several factors:

1. *Seizure types and EEG findings*. Limited spectrum agents are most appropriate for children with seizures associated with clearly focal features at onset and an EEG pattern without bisynchronous abnormalities.[140]
2. *Frequency of seizures*. Medications that require slow titration, such as lamotrigine, are inappropriate for a child having several seizures per week.
3. *Unique side effect and interaction profile of a drug*. Drugs known to cause behavioral activation, such as levetiracetam and phenobarbital, should not be used as first-line agents in children with significant behavioral concerns. Enzyme-inducing or inhibiting drugs may interact with chemotherapy, antibiotics, or other common treatments in children with brain tumors (see Tables 5.5a and 5.5b). Several drugs have been associated with liver enzyme abnormalities or blood dyscrasias, which are more likely to occur in children undergoing antitumor treatment. Specific modes of excretion must be considered in children with impairment of liver and renal function. Valproate is associated with platelet dysfunction and should be avoided in children undergoing resection and those with tumors associated with a high risk of hemorrhage.
4. *Effectiveness for comorbid conditions*. Anticonvulsant medications may have effects on the brain other than seizure control that may be useful to treat other conditions. Gabapentin and valproate stimulate appetite. Gabapentin and pregabalin may be used to treat chemotherapy-induced neuropathic pain.[204–207] Valproate has been found to have antitumor properties against astrocytic tumors and may act synergistically with certain chemotherapeutic agents, such as temazolamide. Other newer antiseizure agents, such as tonabersat, a gap junction inhibitor with antiseizure properties, and perampanel, an AMPA-receptor antagonist, may exert antiseizure effects through mechanisms specific to tumor-related epilepsy.[208]
5. *Out-of-pocket cost, availability, and administrative burden*. Newer drugs are not available in child-friendly formulations in all countries. Children covered by insurance often require assistance with paperwork that justifies the need for a certain drug.
6. *Ease of use*. Medication regimens that require extra steps (e.g., crushing pills) or more than twice-daily dosing are associated with poor adherence.[209] Enzyme-inducing or inhibiting drugs require monitoring of labwork (drug level, blood count, electrolytes and liver enzymes) every 2 to 6 months.

Following initiation of antiseizure medicine, children must be closely monitored for treatment responsiveness and intolerable side effects. All patients receiving antiseizure drugs and their caregivers should be queried regarding type and frequency of seizures (including any seizure types not previously documented), adverse effects, and adherence at each visit.[200]

Any new medication should ideally be slowly titrated to a typical maintenance dose over the course of 3-4 weeks (longer for lamotrigine), especially in children who have a low seizure frequency (one seizure or less per month). If unwanted neurocognitive side effects occur, the dose may be decreased to the highest tolerated dose and a slower titration may be attempted. This strategy may improve tolerance of common side effects, such as somnolence, cognitive slowing, and behavioral disturbances.[210] Idiosyncratic reactions to antiseizure drugs are more common in children and, by definition, do not typically improve with time or dose reduction.[211]

Drug doses should be increased for any breakthrough seizure that is unprovoked or due to provoking factors that are difficult to avoid and likely to recur (e.g., febrile illness, missing or delaying a single medication dose due to vomiting or forgetting). Provoking factors for breakthrough seizures should always be sought and thoroughly documented. Inconsistency of drug dosing (e.g., forgetting multiple doses per month, administering drugs at too long of an interval) is a common cause of apparent resistance to a drug.[212] Children and young teenagers are frequently expected to self-administer medications, but do not reliably do so. Simple interventions can be effective, such as use of a medication log, medication alarms, and pill boxes. More sophisticated measures designed specifically for children with epilepsy have been developed and appear effective in preliminary research.[213]

Drugs that are ineffective, but tolerated at typical maintenance doses may be increased in a step-wise fashion using one of two approaches. The first is the use of 3 dose tiers: "low," "moderate," and "high." The second is an increase in total drug amount by 10-20% increments. The first approach may result in more rapid determination of drug responsiveness or resistance. The second may be more advantageous in children with brain tumors. This population is at high risk of drug discontinuation due to both dose-dependent and idiosyncratic adverse drug reactions.[202,214]

Although monotherapy is associated with fewer side effects, there is little agreement regarding the use of serial monotherapy versus add-on therapy in regards

TABLE 5.5A Commonly Used Limited Spectrum AEDs

Antiseizure Drug	Typical Starting Dose (mg/kg/day)	Typical & Max Maint. Dose (mg/kg/day)	Max Adult Dose (mg/day)	Typical Dosing Interval	Interactions (Nonchemotherapy)	Other Special Considerations
Carbamazepine (CBZ)	<12 y: 5-10	<12 y: 20-25 Max: 35	<12:1000 >12:2400	Tab,CT, Sus:TID XR tab: BID	↓[o]CLB, LTG, OXC, TPM, VPA, LCM, steroids, antifungals, antipsychotics, doxycycline, erythromycin, trazodone, HC ↑[o]PHT ↓[b]PB, PHT, rifampin ↑[b]VPA,LTG, haloperidol	Auto-induction leads to poor efficacy at lower levels. CBC, LFT at baseline, then draw with drug level at 6 weeks, 3 months, 6 months, and every 6 months thereafter
Gabapentin (GBP)	<3 y:25-40 3-12 y:10-20	<12 y:30-60 Max:60	4800	Sol,tab: TID	↓[b]Antacids	
Lacosamide (LCM)	<16 y:1-2	<16 y:5-8 Max:10	600	Sol, tab, IV:BID	↓[b]CBZ, PB, PHT	May be loaded quickly at therapeutic dose. May have a broad spectrum of effectiveness
Oxcarbazepine (OXC)	<16 y:8-10	<16 y:20-40 Max:60	2400	Sus, tab: BID XR:QD	↓[o]HC, LTG ↑[o]PB, PHT ↓[b]CBZ, PHT, PB	Increased risk of skin reactions in patients receiving radiatiotherapy. Check sodium in any patient with worsening seizures or encephalopathy
Phenobarbital (PB)	Neonate: 3-5 Older: 1-3	2 m-1 y: 4-11 1-3 y: 3-7 3-6 y:2-5 >6 y:1.5-4 Max:10	250	Sol, tab, IV: QD-BID	↓[o]CBZ, LTG, TPM, VPA, corticosteroids, HC, promethazine, quetiapine, voriconazole ↑[b]VPA	May be loaded quickly at therapeutic dose. Long-term use associated with slightly lower IQ. Increased risk of skin reactions in patients receiving radiotherapy

CT, chew tab; Sol, oral solution; Sus, oral suspension (must be shaken vigorously before each use to assure uniformity of dosing); Spr, sprinkle cap; BID, twice daily; TID, three times daily; NE, not established; neo, neonate; DR, delayed-release; XR, extended-release; PHT, phenytoin; ↓[o], causes a decrease in the blood levels of; ↓[b], blood level is decreased by; ↑[o], causes an increase in the blood levels or toxicity of; ↑[b], blood level or toxicity is increased by; HC, oral contraceptives; CBC, complete blood count; lytes, electrolytes; LFT, liver function tests.
Adapted from Ref. [72].

to drug effectiveness in children who do not respond to the first drug tried. Such decisions should be made based on a case-by-case basis, taking into account the synergistic effects, desired or not, of drug combinations.[214]

Drugs may be discontinued for several different reasons, including unsatisfactory seizure control, adverse effects, interaction with other medications, long-term seizure freedom, psychosocial reasons (e.g., parental fear of adverse effects), or administrative/financial reasons (e.g., change of insurance coverage, loss to follow-up).[72]

Except in the case of drug-induced worsening of seizures, severe side effects, or inability to administer (e.g., in the perioperative period), drugs that have been used for longer than 1 month should be discontinued slowly to prevent exacerbation of seizures. For those in whom the drug is being replaced with concurrent titration of another drug, discontinuation over the course of about 6 weeks is standard practice (longer for phenobarbital).[215] Drugs that require immediate discontinuation for less than a few days (e.g., medications without intravenous formulation in the perioperative period) can be temporarily replaced by a bridge of maintenance dosing of benzodiazepines, levetiracetam, and/or lacosamide, but if discontinuation is likely to be more than a few days or permanent (e.g., due to drug allergy), it should be replaced by another drug that can be quickly loaded (see Tables 5.5a and 5.5b).

In the case of children who have attained long-term seizure freedom, a trial off of antiseizure medications should be attempted before they reach adulthood, especially in those who are expected to achieve a significant degree of independence. One drug should be weaned at a time, each over a period of 6-12 weeks.[215] Standard practice in those who undergo surgical resection is to wean off of medications in the absence of seizures or auras for at least 1 year following surgery, although some have proposed earlier weaning schedules. Because of the high risk of recurrent seizures, a well-tolerated and effective drug regimen should not be discontinued in most children who have not undergone resection, but doses may be lowered and efforts should be made to achieve monotherapy as polytherapy is associated

TABLE 5.5B Commonly Used Broad-Spectrum AEDs

Antiseizure Drug	Typical Starting Dose (mg/kg/day)	Typical & Max Maint. Dose (mg/kg/day)	Max Adult Dose (mg/day)	Typical Dosing Interval	Interactions (Nonchemotherapy)	Other Special Considerations
Clobazam (CLB)	<12 y: 0.25-0.5	<12 y: 0.4-1 Max:NE	NE (typically not higher than 40)	Tab, Sus: QD-BID	↓[b] CBZ ↑[b] PHT, antifungals	Useful for children with epileptic encephalopathy
Levetiracetam (LEV)	<12 y:10-20	<16 y:30-40 Max:60-80	3000	Sol, tab, IV:BID XR tab: QD	None	May be loaded quickly at therapeutic dose. IV formulation available
Lamotrigine (LTG)	<12 y:0.5-0.8	<12:4-8 Max:15	800	CT, tab: BID XR tab: QD	↑[o]CBZ, folate inhibitors ↓[b] CBZ, PHT, OXC, PB, HC ↑[b] VPA, sertraline	Titrate slowly over 6-8 weeks. Stop immediately if drug rash develops. Lower doses needed when adding to VPA
Topiramate (TPM)	<16 y:1-3	<16 y:5-9 Max:15	800	Spr, tab: BID XR:QD	↓[o]HC, VPA ↑[o]PHT ↓[b] CBZ, PHT, PB, VPA	May be loaded quickly at therapeutic dose. Monitor for acidosis during acute illness
Valproic acid/ Divalproex/ Valproate (VPA)	<16 y:15	<16 y:20-40 Max:60	3000	Sol:TID Spr:BID DR tab: TID XR tab: BID IV: QID	↑[o]PB, LTG, CBZ, TPM ↓[b] PB, PHT, LTG, rifampin ↑[b] erythromycin, PB	May be loaded quickly at therapeutic dose. Useful for children with epileptic encephalopathy
Zonisamide (ZNS)	<16 y:1-3	<16 y:4-8 Max:12	600	Cap: QD-BID		Monitor for acidosis during acute illness

CT, chew tab; Sol, oral solution; Sus, oral suspension (must be shaken vigorously before each use to assure uniformity of dosing); Spr, sprinkle cap; BID, twice daily; TID, three times daily; NE, not established; neo, neonate; DR, delayed-release; XR, extended-release; PHT, phenytoin; ↓[o], causes a decrease in the blood levels of; ↓[b], blood level is decreased by; ↑[o], causes an increase in the blood levels or toxicity of; ↑[b], blood level or toxicity is increased by; HC, oral contraceptives; CBC, complete blood count; lytes, electrolytes; LFT, liver function tests.
Adapted from Ref. [72].

with adverse psychiatric outcomes for children with epilepsy and their caregivers.[216–218]

Prospective documentation is critical to the retrospective determination of adequate drug trials, which is the most important determination of likelihood of failure of current or future medication trials (see Section on Drug Resistant and Drug Responsive Epilepsy). Every effort should be made to thoroughly document all medication trials (at minimum, medication name, formulation, maximum milligram per kilogram dose tried, dosing interval, adherence, duration of exposure, use prior to or after any resection, effect on seizure control, adverse effects, attempts at optimizing dose, and reason for discontinuation). Only drugs that are discontinued after an adequate trial (given consistently and appropriately at typical maintenance doses long enough to determine treatment response) should be documented as a "failure."[72]

Rescue Antiseizure Drugs

Short seizures at onset of epilepsy do not protect against the possibility of longer seizures and status epilepticus later in the course of the disease.[219] The longer that a seizure continues beyond 5 min without being treated, the less likely it is to spontaneously abort.[220] A rescue medication, such as intravenous, rectal diazepam or intranasal or intramuscular midazolam, should be available in all settings (i.e., hospital, home, school, daycare) and care providers, parents and other caregivers should receive a seizure action plan and be trained in the proper use of the chosen medication.[221–223] A longer-acting benzodiazepine, such as clonazepam or clorazepate, should also be available for children who are known to have clusters of seizures over the course of several hours.[224]

DRUG RESISTANT AND DRUG RESPONSIVE EPILEPSY

The ILAE defines drug resistant (a term used more or less interchangeably with the terms "medically intractable/refractory" and "pharmacoresistant") epilepsy as that in which "...seizures persist and seizure freedom is very unlikely to be attained with further manipulation of antiepileptic drug therapy." The practical consensus definition for consideration of candidates for other therapies, such as epilepsy surgery, is "failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom." Drug responsive ("pharmacoresponsive") epilepsy is that in which "...the patient receiving the current AED regimen has been seizure-free for a minimum of three times the longest pretreatment interseizure interval or 12 months, whichever is longer."[72] The rationale for this definition is that seizures, provoked and unprovoked, occur at unpredictable intervals (sometimes 6 months or more); thus, in some patients, determination of responsiveness may require a prolonged interval of complete seizure freedom.

There is no consensus definition of either category in children; however, based on current knowledge, the use of the above definitions are statistically sound and practical for clinical and research purposes in children with brain tumors. Less than 10-20% of children with structural epilepsy who have had incomplete seizure response to two drugs will achieve sustained seizure remission with subsequent drug trials[225,226]; nevertheless, responsiveness and resistance are dynamic concepts that do not necessarily predict lifelong response to drugs. Seizures may remit after use of more than two agents over an extended period of time and may recur after long-term remission even in those with static processes and stable treatment regimens.

The presence of a structural lesion with potential for growth during a period of dynamic biological and psychosocial development increases the complexity of predicting the course of childhood brain-tumor-related epilepsy. Mixed series of children and adults with epilepsy indicate that those with brain-tumor-related epilepsy have a similar prognosis for achieving long-term seizure freedom with medications alone compared with others with epilepsy with focal-onset seizures[227]; however, the only prospective series examining children with brain-tumor-related epilepsy (which included eight children with low-grade temporal lobe tumors) indicated that all eventually developed pharmacoresistance.[228] No prospective study has determined risk factors for, incidence of, or time to pharmacoresistance or tumor progression in children with unresected low-grade brain tumors and seizures.

According to epidemiologic data from the Connecticut Study of Epilepsy,[229] 13-24% of children with epilepsy due to a confirmed or suspected structural brain abnormality met criteria for pharmacoresistance at some point during long-term follow-up. Of this group, about half did not meet criteria for pharmacoresistance until 3 or more years after diagnosis, but about one in five eventually went into long-term remission. About 40% of children with a confirmed or suspected brain lesion that did not yet meet criteria for resistance at 2 years postdiagnosis had sustained seizure freedom in long-term follow-up.[225,226,229] Most patients with brain tumors in that series underwent resection prior to developing pharmacoresistance, which somewhat limits the ability to extrapolate these results to patients with brain tumors.[47] While the presence of a temporal lesion was strongly predictive of pharmacoresistance in other series, this was not the case in this group of patients.

Across all "natural history" studies of children with structural epilepsy, the most consistent predictors of pharmacoresistance were age less than 1 at onset of seizures, structural etiology, low IQ, and development of an epileptic encephalopathy. While it is unlikely that the two-drug definition for pharmacoresistance will change in the near future, most authors now advocate for beginning evaluation for epilepsy surgery in children with any of these risk factors after a single drug failure in order to offer surgical resection as soon as criteria for pharmacoresistance have been met.

Role of Antiseizure Drugs in Children Without a History of Seizures

There is clear evidence that the use of antiseizure prophylaxis in adults with brain tumor does not decrease the incidence of seizures or epilepsy in those who have not had a seizure. Combined series of adults and children indicate that the same is likely true for children.[230]

Despite this evidence, use of prophylaxis in the perioperative period has become standard practice because of concern for the potential for additional morbidity during this critical period. A single retrospective series examined perioperative seizures in children without history of seizure. Ten percent of patients with and 7% of patients without exposure to antiseizure prophylaxis had perioperative seizures. Based on analysis of risk factors, the authors suggested that perioperative prophylaxis should be further studied in children under the age of 2 and in those at risk for severe or progressive hyponatremia.[231] Close surveillance and correction of sodium disturbances (i.e., cerebral salt-wasting, the syndrome of inappropriate antidiuretic hormone, and diabetes insipidus) in the perioperative period would likely reduce the occurrence of encephalopathy and seizures as well. No studies have examined prophylaxis for acute radiation-induced seizures.

Chemotherapy, Biologic Agents, and Steroids

Tumor regimens that include chemotherapy may be comprised of high-dose systemic or regional (intrathecal, intraventricular, convection-enhanced delivery, intra-arterial, or interstitial administration) delivery. Evidence for effectiveness of chemotherapy for seizure control in children with brain tumors is anecdotal. During the acute phase of treatment, seizures may occur as a direct or indirect complication of several agents, including vincristine, cisplatin, cyclophosphamide, and methotrexate.[232]

Biologic therapies, such as receptor tyrosine kinase inhibitors, immunotherapy, and gene therapy are also under development, but no trials with these agents have addressed seizure occurrence or control.

Steroids contribute meaningfully to reduction of neurologic symptoms in children with significant tumor- or treatment-related parenchymal edema. They are routinely given in the postoperative period to reduce short-term risk of seizure and exacerbation of neurologic deficits, which may affect the ability to record seizures with extraoperative intracranial EEG recordings.[233] Long-term use is generally not recommended due to the association with multiple adverse effects.

Dietary Considerations and Alternative Therapies

All providers who care for children with cancer or epilepsy encounter caregivers questions about alternative therapies and lifestyle, although their use is not always disclosed to the provider.[234–237] While some of these strategies have been found to be effective in the laboratory setting, they remain as "alternative" therapies because they have not been supported by a well-designed placebo-controlled trial in children with brain tumor or epilepsy. Until such trials are conducted and safety, efficacy, and relevant interaction data is published, we recommend use of proven antiseizure drugs as first-line therapy. Nevertheless, providers should inquire about their use and, if caregivers choose to use them, appropriate guidance should be given.

Despite a lack of class 1 evidence, carbohydrate-restricted diets (i.e., ketogenic, modified Atkins, and low-glycemic index therapy) are now accepted as proven and effective treatment for pharmacoresistant epilepsy.[238] Benefit of a calorie-restricted ketogenic diet has been proposed for brain tumors and inhibition of tumor growth has been found in lab animals and a few cases of children with malignant astrocytoma.[239] These findings are encouraging and demand further study; nevertheless, dietary restriction is a difficult undertaking, requiring close laboratory and clinical monitoring and ideally utilizing a specially trained dietician. Until further data is available, diet therapy should only be considered for routine clinical use as adjunctive therapy in children with pharmacoresistant epilepsy and should not delay the use of more definitive strategies, such as resection.

Recently, there has been increasing interest in the use of marijuana derivatives in children with neurologic conditions, including epilepsy and brain tumors. Short-term reduction of induced seizures following administration of cannabidiol has been reported in animal models. Uncontrolled studies thus far have indicated that caregivers of children with severe epileptic encephalopathies report improvements in seizure control and alertness following initiation of a variety of marijuana derivatives at nonstandardized doses.[240] Caregivers of children with treatment- and cancer-related nausea and anorexia also report improvement.[241,242] Concerns have been raised regarding adverse neurodevelopmental and social effects of use of marijuana derivatives in children.[243] Prospective data on short- and long-term seizure and neuropsychological outcomes in children with epilepsy and/or brain tumors is absent[240,244–247].

Dietary supplementation of certain micronutrients may reduce idiosyncratic drug effects for patients with epilepsy. Of greatest interest to oncologists is the recommendation that all women of childbearing age (including girls above the age of 11) who are taking antiseizure drugs be given 0.4-4 mg of folate daily in order to reduce the risk of drug-induced neural tube defects in the event of a pregnancy.[248] Concerns have been raised about folate supplementation in women with brain tumors, with studies yielding seemingly contradictory results. Folate deficiency during pregnancy increases the risk of brain tumors in childhood. On the other hand, folate accelerates the growth of some cancer types. In addition, inhibition of folate metabolism is the primary mechanism of action of several antitumor agents.[249] Reasonable approaches to this issue may include supplementation of at least the minimum recommended daily intake (400 μg) of folate (unless prohibited by oncologic trial enrollment) and counseling of caregivers and young women with epilepsy and brain tumors about contraception that accounts for interactions with antiseizure medications.

SURGICAL MANAGEMENT

Goals and Approaches

Open resection remains the "gold standard" approach to children with primary brain tumors of any grade. The goal is usually to remove as much tumor as safely as possible in order to prevent or lengthen time to recurrence. Additional goals, especially in tumors of

uncertain or high malignancy potential, include relief of compression of tumor on areas of importance to neurological function and flow of cerebrospinal fluid and providing a tissue diagnosis.[35] In children who have epilepsy, long-term seizure control is also considered and may require additional resection of highly epileptogenic regions such as the hippocampus.[250] Thus, the approach to surgery in children with seizures related to supratentorial tumors falls into two broad categories, one in which the primary goal is seizure freedom (i.e., "epilepsy surgery") and the other in which the goals are survival and prevention of tumor progression and recurrence (i.e., "tumor surgery"). While there is an appropriate overlap in these approaches, there are substantial differences between the populations that ultimately undergo one or the other.

Brain tumors account for about one in five epilepsy surgeries done in children.[251] Surgical series reporting epilepsy outcomes in children who predominantly underwent tumor resection because of uncontrolled seizures reveal a significant overrepresentation of temporal localization and very few cases of occipital tumors.[65,122] The tumors were almost exclusively supratentorial, and the most common tumors found were dysembryoplastic neuroepithelial tumor and ganglioglioma. Diagnosis of tumor was often delayed by more than 1 year following onset of seizures. The majority of children had normal neurological examinations at the time of surgery. In addition to a neurosurgeon, the authors of these papers were most often neurologists.

These characteristics differ from those found in seizure series from brain tumor consortia, single center tumor series, and surveillance programs. Seizures reported by these authors were often based upon assumptions (e.g., all events associated with lost consciousness were counted as seizures) and were not typically differentiated in regards to provocation or drug responsiveness. The majority of patients developed other neurologic signs or symptoms and were found to have brain tumor within 1 year of seizure onset. There was a predominance of supratentorial tumors, but more infratentorial tumors were represented than in the epilepsy series. The most frequent supratentorial pathologies in these series were anaplastic astrocytoma, low-grade astrocytoma, ependymoma, and primitive neuroectodermal tumors. In the largest cohort that reported tumor localization in patients with seizures, the parietal lobe was most commonly affected (40%), followed by the temporal (38%), frontal (34%), and occipital lobes (30%).[43,48,252,253] Authorship in these reports was primarily comprised of neurosurgeons and oncologists.

The retrospective nature of these studies, availability of advanced imaging over the time period studied, tendency toward studying localization-related versus pathological entities (e.g., temporal lobe tumors versus ganglioglioma) and other sources of bias may partly explain the differences between these groups; however, it is more likely that differences in tumor biology account for the ways in which children with seizures present and are referred for subspecialty care. Prospective studies enrolling children with seizures at the time of diagnosis of brain tumor are needed to confirm the contribution of tumor biology to the pre-surgical course of tumor-related epilepsy in children.

Timing of Surgical Resection

Very large and high-grade tumors that present in surgically accessible locations are typically operated on urgently, limiting the ability to use studies to define the seizure-onset zone; nevertheless, in these situations, if long-term survival without seizure freedom is achieved following initial resection, repeat surgery with further consideration of seizure-onset zone is often successful.[254]

Management of low- and intermediate-grade tumors is more nuanced.[255] Proponents for early surgical resection in patients with lower-grade tumors associated with generally good overall prognosis for survival cite several supporting arguments. There is a small risk of progression or malignant transformation of low-grade tumors. There is also a theoretical risk of allowing epileptogenesis to proceed unchecked in a patient with a lesion that is actively contributing to epileptogenesis (see Chapter 7). Younger age, shorter duration of epilepsy (especially duration of less than 1 year), and treatment responsiveness at resection are among the primary determinants of improved postresection epilepsy outcomes for all tumor types.[256,257] Furthermore, it is thought that the long-term side effects of medication are more deleterious to neurological and neuropsychological development than resection and that eventual pharmacoresistance or progression is the rule. Finally, resection is associated with a sense of being permanently freed from a disease in children with lower-grade tumors and their caregivers.[258]

While most agree that such an approach is warranted for a child with pharmacoresistant epilepsy; controversy exists over the approach to the child with well-controlled seizures, minimal side effects, and a nonprogressing brain tumor that is otherwise associated with an excellent prognosis. Resection is associated with non-negligible risk of perioperative complications and long-term neurological and neuropsychological morbidity and mortality.[259–263] Children with low-grade glial tumors generally survive longer than adults with similar tumors. Improved survival in patients with intermediate-grade glial tumors presenting with seizures suggests that the approach to these children may not need to be as aggressive as

patients without seizures.[6,264] Despite evidence of stable or improved overall cognitive trajectory in young children who undergo epilepsy surgery at a younger age and become seizure free,[265] no studies have examined long-term and comparative neuropsychological profiles of children who do or don't undergo epilepsy surgery. Adults with long-standing pharmacoresistant epilepsy and low-grade tumors who undergo lesionectomy alone have relatively good epilepsy and neuropsychological outcome, arguing against the theoretical risks of uncontrolled seizures on the mature peritumoral brain (see Chapters 9 and 15); however, the extent to which epileptogenic brain tumors affect cognitive development and the epileptogenic network in the absence of seizure recurrence or tumor progression is unknown. Assertions of eventual pharmacoresistance or progression and the comparative effects of long-term antiseizure drug use and resection are based on generalizations regarding the natural history of structural epilepsy and/or uncontrolled series of adults and children who eventually went to surgery and are, thus, subject to significant ascertainment bias. Finally, those who obtain seizure freedom without undergoing surgery have better psychological outcomes than those who become seizure free following surgery.[258]

No studies have compared the surgical outcomes of epileptic children with pharmacoresistant versus pharmacoresponsive epilepsy or with early versus delayed drug resistance patterns. Likewise, there are no studies that have compared neurological and neuropsychological outcomes of children with epilepsy who achieve remission of seizure with or without resection. Considering that such studies in children with brain tumors would have to control for important confounding factors, such as the site, size, and type of tumor and the surgical approach, it is unlikely that these questions will have a definitive answer outside of a large prospective multicenter collaborative study.

Early resection should be considered in children who have pharmacoresistant epilepsy or have additional risk factors for pharmacoresistance (see Section on Drug Resistant and Drug Responsive Epilepsy).

Lesionectomy (Tumorectomy) Versus Lesionectomy "Plus"

It is becoming increasingly apparent that a single resection strategy for all children with any given tumor type is untenable. Localization of tumor (including juxtaposition to vital structures) and association of other pathologies (i.e., focal cortical dysplasia and mesial temporal sclerosis) are likely of importance to achieving the best surgical outcome. Complete tumor resection is the most important determinant of long-term seizure and survival outcome following surgery in children as well as adults with tumors of any pathology, but there is considerable debate regarding the additional utility of determining and/or resecting the apparent extent of seizure onset zone while avoiding precisely determined eloquent structures.[65,121–123,160] Outside of the mesial temporal region, such strategies vary from a priori resection of a margin of peritumoral cortex (avoiding presumed vital structures)[266,267] to resection of electrically "active" regions and avoidance of vital cortex and tracts as determined by multiple noninvasive and invasive studies. Those studies typically include the use of intracranial EEG before, during, and/or immediately following tumor resection. No approach has been shown superior to another with respect to any tumor localization or pathology; however, all generally result in improved seizure outcome over lesionectomy following initial surgery. In the mesial temporal region, additional a priori selective amygdalohippocampectomy or anterior temporal lobectomy is supported by superior seizure outcomes in patients with tumors adjacent to mesial temporal structures[121,123]; however, seizure freedom with lesionectomy alone in this region has been reported and the extent to which additional resection in this region influences memory and language outcomes in children is poorly understood.[123]

Several concerns have been raised about the "lesionectomy-plus" approach. Such an undertaking may involve costly and time-consuming noninvasive and invasive procedures that do not always lead to additional resection beyond tumor and may increase perioperative morbidity.[50,268–270] Similar to children with high-grade tumors, children with low-grade tumors who do not become seizure free following lesionectomy as an initial strategy can achieve similar results (to those who undergo lesionectomy-plus as an initial strategy) by undergoing a second, tailored resection.[121,271] Nevertheless, children and their caregivers may be reluctant to return to the operating room when initial resection does not result in sustained seizure freedom.[272] Concerns that determinations of eloquent structures may result more often in subtotal tumorectomy are unfounded—neither the initial approach to workup nor the ultimate resection strategy employed affected the totality of lesion resection.[50,65,121–123,160,266–270]

At a minimum, all centers that treat children with seizures and brain tumors should become familiar with and routinely employ intraoperative electrocorticography and basic intracranial motor and somatosensory evoked potentials, which are relatively fast, inexpensive, and safe procedures with minimal potential for morbidity. Prospective research examining the optimal use of electrocorticography and the utility of other studies mentioned above is ongoing, but requires appropriate, universal, and comprehensive outcome measures (see Section on Outcome).

Palliative Strategies

Uncontrolled seizures related to tumors that are not amenable to surgical resection or in patients with ongoing seizures following resection have substantial impact on quality of life. In these situations, palliative approaches are associated with seizure reduction (and sometimes freedom) and substantial improvements in postoperative quality of life.[273–275] Transection of pathways important to the seizure network (corpus callosotomy and hemispherectomy/hemispherotomy) and vagus nerve stimulation are the most well studied in children with structural epilepsy for whom definitive resection is not possible. Candidates are typically considered for transection in the setting of frequent uncontrolled seizures and significant comorbidities, including hemiparesis (for hemispherectomy candidates) and frequent fall-related injuries (for callosotomy candidates). Literature on the use of these strategies for seizure reduction in children with brain tumors is limited to a few cases within larger series.[275–279]

The use of cranial radiotherapy, including conformal radiation, stereotactic radiosurgery, and brachytherapy for patients with brain-tumor-related seizures is reviewed in Chapters 4 and 14. The literature on the effect on seizures of radiotherapy in adults with brain tumors is mixed. Outside of the use of radiosurgery for hypothalamic hamartoma, there is very little evidence of the effect of irradiation on seizure control in children. While routinely employed in older children with incompletely resected or progressive low-grade astrocytoma, anaplastic astrocytoma, glioblastoma, primitive neuroectodermal tumor, and ependymoma, use of radiotherapy in initial presentation of glial and glioneuronal tumors that are associated with a better prognosis (i.e., low grade, complete resection possible, cerebral localization, presentation with seizures) remains controversial.[244–247]

Most radiation protocols in children have been determined empirically. Radiation is typically avoided in young children with low-grade tumors as they are more susceptible to acute toxicity and late effects of radiation (e.g., secondary tumors, developmental delay, inhibition of growth) than adults.[247] Radiation toxicity is highly variable in older children, possibly related to genetic predisposition and the extent of pre-existing neurologic injury.

Due to concerns regarding long-term morbidity related to invasive surgical approaches and exposure to chemotherapy and ionizing radiation, there has been increasing interest in ablative technologies. Ablation is a non- or minimally invasive procedure that destroys a small area of tissue by inducing rapid electrochemical, thermal, and/or hydro-mechanical changes that result in tissue necrosis and apoptosis by multiple mechanisms. The "zone of efficacy" of ablation may be considered complementary to that of ionizing radiation. Whereas the former is dependent upon the "concentration" of destructive force (highest at the center of the target), the latter is dependent upon the development of cytotoxic free radicals (an oxygen-dependent process that is most effective in the relatively oxygen-rich tumor periphery). Currently available technologies can be divided into primary mechanisms of tissue injury: hyperthermic ablation (radiofrequency, microwave, laser, and focused ultrasound (FUS)), cryoablation, electrical ablation (percutaneous irreversible electroporation), and chemical ablation.[280]

Ablation of central nervous system tumors is a relatively recent development. Some techniques, such as transcranial MRI-guided FUS, are applied over a broad field through the intact skull and stereotactically focused on a single location in a manner similar to radiosurgery. Methods that require proximity to the area of interest, such as MRI-guided laser interstitial thermal therapy (LITT), cryotherapy, and microwave ablation typically employ a stereotactically positioned catheter or antenna introduced through a burr hole. Most currently used techniques have incorporated imaging guidance: real-time structural and/or thermal imaging that assist in delivering optimal doses to the target tissue. The primary determinants of totality of tumor ablation are tumor size and accessibility of tumor to the method used. Preliminary evidence indicates that even incomplete ablation with FUS[281] (E. Martin, personal communication, April 30, 2014) or LITT[282,283] may result in sustained seizure freedom in tumors with high potential for morbidity with open resection. There is also increasing interest in the use of ablation to augment the effectiveness of chemotherapy and radiotherapy.[280]

OUTCOME

There are no studies available that examine the outcomes of children with brain tumors who have not undergone resection. Following resection, the prognosis for seizure freedom in children with LEATs is generally good. Sixty-nine to one hundred percent of children who have reported seizures at the time of surgery achieve seizure freedom on or off of antiseizure medications following surgery.[67,121,250,269,284] In the only study in which medication wean was attempted following surgery for children with brain-tumor-related epilepsy, 27% had seizure recurrence.[97]

While cancer-related mortality in children has substantially declined (about 50%) over the past 4 decades, there has been a more modest (15-20%) improvement in overall survival of children with brain tumors, with an estimated 5-year survival rate of 66%. Central nervous

system tumors now account for the highest number of childhood cancer deaths, although the mortality remains well below that of adults with brain tumors. Males have a higher mortality (5.2/100,000) than females (3.5/100,000). It should be emphasized that presentation with seizures, at least for patients with low- or intermediate-grade glial tumors, portends a better prognosis. Additional good prognostic indicators include diagnosis in the last half of the first decade of life, limited malignant features on histology, and long duration of symptoms before diagnosis; whereas neoplasms in infancy, brainstem and thalamic location, and evidence of histologic aggressiveness are considered poor prognostic signs.[1,2] Following resection, poor seizure control in children with high-grade tumors is associated with reduced survival.

Improved survival has resulted in an increasing recognition that even disease- and progression-free survivors are at high risk of substantial long-term medical, neurological, and psychosocial morbidity. As might be expected, morbidity is generally higher in children who require more aggressive interventions in order to achieve tumor remission or cure. A large series examining outcomes of children with brain tumors found that half of all long-term survivors self-reported new focal neurologic deficits and about 25% had new-onset seizures or seizure-like events after tumor diagnosis, with a higher incidence in children younger than 5 years of age at diagnosis. The incidence of new-onset seizures declined from 54 per 1000 person-years during treatment to 23 per 1000 person-years in the 5 years following treatment, and 10 per 1000 person-years thereafter. Seizures, either related to stroke or mineralizing microangiopathy, were common long-term sequellae of children who receive radiation doses higher than 30 Gy.[252]

Educational attainment is lower in children with brain tumors than in any other childhood cancer. Compared to healthy siblings, children with brain tumors are 2-10 times more likely to report academic or school-related problems, including receiving a diagnosis of a learning disability, repeating or failing a grade, or being enrolled in a special education program. Less than 60% report at least some college level education. Survivors diagnosed before the age of 5 are more likely to need special education.

Children with brain tumors also have poorer psychosocial outcomes in adolescence and adulthood, including a majority reporting having no close friends and not being married. On the other hand, almost 70% find meaningful employment and the rate of mood disorder diagnosis is relatively similar to that of siblings of survivors. Limitation of physical and cognitive abilities are the most important risk factors for low psychosocial attainment.[285,286]

Structural epilepsy is associated with substantial long-term risk of mortality due to direct sequellae of seizures (e.g., status epilepticus, sudden unexplained death in patients with epilepsy, drowning, motor vehicle accident) as well as other causes (e.g., suicide, medical comorbidities). In a 40-year follow-up study of patients diagnosed with childhood epilepsy, 37% of children with remote symptomatic etiology of epilepsy (which includes patients with structural epilepsy) died, with the most important risk factor being uncontrolled seizures.[287]

Prospective studies of cognitive deficits in children with epilepsy indicate that such deficits are present early on and that progressive deficits may occur even in the setting of treatment, especially in children with early age of seizure onset and very frequent (daily) seizures. Epilepsy surgery is associated with stabilization or improvement in general cognitive and behavioral outcomes in young children or children with intellectual disabilities who become seizure free after surgery.[265,288]

In terms of psychosocial outcomes, children with epilepsy are at high risk of depression, anxiety, attention deficit hyperactivity disorder, and behavioral problems in the short term.[289] In the long term, roughly one-quarter do not graduate from high school, two-thirds do not have an intimate partner, one-third are financially dependent or unemployed, one-sixth are socially isolated, and about one-sixth are dependent on full-time caregivers. Among survivors in long-term follow-up cohorts of epilepsy of varying etiology, the majority had comorbid somatic illnesses, half developed intellectual disabilities, and one-quarter developed psychiatric disorders. Again, the primary determinants of psychosocial outcome in these series were neurological or cognitive deficits. Surprisingly, seizure control and medication status did not have a major effect on reported comorbidities, although patient- and caregiver-reported outcomes clearly implicate these factors in dissatisfaction with overall and health-related quality of life.[290–292] A single study examining short-term change in behavior found improvements following surgery.[293]

FUTURE DIRECTIONS

Children with brain tumors and children with epilepsy are at high risk of poor long-term socioeconomic, cognitive, psychiatric, and medical outcomes. The co-occurrence of these two conditions is a perfect storm with potential for severe consequences; nevertheless, there are significant differences in biology, behavior, and localization-related effects of epilepsy-associated supratentorial tumors compared with the larger group with brain tumors (which is dominated by infratentorial pathology) or other structural etiologies of epilepsy. Thus, it is likely that children with brain-tumor-related epilepsy have different and more varied outcomes from those with epilepsy of other causes or those with brain tumors that have not had seizures.

The fragmented and myopic problem-based approach of each specialty to children with both of these conditions is, in part, to blame for the challenges that these children apparently face into adulthood.[36] Early and appropriate interventions based on predictive integrative models in children with brain-tumor-related epilepsy are necessary to make a substantial impact on mortality, morbidity, pharmacoresistance, progression, and other survival outcomes. Such models have been proposed, but no attempt has been made at prospective collection of data that accounts for the interactions between tumor biology, the epileptogenic network, and the dynamic changes in childhood psychological, social, and neurological development.[294,295]

Current limitations in development of this model can be addressed by the use of standardized, meaningful, and comprehensive brain-tumor-related epilepsy outcome measures for children and reliable early stage biomarkers of epileptogenesis and tumor onset, recurrence, or progression for all tumor types across the spectrum of childhood. These challenges will best be met in the setting of multicenter multispecialty prospective basic science, clinical, and translational research collaboratives.

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CHAPTER

6

Mechanisms of Focal Epileptogenesis

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CHAPTER CONTENTS

This chapter reviews the mechanisms underlying the process that characterizes the progression of epileptogenesis, based on the analysis of the data obtained from animal models of focal epilepsy. These models tend to reproduce temporal lobe and posttraumatic epilepsy because the extent or quality of brain damage in these forms of progressive epilepsies are likely to be active in the presence of a brain tumor. Secondary focal epilepsies are progressive diseases that develop according to the nature of the underlying primary lesion. A latent period elapses between the early presentation of an epileptogenic lesion and the appearance of the first epileptic manifestation. During this period, complex tissue changes occur, and these changes characterize the *epileptogenic process*. The primary alteration may present as a critical acute event, such as a stroke or a traumatic lesion, which independently induces cerebral tissue damage associated with acute seizures. These are due to massive tissue destruction that releases into the extracellular space proconvulsive compounds, such as glutamate and potassium. Acute seizures are symptomatic of brain damage and usually remit within hours or days. A latent period without seizures occurs between the acute "symptomatic" seizures and the development of a late, chronic epileptic condition. This is also true for slowly growing, low-grade, cortically based tumors more often arising at younger ages, defined as long-term epilepsy-associated tumors (LEAT)[1] that are mostly epileptogenic and are commonly responsible for drug-resistant epilepsy.[2] Early and late factors that modify excitability of the peritumoral tissue in the course of epileptogenesis are further discussed in the following paragraphs. These may differ in slow-growth tumors (such as LEAT) and in high-grade, rapidly progressive tumors.[3] Considering LEATs, the occurrence of acute seizures is usually missing, and the first seizure is assumed to be the result of the process of epileptogenesis evolving in the tissue that surrounds the expansive lesion, in particular when they are positioned in cortical structures. Rapid-growth tumors may generate seizures through other phenomena, which may include increased intracranial pressure and alterations of blood-brain barrier (BBB) permeability. In cerebral neoplasm, as well as in most lesional epilepsies, seizures emerge from the perilesional brain tissue, because the tumor itself is not generating activity and is considered to be electrophysiologically inert.

The details of the epileptogenic process have been studied in two forms of epilepsy, temporal lobe epilepsy and posttraumatic epilepsy, mainly because the extent and quality of brain damage can be reliably reproduced in animal models of these two conditions. The evidence that is discussed in this chapter is mainly based on research performed on these forms of experimental focal epilepsy. Most importantly, the experimental data obtained from animal models have been validated in human brain tissue removed from patients with focal epilepsy resistant to available antiepileptic drugs and treated with epilepsy surgery. In those cases, the epilepsies tended to be secondary to mesial temporal sclerosis, focal cortical dysplasia (FCD), low-grade tumors, and glial scars. An increasing number of publications also address focal epilepsy secondary to cortical dysplasia,

even though, for this condition, animal model studies on the progression of the epileptogenesis process are less advanced.[4] Several reviews on this topic have appeared in the last 20 years,[5,6] and only recently, review articles specifically dedicated to tumor-associated epileptogenesis have been published.[2,7,8] This chapter examines general concepts on mechanisms of epileptogenesis that characterize acquired focal epilepsies.

TIME COURSE AND SPECIFICITY OF ACQUIRED EPILEPTOGENESIS

As mentioned above, the time required to develop the epileptogenic process, or to transform a normal brain area into one capable of generating spontaneous epileptiform activity, depends on the features of the epileptogenic lesion. In addition to the early damage that may occur in focal epilepsies due to acute cerebral injuries, the early days or weeks of epileptogenesis are characterized by changes in the lesional and postlesional microenvironment associated with the altered transcriptional expression of genes. These events are followed by molecular, neuronal, and circuit reorganization that may involve dendritic or axonal sprouting, neuronal degeneration, cell loss, gliosis, inflammatory reactions, neurogenesis, and molecular and tissue reorganization, among other processes (see Figure 6.1).[5] These events may have an unfavorable effect on tissue excitability, but they could also represent a reparative process that counteracts or stabilizes cerebral tissue damage. It is commonly assumed that the cascade of events that characterize the early epileptogenic process are lesion-specific, but later reorganization is rather independent of the primary cause of damage. Part of late epileptogenesis is believed to be due to the occurrence of subclinical hyperexcitability that by itself may promote further tissue damage (Figure 6.1). These hyperactivity-dependent alterations are supposed to continue and to be enhanced when recurrent seizures become manifest at the end of the latent period. The concept that "seizures beget seizures" is commonly accepted, even though the conclusive demonstration that seizure activity by itself is sufficient to induce a chronic progression of the epileptogenic process is still lacking.[9,10] Intense and sustained seizure activity, such as that occurring during *status epilepticus* (i.e., continuous, uninterrupted seizure discharges for more than 30 min), may promote further damage through associated secondary changes, such as BBB alterations and breakdown of brain metabolic

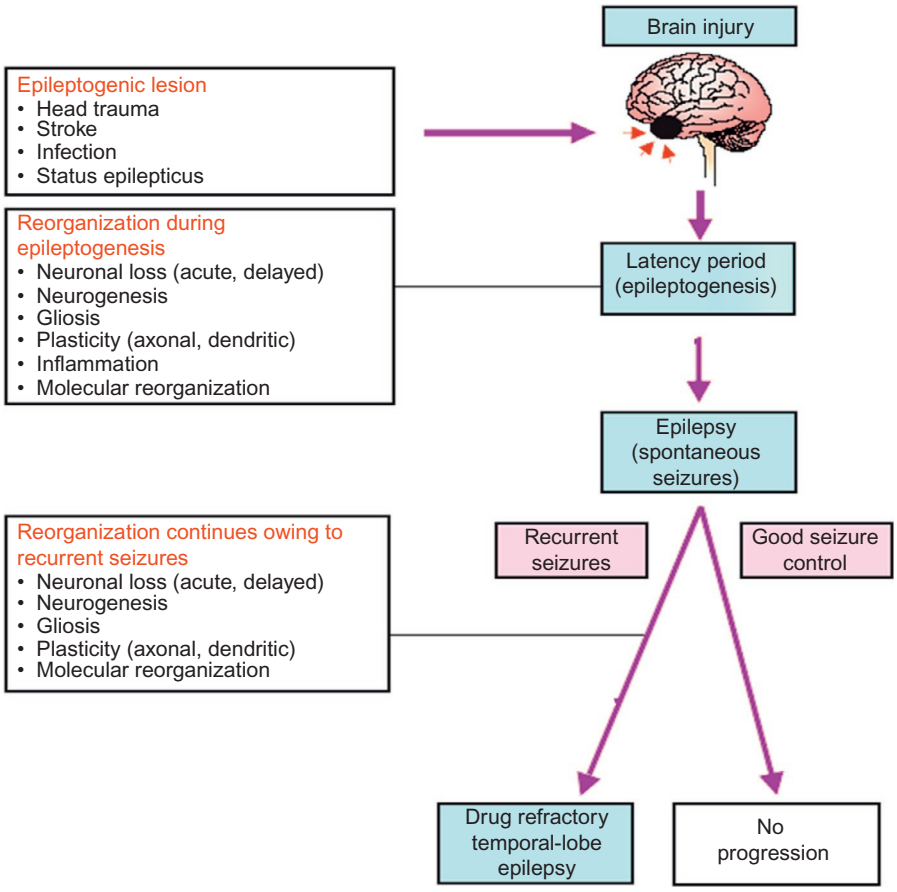

FIGURE 6.1 Scheme of the process of epileptogenesis. Modified from Pitkänen and Sutula [5] with permission from Elsevier

homeostasis. Similar transient events may occur during prolonged single seizures that are usually mild and are well compensated. The possibility that tissue damage by itself may be the cause of further damage via the activation of transcriptional events should also be considered. In conclusion, solid evidence suggests that, whatever the cause, the epileptogenic process does not stop when spontaneous seizures become evident. The causes of such a progression are still largely undetermined. This chapter largely focuses on structural and functional alterations during epileptogenesis and refers to other chapters for the discussion of posttranscriptional changes in early genes and gene expression.[6,11] We exclude from the present discussion the possible effects of tumor-specific treatments, such as radiotherapy or chemotherapy, which should also be considered as potential causes of epileptogenic brain damage.

The study of epileptogenesis is founded on the use of animal models of epilepsy. The ideal strategy for studying epileptogenesis should first recognize the type of focal epilepsy that is considered and human model to refer to for the interpretation of the findings. Even though brain changes likely follow the initial insult and the occurrence of spontaneous seizures is similar for different forms of focal epilepsies, specific changes may coincide with different conditions characterized by different causes and possibly by different time courses of brain damage. For this reason, the epileptogenic changes that may occur after a hemorrhagic stroke would probably be different from those developing from a (possibly congenital) FCD. The choice of the correct animal model to study lesion-specific or insult-specific epileptogenesis is a crucial step in correctly identifying changes occurring in different focal brain diseases associated with epilepsy. As mentioned above, researchers are increasingly able to investigate the process of epileptogenesis in different forms of focal epilepsies by using morphological, functional, and molecular neuroscience techniques to analyze the epileptogenic cortical tissue of patients with different forms of focal epilepsy who received epilepsy surgery treatment.[12] Epilepsy surgery is performed on patients who present with either a clear lesional epilepsy or a form with severe seizures and neurological or cognitive impairments that is resistant to pharmacological treatment. State-of-the-art techniques can be applied to the epileptogenic tissue that has been surgically removed to confirm and validate hypotheses that were developed on the basis of experimental studies on animal models. This approach is particularly appealing and relatively unexplored for lesional epilepsies associated with tumors.

One final issue to be considered when discussing acquired focal epileptogenesis is its pattern of progression. This problem has been analyzed in animal models of mesial temporal lobe epilepsy[13,14] and in a hypoxia-ischemia model induced in juvenile rats.[15,16] The experimental data indicate that there is a time window between the initial insult and the occurrence of the spontaneous chronic seizures (latent period) and that there is a progressive increase in seizure frequency over time after their first appearance. These trends have exceptions, because it has been reported that a subpopulation of animals submitted to electrically induced status epilepticus show a nonprogressive appearance of seizures with a short delay from the status.[17] The existence of a progression suggests that changes in the brain support a process of progressive increase in excitability that eventually results in seizures and epilepsy. As mentioned above, whether the increase in seizure frequency after the appearance of the first seizure from the latent period is due to the evolution of the initial brain damage or to the occurrence of seizures is still undetermined.

In the following paragraphs, we review the changes that are observed during focal epileptogenesis.

Cellular death is not a common feature of tumor epileptogenesis, although it is always observed in other forms of acquired focal epilepsies, such as mesial temporal lobe epilepsy with hippocampal sclerosis and posttraumatic and postinfarct epilepsies. Neuronal cell loss may occur in fast-growing tumors, as a result of vascular-mediated events, such as deafferentation by vessel compression[18] or micro- and macroischemic/hemorrhagic damage that induces necrosis. Mechanisms of neuronal or glial damage due to hypoxia include cell swelling resulting from ion and pH unbalance.[19] The role of cell loss in epileptogenesis is still discussed. In models of temporal lobe epilepsy, cell loss is observed in CA1 and CA3 regions and in the hilus of the dentate gyrus, as well as in layer III of the entorhinal cortex. In poststatus models diffuse cell loss in the thalamus, piriform cortex, and other cortical areas has been demonstrated. In posttraumatic epilepsy cell death occurs at the site of trauma in the neocortex (at the percussion site in the most diffuse model of fluid-percussion injury),[20] but also in the hippocampus and thalamus. In human postsurgical samples obtained after epilepsy surgery, similar patterns of cell loss were observed.[21,22] Cell loss is due to the initial insult, but it can be worsened by seizure activity. The selective death of specific cell subpopulations has been proposed to explain an increase in excitability in the epileptogenic tissue. Inhibitory GABAergic neurons decrease in number in the dentate gyrus of the hippocampus of temporal lobe epilepsy models[23–25] and inhibitory postsynaptic currents have been shown to be reduced in granule cells of the dentate gyrus and in pyramidal neurons of the CA1 region.[26,27] The loss of mossy cells in the dentate gyrus has also been confirmed in experimental and human temporal lobe epilepsy[22,28] and in posttraumatic epilepsy.[29] Even though it is commonly and simplistically assumed that epilepsy should correlate with a

decrease in inhibitory activity (and thus a loss of inhibitory neurons), the existence and the role of selective loss of inhibitory neurons in focal epilepsies have been questioned. In several forms of drug-resistant epilepsies, indeed, inhibitory neurons are not reduced, and GABAergic function can be "paradoxically" enhanced.[30–32] In light of recent findings on the pro-ictal effects of enhanced inhibitory network activity,[33,34] the selective loss of interneurons in ictogenesis and epileptogenesis should be reconsidered. It is more likely that the tissue process associated with necrotic-apoptotic cell death (inflammation, gliosis, etc.) provides an epileptogenic potential more effective than the cell loss that results from cell death.

Inflammation: Increasing evidence demonstrates the involvement of brain inflammation in epilepsy and seizures. Glial cells, such as astrocytes and microglia, produce proinflammatory molecules that regulate neuron-glia interactions and contribute to modulate brain excitability.[35,36] It has been demonstrated that proinflammatory factors, such as interleukin 1 beta, complement molecules and toll-like receptors are overexpressed in different types of human focal epilepsies, including mesial temporal lobe epilepsy,[37,38] epilepsy secondary to cortical dysplasias,[39,40] tuberous sclerosis,[41] and glial tumors such as gangliogliomas and dysembryoplastic neuroepithelial tumors.[39,42] Researchers are still debating whether inflammation is a protective reaction of brain tissue against both the initial insult or seizure activity or a detrimental factor in the development of epileptogenesis. Microarray gene expression profiles and immunohistochemical studies performed in animal models of temporal lobe epilepsy and posttraumatic epilepsy have demonstrated that inflammation-related genes[11,43,44] and molecules[36,45,46] are upregulated or overexpressed both in the acute phase after status epilepticus and in the latent phase associated with the epileptogenic process. The persistence of the enhanced expression of proinflammatory molecules in tissue obtained from chronically epileptic animals and in postsurgical specimens removed from patients with drug-resistant focal epilepsies suggests that focal inflammation accompanies focal epilepsy throughout its clinical course. One possible explanation for these findings may be that the recurrence of seizure activity per se sustains inflammation. Several findings support this hypothesis. Seizure activity induced in vivo enhances the expression of cytokines and inflammatory mediators.[36,47,48] This could be due to either a direct effect of seizures on neurons and glia (brain-borne inflammation) or by the activation of blood-borne elements during seizures.[49] A recent study demonstrated that seizures induce a rapid increase in production of IL-1beta in the absence of peripheral contributes in the in vitro isolated whole brain preparation,[50] demonstrating the primary contribution of local cerebral inflammatory activation during epilepsy. A peripheral contribution should also be considered, because status epilepticus and seizures have reportedly induced leucocyte activation,[49,51] expression of adhesion molecules in cerebral endothelial cells,[52] and alterations of BBB permeability. These events can reinforce brain inflammation and may promote further brain hyperexcitability. It is now well established that the expression of inflammatory cytokines sustains seizure activity,[36,45,47,53] therefore perpetuating a loop of inflammation-seizure-inflammation that may be crucial to sustaining and worsening the epileptogenic process via both transcriptional and nontranscriptional events.[36] Finally, several preclinical trials with anti-inflammatory drugs demonstrated a protective action by slowing down the epileptogenic process, thus affecting the progression of the focal epilepsy.[11,36]

Gliosis: The upregulation of intermediate filament (IF) proteins, in particular glial fibrillary acidic protein (GFAP), by reactive astrocytes and activated microglia in the lesional and epileptogenic areas serves as a marker of focal epilepsy. Independent of the type of primary alteration or insult, astrocytes react by expanding their soma and processes, by increasing synthesis of GFAP, and by re-expressing progenitor markers, such as vimentin and nestin. Enhanced expression of these specific astrocytic markers observed with immunohistochemical staining has been considered to be a phenomenon of reactive astrocytosis. Researchers are still debating whether the enhanced expression of GFAP signaling in the epileptogenic tissue originates from proliferating cells, such as NG2 progenitors,[54] or from astroglial cells that restart proliferation after brain insult. Quiescent astrocytes re-enter the cell cycle after a traumatic lesion and, if exposed to specific growth factors, are able to generate to self-renewing multipotent neurospheres. Notably, this response does not occur with cells isolated from intact parenchyma.[55] Such potentials to self-renew and to acquire neural stem cell features are not expressed in vivo, where reactive astrocytes only give rise to other astrocytes.[56] In summary, although NG2+ cells actively possess a significant degree of plasticity in the intact brain, astrocytes do not exhibit progenitor function even if, upon injury and epilepsy, they are able to reacquire immature traits, as suggested by the activation of proliferation and acquisition of immature and germinal astroglia.

In human temporal lobe epilepsy and in related animal models, the relevant alteration of astrocytic morphology and function has been demonstrated. Astrocytes express ionotropic glutamate receptors (GluRs) and glutamate transporters (GluTs). GluR cells are characterized by the expression of voltage-ion channels. GluR cells receive synaptic input from GABAergic interneurons and glutamatergic CA1 pyramidal neurons.[57]

Most GluR cells are immunoreactive for NG2, but not for GFAP. GluT cells are intensively coupled via gap junctions, enwrap blood vessels with their endfeet, and show immunoreactivity for GFAP. Interestingly, although GluR astrocytes have been found in both the sclerotic and nonsclerotic forms of TLE, a dramatic loss of GluT cells is observed in the CA1 region of AHS patients.[58] A significant reduction of astrocytic Kir 4.1 channel expression resulting in a reduced $I_{k(IR)}$ current was also demonstrated in human sclerotic hippocampi of temporal lobe epileptic tissue.[59,60] Interestingly, Kir4.1 colocalizes with astrocytic water channels, aquaporine 4 (AQP4), which is also downregulated in the ASH,[61,62] and in epileptic tissue with FCD.[63] A downregulation of Kir4.1 and AQP4 channels has also been observed in the kainic[64] and pilocarpine models of epileptogenesis.[65] These alterations may contribute to astrocyte swelling and derangement of potassium and glutamate homeostasis in the epileptic tissue, thus promoting hyperexcitability.[64] An increase in extracellular glutamate levels has also been described in human epileptic tissue from TLE patients as a result of a decrease in the rate of the glutamate or glutamine cycle[66,67] or due to an altered expression of the glial glutamate transporters (EAAT2).[68,69]

BBB impairment represents another marker of incoming astrocyte activation. Friedman and colleagues postulated a link between the changes in BBB permeability during seizures and astrocyte dysregulation.[70] In particular, serum-derived albumin uptake by astrocytes is followed by the upregulation of the astrocytic marker GFAP, suggesting a BBB damage-induced astrocyte transformation and dysfunction.[71]

Serum albumin-induced astrocytic transformation is mediated via transforming growth factor b receptor 2 (TGFbR2). Experimental studies in animals submitted to both amygdala kindling and status epilepticus showed TGFβ upregulation in hippocampal neurons and astrocytes, respectively.[72,73] Astrocytic TGFβR2 activation would induce rapid transcriptional changes resulting in downregulation of K^+ inward-rectifying (Kir 4.1) channels[74] and water channels AQP4[75], as previously discussed. This would lead to astrocyte swelling, reduced clearance of both extracellular potassium and glutamate, an increase in glutamate release, and, within weeks or months, a condition of steady increased excitability. The described modifications occur in reactive astrocytes during epileptogenesis and include the production and release of inflammatory molecules (IL-1β, TNFα, PGE_2, etc.).

Immunological abnormalities are found in routine epilepsy specimens, suggesting a broad role for immune system activation in the etiology of epilepsy. Following an acute or chronic brain pathological insult, microglia activation precedes synaptic alterations. Indeed, recent data has demonstrated that prenatal activation of microglia is sufficient to impact synaptic function in adulthood.[76] Microglial cells express membrane neurotransmitter receptors, and this characteristic makes them sensitive to neuronal activity. Accumulating evidence suggests that activated microglia and reactive astrocytes work in concert to promote the Ca^{+2}-dependent release of ATP, glutamate, adenosine, and other gliotransmitters. Microglial cells trigger the activation of resting astrocytes, stimulating Ca^{+2} mobilization from internal stores through the release of ATP and proinflammatory molecules that support regenerative and propagating calcium waves through autocrine or paracrine activation. As a result of such activation, reactive astrocytes respond with the release of inflammatory mediators in the extracellular space.[77–79] These events promote further gliotransmitter release. All these molecules act in concert generating and amplifying intercellular astrocyte Ca^{+2} waves and increasing neuronal excitability.[80,81] In line with these data, a recent paper supports the possibility that activated microglia could represent an upstream partner of astrocytes, transforming the astrocytes themselves into glutamate-releasing cells, thus helping to modulate neuronal excitability early in the inflammatory process and to initiate bursting neuronal activity in the epileptic brain.[82]

Neurogenesis: Evidence suggests that neuronal death and glial proliferation in temporal lobe epilepsy are coupled with the formation of new neurons. The first indication of neurogenesis in epilepsy was the demonstration of newly differentiated granule cells in the dentate gyrus in animal models of temporal lobe epilepsy.[83,84] Increased neurogenesis is observed for 3-4 weeks in the subventricular zone of the forebrain and in the subgranular zone of the dentate gyrus after status epilepticus induced by pilocarpine treatment.[83,85] Newly formed granule cells migrate in the dentate hilus and may enlarge the dentate gyrus layer, which acquires a dispersed structure.[86]

Tissue reorganization: The above-described events (cell death, gliosis, neurogenesis, changes in gene expression and molecular plasticity) change the environment at the epileptic focus and may induce a reorganization of the neuronal networks and of the interactions between neurons, glia, and cerebral vessels. These events usually occur weeks or months after the original epileptogenic insult. Plasticity changes in the axons and dendrites of neurons in the epileptogenic region have been demonstrated in models of temporal lobe epilepsy.[87] Axons of granule cells in the dentate gyrus are released from their targets when neurons in the hilus degenerate in the acute phases after status epilepticus, and these axons may sprout to form re-entrant excitatory loops by targeting neighboring granule cells. These findings are confirmed by physiological evidence of enhanced

excitatory synaptic potentials in granule cells recorded in slices of hippocampus from temporal lobe epilepsy rats.[88] Granule cell axons are enriched with zinc and can be revealed by Timm's histochemical staining.[22,89–91] A newly formed band of zinc staining due to axon sprouting in the inner molecular layer of the dentate gyrus becomes apparent weeks after status epilepticus and has been demonstrated in human mesial temporal lobe epilepsy.[89,92,93] Axonal sprouting is not limited to the dentate gyrus in temporal lobe epilepsy models; recurrent excitation has also been shown in the CA1 region.[94,95] Moreover, mossy fiber sprouting in the dentate gyrus reportedly occurred in several animal models of focal epilepsy, in addition to temporal lobe epilepsy models.[96]

Axonal sprouting is associated with the formation of new functional synapses on dentate gyrus granule cells.[94,97,98] Modifications in postsynaptic dendrite morphology and function has also been demonstrated. Alterations of neurotransmitter receptors and voltage-gated channels at synapses and dendrites are known to occur in temporal lobe epilepsy and posttraumatic models.[11] A reduction of postsynaptic GABAa receptor function possibly mediated by receptor internalization was demonstrated after status epilepticus in rats.[99] Glutamate receptors (AMPA subtype) are also increased in the granule cells of temporal lobe epilepsy models.[100] In addition, the dendrite structure and morphology of the basal dendrites of granule cells in the dentate gyrus (basal dendrites that are not usually present in this type of neuron in control conditions) become apparent after status epilepticus in epileptic rats[101] and grow into the hilus, contributing to hyperexcitability via recurrent excitatory circuit via sprouted axons.[102] Increased dendritic ramification in principal cells and interneurons of the hippocampus have been described in Ammon's horn sclerosis as well.[103] Dendrite calcium conductances, in particular *t*-type conductances, are enhanced in epileptic rats[104,105] during the latent period of epileptogenesis, and these increased conductances promote enhanced burst firing and synchronization in the CA3 and CA1 regions of epileptic animals.

Several of the epileptogenic elements described for temporal lobe epilepsy, focal dysplasias, and posttraumatic epilepsy are likely to be active in the presence of a brain tumor. In the case of expanding lesions, the continuous challenge of the perilesional tissue undoubtedly plays a primary role in worsening tissue damage, thus promoting further epileptogenesis. Immunohistochemical or molecular analysis has demonstrated that increased expression of proepileptic and proepileptogenic factors in peritumor tissue occur and are responsible for a progressive molecular reorganization of the tissue, both inside and around the tumor lesion. Upregulation of glutamate receptors and downregulation of GABAergic receptor subunits and of ion channel transporters have been reported[38,42,106,107] and could be responsible for maintaining hyperexcitability in the tissues that surround the lesion. A contribution could also be mediated by the altered (enhanced) expression of connexins (connexin 43 and 32, forming the pore of the gap junction), observed in tumor and peritumor tissue, that facilitate interneuronal transfer of excitation.[108] Peritumoral changes in inward rectifier potassium channels[42] that reduce the buffering of extracellular potassium generated during epileptiform discharges by glial cells also contribute to seizure generation.

Based on the above observation, the exploitation of the knowledge derived from the studied animal models of focal epilepsy could help to address future research directions, thus allowing a better understanding of the mechanisms of epileptogenesis in BTRE and how these mechanisms contribute to the appearance and expression of seizures.

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CHAPTER

7

Pathophysiology of Brain Tumor-Related Epilepsy

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CHAPTER CONTENTS

INTRODUCTION

This chapter will focus on brain tumor-related epilepsy (BTRE). It is important to underline that the pathogenesis of BTRE is poorly understood to date and there is ongoing debate about whether tumor environment or its margins are responsible for epileptiform activity. Literature data supports a significant role for each and it is conceivable that both tumor-related factors and peritumoral changes contribute to the development of epileptic seizure. Moreover different mechanisms are likely to play different roles in the different types of tumors.

The purpose of this chapter is to provide an overview of the various mechanism involved in the pathophysiology of BTRE. We think that a more detailed knowledge of these mechanisms can provide new strategies or surgical and medical treatment of this condition.

EPIDEMIOLOGY OF BTRE

The association between epilepsy and brain tumors has been observed for over a century. In his pioneering study, Jackson made two important observations: that epilepsy often represents the initial symptom of tumor and that the epileptogenicity of tumors is related with the involvement of cortical gray matter.[1] In the years following his study, several clinical studies confirmed these observations and clarified that the presence of epilepsy varies according to the site, histology, grade, growth pattern of tumor, and possibly to hitherto unknown host-related features.

The incidence of seizures among patients with brain tumors is reported in most series at approximately 30% or more, depending on tumor type.[2] Epilepsy has the highest frequency in patients with low-grade tumors (i.e., WHO gliomas grade I and II, DNETs), in which it is often the initial and only clinical symptom, with a significant impact on the quality of life; whereas it is less frequent in patients with fast-growing tumors such as grade III and IV gliomas and brain metastases.[3] A seizure frequency of up to 100% is seen with dysembrioblastic neuroepithelial tumors, and of 60-85% in low-grade astrocytomas and oligodendrogliomas. In glioblastoma multiforme, the frequency of epilepsy varies from 30% to 50%. About 25% of patients with meningioma present with seizures, whereas for patients with brain metastases, the frequency of seizures ranges from 20% to 35%.[4] (Table 7.1)

The location of the tumor within the brain is relevant to the development of epilepsy; tumors arising in the context of/near the cortex are more epileptogenic, as are those compressing the cortex (i.e., meningiomas), whereas deep-seated tumors are rarely epileptogenic. Tumors that affect the frontal, temporal, and parietal lobes are more commonly associated with seizures than are occipital lesions.[5] Infratentorial and sellar tumors are

TABLE 7.1 Seizure Frequency and Type of Brain Tumor

Tumor Histology	Seizure Frequency (%)
Dysembryoblastic neuroepithelial tumor	100
Ganglioglioma	80-90
Low-grade astrocytoma	75
Meningioma	29-60
Oligodendroglioma	53
Anaplastic astrocytoma	43
Glioblastoma multiforme	25
Ependymoma	25
Metastasis	20-35
Leptomeningeal tumor	10-15
Primary CNS lymphoma	10
Hemangioblastoma	0
Medulloblastoma	0
Schwannoma	0

Adapted from Van Breemen et al.[4]

only rarely associated with seizure activity unless they extend to involve cerebral hemispheres. Proximity to the Rolandic fissure increases seizure frequency as does proximity to the central sulcus.[6]

The lower frequency of epilepsy in high-grade gliomas as compared with low-grade gliomas may be explained by the less frequent involvement of the cortex in the former; however, the frequent underdiagnosis of non-generalized seizures in severely impaired patients and the short survival may also partly account for the reported low incidence of seizures in patients with high-grade tumors.

PATHOPHYSIOLOGY OF BTRE

The debate of whether the tumor itself or its margins are responsible for the epileptiform activity has led to the conclusion that although some evidence exists favoring the role of tumor cells themselves in the generation of abnormal discharges,[7] a relevant role is also played by the area at the border between the tumor and the healthy brain tissue. This latter hypothesis is supported not only by experimental data but also by the clinical observation that in gliomas, clinical and EEG foci of seizures often are located at some distance from the tumor mass. Kohling *et al.*[8] observed that rats, implanted intracranially with rodent C6 glioma cells and monitored by EEG, exhibited spontaneous epileptiform discharges throughout the 12- to 15-day recording period and that epileptiform activity originated outside the tumor within 1-2 mm from the tumor border.

Patt *et al.*[9] used EEG dipole localization techniques to identify the foci of epileptic activity in glioma patients and found that within a 15-min recording period, all patients exhibited abnormal activity consisting of sharp waves, spikes, and/or polyspikes. They found a strong correlation between tumor histological grade and distance between the seizure foci and tumor border; in general, the focus in low-grade glioma patients was closest to the tumor border, while most of the foci in high-grade glioma patients were found to be more distant from the border.

It is conceivable that tumors may cause epilepsy via different mechanisms that include both tumor-related factors (site, size, and histology of the mass with the resulting changes in cellular excitability) and peritumoral changes (modification of the neighboring neurons, metabolic and vascular changes, possibly associated cortical malformations) (Figure 7.1). The different mechanisms are likely to play different roles in the different tumors; nonetheless understanding the pathogenesis of seizures in tumor may help to identify targeted antiepileptic treatments.

A recent retrospective study on 124 patients with newly diagnosed supratentorial tumors has confirmed the influence of size and location of the tumors on their propensity to cause seizures. The magnetic resonance imaging-based analysis demonstrated that low-grade gliomas were larger in patients presenting with seizures compared to those found in patients without seizures, and that, conversely, in high-grade gliomas, tumors presenting with seizures were smaller than tumors presenting with other neurological symptoms. Moreover, seizures were more likely to be the presenting symptoms in patients with low-grade gliomas in the temporal lobe or in the insular region.[10] The latter data are in line with previous reports in the literature that indicate a high incidence of epilepsy in tumor arising in the frontal and temporal lobes. Subcortical location, compression of the cortex by the tumor, or edema may also explain occurrence of seizures in brain metastases and meningiomas, respectively.

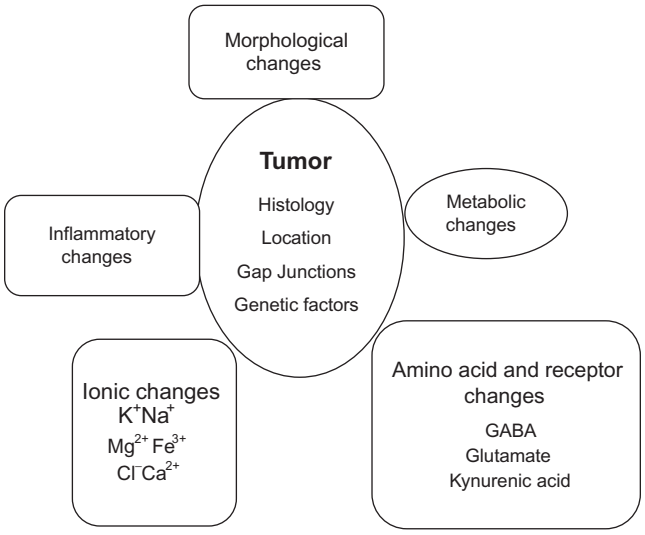

FIGURE 7.1 Possible intra- and peritumoral factors involved in the pathogenesis of tumor-related epilepsy.

In low-grade gliomas, the infiltrative nature of the lesion leads to abnormal glial tumoral cells interspersed with "normal" neurons, which may be subject to an altered profile of neurotransmitter stimuli in this abnormal microenvironment. The tissue disruption/infiltration with subsequent deafferentation of brain areas is a mechanism that may play a role in slow-growing tumors. This is supported by the clinical EEG observation that epileptogenic foci associated with low-grade brain tumors may be at a distance from the tumor itself. In low-grade gliomas, necrosis is typically absent, and hypoxia is rare and probably not relevant in epileptogenesis. Necrosis and hypoxia, together with vasculature abnormalities, are conversely prominent in glioblastoma, the most malignant glial tumor. In this tumor, moreover, a role in epileptogenesis is probably also played by the microhaemorrhages that lead to hemosiderin deposition.

The different propensity to generate seizures in the different types of tumors is also related to the changes observed at the level of interaction between different cell types, which include intrinsic neuronal epileptogenicity, imbalanced expression of excitatory and inhibitory receptors, abnormalities in synaptic and gap junctional transmission, altered expression of inflammatory molecules, and molecular genetic changes. The hypothesis that a neuronal component of the tumor itself may contribute to epileptogenic activity is supported by the electrocorticographic demonstration of spiking or recruiting discharges in patients with glioneuronal tumors.[7] The intrinsic hyperexcitability probably results from the imbalance between excitation and inhibition, as suggested by immunocytochemical and gene expression studies that demonstrated overexpression of glutamate and downregulation of Gaba receptors.

Synaptic and gap junction abnormalities may also contribute to epileptogenesis. The intercellular communications via gap junctions take place through transmembrane proteins termed connexins (CX). They represent an important pathway in maintaining tissue homeostasis, controlling cell growth and differentiation, and regulating the propagation of action potential in excitable cells. The possible contribution of altered CXs in generating seizures has been suggested by Aronica and coworkers,[11] who studied the expression of CX43 (normally expressed in astrocytes) and of CX32 (normally expressed in oligodendroglia) on surgical specimens of brain tumors taken from patients with drug resistant seizures, compared with high-grade tumors and control tissues. Increased CX43 immunoreactivity was observed in low-grade glioma and in the peritumoral reactive astrocytes, whereas increased CX32 reactivity was evident in oligodendroglioma. A reduction of the typical plasma membrane CX43 immunoreactivity and aberrant intracytoplasmic localization was conversely observed in high-grade astrocytomas.

The key role of glutamate-mediated hypercitability, which also involves peritumoral tissue, has been recently demonstrated by the relevant contribution of Buckingham and colleagues.[12] After implanting immunodeficient mice with human-derived glioblastoma cells, the authors have shown that the high release of glutamate by glioma cells was associated *in vivo* with the development of spontaneous electroencephalographic epileptic activity closely resembling those occurring in human gliomas. More importantly, inhibition of this release and blocking of glutamate receptor-ligand interaction proved to be effective in abolishing epileptogenic activity *in vivo* and *in vitro*. This evidence together with the previous data from literature confirm that increased glutamate coupled with reduced inhibitory gabaergic transmission highly contribute to peritumoral changes leading to epileptogenesis in high-grade glioma.

Further changes that probably contribute to peritumoral abnormal excitability include: changes in cellularity, pH, oxygenation, neurotransmitters and amino acids, ions, and water content of the intra- and extracellular compartments. Alterations in local metabolism, supported by neurochemical studies and pathological analyses at the level of cells and interstitium,[13] have been confirmed by the development of spectroscopic MRI; this technique has allowed detection of loss in the concentration of NAA (*N*-acetyl-aspartate), a neuronal metabolite, together with an increase in choline and—more recently—in glutamate.[14,15]

In high-grade gliomas, a central necrotic area is characterized by a very low pH. Acidosis, aggravated by ongoing anaerobic glycolysis by the tumor, may extend to the peritumoral area; causing functional and/or anatomical damage to the glial cells, which may in turn interfere with neuronal stability leading to uncontrolled firing and seizures.

In *in vivo* experimental models, high levels of extracellular sodium and calcium have been reported to possibly enhance neuronal excitability.[16] Extracellular iron may induce perioxidative damage of neuronal membranes.[17]

Recently, Conti and coworkers[18] have shown that alterations in the regulation of intracellular chloride concentration, due to imbalance between NKCCl and KCC2, may decrease the hyperpolarizing effects of GABA; facilitating epileptogenesis in human brain tumors.

In high-grade glial tumors, activation of pathways involved in coagulation has been described; this in turn parallels the occurrence of both thrombosis and hemorrhages within the context of the tumor, typically in glioblastoma. Pathological studies have shown that tissue plasminogen activator and urokinase plasminogen activator are upregulated in human epileptogenic diseases, among which gangliogliomas.[19]

In high-grade gliomas and possibly in brain metastases, brain edema may partly be responsible for seizure triggering or worsening, as suggested by the clinical observation of seizure fluctuations depending on steroid dose. Dysregulation of molecules involved in the control of interstitial water content in the brain, such as Aqp4,

may be involved in this phenomenon[20]; together with vascular endothelial growth factor (VEGF) upregulation and release, with subsequent enhancement of permeability of the blood-brain barrier. Also transforming growth factor-beta (TGF-β), an immunosuppressive cytokine, produced at high levels by high-grade gliomas, is possibly involved in BTRE via facilitation of *N*-methyl-D-aspartate (NMDA) receptor-mediated hyperexcitability.[21]

The role of the BBB in the development of some tumor-related seizures is supported by the study of Marchi and colleagues,[22] in which focal seizures occurred after intra-arterial administration of chemotherapeutic agents, only after osmotic disruption of the BBB. Relevant molecular changes in brain tumors that affect BBB structure and function include decreased expression of transmembrane junctional proteins and heightened release of VEGF.[23,24] Diffusion of VEGF into the peritumoral brain may aggravate the edema surrounding the lesion. Stewart *et al.* reported structural defects in endothelial tight cell junctions surrounding human gliomas.[25] A recent study suggested that neuronal hypersynchronization may be mediated by TGF-β receptor stimulation, causing activity-dependent accumulation of extracellular potassium, facilitation on NMDA receptor-mediated neuronal hyperexcitability, and eventually epileptiform activity.[26] Blockade of TGF-β receptors *in vivo* reduced the likelihood of epileptogenesis.[21] These data taken together suggest that pathological disruption of the BBB in brain tumor patients may contribute to seizure activity.

Most high-grade gliomas are characterized by hypoxia and acidosis. On one hand, tumors with insufficient blood supply often cause interstitial hypoxia, which subsequently contributes to acidosis. On the other hand, large tumors usually cause peritumoral hypoxia because of direct compression. Both these factors cause glial cell swelling and damage. This is of particular interest because astroglial cells control the acidity of the environmental fluid and, under these conditions, the astrocytic cell membrane becomes prone to inward sodium flow with an increased risk of seizures.[27]

Certain morphological changes in the peritumoral brain tissue, such as persistent neurons in the white matter, inefficient neuronal migration, and changes in synaptic vesicles, might contribute to seizure generation.[28] It is presumable that peritumoral cells have an altered or anomalous phenotype, which is commonly seen in glioneural or dysplastic brain tumors. Comparison of the ultrastructure of the peritumoral cortex, in patients with and without epilepsy, has demonstrated statistically significant changes in the form, size, distribution, and number of synaptic vesicles. Another type of cellular change associated with tumor growth is a decrease in inhibitory synapses and an increase in excitatory synapses in peritumoral pyramidal neurons.[29] Finally, dysfunctional astrocytes in peritumoral regions may contribute to epilepsy through disruption of glutamate/potassium homeostasis.[30]

A further aspect is that of putative common genetic pathways contributing to tumor development and to seizure occurrence. The tumor-suppressor gene LGI1, which could contribute to glioma progression by increasing cell growth and migration when downregulated, is low or absent in high-grade gliomas.[31] This gene has also been implied in a form of genetically transmitted epilepsy.[32] Brodtkorb *et al.* suggested that LGI1 may be correlated with epileptic susceptibility in patients with a brain tumor.[33] However, some other studies have not supported a tumor-suppressor function of LGI1.[34] Moreover, tumors have genomic and chromosomal instability, including DNA strand breaks and rearrangements. These alterations may be associated with changes in gene expression that have negative effects on the stability of DNA repair mechanism and on the likelihood of mutations. Under these conditions, the tumor cells might become epileptogenic.

TREATMENT OF BTRE

Whatever the mechanism(s), one of the characteristic features of BTRE is pharmacoresistance. Treatment of BTRE includes surgery aimed at removing the tumor and/or the tumor-associated epileptogenic focus, non-surgical oncological treatments (i.e., radio- and chemotherapy), and antiepileptic drugs (AEDs). Early treatment of BTRE is necessary in order to increase the likelihood of satisfactory seizure control; as a matter of fact, one of the predictive factors for successful seizure control after surgery for low-grade glioma is the short duration between the clinical onset of epilepsy and surgery.[35] This supports the hypothesis that at least some of the mechanisms involved in pharmacoresistance, in this type of epilepsy, may be similar to those acting in non-tumor-related epileptic patients undergoing surgery for intractable epilepsy.

To some extent, the effects of various forms of therapies on epileptic seizures associated with brain tumors may lead to an understanding of some factors involved in the pathogenesis of this complex phenomenon.

Many works have dealt with the effect of surgery on BTRE. Slow-growing brain tumors or tumors with neuronal component have been included in the majority. A review by Englot[35] on the effects of surgery on BTRE in low-grade gliomas has shown that an earlier surgery is more frequently successful in controlling epilepsy in these patients. Thus, not only does early surgery seem to be effective from an oncological point of view, but it also seems to prevent the development of alterations leading to pharmacoresistance.

It has been suggested that some effects of radiation therapy on BTRE may not relate only to the radiologically documented antitumor effect (i.e., tumor "shrinkage"), since they seem to precede this phenomenon by

far; a reduction in seizure frequency has been shown in two small series of patients, with a more than 75% decrease in seizures persisting after a median follow-up of 12 months.[36,37]

The mechanism(s) whereby this effect occurs is so far unknown, even if its rapidity of action suggests that short-acting phenomena are involved (for instance, modulation of soluble factors released by the tumor cells that may exert an epileptogenic role).

A few reports seem to indicate that a reduction in seizure frequency may also occur due to chemotherapy administered for the brain tumor; temozolomide has been reported to reduce by 60% the frequency of seizures in glioma patients, with a non-negligible proportion of patients achieving a seizure-free condition.[38,39] A similar effect has been reported for nitrosureas.[40]

Approximately one-third of patients with BTRE are refractory to antiepileptic medication. This is probably due to a number of factors. First, AEDs could be affected by the clinical milieu of the peritumoral space. Second, interactions between AEDs and chemotherapeutics may affect antiepileptic effectiveness by influencing the cytochrome P450 system. Several AEDs (e.g., phenobarbital, primidone, carbamazepine [CBZ], and phenytoin) induce cytochrome P450 coenzymes, whereas new AEDs such as gabapentin (GBP), levetiracetam (LEV), and pregabalin (PGB) do not. Third, treatment resistance may also arise from overexpression of multidrug resistance-related proteins (MPRs) in tumors that restrict the penetration of lipophilic substances into the brain. An increased expression of transporter molecules belonging to the families of the so-called "drug-resistance proteins" has been detected at the cellular level in the brains of patients who have had surgery for long-standing temporal lobe epilepsy[41] and also in tumor and endothelial cells in the context of glial tumors[42] (Figures 7.2 and 7.3). In healthy brains, the multidrug resistance gene MDR1 and MRPs contribute to the function of the blood-brain barrier. CBZ, phenytoin, phenobarbital, lamotrigine (LTG), and felbamate are

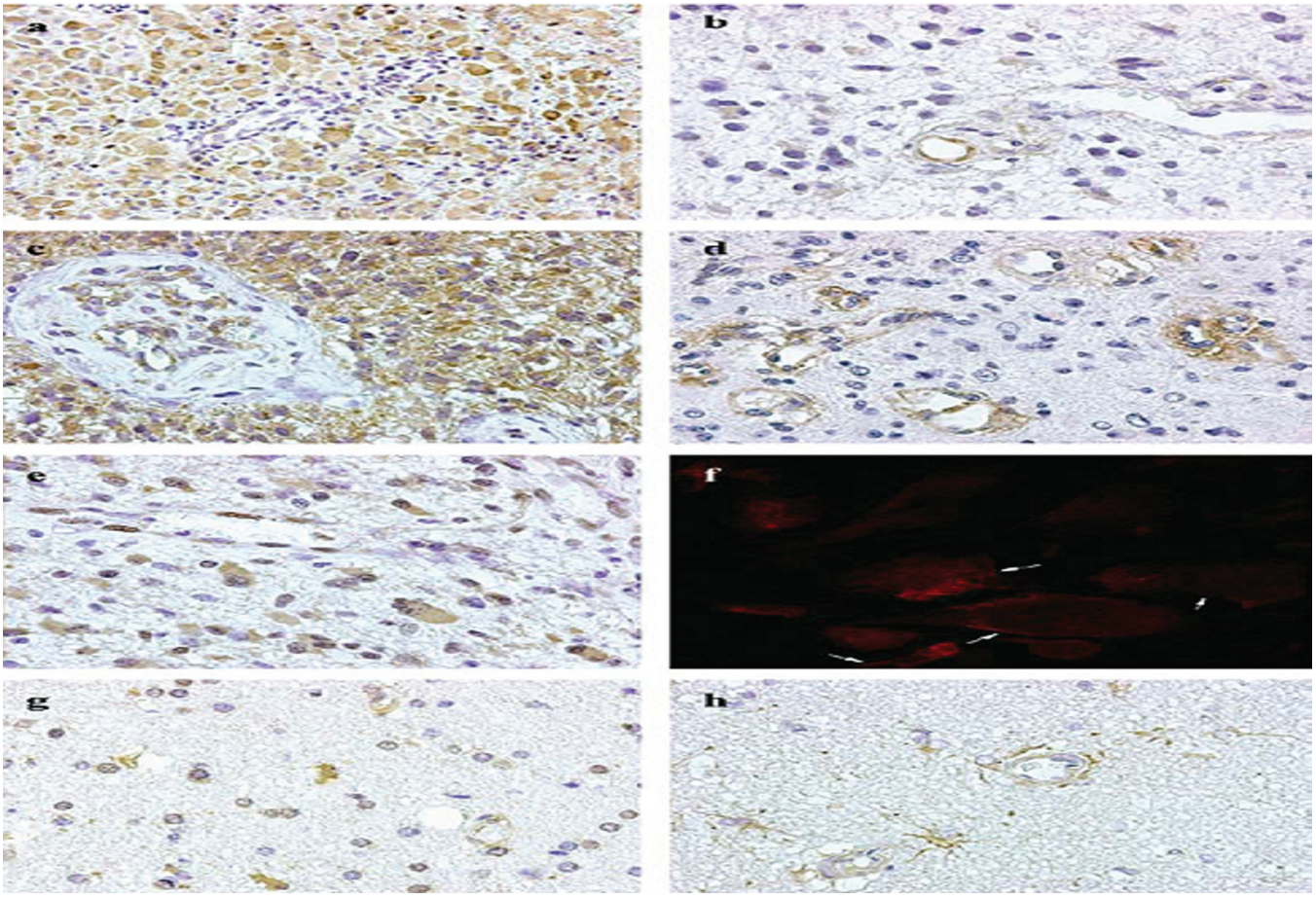

FIGURE 7.2 Immunohistochemistry: (a) MRP1 expression in an astrocytoma sample (WHO grade II): Tumoral cell (TC) −, Endothelial cell (EC) + and (b) in a GBM sample (WHO grade IV): TC++, EC−. (c) MRP3 expression in an astrocytoma sample (WHO grade II): TC−, EC+ and (d) in an anaplastic astrocytoma sample (WHO grade III): TC−, EC++. (e) Pgp expression in an oligodendroglioma sample (WHO grade II): TC−, EC+ and (f) in a GBM sample (WHO grade IV): TC±, EC+. (g) GST-p expression in an astrocytoma sample (WHO grade II): TC+, EC− and (h) in an anaplastic astrocytoma sample (WHO grade III): TC++, EC−. With kind permission from Springer Science+ Business Media B.V. From J Neurooncol 2012; 110:129–135. Multidrug resistance proteins expression in glioma patients with epilepsy. C. Calatozzolo et al.

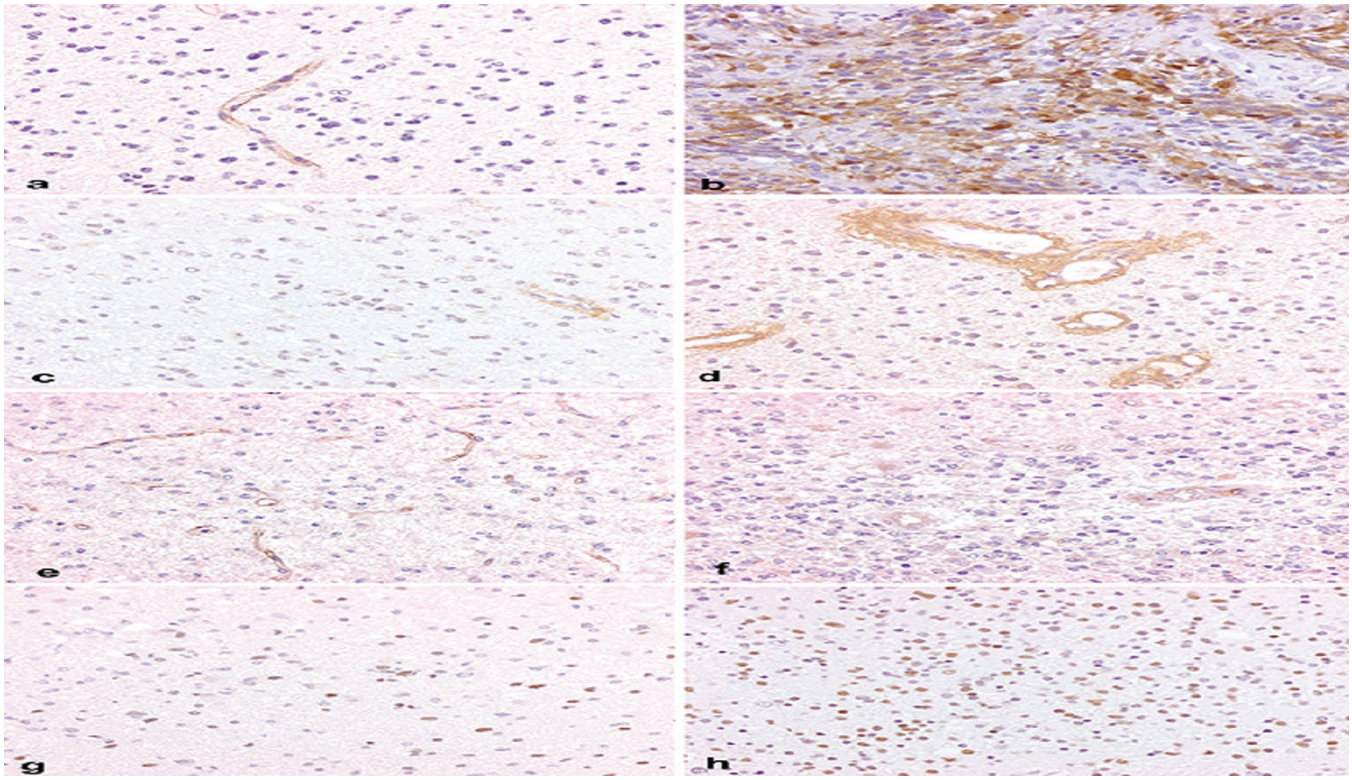

FIGURE 7.3 Immunohistochemical detection of multidrug resistance proteins on paraffin sections of human glioma and non-tumor specimens: indirect immunoperoxidase staining with monoclonal antibodies which recognize (a) MRP1 on a glioblastoma with gemistocytic areas, (b) MRP3 on a oligoastrocytoma (grade II), (c) MRP5 on a glioblastoma, (d) Pgp on an astrocytoma (grade II), (e-f) GST-π on a glioblastoma, (g) MRP1 and (h) MRP5 on a non-tumor brain sample. Slides were counter-stained with heamtoxylin. Immunofluorescence staining of primary cell culture grown on chamber-slides with anti-MRP5 antibody at confocal microscopy. With kind permission from Springer Science+ Business Media B.V. From J Neurooncol 2005; 74:113–121. Expression of drug resistance proteins Pgp, MRP1, MRP3, MRP5 and GST-*p* in human glioma. C. Calatozzolo et al.

substrates for this gene product; it is not sure that this holds true for LEV. Insufficient concentration of AEDs at the target can be the result of an active defense mechanism by MDR1. Overexpression of MRD1 and MRP has been reported in samples of brain tissue from patients with focal cortical dysplasia and ganglioglioma.[43] Breast-cancer-resistance protein (ABCG2) is another member of transporter molecules, the expression of which is increased in brain tumor tissue compared with healthy brain tissue.[44]

Two meta-analyses of AEDs in patients with brain tumor who did not have seizures suggested no efficacy as prophylaxis.[45,46] A consensus statement from the Quality Standards Subcommittee of the American Academy of Neurology recommends not using AEDs routinely as prophylaxis in patient with brain tumors and withdrawing these drugs in the first week after surgery if patients have never had seizures.[45] No randomized clinical trials have evaluated the efficacy of traditional AEDs such as CBZ, phenytoin (PHT), phenobarbital (PHE), and valproic acid (VPA) in patients with brain tumors. VPA is thought to inhibit epileptic discharges by stabilizing neuronal membranes and enhancing GABA transmission. Moreover, it can induce apoptosis, growth arrest, and cell differentiation of tumor cells through inhibition of histone deacetylase.[47] Fu *et al.*[48] reported that VPA induced autophagy in glioma cells and this action was independent of apoptosis; Weller *et al.*[49] indicated potential antitumor activity of VPA in patients with GBM who required an AED during temozolomide-based chemotherapy. These data suggest that VPA could be considered as a first-line therapy in treating tumor-related epilepsy; new AEDs such as LEV, LTG, topiramate, GBP, and PGB have been recommended in patients with BTRE. These drugs have different antiepileptic mechanisms, including GABA receptor agonism, calcium channel modulation, and NMDA receptor antagonism. In their review, Vecht and van Breemen[50] suggested that first-line anticonvulsants should include LEV and LTG, because they lack significant drug-drug interactions with chemotherapy agents. Studies evaluating the effects of LEV have found it beneficial for both monotherapy and add-on therapy in tumor-related epilepsy.[51,52] In a recent study, carbenoloxon has been evaluated in organotypic hippocampal slice cultures as a gap junction inhibitor; with findings that it

inhibited both spontaneous and evoked seizure-like events.[53] In the same study, evaluation of synthetic CX-mimetic peptides, homologous to the second extracellular loop of CX43, provided greater specificity in selectively inhibiting only recurrent epileptiform activity by antagonizing gap junction coupling. The clinical utility of this strategy remains uninvestigated but it certainly may be valuable in the context of low-grade gliomas with heightened CX43 expression.

Current research into both tumor biology and the peritumoral microenvironment has provided insight into the pathophysiology of BTRE; however, many aspects remain largely unclear. Increased understanding of the dynamic process at the tumor-brain interface may lead to novel concepts and treatment strategies for tumor-related epilepsy in the future.

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CHAPTER

8

The Neurophysiology of Central Nervous System Tumors

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CHAPTER CONTENTS

INTRODUCTION

The neurophysiology of central nervous system (CNS) tumors involves the use of electroencephalography (EEG) and its various permutations (e.g., ambulatory EEG, inpatient EEG monitoring), to assess the patient for the presence of epileptiform activity or ongoing seizure activity. The first reports of the use of EEG to record human cerebral electrical activity from the scalp were by the German psychiatrist Hans Berger between 1928 and 1935.[1] After these initial crude attempts to record the voltage changes generated in the cerebral cortex, further advances were made by neurological clinicians with an advanced understanding of electronics, such as Lord Adrian.[2] By the end of the 1930s, EEG recording devices had improved, typically with three channels, and were tested on patients with various neurological diseases, resulting in the "Harvard Studies" of Gibbs, Gibbs, and Lennox from 1937 to 1943.[3] This series of studies gave the first descriptions of EEG changes during epileptic seizures. These early studies also determined that grand mal or generalized epilepsy was associated with electrical activity at 20-29 Hz, petit mal epilepsy was associated with activity at 2-3 Hz, and psychomotor seizures were associated with activity at 4-7 Hz.

Since the early history of EEG, it has been known that space-occupying lesions may induce some degree of change in the normal background of both scalp and intracranial electroencephalographic recordings (i.e., focal slow waves). Prior to the routine use of noninvasive neuroimaging (e.g., CT, MRI), the EEG was used as a primary tool in the localization of intracranial and intracerebral lesions. These findings, along with abnormalities on the clinical examination and available radiographic techniques of the time (e.g., skull roentgenogram, air-contrast roentgenogram), were used in the presurgical planning of operations. Since the advent of a wide spectrum of advanced noninvasive imaging, the role of EEG for the localization of intracerebral pathology and CNS neoplasms has largely been supplanted. In some cases,

intractable epilepsy in particular, EEG still plays a critical role in planning of neurosurgical procedures and is also vital in long-term management of persons with recurrent unprovoked seizure activity (i.e., epilepsy). This chapter will focus on the EEG findings typically found in CNS tumors as well as the potential neurophysiologic changes accompanying these lesions.

EEG MODALITIES AND APPLICATIONS

Routine EEG. Over the past two to three decades, there has been a significant modernization of the equipment used to record EEGs—mainly computerization.[4,5] With the advent of computerization, the scalp recordings of electrical signals could be digitized, allowing for the information to be reformatted in various ways or to be subjected to mathematical analysis (e.g., spectral analysis). Digitization also allowed for much longer recordings to be made, with minimal artifact. In addition, it made it possible to combine EEG recordings with video recording data, leading to a better correlation of behavioral manifestations and electrical abnormalities. Standard recordings now use the 10-20 International System of electrode positions, using silver/silver chloride electrodes, which have been proven to be the most reliable and give the least electrode artifact.[4] The EEG should be long enough to capture time while the patient is awake and relaxed, drowsy, and asleep and should include activating procedures such as hyperventilation and intermittent photic stimulation. The purpose of the EEG recording is to find proof or verification of an underlying seizure disorder or epilepsy syndrome, in the form of interictal epileptiform activity or an actual seizure. During routine studies, it is uncommon to capture an actual seizure; in most cases, the hope is to at least record interictal epileptiform abnormalities, which are highly correlated with the presence of underlying epilepsy. Interictal epileptiform activity includes 3 Hz generalized high-amplitude spike-slow wave complexes, focal spikes, focal sharp waves, a combination of focal spikes and sharp waves, and photosensitivity.[4] Even after only one event, the presence of epileptiform discharges on a routine EEG is a strong predictor for further seizure activity.

Ambulatory EEG. If there is still clinical doubt regarding the etiology of "spells" or similar paroxysmal episodes, and the routine EEG has not clarified the diagnosis, then ambulatory EEG may be considered.[4] It is a form of prolonged EEG monitoring in which the patient has a full set of scalp electrodes and a very compact digital recording device. Ambulatory EEG is typically performed over a 48- to 72-h period, in which the patient is supposed to adhere to normal routines of natural sleep and activity in an attempt to capture interictal epileptiform discharges or a paroxysmal event that is typical for that patient. Ambulatory EEG is superior to routine EEG in capturing interictal abnormalities, especially in relation to natural sleep, circadian variations, and the patient's typical daily lifestyle.[4,6] If the patient is having daily or frequent episodes, there is a high likelihood of capturing one during the monitoring. The presence of ictal electrographic rhythms or discharges temporally related to the patient's typical symptoms will confirm the diagnosis of epilepsy and help define the seizure type. In some cases, home video can be added to ambulatory EEG to further help clarify the presence or absence of epileptic events.[7] In the series by Goodwin and colleagues, when offered the chance to use a camcorder to record events while undergoing ambulatory EEG, 45 out of 130 patients (35%) accepted the offer and recorded ictal events on video. The authors felt this additional technology was very helpful in defining the nature of paroxysmal events in the home setting.

Epilepsy Monitoring. In patients where routine EEG and ambulatory EEG have not clarified the nature of persistent paroxysmal events, the next step would be epilepsy monitoring under video surveillance (i.e., video-EEG telemetry)—typically in an inpatient setting: the epilepsy monitoring unit (EMU).[4,5] Evaluation in the EMU is the definitive investigation for the vast majority of patients. Most patients are monitored until one or more of their "typical spells" can be captured on EEG and video. In the patients with true epilepsy, there will be very strong temporal synchronization between electrographic changes and evidence for an ictal event and behavioral changes that are "typical" or consistent with their usual seizure. For patients who are having panic attacks, cardiac syncope, psychogenic seizures, or other nonepileptic paroxysmal events (see Chapter 10 for a complete differential diagnosis), there will not be any electrographic correlates of the events captured on video monitoring. This type of specialized video-EEG monitoring is also very helpful in working up patients undergoing evaluation for epilepsy surgery for their brain tumor-related epilepsy. In these cases, the data can help clarify if the seizures are of a single type, if they are clinically and electrographically consistent with the lesion or tumor under consideration for surgery, if they are localized to the lesion in question, and if they are all originating from the same locus around the mass. In general, to adequately answer these questions, several seizures have to be recorded. From a statistical point of view, recording 5 or more consecutive seizures of the same type will give a 95% probability that 9 out of 10 of all ictal events will be of the same variety.[4,5] During the monitoring sessions, it is imperative to localize the epileptogenic zone around the tumor and to be absolutely sure that the entire region of the zone is delineated.

Invasive EEG Monitoring. In selected cases, video-EEG monitoring will not be adequate enough to completely define the epileptogenic zone around a tumor, and so further testing is indicated, using more invasive techniques.[4,5,8,9] Invasive monitoring can include the placement of sphenoidal or other types of depth electrodes, subdural electrode arrays, and cortical function mapping.[8,9] These techniques are most helpful in mesial temporal tumor-related epilepsy to confirm the side of ictal onset when doubt persists after video-EEG monitoring. In addition, they are also critical in locating the site of ictal onset from the neocortex in lesional cortical epilepsy. In selected patients, cortical function mapping may also be necessary to determine the location of ictal onset in relation to nearby regions of eloquent cortex (e.g., language areas, primary motor cortex, primary sensory cortex), thereby reducing the risk of permanent neurological injury after cortical resection. In some reports, invasive EEG monitoring is used in up to 10% of patients with tumor-related epilepsy undergoing evaluation for epilepsy surgery.[8]

EEG BACKGROUND CHANGES

As early as 1936, localized EEG background slow-wave activity was described (i.e., "Delta Waves") by W. Grey Walter and associated with intracerebral tumors.[10] Interestingly, being that it was among the first investigations into EEG and cerebral tumors, several other observations were made in the same article, although they have received less attention over time. Specifically, Walter stated that EEG recordings from the scalp "closely resemble those obtained directly from underlying brain, except in regard to the size of potential changes, which are attenuated by the skull." He described scalp potentials as a "faithful miniature" of cortical activity. He also noted that similar "slow waves"—which he later named "Delta Waves"—were present under the influence of anesthesia as well as in the setting of elevated intracranial pressure. These observations and many others in the early history of EEG were made using technically unsophisticated equipment that was often constructed by the operator himself. Walter's instrument had just three lead placements of electrodes that were only described by drawings. The International 10-20 System of Electrode Placement would not even come into use as a standardized method for recording until after being introduced by Jasper in 1958.[11]

Prior to common availability of CT and MRI imaging, a great deal of effort was employed in attempting to characterize and quantify abnormalities in EEG that localized cerebral lesions.[12] Abnormalities in EEG recordings were present in the vast majority of patients (>90%) with primary or metastatic lesions.[13,14] In most cases when abnormalities were not recorded, it was related to tumor location, with abnormalities being less common in neoplasms involving the cerebral ventricles and posterior fossa. The abnormalities recorded may be *generalized*, indicating a widespread change in normal electrographic activity, or they may be *focal* (see Figures 8.1 and 8.2), indicating a more regional or localized area of cerebral dysfunction. It is also not unusual for there to be both generalized and focal abnormalities in the same individual (see Figures 8.3 and 8.4). The presence of slower than normal frequency EEG activity, typically in the delta frequency range (<4 Hz) is the most commonly encountered abnormality, although slow activity can also include increased activity in the theta frequency (<8.5 Hz). Both of these patterns, depending on amplitude, persistence, and patient state (e.g., awake versus asleep) may be abnormal. Delta activity may be generalized or focal and may also be classified as rhythmic (such as FIRDA; see Figure 8.5) or as polymorphic (arrhythmic). While both types of delta activity are similar in frequency and occasionally in amplitude, they have different clinical significance. Rhythmic delta activity (alternatively called monomorphic or monorhythmic) is typically of maximal amplitude over the occipital (OIRDA) or frontal (FIRDA) regions. The difference in its distribution is related to the age of the patient, with OIRDA being characteristically found in children and is more closely associated with generalized epilepsy syndromes, although it can also be seen in encephalopathy.[15,16] In contrast, FIRDA is generally seen in cases of diffuse encephalopathy and may be the most common finding in tumors of the ventricles and posterior fossa.[17,18] This pattern does not have localizing value as does polymorphic delta. Rhythmic delta activity is intermittent, and the EEG in between the paroxysms of this pattern may be normal. Intermittent rhythmic delta usually goes away during sleep. It can also be recorded as a result of most causes of acute encephalopathy such as elevated intracranial or intraventricular pressure (as is seen in posterior fossa and ventricular lesions), medication effect, or as a postictal phenomena.[19] As its name implies, IRDA also has a characteristic rhythmic morphology, with a more rapid first (negative) phase in what has been described as a "saw-tooth" appearance. These paroxysms are characteristically short but repetitive. In contrast to IRDA, polymorphic or arrhythmic delta activity (ADA) is typically invariant, persistent, and commonly lateralizing if not localizing. Its presence in patients with cerebral neoplasms often localizes the lesion and it is more resistant to changes in the state of the patient (such as wakefulness and sleep).[20,21] While the amplitude of IRDA is characteristically higher than

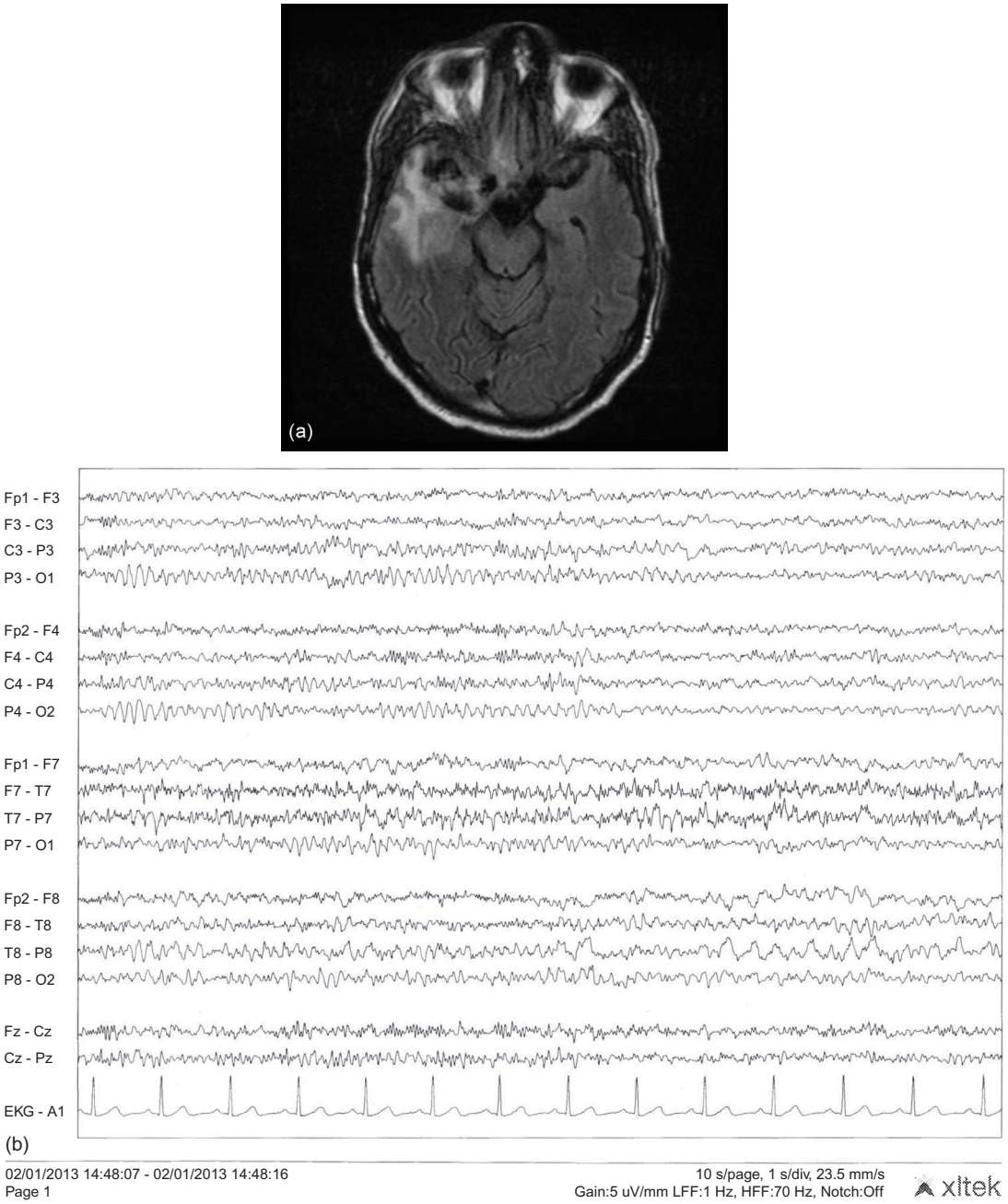

FIGURE 8.1 Sixty three-year-old male with a gliosarcoma, admitted with possible seizure activity. (a) The MRI scan (FLAIR) shows a heterogeneous mass with abnormally high signal in the medial and anterior right temporal lobe. (b) The bipolar longitudinal EEG tracing is abnormal, demonstrating intermittent slowing in the right temporal head region.

that of normal background EEG activity (>100 mV), the delta activity in ADA may be higher or may be lower in amplitude (see Figures 8.1 and 8.2). And, perhaps counterintuitively, the presence of lower amplitude and more irregular ADA is suggestive of a larger and more destructive lesion or may be seen in more chronic lesions.[22] In either case, its presence should be definitively alerting to the interpreter of underlying cerebral pathology (Figures 8.6 and 8.7).

EPILEPTIFORM ACTIVITY

The most common neurophysiologic test is the scalp EEG. EEG has value in localization of cerebral lesions as well as in diagnosis of epileptic seizures.[4,12] Certain sharply contoured waveforms are rarely seen outside of persons with epileptic seizures. These waveforms are referred to as epileptiform discharges and, depending on location, are specific for epileptic seizures (see

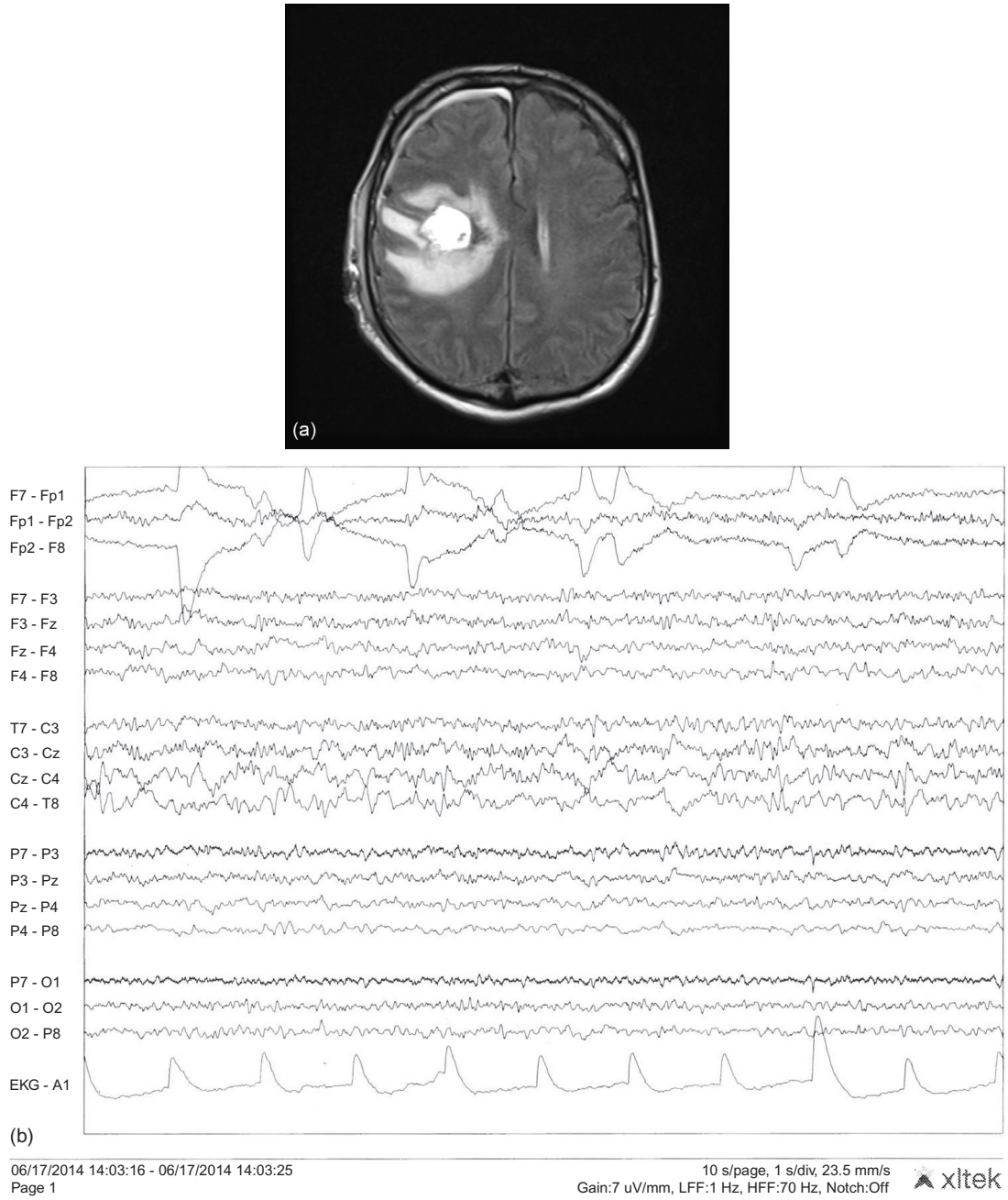

FIGURE 8.2 Seventy-year-old male with a right parietal high-grade glioma, 5 days after resection. (a) The MRI (FLAIR) demonstrates a right-sided skull defect and underlying postsurgical changes, with a fluid collection and edema around the resection cavity. (b) The routine bipolar transverse EEG shows continuous right central slowing, with intermittent sharps and breach effect.

Figure 8.2). As is the case in other types of epilepsy, focal epileptiform activity, when present, should alert the clinician to the risk for seizures, although its absence should not be used as criteria to "rule out" seizures. Given the relatively large volume of cortical tissue that is required to generate an electrical discharge of sufficient amplitude to be demonstrable on scalp EEG recordings, it is not surprising that the presence of interictal epileptiform discharges has been reported more commonly in patients with slower-growing neoplasms.[23–26] Patients with more rapidly growing lesions or with more edema also have seizures, therefore the lack of epileptiform EEG abnormalities should not be the sole consideration in the management of patients with cerebral neoplasms (see Figures 8.1–8.4). The incidence of clinical seizures may be higher than that of epileptiform discharges depending on the location of the lesion.[27–29] Another potential confounding

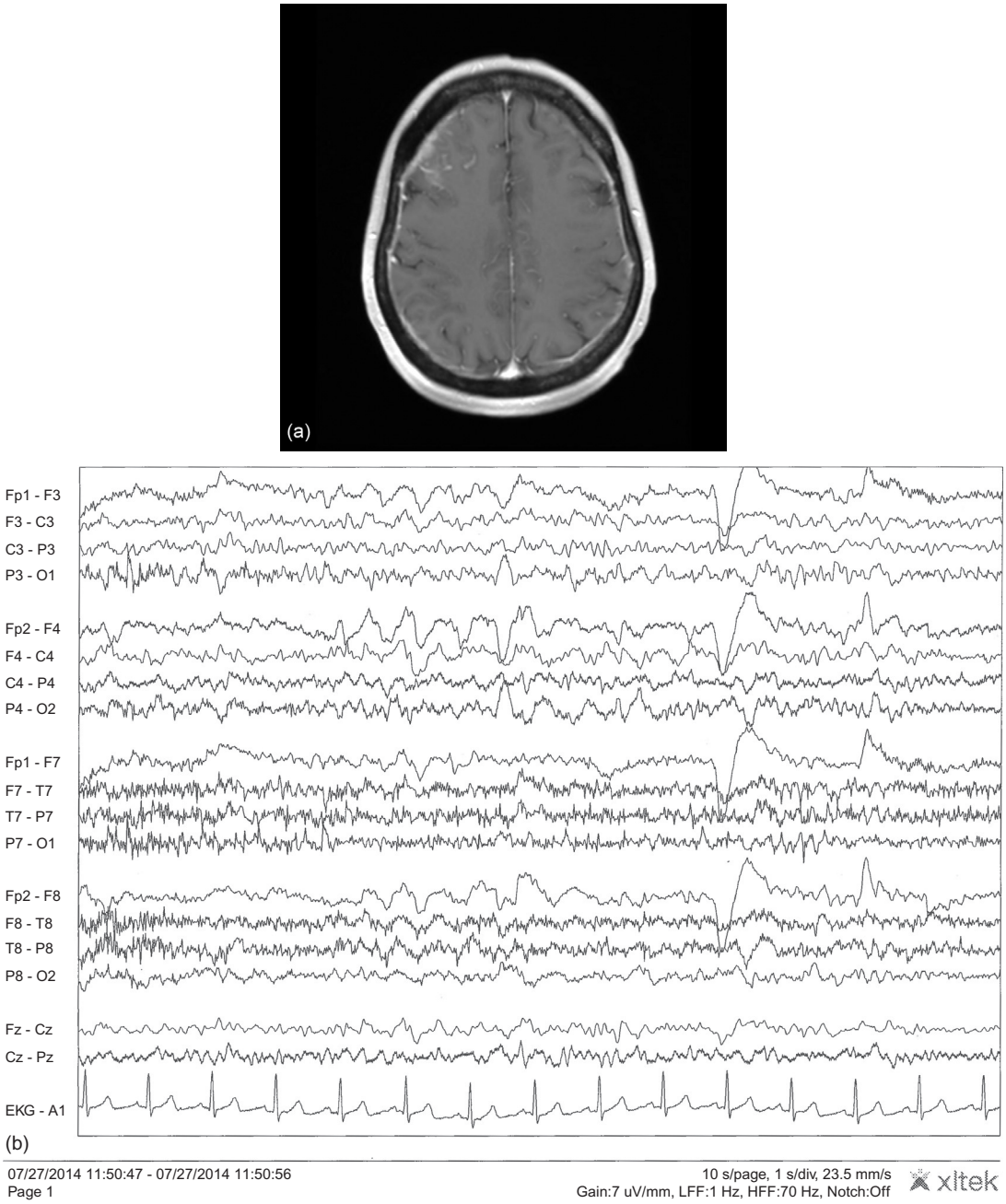

FIGURE 8.3 Forty one-year-old female with a history of metastatic breast cancer and known CNS metastasis, admitted with a first seizure. (a) The MRI (T1 GAD) shows right frontal leptomeningeal enhancement and thickening. (b) The bipolar longitudinal EEG awake recording shows moderate diffuse slowing, along with superimposed more acute slowing in the right frontal and central head regions.

factor is that scalp EEG localization of these interictal abnormalities may be misleading, depending on the location of the underlying lesion and technical factors from the study.[30,31] Since the locations of the lesion is typically known from noninvasive imaging, the clinician should not be overly concerned with the presence of interictal abnormalities recorded from scalp electrodes that are not adjacent or overlying the known lesion.

MENINGIOMAS

The evaluation and management of patients with meningiomas present multiple unique challenges, both clinically and neurophysiologically. They are the most common benign intracranial tumor and can present with widely varying clinical symptoms, depending on the size and location of the mass.[32] With increased utilization of neuroimaging, they can also be found incidentally

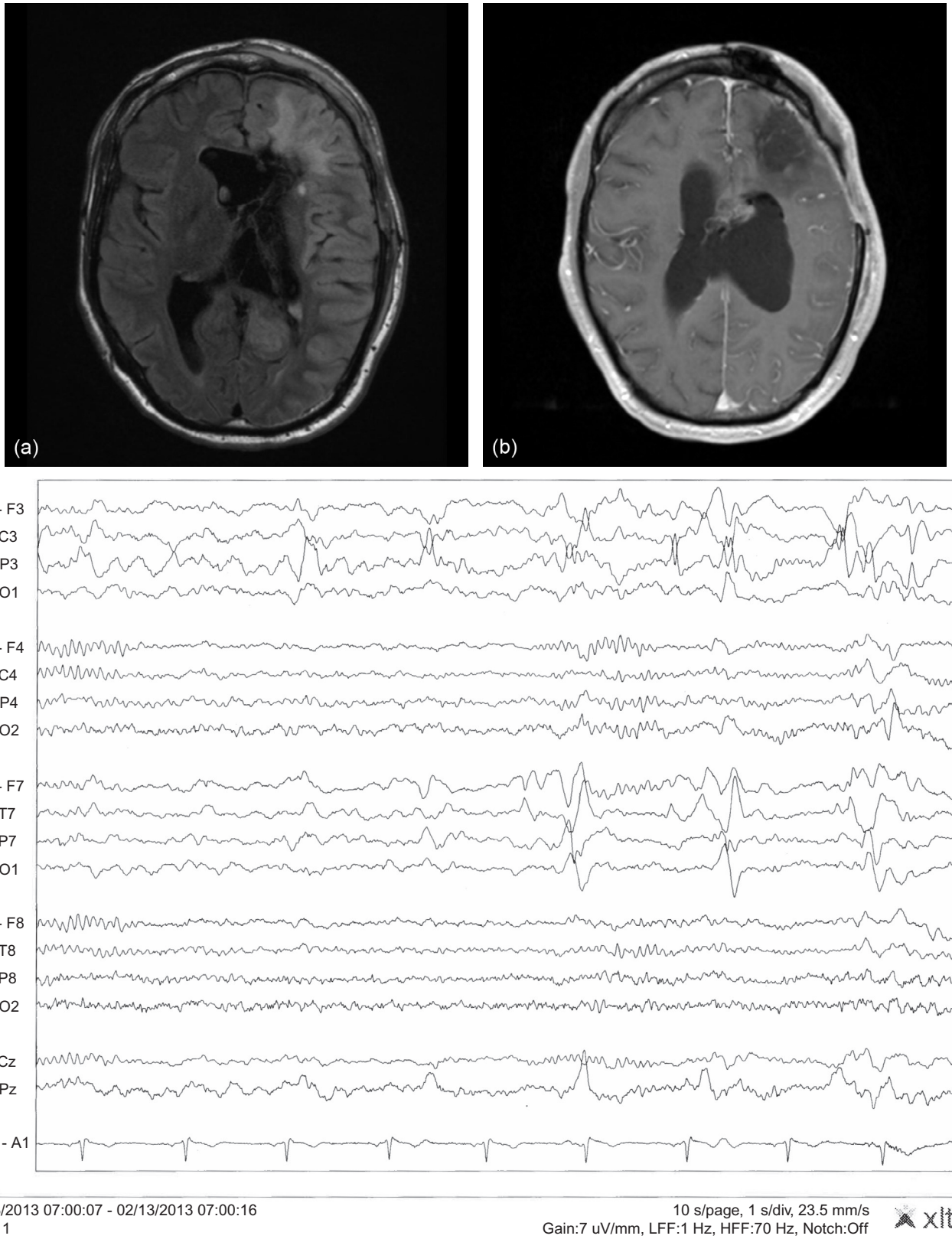

FIGURE 8.4 Thirty eight-year-old male with a history of a central neurocytoma, found down at home after multiple recent seizures. (a, b) The MRIs (T1 GAD & FLAIR) demonstrate the left frontal lobe tumor and surgical skull defect, with surrounding high signal abnormality, along with left hemispheric gyral enhancement and edema due to recent seizure activity. (c) The bipolar longitudinal EEG tracing obtained during sleep shows a marked background asymmetry, with continuous delta slowing over the left hemisphere, along with frequent centrotemporal sharp waves.

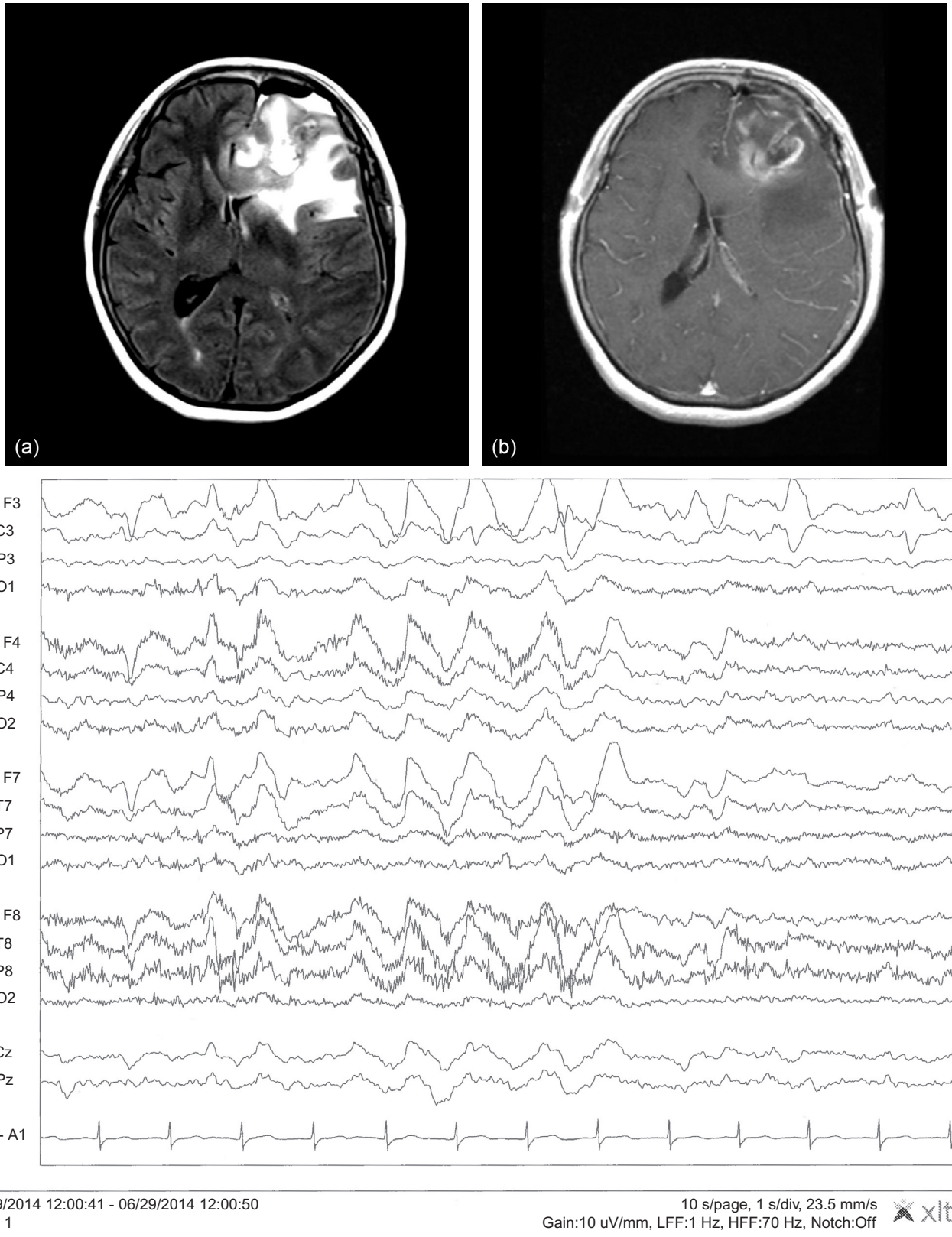

FIGURE 8.5 Sixty three-year-old female admitted with altered mental status and newly diagnosed intracranial mass. (a, b) The MRIs (T1 GAD & FLAIR; postoperative) demonstrate a large mass in the left frontal lobe region that is high signal on FLAIR, with surrounding edema and infiltration, that crosses the midline. Rim enhancement is present. (c) The bipolar longitudinal EEG tracing demonstrates mild to moderate diffuse slowing and background asymmetry with relative left hemispheric attenuation and bursts of FIRDA. On pathological evaluation, the mass was consistent with a glioblastoma multiforme.

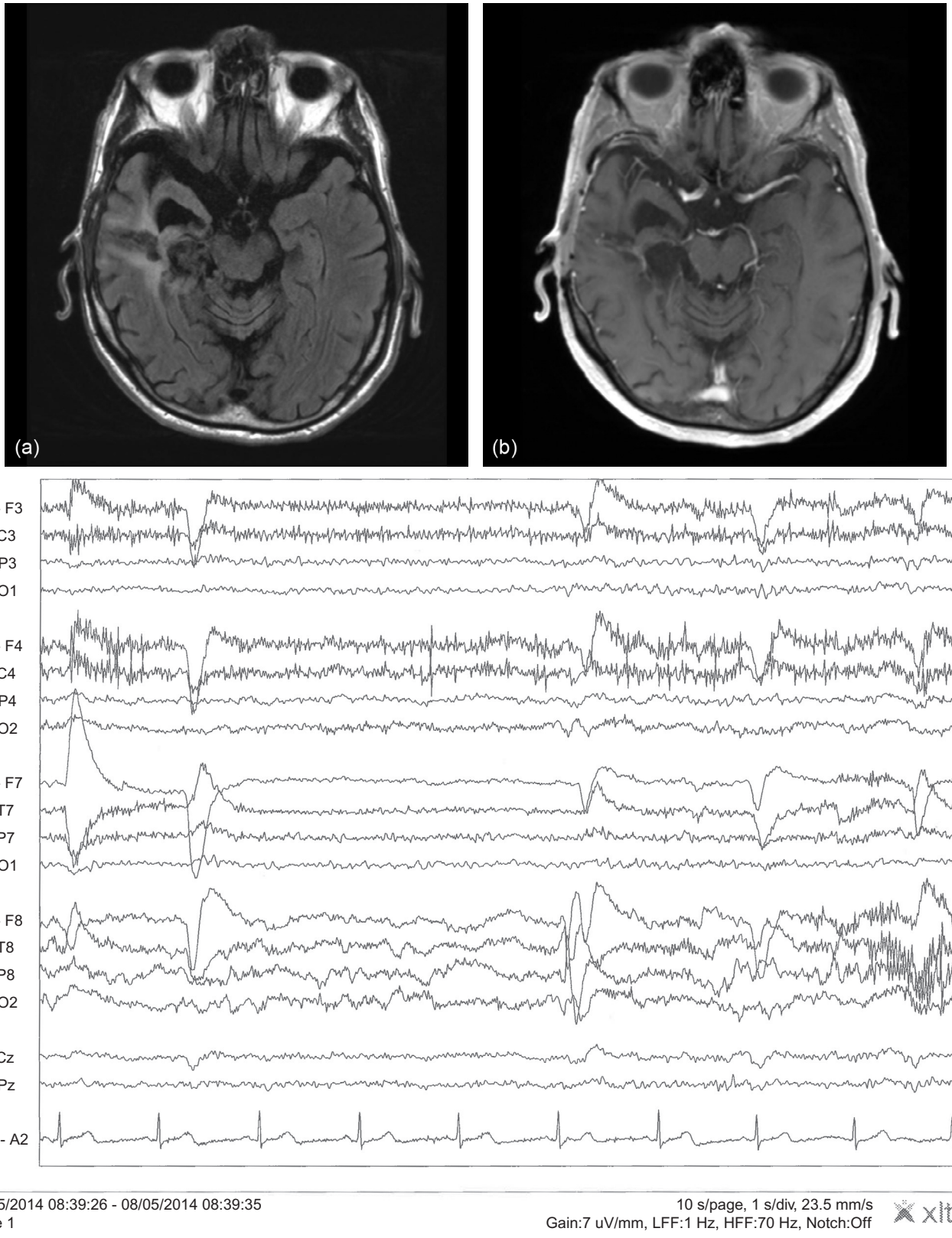

FIGURE 8.6 Seventy four-year-old male with a right temporal tumor of unknown histology—removed 15 years prior to admission, currently with multiple seizures. (a, b) The MRI (FLAIR & T1 GAD) demonstrates postsurgical changes, gliosis, and dilatation of the right temporal horn due to volume loss. (c, d) The bipolar longitudinal video-EEG tracings show continuous right temporal slowing during the awake recording (c), along with marked activation of sharps during sleep (d).

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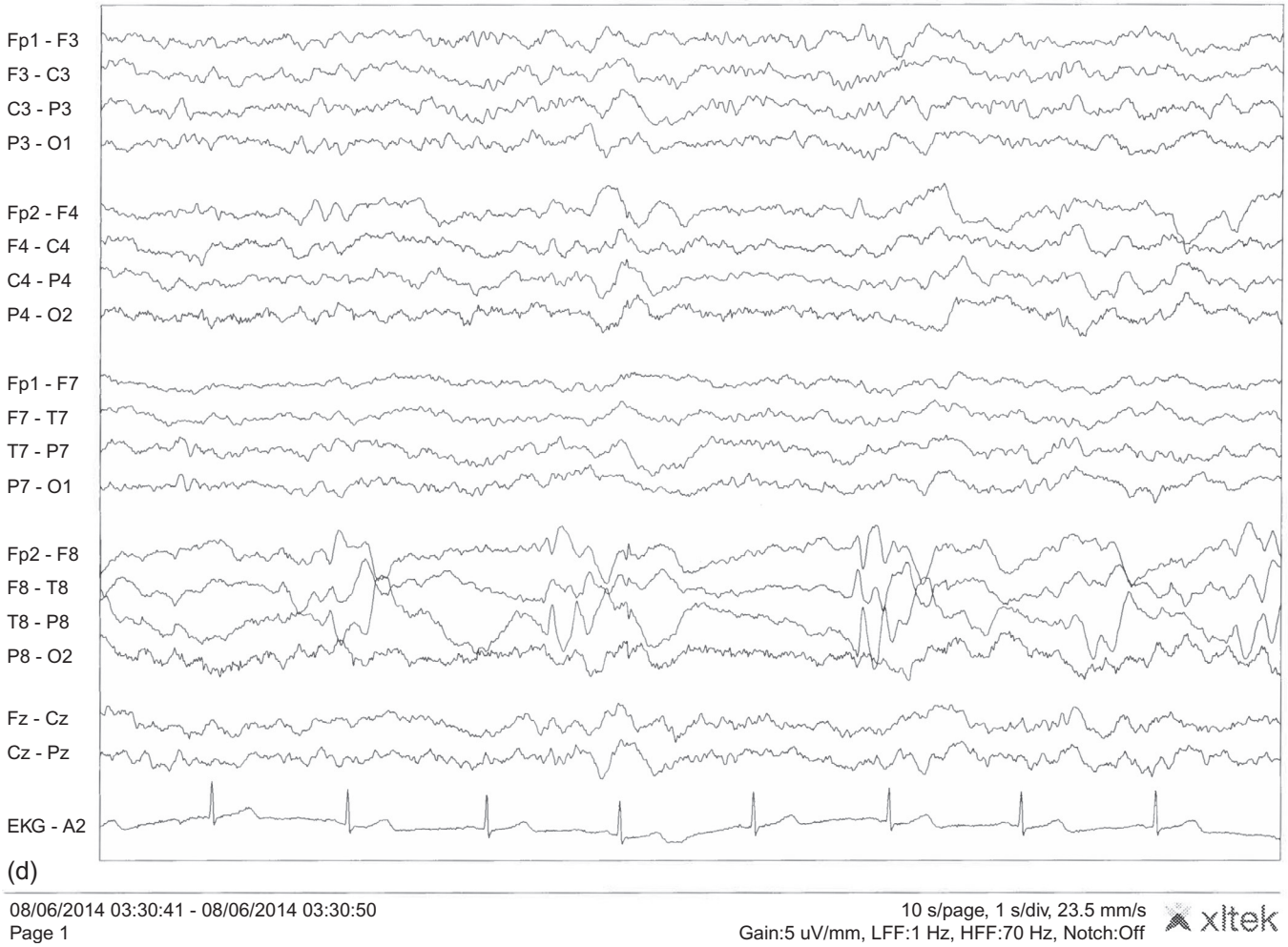

FIGURE 8.6, CONT'D

prior to the onset of clinically relevant signs or symptoms.[33] Seizures are one of the most common symptoms associated with these neoplasms and can be the presenting symptom in up to 50%.[34–36] Similar to other intracranial lesions, the overall incidence of seizure activity is most common in supratentorial lesions.[35] Multiple case series have attempted to address the relative risk of epilepsy based on the location of meningiomas with varying results. The majority of evidence favors the highest risk being among patients with temporal, parasaggital, or parietal lobe lesions.[36–38] Although it is difficult to estimate clinically, the risk may also be related to the prolonged clinical course that is typical for these tumors.

The EEG findings in these neoplasms can vary widely depending on the size and location of the tumor. A relatively small lesion can compress or obstruct the flow of cerebrospinal fluid, or a larger lesion may only displace normal cerebral tissue. The absence of scalp EEG abnormalities in patients with seizures may be more closely related to the location of the meningioma relative to the recording electrodes than the size of the tumor itself. In one larger case series, the preoperative incidence of abnormalities included focal slowing in 48% of patients and epileptiform abnormalities in only 13% of patients.[39] Multiple case series have attempted to determine if these preoperative abnormalities predict postoperative outcomes and have been unable to come to a clear conclusion, although several of these authors evaluated mixed tumor types.[39–41] In more unusual cases involving multiple meningiomas, the EEG evaluation may be a useful adjunct in determining which lesion is symptomatic.

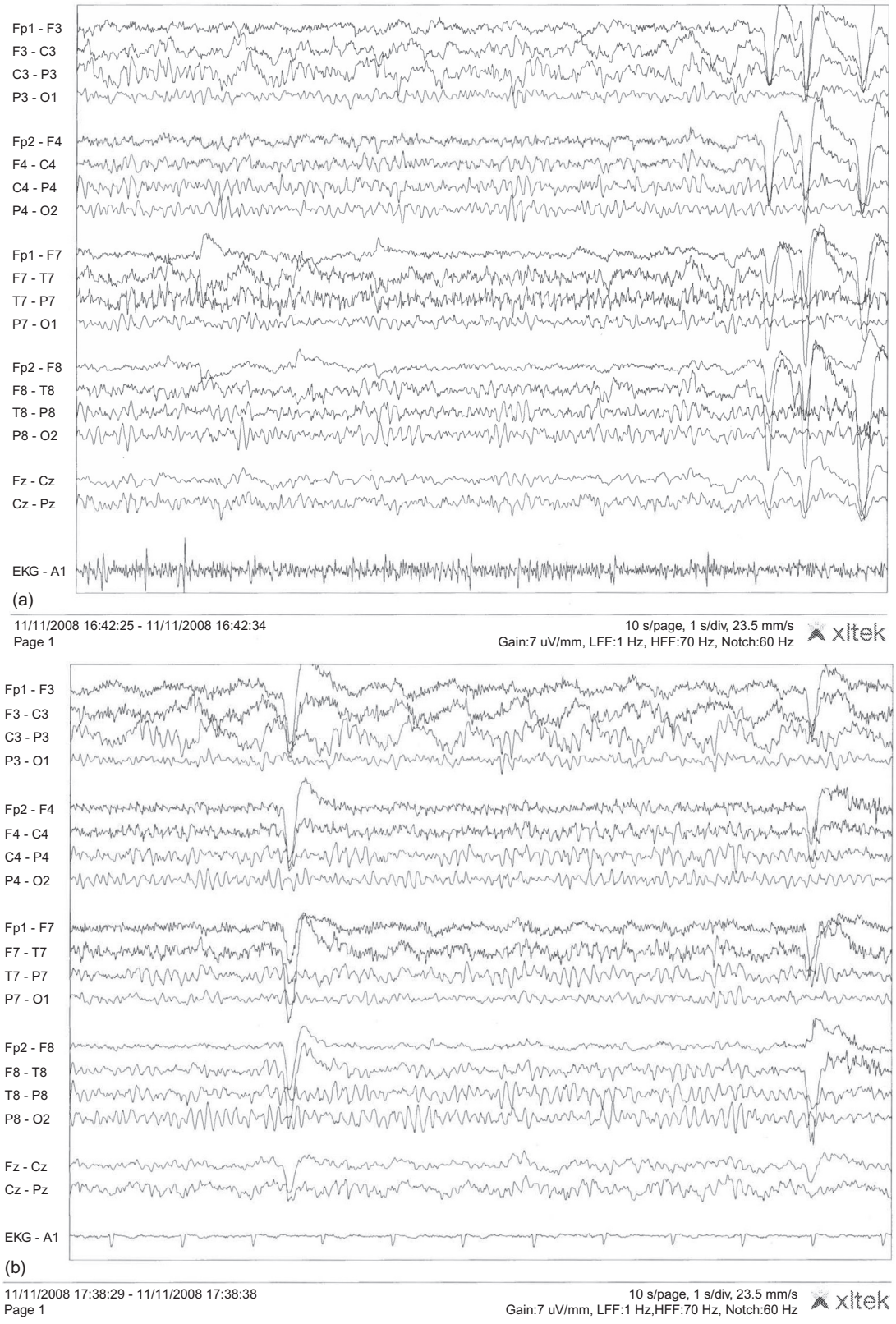

FIGURE 8.7 Fifty three-year-old female with a history of a left frontal ganglioglioma, off of active treatment for many years, who was admitted with episodes of dysarthria, aphasia, and abnormal vocalizations. (a) EEG tracing demonstrating left central slowing at baseline. (b) Bipolar longitudinal EEG tracing recorded during an event, showing rhythmic delta in the left centroparietal head region.

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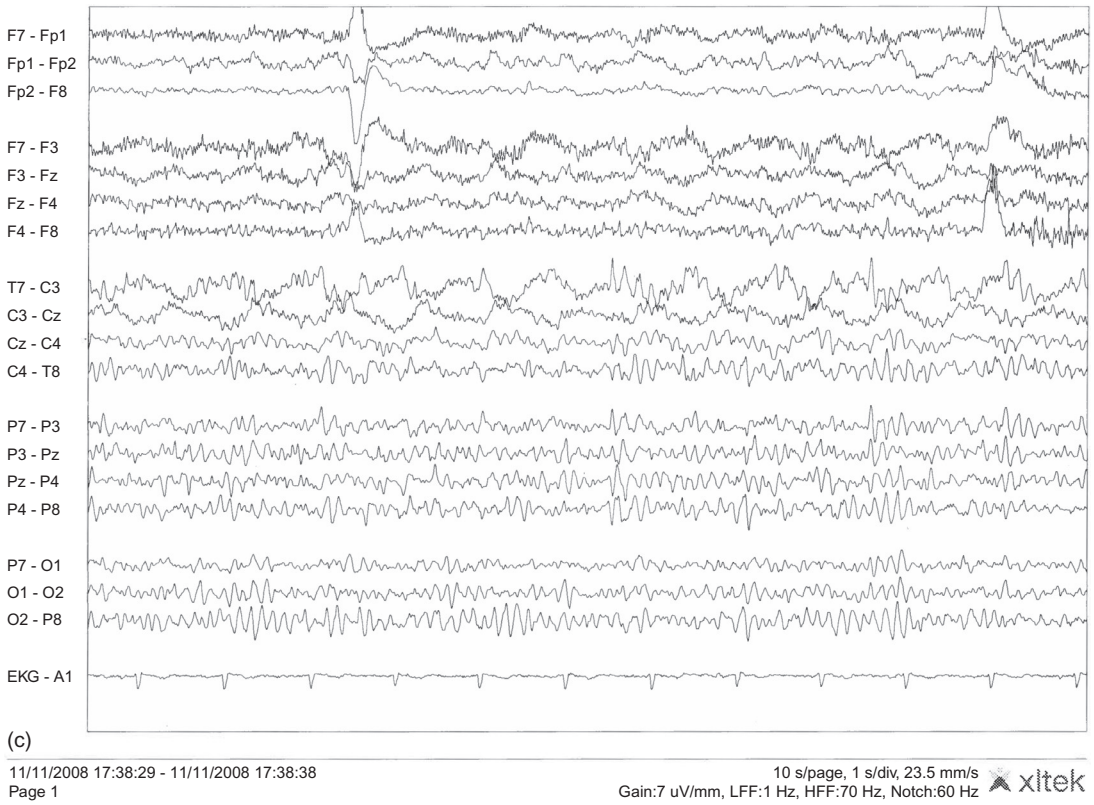

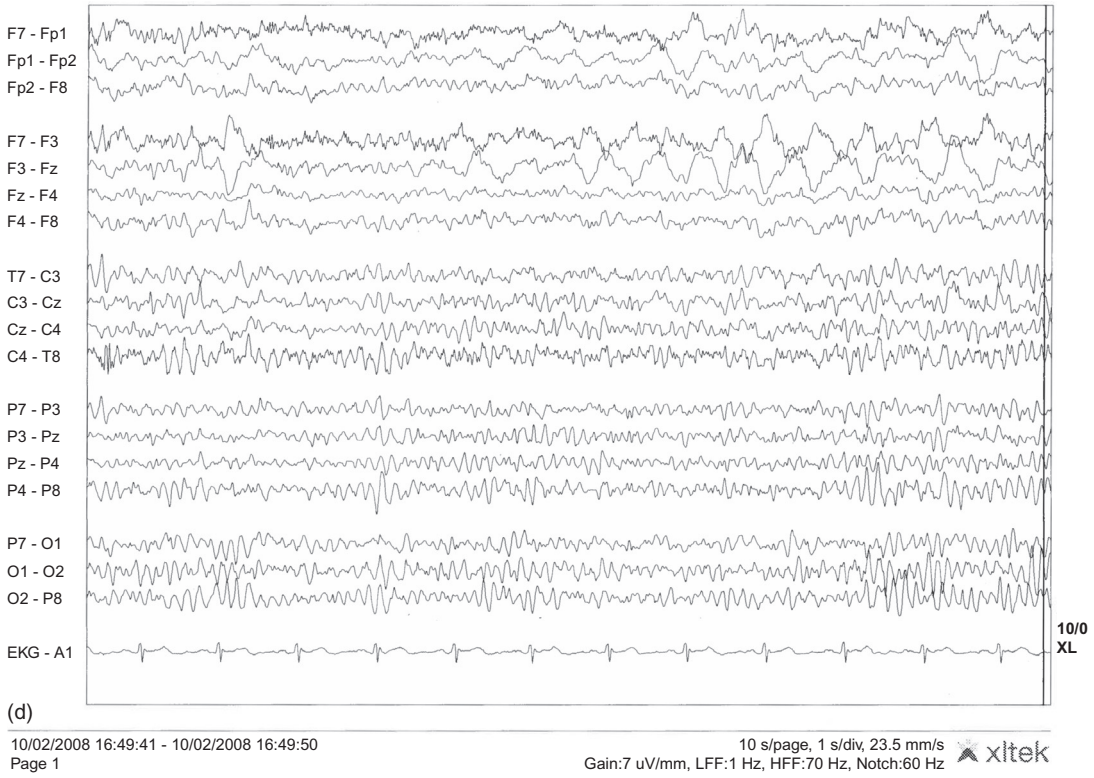

FIGURE 8.7, CONT'D (c) Bipolar transverse EEG tracing recorded during the same event as b, showing rhythmic delta wave activity. (d) Bipolar transverse EEG tracing recorded later on during the same event as b and c, demonstrating rhythmic delta activity originating in the frontocentral head region.

GENERATION OF ABNORMAL CEREBRAL ACTIVITY

The relationship between tumor size, location, and the incidence of seizures has been recognized since the nineteenth century, when John Hughlings Jackson noted that seizures can be the initial manifestation of cortical lesions.[42] As noted earlier, epilepsy is more common with slower-growing tumors, and this increased prevalence reflects underlying mechanisms of epileptogenesis. Early recordings from neurophysiologists largely reflected the concept that epileptiform activity, and therefore seizures, was largely due to changes in peritumoral tissue.[43,44] These studies and more recent investigations into higher-grade tumors have continued to demonstrate that epileptiform activity in these lesions is typically generated not from within the tumor itself but instead from the surrounding tissues.[45] However, with some lower-grade tumors, this is not the case.[46] Research in epilepsy surgery, where it is far more common to encounter low-grade tumors, has demonstrated increasing evidence for a tumoral component in the development and maintenance of epilepsy. These low-grade tumors are grouped as long-term epilepsy-associated tumors and are typically WHO grade I tumors. They include dysembroplastic neoroepithelial tumors; papillary glioneuronal tumors; gangliogliomas; and other less common tumor types such as gangliocytomas, pleomorphic xanthoastrocytomas, pilocytic astrocytomas, and rosette-forming glioneuronal tumors.[47] With these lower-grade tumors, studies have indicated that there are changes in ion channels as well as receptors for neurotransmitters capable of upregulating excitatory neurotransmission and downregulating inhibitory neurotransmission.[48] Glutamate receptor modulation as well as changes in the extracellular glutamate concentration favoring increased excitatory neurotransmission has been demonstrated in both *in vivo* and *in vitro* studies.[49–51] Additionally, downregulation of GABA receptor expression in tumor specimens has also been indicated as a possible mechanism for increased neuronal hyperexcitability.[52] There have also been multiple proposed mechanisms to explain how peritumoral tissue transforms into an area capable of generating ictal activity. Potential mechanisms include changes in local and regional connectivity of normal tissue adjacent to tumor lesions,[53] changes in the extracellular environment with respect to vascular organization and biochemical profile,[54] changes in the amino acid profile of GABA and its uptake by peritumoral tissues,[55–57] and changes in intercellular communications.[58,59] Depending on tumor histology, disruption of the blood-brain barrier and increased inflammatory responses in the peritumoral region have also been implicated in the development and maintenance of intractable epilepsy.[60] It is most likely that with a given tumor type there are multiple mechanisms and targeted therapy with anticonvulsants may be a future possibility.

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CHAPTER

9

Surgical Treatment for Epilepsy

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CHAPTER CONTENTS

INTRODUCTION

The International League Against Epilepsy (ILAE) defines epileptic seizures as the transient occurrence of signs and symptoms due to abnormally excessive or synchronous neuronal activity of the brain.[1] According to the ILAE, a person is diagnosed with epilepsy if he or she has one of the following: the occurrence of two unprovoked epileptic seizures more than 24 hours apart, the diagnosis of an epilepsy syndrome, or a history of one unprovoked seizure with a greater-than-60% probability of further seizures.[1,2] The median incidence of epilepsy in the developed world is approximately 50 for every 100,000 persons per year, and the prevalence is approximately 5 in every 1000 persons.[3–6] Among those patients, approximately 20-40% suffer from drug-resistant epilepsy (DRE).[7–9] The ILAE recently defined DRE as epilepsy in a patient who does not achieve sustained seizure freedom after adequate, tolerated trials of two appropriately chosen and executed AED schedules (whether as monotherapies or in combination).[10] The lifetime cost for yearly cases of epilepsy in the United States is estimated to be 11 billion dollars, with the majority of the cost attributable to DRE cases.[11] As shown in multiple cohort studies and one randomized controlled study, surgery can be more effective than prolonged medical therapy for carefully chosen patients suffering from DRE,[12–15] and current practice guidelines urge physicians to refer all patients with DRE to epilepsy surgery centers.[13]

In this chapter we discuss the role of surgery in the management of DRE. We focus our discussion on the surgical tools available for treatment of various forms of DRE. We start by considering the selection and workup of surgical candidates, including helpful imaging and electrophysiological techniques. We then describe the available surgical options, organizing the surgical armamentarium into three broad categories: resection techniques, disconnection surgeries, and functional techniques involving electrical stimulation.

EVALUATION AND SELECTION OF THE SURGICAL CANDIDATE

As stated above, current practice guidelines recommend that all patients with DRE should be referred to a center that specializes in the surgical treatment of epilepsy. Unfortunately, despite the many published studies and class 1 evidence for the efficacy of surgery in treating DRE, the utilization of epilepsy surgery and referrals to epilepsy treatment centers have not increased.[16,17]

Patients who have failed two or more appropriately chosen antiepileptic regimens and who are not high-risk surgical candidates should undergo further testing. Discussion of the general risk of surgery and the potential for invasive monitoring should precede further testing, however, and only patients who are willing to accept the risks of resective or palliative surgeries should undergo further testing.

Initial testing should include volumetric a multiplanar MRI and an ictal and inter-ictal scalp EEG, as well as neuropsychological and psychiatric testing and social evaluation. The workup of patients with DRE should occur in epilepsy centers equipped with the appropriate services, personnel, and facilities.[18] Patient should not have pre-existing psychiatric conditions that can be worsened by surgery or can interfere with surgical outcome. Social evaluation ensures that the patient has the social support needed after surgery, and extensive neuropsychological testing determines whether the clinical manifestation of epilepsy corresponds to the localization of the seizure focus on the EEG and any lesions visible on the MRI. Patients who have concordant findings on the EEG and imaging (e.g., a lesion that coincides with the seizure focus in a noneloquent area) are candidates for surgical resection. Patients without concordant findings can undergo further testing, including invasive electrocorticography and further imaging. Those deemed unsuitable candidates for surgical resection should be referred for palliative surgeries such as neurostimulation or disconnection surgery, as discussed below.[19]

RESECTION PROCEDURES

Epilepsy is typically categorized as partial or generalized epilepsy. Partial epilepsy refers to epilepsy that emanates from a focal cortical area while generalized epilepsy involves many cortical areas at once. Because of its focal nature, drug resistant partial epilepsy can potentially be treated by resection of the abnormal cortical tissue. In this section, we will discuss the surgical approach to various forms of drug-resistant focal epilepsy. We start by focusing on temporal lobectomy, as it is the most commonly performed surgical resection. We will then discuss the surgical treatment of extratemporal focal drug-resistant epilepsy focusing on the approach to non-lesional focal epilepsy. We end this section with discussion of surgical approach to hemispheric epilepsy.

Temporal Lobectomy

Patients with temporal lobe epilepsy present with simple or complex partial seizures of well-defined semiology involving auras and automatisms.[15] The most commonly encountered pathology in temporal lobe epilepsy is mesial temporal lobe sclerosis. Other commonly encountered pathologies include focal cortical dysplasia, trauma, infection, vascular malformations, and neoplasms.[20,21]

Evaluation of these patients as with others starts with high-resolution MRI scans and prolonged EEG. At this point, patients can be categorized into three categories: those that have a lesion on MRI that corresponds to the EEG and clinical abnormality (lesional temporal lobe epilepsy), those that have temporal lobe lesions in addition to other lesions (temporal lobe plus), and those that have no MRI abnormalities (non-lesional temporal lobe epilepsy). In this section, we will discuss surgical management of patients who fall into the first two categories. Workup of patients with non-lesional temporal lobe epilepsy follows that of non-lesional extratemporal lobe seizures except for the use of a temporal lobectomy if the workup confirms a temporal lobe focus for the seizure. Workup of patients with non-lesional temporal lobe epilepsy follows that of non-lesional extratemporal lobe seizures discussed in the next section.

Once the origin of the seizure is confirmed, the next step is surgical resection. All surgical approaches focus on resection of the mesial temporal structures but there is continued debate about the extent of resection.

Common Complications

Traditionally, patients with left sided temporal lobe epilepsy underwent a sodium amobarbital intracarotid injection (Wada test) to establish their memory and language laterality. However, earlier data suggested that the test can be useful in predicting patients who will have poor post-resection cognitive outcome.[22] Recent data and more experience with temporal lobectomies suggest that the a positive Wada test may not preclude good memory outcomes after temporal lobe epilepsy.[23] Indeed, the test is now rarely utilized by most epilepsy centers.[24]

Efficacy of surgery for drug-resistant temporal lobe epilepsy has been established in a randomized clinical trial.[15] These results are confirmed by long-term follow up studies. Between 50 to 60% of patients achieve a seizure free outcome in large series with up to 90% achieving a substantial decrease in seizure frequencies.[12,25]

Extra-temporal Cortical Resections

Extra-temporal epilepsy can be categorized into lesional and nonlesional epilepsy. Lesional epilepsy is related to an MRI visible cortical lesion responsible for

generation of a seizure focus. Nonlesional epilepsy refers to focal epilepsy with an MRI occult seizure focus.

The approach for lesional extra-temporal lobe epilepsy focuses on management of the underlying lesion. Commonly encountered lesions include tumors, infarcts, vascular malformation, cavernous malformation, and malformations of cortical development.[26]

The approach for patients with non-lesional neocorical focal epilepsy is more complicated. The spatial and temporal localization of seizure onset with scalp EEG is poor. Therefore, for an extra-temporal focus localization, invasive localization is often necessary in the form of a large subdural grid and sometimes stereotactic depth electrodes. Invasive EEG monitoring is always necessary for cortical resection when the epileptic focus is not clear. Subdural strip electrodes are limited in their ability and are basically useful to lateralize an epileptogenic focus, while large subdural grids and depth electrodes are used to localize a focus. Subdural strip electrodes are placed through burr holes while subdural grid electrodes are placed through a craniotomy and can also be used for functional mapping. There are no anatomically standard respective procedures for extra-temporal cortical resection. The extent of resection is based on the results of elctrocorticography, functional mapping and proximity of focus to eloquent areas and is individually tailored to each case. Non-lesional resection of neo-cortical focal epilepsy generally results in seizure-free rates of 45% and improvement in 35%.

Hemispherectomy

Walter Dandy first introduced hemispherectomy as a treatment for hemispheric glioma and over the next few decades it gained attention as a resection technique for intractable hemispheric epilepsy. The procedure fell out of favor due to its high perioperative mortality in addition to its serious long-term complications of superficial cerebral hemosiderosis and hydrocephalus. Most of these complications were thought due to the extensive degree of brain resection. Attempts to modify the procedure by decreasing the amount of tissue resected led to a decrease in the complication rates but decreased the efficacy of the procedure.[27] The use of the procedure increased with the development of functional hemispherectomy or hemispherotomy that substituted anatomic resection with functional disconnection of the two hemispheres. Rates of superficial cerebral hemosiderosis and hydrocephalus along with perioperative mortality decreased significantly while seizure control rate was similar to those observed with anatomic hemispherectomy.

The procedure is indicated for drug-resistant hemispheric epilepsy resulting from disease processes that affect one hemisphere such as Rasmussen encephalitis, hemimegalencephaly, or multiple hemispheric strokes. It is controversial whether patients with bilateral anatomic abnormalities have worse outcomes.[28,29]

There are two main surgical techniques to perform hemispherectomies. Anatomic hemispherectomy aims to resect all cortical tissue on one hemisphere with various amounts of subcortical tissue resection. Functional hemispherectomy on the other hand aims to disconnect one hemisphere from the others and may be classified as a functional disconnection procedure (see below) rather than an anatomical resection. There are three main techniques to perform a functional hemispherectomy: (1) Rasmussen's functional hemispherectomy; (2) Vertical functional hemispherectomy; (3) Lateral functional hemispherectomy.[30] All three share the same components of corpus callosotomy, resection of medial temporal structures, disruption of frontal horizontal fibers, and interruption of the corona radiata and internal capsule.[31]

Regardless of the technique used, hemispherectomy is an efficacious procedure in properly selected patients. Approximately two-thirds of patients become seizure free. Reported rates of seizure free outcome range from 60 to 90% in case series.[30,32,33,34,35] The most common complications are hydrocephalus (2–33% of cases) and superficial cerebral hemosiderosis (0–30%).[30] Those complications are more common in cases when anatomic hemispherectomy is performed. Operative mortality range for modern cases series range from 2 to 7%.[30]

NONRESECTIVE TECHNIQUES

The resective techniques described above remain the best option for most patients with DRE. However, a subset of patients with DRE are not candidates for those interventions. This may be due to the nonlocalizable or multifocal nature of their epilepsy or the fact that the seizure focus originates in an eloquent cortical area, making resection a highly morbid or not feasible. These patients might benefit from a variety of techniques that do not involve the resection of neuronal tissue.

We split the nonresective surgical options into the disconnection procedure and the functional stimulation procedure. The disconnection procedure involves cranial surgery and focuses on disconnecting the seizure focus from the rest of the cerebrum, therefore preventing the seizure from generalizing. The two main disconnection procedures are corpus callosotomy and multiple subpial disconnections. Functional procedures aim to use electrical stimulation to abort or interfere with the initiation or generalization of seizures. The main electrical stimulation techniques available or under investigation today include vagal nerve stimulation (VNS), deep brain stimulation

(DBS) of various deep brain nuclei, and responsive neural stimulation (RNS).

DISCONNECTION SURGERIES

Corpus Callosotomy

In the early part of the twentieth century, physicians noted that patients with intractable epilepsy who suffered damage to the corpus callosum experienced a significant decrease in the number of seizures.[36] This observation lead to the introduction of corpus callosotomy surgery for the treatment of intractable epilepsy in the 1940s.[37] Corpus callosotomy might lead to decreased seizure frequency due to interruption of the spread of seizure activity from one hemisphere to the other. However, partial corpus callosotomy (e.g., anterior callosotomy) can be as effective as complete callosotomy in decreasing the seizure frequency, suggesting that interruption of bihemispheric communication is not the sole mechanism by which callosotomy leads to improvement in seizure frequency.[38,39] Studies suggest that the interruption of corpus callosum fibers leads to decreased overall epileptogenicity, in addition to decreasing the cross-hemispheric spread of seizure activity.[40] One hypothesized mechanism by which corpus callosotomy can decrease epileptogenicity is by decreasing the cross-hemispheric back-and-forth volleys of electrical activity that can synchronize cortical networks leading to seizures. Nonetheless, the mechanism by which corpus callosotomy leads to decreased seizure frequency remains unclear and subject to further studies.

Regardless of the mechanism, corpus callosotomy appears to be efficacious in reducing the frequency of generalized seizures and drop attacks in patients with DRE. Studies show a significant decrease in frequency or complete elimination of drop attacks in 50-100% of patients, as well as a 70-85% decrease in the frequency of generalized tonic-clonic seizures.[38,39,41–46] Improvement in the frequency of other seizure types is generally poor, however.

Current candidates for corpus callosotomy are patients with DRE who have no identifiable lesions that might correspond to the EEG abnormalities, those who fail other surgical resections, and those who have multiple bihemispheric lesions not amenable to resection. Meta-analysis comparing the efficacy of corpus callosotomy to VNS show that the procedures have equivalent seizure control efficacy for most seizure types, except for drop attacks for which corpus callosotomy shows higher efficacy.[47] Given that VNS is a less invasive approach, physicians suggest that patients whose predominant seizure type is not drop attacks undergo VNS prior to considering corpus callosotomy. On the other hand, patients whose predominant seizure type is drop attacks should strongly be considered for corpus callosotomy.

The surgical technique for corpus callosotomy requires a linear or curved incision that allows visualization of the midline, while creating an opening for an approximately 5 cm (AP dimension) by 4 cm (lateral extent) craniotomy. A nondominant-side craniotomy is usually chosen to minimize retraction and damage to the dominant hemisphere. Some authors recommend testing language laterality in patients undergoing callosotomy because of the more frequent incidence of right-sided dominance in these patients. The surgical procedure proceeds with interhemispheric blunt dissection to reach the corpus callosum. Care is taken to avoid injury to cortical bridging veins and the superior sagittal sinus. For this reason among others, the procedure is usually carried out using the operative microscope, and care is taken to divide the corpus callosum in the midline between the two anterior cerebral arteries and to avoid entrance into the ventricles, which might lead to postprocedural hydrocephalus and/or development of chemical meningitis.

The required extent of the corpus callosotomy is subject to much debate. Studies show that complete callosotomy generally leads to better seizure outcomes.[38,39,43,46,48] The tradeoff is that complete corpus callosotomy is associated with higher chances of neurological dysfunction. However, the incidence of disconnection syndrome is reportedly similar for anterior callosotomy or complete callosotomy.[41,49] Therefore, most centers carry out anterior 2/3 or anterior 1/2 callosotomy, followed by completion a few weeks later if there is no improvement in symptoms and no neurological dysfunction occurs.[38,39,41,45,46,48] This is especially true for higher-functioning pediatric patients and adult patients.[41,50] For pediatric patients, especially those with significant baseline neurological symptoms, some suggest that complete callosotomy at the outset is associated with better outcomes without increases in significant side effects.[43,48]

The complications of corpus callosotomy include those of any other craniotomy, including stroke, hemorrhage, and infections. Accidental entry into the ventricle may lead to the development of hydrocephalus or chemical meningitis. Patients should be educated about the rare risk of developing postoperative disconnection syndromes. The syndromes arise due to the interruption of functional areas of the dominant and nondominant hemispheres. The most commonly seen syndrome is an acute SMA syndrome. Chronic disconnection syndromes include alien hand syndrome, tactile dysnomia, hemispatial neglect, and alexia without agraphia.[50] Patients should be educated that the risk of developing any disconnection syndrome is small. The development of new seizure types after corpus callosotomy has been

reported, however, and patients need to be educated about it. In modern studies the chance of developing lasting disabling effects range from 0% to 20%.[41,48,49] Studies suggest that disconnection syndromes are usually transient with little long-lasting effects, and these syndromes are less likely with incomplete corpus callosotomy. The medical field has widely accepted that the benefits of the procedure, especially for patients with drop attacks, outweigh the risks of developing disabling neurological deficits.

Multiple Subpial Transections

Multiple subpial transection (MST) is a technique first described by Morrell in 1989 for the treatment of DRE in which the seizure focus involves eloquent cortical areas.[51] The rational for the procedure is that spread of seizure activity follows cortical communication fibers that travel horizontally between cortical areas. On the other hand, cortical output is thought to travel along vertically oriented fibers. The technique involves the transection of horizontal intracortical connections, leaving the vertical connection intact and therefore preserving cortical function.

MST has largely been practiced in conjunction with resection surgery, and no large studies address the efficacy of MST alone. There are also no agreed-upon indications for the use of MST. Currently, the procedure is usually described in the literature for treatment of DRE with lesions in eloquent brain areas where resection is not possible without significant neurological compromise. In the largest meta-analysis to date, MST with cortical resection lead to a >95% reduction in seizure frequency in 87% of patients with generalized epilepsy, and MST alone resulted with similar results in 71% of patients.[52] Other small single-center studies show a much smaller efficacy for the techniques, with 30-50% of patients achieving significant reductions in seizure frequency.[53,54]

The surgical technique is well described in the literature. In summary, the affected region of the cortex is exposed and surface electrocorticography is performed to outline the eloquent areas. The surgeon then uses an epilepsy knife to make cuts under the pia in a direction perpendicular to the long axis of the gyrus. This is repeated at 5-mm distances along the affected gyrus.[53] The majority of patients develop neurologic deficits after the procedure. These deficits are related to the function of the cortical areas where the subpial transections are being made, and most of the deficits improve with time.[52–54] Thus, MST is a novel technique with promising results when used in conjunction with resective techniques. As a stand-alone therapy for DRE, this technique needs further study to better understand its efficacy.

Vagal Nerve Stimulation

Animal studies in the 1930s showed that stimulation of the vagal nerve can influence cortical activity.[55] Investigations into this phenomenon continued in the late 1980s and early 1990s, and the first human studies on VNS for the treatment of DRE were published with encouraging results.[56–58] Class 1 evidence for the efficacy of VNS was published with the results of two pivotal multicenter randomized and blinded studies known as the E03 and E05 studies,[59,60] and in 1997, VNS was FDA-approved for the adjunctive treatment of drug-resistant partial-onset epilepsy in patients 12 years and older.

The mechanism of action in VNS is not well understood. The vagus nerve is composed of about 80% afferent fibers. Its main target is the nucleus of the solitary tract (NTS). The NTS, in turn, has widespread projections to many areas, such as the reticular activating system, which includes the locus coeruleus (LC) and raphe nucleus, thalamus, hypothalamus, and amygdala. Researchers hypothesize that VNS acts by desynchronizing neuronal activity.[61,62] This desynchronization may involve increasing levels of various neurotransmitters through indirect stimulation of the reticular activating system. Lesioning of the LC interferes with the antiseizure effect of VNS.[63] Furthermore, it has been shown that levels of neurotransmitter metabolites rise in the CSF in response to VNS.[64] Despite this evidence, the exact mechanism of VNS action remains poorly understood.

Candidates for the implantation of a vagal nerve stimulator include all patients with DRE who are not candidates for resection, those who have failed prior surgical resection, and patients who want to avoid cranial surgery. Patients are not suitable for resection surgeries because they suffer from seizures originating in eloquent areas, have multiple seizure foci, or have no identifiable surgical lesion. Contraindications for vagal nerve implantation include prior damage to the left vagal nerve, bradycardia, dysautonomia, and pulmonary disease. Although FDA approval does not extend to children younger than 12 years of age, emerging evidence supports of use of VNS in children.[65–68] Similarly, patients with generalized onset seizures, although not included in the FDA approval statement, have benefited from VNS therapy and should not be excluded.[60,25,69]

The implantation of a vagal nerve stimulator is a simple procedure compared to other surgical interventions for epilepsy. The procedure is carried out under general anesthesia and requires two incisions. One small horizontal incision on the left side of the neck is used to implant the electrode around the vagus nerve. The left side is chosen to avoid unwanted vagal stimulation of the heart, because the majority of efferent fibers to the heart travel along the right vagal nerve. However, small studies have shown that right vagus nerve stimulation is safe and

effective.[70–72] The platysma is divided and dissection is carried out along the medial edge to the sternocleidomastoid muscle in order to arrive at the carotid sheath. The sheath is opened up and the vagus nerve is dissected out between the carotid artery and jugular vein. The electrodes are then implanted around the vagus nerve. Another incision is made in the infraclavicular region or midsternal area to allow for implantation of the battery or pulse generator above the pectoral fascia. The electrode leads are then tunneled from the cervical incision to the battery and connected. The electrode is subsequently turned on and its function verified. After implantation, the stimulation paradigm is programmed on an outpatient basis over the following weeks, and in most centers, the entire procedure is done on an outpatient basis, with patients going home after surgery.

In terms of expected outcomes, the EO3 and E05 showed a mean reduction of seizure frequency of approximately 30% in the 3 months after implantation.[59,60] Long-term follow up shows improved results with time. Up to 50% of patients can expect at least a 50% decrease in seizure frequency. Patients should also be educated that, on average, 25% of patients don't benefit from VNS.[68,69,73,74] The procedure is usually well tolerated, however. The most common reported side effects include hoarseness and voice changes (37%), tingling and throat pain (18%), and coughing (8%). Less frequent side effects include dyspepsia and permanent vagus nerve injury.[59,60] Most of these side effects become less noticeable with time, and more than 75% of patients implanted with VNS chose to continue therapy.[25] Cardiac complications, including symptomatic bradycardia, asystole, and heart block, are extremely rare. It has been reported that about 1 in 1000 patients will suffer transient bradycardia during the initial testing of the lead at the time of implantation.[75,76] Rare complications include lead fractures and premature battery or pulse generator failure.[77] Reported hardware and tissue infection rates are less than 10%,[68,25,66,77] and there have been no reported device-related mortalities in any of the major trials.

Deep Brain Stimulation

The idea of using electrical stimulation to treat epilepsy dates back to the 1970s.[78] Initial attempts stimulated the cerebellum, but they did not show efficacy in clinical trials. More recently, improvements in the technology of DBS and the availability of more accurate methods for targeting deep nuclei renewed the field's interest in stimulating deep brain nuclei in an attempt to treat epilepsy. The literature is full of case reports and small case series on the targeting of various deep brain nuclei for stimulation with the goal of treating epilepsy, and the stimulation of the anterior thalamus was recently found to be effective in a blinded randomized clinical trial.[79]

Interest in the stimulation of the anterior thalamic nuclei to treat epilepsy relates to the involvement of that region in the limbic circuit. Researchers postulate that modulation of the activity of the anterior nucleus of the thalamus leads to changes in the activity downstream in the amygdala and hippocampus, areas well known for their involvement in initiating and propagating epileptic discharges. Although this relationship may be plausible, it is not proven, and the exact mechanism of action for DBS of the anterior nucleus is not well understood.

In the SANTE clinical trial, 109 patients underwent implantation of bilateral anterior thalamic nuclei stimulators. The patients ranged in age from 18 to 65 years old. The control group underwent implantation of the device, but they never had it turned on. All patients were followed for 3 months after implantation. The patients were then unblinded and followed for additional time. After 3 months, the patients receiving stimulation had a decrease in seizure frequency of approximately 40%, compared to 15% in the control group. At the 2-year mark, about 50% of the patients enjoyed a more-than-50% decrease in their seizure incidence.[79]

The major side effects of DBS implantation include all the possible side effects of DBS surgery, such as infection, stroke, hemorrhage, and hardware failure. Specific to ANT stimulation, encountered side effects have included memory impairment (13%) and depression (15%). Despite the above encouraging results DBS stimulation of bilateral ATN is not yet FDA-approved in the United States. On the other hand, the device has been approved in the European Union for use in the treatment of epilepsy.

Responsive Neurostimulation

Responsive neurostimulation refers to the electrical stimulation of a seizure focus in response to the detection of a seizure arising from that focus. The only responsive neurostimulation device on the market (Neuropace) went into trials in 2005. Based on the results of those trials and the long-term follow up of the participating patients, the Neuropace device was FDA-approved in 2013 for the treatment of DRE. The Neuropace device consists of a pulse generator and one or two subdural grids or depth electrodes. The system records activity from the grids or depth electrodes. When a seizure is detected according to a prespecified algorithm, the pulse generator delivers an electrical stimulus to the seizure focus to attempt to disrupt the evolution of the seizure.

The pivotal RNS trial is the only prospective randomized blind trial on the use of the Neuropace device.[80,81]

This trial enrolled 191 patients who were randomly assigned to the control or treatment groups. Both groups underwent implantation of the device, but only the treatment group had the device turned on. The patients were followed for 3 months, and initial results showed a decrease in seizure frequency of 38% in the stimulation group, compared to 17% in the control group.[81] Follow up of these patients for 2 years after implantation revealed sustained and increasing effects of RNS on seizure frequency. At the end of 2 years, the median reduction in seizure frequency was 53%.[80] Few significant side effects have been reported for RNS. The infection rate was about 5%. Otherwise, the main significant side effects were memory impairment (5%), depression (3%), and infection (3%).

Choosing patients to undergo VNS, DBS, or RNS is difficult. The three devices have similar indications, and they have similar and comparable efficacy when compared to placebo. The degree of reduction in seizure frequency compared to baseline is also similar across these devices. The complications of the procedures and their rates are also similar. VNS does not require cranial surgery for implantation and therefore has a smaller risk for strokes and brain injury compared to DBS and Neuropace. The Neuropace only stimulates in response to detected seizure emergence and, as such, has lower power requirements and less need for frequent battery replacements, compared to DBS and VNS. The Neuropace system is not well supported for epilepsies with more than two seizure foci or in generalized seizures, however, especially when compared to VNS or DBS, which have a more generalized effect on cortical electrophysiological activity. Trials comparing these technologies are needed to help clinicians choose the most effective treatment for any particular patient.[82]

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CHAPTER

10

Clinical Evaluation of Epilepsy in the Brain-Tumor Patient

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CHAPTER CONTENTS

Epilepsy is one of the most common neurological conditions and affects up to 1% or more of the entire population.[1,2] Seizure activity and epilepsy have been described since ancient times (e.g., Hippocrates in 400 BC) and do not discriminate in terms of age, race, social class, or geographic location. It is estimated that at least 50 million people have epilepsy worldwide, and many of these people live in resource-poor countries with limited access to health care.[3] The annual rate of new cases of epilepsy is estimated to be approximately 40-50 per 100,000 in the USA, Europe, and other Western countries.[4] In resource-poor countries, the annual rate is much higher, with an overall incidence of 65-70 per 100,000. However, in some regions (e.g., South America), the incidence can be even higher—in the range of 100-150 per 100,000. The majority of these patients with new-onset seizure activity and epilepsy do not have a brain tumor. Instead, they have more common causes of seizures such as idiopathic epilepsy (the most common cause), cerebral infarction, alcohol-related seizures, sepsis, CNS infection, metabolic derangement (e.g., hyponatremia, uremia, hepatic failure), and intracranial hemorrhage (see Table 10.1).[1,2]

It is clear from Table 10.1 that for patients with a new-onset seizure and epilepsy, the majority will not have a brain tumor, but will instead have a more common illness such as idiopathic epilepsy, stroke, infection, sepsis, drug toxicity, or metabolic disturbance.[1,2,4] The overall incidence of brain-tumor patients among the cohort with seizures and epilepsy ranges from 4% to 8%, depending on the source of epidemiological data.[1,2,5,6] The age of onset at the time of the event is very important in assessing the risk of the seizure being brain tumor-related. If the seizure occurs before the age of 45, then the risk is low, in the 2-3% range. However, if the seizure occurs after the age of 45, the risk is much higher, in the 11-12% range. In addition,

TABLE 10.1 Common Causes of Seizures and Epilepsy in Teens and Adults

Cause	Percent (%)
Idiopathic epilepsy	25-30
Cerebral infarction and vascular events	22-25
Ischemic, focal and global	
Hemorrhagic	
Aneurysmal rupture	
Alcohol withdrawal	10-12
Drug withdrawal, other	
CNS infection	8-10
Bacterial	
Viral	
Fungal	
Mass lesion in the brain	
Brain tumor	6-8
Vascular malformation	5-7
Abscess	
Primary hemorrhage	
Cranial trauma	3-5
Drug toxicity and poisoning	2-4
Subdural hematoma	2-3
Metabolic	1-2
Hyperglycemia/hypoglycemia	
Uremia	
Hyponatremia	
Hypocalcemia	
Hypomagnesemia	
Hypoxia	
Hepatic failure	
Other	0.5-1
Mitochondrial diseases	
Neurodegenerative conditions	
Drug-related (e.g., chemotherapy)	
Treatment-related (e.g., radiation necrosis)	
Psychiatric disorders	

Adapted from the Refs. [1,2]

the presence or absence of focal findings on the neurological examination is also an important variable. If there is an intact and nonfocal neurological examination, then the risk for an underlying brain tumor across all ages is reduced to 4.5%. If there are focal findings, then the risk for a brain tumor is substantially higher, especially in the presence of high-grade disease.

The overall incidence of seizure activity and epilepsy in brain-tumor patients is approximately 30-35%, when all locations and histological types are considered.[5,6] Of this group, between 30% and 50% will have a single seizure or multiple seizures as part of the tumor presentation. Another 10-30% will develop seizure activity at a later time in the course of their disease. In general, the lower-grade brain tumors have the highest incidence of seizure activity and epilepsy.[5,6] For example, dysembryoblastic neuroepithelial tumors (DNET) have an incidence of epilepsy approaching 100%, and low-grade astrocytomas and oligodendrogliomas have an incidence in the 60-80% range (see Table 10.2). Patients with high-grade tumors such as glioblastoma multiforme (GBM) have a much lower incidence of seizures at presentation, in the 30-45% range. However, seizures at presentation are even less common in patients with primary CNS lymphoma (10-15%). Extra-axial tumors such as meningioma can also present with seizure activity, with an incidence in the 30-60% range. Brain metastases can also induce seizures and epilepsy through compression of the underlying brain, in the range of 20-35%. The more cortically based the tumor, the more likely it is to induce seizures. Therefore, tumors arising in the frontal, temporal, and parietal lobes are commonly associated with brain tumor-associated epilepsy, whereas tumors in the occipital lobes and deeper locations are not as likely.

Once seizure activity and brain tumor-associated epilepsy is suspected in a brain tumor patient, the patient must undergo a thorough assessment and evaluation to determine if the "spell" was an actual seizure—deserving of specific anti-seizure therapy—or some other paroxysmal event with similar features, unrelated to the brain tumor and abnormal electrical activity in the brain.[5,6] The differential diagnosis of seizure activity and epilepsy is very extensive and we review it in detail in the next section.[7]

TABLE 10.2 Listing of Brain Tumor Types and Seizure Frequency

Brain tumor	Frequency (%)
DNET	100
Gangliocytoma	80-90
Low-grade oligodendroglioma	75-80
Low-grade astrocytoma	70-75
Meningioma	30-60
Glioblastoma multiforme	30-45
Brain metastases	20-35
Primary CNS lymphoma	10-15

Adapted from the Refs. [5,6]

DIFFERENTIAL DIAGNOSIS

The cause of seizure activity related to a brain tumor is very specific: abnormal cortical excitability and aberrant electrical discharges in the region of the brain around the primary mass of the tumor. However, there are numerous paroxysmal events with transient alterations of neurological function that can appear, superficially at least, to be similar to a seizure, without being related to abnormal electrical activity in the brain.[7,8] The differential diagnosis of seizure activity and epilepsy is very broad and includes syncope of cardiac origin, syncope of noncardiac origin, stroke and transient ischemic attack (TIA), migraine, toxic and metabolic disturbances, psychiatric diseases, sleep disorders, and many other diagnoses (see Table 10.3).

Syncope is defined as a sudden and transient loss of consciousness and postural tone—often leading to a fall—that is associated with rapid spontaneous recovery and no neurological sequelae.[7–9] The cardiological definition of syncope is limited to transient global cerebral hypoperfusion as the underlying mechanism.[8,9] However, the neurological definition is more expansive and also includes other noncardiovascular causes of syncope, as listed in Table 10.3. In general, syncope occurs secondary to reversible anoxia in the brain, induced by a drop in cerebral perfusion pressure. Syncopal events are often very difficult to distinguish from seizures, and they often require a detailed work-up.[7–9] For example, in a study of 946 patients with episodic bouts of unconsciousness, the final diagnoses included 417 with pure syncope (mostly of cardiogenic origin) and 377 with epilepsy.[11] Syncope of cardiac origin is suggested when the patient reports the episode occurred in the supine position or during physical exertion or effort, without any type of prodrome (e.g., cardiac asystole), especially when the patient has an established structural heart disease or abnormal EKG, or when there is a family history of sudden death.[8,10] Cardiogenic syncope can be grouped mechanistically into four categories: (1) cardiac arrhythmias, (2) reduced cardiac output, (3) reflex-triggered drop in heart rate or systemic vascular resistance, and (4) drop in systemic vascular resistance from medications or autonomic nervous system dysfunction.[8,9,12] Common cardiac arrhythmias that can lead to cerebral anoxia severe enough to cause syncope include atrial fibrillation, bradycardia (i.e., less than 40 beats/min), and ventricular tachycardia (i.e., greater than 150 beats/min). Overall, bradyarrhythmias are more commonly associated with syncope than tachyarrhythmias. Specific types of arrhythmias include paroxysmal atrial tachycardia, sick sinus syndrome, paroxysmal ventricular bradycardia and tachycardia, Stokes-Adams attacks (bradycardia due to atrioventricular block), bundle-branch block, atrioventricular node block, various forms of ventricular dysrhythmia, and long QT syndrome.[8,9,12] Numerous types of structural cardiac disease can also

TABLE 10.3 Differential Diagnosis of Epileptic Seizures in Adults

Syncope of cardiac origin	Amyloidosis
Arrhythmias	Hypovolemia
Supraventricular arrhythmias	Valsalva maneuvers
Atrial fibrillation	Medication-induced (i.e., drop in systemic vascular resistance)
Paroxysmal atrial tachycardia	Tricyclic antidepressants
Sick sinus syndrome	Levodopa
Ventricular dysrhythmias	Antihypertensives
Paroxysmal tachycardia or bradycardia	Phenothiazines
Stokes-Adams attacks	Hyperventilation
Heart block/asystole	Benign paroxysmal vertigo
Bundle-branch block	Migraine
Atrioventricular node block	Transient global amnesia
QT prolongation	Cerebrovascular disease and vascular
Structural cardiac disease	Stroke
Acute coronary syndrome	Transient ischemic attack
Acute myocardial infarction	Vertebrobasilar insufficiency
Acute aortic dissection	Subclavian steal syndrome
Valvular heart diseases	*Toxic disturbance*
Aortic stenosis	Alcohol
Pulmonary stenosis	Strychnine
Pulmonary embolism	Carbon monoxide poisoning
Pericardial tamponade	Cyanide
Congenital heart disease	Medication overdose
Hypertrophic cardiomyopathy	Illicit drug usage
Atrial myxoma	*Metabolic disturbances*
Syncope of noncardiac origin	Hypoglycemia
Neurally mediated (Reflex)	Porphyria
Vasovagal	Renal and hepatic disease
Situational	Pheochromocytoma
Tussive	*Sleep disorders*
Micturition	Narcolepsy
Exercise	Parasomnias
Pain	Paroxysmal nocturnal choreoathetosis
Carotid sinus syndrome	Psychiatric disease
Orthostatic	Anxiety/panic disorder
Shy-Drager syndrome	Conversion disorder
Parkinson's disease	*Movement disorders*
Autonomic neuropathies	Paroxysmal dyskinesias
Porphyria	Psychogenic seizures
Familial dysautonomia	
Diabetes	

Adapted from the Refs. [1,2,7–10]

lead to cardiogenic syncopal episodes (see Table 10.3).[7–9] In general, syncope due to nonacute structural heart disease is common during exercise, when the differences between body demands for oxygen and cardiac output substantially increase. Nonacute types of structural heart disease that have been implicated in syncopal events include valvular heart disease (i.e., aortic stenosis, pulmonary stenosis), congenital heart disease, hypertrophic cardiomyopathy, and atrial myxoma. Acute forms of structural heart disease can also lead to syncope, including acute coronary syndrome, acute myocardial infarction, acute aortic dissection, pericardial tamponade, and severe pulmonary embolism.

Noncardiogenic types of syncope are common (see Table 10.3), especially in older patients, and include neurally mediated syncope (NMS), orthostatic syncope, valsalva-related syncope, and medication-induced syncope.[7–9,11,13] NMS (also known as vasovagal syncope and reflex syncope) can be subdivided into vasovagal syncope (induced by standing), situational syncope (triggered by different stimuli/situations), and carotid sinus syndrome.[8] Episodes of NMS usually present with a prodrome that precedes the loss of consciousness by 30-60 s; however, in some elderly patients, it is due to less autonomic activation.[13] The prodromal manifestations include facial pallor (which is often first), cold sweating, salivation, palpitations, and pupillary dilatation. Soon after, more severe symptoms related to cerebral and/or retinal hypoperfusion occur, such as mental changes, lightheadedness, fatigue, visual and hearing changes, and even the possibility of hallucinations and near-death experiences. Actual loss of consciousness is quite variable but typically brief—in the range of 10-20 s—although it can sometimes extend to several minutes. Generalized "jerking" or "twitching" of the extremities can occur during the bout of unconsciousness, but without tongue biting or bladder incontinence. The recovery from loss of consciousness is very rapid and complete. Syncopal episodes related to NMS are suggested by the following features in the history: the spell follows a sudden unexpected sight, sound, smell, or pain; the spell occurs after pressure on the carotid sinus (e.g., head rotation, shaving, tight collar); the spell occurs during prolonged standing in a crowded and/or hot location; the spell occurs after eating and alcohol intake; or the spell follows a bout of exertion.[8,13] Physiologically, the episodes of NMS lead to an abnormal baroreflex response, which typically involves sympathetic activation, with increased systemic vasoconstriction and cardiac output, and reduced parasympathetic activity. In NMS, the response is abnormally activated and eventually reversed, so that efferent pathways induce a decrease in blood pressure, and sometimes even to brief asystole, which leads to transient cerebral hypoperfusion. Vasovagal syncope is characterized by a sudden loss of postural tone and consciousness, associated with a drop in systolic blood pressure. It is most common in young subjects and can be precipitated by stress, emotions, pain, fright, and many other stimuli. The common forms of situational syncope include micturition syncope, tussive syncope, and pain-related syncope. However, there are many other forms that can be triggered by exercise, other urogenital causes (e.g., prostatic massage), gastrointestinal causes (e.g., rectal examination), respiratory causes (e.g., airway instrumentation), and many others. Carotid sinus syndrome is considered to be an exaggeration of the normal carotid sinus reflex, which regulates blood pressure.[8,11,13] The syndrome is characterized by a ventricular pause lasting at least 3 s, bradycardia, and a fall in systolic blood pressure of greater than 50 mmHg or more.[11,14] Carotid sinus syndrome is most common in older men, and it typically presents with syncope or similar symptoms such as drop attacks or dizziness, often induced by head rotation or shaving. Other triggers include tight shirt collars or ties, or manipulation or pressure in the upper neck region. The cause of the baroreceptor sensitivity remains unclear; atherosclerosis, coronary artery disease, and other vascular risk factors are often present, along with rare cases of head and neck malignancies. Carotid sinus syndrome is diagnosed when manual stimulation of the carotid artery leads to bradycardia (greater than a 50% reduction of sinus rate) or hypotension (systolic decrease of at least 40 mmHg).

Another common form of noncardiogenic syncope is orthostatic or postural hypotension.[7–9,13] Orthostatic hypotension (OH) is defined as a sustained drop in systolic blood pressure of greater than 20 mmHg or in diastolic blood pressure of greater than 10 mmHg, within 3 min of standing or during head-up tilt to at least 60° on a tilt table.[8,15] The degree of symptomatology is quite variable, however, and some patients can be completely asymptomatic. One of the important differentiating features of OH, in comparison to NMS, is that it is only rarely preceded by autonomic manifestations. Yet, symptoms related to cerebral and/or retinal hypoperfusion are very similar. The symptoms typically develop over several minutes and improve upon lying back down. Upon immediately standing up, there is a presyncope phase or "gray-out," which is usually brief and benign and can be noted in young and old patients. After the patient is up for a more prolonged period of time (typically a few minutes), the symptoms of hypoperfusion arise, followed by the full-blown syncopal event. In addition, there are a few symptoms typically associated with OH-related syncope, including visual hallucinations (secondary to occipital lobe ischemia), neck pain radiating to the shoulders and head (i.e., "coat-hanger" pain, resulting from ischemia in the postural neck muscles), and chest pain resulting from cardiac ischemia. All

of the following features are very suggestive of orthostatic syncope (some of these overlap with NMS): spells that occur upon standing up, spells during prolonged sitting or standing, spells in crowded and/or hot locations, spells that occur after the initiation or changing doses of antihypertensive medications, spells after eating and after alcohol intake, spells immediately after exertion, improvement after lying back down, lack of any autonomic prodrome, coat-hanger pain and chest pain, and the presence of autonomic neuropathy or parkinsonism.[8,13,15]

Changing from the supine to the upright position causes an immediate shift of approximately 800 mL of blood from the central intravascular compartment to the peripheral vascular bed of the abdomen and legs.[16] This volume shift causes a drop in venous return, cardiac output, and blood pressure. These changes are usually countered by feedback through the baroreceptors to increase sympathetic tone, as well as vagal inhibition, resulting in an increase in cardiac output and an increase in peripheral vascular resistance. OH occurs when there is an insufficient response to the initial blood volume shifts, reduced cardiac output, and inadequate vascular tone. The poor vasoconstrictor response is thought to be mainly due to an inadequate release of noradrenaline (norepinephrine) from sympathetic vasomotor neurons.

The etiology of syncopal episodes from orthostatic mechanisms is very extensive and covers a broad range of diagnoses (see Table 10.3).[8,13] The most common cause is related to the use of medications that affect blood pressure, vascular tone, and intravascular volume (listed separately in Table 10.3). Medications that can lower blood pressure include vasodilators, diuretics, common antidepressants (especially the tricyclics), and antiparkinsonian agents. Other factors that predispose a person to OH include diseases that can lead to an autonomic neuropathy, such as diabetes, chronic alcoholism, porphyria, amyloidosis, and familial dysautonomia. Diseases that can cause central autonomic failure, such as Parkinson's disease and Shy-Drager syndrome, are also associated with OH and syncopal events. Hypovolemia can also lead to OH, and can be caused by dehydration, prolonged heat exposure, inadequate fluid intake, and volume depletion (e.g., hemorrhage, diarrhea).

Valsalva maneuvers can also lead to syncopal episodes in some patients, often in the setting of heart failure or other diseases that may limit venous return to the heart.[7–9,12,13,17] Valsalva maneuvers are part of the physiological process in tussive syncope, as well as other settings such as "straining at stool"—so-called defecation syncope. During the maneuver, an increase in intrathoracic pressure leads to a reduction in venous return to the heart, with a subsequent reduction of cardiac output and cerebral blood flow. Other mechanisms may also be involved, such as a reduction in cerebral blood flow velocities and an increase in cerebral vasoconstriction.[18]

There are numerous other paroxysmal, nonsyncopal disorders and conditions that are in the differential diagnosis for brain tumor-related seizures (see Table 10.3).[7,8] For example, hyperventilation attacks can sometimes be mistaken for a seizure event.[7] They are most common in adolescent girls and others with anxiety disorders. During the hyperventilation episode, the patient will complain of dyspnea, chest pain, tachycardia, lightheadedness, circumoral numbness, and carpopedal spasms, along with rapid and pronounced respiratory excursions. All of the symptoms worsen as the respirations become more rapid and irregular, including the possibility of absence-like spells and transient loss of consciousness. The underlying physiology is related to hyperventilation-induced hypocapnia, which then causes vasoconstriction of the cerebral vasculature, with subsequent reduction in cerebral blood flow and perfusion pressure.[19] Patients with hyperventilation will have a normal EEG during and after the event.

Migraine headaches present as a recurring paroxysmal disorder of the CNS, and they can sometimes appear similar to seizures (see Table 10.3).[7,8] In fact, certain epilepsy syndromes can even have migrainous phenomenon as part of the symptom complex, such as benign epilepsy of childhood with occipital spike and wave complexes, benign nocturnal childhood occipital epilepsy, and benign Rolandic epilepsy.[20] In these patients, the headache is usually postictal, particularly after convulsive episodes. In most other patients, however, the coexistence of epilepsy and migraine headaches is coincidental and unrelated. Patients with brain tumor-related seizure activity experience paroxysmal events related to abnormal and excessive neuronal discharges, while those with migraine headaches have episodic events that are related to spreading depression in the brain. Recent research suggests that genetic (e.g., affecting ion channel sensitivity), molecular, and environmental factors are able to trigger a wave of cortical spreading depression (CSD) within the brain, heralding the onset of a migraine attack.[21] During CSD, the trigeminovascular system is activated, thereby releasing calcitonin gene-related peptide (CGRP), which helps mediate the process. Treatment with triptans (i.e., 5-HT (1B/1D) receptor agonists) causes the headache to resolve, and it also normalizes the levels of CGRP. CGRP receptor antagonists have also been shown to abort acute migraine headaches. Migraine episodes can occasionally mimic a seizure, especially if the event has features such as visual, olfactory, or auditory phenomena, paresthesias, motor dysfunction, clouding of consciousness or reduced awareness, nausea, or emesis. Posterior circulation migraines can also appear similar to seizures, with symptoms including loss of vision, vertigo, ataxia,

tinnitus, and confusion. Migraine episodes rarely result in complete loss of consciousness and do not involve tonic-clonic motor behavior. In addition, during a migraine headache, the EEG may demonstrate focal slowing, but it will not have any epileptiform or convulsive activity.

Transient global amnesia (TGA) is a syndrome that most often occurs in middle-aged or elderly individuals, and is characterized by the acute onset of sudden agitation and confusion in association with severe, acute, and nearly total loss of memory (see Table 10.3).[7,22] The episode often arises during or right after a period of exertion, such as exercise, defecation, or sexual activity. The anterograde and retrograde amnesia is not accompanied by cognitive impairment, although in rare cases there can be mild focal findings (e.g., visual field deficits, subtle hemiparesis). The symptoms of TGA typically resolve in a matter of hours, but may last days or recur in some cases. The etiology of TGA remains unclear, but most experts suggest a vascular mechanism, most likely ischemia in the posterior circulation, with dysfunction of the medial temporal and hippocampal region.[22] Episodes of TGA can appear similar to seizures in some cases, and they must be differentiated from ictal or postictal amnesia. Pure amnestic seizures occur in the setting of bilateral hippocampal ictal discharges, and these seizures present as an amnestic syndrome without other behavioral changes. However, these patients always have other forms of partial seizures as well, and they will also have typical EEG abnormalities and epileptiform activity in the temporal lobes.

Cerebrovascular disease that causes syncope, or transient or fluctuating neurological dysfunction, can also be mistaken for a tumor-related seizure (see Table 10.3).[7,8] In fact, several recent studies reveal how commonly these two disorders can be mistaken for each other.[23,24] In two large reviews of suspected stroke, numerous patients were admitted with nonstroke diagnoses, including syncope (approximately 12%), seizure activity (approximately 6%), and brain tumors. Patients with TIAs that are brief, repetitive, and stereotyped (e.g., aphasia, sensory deficits, motor deficits) are especially difficult to differentiate from simple partial seizures. Vertebrobasilar insufficiency can also resemble an ictal event with sudden atonia, vertigo, ataxia, dysarthria, and visual dysfunction, as well as memory disturbances similar to TGA. Vascular-related syncopal events can arise from TIAs, vertebrobasilar insufficiency, unilateral or bilateral carotid artery stenosis, and, on occasion, subclavian steal syndrome. Patients with TIAs and stroke tend to be older than patients with idiopathic epilepsy; however, tumor-related epilepsy patients can be older and considerably overlap the cerebrovascular disease group. Patients with TIAs and stroke will have a nonepileptiform EEG, although there may be slow-wave abnormalities.

Toxic and metabolic disturbances are also well known to cause transient and fluctuating neurological dysfunction, as well as syncope and loss of consciousness, which can sometimes appear similar to seizure activity (see Table 10.3).[7,8] This group of disorders is very broad and includes alcohol intoxication, hypoglycemia, renal and hepatic encephalopathy, porphyria, pheochromocytoma, poisoning (e.g., strychnine, carbon monoxide, cyanide), and medication overdoses. Numerous medications can lead to alterations of mental status and fluctuations in neurological function, such as sedatives, antidepressants, antipsychotics, anxiolytics, anticholinergics, dopaminergic agents, and sympathomimetics. In addition, illicit drugs such as LSD, phencyclidine, cocaine, amphetamines, and methamphetamine can lead to agitation, hallucinations, encephalopathy, and psychosis. All of these disease states can be differentiated from seizure activity through physical examination, laboratory and toxicology testing, and EEG monitoring.

Sleep disorders, in particular narcolepsy, have many clinical features that can be confused with seizure activity (see Table 10.3).[7,8] Narcolepsy involves recurrent and irresistible attacks of daytime somnolence and sleepiness, often in conjunction with the triad of cataplexy, sleep paralysis, and hypnogogic hallucinations.[25] Cataplexy is associated with narcolepsy in approximately 50% of patients, and it consists of sudden falls from loss of muscle tone in the extremities, often precipitated by laughter, fright, or other strong emotions. Cataplexy can be differentiated from atonic seizures by a normal EEG during and after the cataplexic event. Sleep paralysis consists of the patient not being able to move after awakening from REM sleep or shortly after going to bed. The paralysis is total, but consciousness is preserved. Hypnogogic hallucinations consist of intense dreams, often with a very strong affective component, that arise during brief daytime episodes of somnolence. They can easily be confused with partial seizures, especially those of temporal lobe origin. Recent studies suggest that narcolepsy is caused by loss of the hypothalamic neuropeptide hypocretin or orexin, and autoimmune mechanisms may be involved, such as exposure to viruses and vaccinations (e.g., H1N1).[25] Narcolepsy can be diagnosed by a multiple sleep latency test and the verification of reduced sleep latency times. Other sleep disorders such as sleep-onset myoclonus, restless leg syndrome, and parasomnias (e.g., sleepwalking) can also resemble seizure activity. However, an EEG during any of these sleep-related conditions will be unremarkable.

Psychiatric diseases can occasionally manifest symptoms that can be mistakenly associated with seizure activity, such as anxiety attacks and panic disorder (see Table 10.3).[7,26] In most cases, patients with acute anxiety present as similar to patients with hyperventilation (discussed above), displaying dyspnea, chest pain,

tachycardia, lightheadedness, circumoral numbness, and carpopedal spasms, in combination with rapid and pronounced respiratory excursions. Absence-like spells and transient loss of consciousness can also occur. In rare patients, a conversion disorder can lead to psychogenic pseudosyncope, in which there is apparent transient loss of consciousness, but without true loss of awareness.[27] In these patients, researchers theorize that the event represents the physical manifestation of internal psychic stressors, and EEG monitoring during panic attacks and psychogenic pseudosyncope does not show epileptiform or seizure-related activity.

Occasionally, transient and intermittent movement disorders can be mistaken for focal motor seizure activity (see Table 10.3).[7] In some patients, localized cramps or focal dystonia can appear similar to the restricted and sustained motor manifestations of epilepsia partialis continua. Paroxysmal dyskinesia (i.e., paroxysmal choreoathetosis) is another movement disorder that can mimic focal motor seizures in some patients.[28] It is characterized by episodic, short paroxysms of unilateral or generalized tonic, choreiform, and athetoid movements and posturing. The disorder can have an autosomal dominant or recessive inheritance, as well as an acquired form that can result from metabolic diseases such as hypoparathyroidism and other neurological disorders such as multiple sclerosis. The paroxysmal dyskinesias do not ever affect the level of consciousness or awareness, and will have a normal EEG during and after attacks.

Psychogenic seizures are behavioral events that can closely resemble seizure activity, but they are not caused by abnormal paroxysmal discharges of cerebral neurons (see Table 10.3).[7,8,29,30] They have also been described as pseudoseizures, hysterical seizures, and nonepileptic seizures. Psychogenic seizures are typically precipitated by psychological factors that, in most patients, remain at the subconscious level. In most cases, patients with psychogenic seizures are young females with somatoform, panic, or dissociative disorders. However, many patients with true epilepsy also have psychogenic seizures as well (estimated between 10-40%), including some with brain tumor-related epilepsy. In many cases, it will be very difficult to differentiate a psychogenic seizure event from a true epileptic seizure. However, there are a few features that are more likely to be related to a psychogenic seizure, including fluctuating, arrhythmic, "struggling"-type movements, pelvic thrusting, bizarre facial grimacing, body posturing, prolonged nonresponsiveness with motor arrest, and directed aggression during or after the ictal event.[29,30] In addition, retained consciousness, in spite of bilateral motor manifestations, is also quite typical for psychogenic seizure events. Routine EEG or prolonged video-EEG monitoring can confirm the psychogenic nature of the events by recording a lack of epileptiform and convulsive brain activity.

CLINICAL HISTORY AND PHYSICAL EXAMINATION

The clinical history is very important in the initial assessment of a "spell" or similar paroxysmal event of a brain-tumor patient.[1,7,8] Certain clinical features of the event, as well as the context of the event, can be helpful in determining if the event was a brain tumor-related seizure or some other type of spell, as listed in the differential diagnosis in Table 10.3. A detailed description of the event should be obtained from the patient, as well as available family and friends, especially if there is evidence of unconsciousness or reduced level of awareness, so that the patient cannot provide all of the essential details. The onset of the event should be explored (i.e., preictal phase)—in particular, if there was some type of aura or prodrome. Auras are typically long in syncopal and/or cardiac-related events and brief (several seconds) in epileptic seizures. Other aspects of the onset that should be discussed include any odors or smells that were present, feelings of déjà vu, auditory or visual hallucinations, sweating, feeling warm or hot, palpitations, facial discolorations, and various motor features (e.g., head turning, limb jerking, "convulsive" movements, or unusual posturing). The details of the actual event itself (i.e., ictal phase) should then be explored in detail, such as any effect on the level of consciousness or awareness, duration of the event, facial coloration, type of fall (if present; atonic, tonic), motor features (e.g., head turning and limb jerking that might be rhythmic, tonic-clonic, or more disorganized; convulsive movements; unusual posturing), tongue biting, and presence of any other injuries. The end of the event should also be discussed (i.e., postictal phase), especially the rapidity of recovery from any alteration of consciousness or awareness, the presence of prolonged confusion or disorientation, headaches, muscle aches, urinary and/or fecal incontinence, and the presence of any focal neurological deficits (e.g., reduced speech, focal weakness, visual loss, gait difficulty). In general, patients with cardiac and noncardiac syncope recover very quickly from the event, while the postictal phase of a seizure can often take much longer (minutes to hours). Tongue biting and urinary or fecal incontinence are rare in syncopal and nonepileptic events. The circumstances and context just prior to the event will also need to be reviewed, including the position of the patient (i.e., standing, sitting, supine), any changes in body position or head turning, strong emotions (e.g., fear, surprise, anger), amount of exercise and activity, eating or drinking, micturition, coughing, sneezing, or defecating. In addition, other clinical information will also need to be reviewed, such as the patient's age and general health, history or evidence of cardiac disease, history of alcohol consumption, family history of sudden death and syncope, and medications.

The medications should be reviewed in detail, to screen for any that have the potential to cause autonomic dysfunction, orthostatic changes, or cardiac arrhythmias. Furthermore, precipitating factors should be explored, such as stress, lack of sleep, dietary items (e.g., coffee, other caffeinated beverages), positional or postural changes, and fatigue.

The neurological examination is typically normal and nonfocal in patients with idiopathic epilepsy, as well as in patients with cardiogenic and noncardiogenic syncope and the other diseases listed in Table 10.3.[1,7,8] However, in patients with brain tumor-related epilepsy, there is a higher probability of having focal findings, especially in patients with higher-grade tumors (e.g., anaplastic astrocytoma, GBM).[5] The presence of focal findings, such as weakness (e.g., monoparesis, hemiparesis), expressive dysphasia, visual deficit with homonymous hemianopsia, ataxia, and asymmetric reflexes, increases substantially in the brain-tumor population. Findings on the general physical examination may be important clues to a nonepilepsy diagnosis for the paroxysmal event, such as the presence of orthostatic blood pressure, a heart murmur, cardiac rhythm abnormalities, carotid bruit, or an unusual affect.

NEUROIMAGING EVALUATION

Neuroimaging can be helpful in several different scenarios during the evaluation of possible brain tumor-related epilepsy. For example, it can be critical for patients with a first seizure, especially for those with focal neurological findings, where a mass lesion needs to be ruled out.[31–33] CTs and MRIs can also be helpful in screening for the presence of other intracranial abnormalities that could lead to a seizure and focal findings, such as an acute or old stroke, abscess, hemorrhage, focal infection, or vascular lesion.[33,34] In addition, neuroimaging can be important for the patient with a known brain tumor, who has never had seizures in the past and now has had a first seizure episode, as well as for the brain-tumor patient with well-controlled seizures who suddenly has a flare-up of seizure activity.[31] In both of these situations, follow-up imaging will be critical for determining whether or not the tumor has begun to grow and progress. Seizures are often one of the first clinical signs that a tumor is enlarging and progressing, because the growing mass often causes more damage and irritation in the peritumoral region where the epileptic foci develop.

MRI of most brain tumors reveals a mass that is hypointense on T1-weighted images and hyperintense on T2-weighted, fluid attenuated inversion recovery (FLAIR) sequences, and proton-density images.[31–33] The degree of enhancement is variable, depending on the vascularity of the lesion and the integrity of the blood-brain barrier (BBB) of intratumoral vessels. For the most common types of adult brain tumors—the gliomas (e.g., GBM, anaplastic astrocytoma, oligodendroglioma)—MRI will often reveal characteristic features, depending on the grade of the lesion. For low-grade tumors (i.e., WHO grades I and II), typical MRI features include mild expansion of affected brain regions, negligible surrounding edema, and minimal to no gadolinium enhancement (see Figure 10.1). These features are

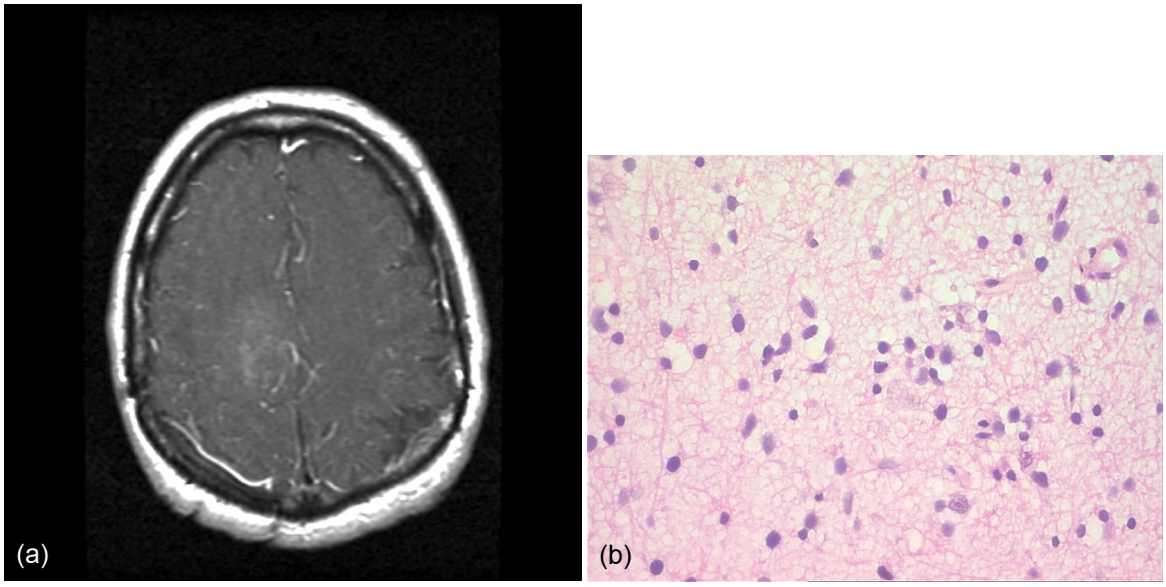

FIGURE 10.1 Fibrillary astrocytoma (WHO grade II). (a) T1-weighted gadolinium-enhanced MRI, demonstrating subtle patchy enhancement in the midsagittal central region of the brain. (b) Microscopic preparation revealing neoplastic astrocytes in a fibrillary matrix, with mildly increased cellularity and pleomorphism. No mitoses or hypervascularity is present (H & E @ 400×).

consistent with the histopathology of low-grade gliomas, which demonstrate mild cellularity and minimal vascular proliferation. High-grade tumors (i.e., WHO grades III and IV) are usually more infiltrative and expansile into surrounding brain (with a large region of T2-weighted hyperintensity that extends beyond the enhancing core), display significant amounts of peritumoral edema and mass effect, and they often demonstrate moderate to intense heterogeneous enhancement, which may have a central nonenhancing zone (i.e., regions of necrosis in GBM) (see Figure 10.2). These more aggressive imaging features are consistent with the pathology of high-grade gliomas, which include a high degree of cellularity, cellular and nuclear atypia, dense vascularity and vascular proliferation, diffuse infiltration into surrounding brain, and regions of necrosis. In general, brain metastases have a different appearance on MRI, presenting as one or more discrete masses that are hyperintense on T2-weighted and FLAIR images and densely enhance with gadolinium (see Figure 10.3).[32,33] Metastatic brain tumors often have significant amounts of peritumoral edema that may seem out of proportion to the size of the mass. These imaging characteristics are consistent with the pathology of brain metastases, which typically show a discrete nodule of tumor with minimal invasion or infiltration of the surrounding brain.

The presence of abnormal enhancement in a mass usually denotes breakdown of the BBB and implies the presence of a high-grade tumor.[31–33] In general, the enhancing region corresponds histologically to areas of tumor that have dense cellularity and neovascularization. Low-grade tumors that may show enhancement, but do not behave in an aggressive fashion, include oligodendrogliomas and pilocytic astrocytomas. Although a lack of enhancement is often consistent with low-grade pathology, up to a third of diffuse gliomas in adults are proven to be of high-grade at the time of biopsy.[35] The risk of a nonenhancing lesion having high-grade pathology is significantly dependent on age ($p = 0.025$), such that patients 45 years of age or older have a 50% chance of having an AA or GBM.

Other intracranial masses that can appear similar to a brain tumor on MRI include subacute infarction, solitary demyelinating plaques, hemorrhage, granulomatous lesions, parasitic infections, regions of necrosis, and vascular malformations (see Table 10.4).[31–33] Although diffusion-weighted images (DWI) can easily differentiate acute infarction from tumor (i.e., markedly hyperintense signal in the area of abnormality), subacute infarction can often be more challenging. If the DW images are equivocal, subacute infarction should be suspected by the presence of a gyral enhancement pattern, negligible or mild surrounding edema, and a lack of infiltration into surrounding brain structures. Large, tumefactive demyelinating lesions can also be difficult to discern from brain tumors in some patients. On MRI, they can appear similar to high-grade gliomas, with ill-defined borders, mass effect, perilesional edema, central necrosis, involvement of gray-matter structures, and variable amounts of enhancement. The presence of infiltration into and enlargement of surrounding brain structures, as well as

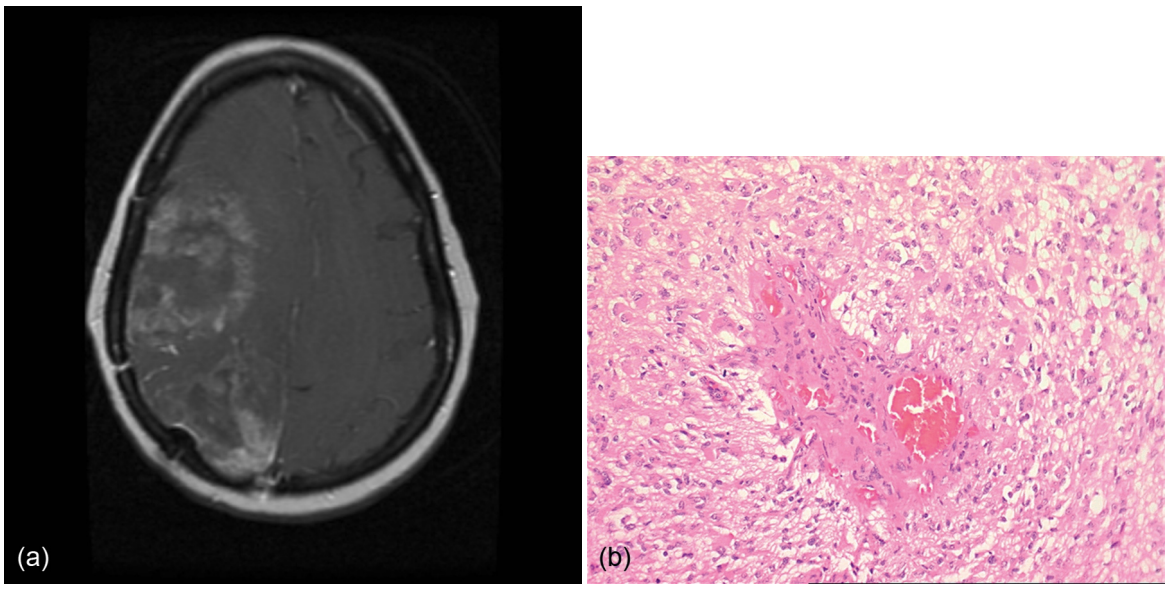

FIGURE 10.2 Glioblastoma multiforme (WHO grade IV). (a) T1-weighted gadolinium-enhanced MRI of a progressive tumor, with several large nodules of dense enhancement, surrounding central regions of nonenhancing necrotic material, peritumoral edema, and mass effect. (b) Microscopic preparation demonstrating a highly cellular tumor with marked cellular and nuclear pleomorphism, numerous mitoses, giant cells, and endothelial proliferation (H & E @ 200×).

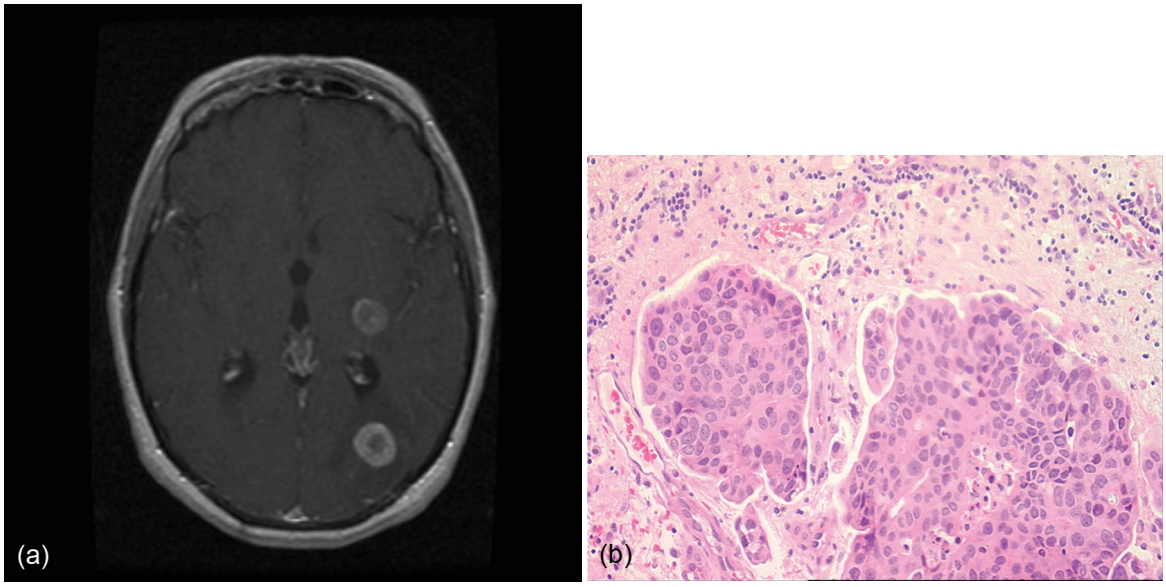

FIGURE 10.3 Metastatic lung carcinoma. (a) T1-weighted gadolinium-enhanced MRI showing two densely enhancing, well-circumscribed nodules of tumor, with mild surrounding edema. (b) Microscopic preparation of tissue from a metastatic brain tumor from a lung primary. Note the tumor nodules are sharply demarcated from surrounding brain parenchyma, with no infiltration (H & E @ 200×).

TABLE 10.4 Differential Diagnosis of Brain Tumor on MRI

Diagnosis	Comments
Abscess	Mature with capsule
Bacterial or fungal	
Infarction	Subacute
Demyelinating lesions	Large solitary plaque
Hematoma	Differentiate from tumor
With hemorrhage	
Granulomatous lesions	Tuberculosis, sarcoidosis
Parasitic infections	Cysticersosis
Necrosis	Postirradiation, etc.
Vascular malformations	Usually arteriovenous

Data adapted from the Refs. [31–33]

a more vigorous enhancement pattern, may be suggestive of a high-grade glioma. Primary intracranial hemorrhage, especially of the lobar variety, may appear similar to a hemorrhagic brain tumor. An underlying mass will usually become more apparent on subsequent neuroimaging as the blood products breakdown and resolve. Granulomatous lesions (e.g., tuberculosis, sarcoidosis), parasitic infections (e.g., cysticercosis), and vascular malformations can usually be differentiated from brain tumors by the pattern of brain involvement, presence of infiltration, amount of perilesional edema, and degree of enhancement.

In addition to DWI, other new MRI techniques that can be of benefit in the differential diagnosis of an intracranial mass lesion include proton magnetic resonance spectroscopy (MRS), perfusion-weighted imaging (PWI) modalities such as dynamic contrast-enhanced MRI (DCE-MRI), and diffusion tensor imaging (DTI).[31–33] Recent reports suggest that MRS can be of benefit in differentiating high-grade tumor from nonneoplastic mass lesions.[36] High-grade gliomas have a characteristic spectrographic signature, demonstrating an increase in the choline (CHO) peak, a decrease in the *N*-acetyl aspartate (NAA) peak, an increased CHO/creatine ratio, and, in some cases, the presence of a lactate peak (see Figure 10.4).[31,36] The increase in the CHO resonance results from amplified synthesis and turnover of membrane phospholipids and correlates with the cell density of high-grade gliomas. The decrease in NAA resonance is due to the loss of neurons within the tumor and infiltrated regions of the surrounding brain. Cerebral abscesses, regions of necrosis, and other nonneoplastic masses will not have an MRS signature consistent with a tumor. In most cases, the mass will not demonstrate a significant elevation of the CHO peak or the CHO/creatine ratio. A more-defined creatine peak in tissues surrounding a mass can be helpful in differentiating gliomas from MBT.[31] Metastatic tumors generally lack a creatine peak while, in the vast majority of gliomas, it is well defined.

PWI techniques rely on an assessment of blood flow into the mass in question, and they measure the relative cerebral blood volume (rCBV) of the lesion in comparison to contralateral normal white matter.[31–33,37] Most high-grade gliomas and MBT are well perfused and demonstrate high rCBV values. In contrast, nonneoplastic mass lesions (e.g., abscess, subacute infarction)

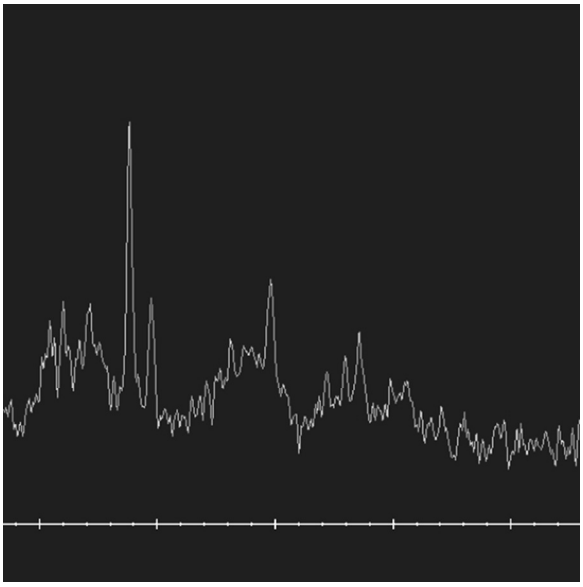

FIGURE 10.4 Magnetic resonance spectroscopy. MRS of an anaplastic glioma, demonstrating the typical features of elevated CHO peak and CHO/creatine ratio, and a reduced NAA peak.

usually have much lower rCBV values. Perfusion techniques can also be helpful in differentiating high-grade gliomas from other PBT and certain types of MBT.[33,37] Primary CNS lymphomas tend to have significantly lower rCBV's than gliomas and have a characteristic intensity-time curve profile, due to intense early leakage of contrast media into the interstitium.

DTI is a new MR technique that analyzes the diffusion properties of water in three-dimensional space in the region around a mass, providing information on the status and integrity of white matter tracts (i.e., displaced, edematous, infiltrated, disrupted).[31–33,38] The physics of DTI involves the principle that the diffusion of water molecules parallel to the white matter tracts is less restricted than water diffusion perpendicular to the tracts. Therefore, there will be higher diffusion-gradient encoded signals perpendicular to the white matter tracts than parallel to the tracts. High-grade gliomas tend to have DTI abnormalities that are larger and more extensive than corresponding T2-weighted images, due to their tendency to invade surrounding normal brain. This is in contrast to nonneoplastic mass lesions (e.g., abscess, subacute infarct, demyelinating plaque), low-grade gliomas, and MBT, which do not demonstrate significant brain invasion and have DTI and T2-weighted images that are of similar size.

Perfusion techniques, in particular DCE-MRI, have also been applied to the preoperative grading of glial tumors.[31–33,37] In general, these methods demonstrate a high correlation between the degree of perfusion of a given lesion and the grade. Tumors with high perfusion tend to have a higher vascular density and to be of higher grade. There appears to be a correlation between rCBV, tumor vessel permeability, and glioma grade, with the ability to discriminate between low-grade (WHO I and II) and high-grade (WHO III and IV) lesions. When correlating with survival, CBV has been shown to be superior to conventional MRI evidence of enhancement. In general, elevated rCBV seems to be a sensitive, but not specific, marker for high-grade histopathology. Some low-grade tumors, especially oligodendrogliomas, may have high rCBV foci.

Some authors have also been attempting to correlate the presence or absence of contrast enhancement with molecular and proteomic signatures.[31–33,39] Preliminary data suggests that contrast-enhanced (CE) and noncontrast-enhanced (NCE) regions have distinct proteomic signatures, indicating differential gene expression profiles between these regions of tumor. In addition, similar to what is observed at the histopathological level, there was heterogeneity in the CE proteomic signature between different regions of the same tumor. NCE areas of tumor tended to have similar proteomic profiles between patients, whereas the CE regions were more distinct and specific to an individual tumor.

CLINICAL AND ELECTROPHYSIOLOGICAL WORK-UP

Once the history of the paroxysmal event has been clarified, and the patient has been examined and imaged as necessary, a work-up and diagnostic evaluation will often be required to finalize the etiology of the spell.[7,8,12] If the history suggests the event involved a syncopal episode or similar transient loss of consciousness and may be cardiac in origin, then several basic investigations will be required.[8,40] All patients will need basic blood work to evaluate hemoglobin, hematocrit, electrolytes, serum creatinine, and blood glucose. A 12-lead ECG will be necessary to screen for potential arrhythmias, including sinus bradycardia (<40 bpm), Mobitz type II AV block, complete AV block, alternating right and left bundle branch block, paroxysmal tachycardia, ventricular tachycardia, pacemaker or implantable cardioverter defibrillator malfunction, Q waves suggesting myocardial infarction, and long or short QT intervals. If the initial ECG is nondiagnostic or the patient is older than 40 years of age, then a prolonged ECG should be performed. Holter monitoring for 24-48 h is recommended for patients with fairly frequent episodes. The gold standard for this type of monitoring would be a strong correlation between a symptomatic event and a documented arrhythmia on the recording. On occasion, arrhythmias without symptoms can also be diagnostic, such as prolonged asystole for longer than 3 s, rapid

supraventricular tachycardia, and rapid ventricular tachycardia. For patients with rare or uncommon episodes (<1-2 per month), external or implantable/internal event monitoring (i.e., loop recorder) is recommended. In patients with a concern for structural cardiac disease, an echocardiogram may be necessary to screen for valvular stenosis, cardiomyopathies, and other abnormalities. In selected patients, head-up tilt table testing will be necessary to differentiate various diagnoses that can cause syncope and transient loss of consciousness.[8,12,40] Tilt testing is very helpful in diagnosing NMS, and in differentiating it from delayed orthostatic syncope. In addition, it can differentiate convulsive syncope from epileptic forms of transient loss of consciousness. A pathological response during tilt table testing is diagnosed when the procedure causes a reflex hypotension or bradycardia with reproduction of syncope (NMS), or of progressive hypotension with or without symptoms (OH-related syncope).[40] Tilt table testing may also be able to discern psychogenic pseudosyncope in some patients. Cardiac electrophysiological testing may be helpful in some patients, in the context of known cardiac disease, to screen for ventricular tachycardia and sinus node dysfunction.[40] Rarely, carotid sinus massage will be required as part of the evaluation, and should be reserved for patients over 40 years of age with syncope and transient loss of consciousness who have a negative cardiac work-up, including tilt table testing.[8,40] It should be performed for 5-10 s in the supine position first, and, if negative, it should then be performed in the upright position. A pathological response is diagnosed if a ventricular pause of at least 3 s coincides with a drop in systolic blood pressure of 50 mmHg. For patients with syncope or transient loss of consciousness that seem to be related to exercise (i.e., occurred during or shortly after; related to coronary artery disease), formal exercise stress testing is indicated.[8,40]

For neurological and noncardiac causes of syncope, as well as nonsyncopal forms of transient loss of consciousness, other diagnostic tests will be necessary to formalize the cause of the paroxysmal event.[7,8,12] Patients with suspected cerebrovascular disease and TGA will require MRI (especially diffusion sequences), MR angiography, carotid ultrasound, echocardiogram, and other testing as needed. Metabolic, toxic, and medication-related events can also be clarified by the appropriate blood work and drug levels. Patients with suspected narcolepsy or other sleep disorders will need to undergo multiple sleep latency testing and polysomnography. Migraine headaches can be diagnosed by a careful and detailed history and negative neuroimaging evaluation.

In the brain-tumor patient with an event that is very suspicious for a seizure, the history may be enough to verify the diagnosis. For example, if the patient is having spells that consist of intermittent episodes of sensing a "bad smell" similar to burnt rubber, or brief intense moments of déjà vu, or a combination of these types of events, and the patient has a glial tumor in the anterior medial temporal lobe, then further testing may not be warranted. Similarly, if the spells consist of abrupt speech arrest and abnormal motor movements or clonic activity of the contralateral upper extremity, and the patient has a tumor in the dominant inferior frontal region near Wernicke's area, then the diagnosis of a seizure is unequivocal. However, many brain-tumor patients have events and spells that are much more vague and difficult to classify. In this large group of patients, further testing will be needed and may require some of the above-noted investigations for syncope, but will often also involve an EEG.[5,7,8] The initial EEG should be performed with the patient awake and asleep, and the test should include activation procedures, including hyperventilation and photic stimulation.[41] Special electrodes (e.g., true temporal, nasopharyngeal, sphenoidal) will sometimes be helpful in increasing the detection of mesial frontal or temporal abnormalities. In some cases, the patient may be asked to reproduce the conditions that are likely to precipitate or induce the spell, while the EEG is recording. It is common for the EEG to show a slow-wave focus in the region overlying the brain tumor. However, not all EEG recordings will show electrographic seizures or epileptiform activity. In fact, interictal epileptiform abnormalities are only detected in approximately 50% of patients using the first EEG.[7,42] Interictal epileptiform abnormalities are detected in roughly 84% of patients by the third EEG and in 92% by the fourth. In rare cases, the EEG may even remain normal during an actual seizure event, especially in the case of partial seizure activity. When the EEG is positive, it can demonstrate electrographic seizure activity or interictal epileptiform abnormalities, including PLEDs (periodic lateralized epileptiform discharges; see Figure 10.5). In selected cases, more prolonged EEG monitoring may be required, including spending time in an inpatient epilepsy monitoring unit (EMU) for a more comprehensive investigation and characterization of ongoing seizure activity, as part of a work-up for consideration of epilepsy surgery and to adjust anticonvulsant regimens (see Figure 10.6).[41,43] Long-term monitoring in an EMU is more likely to delineate the seizure-onset zone, which is critical for consideration of brain-tumor epilepsy surgery. In addition, it can demonstrate additional information regarding seizure activity that can prompt a change in the anticonvulsant regimen in up to 28% of cases.[44] A more detailed and comprehensive review of the neurophysiological evaluation of epilepsy patients can be found in Chapter 8.

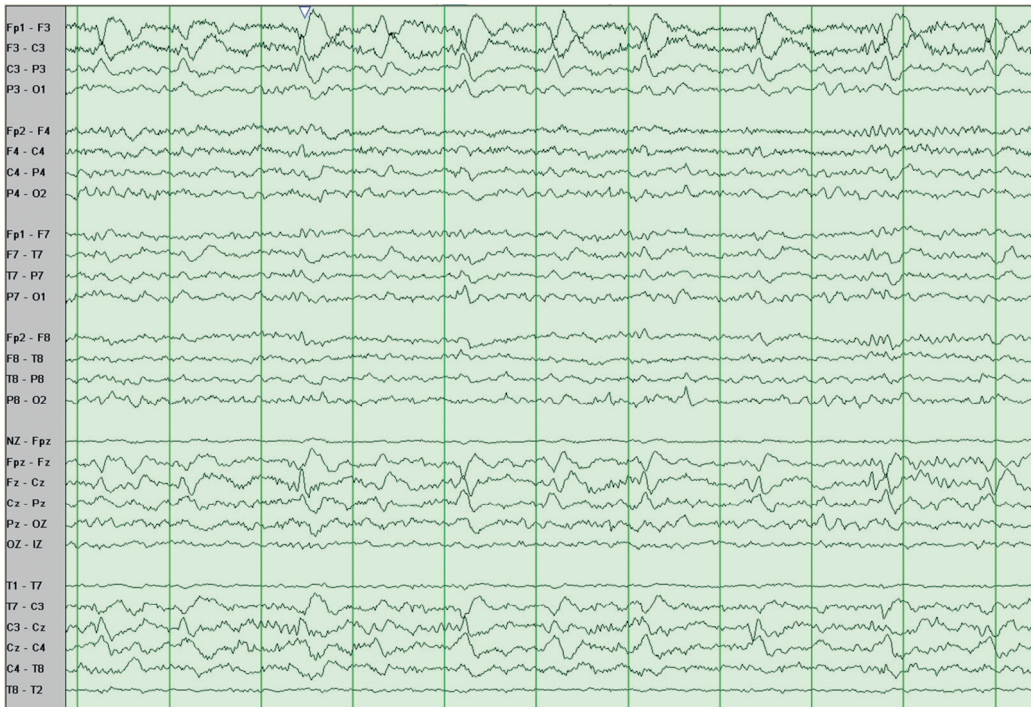

FIGURE 10.5 Routine EEG from a 37-year-old male with an anaplastic oligodendroglioma of the deep left frontal region. The EEG shows PLEDs in the left central region.

EFFECTS OF ONCOLOGICAL THERAPY ON BRAIN TUMOR-RELATED EPILEPSY

In addition to the use of anticonvulsant medications, which we address in detail in Chapters 11-13, tumor-directed oncological therapies have also been shown to reduce seizure frequency and intensity in patients with brain tumor-related epilepsy.[5,45,46] Surgical resection of the tumor with or without attention to the epileptogenic focus, radiotherapy, and chemotherapy have all been demonstrated to potentially improve seizure control. Surgical removal of tumor tissue—especially an aggressive gross total resection or extensive subtotal resection—has also been associated with an improvement in seizure control and a reduction in seizure frequency by up to 70% or more.[5,45,46] When more sophisticated neurosurgical techniques are used to define the complete extent of tumor involvement and the epileptogenic focus, such as fMRI, Wada testing, DTI, awake craniotomy with electrostimulation, depth electrodes, and magnetoencephalography, the reduction in seizure frequency and percentage of patients with seizure freedom will be even higher. For example, when patients with medical refractory brain tumor-related seizure activity are treated with an aggressive oncological surgical resection, the percentage that achieve seizure freedom ranges from 65% to 77%.[47,48] When the tumor resection is combined with an epileptic focal lesionectomy, the percentage of seizure freedom increases to 82-92%.[49–51] The more aggressive approach, with lesionectomy of the epileptic focus in addition to an attempted gross total resection of the tumor, should always be considered in patients with a low-grade glioma (i.e., WHO grade I and II) who do not have any neurological deficits and have poor seizure control as their main symptom. This approach would not be recommended for highly infiltrative gliomas or for higher-grade tumors that are rapidly growing and cannot have treatment delayed for a lesionectomy work-up. Surgical tumor resection with epileptic-focus lesionectomy is most likely to be successful and result in seizure freedom in patients with seizure activity durations of less than 1 year.[52] Those with medically refractory epilepsy and simple partial seizures are less likely to attain seizure freedom from this procedure.

Radiotherapy (RT) has also been shown to reduce seizure frequency in selected patients.[5,45,46] In a report by Rogers and colleagues, five patients with biopsy-proven but unresected cerebral low-grade astrocytomas had medically refractory epilepsy for 7 months to 27 years.[53] They were all treated with irradiation at 5400-6120 cGy, which reduced seizure frequency by more than 90% in three patients and by more than 75% in another patient, with one patient showing no response. In three of the four patients with reduced seizure frequency, CT or MRI produced evidence of tumor shrinkage. In a similar study of nine patients with brain tumors and refractory epilepsy treated with RT, five achieved seizure freedom,

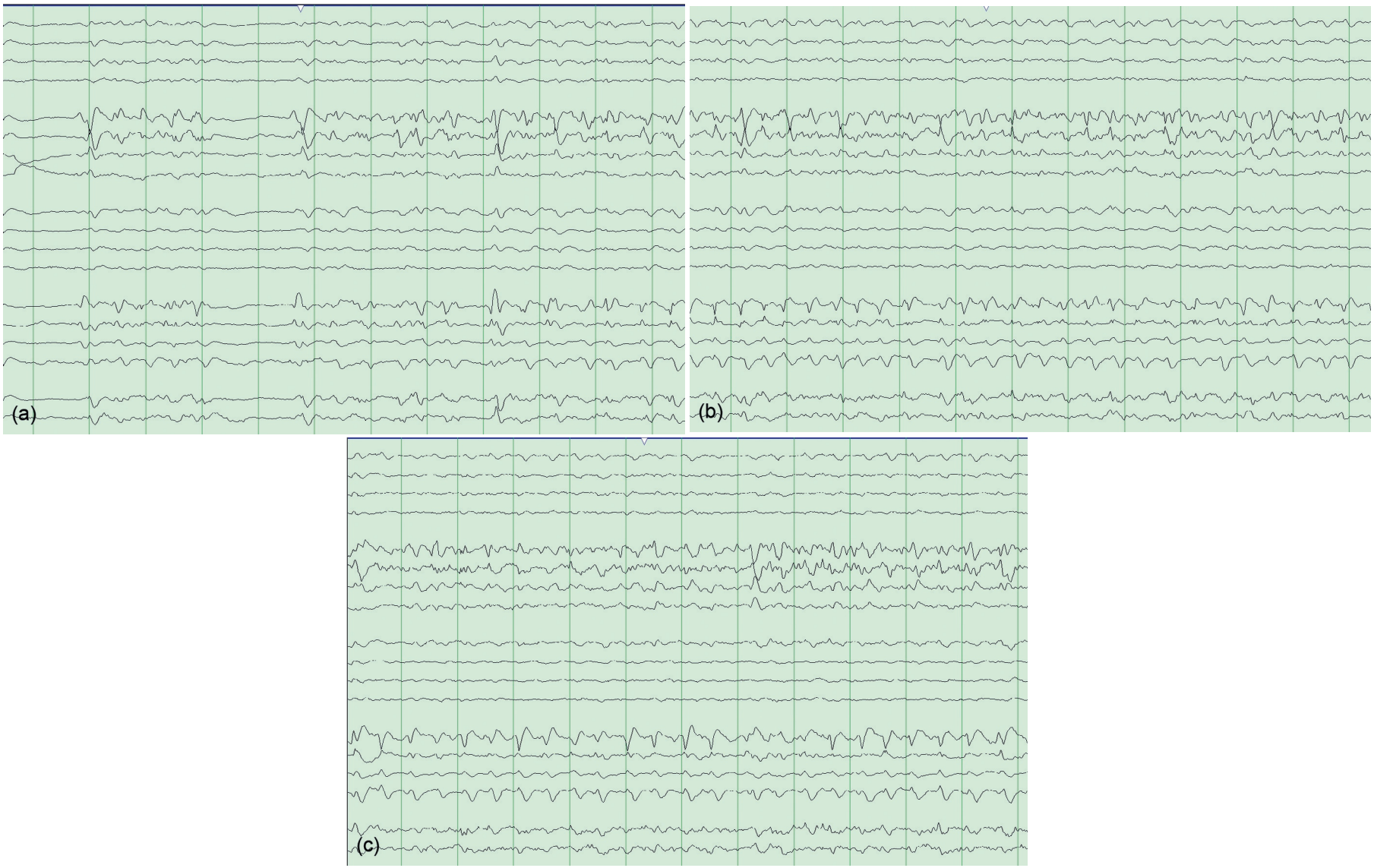

FIGURE 10.6 EMU recordings from a 66-year-old male with a GBM in the right frontal-temporal region. (a–c) The EEG demonstrates PLEDs that evolve into an electrographic seizure, before resolving into focal slowing and sharp waves.

and the other four experienced seizure reductions of greater than 75%.[54] Stereotactic radiosurgery with Gamma Knife has also been reported to reduce seizure frequency in brain-tumor patients.[55]

Several studies also suggest that chemotherapy can have a positive impact on seizure frequency in brain-tumor patients.[5,46,46] In a report from Pace and colleagues, 43 patients with low-grade gliomas were treated with temozolomide (TEM) at the time of documented tumor progression.[56] In 31 of the patients, the predominant presenting symptom was uncontrolled seizure activity. There was a reduction in seizure frequency in 15 (48%) of the seizure cohort, with 6 cohort members achieving complete seizure control and nine achieving partial seizure control. A similar study by Brada and colleagues evaluated 30 patients with low-grade gliomas who had undergone surgery followed by TEM chemotherapy.[57] Fifteen of the 28 patients (54%) with epilepsy as their main symptom experienced a reduction in seizure frequency while on TEM treatment, and 6 were able to achieve complete seizure freedom. A more recent study evaluated 39 patients with low-grade gliomas who were treated with surgery and TEM and compared them to 30 patients treated with surgery alone.[58] There was a significant difference in reduced seizure frequency in favor of the cohort receiving active treatment with TEM: 59% of the TEM group and only 13% of the nontreatment group showed a reduction of >50% ($p < 0.001$). In a small study of 10 patients with symptomatic nonresectable low-grade astrocytomas, treatment consisted of "first-line" chemotherapy with a nitrosourea-based regimen.[59] All of the patients responded with an improvement in seizure frequency, with 60% of them becoming seizure-free.

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CHAPTER

11

Antiepileptic Drugs: First Generation

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CHAPTER CONTENTS

Anticonvulsant medications, often called antiepileptic drugs (AEDs), are sometimes classified by the "generation" in which they were developed and introduced. This chapter focuses on pharmacologic properties and clinical use of first-generation AEDs; i.e., those anticonvulsants developed and introduced between 1912 and 1978 prior to the more rigorous placebo controlled trials currently required by the Food and Drug Administration and that are still in common use. These include carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, and valproate.[1,2] Anticonvulsants are different from other drugs in that they are not classified by mechanism of action, but simply grouped under the heading of anticonvulsant secondary to the mechanism of action of each drug being both not fully understood and likely multiple in nature.[3]

CARBAMAZEPINE

Developed for the treatment of epilepsy in Europe in 1960 and quickly explored for the treatment of trigeminal neuralgia, carbamazepine was introduced into use in the United States in 1974.[1,4] In addition to its ongoing use in the industrialized world, carbamazepine is one of the most used AEDs in the developing world.[5] The main mechanism of action attributed to carbamazepine is blockade of voltage-gated sodium channels with selective binding to the inactive form of the channel. The clinical contribution of carbamazepine's binding ability at benzodiazepine receptors and antagonistic actions at calcium channels is unclear.[6] Carbamazepine has been successfully tested in animal models of epilepsy such as the maximal electroshock seizure model and amygdaloid electrically kindled seizures.[7]

Carbamazepine demonstrates a bioavailability of 70-80%, and protein-binding estimates range from 72% to 81%.[6,8] The metabolism of carbamazepine occurs mainly in the liver, mostly by isoenzyme CYP3A4.[6,9] Less than 2% of carbamazepine is excreted in the urine. No dose adjustment is needed in renal disease.[6,10]

Carbamazepine is available in immediate and extended-release formulations. Recommended dosing of carbamazepine in adults is 400-1600 mg a day divided two to three times a day.[11] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for carbamazepine is 4-12 mg/L.[9] See Table 11.1 for clinical characteristics. The half-life of carbamazepine in adults ranges from 12-35 h, which changes with metabolic auto-induction. Steady state is reached in 3-4 days.[6,9] Enteral feeding may interfere with carbamazepine absorption and thus lower serum level.[6]

TABLE 11.1 First-Generation AED Clinical Characteristics

First-Generation AED	Seizure Type	Starting Dose		Half-Life (h)	Target Therapeutic Range (mg/L)
		Oral (mg/day)	Intravenous in Status Epilepticus		
Carbamazepine	Partial onset with secondary generalization	400	n/a	12-35	4-12
Ethosuximide	Absence	250	n/a	30-60	40-100
Phenobarbital	Generalized	60	10-20 mg/kg	75-120	10-40
Phenytoin	Partial onset with secondary generalization	300	10-20 mg/kg	8-42	10-20
Primidone	Generalized	100	n/a	6-12	5-12
Valproate	Generalized	250	25-30 mg/kg	6-17	50-100

Carbamazepine is indicated for complex partial and generalized tonic clonic seizures.[11] Multiple randomized and double-blind studies have been performed comparing carbamazepine to phenobarbital, phenytoin, primidone, and valproate; they have demonstrated no difference in total efficacy among these medications, with the percent of patients achieving total seizure control on carbamazepine ranging from 34% to 66%.[12–16] There have been mixed results in the same studies regarding the subgroup of patients with generalized tonic clonic seizures. Equal efficacy has been demonstrated in this subgroup (carbamazepine 48% seizure control) compared with phenytoin, phenobarbital, and primidone and inferior efficacy when compared to phenytoin (carbamazepine 39% seizure control).[14] Of note, this last population of patients included a mixture of primary generalized and secondary generalized epilepsies. In comparisons made on patients with complex partial seizures, carbamazepine has demonstrated equivalent efficacy of total seizure control (34%) in one study[14] and superiority (43%) compared to phenobarbital and primidone in another.[13] Additionally, in patients with complex partial seizures who did not reach total seizure control, carbamazepine demonstrated superior action compared to valproate in decreasing the rate of seizures experienced per month.[15] Three meta-analyses have been performed comparing carbamazepine with phenytoin, phenobarbital, and valproate respectively.[17–19] The main measures of the analysis were time to withdraw, time to 12-month remission, and time to first seizure. Carbamazepine was superior to phenobarbital and valproate in control of partial onset seizures on the measure of time to first seizure following randomization and superior to valproate on the measure of time to 12-month remission. There were no other significant differences in comparable efficacy noted. Carbamazepine was found to have a clear advantage compared to phenobarbital on the metric of time to withdrawal mostly because of adverse effects in the latter. In an evidence-based, structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis.[20,21] In this, carbamazepine had Class I evidence (randomized trial meeting select criteria for superior clinic design) of superior efficacy and thus evidence of established efficacy (Level A recommendation) for monotherapy of partial onset seizures in adults. With a paucity of Class I and II randomized trials for adults with generalized tonic clonic seizures, carbamazepine has evidence of possible efficacy (Level C recommendation) for monotherapy in primary generalized onset seizures. Given carbamazepine's efficacy in partial onset seizures, more recent studies with newer medications have adopted carbamazepine as the standard to which noninferiority of the new drugs are compared.[22] There is, however, Class IV (nonrandomized or uncontrolled) evidence suggesting that carbamazepine can aggravate generalized type seizures, which can include tonic clonic seizures.[20,21]

The most common adverse reactions with the use of carbamazepine are dizziness, drowsiness, unsteadiness, nausea, and vomiting.[6,9,11] Transient leukopenia can be seen in 10-20% of patients with persistence in about 2%. Idiosyncratic hyponatremia may also appear.[6,9,11] This is frequently asymptomatic, but with longer use of higher doses may become symptomatic, including the aggravation of seizures. As with many of the AEDs, carbamazepine carries a warning of increased risk of suicidal ideation.[11] Severe idiopathic responses have also been documented, including toxic epidermal necrolysis, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), hepatotoxicity, and aplastic anemia.[6] The serious dermatologic reactions are strongly associated with Asian ancestry and the presence of the HLA-B*1502 or the HLA-A*3101 allele.

Carbamazepine is Pregnancy Category D with a relative risk of major congenital malformation, mostly cleft

palate, of 1.6. This risk is enhanced in the setting of polytherapy. There have been reports of blood clotting deficiency in infants born to women taking carbamazepine with subsequent recommendations of oral vitamin K supplementation during the last month of pregnancy, although this has not been supported adequately in the literature.[23]

Carbamazepine induces multiple liver isoenzymes and thus has significant interactions with other drugs, including antiepileptic and antineoplastic preparations (see Table 11.2). Of note, carbamazepine demonstrates auto-induction of its own metabolism within the first month decreasing its half-life to 10-20 h for chronic therapy. The main isoenzymes induced by carbamazepine are CYP1A2, CYP2C, CYP3A, and UGT.[6,9] Medications with increased clearance secondary to administration of carbamazepine include 9-aminocamptothecin, acetaminophen, albendazole, alprazolam, aprepitant, azoles, bupropion, calcium channel blockers, citalopram, CCNU, clobazam, clonazepam, clozapine, corticosteroids, cyclophosphamide, cyclosporine, desipramine, dicoumarol, dihydropyidine, doxepin, doxycycline, erythromycin, ethosuximide, everolimus, felbamate, glufosfamide, haloperidol, imatinib, lamotrigine, lapatinib, levothyroxine, midazolam, methadone, methotrexate, olanzapine, oral contraceptives, oxcarbazepine, paliperidone, paclitaxel, phenytoin, primidone, praziquantel, procarbazine, protease inhibitors, remacemide, rifampicin, risperidone, sirolimus, tadalafil, temozolomide, temsirolimus, teniposide, thiotepa, theophylline, tiagabine, topiramate, tramadol, trazodone, tricyclic antidepressants, valproate, vincristine, warfarin, ziprasidone, and zonisamide.

Conversely, serum carbamazepine levels are also influenced by other drugs.[6,8] Agents that inhibit CYP3A4 metabolism increase carbamazepine levels. These include acetazolamide, aprepitant, azoles, cimetidine, ciprofloxin, danazol, dantrolene, diltiazem, fluoxetine, fluvoxamine, ibuprofen, isoniazid, lithium, loratadine, loxapine, macrolides, nefazodone, niacinamide, olanzapine, omeprazole, oxybutynin, propoxyphene, protease inhibitors, quetiapine, quinine, remacemide, terfenadine, ticlopidine, trazodone, verapamil, and valproate. Agents that induce CYP3A4 and thus decrease plasma carbamazepine levels include aminophylline, cisplatin, cyclosporine, doxorubicin, felbamate, phenobarbital, phenytoin, primidone, rifampin, sertraline, theophylline, zonisamide, zopiclone.

ETHOSUXIMIDE

Preceded by several forerunning related compounds with significant adverse side effect profiles, ethosuximide was developed for use in childhood onset absence (petit mal) epilepsy in 1958 by Zimmerman and Burgemeister.[26] Although restricted in scope of applicable seizure types, it remains a first-line agent for the treatment of childhood onset absence epilepsy.[27]

The main mechanism of action attributed to ethosuximide is alteration of spontaneous thalamic synchronizing mechanisms via reduction of low-threshold T-type calcium currents in thalamic neurons.[28] Ethosuximide is effective in animal models of primary generalized epilepsy, including subcutaneous pentylenetetrazol induced seizures and spike wave discharges in genetically prone mice.[7]

Ethosuximide has near total bioavailability (95%) with 0% protein binding and a volume of distribution of 0.6-0.7 L/kg. The half-life is long and varies by age, with 30-40 h in kids and 40-60 h in adults.[8,28] In adults, ethosuximide reaches steady state in 10-12 days. The primary elimination is metabolism via CYP3A and only 10-20% excreted unmetabolized in the urine.[28,29] There are no recommended dosage adjustments in renal or liver disease, but given the lack of protein binding, there is a significant likelihood of removal by dialysis and close monitoring and subsequent supplementation is recommended.[10,28]

Starting dosage for ethosuximide differs between children and adults. In children, the starting dose is 10-15 mg/kg/day with titration to a response range of 15-40 mg/kg/day. In adults, dosing begins at 250 mg and the medication is titrated to a response range of 750-1500 mg/day. Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for ethosuximide is 40-100 mg/L.[29,30] See Table 11.1 for clinical characteristics.

Ethosuximide is indicated only for absence (petite mal) epilepsy.[30] Initial small, nonrandomized studies of the compound demonstrated varying efficacy (19-73%).[31–33] Later, small, randomized, but unblinded trials also demonstrated efficacy of ethosuximide in the treatment of absence seizures.[34] There remains a dearth of randomized double-blind clinical trials of ethosuximide in epilepsy.[35] In an evidence-based, structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis. With a paucity of Class I and II randomized trials for children with absence seizures, ethosuximide has evidence of possible efficacy and carries a Level C recommendation for monotherapy in this population.[20,21]

Common adverse reactions to ethosuximide include gastric discomfort, anorexia, nausea, vomiting, tiredness, headache, and imbalance. Psychosis in children with a history of mental illness has also been reported. Rare, severe idiosyncratic reactions include leucopenia, pancytopenia, and aplastic anemia and systemic lupus

TABLE 11.2 First-Generation AED Interaction with Other AEDs and Antineoplastic Agents

First-Generation AED	Other Drugs Affected by the First-Generation AED		Effect of Other Drugs on the First-Generation AED	
Carbamazepine	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	AEDs: Clobazam Ethosuximide Felbamate Lamotrigine Oxcarbazepine Phenytoin Primidone Tiagabine Topiramate Valproate Zonisamide Antineoplastic: 9-Aminocamptothecin CCNU Cyclophosphamide Everolimus Glufosfamide Imatinib Lapatinib Methotrexate Paclitaxel Procarbazine Temozolomide Temsirolimus Teniposide Thiotepa Vincristine		AEDs: Felbamate Phenytoin Phenobarbital Primidone Zonisamide Antineoplastic: Cisplatin Doxorubicin	AEDs: Valproate
Ethosuximide	Addition to phenobarbital may exacerbate absence seizures			
	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
			AEDs: Carbamazepine Phenobarbital Primidone	
Phenobarbital	Addition to ethosuximide may exacerbate absence seizures The combination with ifosfamide my result in encephalopathy The interaction with phenytoin is unclear, level monitoring of each drug is recommended			
	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	AEDs: Carbamazepine Clobazam Ethosuximide Lamotrigine Tiagabine Topiramate Valproate Zonisamide Antineoplastic: 9-Aminocamptothecin Cyclophosphamide Etoposide Glufosfamide Irinotecan Methotrexate Paclitaxel Procarbazine		AEDs: Carbamazepine	AEDs: Felbamate Stiripentol Valproate

TABLE 11.2 First-Generation AED Interaction with Other AEDs and Antineoplastic Agents—cont'd

First-Generation AED	Other Drugs Affected by the First-Generation AED		Effect of Other Drugs on the First-Generation AED	
Phenytoin	The interaction with phenobarbital is unclear, level monitoring of each drug is recommended			
	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	AEDs: Carbamazepine Clobazam Ethosuximide Felbamate Lamotrigine Oxcarbazepine Primidone Tiagabine Topiramate Valproate Zonisamide Antineoplastic: 9-Aminocamptothecin Cyclophosphamide Etoposide Gefitinib Glufosfamide Ifosfamide Imatinib Irinotecan Methotrexate Paclitaxel Procarbazine Temozolomide Temsirolimus Teniposide Thiotepa Topotecan Vincristine		AEDs: Vigabatrin Antineoplastic: Bleomycin Methotrexate Carmustine Vinblastine Vincristine	AEDs: Oxcarbazepine Rufinamide Stiripentol Topiramate Antineoplastic: Fluorouracil
Valproate	Coadministration with topiramate may result in hyperammonemia Coadministration with cisplatin, etoposide or fotemustine increases risk of thrombocytopenia			
	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	Antineoplastic: Irinotecan	AEDs: Carbamazepine Ethosuximide Lamotrigine Phenytoin Phenobarbital Antineoplastic: Paclitaxel	AEDs: Carbamazepine Phenytoin Phenobarbital	AEDs: Felbamate

erythematosus-related syndromes can occur. Ethosuximide is Pregnancy Category C.[28–30]

Ethosuximide demonstrates few interactions with other drugs (see Table 11.2). Adding ethosuximide to phenobarbital therapy may exacerbate absence seizures. Carbamazepine, phenobarbital, primidone, and rifampicin increase clearance of ethosuximide. Isoniazid reduces clearance of ethosuximide. Data is mixed on the effects of valproate on ethosuximide clearance.[24,28,29]

PHENOBARBITAL

Phenobarbital was introduced for the treatment of epileptic seizures in 1912 by Hauptmann, who was fortuitously utilizing the drug as a hypnotic in this population.[36–38] Given its efficacy, by 1940, it was the most widely used antiepileptic but had already garnered a reputation for lack of tolerability.[38,39] Currently, it is not a favorite choice in industrialized countries but remains widely used in the developing world.[5,37,40]

The main mechanism of action put forth for phenobarbital is enhancement of GABA inhibition through enhanced postsynaptic $GABA_A$ chloride currents.[28] Phenobarbital has been demonstrated in animal models of epilepsy, including minimum and maximum electroshock seizures, chemically induced myoclonic seizures, light-induced seizures, and amygdaloid electrically kindled seizures.[7]

Phenobarbital demonstrates a near full bioavailability at 80-90% with a volume of distribution of 0.5-0.9 L/kg in adult patients. Phenobarbital is not highly protein bound, with data estimates varying between 45% and 60% in adults.[8,28] Although it is mainly eliminated by metabolism through glucosides, CYP2C9, CYP2C19, and CYP2E1, up to 25% of phenobarbital can be excreted by renal mechanisms.[28,41] Given this, there is a risk of intoxication with drug and metabolite buildup in renal disease. Monitoring the patient with a possible slight reduction in dosing may be necessary. Supplementation after dialysis may be required.[10,28]

Recommended dosing of phenobarbital in adults is 60-200 mg/day, with the data suggesting that 0.9-1.75 mg/kg/day in adults over the age of 15 yields an average plasma concentration of 15 mg/L.[42] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for phenobarbital is 10-40 mg/L.[8] See Table 11.1 for clinical characteristics. With a long half-life in adults of 75-120 h, phenobarbital slowly reaches steady state in about 3 weeks.[28,41]

Intravenous phenobarbital is used in the treatment of refractory status epilepticus. Dosing can range from 10 to 20 mg/kg. The use of such high doses of phenobarbital can cause respiratory depression and depression of central cardiovascular function, which can contribute to a "shock-like" condition requiring medical support.[43–45]

Phenobarbital is indicated for the treatment of partial and generalized seizures and is considered by the World Health Organization as first-line therapy for both in developing countries.[5,42] A randomized, double-blind control study compared phenobarbital with phenytoin, carbamazepine, and primidone in patients with "untreated and undertreated" seizures.[13] Overall, the probability of obtaining complete seizure control was not different between the drugs, with phenobarbital garnering a 36% remission rate. Complete control of tonic clonic seizures was also similar among the drugs, as phenobarbital reached a 43% rate of seizure control. Phenobarbital was, however, inferior to carbamazepine in total control of partial seizures with a 16% rate. When studied in patients with newly diagnosed epilepsy, phenobarbital, phenytoin, carbamazepine, and sodium valproate demonstrated no significant difference in efficacy, with phenobarbital achieving a 35% 1-year remission rate.[16] Phenobarbital was found, however, to be inferior in tolerability, with a significantly greater number of patients withdrawn from the study secondary to adverse side effects, predominantly drowsiness and lethargy. Two meta-analyses have been performed comparing phenobarbital with carbamazepine and phenytoin, respectively.[17,46] The main measures of the analysis were time to withdraw, time to 12-month remission, and time to first seizure. For efficacy, phenobarbital was equally efficacious in seizure control overall with inferiority demonstrated when compared to carbamazepine in regard to partial onset seizures. In both meta-analyses phenobarbital was inferior in tolerability with decreased time to withdraw compared with either carbamazepine or phenytoin. In an evidence-based, structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis. In this, phenobarbital had evidence of possible efficacy (Level C recommendation) for monotherapy of partial onset seizures in adults given Class I evidence (randomized trial meeting select criteria for superior clinic design) for inferior efficacy compared to carbamazepine but equal efficacy demonstrated in three Class III (randomized but inferior comparison design) trials. Phenobarbital also carries a Level C recommendation for monotherapy in primary generalized onset seizures.[20,21] A review of observational studies performed in developing countries calls into question the purported neurotoxicity of this agent.[37,40]

The primary side effects of phenobarbital are secondary to central nervous system depressant effects with somnolence, lethargy, and vertigo being most common. Barbiturates may be habit forming with tolerance, psychological dependence, and physical dependence potentially occurring.[28,42]

Phenobarbital is Pregnancy Category D with a relative risk of major congenital malformation of 4.2. This risk is enhanced in the setting of polytherapy. There have been reports of blood clotting deficiency in infants born to women taking phenobarbital with subsequent recommendations of oral vitamin K supplementation during the last month of pregnancy, although this has not been supported adequately in the literature.[23]

Phenobarbital has significant interactions with other medications (see Table 11.2). The concomitant use of central nervous system depressants, including sedatives, hypnotics, antihistamines, tranquilizers, or alcohol, may produce additive depressant effects.[28,42] Phenobarbital can interact in a pharmacodynamic way with ifosfamide to result in encephalopathy.[25]

Phenobarbital is a general inducer of liver enzymes, including CYP1A, CYP2A6, CYP2B, CYP2C, CYP3A, and UGT.[28,42] Given this, phenobarbital increases the clearance of many drugs, including many antineoplastic drugs and other AEDs.[24,25,28,41] These medications include acetaminophen, 9-aminocamptothecin,

aminopyrine, amitriptyline, antipyrine, amoxapine, bishydroxycourmarin, carbamazepine, chloramphenicol, chlorpromazine, cimetidine, clobazam, cyclosporine, cyproheptadine, cyclophosphamide, diazepam, dicoumarol, digitoxin, dipryrone, doxycycline, etoposide, felodipine, flunarazine, glufosfamide, glyceryl trinitrate, griseofluvin, haloperidol, irinotecan, isoniazid, lignocaine, mebendazole, meperidine, mesoridazine, methadone, methotrexate, metoprolol, morphine, nimodipine, nortriptyline, oral contraceptives, paclitaxel, phenylbutazone, prednisolone, procarbazine, propranolol, quinidine, teniposide, theophylline, thioridazine, valproate, and warfarin. Based on hepatic enzyme induction, there are further AEDs that may demonstrate lower serum concentrations with coadministration of phenobarbital, including ethosuximide, lamotrigine, tiagabine, topiramate, and zonisamide.[8] Of note, the effect of phenobarbital on phenytoin levels is not predictable and the monitoring of serum concentrations of both agents is recommended with concomitant use.[28] Phenobarbital may lower levels of vitamin D and contribute to osteoporosis.[47]

Conversely, the metabolism of phenobarbital may also be influenced by the administration of other drugs.[24,25,28,41] Increases in plasma concentration of phenobarbital may occur with the use of acetazolamide, chloramphenicol, dicoumarol, felbamate, methylphenidate, phenothiazines, propoxyphene, quinine, stiripentol, and valproate. Phenobarbital plasma concentrations may be decreased with coadministration of folate, pyridoxine, chloramphenicol, dicoumarol, phenylbutazole, thioridazine, tipranavir/ritonavir combination, troleandomycin, and agents used to alkalinize urine. Based on hepatic enzyme induction, there are further possible AEDs that may decrease serum phenobarbital levels, including carbamazepine. Similar to phenobarbital's effect on phenytoin, the effect of coadministration of phenytoin on phenobarbital concentrations is unpredictable, and monitoring of serum levels is recommended.[28]

PHENYTOIN

In searching for a nonsedating barbiturate relative, phenytoin was developed for use in epileptic seizures by Merritt and Putnam in 1938.[38,48] Phenytoin remains in significant use around the world.[5] The main mechanism of action of phenytoin is believed to be the reduction of repetitive firing of voltage-dependent sodium channels from a shift to an inactive state following initial depolarization.[49] The effectiveness of phenytoin has been demonstrated in animal models of epilepsy such as the maximal electroshock seizure model and amygdaloid electrically kindled seizures.[7]

In adults, phenytoin demonstrates a near full bioavailability at 70-100%, with a volume of distribution ranging from 0.5 to 1.0 L/kg and an average of 0.78. Absorption occurs in the duodenum and can be changed by rate of elimination and enteral feeding. Phenytoin is highly protein bound with data estimates varying between 88% and 93%. Phenytoin is eliminated by metabolism through CYP2C9 and CYP2C19. Little is removed though renal filtration and less than 5% removed by dialysis. However, the protein-binding capacity of uremic plasma is decreased and this may lead to a lower half-life of the drug in patients with renal disease.[8,49]

Recommended dosing of phenytoin in adults is 100 mg three times a day with conversion to a once a day 300 mg given seizure control.[50] See Table 11.1 for clinical characteristics. Once saturation kinetics have been reached, increases in dosing should be performed carefully, as small changes in the maintenance dose can lead to large changes in serum concentration.[49,51] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for phenytoin is 10-20 mg/L total or 1-2 μg/mL unbound or "free" phenytoin.[8] The half-life of phenytoin is 8-42 h, dependent on preexisting plasma concentration, with steady state generally reached in 7-14 days.[49,50]

Intravenous administration of phenytoin is used in the treatment of status epilepticus; however, phenytoin per se has poor aqueous solubility and is dissolved in propylene glycol and alcohol. This formulation is caustic to tissues and is associated with adverse cardiovascular responses such as hypotension and bradycardia. Fosphenytoin is a water soluble pro-drug that is rapidly metabolized to phenytoin. Original dosing for treatment of status epilepticus was 20 mg/kg of phenytoin.[43–45] Given the different weights of the drugs fosphenytoin is dosed as 20 mg/kg of "phenytoin equivalence". Substitution dosing of intravenous fosphenytoin for oral phenytoin is equivalent.[50,52]

Phenytoin is indicated for the treatment of partial and generalized seizures as well as the prevention and treatment of seizures following neurosurgical procedures.[50] Early randomized but non-blinded comparison trials of phenytoin to either carbamazepine, valproic acid, or phenobarbital in previously untreated or not recently treated adults demonstrated equal efficacy of seizure control in all drugs, with phenytoin achieving full 6-month to 2-year overall seizure freedom, ranging from 37% to 63% of patients in the respective trials.[15,16,53,54] In a randomized comparison between phenytoin, carbamazepine, and valproate in previously untreated adults, there was no difference in the control of partial seizures among the drugs, with phenytoin reaching 57% in seizure freedom.[14] Phenytoin was superior to carbamazepine in control of generalized seizures, with a rate of 73% seizure freedom. However, it is worth noting that the generalized seizure population contained a mix of patients, with both primary and secondary onset generalized seizures. In a double-blind randomized trial,

phenytoin, phenobarbital, primidone, and carbamazepine were compared with overall efficacy being equal between the drugs in overall seizures control (phenytoin 38%) or control of tonic clonic seizures (phenytoin 43%).[13] In a breakdown of partial seizures, phenytoin demonstrated an "intermediate" level of control at 26% between the highest performing carbamazepine and the lowest performing primidone, which were statistically different from each other. Three meta-analyses have been performed comparing phenytoin with phenobarbital, carbamazepine, and valproic acid respectively.[19,46,55] The main measures of the analysis were time to withdraw, time to 12-month remission, and time to first seizure. There were no differences in efficacy between phenytoin and any of the other drugs. Phenytoin was found to have a clear advantage compared to phenobarbital on the metric of time to withdrawal, mostly because of adverse effects in the latter. In an evidence-based, structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis.[20,21] In this, phenytoin had Class I evidence (randomized trial meeting select criteria for superior clinic design) of superior efficacy and thus evidence of established efficacy (Level A recommendation) for monotherapy of partial onset seizures in adults. With a paucity of Class I and II randomized trials for adults with generalized tonic clonic seizures, phenytoin has evidence of possible efficacy and carries a Level C recommendation for monotherapy in primary generalized onset seizures. There is, however, Class IV evidence (nonrandomized or uncontrolled), suggesting phenytoin can aggravate generalized type seizures, which can include tonic clonic seizures.

The most common adverse effects associated with phenytoin use are referable to the central nervous system. The most common of these include nystagmus, ataxia, slurred speech, decreased coordination, somnolence, cognitive changes, and dyskinesias. As with many of the AEDs, phenytoin carries a warning of increased risk of suicidal ideation.[50] Severe idiopathic responses have also been documented including toxic epidermal necrolysis, Stevens-Johnson syndrome, DRESS, hepatotoxicity, serum sickness, and aplastic anemia. The serious dermatologic reactions are strongly associated with Asian ancestry and the presence of HLA-B*1502 allele. Phenytoin is also associated with long-term side effects, including coarsening of facial features, acne, gingival hypertrophy, osteoporosis, lymphadenopathy, and cerebellar atrophy.[49,52]

Phenytoin is Pregnancy Category D, with a relative risk of major congenital malformation, mostly cleft palate, of 1.6. This risk is enhanced in the setting of polytherapy. There have been reports of blood clotting deficiency in infants born to women taking phenytoin with subsequent recommendations of oral vitamin K supplementation during the last month of pregnancy, although this has not been supported adequately in the literature.[23]

Phenytoin has multiple interactions with other drugs. Acute alcohol intake may increase serum levels while chronic intake may decrease them.[49] Phenytoin induces CYP2C, CYP3A, UGT, and subsequently increases clearance of many drugs including many antineoplastic drugs and other AEDs (see Table 11.2).[24,25,49,52] These drugs include 9-aminocamptothecin, antiretrovirals, atorvastatin, azoles, carbamazepine, CCNU, clobazam, clonazepam, corticosteroids, cyclophosphamide, cyclosporine, dicoumarol, digitalis, digoxin, disopyramide, doxycycline, estrogens, etoposide, felbamate, fluvastatin, furosemide, gefitinib, glufosfamide, haloperidol, ifosfamide, imatinib, irinotecan, lamotrigine, meperidine, methadone, methotrexate, mexiletine, nisoldipine, nortriptyline, oral contraceptives, oxcarbazepine, paclitaxel, paroxetine, praziquantiel, primidone, procarbazine, quinidine, quetiapine, rifampin, sertraline, simvastatin, temozolomide, temsirolimus, teniposide, thiotepa, theophylline, thyroxine, topiramate, topotecan, valproate, vincristine, vitamins D and K, and zonisamide. Based on hepatic enzyme induction, there are further AEDs that may demonstrate lower serum concentrations with coadministration of phenytoin, including ethosuximide and tiagabine.[8] Of note, the effect of phenytoin on phenobarbital levels is not predictable, and the monitoring of serum concentrations of both agents is recommended with concomitant use.[49]

Serum phenytoin levels are also influenced by other drugs, most especially inhibitors/cosubstrates on CYP2C9 and CYP2C19.[24,25,49,52] Drugs that decrease clearance of phenytoin include amiodarone, azapropazone, azoles, bleomycin, capecitabine, carmustine, chloramphenicol, chlordiazepoxide, cimetidine, diazepam, dicoumarol, diltiazem, disulphiram, ethanol, ethosuximide, felbamate, fluorouracil, fluoxetine, imipramine, isoniazid, methotrexate, nafimidone, omeprazole, oxcarbazepine, phenothiazines, phenylbutazone, proguanil, propranolol, propoxyphene, rufinamide, stiripentol, sulfonamides, sulthiamine, tolbutamide, topiramate, trazodone, vigabatrin, viloxazine, vinblastine, vincristine, and warfarin. Similar to phenytoin's effect on phenobarbital, the effect of coadministration of phenytoin on phenobarbital concentrations is unpredictable and monitoring of serum levels is recommended.

PRIMIDONE

Developed in 1954 as a congener to phenobarbital, primidone functions mainly through biotransformation to phenobarbital.[38,41] Only the differences between primidone and phenobarbital are highlighted here.

Primidone has a similar bioavailability and volume of distribution as phenobarbital. Estimates of unmetabolized urinary excretion ranges from 15% to 66%. Primidone itself has a half-life of 6-12 h, with the subsequent half-life of the derived phenobarbital being significantly longer. Adverse effects and drug interactions of primidone are similar to phenobarbital.[28,41]

The recommended starting dose of primidone is 100 mg, with slow titration up to 750 mg divided three times a day. Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for primidone is 5-12 mg/L.[56] See Table 11.1 for clinical characteristics.

Clinical efficacy of primidone was reviewed in the International League Against Epilepsy treatment guidelines. Primidone was inferior to carbamazepine in the control of partial onset seizures in adults and was given a level D recommendation for being potentially effective as initial monotherapy in this population. Data was inadequate for a recommendation for use of primidone for initial monotherapy in adults with newly diagnosed generalized tonic clonic seizures.[20,21]

VALPROATE

Valproate was discovered as having anticonvulsant activity in 1962 when it was being utilized as an inert solvent for compounds being tested in an animal model of epilepsy. Valproate is considered to have a broad spectrum of activity and is used worldwide.[57] The mechanism of action of valproate is most commonly believed to be an increase in brain GABAergic activity, with a decrease in degradation and an increase in synthesis and potentiation of postsynaptic GABAergic inhibition. There is evidence for activation of calcium dependent potassium conduction.[58] The effectiveness of valproate has been demonstrated in animal models of epilepsy such as maximal electroshock seizure model, subcutaneous pentylenetetrazole, and electrical amygdaloid kindling.[7]

In adults, valproate demonstrates a near full bioavailability at 90% with a small volume of distribution ranging from 0.14 to 0.23 L/kg. Valproate is highly protein bound at 90%.[58,59] Valproate is eliminated mostly by hepatic biotransformation. The protein-binding capacity of uremic plasma is decreased, but this does not necessitate a change in dosing.[8,58]

Recommended dosing of valproate for epilepsy in adults is 250-4000 mg/day, with starting dosing typically at 5 mg/kg/day and maximal dosing at 60 mg/kg/day. See Table 11.1 for clinical characteristics. There are immediate and extended-release formulations available.[60] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for valproate is 50-100 mg/L.[8] The half-life of valproate in adults is 6-17 h, with steady state generally reached in 2-4 days.[58,60]

Intravenous administration of valproate has been used in the treatment of status epilepticus. Data demonstrates efficacy of intravenous valproate as a second-line agent in the treatment of status epilepticus similar to that of phenytoin.[61] Dosing is approximately 25-30 mg/kg.

Valproate is indicated for the use of partial and generalized onset seizures.[60] Multiple randomized and double-blind studies comparing valproate to carbamazepine, phenobarbital, phenytoin, and primidone have demonstrated no difference in total efficacy among these medications, with the percent of patients achieving total seizure control on valproate ranging from 30% to 59%.[14–16,18] Subgroup analysis in these studies demonstrated differential efficacy between generalized and partial seizures, with rates of control of tonic clonic seizures between 59% and 73% and partial seizures between 27% and 47%.[14] A retrospective review of patients with primary generalized epilepsy demonstrated 79% control.[62] A randomized prospective trial in the same population demonstrated 83% of patients reached seizure freedom with a decline in interictal discharges recorded in 88% of patients prior to treatment, to 32% following treatment.[63] Valproate was inferior to carbamazepine in the control of complex partial seizures with a higher per month seizure frequency in those patients with uncontrolled seizures.[15] Two meta-analyses have been performed comparing valproate with carbamazepine and phenytoin, respectively.[18,55] The main measures of the analysis were time to withdraw, time to 12-month remission, and time to first seizure. Valproate was inferior to carbamazepine in control of partial onset seizures on the measure of time to first seizure following randomization and time to 12-month remission. There were no other significant differences in comparable efficacy or tolerability found. In an evidence-based, structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis. In this, valproate had Class II evidence (randomized trial with intermediate level of comparative study design) of probable efficacy (Level B recommendation) for monotherapy of partial onset seizures in adults. With a paucity of Class I and II randomized trials for adults with generalized tonic clonic seizures, valproate has evidence of possible efficacy and carries a Level C recommendation for monotherapy in primary generalized onset seizures.[20,21]

The most common adverse effects of valproate therapy include gastrointestinal distress, somnolence, weight gain, hair loss, and tremor.[58–60] As with many of the AEDs, valproate carries a warning of increased risk of suicidal ideation.[60] Severe idiopathic responses have also been documented, including hepatotoxicity,

pancreatitis, hyperammonemia, and thrombocytopenia.[58] The risk of hepatic failure is particularly significant, and valproate should be avoided if possible in patients with liver disease. Although the reaction is idiosyncratic and may not be heralded by a rise in liver enzymes, patients at particular risk for valproate-induced hepatic toxicity include children and individuals with mitochondrial or other inborn metabolic disorders. The use of L-carnitine may aid in the recovery from valproate-induced hepatic failure.[64] Additionally, valproate may induce hyperammonemia without hepatic dysfunction and patients with new encephalopathy on valproate should have an ammonia level checked.[59] Valproate use may be associated with an idiosyncratic pancreatitis, and reports of abdominal pain should prompt investigation into pancreatic function.[59] Valproate-associated thrombocytopenia in one study occurred in 27% of the population, may be dose dependent, and can normalize without intervention.[58,59]

Valproate is Pregnancy Category D with a relative risk of major congenital malformation of 4.0. This risk is enhanced in the setting of polytherapy. Additional data have suggested unfavorable developmental outcomes in children with *in utero* exposure to valproate.[23,65]

Valproate has multiple interactions with other drugs.[24,25,58,59] Concomitant use of valproate and clonazepam may induce absences status in patients with a history of absence seizures. Administration of valproate with topiramate has been associated with development of hyperammonemia. Simultaneous use of valproate and cisplatin, etoposide, or fotemustine is associated with increased risk of thrombocytopenia and neutropenia.

Valproate inhibits epoxide hydrolase, CYP2C9, UDP glucuronyltransferases, and UDP glucosyltransferases.[24,25,58,59] Subsequently, decreased clearance of many drugs, including many antineoplastic drugs and other AEDs, may result (see Table 11.2). These drugs include carbamazepine, carbapenem antibiotics, diazepam, ethosuximide, lamotrigine, lorazepam, paclitaxel, phenytoin, phenobarbital, rifampin, and zidovudine. Valproate use can be associated with a decrease in irinotecan plasma levels.

Serum valproate levels are also influenced by other drugs.[24,25,58,59] Coadministration of enzyme-inducing agents, such as carbamazepine, phenytoin, and phenobarbital, can produce a twofold increase in valproate clearance. Conversely, aspirin and felbamate have been associated with decreased valproate clearance.

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CHAPTER

12

Antiepileptic Drugs: Second and Third Generation

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CHAPTER CONTENTS

INTRODUCTION

Anticonvulsant medications, often called antiepileptic drugs (AEDs), are sometimes classified by the "generation" in which they were developed and introduced. This chapter focuses on pharmacologic properties and clinical use of second- and third-generation AEDs. Three-quarters of the drugs we now use regularly have been developed and brought to market since 1990: they are called second- and third-generation AEDs.[1] Second-generation "designer" AEDs were introduced in a 15-year period beginning in 1989; while third-generation AEDs were introduced beginning in 2008.[2] These include clobazam, eslicarbazepine acetate, ezogabine/retigabine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide. Anticonvulsants are different in their classification from other drugs in that they are not classified by mechanism of action, but simply grouped under the heading of anticonvulsant secondary to the mechanism of action of each drug being both not fully understood and likely multiple in nature.[3]

CLOBAZAM

Developed with a goal of improvement in efficacy and decrease in sedation and hypotonia, clobazam, a 1,5-benzodiazepine agonist, was first synthesized in 1966 and introduced into practice in Australia in 1970 and France in 1974.[4,5] Clobazam received United States Food and Drug Administration approval in 2011.

Clobazam is a Schedule Class IV controlled substance in the United States.[4–6]

The main mechanism of action is thought to be modulation of gamma-aminobutyric acid (GABA) induced chloride influx via binding to the benzodiazepine receptor on $GABA_A$ channels. Clobazam demonstrates greater selectivity for anxiolytic and antiepileptic compared to sedative subunit types.[4–8] Clobazam has been successfully tested in animal models of epilepsy such as the maximal electroshock, subcutaneous pentylenetetrazol model, metrazol, bicuculline, picrotoxin- and strychnine-induced seizures models in mice and rats, and photically induced seizures in the baboon.[8,9]

Clobazam demonstrates a bioavailability of 90-100% and protein-binding estimates range from 80% to 90% for clobazam itself and 70% for the active metabolite *N*-desmethylclobazam.[4,7,8,10] The metabolism of clobazam occurs mainly in the liver, mostly by isoenzyme CYP3A4; however, *N*-desmethylclobazam is mainly metabolized by CYP2C19.[7,10] Children metabolize clobazam and *N*-desmethylclobazam more rapidly than adults.[4,6] There is a high risk of intoxication in patients with hepatic compromise and dose reduction is indicated.[7,11] No dose adjustment is needed in renal disease.[7]

Clobazam is available in 10 and 20 mg tablets and oral suspension. Recommended dosing of clobazam in adults is 5-40 mg a day administered one to two times a day[7] and in children 0.25-1.0 mg/kg/day.[4] The half-life of clobazam in adults ranges 12-42 h, with the half-life of the *N*-desmethylclobazam ranging from 71 to 82 h.[4–7,10] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for clobazam is 0.03-0.3 mg/L with the corresponding range for *N*-desmethylclobazam being 1-4 mg/L.[12,13] See Table 12.1 for clinical characteristics.

Clobazam is indicated for adjunctive therapy for multiple seizure types in patients with Lennox-Gastaut syndrome (LGS).[7] The clinical effectiveness of clobazam was studied in the United States with two multicenter controlled trials in which drop seizures in patient with LGS were decreased by 41.2-68.3% compared to the 12% drop seen in placebo-treated patients. This response was dose dependent, with patients receiving a 40 mg dose demonstrating a 93% decline and those receiving a 10 mg dose demonstrating a 29% decline.[5,7] International efficacy trials of clobazam demonstrated responder rates (50% or greater decrease in seizure frequency) of 56.3-83% in patients with LGS and 40-61% in patients with refractory epilepsy.[4,5] Open-label studies suggest that clobazam may be equally efficacious as monotherapy for partial-onset seizures as phenytoin or carbamazepine[4] and a meta-analysis of open-label studies documented clinical improvement in 67% of patients treated.[14] A retrospective multi-practitioner review of patients treated with clobazam documented clinical improvement in at least 50% of patients, with a $\geq$50% reduction in 40-50% of patients.[15] In an evidence-based structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis in which clobazam was found to have an inadequate efficacy or effectiveness data available for consideration of use as monotherapy for new or untreated partial or generalized epilepsy. However, data was found to support a classification of potentially efficacious (level D) for clobazam use in elderly adults with partial-onset seizures.[16,17]

The issue of tolerance is of question with the use of clobazam. Reports of tolerance range from 10% to 87% of patients and appear to depend on the definition and the time period over which data is measured.[5] In a retrospective multi-practitioner study, "tolerance" was cited as a reason for discontinuation in 9.2% of the treated population.[15] In a retrospective study of patients who responded with a >75% reduction of seizures, 50% relapsed to a level $\geq$50% of previous seizure frequency, with longer epilepsy duration being correlated with possibility of relapse.[18] An additional small prospective study demonstrated that out of 11 patients, 72% demonstrated a return to baseline seizure frequency.[19]

The most common adverse reactions with the use of clobazam are somnolence, ataxia, aggression, fatigue, and insomnia. Withdrawal symptoms are common upon discontinuation. As with all AEDs, clobazam carries a warning of increased risk of suicidal ideation.[7] Severe idiopathic responses have also been documented, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and hepatotoxicity.[4,7] Clobazam is Pregnancy Category C but considered to be of low risk for teratogenicity.[5,7] No pregnancy registry data is currently available for clobazam. Some infants do demonstrate withdrawal symptoms after *in utero* exposure.[20]

Clobazam has effects on other drugs (see Table 12.2). Clobazam is an inhibitor of valproate concentrations,[5] increases plasma concentrations of dextromethorphan through CYP2D6 interactions, and decreases plasma concentrations of oral contraceptives through changes in CYP34A metabolism.[7] Clobazam use is also associated with decreased plasma levels of eslicarbazepine, felbamate, lamotrigine, levetiracetam, oxcarbazepine, perampanel, retigabine, rufinamide, stiripentol, tiagabine, topiramate, valproate, and zonisamide.[21]

Serum clobazam and *N*-desmethylclobazam levels are influenced by other drugs.[7,22] Agents that inhibit CYP3A4 and CYP2C19 metabolism increase clobazam and *N*-desmethylclobazam levels. These include amprenavir, atazanavir, cimetidine, danazol, darunavir, diltiazem, erythromycin, eslicarbazepine acetate, etravirine, fluconazole, fluvoxamine, grapefruit juice, indinavir, itraconazole, isoniazid, ketoconazole, miconazole, omeprazole, propoxyphene, quinupristin, ritonavir,

TABLE 12.1 Second- and Third-Generation AED Clinical Characteristics

AED	Indication	Starting Dose	Half-Life	Target Therapeutic Range (mg/L)
Clobazam	Multiple seizures types in LGS	Adults: 5 mg/day Children: 0.25 mg/kg/day	Clobazam: 12-42 h NDMC: 71-82 h	Clobazam: 0.03-0.3 NDMC: 1-4
Eslicarbazepine	Partial-onset seizures	400 mg/day	13-20 h	5-35
Ezogabine/ retigabine	Severely refractory partial-onset seizures where risk for visual loss outweighed by epilepsy benefit	300 mg/day	7-11 h	n/a
Felbamate	Multiple seizure types in LGS where risk of aplastic anemia outweighed by epilepsy benefit	1200 mg/day	20-23 h	30-80
Gabapentin	Partial-onset seizures	900 mg/day	5-9 h	2-20
Lacosamide	Partial-onset seizures	100 mg/day	13 h	10-20
Lamotrigine	Partial-onset seizures, primary generalized seizures Multiple seizure types in LGS	*Slow escalation* Adults: 200 mg/day Children: 7.5 mg/kg/day	Alone: 25-38 h Enzyme inducer: 12-14 h Enzyme inhibitor: 48-70 h	2-20
Levetiracetam	Partial-onset seizures Myoclonic seizures Primary generalized seizures	Adults: 1000 mg/day Children: 14 mg/kg/day	6-8 h	12-46
Oxcarbazepine	Partial-onset seizures	600 mg/day	Oxcarb: 2 h MHD: 9 h	MDH: 2-55
Perampanel	Partial-onset seizures	2 mg/day	105 h	n/a
Pregabalin	Partial-onset seizures	150 mg/day	6-10 h	2.8-8.3
Rufinamide	LGS	Adults: 400 mg/day Children: 10 mg/kg/day	6-10 h	10-40
Tiagabine	Partial-onset seizures	4 mg/day	3-9 h	5-70
Topiramate	Partial-onset seizures Primary generalized seizures	200 mg/day	20-30 h	5-20
Vigabatrin	Partial-onset seizures and infantile spasms where risk for visual loss outweighed by epilepsy benefit	Adults: 1000 mg/day Infants: 50 mg/kg/day	5-8 h	0.8-36
Zonisamide	Partial-onset seizures	100 mg/day	27-70 h	10-40

LGS, Lennox-Gastaut Syndrome; NDMC, *N*-desmethylclobazam (active metabolite); MHD, monohydroxy metabolite (active metabolite).

saquinavar, stiripentol, telithromycin, ticlopidine, troleandomycin, and verapamil. Drugs that can induce hepatic enzyme metabolism, including felbamate, lamotrigine, oxcarbazepine, perampanel, phenobarbital, phenytoin, and topiramate, can decrease clobazam serum concentrations.[4,10,21]

ESLICARBAZEPINE ACETATE

Developed from a program to identify analogs of carbamazepine and oxcarbazepine, eslicarbazepine is the S-enantiomer of the active metabolite of oxcarbazepine.[23] Introduced into clinical practice in 2009, eslicarbazepine acetate received United States Food and Drug Administration approval in 2013.[23,24] The main mechanism of action of eslicarbazepine acetate is thought to be modulation of voltage-gated sodium channels.[21,25] Eslicarbazepine acetate has been successfully tested in animal models of epilepsy such as maximal electroshock seizures, amygdala kindling, and chemically induced seizures by agents such as metrazol, bicuculline, 4-amino-pyridine, latruncullin A, and picrotoxin.[25]

Eslicarbazepine acetate demonstrates a bioavailability of 90% and a protein binding that is low at less than 40%. Eslicarbazepine acetate is quickly transformed by

TABLE 12.2 AED Interaction with Other AEDs and Antineoplastic Agents

AED	Other Drugs Affected by the AED		Effect of Other Drugs on AED	
Clobazam	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	Eslicarbazepine Ezogabine Felbamate Lamotrigine Levetiracetam Oxcarbazepine Perampanel Rufinamide Stiripental Tiagabine Topiramate Valproate Zonisamide		Felbamate Lamotrigine Perampanel Phenobarbital Phenytoin Topiramate	Eslicarbazepine Stiripentol *Active metabolite* increased by felbamate
Eslicarbazepine	Eslicarbazepine should not be taken with oxcarbazepine			
	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	Carbamazepine Lamotrigine Topiramate Valproate	Clobazam Phenobarbital Phenytoin	Carbamazepine Clobazam Phenobarbital Phenytoin Topiramate	
Ezogabine/ retigabine	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	Lamotrigine	Phenobarbital	Carbamazepine Clobazam Phenytoin	Lamotrigine Phenobarbital
Felbamate	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	Carbamazepine Clobazam Phenobarbital Phenytoin Vigabatrin	Lamotrigine Valproate *Active metabolite of clobazam increased by felbamate	Carbamazepine Clobazam Phenobarbital Phenytoin	Gabapentin Valproate
Gabapentin	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	Pregabalin	Felbamate		
Lacosamide	Toxic interactions, not related to plasma concentrations, have been seen with carbamazepine, lamotrigine, oxcarbazepine and phenytoin			
	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	*Active metabolite of oxcarbazepine decreased by lacosamide		Phenobarbital Phenytoin	
Lamotrigine	Toxic interactions, not related to plasma concentrations, have been seen with lacosamide.			
	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	Clobazam Levetiracetam Oxcarbazepine Valproate	Ezogabine	Carbamazepine Clobazam Eslicarbazepine Ezogabine Oxcarbazepine	Felbamate Valproate

TABLE 12.2 AED Interaction with Other AEDs and Antineoplastic Agents—cont'd

AED	Other Drugs Affected by the AED		Effect of Other Drugs on AED	
			Perampanel Phenobarbital Phenytoin Primidone Rufinamide	
Levetiracetam	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
			Carbamazepine Clobazam Lamotrigine Oxcarbazepine Phenytoin Phenobarbital Primidone	
Oxcarbazepine	Oxcarbazepine should not be taken with eslicarbazepine; toxic interactions not related to plasma concentrations have been seen with lacosamide			
	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	AEDs: Carbamazepine Lamotrigine Levetiracetam Perampanel Rufinamide Topiramate Antineoplastic: Cyclosporine Imatinib	Phenobarbital Phenytoin	Carbamazepine Clobazam Lacosamide Lamotrigine Phenobarbital Phenytoin Topiramate	Perampanel
Perampanel	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	Carbamazepine Clobazam Lamotrigine Valproate	Oxcarbazepine	Carbamazepine Clobazam Oxcarbazepine Phenytoin Topiramate	
Pregabalin	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	Tiagabine		Gabapentin	Phenytoin
Rufinamide	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	Carbamazepine Lamotrigine	Phenobarbital Phenytoin	Carbamazepine Clobazam Oxcarbazepine Phenobarbital Phenytoin Primidone Vigabatrin	Valproate
Tiagabine	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	Valproate		Carbamazepine Phenobarbital Phenytoin Pregabalin Primidone	

Continued

TABLE 12.2 AED Interaction with Other AEDs and Antineoplastic Agents—cont'd

AED	Other Drugs Affected by the AED		Effect of Other Drugs on AED	
Topiramate	Coadministration with valproate increases the risk of hyperammonemia, hypothermia; use with other carbonic anhydrase inhibitors like zonisamide increases the risk of metabolic acidosis and nephrolithiasis.			
	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	AEDs: Carbamazepine Clobazam Eslicarbazepine Ethosuximide Oxcarbazepine Perampanel Valproate Antineoplastic: Imatinib	Phenytoin	Carbamazepine Clobazam Eslicarbazepine Oxcarbazepine Phenobarbital Phenytoin Primidone Vigabatrin	
Vigabatrin	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
	Phenytoin Rufinamide Topiramate		Felbamate	
Zonisamide	Use with other carbonic anhydrase inhibitors like topiramate increases the risk of metabolic acidosis and nephrolithiasis.			
	Decreased plasma concentration	Increased plasma concentration	Decreased plasma concentration	Increased plasma concentration
			AEDs: Carbamazepine Clobazam Phenobarbital Phenytoin Primidone Antineoplastic: Cyclosporine	

first-pass hydrolytic metabolism to the main active metabolite eslicarbazepine. Eslicarbazepine is then excreted in the urine unchanged or in glucuronide conjugate form. Eslicarbazepine acetate dosing should be decreased in patients with renal failure and its metabolites are removed by dialysis.[21,24]

Eslicarbazepine acetate is available in 200, 400, 600, and 800 mg tablets. Recommended dosing of eslicarbazepine acetate in adults is 400-1200 mg a day administered once a day. The half-life of eslicarbazepine acetate ranges from 13 to 20 h.[24] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for eslicarbazepine acetate is 5-35 mg/L.[2] See Table 12.1 for clinical characteristics.

Eslicarbazepine acetate is indicated for adjunctive therapy for partial-onset seizures. Three initial studies of efficacy were performed with eslicarbazepine acetate dosing ranging from 400 to 1200 mg/day. Patients demonstrated decreases in seizure frequency from 28% to 39% compared to placebo responses of 6-20%.[24] Further Phase II and III clinical trials have documented similar rates of efficacy, with significant decreases in seizure frequency ranging from 36% to 41.9% and responder rates (>50% seizure reduction) of 34-43%.[26–30] Longer-term data has been examined and responder rates up to a year ranged between 48% and 53% while the proportion of seizure-free patients per 12-week interval ranged between 8.7% and 12.5%.[26,31] A meta-analysis was performed with data supporting reduced seizure frequency when used as add-on treatment for partial-onset epilepsy.[31]

The most common adverse reactions with the use of eslicarbazepine acetate are dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, tremor, and cognitive dysfunction. As with all AEDs, eslicarbazepine acetate carries a warning of increased risk of suicidal ideation. Severe idiopathic responses have also been documented including toxic epidermal necrolysis, Stevens-Johnson

syndrome, drug reaction with eosinophilia and systemic symptoms/multiorgan hypersensitivity, anaphylaxis, angioedema, and hepatotoxicity.[24] Hyponatremia can occur in up to 5% of patients. Eslicarbazepine acetate is Pregnancy Category C.[24] No pregnancy registry data is currently available for eslicarbazepine acetate.

Eslicarbazepine acetate has varied effects on other drugs (see Table 12.2). Eslicarbazepine acetate should not be taken with oxcarbazepine. Eslicarbazepine acetate can inhibit CYP2C19 and induce CYP3A4. Eslicarbazepine acetate increases serum concentrations of clobazam, omeprazole, phenobarbital, and phenytoin and decreases in plasma concentrations of carbamazepine, digoxin, hormonal contraceptives, lamotrigine, metformin, simvastatin, topiramate, valproate, and warfarin have been seen with concomitant use of eslicarbazepine.[21,25,33]

Serum eslicarbazepine levels can be influenced by other drugs.[21,24] Agents that induce hepatic enzyme function may enhance metabolism of eslicarbazepine acetate. These include carbamazepine, clobazam, phenobarbital, phenytoin, and topiramate.[21,24]

EZOGABINE/RETIGABINE

First introduced clinically and approved in the United States in 2011, ezogabine/retigabine was developed from a screening program for derivatives of an analgesic with anticonvulsant properties. Ezogabine/retigabine is a Schedule Class V controlled substance in the United States.[23,34] The main mechanism of action of ezogabine/retigabine is thought to be potassium channel opening-KCNQ activation and neuronal-specific M-type potassium currents mediated by Kv7 channels.[2,34] Ezogabine/retigabine has been successfully tested in animal models of epilepsy such as 6 hertz psychomotor seizures, audiogenic seizures, maximal electroshock seizure, subcutaneous pentylenetetrazol, and amygdala kindling models.[2]

Ezogabine/retigabine demonstrates a bioavailability of 60% and protein binding of 80%. Ezogabine/retigabine undergoes glucuronidation and acetylation. Ezogabine/retigabine and its metabolites are 85% eliminated by urinary excretion with 36% being unchanged drug. The dosage of ezogabine/retigabine should be reduced by approximately 50% in patients with renal disease, or moderate or greater hepatic disease.[34]

Ezogabine/retigabine is available in 50, 200, 300, and 400 mg tablets. Recommended dosing of ezogabine/retigabine is 100 mg three times a day to start, with maximum dosing of 400 mg three times a day. The half-life of ezogabine/retigabine ranges from 7 to 11 h.[33] A recommended therapeutic range for ezogabine/retigabine has not been established. See Table 12.1 for clinical characteristics.

Ezogabine/retigabine is indicated for adjunctive therapy partial-onset seizures only in severely refractory patients in whom the risk for visual loss is outweighed by the possible benefits of seizure control.[34] There have been three major Phase III trials demonstrating the efficacy of ezogabine/retigabine. Each study was conducted with adjunctive therapy of in patients with refractory partial-onset epilepsy with 600, 900, and/or 1200 mg ezogabine/retigabine dosing groups. Significant decreases in seizure frequency of 23-43% were seen compared to the 13-28% seen in the placebo groups. Significant responder rates (>50% seizure reduction) ranged from 31.6% to 47% compared to 15.6% to 18.9% in control groups.[23,34–37]

The most common adverse reactions with the use of ezogabine/retigabine are dizziness, somnolence, confusional states, fatigue, vertigo, tremor ataxia, and diplopia. Withdrawal symptoms are common upon discontinuation. As with all AEDs, ezogabine/retigabine carries a warning of increased risk of suicidal ideation. Ezogabine/retigabine is also associated with retinal pigment abnormalities and vision loss requiring visual screening prior to initiation and every 6 months thereafter. Additionally, blue/gray skin discolorations have been reported. Other severe reactions to ezogabine include urinary retention, confusion, and hallucinations.[34] Ezogabine/retigabine is Pregnancy Category C.[34] No pregnancy registry data is currently available for ezogabine/retigabine.

Ezogabine/retigabine has few effects on other drugs (see Table 12.2). Ezogabine/retigabine decreases lamotrigine levels and increases digoxin plasma concentrations through inhibition of renal clearance.[21,34] Serum phenobarbital levels may be increased by coadministration of ezogabine/retigabine.[21] Serum ezogabine/retigabine levels are influenced by other drugs. Carbamazepine, clobazam, ethanol, and phenytoin can act to decrease ezogabine/retigabine plasma concentrations[33,34] while lamotrigine and phenobarbital can act to increase plasma concentrations of ezogabine/retigabine.[21]

FELBAMATE

Developed as a potential sedative, felbamate was licensed for clinical use and FDA approved in 1993.[21,23,38,39] The main mechanism of action of felbamate is thought to include inhibition of *N*-methyl-D-aspartate receptor responses and action on gamma-amino butyric acid $(GABA)_A$ receptors. Felbamate has been successfully tested in animal models of epilepsy such as the maximal electroshock, electrical kindling,

phenytoin-resistant kindled rat, and subcutaneous pentylenetetrazol models of epilepsy.[40,41]

Felbamate demonstrates a bioavailability of 90% and protein-binding estimates range from 22% to 25%.[10,41] The metabolism of felbamate is primarily via UDP glucuronosyltransferase with some contribution from CYP3A4.[10] Forty to fifty percent of the dose is excreted unchanged in the urine. Felbamate should be used with caution with dosing reduction in patients with renal disease and not used in patients with hepatic impairment.[11,41]

Felbamate is available in 400 and 600 mg tablets and oral suspension. Recommended dosing of felbamate begins at 1200 mg/day administered three to four times a day with maximum dosing at 3600 mg/day.[10,41] The half-life of felbamate ranges from 20 to 23 h.[10,41] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for felbamate is in the range of 30-80 mg/L.[10,42] See Table 12.1 for clinical characteristics.

Felbamate is indicated for adjunctive therapy or monotherapy for multiple seizure types in patients with LGS in whom the risk of aplastic anemia and hepatic failure are outweighed by the possible benefit of seizure control.[41] A randomized study in patients with LGS demonstrated significant decreases in total seizures of 26% compared to 5% in placebo-treated patients. Atonic seizures decreased by 44% compared to 7% and generalized tonic-clonic seizures decreased by 40% compared to 12% in controls.[41,43] Further, felbamate was studied as monotherapy in adults under the novel trial design of not reaching escape criteria of worsening seizures when compared to a very low dose of valproate. In these studies, felbamate met escape criteria in significantly fewer numbers than patients given low-dose valproate.[41,43] In a meta-analysis regarding the efficacy of felbamate in refractory partial-onset seizures, no reliable evidence was found to support the use of felbamate in this population.[44] In an evidence-based structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis.[16,17] Felbamate was found to have an inadequate efficacy or effectiveness data available for consideration of use as monotherapy for partial or generalized epilepsy.

The most common adverse reactions with the use of felbamate are anorexia, vomiting, insomnia, nausea, headache, and dizziness. As with all AEDs, felbamate carries a warning of increased risk of suicidal ideation.[41] Felbamate use is associated with a risk of aplastic anemia and hepatic failure. Although all cases of aplastic anemia were reported within the first year of exposure to felbamate, serological evaluation for these conditions should be performed in an ongoing manner.[41,45,46] Felbamate should be reserved for use in patients for whom the risk-benefit ratio is favorable, including patients unresponsive to standard therapies at therapeutic dosing.[46] Felbamate is Pregnancy Category C.[41] No pregnancy registry data is currently available for felbamate.

Felbamate is an inducer of CYP3A4 and has significant interactions with other drugs (see Table 12.2). Felbamate increases the clearance of carbamazepine, clobazam, hormonal contraceptives, lamotrigine, phenobarbital, phenytoin, valproate, vigabatrin, and warfarin.[10,21,33,41,42] Felbamate increases the plasma concentration of the pharmacologically active metabolite of clobazam-*N*-desmethylclobazam.[21]

Conversely, serum felbamate levels are influenced by other drugs. The elimination of felbamate is decreased by gabapentin via an interaction at the level of renal excretion.[21] Hepatic enzyme-inducing agents increase the clearance of felbamate and subsequently decrease plasma concentrations. These include carbamazepine, clobazam, phenobarbital, and phenytoin.[10,21,41,42] Valproate inhibits the metabolism of felbamate.[21]

GABAPENTIN

Developed as a potential GABA mimetic and spasmolytic that could cross the blood-brain barrier, gabapentin was first introduced into clinical practice in 1993 and first received United States Food and Drug Administration approval in 1993.[23,38,39,47] The main mechanism of action of gabapentin is thought to be action at α_2-δ-1 and α_2-δ-2 subunits of voltage-gated calcium channels.[21] Gabapentin has been successfully tested in animal models of epilepsy such as the maximal electroshock, electrical kindling, subcutaneous pentylenetetrazol, and genetic epilepsy models in mice.[40,48]

Gabapentin demonstrates bioavailability inversely proportional with absolute dose with absorption of 60% of a 900 mg/day dosing and 27% or a 4800 mg/day dosing. Gabapentin has minimal protein binding at less than 3%.[10,48] One hundred percent of gabapentin is excreted unchanged in the urine and dosing reduction is recommended in the setting of renal disease. No adjustment is needed in patients with hepatic disease.

Gabapentin is available in 100, 300, 400, 600, and 800 mg pills and in oral suspension. Recommended dosing of gabapentin starts at 900 mg/day divided three times a day to a maximum of 3600 mg/day.[48] The half-life of gabapentin is 5-9 h.[10,48] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for gabapentin is in the range of 2-20 mg/L.[10] See Table 12.1 for clinical characteristics.

Gabapentin is indicated for adjunctive therapy for partial-onset seizures with or without secondary generalization.[48] Initial approval for gabapentin was

based on three randomized clinical trials in adults with partial-onset epilepsy where significant decreases in seizure frequency of 17-31% compared to 0.3-12.5% in placebo-treated patients were recorded. Responder rates (>50% seizure reduction) ranged from 22% to 34% compared to 8% to 14% in control groups.[48–51] Open-label extensions of these trials revealed stable response ratios with median reduction of seizure frequency ranging from 33% to 60% and responder rates ranging from 35% to 71%.[49,50] Post-marketing data suggests that optimal dosing is from 900 to 1800 mg.[51] One open-labeled study demonstrated a responder rate of 33.9% with seizure freedom documented in 13.4%.[51] A meta-analysis concluded that gabapentin demonstrated efficacy as adjunctive therapy in patients with refractory partial-onset seizures.[52] In an evidence-based structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis.[16,17] Gabapentin was found to have evidence for a level D recommendation (potentially efficacious) for monotherapy in children with partial-onset seizures, children with benign epilepsy with centrotemporal spikes, and adults with generalized tonic-clonic seizures and a level C recommendation (possibly efficacious) in adults with partial-onset seizures. Additionally gabapentin has evidence for a level A recommendation (established efficacy) for monotherapy for partial-onset seizures in elderly adults.

The most common adverse reactions with the use of gabapentin are dizziness, somnolence, peripheral edema, ataxia, and fatigue.[47,48] As with all AEDs, gabapentin carries a warning of increased risk of suicidal ideation.[48] Increased emotional lability has been documented in children under the age of 12. Severe idiopathic responses have also been documented including drug reaction with eosinophilia and systemic symptoms/multiorgan hypersensitivity.[48] Gabapentin is Pregnancy Category C.[48] The relative risk of major malformations identified in a pregnancy registry was 0.6.[53]

Gabapentin has few effects on other drugs (see Table 12.2). Gabapentin decreases elimination of felbamate at the level of renal excretion[21] and works to decrease plasma levels of pregabalin. Gabapentin decreases plasma hydrocodone levels.[21,48] Serum gabapentin levels are influenced by only a few other drugs. Morphine and naproxen increase while cimetidine and Maalox can decrease plasma gabapentin concentrations.[33,48,54]

LACOSAMIDE

Developed as part of a formal anticonvulsant screening program, lacosamide was first introduced into clinical practice and received United States Food and Drug Administration approval in 2008. Lacosamide is a Schedule Class V controlled substance in the United States.[23,39,55,56] The main mechanism of action of lacosamide is thought to be enhancement of slow inactivation of voltage-gated sodium channels.[21,55] Additionally, lacosamide has interaction with the collapsing response mediator protein 2, possibly inhibiting axonal sprouting that may underlie the progression reported in chronic epilepsy.[57] Lacosamide has been successfully tested in animal models of epilepsy including 6 Hz psychomotor seizures, audiogenic seizures, maximal electroshock, and electrical kindling.[2,40]

Lacosamide demonstrates a bioavailability of 100% and protein-binding estimates are less than 15%.[10,55] The metabolism of lacosamide occurs mainly in the liver, mostly by isoenzymes CYP3A4, CYP2CP, and CYP2C19.[55] Lacosamide and its metabolites are 95% excreted in the urine, with 40% unchanged drug. Dosing should be decreased in patients with hepatic disease and not used in patients with severe hepatic impairment. No dose adjustment is needed in mild or moderate renal disease, and dosing should be decreased in patients with severe renal disease. Lacosamide is removed by hemodialysis.[11,55]

Lacosamide is available in 50, 100, 150, and 200 mg tablets, oral suspension, and intravenous solution. Recommended dosing of lacosamide starts at 50 mg twice a day to a maximum of 400 mg a day divided two times a day.[55] The half-life of lacosamide is 13 h.[10,55] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for lacosamide is in the range of 10-20 mg/L.[2] See Table 12.1 for clinical characteristics.

Lacosamide is indicated for adjunctive therapy for partial-onset seizures.[55] Initial studies of lacosamide as add-on therapy in patients with refractory partial-onset seizures demonstrated decreases in seizure frequency from 26% to 38% compared to 10% to 21% for placebo-treated patients.[55] Response rates (>50% seizure reduction) occurred in 33-41% compared to 18-26% in the control group[20,58–61]. Open-label extensions of initial studies out to 5-year completion rates documented median percent reduction in seizure frequency of 53-62%.[56] Post-marketing studies report responder rates of 32-68%.[60,61]

Lacosamide also comes in an intravenous formulation. The role of the use of lacosamide in status epilepticus is distinctly unclear. Lacosamide is highly potent in animal models of acute status epilepticus.[57] However, randomized clinical data in humans is not currently available. Reviews with summative data are complicated by inclusion of a preponderance of case reports and retrospective case series typically with very small sample size. Additionally, these retrospective series are complicated by coadministration of other seizure abortive agents and consist of mixed populations with

epilepsia partialis continua, prophylaxis following first-time seizures, post-operative prophylaxis, and seizure clusters with very few generalized tonic-clonic seizures and documented nonconvulsive status epilepticus.[62] Retrospective case studies with total sample sizes of 4-48 patients have reported subpopulations of patients with 0-11 generalized tonic-clonic seizures, 0-10 generalized nonconvulsive status epilepticus, and 4-10 complex partial status for respective totals of 13, 19, and 42 summed over six studies.[63–69] Efficacy in these small retrospective trials ranged from 38% to 100% with almost all patients having received other antiepileptic agents.

The most common adverse reactions with the use of lacosamide are dizziness, ataxia, vomiting, diplopia, nausea, vertigo, and blurred vision. As with all AEDs, lacosamide carries a warning of increased risk of suicidal ideation. Lacosamide increases the cardiac PR interval and has been associated with syncope, atrial fibrillation, and atrial flutter. Severe idiopathic responses have also been documented including drug reaction with eosinophilia and systemic symptoms/multiorgan hypersensitivity.[55] Lacosamide is Pregnancy Category C.[55] No pregnancy registry data is currently available for lacosamide.

Lacosamide has few effects on other drugs, and serum lacosamide levels are not influenced by many other drugs given its metabolism by demethylation, a pathway not susceptible to much modulation.[21,55] Mild decreases in plasma concentrations of lacosamide have been documented with the use of phenobarbital and phenytoin.[21] Decreases in the active metabolite of oxcarbazepine, H10-hydroxycarbazepine, have been seen with lacosamide use. However, neurotoxicity unrelated to plasma concentrations has been reported with coadministration of lacosamide with carbamazepine, lamotrigine, oxcarbazepine, and phenytoin.[21]

LAMOTRIGINE

Developed from a line of compounds initially chosen for their antifolate properties, lamotrigine was introduced into clinical practice in 1990 and received United States Food and Drug Administration approval in 1994, without significant proven antifolate effects.[23,39,70,71] The main mechanism of the action of lamotrigine is thought to be the inhibition of voltage-sensitive sodium channels,[70] although calcium channels may also be a target for lamotrigine's effects as well.[71] Lamotrigine has been successfully tested in animal models of epilepsy such as the maximal electroshock, subcutaneous pentylenetetrazol, spike-wave discharges, electrical kindling, phenytoin-resistant kindled rat, and visually and electrically evoked after discharges.[40,70]

Lamotrigine demonstrates a bioavailability of 98% and protein binding of 55%.[10,70] The metabolism of lamotrigine occurs by glucuronic acid conjugation.[70] No adjustment is needed for mild to moderate hepatic disease, but reduced dosing is recommended in patients with severe disease with ascites.[70] Use in renal disease is unknown and should be used with caution. Twenty percent of the plasma concentration is removed by hemodialysis.[70]

Lamotrigine is available in 25, 100, 150, and 200 mg tablets; 2, 5, and 25 mg chewable tablets; 25, 50, 100, and 200 mg oral disintegration tablets; and 25, 50, 100, 200, 250, and 300 mg extended-release tablets. Recommended dosing of lamotrigine in adults is to start with a very slow escalation to 100 mg twice a day with maximum dosing at 400 mg/day. Dosing in children also involves very slow escalation, starting at 0.3 mg/kg/day to a target of 7.5 mg/kg/day and a maximum of 300 mg/day. The half-life of lamotrigine varies based on other medications that are coadministered. Alone in adults, the half-life varies from 25 to 38 h. In the presence of enzyme-inducing agents, the half-life is changed to 12-14 h; with coadministration of valproate, the half-life varies from 48 to 70 h.[70] In children, the half-life is 19 h with coadministration of carbamazepine, resulting in a decrease to 7 h and valproate resulting in an increase to 45-65 h.[70] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for lamotrigine is from 2 to 20 mg/L.[10] See Table 12.1 for clinical characteristics.

Lamotrigine is indicated for monotherapy and adjunctive therapy for partial-onset seizures, primary generalized epilepsy, and multiple seizure types in patients with LGS.[70] Initial clinical data of adjunctive use of lamotrigine in adults with partial-onset seizures demonstrated a decrease in seizure frequency from 20% to 36% compared to 8% to 21 % in placebo-treated patients. In two crossover trials, lamotrigine demonstrated a decrease in seizure frequency of 25% compared to a placebo arm. In pediatric patients with partial-onset seizures, a 36% reduction in seizure frequency compared to 7% in controls was documented. Adults and pediatric patients with primary generalized tonic-clonic seizures demonstrated a 66% drop compared to 34% in the control group. In patients with LGS, there were decreases in major motor seizures, drop attacks, and tonic-clonic seizures of 32-36% compared to 9-10% for placebo. Monotherapy trials in adults with partial-onset seizures have also been performed with a trial design of escape criteria of increase seizures in comparison to low-dose valproate; lamotrigine had a favorable outcome of 42% reaching escape criteria compared to 69% in the control group. Review of multiple double-blind, placebo-controlled trials in parallel or crossover design demonstrated responder rates (>50% seizure reduction) of 7-67%.[72–75] In newly diagnosed patients,

lamotrigine demonstrated efficacy in patients with partial-onset and idiopathic generalized tonic-clonic seizures.[74,76–78] Of note, in these trials, patients treated with lamotrigine endorsed fewer adverse effects, with the exception of rash, compared to carbamazepine, phenytoin, and valproate. Open-label studies have been conducted with documented clinical efficacy of lamotrigine in patients with idiopathic primary generalized epilepsy, such as childhood absence and juvenile myoclonic epilepsy.[75,79–81] Multiple meta-analyses have been performed on the lamotrigine literature.[82–85] In these, the authors concluded that lamotrigine was effective as add-on therapy in patients with drug-resistant partial epilepsy; limited data suggests that lamotrigine decreases primary generalized tonic-clonic seizures. Lamotrigine was significantly less likely to be withdrawn than carbamazepine, but data was insufficient to determine efficacy as monotherapy in partial-onset seizures or in the treatment of childhood absence epilepsy. In an evidence-based structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis.[16,17] Lamotrigine was found to have evidence for a level D recommendation (potentially efficacious) for monotherapy in children with partial-onset seizures and a level C recommendation (possibly efficacious) in adults with partial and generalized onset seizures and children with absence seizures. Additionally, lamotrigine has evidence for a level A recommendation (established efficacy) for monotherapy for partial-onset seizures in elderly adults.

The most common adverse reactions with the use of lamotrigine are dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rash, GI upset, and insomnia. As with all AEDs, lamotrigine carries a warning of increased risk of suicidal ideation.[70] Severe idiopathic responses have also been documented including aseptic meningitis, blood dyscrasias, and drug reaction with eosinophilia and systemic symptoms. Stevens-Johnson syndrome occurs in 0.8% of children and 0.3% of adults.[70] Generally, the risk for development of a serious rash appears to be increased with high starting doses or rapid escalation.[86]

Lamotrigine is Pregnancy Category C.[70] The relative risk of major malformations identified in a pregnancy registry was 1.8.[53] Compared with baseline, lamotrigine plasma levels fall precipitously during pregnancy and may be reduced up to 60% with the clearance increasing more than 330% from preconception to the third trimester.[87–89] Lamotrigine dosing requires an average increase of 250% during pregnancy.[88,90] Following delivery, the elimination rate drops quickly, with plasma concentrations rising in the first 2-3 postpartum weeks.[88,90]

Lamotrigine has few effects on other drugs (see Table 12.2). Minor decreases in plasma concentrations of aripiprazole, clobazam, clonazepam, levetiracetam, lithium, quetiapine, and valproate have been documented,[21,33] while increases in atorvastatin and retigabine concentrations have been seen.[21,33] However, neurotoxicity unrelated to plasma concentrations has been reported with coadministration of lamotrigine with lacosamide.[21]

Lamotrigine is sensitive to interactions with coadministration of other medications via alterations in glucuronidation. Agents that inhibit glucuronidation increase levels of lamotrigine. The most important of these is valproate, with significant increase in plasma levels of lamotrigine; however, felbamate can also inhibit lamotrigine clearance. Agents that induce glucuronidation significantly decrease lamotrigine levels. These include aripiprazole, carbamazepine, ertapenem, eslicarbazepine acetate, fluoxetine, hormonal contraceptives with estrogen, lithium, lopinavir/ritonavir, methsuximide, olanzapine, orlisat, oxcarbazepine, imipenem, meropenem, panipenem, perampanel, phenobarbital, phenytoin, primidone, retigabine, rifampin, and rufinamide.[10,21,33,70]

LEVETIRACETAM

Developed as part of a formal anticonvulsant screening program, but nearly dismissed for lack of efficacy in the maximal electroshock and subcutaneous pentylenetetrazol models,[91] levetiracetam was first introduced into clinical practice in 1999 and received United States Food and Drug Administration approval in 1999.[23,39,92] The main mechanism of action of levetiracetam is thought to be binding to synaptic vesicle protein SV2A.[92] Levetiracetam is active in animal models of chronic epilepsy, but not acute seizures.[93] Levetiracetam has been successfully tested in animal models of epilepsy such as pilocarpine- and kainic-acid-induced secondarily generalization, spike-wave discharges, electrical kindling, phenytoin-resistant kindled rat, and 6 Hz electroshock.[40,92]

Levetiracetam demonstrates a bioavailability of 100% and minimal protein binding of less than 10%.[10,92] The metabolism of levetiracetam occurs by enzymatic hydrolysis of the acetamide group, independent of liver function. No adjustment is needed for hepatic diseases. Dose adjustment in renal disease is correlated with creatinine clearance and should be decreased for moderate to severe disease. Fifty percent of the plasma concentration is removed by hemodialysis.[92]

Levetiracetam is available in 250, 500, 750, and 1000 mg tablets; 500 and 750 mg extended-release tablets; oral solution; and intravenous formulation. Recommended dosing of levetiracetam in adults is to start at 1000 mg a day with advancement to a maximum of 3000 mg a day. Higher doses have been used, but there

is no systematic data as to their effectiveness. In children 1-6 months old, dosing is started at 7 mg/kg twice a day and advanced to a maximum of 21 mg/kg twice a day. In children 6 months to 4 years, dosing is recommended to start at 10 mg/kg twice a day and advanced to a maximum of 25 mg/kg twice a day. Children 4-16 years old are started at 10 mg/kg twice a day to a maximum of 30 mg/kg twice a day.[92] The half-life of levetiracetam is 6-8 h.[10,92] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for lamotrigine is from 12 to 46 mg/L.[10] See Table 12.1 for clinical characteristics.

Levetiracetam is indicated for adjunctive therapy for partial-onset seizures, myoclonic seizures, and primary generalized tonic-clonic seizures.[92] In pivotal double-blind trials, levetiracetam demonstrated seizure reduction rates of 17.7-55.9% compared to 6.1-13.7% in placebo-treated patients[92,94,95] with responder rates (>50% seizure reduction) of 22.8-55.9% compared to 10.4-26% in the control groups.[92–95] Of note in one study was the rapid onset of efficacy with significant seizure reductions seen in the first 2 weeks of the titration period.[96] Combined analysis of these studies in adults with localization-related epilepsy yielded overall responder rates of 35% compared to 9.4% in placebo-treated groups.[97] Long-term extensions of double-blind trials demonstrated continuation rates similar to other anticonvulsant agents of 60% at 1 year, 37% at 3 years, and 32% at 5 years.[98] Two double-blind placebo-controlled studies of levetiracetam as add-on therapy in children with partial-onset seizures documented a responder rate of 44.6% compared to 19.6% placebo in older children and 43.1% compared to 19.6% in infants and small children.[91,99,100] In a supplementary analysis of two placebo-controlled studies, patients treated with levetiracetam had a responder rate of 53.3-61.9% vs. placebo rate of 24.7-29.6% for idiopathic generalized epilepsy syndromes.[91,92,98,101] In a study of potential monotherapy, fewer patients taking levetiracetam (80.1%) met escape criteria of worsening seizures than the placebo group (90.5%).[95,102] Additionally, levetiracetam was demonstrated to be not inferior to carbamazepine in newly diagnosed patients with epilepsy.[94,98,103] Two meta-analyses have concluded that levetiracetam is an effective adjunctive agent for refractory epilepsy,[104,105] but data was lacking to support the use of monotherapy or use specifically for primary generalized seizures. In an evidence-based structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis.[16,17] Levetiracetam was found to have evidence for a level D recommendation (potentially efficacious) for adults with generalized tonic-clonic seizures and children with benign epilepsy with centrotemporal onset. Additionally, levetiracetam has evidence for a level A recommendation (established efficacy) for monotherapy for partial-onset adults.

Levetiracetam also comes in an intravenous formulation. The role of the use of levetiracetam in status epilepticus is distinctly unclear. Reviews with summative data are complicated by the inclusion of a preponderance of case reports, and the retrospective case series typically have very small populations. The reports are complicated by coadministration of other seizure abortive agents and consist of mixed populations with epilepsia partialis continua as well as first-time seizures, postoperative prophylaxis, and seizure clusters with very few generalized tonic-clonic seizures and nonconvulsive status epilepticus reported.[62] Retrospective case studies with total sample sizes of 10-73 patients have reported subpopulations of patients with generalized tonic-clonic seizures of 1-8, generalized nonconvulsive status epilepticus of 6-7, and complex partial status of 9-20 for respective totals of 37, 21, and 91 summed over 10 studies.[106–115] The most common reason for levetiracetam use was that standard treatment was deemed inappropriate.[116] Higher-efficacy rates have been reported by these retrospective trials than the few prospective trials. Not all trials reported treatment success by seizure type; however, when reported, levetiracetam appeared to have the best efficacy in complex partial status. This is congruent with data from a prospective trial in which the status was terminated with levetiracetam use in 3/5 cases of simple focal, 11/18 complex focal, 2/2 myoclonic, 2/8 generalized nonconvulsive, and 0/8 generalized tonic-clonic seizures.[117] In a prospective randomized comparison trial, levetiracetam demonstrated similar efficacy to lorazepam as first-line treatment for prolonged seizures.[118] A prospective registry with retrospective analysis of status epilepticus demonstrated that the use of levetiracetam was related to a higher risk of second-line treatment failure, even adjusting for mortality, and statistically corresponded to 16.8% treatment failures attributable to its use.[119]

The most common adverse reactions with the use of levetiracetam are psychiatric reactions such as irritability, aggression, anxiety, depression, emotional lability, and psychosis. Other common adverse events include somnolence and fatigue. There is a minor but statistically significant decline in complete blood count with levetiracetam. As with all AEDs, levetiracetam carries a warning of increased risk of suicidal ideation. Severe idiopathic responses have also been documented, including Stevens-Johnson syndrome and toxic epidermal necrolysis.[92]

Levetiracetam is Pregnancy Category C.[92] The relative risk of major malformations identified in a pregnancy registry was 2.2.[53] There is a gradual decline in plasma levels throughout pregnancy, which is most pronounced

in the third trimester.[87,92] These levels may fall as low as 40% of baseline plasma levels.[87]

Levetiracetam has few effects on other drugs (see Table 12.2). Probenecid decreases renal clearance of levetiracetam.[33,92] Carbamazepine, clobazam, lamotrigine, oxcarbazepine, phenytoin, phenobarbital, and primidone can increase clearance of levetiracetam.[21]

OXCARBAZEPINE

Designed as an analogue of carbamazepine, oxcarbazepine was first introduced in Denmark in 1990 and is available in multiple other countries.[13,23,120] Oxcarbazepine received United States Food and Drug Administration approval in 2000.[39,121] The main mechanism of action of oxcarbazepine is thought to be blockade of voltage-sensitive sodium channels.[121] Oxcarbazepine has been successfully tested in animal models of epilepsy such as maximal electroshock test, electrically induced tonic seizures, and focal seizures in Rhesus monkeys.[121]

Oxcarbazepine demonstrates a bioavailability of 100% and protein binding of 40-60%.[10,121] Oxcarbazepine undergoes extensive metabolism by cytosolic enzymes to the active form of 10-monohydroxy metabolite (MHD). The metabolism of MHD is by glucuronic acid conjugation. Ninety-five percent of oxcarbazepine metabolite is excreted in the urine, with 27% of MHD excreted unchanged. Metabolism mainly occurs by enzymatic hydrolysis of the acetamide group independent of liver function. No adjustment is needed for mild to moderate hepatic diseases with unknown effect in severe cases.[121] Dose adjustment in renal disease should be half of the regular prescribed dose.

Oxcarbazepine is available in 150, 300, and 600 mg tablets and oral solution. Recommended dosing of oxcarbazepine in adults is to start at 300 mg twice a day with an advancement to a maximum of 1200 mg twice a day. In children 2-4 years old, a starting dose of 8-10 mg/kg twice a day is recommended. For children 4-16 years old, an initiation dose of 4 mg/kg twice a day to a maximum of a total of 60 mg/kg/day. The half-life of oxcarbazepine is 2 h and of the active metabolite MHD is 9 h.[121] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for oxcarbazepine's main active metabolite MDH is 2-55 mg/L.[122]

Oxcarbazepine is indicated for adjunctive and monotherapy for partial-onset seizures.[121] Initial approval studies with oxcarbazepine as adjunctive therapy in adults and children with partial-onset seizures demonstrated median seizure reductions of 26.4-49.9% compared to 7.6-9.4% in placebo-treated patients and up to 22% of patients on the highest dose demonstrating seizure freedom during the trials.[121,123] Additional data from a randomized study in children with focal-onset epilepsy demonstrated a significant reduction in seizure frequency with oxcarbazepine (35%) compared to placebo (9%) with a responder rate (>50% seizure reduction) of 41% vs. 22%.[123–125] In evaluations of potential for monotherapy, oxcarbazepine had favorable times to reach exit criteria of worsening seizures compared to placebo controls in two studies.[121] Oxcarbazepine demonstrated noninferiority to carbamazepine treatment in both retrospective and double-blind cross over studies[14,124,126,127] as well as noninferiority to phenytoin[97,127,128] and valproate[97,123,127,129] in reducing partial and generalized tonic-clonic seizures. Meta-analyses on oxcarbazepine have concluded that it has efficacy as add-on treatment for patients with drug-resistant partial epilepsy,[130] and that oxcarbazepine is similarly effective as carbamazepine.[131] An additional meta-analysis concluded that data was not present to support a comparison of oxcarbazepine's efficacy to phenytoin, but it appeared to be better tolerated.[132] In an evidence-based structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis.[16,17] Oxcarbazepine was found to have evidence for a level D recommendation (potentially efficacious) for monotherapy in children with generalized tonic-clonic seizures and children with benign epilepsy with centrotemporal spikes and a level C recommendation (possibly efficacious) in adults with partial-onset seizures and generalized onset tonic-clonic seizures. Additionally, oxcarbazepine has evidence for a level A recommendation (established efficacy) for monotherapy for partial-onset seizures in children.

The most common adverse reactions with the use of oxcarbazepine are dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, and abnormal gait. As with all AEDs, oxcarbazepine carries a warning of increased risk of suicidal ideation. Severe idiopathic responses have also been documented, including angioedema, psychomotor slowing, somnolence, fatigue, ataxia, multiorgan hypersensitivity, Stevens-Johnson syndrome, and toxic epidermal necrolysis.[121] Rarely, the use of oxcarbazepine has been associated with pancytopenia, agranulocytosis, and leukopenia. Hyponatremia has been documented in 2.5% of patients.

Oxcarbazepine is Pregnancy Category C.[121] The relative risk of major malformations identified in a pregnancy registry was 1.1.[53] There is a gradual decline in plasma levels of the active metabolite MHD throughout pregnancy to at least 36% lower than pre-pregnancy levels.[87,121]

Oxcarbazepine acetate should not be taken with eslicarbazepine. Oxcarbazepine affects the metabolism of

other medications through the inhibition of CYP2C19 and induction of CYP3A4 and CYP3A5 (see Table 12.2). Decreased plasma levels are seen in hormonal contraceptives, carbamazepine, cyclosporine, felodipine, imatinib, lamotrigine, levetiracetam, perampanel, rufinamide, and topiramate.[21,33,121] Increased plasma levels of phenobarbital and phenytoin can be seen with coadministration of oxcarbazepine.[21] However, neurotoxicity unrelated to plasma concentrations have been reported with coadministration of oxcarbazepine with lacosamide.[21]

Oxcarbazepine metabolism is affected by several other drugs (see Table 12.2). Oxcarbazepine plasma levels are decreased by carbamazepine, clobazam, lacosamide, lamotrigine, phenobarbital, phenytoin, topiramate, viloxazine, and verapamil.[21,33,121] Coadministration of perampanel increases oxcarbazepine levels.[21]

PERAMPANEL

Developed during a screening search for a noncompetitive AMPA receptor antagonist, perampanel received United States Food and Drug Administration approval in 2012.[133,134] Perampanel is a Schedule Class III controlled substance in the United States secondary to a potential for abuse.[133] The main mechanism of action of perampanel is thought to be noncompetitive AMPA-glutamate receptor antagonism.[133] Perampanel has been successfully tested in animal models of epilepsy such as maximal electroshock, subcutaneous pentylenetetrazol-induced seizures as well as audiogenic and 6 Hz seizures.[135]

Perampanel demonstrates a bioavailability of 100% and protein binding of 95%. Perampanel is metabolized mainly by the CYP3A4 and CYP3A5 enzymes. Twenty-two percent of perampanel is excreted in the urine primarily as metabolites. Maximal dosing in mild and moderate hepatic impairment should be reduced to 6 and 4 mg respectively. Perampanel should not be used in severe hepatic impairment. No dosing adjustment is needed in mild renal disease but should be used with caution in moderate disease and not used in severe renal impairment.[133]

Perampanel is available in 2, 4, 6, 8, 10, and 12 mg tablets. Recommended initiation dosing of perampanel is 2 mg once at bedtime with advancement to a maximum of 12 mg once a day. The half-life of perampanel is 105 h.[133] A recommended therapeutic range for perampanel has not been established. See Table 12.1 for clinical characteristics.

Perampanel is indicated for adjunctive therapy for partial-onset seizures.[133] Initial clinical trial data from three randomized trials demonstrated significant declines in seizure frequency from 23.3% to 34.5% compared to 9.7% to 21.0% for placebo-treated patients with responder rates (>50% seizure reduction) in 33.3-37.6% compared to 14.7-26.4% in the control groups.[136] Extension studies have documented responder rates from 43.8% to 51.5% over 1- to 4-year extensions in those patients choosing to continue the medication.[136,137]

The most common adverse reactions with the use of perampanel are dizziness, psychomotor impairment, somnolence, vertigo, aggression, anger, ataxia, blurred vision, irritability, and dysarthria. As with all AEDs, perampanel carries a warning of increased risk of suicidal ideation. Perampanel is associated with life-threatening behavioral reactions, including aggression, hostility, anger, and homicidal ideation.[133] Perampanel is Pregnancy Category C.[133] No pregnancy registry data is currently available for perampanel.

Perampanel demonstrates superadditive effects on alertness when used with alcohol.[33] Perampanel is a weak modulator of hepatic enzymes and affects the metabolism of other medications (see Table 12.2). Decreased plasma levels are seen in carbamazepine, clobazam, hormonal contraceptives, lamotrigine, midazolam, and valproate with coadministration of perampanel.[21,33,133] Perampanel induces CYP3A and should be avoided in conjunction of other strong CYP3A inducers such as St. John's wort and rifampin.[133] Plasma levels of oxcarbazepine are increased with coadministration of perampanel.[21]

Perampanel metabolism is affected by several other drugs (see Table 12.2). Perampanel plasma levels are decreased by carbamazepine, clobazam, oxcarbazepine, phenytoin, rifampin, St. John's wort, and topiramate.[20,133] Ketoconazole increases perampanel plasma levels.[33,133]

PREGABALIN

Developed as a potential lipophilic analogue of GABA modified to diffuse more easily across the blood-brain barrier, pregabalin was first introduced into clinical practice in 2004 and received United States Food and Drug Administration approval in 2004.[23,138] Pregabalin is a Schedule Class V controlled substance in the United States secondary to withdrawal symptoms on discontinuation.[138] Despite its design intentions, the main mechanism of action of pregabalin is thought to be binding to the α_2-δ subunit of the calcium channel rather than GABA-related function.[136] Pregabalin has been successfully tested in animal models of epilepsy such as maximal electroshock and subcutaneous pentylenetetrazol-induced seizures.[40]

Pregabalin demonstrates a bioavailability of 90% and no protein binding.[10,138] Pregabalin undergoes minimal (less than 2%) metabolism and is excreted in the urine unchanged.[138] No dosing adjustment is required in

patients with hepatic disease. Maximal dosing in patients with mild, moderate, and severe renal disease should be reduced to 300, 150, and 75 mg respectively and dosing should be once daily.[138]

Pregabalin is available in 25, 50, 75, 100, 150, 200, 225, and 300 mg tablets as well as an oral solution. Recommended initiation dosing of pregabalin is 150 mg/day divided two or three times a day. The recommended maximum dosing is 600 mg/day.[138] The half-life of pregabalin is 6 h.[10,138] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the proposed therapeutic range for pregabalin is 2.8-8.3 mg/L.[13,139] See Table 12.1 for clinical characteristics.

Pregabalin is indicated for adjunctive therapy for partial-onset seizures.[138] In initial clinical studies in adults with refractory partial-onset epilepsy, pregabalin was associated with a decrease in seizure frequency of 9-48% compared to the 0-1% in the placebo-treated group. Responder rate (>50% seizure reduction) was 31-51% compared to 8-14% in controls.[138,140] Open-label extension trials demonstrated retention rates of 25-42%. Responder rates or "markedly improved patients" of 14-60% were recorded in these self-selected populations.[140–142] The data on pregabalin has been subjected to two meta-analyses. Pregabalin was found to be efficacious in treatment of drug-resistant partial epilepsy.[143] However, comparisons to lamotrigine have been inconsistent, and potentially subject to trial design with possible inferiority to lamotrigine in efficacy.[144] In an evidence-based structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis.[16,17] Pregabalin was found to have an inadequate efficacy or effectiveness data available for consideration of use as monotherapy for epilepsy.

The most common adverse reactions with the use of pregabalin are dizziness, somnolence, ataxia, dry mouth, edema, blurred vision, weight gain, and decreased concentration.[47,138] As with all AEDs, pregabalin carries a warning of increased risk of suicidal ideation. Severe idiopathic responses have also been documented, including angioedema and hypersensitivity reactions. The use of pregabalin has been associated with elevations in creatinine kinase levels and decreases in platelet counts. Prolongation of the cardiac PR interval has also been documented.[138] Pregabalin is Pregnancy Category C.[138] No pregnancy registry data is currently available for pregabalin.

Pregabalin has minimal interactions with other medications (see Table 12.2). Additive effects on cognition and motor functions are seen with concomitant use of oxycodone.[33] The coadministration of gabapentin and phenytoin can decrease plasma pregabalin levels. Decreases in plasma concentration of tiagabine has been documented.[21,138]

RUFINAMIDE

Discovered as part of a sponsored anticonvulsant drug screening program, rufinamide was first introduced into clinical practice in 2007 and received United States Food and Drug Administration approval in 2008.[23,145] The main mechanism of action of rufinamide is thought to be prolongation of the inactive state of sodium channels.[145] Rufinamide has been successfully tested in animal models of epilepsy such as maximal electroshock and subcutaneous pentylenetetrazol-induced seizures.[40]

Rufinamide demonstrates a bioavailability of 85% and protein binding of 34%.[10,145] Rufinamide undergoes hydrolysis by carboxylesterase. Less than 2% of rufinamide or its metabolites are excreted in the urine, however, 30% is removed by hemodialysis. No adjustment is needed in patients with renal disease. The use of rufinamide in patients with hepatic impairment has not been studied.[145]

Rufinamide is available in 200 and 400 mg tablets and an oral solution. Recommended dosing of rufinamide in adults is to start at 400 mg/day divided twice a day with advancement to a maximum of 3200 mg/day divided twice a day. In children, a starting dose of 10 mg/kg/day divided twice a day is recommended to a maximum of 45 mg/kg/day or a total of 3200 mg/day, whichever is less.[145] The half-life of rufinamide is 6-10 h.[10,145] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for rufinamide is 10-40 mg/L.[10]

Rufinamide is indicated for adjunctive therapy for seizures in patients with LGS. Initial studies in patients with LGS showed a 32.7% decrease in total seizures and a 42.5% decrease in atonic seizures compared to 11.7% and 1.4% respectively for placebo-treated patients with responder rates (>50% seizure reduction) of 42% compared to 16.7% in controls.[145,146] Rufinamide was tested in a small number of patients with refractory partial-onset seizures with significant decrease in seizure frequency compared to controls, but the responder rate of 39% compared to control group 16% did not reach statistical significance.[147] Short-term (28 day) data from a double-blind trial in adults with refractory partial or primary generalized tonic-clonic seizures documented a significant decline in seizure frequency (−41% vs. +52% control).[148,149] A retrospective review of patients with varied refractory epilepsy syndromes captured a responder rate of 46.7%,[150] while a longer prospective trial in patients with partial-onset epilepsy had a responder rate of 11.6-16% compared with placebo response of 9%.[151,152]

The most common adverse reactions with the use of rufinamide are somnolence, fatigue, dizziness, ataxia, headache, nausea, and vomiting.[145,152] As with all AEDs,

rufinamide carries a warning of increased risk of suicidal ideation. Severe idiopathic responses have also been documented, including multiorgan hypersensitivity and increased risk for status epilepticus. The use of rufinamide has been associated with leukopenia, and shortening of the cardiac QT interval has also been documented.[145] Rufinamide is Pregnancy Category C.[145] No pregnancy registry data is currently available for rufinamide.

Rufinamide affects the metabolism of other medications (see Table 12.2). Decreased plasma levels are seen in carbamazepine, hormonal contraceptives, lamotrigine, and triazolam,[21,33,145] while increased plasma levels are seen in phenobarbital and phenytoin[21] with concurrent rufinamide use.

Rufinamide metabolism is affected by several other drugs (see Table 12.2). Rufinamide plasma levels are decreased by carbamazepine, clobazam, oxcarbazepine, phenobarbital, phenytoin, primidone, and vigabatrin. Valproate increases plasma levels of rufinamide.[21,145]

TIAGABINE HYDROCHLORIDE

Developed specifically to influence the GABAergic system[14,153] tiagabine was first introduced into clinical practice and received United States Food and Drug Administration approval in 1997.[23,39,154] The main mechanism of action of tiagabine is thought to be enhancement of GABA activity through blocking GABA uptake.[154] Tiagabine has been successfully tested in animal models of epilepsy such as subcutaneous pentylenetetrazol-induced tonic seizures, audiogenic seizures in genetically prone mice, and amygdalar kindled seizures.[40,154]

Tiagabine demonstrates a bioavailability of 90% and protein binding of 96%. Tiagabine undergoes metabolism by thiophene ring oxidation and glucuronidation. Twenty-five percent of tiagabine and its metabolites are excreted in the urine, with only 2% unchanged.[154] When adjusted for body weight, tiagabine elimination is up to two times higher in children.[155] No adjustment is needed in patients with renal disease. Given that moderate hepatic impairment increases tiagabine dosing by 60%, total dosing should be reduced and the dosing interval should be increased in this population.[154]

Tiagabine is available in 2, 4, 12 and 16 mg tablets. Recommended initial dosing of tiagabine is 4 mg/day divided in two to three times a day with advancement to a maximum of 32 mg/day divided two to three times a day. The half-life of tiagabine is 3-9 h. Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for tiagabine is 5-70 mg/L.[154] See Table 12.1 for clinical characteristics.

Tiagabine is indicated for adjunctive therapy for partial-onset seizures.[154] Initial clinical trials of tiagabine in adults with refractory partial-onset seizures demonstrated a median reduction of 13-36% compared to 3-9% in placebo-treated patients. In a study restricted to complex partial seizures, tiagabine demonstrated a decrease of 11-14% compared to increases in seizure frequency in the placebo groups.[154,156–158] Integrated and meta-analysis of five double-blind, placebo-controlled trials, stratified by seizure type, yielded seizure reductions of 27% for simple partial seizures, 20% for complex partial seizures, and 38% for secondarily generalized seizures compared to 6%, 4%, and 7% respective reductions in the placebo-treated patients.[153,159] Responder rates (>50% seizure reduction) were similarly analyzed with patients responding 30-32% for simple partial seizures, 24-27% for complex partial seizures, and 40-45% for secondarily generalized seizures compared to 10-11%, 8-13%, and 30% respective responder rates in the control groups.[153,159] Results in trials for monotherapy have been mixed, with data including a responder rate of 30% for complex partial seizures but a nonsignificant decrease in overall median seizure reduction, and a 61% responder rate for a study with highest allowable dosing and a 100% incidence of adverse events.[153,159] A meta-analysis concluded that tiagabine reduces seizure frequency but is associated with some adverse effects in patients with refractory partial-onset epilepsy.[160] Use of tiagabine is associated with an increased risk of status epilepticus and worsening of spike and wave discharges on the electroencephalogram up to nonconvulsive status epilepticus.[154] In an evidence-based structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis.[16,17] Tiagabine was found to have inadequate efficacy or effectiveness data available for consideration of use as monotherapy for epilepsy.

The most common adverse reactions with the use of tiagabine are decreased concentration, confusion, somnolence, fatigue, nervousness, dizziness, and tremor.[154,155] As with all AEDs, tiagabine carries a warning of increased risk of suicidal ideation. Use of tiagabine is associated with an increased risk of status epilepticus and worsening of spike and wave discharges on the electroencephalogram up to nonconvulsive status epilepticus.[154] Tiagabine is Pregnancy Category C. No pregnancy registry data is currently available for tiagabine.

Tiagabine has minimal effects on the metabolism of other medications (see Table 12.2).[154] Valproate levels are decreased by coadministration of tiagabine.[21] Tiagabine metabolism is affected by several other drugs. Tiagabine plasma levels are decreased by carbamazepine, cimetidine, clobazam, phenobarbital, phenytoin,

pregabalin, and primidone.[21,33,154] Tiagabine is displaced from serum proteins by naproxen, salicylates, and valproate.[161] Gemfibrozil has been reported to increase tiagabine plasma concentrations.[33]

TOPIRAMATE

Discovered serendipitously in the search for a sugar sulfamate in an antidiabetic project,[162] topiramate was first introduced into clinical practice in 1995 and received United States Food and Drug Administration approval in 1996.[23,39,163] The main mechanisms of action of topiramate are thought to be blockade of voltage-sensitive sodium channels, augmentation of GABA, antagonism of AMPA receptors, and inhibition of carbonic acid enzyme.[163] Topiramate has been successfully tested in animal models of epilepsy such as maximal electroshock test, subcutaneous pentylenetetrazol-induced seizures, spike-wave discharges, phenytoin-resistant kindled rat, seizures in spontaneous epileptic rat, and amygdalar and global ischemia-induced seizures.[39,163]

Topiramate demonstrates a bioavailability of 80% and protein binding of 9-41%.[10,163] Topiramate is metabolized by hydroxylation, hydrolysis, and glucuronidation. Topiramate is excreted 70% unchanged in the urine. Dose adjustment in renal disease should be half of the regular prescribed dose. Hemodialysis removes topiramate at a rate of four to six times clearance in healthy individuals.[163]

Topiramate is available in 25, 50, 100 and 200 mg tablets, 15 and 25 mg sprinkle capsules, 25, 50, 100, and 200 mg extended-release tablets. Recommended initial dosing of topiramate is to start at 400 mg/day divided twice a day with advancement to a maximum of 1600 mg divided twice a day, although many advocate the use of much lower starting doses of 100 mg/day. In children up to age 11 are started at 150 mg/day to a maximum of 250 mg/day.[163] The half-life of topiramate is 20-30 h.[13] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for topiramate is 5-20 mg/L.[10]

Topiramate is indicated for adjunctive and monotherapy for partial-onset and primary generalized seizures.[163] Initial clinical trials with topiramate as adjunctive therapy in adults with partial-onset seizures demonstrated a median seizure reduction of 24.3-47.5% compared to a 20.6% seizure increase to a 20% seizure reduction in placebo-treated patients. The responder rate (>50% seizure reduction) was 24-47% compared to 0-24% in the control groups.[163,164] Pooled analysis of six trials of adjunctive therapy in adults with partial-onset seizure revealed a responder rate of 44% compared with 12% for the placebo controls.[165,166] Pediatric patients with partial-onset seizures had a median reduction of seizures of 33.1% compared to 10.5% for placebo and a responder rate of 39% compared to 20%.[163] Topiramate was also found to be efficacious in primary generalized seizures, with a median reduction of 56.7% (vs. 9% placebo) and a responder rate of 56% (vs. 20% placebo) in a pediatric population and a median seizure reduction of 14.8% (vs. 5.1% increase placebo) and a responder rate of 28% (vs. 14% placebo) in a population with LGS.[162,163,165] Open-label extension in one of these trials documented an ongoing responder rate of 58-91% of the self-selected population.[162] In studies toward evaluation of monotherapy, a higher dose of topiramate demonstrated a favorable time to first seizure after therapy compared to a lower dose and retrospective, and open-label extension studies demonstrated a 33% rate of successful conversion to monotherapy.[162,163,165,167] A study of topiramate use as first-line treatment in adults and children with partial and generalized onset seizures demonstrated a 59-76% 1-year seizure freedom rate.[168,169] An open-label trial with flexible dosing documented a responder rate of 76.3%.[167,168] In an evidence-based structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis.[16,17] Topiramate was found to have evidence for a level D recommendation (potentially efficacious) for monotherapy in elderly adults with partial-onset seizures and juvenile myoclonic epilepsy. Topiramate had evidence for a level C recommendation (possibly efficacious) in adults and children with partial-onset seizures and generalized onset tonic-clonic seizures.

The most common adverse reactions with the use of topiramate are paresthesias, anorexia, weight loss, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, decreased memory, decreased cognition, mood, fever, infection, and flushing.[163] Although not documented in double-blind trials of monotherapy with topiramate, word-finding difficulty is intensely researched.[166] As with all AEDs, topiramate carries a warning of increased risk of suicidal ideation. Topiramate is associated with the development of nephrolithiasis and secondary angle closure glaucoma. In children, there have been reports of oligohydrosis and hyperthermia. The use of topiramate is associated with the development of metabolic acidosis and hyperammonemia.[163]

Topiramate is Pregnancy Category D secondary to increased risk of cleft palate.[163] Relative risk of major malformations identified in a pregnancy registry was 3.8.[53] Topiramate levels can fall by 30-40% during pregnancy.[87]

When coadministered with other agents, topiramate can contribute to the development of metabolic abnormalities. Coadministration with valproate increases the

risk of hyperammonemia and hypothermia. Use with other carbonic anhydrase inhibitors such as acetazolamide dichlorphenamide, and zonisamide increases the risk of metabolic acidosis and nephrolithiasis.[163]

Topiramate induces CYP3A4 and affects the metabolism of other medications (see Table 12.2). Coadministration of topiramate can result in decreased plasma levels of carbamazepine, clobazam, digoxin, eslicarbazepine acetate, ethosuximide, glyburide, hormonal contraceptives, imatinib, oxcarbazepine, perampanel, pioglitazone, risperidone, and valproate.[21,32,163,170,171] Use of topiramate at high doses increases lithium plasma concentrations, while some increase in plasma concentrations of amitriptyline, diltiazem, haloperidol, metformin, phenytoin, and sumatriptan have been documented.[21,33,163]

Topiramate clearance is affected by several other drugs (see Table 12.2). Topiramate plasma levels are decreased by carbamazepine, clobazam, eslicarbazepine acetate, metformin, oxcarbazepine, phenobarbital, phenytoin, primidone, and vigabatrin.[33,163,170] Diltiazem, hydrochlorothiazide, posaconazole, and propranolol can increase topiramate concentrations.[32,163]

VIGABATRIN

Vigabatrin was synthesized in 1974 as a structural analog of GABA and used in 1977 as a selective inhibitor of 4-aminobutyric acid aminotransferase. Introduced into clinical practice in 1989, multiple studies were conducted through the 1980-1990s regarding clinical efficacy. Vigabatrin received United States Food and Drug Administration approval for use in for adjunctive therapy for partial-onset seizures and monotherapy in infantile spasms in 2009.[23,38,39,172–174] The main mechanism of action of vigabatrin is thought to be irreversible inhibition of GABA transaminase resulting in increased GABA levels.[172] Vigabatrin has been successfully tested in animal models of epilepsy such as subcutaneous pentylenetetrazol-induced seizures and electrical kindling.[40]

Vigabatrin demonstrates a bioavailability of 50-60% and no protein binding.[10,172] Vigabatrin is eliminated primarily by renal excretion. Dosing in renal disease should be decreased by 25% in mild renal disease, by 50% in moderate disease, and by 75% in severe disease.[172]

Vigabatrin is available in 500 mg tablets and a powder for oral solution. Recommended dosing of vigabatrin in adults is to start at 500 mg twice a day with advancement to a maximum of 1500 mg twice a day. In children age 10-16 years old, the starting dose is 250 mg twice a day with advancement to a maximum of 1000 mg twice a day. Recommended dosing for infants is 50 mg/kg/day divided twice a day to a maximum of 150 mg/kg/day divided twice a day.[172] The half-life of vigabatrin is 5-8 h.[13] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for vigabatrin is 0.8-36 mg/L.[10] See Table 12.1 for clinical characteristics.

Vigabatrin is only available on a limited basis and is indicated for adjunctive therapy for partial-onset seizures and monotherapy in infantile spasms.[172] Multiple studies have been conducted on vigabatrin use in infantile spasms. Retrospective studies have documented spasm freedom in 42.5-82% of subjects.[175] Prospective studies have documented spasm reduction of 68.9-77.9% compared to 17-25.9% with placebo[172,176] and spasm freedom ranging from 26% to 100% if data is gathered out to 1 month compared to 16-26% in placebo controls.[176,177] There is some suggestion in retrospective data that vigabatrin may be more effective in patients with tuberous sclerosis as the etiology of the infantile spasms, with spasm freedom in 73% of this population.[175] Vigabatrin has also been studied extensively as adjunctive therapy in refractory complex partial seizures. Seizure reduction in double- and single-blinded studies have ranged from 33.7% to 56.5% compared to 2% to 16.7% in placebo-treated patients.[172,176] Responder rates (>50% seizure reduction) of 24-70% compared to 16-26% in placebo controls have been documented[177,178] with a 40-50% responder rate calculated over all trials.[174] In studies of long-term use of vigabatrin, 39-72% elect to stay on vigabatrin 3 years after initiation of therapy[174] with maintained 24-54% responder rates documented.[179] Meta-analysis on data on vigabatrin for treatment of refractory partial epilepsy concluded that vigabatrin reduces seizure frequency in this population while a separate analysis had insufficient data to address the risk-benefit balance of using vigabatrin compared to carbamazepine given the high incidence of visual field defects with the former.[180,181] In an evidence-based structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis.[16,17] Vigabatrin was found to have evidence for a level D recommendation (potentially efficacious) for monotherapy in adults with generalized onset seizures and a level C recommendation (possibly efficacious) in adults and children with partial-onset seizures.

The most common adverse reactions with the use of vigabatrin are permanent vision loss, fatigue, somnolence, nystagmus, tremor, blurred vision, memory impairment, weight gain, arthralgia, abnormal coordination, and confusion. As with all AEDs, vigabatrin carries a warning of increased risk of suicidal ideation.[172] Vigabatrin is associated with a high incidence of progressive, permanent visual field constriction requiring periodic vision assessment.[182] Vigabatrin is also associated with the development of anemia, peripheral neuropathy,

psychosis, and edema.[172,183] Vigabatrin is Pregnancy Category C. No pregnancy registry data is currently available for vigabatrin.

Vigabatrin interacts with the metabolism of few other medications (see Table 12.2). Coadministration of vigabatrin can result in decreased plasma levels in clonazepam, phenytoin, and rufinamide.[21,172] Vigabatrin levels can be decreased with felbamate use.[21]

ZONISAMIDE

Developed through routine screening of 1,2-benzisoxazole derivatives, zonisamide was introduced into clinical practice in 1989 and received United States Food and Drug Administration approval in 2000.[23,39,184,185] The main mechanism of action of zonisamide is thought to be blockade of sodium channels and reduction of voltage-dependent transient induced currents (T-type calcium channels).[184] Zonisamide has been successfully tested in animal models of epilepsy such as maximal electroshock test, electrical kindling, tungstic acid gel in rats, and cortical freezing in cats.[40,184]

Zonisamide demonstrates a bioavailability of 90% and protein binding of 40%.[10,184] Zonisamide undergoes metabolism by CYP3A4 and glucuronide. Zonisamide and its metabolites are primary excreted in the urine. Dose adjustment should be made in marked renal impairment. Use has not been studied in patients with hepatic diseases.[184]

Zonisamide is available in 25 and 100 mg tablets. Recommended initial dosing of zonisamide is 100 mg a day with advancement to a maximum of 600 mg,[184] although doses past 400 mg/day have not been consistently associated with increased efficacy.[186] The half-life of zonisamide is 27-70 h.[10] Although therapeutic dosing is determined based on seizure frequency and toxic side effects, the recommended therapeutic range for zonisamide is 10-40 mg/L.[10,185] See Table 12.1 for clinical characteristics.

Zonisamide is indicated for adjunctive therapy for partial-onset seizures.[184] Initial clinical data for adjunctive treatment of partial-onset seizures in adults demonstrated median reduction in seizure frequency ranging from 20.4% to 51.3% compared to placebo −6.6% to 22.5% and responder rates (>50% seizure reduction) ranging from 25% to 51.2% compared to 9.6% to 22.2% in the placebo-treated groups.[184,187–189] A large open-label extension study has also been performed with 45% 1-year retention rate and an overall 41% decrease in all seizures and a 67.5% decrease in generalized tonic-clonic seizures.[187] Other extension studies carried out of 12, 24, and 36 months documented median reduction in seizures of 45%, 45.7% and 47% with responder rates ranging from 33% to 55% in the respective 65.3%, 44.5%, and 28.8% of individuals choosing to remain on zonisamide.[188] Similar data was obtained from open-label studies with responder rates in the low 40%.[190] Monotherapy for adults with newly diagnosed partial-onset seizures has been investigated with noninferiority comparison to carbamazepine, which demonstrated no significant differences in seizure freedom between the two treatment groups out to 52 weeks (67.6% zonisamide, 74.7% carbamazepine).[188,189] Zonisamide use in pediatric population with primary generalized epilepsy demonstrated a 81.2% decrease in generalized tonic-clonic seizures compared to 43.8% low-dose valproate.[187] Additionally, other small open-label studies as well as case reports exist for successful use of zonisamide in other idiopathic generalized epilepsies including myoclonic seizures, infantile spasms, and absence seizures. A 50% responder rate has been documented in a small LGS population.[187] In a meta-analysis, the authors concluded that zonisamide had efficacy as add-on treatment for drug-resistant partial-onset epilepsy.[191] In an evidence-based structured literature review, the International League Against Epilepsy put forth treatment guidelines regarding seizure prophylaxis.[16,17] Zonisamide was found to have evidence for a level D recommendation (potentially efficacious) for monotherapy in children with partial-onset seizures. Additionally, zonisamide has evidence for a level A recommendation (established efficacy) for monotherapy for partial-onset seizures in adults.

The most common adverse reactions with the use of zonisamide are somnolence, anorexia, dizziness, ataxia, agitation, irritability, memory impairment, and decreased concentration. As with all AEDs, zonisamide carries a warning of increased risk of suicidal ideation. Severe idiopathic responses have also been documented including Stevens-Johnson syndrome, toxic epidermal necrolysis, aplastic anemia, and agranulocytosis. In children, there have been reports of oligohydrosis and hyperthermia. Use with other carbonic anhydrase inhibitors such as topiramate, acetazolamide, and dichlorphenamide increases the risk of metabolic acidosis and nephrolithiasis.[184] Zonisamide is Pregnancy Category C. No pregnancy registry data is currently available for zonisamide. Some reports suggest that zonisamide clearance may be increased during pregnancy.[86]

Zonisamide affects the metabolism of few other medications, but zonisamide clearance is affected by several other drugs (see Table 12.2). Zonisamide plasma levels are decreased by carbamazepine, clobazam, cyclosporine, phenytoin, phenobarbital, primidone, and risperidone.[21,33,184,186] Coadministration with other carbonic anhydrase inhibitors, like topiramate, can increase the risk of metabolic acidosis and nephrolithiasis.

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CHAPTER

13

Antiepileptic Drugs and Brain Tumor Patients

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CHAPTER CONTENTS

INTRODUCTION

Epilepsy is a common problem among patients with central nervous system tumors. The frequency of epilepsy depends on a number of factors, including tumor type (low grade, high grade, or metastasis), histology, and location within the brain parenchyma. Anywhere from 30% to 80% of patients with a brain tumor will struggle with epilepsy.[1,2] In approximately 20-40% of those patients, the seizures will arise at the onset of symptoms, while another 20-45% will develop seizures during the course of their disease. Twenty to forty percent of patients with brain metastases will present with seizure activity, especially when there are multiple metastases.[2] Seizures appear in 67% of patients with brain metastases from melanoma, in 48% with lung cancer, in 33% with breast cancer, and in 55% of those with an unknown primary.

Epilepsy can significantly impair quality of life (QoL) and even cognitive function. In addition to potential injury, epilepsy can lead to forfeiture of driving privileges and employment.[2,3] Not only is epilepsy itself common in brain tumor patients, refractory epilepsy is also common, unfortunately. Twelve to fifty percent of patients with a structural brain lesion (including brain tumors) experienced seizures despite using antiepileptic drugs (AEDs) with adequate serum levels.[2–4]

PATHOPHYSIOLOGY

The pathophysiological mechanisms underlying tumor-associated seizures (TAS) remain unclear.[5–8] Epileptogenesis is most likely multifactorial and influenced by tumor type, location, peritumoral microenvironment, morphology, and genetic changes. Cortical tumors are

the most epileptogenic, and tumors affecting the frontal, temporal, or parietal lobes are more often associated with epilepsy than occipital, infratentorial, or sellar lesions.[1,2] Slow-growing tumors, mostly low-grade gliomas, are the most epileptogenic. Developmental and slow-growing tumors may partially isolate brain regions by means of mechanical or vascular mechanisms. A relative deafferentation of circumscribed cortical areas is known for its intrinsic epileptogenic propensity.[4,8–10]

Recent evidence using direct brain recordings of electrical activity suggest that TAS originate from intact, noninfiltrated, neural tissue adjacent to tumors, and not from within the tumor mass itself.[7–10] Histologically, epileptogenic regions of brain demonstrate gliosis and mild reactive astrocytosis, without evidence for tumor cells. It is now theorized that these peritumoral epileptogenic foci develop an imbalance between excitatory and inhibitory inputs, due to multifactorial alterations in the local milieu from the tumor. The intra- and extracellular pH is slightly alkaline in peritumoral tissues, which enhances excitatory neuronal pathways and induces a 30% reduction of activity in GABAergic inhibitory pathways.[7] In biopsy samples from peritumoral epileptic foci, the number of GABA- and somatostatin-containing neurons are decreased.[11] Similar biopsy studies have noted an elevated concentration of glutamine, the direct precursor of glutamate, in peritumoral epileptogenic foci.[12] Glutamine is taken up and secreted by normal glia and glioma cells, thus providing a large reservoir of precursor for peritumoral neurons to convert to glutamate. In addition, recent evidence suggests that glioma cells directly secrete glutamate, causing significantly increased, excitotoxic concentrations in peritumoral tissues.[13,14] *In vitro* experiments have demonstrated extensive NMDA and AMPA receptor stimulation and delayed Ca^{2+}-dependent cell death in exposed neurons. These reports suggest that exposure of peritumoral neurons to chronically elevated concentrations of glutamate could contribute to neuronal injury, abnormalities of neuronal circuitry, and the development of epileptiform activity. Other peritumoral alterations that may contribute to epileptogenic potential include increased extracellular Fe^{3+}, dysfunction of astrocytic syncytial gap junctions due to the infiltration of tumor cells, and the presence of proinflammatory cytokines (e.g., TNF-α), which can increase membrane excitability.[5]

Genetic alterations may additionally play a role in the mechanism of epileptogenesis in patients with brain tumors.[7–10] A possible role of the LG1 gene has been suggested.[15] The LF1 gene is involved in glioma progression and is the cause of the rare syndrome of autosomal dominant lateral temporal lobe epilepsy. Any and all of these factors may play a role in the development of brain tumor-related epilepsy (BTRE).

In addition, the development of refractory epilepsy is common in patients with brain tumors, a process that is likely multifactorial as well.[1–4] An increase in seizure frequency may be the result of tumor growth, tumoral hemorrhage, or insufficient plasma levels of AEDS. In addition, AEDs may not act as well with brain tumors due to the potential for different mechanisms for the development of epilepsy or possibly the mechanism of action of AEDs do not sufficiently prevent the spread of epileptic discharges. Lastly, malignant cells may have increased expression of multidrug resistant proteins. In the normal brain, multidrug resistant gene-I (MDR1) and multidrug resistant associated protein-1 (MRP1) contribute to the blood-brain barrier and the blood-cerebrospinal fluid barrier. Overexpression of MDR1 and MRP1 may lead to insufficient AED levels in brain and tumor tissue.[1,2]

TYPE OF SEIZURE

The type of epileptic seizure in patients with brain tumors, for the most are, are partial, either simple or complex.[2] Partial seizures with secondary generalization are also frequent, but they may be difficult to recognize clinically. Occasionally, repeated complex partial seizures (often occurring in the temporal lobe) can cause a nonconvulsive epileptic state with variable duration that can last up to several hours. Clinical manifestations of these types of seizure may involve a confusional state, automatisms or behavioral modifications, which may be confused with psychiatric disorders. Primary generalized seizures rarely occur in these patients.[2] Treatment of TAS often follows the principles of treating partial seizures among the general population of primary epilepsy patients.

TREATMENT OF SEIZURES

Despite the frequent occurrence of seizures in patients with brain tumors, prospective studies on the medical treatment of epilepsy in this patient population are scarce. In contrast, much is known about the surgical management of treatment-resistant forms of epilepsy, including those associated with brain tumors that are mainly low grade.[4] Because seizures in patients with brain tumors are partial in nature, medical treatment is often extrapolated from treatment of partial seizures in the general population. Of course, there are limitations to this practice. The general approach to treating seizures in these patients is to treat using a single AED at the lowest dose that effectively controls seizures, followed by one or two serial monotherapy trials, as necessary. Treatment with multiple AEDs is generally reserved for refractory cases.[16]

First-Generation AEDs

The mechanism of action of the first-generation AEDs is mainly through interactions with voltage-gated and

ligand-gated ion channels (see Table 13.1). For adult patients with generalized seizures that are not tumor related, phenytoin, carbamazepine, and valproate have relatively equivalent efficacy for reducing seizure activity.[17,18] Similarly, all three drugs are effective for partial motor, partial sensory, and partial complex seizures.

Almost 20 years ago, Moots and colleagues set out to describe the morbidity associated with seizures and the efficacy of anticonvulsant therapy in adult patients with malignant gliomas.[19] AEDs used for the 65 patients in this retrospective review included phenytoin (62 patients), phenobarbital (18), carbamazepine (12), and valproate (4). One of the notable conclusions the authors made was that these AEDs have limited efficacy in patients with malignant gliomas. They made this conclusion due to the high number of patients (72%) with recurrent seizures. In addition to the high frequency of seizure recurrence, patients also reported a notable amount of adverse events. Twenty-eight AED side effects were encountered in 22 patients. The most common toxicity reported was rash. Rash was associated with the start of phenytoin therapy and common with carbamazepine as well. Transient dose-related encephalopathy that was sufficient to require hospitalization occurred in three patients. Two patients on phenytoin experienced nausea, vomiting, and weight loss with therapeutic blood levels that resolved when phenytoin was stopped. Hematologic side effects that required change in AEDs to proceed with chemotherapy occurred in two patients: thrombocytopenia with valproate and neutropenia due to carbamazepine. Though this study is limited by its retrospective design and abundant use of prophylactic AEDs (a practice no longer recommended), the results outline the difficulty associated with the use of conventional AEDs in this population. Refractory seizures in the face of therapeutic drug concentrations, along with significant side effects, limit their use.

In addition to these concerns, first-generation AEDs have a significant amount of drug-drug interactions. These interactions may lead to insufficient control of the tumor or epilepsy, or an increase in AED-related side effects. The most common mechanism of action is enzyme induction of the cytochrome P450 coenzymes, such as 3A4, 2C9, or 2C19. AEDs that cause this induction are frequently referred to as enzyme-inducing antiepileptic drugs (EIAEDs) and include phenytoin, phenobarbital, and carbamazepine. EIAEDs decrease the effectiveness of corticosteroids and several chemotherapeutic agents, such as nitrosoureas, paclitaxel, cyclophosphamide, etoposide, topotecan, irinotecan, doxorubicin, thiotepa, and methotrexate.[2,4]

Oberndorfer and colleagues did a retrospective study of patients with GBM who were given adjuvant chemotherapy, most often including lomustine.[20] They found that the overall survival of patients that received EIAEDs (most often carbamazepine) was significantly shorter

TABLE 13.1 Proposed Mechanisms of Action of Anticonvulsant Drugs and Associated Epilepsy Syndromes

Mechanism of Action	Epilepsy Syndromes	AEDs
VOLTAGE-GATED ION CHANNELS		
Sodium channels	GEFS	PHT, CBZ, TPM, LTG, OXC, FBM, VPA, ZNS
Calcium channels		
L-type	–	PB, FBM
P/Q type	AEA	LTG, OXC, LEV
N-type	–	LTG, GBP, PG
T-type	Absence	ESM
Potassium channels		
Kv	Absence, ADLTLE	Retigabine
	EAT1-MK-PS	
Kir 4.1	–	LEV, TPM
HCN channels		
HCN-2	Absence	LTG
LIGAND-GATED ION CHANNELS		
$GABA_A$ receptor	JME, GEFS	PB, BZD, FBM, TPM, propofol
Nicotinic cholinergic receptors	ADNFLE	CBZ
Glutumate receptors		
AMPA receptors	–	PB, TPM
NMDA receptors	–	FBM
kianate receptors	–	TPM
Synaptic vesicle proteins		
SV2A	–	LEV, BRIV
Enzymes		
GABA-transaminase	–	Vigabatrin
Carbonic anhydrase	–	TMP, ZNS
GABA metabolism		
Increase synthesis	–	VPA, GBP
Decrease metabolism	–	VPA
Prevent reuptake	–	TGB

ADLTLE, autodominant lateral temporal lobe epilepsy; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; AEA, absence epilepsy with ataxia; BRIV - brivaracetam; CBZ, carbamazepine; EAT1-MK-PS, episodic ataxia type 1 with myokymia and partial seizures; ESM, ethosuxumide; BZD, benzodiazepines; FBM, felbamate; GBP, gabapentin; GE, generalized epilepsy; GEFS, generalized epilepsy with febrile seizures; HCN, hyperpolarization-activated cycle nucleotide-gated cation; JME, juvenile myoclonic epilepsy; LEV, leveritacetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbitol; PHT, phenytoin; TGB, tiagabine; TPM, topiramate; VPA, valproic acid; ZNS, zonisamide.
Adapted from Refs. [1–6,17,18].

than those who received nonenzyme inducing AEDs (NEIAEDs, mostly valproic acid (VPA)). A difference in survival of approximately 3 months was noted: 10.8 months with EIAEDs vs. 13.9 months with NEIAEDs. This is consistent with the understanding that the blood concentration of chemotherapeutic drugs is decreased with EIAEDs and thus the effectiveness and efficacy are decreased.

In addition to enzyme induction, VPA is a broad-spectrum enzyme inhibiting AED.[2,4] Therefore, VPA can increase the toxic effects of CYP metabolized drugs given concomitantly. Enhanced toxic effects of nitrosoureas given either alone or with cisplatin and etoposide have been reported with concomitant administration of VPA.[2,4]

Newer AEDs

The newer generation of AEDs have a broader range of mechanisms of action than the first-generation drugs, including interactions with K^+ channels, ligand-gated channels, synaptic vesicle proteins, enzymes, and GABA metabolism (see Table 13.1). The new generation of anticonvulsants has been particularly appealing for the management of seizures in patients with cancer for multiple reasons. First, patients with primary brain tumors are more likely to suffer side effects of AEDs, and new anticonvulsants typically have fewer side effects.[2] Second, drug interactions may be of significant concern in this patient population. Numerous interactions between first-generation AEDs and chemotherapy—based on cytochrome P450 enzyme interactions—have been reported. Particularly, strong CYP3A4 inducers such as phenobarbital, phenytoin, and carbamazepine are known to significantly decrease levels of vincristine, paclitaxel, irinotecan, methotrexate, and busulfan.[1,21,22] This decrease in levels of chemotherapeutic agents may lead to a decrease in overall efficacy. Many of the newer AEDs do not interact with the cytochrome P450 enzyme system. However, patients with low serum protein from malnutrition or cancer-induced cachexia may also have altered protein binding of AEDs, leading to increased toxicity of these drugs. Most of the newer generation AEDs are less protein bound than first-generation AEDs previously discussed. Lastly, newer anticonvulsants are less like to require close serum monitoring of drug concentration. While large, randomized studies are not available, smaller studies have been performed evaluating newer generation AEDs such as levetiracetam, oxcarbazepine, and lacosamide in patients with brain tumors.

LEVETIRACETAM

Levetiracetam was one of the first newer generation AEDs on the market. Levetiracetam was approved by the FDA at the end of 1999 as adjuvant therapy for the treatment of partial onset seizures in adults with epilepsy (see Chapter 12 and Table 13.2).[33] The exact mechanism of action is unknown, but it is known that levetiracetam offers a novel mechanism—interaction with the synaptic vesicle protein SV2A (see Table 13.1). The other benefits of levetiracetam are that it is rapidly and completely absorbed orally, is less than 10% protein bound, and does not affect cytochrome P450 enzymes. The most common adverse reactions noted with levetiracetam include weakness, somnolence, and dizziness. Behavioral changes including irritability, aggression, anxiety, and personality changes have also been reported with the use of levetiracetam and may limit its use in some patients. Since the approval of levetiracetam, numerous small studies have been conducted to evaluate its use in for patients with BTRE (see Table 13.2).[23]

TABLE 13.2 Studies of Levetiracetam in Patients with Brain Tumor-Related Epilepsy from Primary and Metastatic Tumors

Author	Design	N	Tumor Type	Results
Wagner[24]	Observational	18	PBT's	LEV "feasible" in BTRE
Maschio[25]	Observational, add-on	19	Glioma	Reduced refractory seizures
Newton[26]	Retrospective	41	PBT, MBT	Effective, 59% seizure free
Newton[27]	Retrospective	13	MBT	77% seizure free
Milligan[30]	retrospective versus PHT	105	Post Craniotomy	Similar efficacy PHT, better tolerated
Lim[31]	Pilot study, switch PHT to LEV; randomized phase II	29	Glioma	SWITCH TO LEV SAFE
Merrell[16]	Retrospective, compare to PHT	76	Glioma	Similar efficacy PHT, better tolerated
Rosati[28]	Retrospective	82	Glioma	91% seizure free
Stevens[29]	Retrospective	278	PBT	>50% reduction in over 60%
Bahr[32]	Prospective	25	Suspected PBT's	Efficacy promising

PBT, primary brain tumor; LEV, levetiracetam; BTRE, brain tumor-related epilepsy; MBT, metastatic brain tumors; PHT, phenytoin.
Adapted from Refs. 23–28,16,29–32

Levetiracetam was first evaluated as an addition to existing AED treatment for patients with persistent seizures.[23,33] The first report was by Wagner *et al.*, who studied the use of levetiracetam in 26 patients with glial brain tumors.[24] They noted a greater than 50% reduction in seizure frequency in 65% of the cohort, with excellent tolerability. The conclusion was that use of levetiracetam was "feasible" in patients with brain tumors. Soon after, Maschio and colleagues published a report on 19 patients with supratentorial gliomas and epilepsy.[25] All patients continued to have seizures at daily to monthly frequency, so levetiracetam was added to their AED treatment at doses of 1000 mg/day. Doses were titrated up to 3000 mg/day on a clinical basis. Seizure frequency was reported before and during levetiracetam therapy. Forty-seven percent (9/19) of patients became seizure free with the addition of levetiracetam, and an additional 25% (5/19) reported improvement in seizure frequency. In this small study, no adverse effects related to levetiracetam were reported. This shows the potential efficacy of levetiracetam to treat persistent seizures when added to other AEDS for BTRE.

Newton and colleagues have also evaluated the use of levetiracetam for patients with primary brain tumors, brain metastases from systemic cancer, and tumor-related seizures.[26,27] The indications for initiating levetiracetam included: persistent seizure activity after maximal therapy with traditional AEDs, potential drug interactions with chemotherapeutic agents or corticosteroids, and unacceptable adverse effects of other AEDs. In the first report, they studied 41 patients with brain tumors (34 primary, 7 metastatic), with a median age of 47.5 years.[26] The baseline seizure frequency for the entire cohort was one seizure per week. After the addition of levetiracetam to the first-line AED regimen (median dose 1500 mg/day; range 500-3500 mg/day), the median seizure frequency was reduced to 0 per week. In 59% of the patients, complete seizure control was achieved, while in 90% there was an overall reduction in seizure frequency ($p < 0.0001$). The most common side effect was somnolence, noted in 37% of the patients. In the second study, the focus was on patients with BTRE secondary to brain metastases.[27] This retrospective study evaluated 13 patients, of whom 7 received levetiracetam as add-on therapy (54%) and 6 patients (46%) received monotherapy. All of the patients had their seizure frequency reduced to less than 50% of their prelevetiracetam baseline frequency, with 10 patients (77%) noting complete seizure control. The median dose of levetiracetam was 1000 mg/day. Forty-six percent of patients (6/13) reported mild adverse side effects from levetiracetam, including somnolence (three), headache (three), blurry vision (two), and nausea/vomiting (one). This demonstrates the potential activity of levetiracetam in the treatment of tumor-related seizures from metastatic cancer.

Rosati and colleagues conducted a single-center, prospective evaluation of 82 patients with a new diagnosis of brain tumor and BTRE, treated with levetiracetam.[28] Patients less than or equal to 70 years of age were started at a dose of 500 mg twice a day while patients older than 70 received half that dose (250 mg twice a day). The dose of levetiracetam was increased to 3000 or 4000 mg/day if necessary. At the last study evaluation, 75 of these 82 patients (91%) remained seizure free with monotherapy. Of this group, 73 patients were still receiving monotherapy with levetiracetam. The other two patients on monotherapy were receiving topiramate and VPA. Levetiracetam was stopped in these two patients because of intolerable diarrhea or visual hallucinations with psychotic thoughts. Sixty percent of patients (49/82) were reported to have had prompt and long-lasting control of seizures with the initial dosage of levetiracetam, ranging from 1500-3000 mg/day. Only 9 of 82 (11%) patients needed an increase in levetiracetam dosage to 4000 mg/day to become seizure free. Fourteen patients with seizure activity that presented at tumor onset experienced a reappearance of seizures due to clinical and radiographic evidence of tumor recurrence (8 patients) or malignant progression (6 patients). In all 14, an increase in levetiracetam dose led to full control of seizure and all became seizure free. This small trial showed the possible efficacy and safety of levetiracetam as monotherapy for the treatment of BTRE.

Merrell and colleagues reported a retrospective, noninferiority comparison of seizure outcomes and side effects in two cohorts of patients with glioma treated with phenytoin or levetiracetam.[16] They identified 76 patients composed of 25 patients receiving treatment with phenytoin and 51 receiving treatment with levetiracetam. Among these 76, 16 patients in the levetiracetam cohort were treated with phenytoin for a short time interval (<3 weeks). Five of the 16 were switched due to side effects of phenytoin while the remaining 11 were switched due to clinician preference. An additional one patient was initially treated with levetiracetam for a short time and switched to phenytoin due to side effects. These brief exposures were not considered long enough to have influenced the analysis of outcomes over the 6-month observation period. None of these patients experienced their second seizure prior to being switched over. The cohorts were equally matched in surgical approach, cortical distribution of tumor, and types of seizures. The proportions of patients with a second seizure were equivalent between the levetiracetam and phenytoin groups ($p = 0.333$). When adjusted for age, sex, type of seizure, type of glioma, and dosage using univariate analysis, there were no significant differences between the groups. The incidence of side effects in the levetiracetam group was 5.9% versus 20% in the phenytoin group ($p = 0.106$). Although this difference was not

statistically significant, this trial did show a possible equivalence in efficacy of levetiracetam and phenytoin, with a trend toward less side effects and toxicity with levetiracetam.

More recent reports have shown similar results and efficacy of levetiracetam in primary and metastatic brain tumors, when used as add-on therapy, monotherapy, and in the perioperative period (see Table 13.2).[23,29–32,34,35] In the report by Stevens and coworkers, 278 patients with various types of brain tumors were treated with levetiracetam over a 36-month period.[29] They noted a greater than 50% reduction in seizure frequency in over 60% of their patient group. Other authors have compared the use of levetiracetam versus phenytoin in the control of perioperative and postoperative seizure activity, and they found that levetiracetam was just as effective, if not more, and had a more tolerable side effect and toxicity profile.[30–32] In addition, levetiracetam has been shown to be an effective and well-tolerated AED for general anti-seizure prophylaxis in brain tumor patients in the perioperative and postoperative period.[34,35]

All of these reports demonstrate the efficacy of levetiracetam as add-on treatment and as monotherapy for patients with BRTE, including those with primary and metastatic brain tumors. Levetiracetam is commonly prescribed for BTRE due to the relatively large number of clinical reports, albeit each small in number, and the favorable properties of the medication (including limited side effects, low protein binding, and lack of drug interactions). Patients on levetiracetam should be monitored for possible behavioral changes. This is a rare complication, but one that typically requires changing to a different AED.

TABLE 13.3 Studies in Tumor-Related Epilepsy with New Generation AEDs

Author	Design	N	Tumor Type	Results
OXCARBAZEPINE				
Mauro[36]	Prophylaxis	150	Gliomas	2.7% early seizures
Maschio[37]	Retrospective	70	PBT	45.6% seizure free
Maschio[38]	Prospective, observational	25	PBT	88% responder rate
LACOSAMIDE				
Newton[40]	Retrospective	13	PBT	46% seizure free
Maschio[41]	Retrospective	14	PBT	42.9% seizure free
Saria[42]	Retrospective	70	PBT	66% responder rate
PREGABALIN				
Novy[43]	Retrospective	9	PBT	56% responder rate
Maschio[44]	Retrospective	25	PBT	Significant Activity
Rossetti[45]	Randomized phase II	27	PBT	75% seizure free
TOPIRIMATE				
Maschio[46]	Retrospective	47	PBT, MBT	55.6% seizure free
ZONISAMIDE				
Maschio[47]	Observational	6	PBT	83% responder rate

PBT, primary brain tumors; MBT, metastatic brain tumors.
Adapted from Refs. 26–28,40–47

OXCARBAZEPINE

Oxcarbazepine is also a newer generation AED that has been shown to be equally as effective as traditional AEDs, but with less drug-drug interactions.[36–39] Although it should be noted that oxcarbazepine is not completely devoid of potential interactions, as it inhibits CYP 2C19 and weakly induces 3A4. The first experience with oxcarbazepine was reported by Mauro *et al.*, who used the drug as prophylaxis against perioperative and postoperative seizure activity in a cohort of 150 glioma patients (see Table 13.3).[36] Only 4 patients (2.7%) had early seizure activity while on oxcarbazepine prophylaxis. Maschio and colleagues first conducted retrospective comparison of 70 patients as a single center treated with either oxcarbazepine (35 patients) or a traditional AED (35 patients), including phenobarbital, carbamazepine, phenytoin, or VPA.[37] Patients in the traditional AED group were chosen based on age, sex, and duration of AED treatment similar to the oxcarbazepine group. The aim of this study was to compare between groups the efficacy of controlling seizures as well as the safety and tolerability of the AEDs. The primary efficacy variable was the mean number of seizures per month. The mean seizure frequency per month before treatment with traditional AEDs was 4.1, and dropped to 1.6 at final follow-up. In this group, 45.6% of patients were seizure free at final follow-up. For the oxcarbazepine group, mean seizure frequency per month before treatment was 2.9 and dropped to 0.6 at final follow-up. Among this group, 62.9% of patients were seizure free. Both groups showed a significant reduction in seizure frequency. However, when compared there was no

difference between groups. When looking at safety and tolerability, two variables were evaluated: dropout rate for side effects and total incidence of side effects. There was a significant difference between groups for both variables. The authors concluded that while both traditional AEDs and oxcarbazepine may reduce seizure frequency equally as well, the higher incidence of serious side effects makes traditional AEDs less tolerable and affect patient's QoL.

Maschio and colleagues again evaluated oxcarbazepine monotherapy in patients with BTRE, but this time they wanted to further evaluate the impact on QoL.[38] This was a prospective observational study to verify the efficacy, tolerability, and impact on QoL, mood, and global neurocognitive performance of oxcarbazepine monotherapy in patients with BTRE. The primary outcome variable was mean weekly seizure rate after 12 months of treatment. Patients in this trial had a primary brain tumor, which included meningiomas and all grades of gliomas. Oxcarbazepine was introduced as monotherapy either as the first drug or after switching from other AEDs. The dose was started at 300 mg/day and titrated up (300 mg/4 days) to a maximum dosage of 2100 mg/day in 4 weeks, depending on seizure control and onset of eventual side effects. Twenty-five patients were evaluated in this trial. At final follow-up, the mean dose of oxcarbazepine was 1230 mg/day. Only 10 patients completed the follow-up at 12 months; 5 died due to tumor progression, 6 dropped out for severe side effects, 3 for uncontrolled seizures, and 1 for lung complications. Among the 10 patients that completed 12 months of treatment, there was a significant reduction in mean weekly seizure number between baseline (2.62 ± 6.35) and final follow-up (0.13 ± 0.37, $p = 0.005$). Responder rate in the intent to treat population was 88%. Unfortunately, there was no significant difference in QoL in epilepsy, QoL in cancer, AE profile related to AEDs, or global neurocognitive performance. Side effects were reported in 28% of patients (7/25), with one mild and six severe enough to discontinue treatment (one confusion, one dizziness, four rash). The authors state that while there was no improvement in QoL perception, it should be noted that while there was disease progression, the QoL tests did not worsen. Despite the lack of impact on QoL demonstrated in the trial, there is still support of efficacy in BTRE with manageable toxicity with a prospective design.

The adverse effects most frequently reported for oxcarbazepine include hyponatremia, drowsiness, headache, and dizziness.[36–39] These are usually of moderate intensity. Most often hyponatremia associated with oxcarbazepine is asymptomatic and does not require suspension of the drug. Serum sodium concentrations should be monitored because some patients may experience symptomatic hyponatremia requiring discontinuation of oxcarbazepine.

LACOSAMIDE

Lacosamide was approved by the FDA in 2008 as an adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy.[48] Lacosamide offers a novel mechanism of action by selectively enhancing slow inactivation of voltage-gated sodium channels. Refractory epilepsy is common in brain-tumor-related seizures, so medications that offer a novel mechanism of action, such as lacosamide, are of particular interest in this patient population.

The first report of Lacosamide being used for BTRE was by Newton and coworkers, who treated 13 patients with gliomas and refractory seizure activity (see Table 13.3).[40] Lacosamide was used as an add-on AED in 11 patients and as monotherapy in 2 patients. The median dose was 100 mg/day (range 50-225 mg/day). The baseline median seizure frequency for the cohort was two per week. After the addition of lacosamide, the seizure frequency was reduced to less than one seizure per month (with 46% of patients with complete seizure control). The overall seizure frequency was reduced in 10 of 13 patients (77%; $p = 0.004$). Lacosamide was well tolerated in most patients, with the main side effect of mild dizziness. A similar study was published by Maschio and colleagues with a series of 14 patients recruited to add-on lacosamide after suffering from BTRE and insufficient control of seizures on one or more other AEDs.[41] AEDs had been at the maximum tolerated dose for the patients. Patients who had at least one seizure in the month preceding treatment were consecutively recruited to this case series. Lacosamide was started at 100 mg/day with a weekly increase of 100 mg/day divided into two oral doses. In order to achieve seizure freedom, the dosage of lacosamide was titrated depending on seizure control and eventual adverse events onset up to the maximum dose of 400 mg/day. The minimal effective dose was considered to be 200 mg/day. Efficacy of lacosamide was evaluated in the overall population (ITT, $n = 14$). In the month prior to the introduction of lacosamide, patients were on polytherapy with the following drugs: clonazepam, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, pregabalin, topiramate, VPA, and zonisamide. The mean seizure number had been 15.4 seizures/month. Mean lacosamide dose was 332.1 mg/day. At last follow-up, mean seizure number was reduced to 1.9/month. Six patients were seizure free (42.9%) and 5 (37.5%) had a seizure reduction of greater than or equal to 50%. Two patients (14.3%) had seizure reduction of less than 50% and one had unmodified seizure frequency (7.1%). A final responder rate of 78.6% was reported. The difference in presence/absence of seizures between baseline and follow-up was statistically significant, as was the difference in mean monthly seizure frequency. Only one patient

dropped out due to side effects (dizziness and blurred vision, grade 2).

Next, Saria and colleague conducted a restrospective chart review of 70 patients from 5 different academic medical centers with primary brain tumors that received lacosamide for seizure management.[42] Indications for initiating lacosamide therapy included seizure activity that did not respond to prior AEDs, unacceptable adverse effects from previous therapy, or prophylaxis. Most of these patients (74%) were started on lacosamide because of recurrent seizure activity and most were taking other AEDs concurrently with lacosamide (58/70, 82.9%). The majority of the patients were on levetiracetam in addition to lacosamide (35; 50%). Sixty-six percent of patients (46/70) reported a decrease in seizure activity after the start of lacosamide, and of these, 38 patients (83%) reported a greater than 50% decrease in seizure frequency. Among the patients started on lacosamide due to seizure activity on other AEDs, 73% had a decrease in seizure frequency. Fifty percent of patients were maintained on a total dose of 200 mg/day and most (77%) did not report any toxicities. Four patients reported more than one toxicity. The most common toxicity was fatigue (four cases, 6%) followed by dizziness, nausea, confusion, and weakness (two cases each). Although this is a retrospective review, it does seem to indicate potential efficacy of lacosamide, especially for breakthrough seizures with minimal toxicity.

The most frequently reported adverse effects of lacosamide are typically related to the CNS and GI and are mild to moderate in nature. These include dizziness, fatigue, headache, ataxia, tremor, and nausea/vomiting.[40–42,48]

PREGABALIN

Pregabalin was approved in 2005 as adjunctive therapy for the treatment of partial-onset seizures.[49] Pregabalin does not undergo any hepatic transformation nor does it have any impact on the hepatic cytochromic system. Pregabalin may be rapidly titrated to target dose and has few reported side effects. For all these reasons, pregabalin appears to be an interesting drug to use for the treatment of BTRE.

Novy and colleagues first described the use of pregabalin in patients with brain tumors (see Table 13.3).[43] They retrospectively studied nine consecutive brain tumor patients on pregabalin in their outpatient epilepsy clinic. All patients had a primary brain tumor, with six patients having a diagnosis of GBM, two patients with low-grade glioma, and one patient with primary CNS lymphoma. Pregabalin was used because of intolerance to previous AED in four patients, to replace EIAEDs in three patients, and for insufficient seizure control in two patients. The median dose of pregabalin given was 300 mg/day. During the follow-up, all four patients that were suffering from seizures experienced at least a 50% seizure reduction, while one became seizure free. The other four subjects remained seizure free under the regimen containing pregabalin. Five patients reported side effects including fatigue, weight gain, peripheral edema, or erectile dysfunction. Fatigue was reported by two subjects receiving 600 mg/day of pregabalin, and was satisfactorily improved by lowering the dose. Although this is a small series, it appears that pregabalin may be useful for the treatment of BTRE.

A few years later, Maschio and colleagues conducted an open pilot study to evaluate the effect of pregabalin as add-on therapy for seizure control, QoL, and anxiety in patients with BTRE.[44] Twenty-five patients with BTRE on standard AED therapy were recruited after they had had at least one seizure in the month preceding recruitment, despite receiving AEDs at the maximum tolerable doses. Pregabalin was added as the first or second add-on drug at 75 mg/day, with an increasing schedule up to the maximum dosage of 600 mg/day over 4 weeks, depending on seizure control and eventual onset of adverse events. Pregabalin was added to the following specific drugs: clobazan, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, valproate, and topiramate. The primary outcome variable for this study was the mean number of weekly seizures after 6 months of treatment. At baseline in the ITT population, the mean weekly seizure frequency was 5.3 ($\pm$10), which dropped to 2.5 ± 5 at the last follow-up visit ($p = 0.016$). At the end, only 48% of patients ($n = 12$) completed the 6-month follow-up. Four patients dropped out due to worsening of seizures, one with unchanged seizure frequency, three due to lack of compliance, and two due to side effects. Despite these issues, the responder rate was 76% in the ITT population. The two patients who dropped out due to significant side effects experienced dizziness for one and irritation and dryness of the eye for the other. Despite the small population and short follow-up, there was a significant reduction in mean weekly seizures with the addition of pregabalin in patients with BTRE.

Most recently, Rossetti and colleagues evaluated the use of pregabalin and levetiracetam as monotherapy for patients with primary brain tumors and epilepsy.[45] This was an open-label, phase 2, randomized trial conducted at two Swiss brain tumor centers. The trial included adult patients with a brain tumor and at least one recent seizure (therefore justifying introduction of AED treatment) and with a potential need of chemotherapy. Patients receiving other AEDS at the time of enrollment were also eligible, especially if they were on EIAEDs, and if these could be discontinued within 2 weeks of enrollment. The study AEDs consisted of an increasing dose of either levetiracetam up to

1500 mg twice daily (starting dose 250 mg twice daily) or pregabalin up to 300 mg twice daily (starting dose 75 mg BID). The primary endpoint evaluated was a survival-free composite reflecting pragmatically the failure of an AED monotherapy and included status epilepticus, two seizures with impaired consciousness, need of a second AED, and need to discontinue the study drug (lack of efficacy or adverse reaction). A total of 52 patients were enrolled. After 1 year of follow-up, over one-third of the patients failed therapy as defined per study endpoints: 9 in the pregabalin cohort and 12 in the levetiracetam group. Globally, 65% of patients on levetiracetam and 75% on pregabalin remained seizure free until the last follow-up. Adverse events most frequently associated with levetiracetam were somnolence, depression, and concentration problems. Similar adverse events were associated with pregabalin and included dizziness, concentration problems, and depression. The authors concluded that these results confirm that levetiracetam and pregabalin represent valuable monotherapy options for the treatment of BTRE.

Tolerability of pregabalin is usually good, with somnolence and peripheral edema reported as the most common side effects.[43–45,49] Side effects of pregabalin observed in the literature for both BTRE and nononcologic patients are reported at ranges from 7% to 60%.

TOPIRAMATE

Topiramate is approved for the treatment of partial-onset or primary generalized tonic-clonic seizures, either as adjunctive therapy or as monotherapy.[50] There was one published prospective observational study on 47 patients with brain tumors and epilepsy who received topiramate (see Table 13.3).[46] This study included both patients with primary brain tumors as well as brain metastases from systemic cancer. Of these 47 patients, 14 received topiramate as the first AED therapeutic choice because of its pharmacokinetics and because there had been no evidence of interactions with antineoplastic agents. The remaining 33 patients received topiramate for the same reasons after they had already been treated with other AEDs. Topiramate was titrated as per the label, at an initial dose of 25 mg/day followed by weekly increments of 25 mg/day during 4 weeks until reaching the dose of 100 mg/day. After the initial titration, doses were adjusted according to patient response with weekly increments of 25 mg/day, not exceeding the maximum dose of 400 mg/day. Starting in the second week of topiramate, previous AEDs were tapered off over a 3-week period or longer if deemed necessary. Seizure frequency was evaluated at 3 months, 6 months, and 12 months after initiation of topiramate and compared to baseline. Two patients dropped out due to cognitive disturbances before the 3-month follow-up, so only 45 patients were observed. At final follow-up, 25 patients were seizure free (55.6%) and 9 (20%) had a seizure reduction of seizure frequency greater than 50%. This decrease in seizure frequency was statistically significant ($p = 0.008$). The remaining 11 patients (24.4%) were stable. Of the total patient population, 4 of 47 patients (8.5%) had mild reversible side effects and 3 had severe side effects (6.4%) leading to discontinuation of topiramate. Two of these patients discontinued topiramate due to cognitive disturbances about 1 month from the first dose and the other patient discontinued due to weight loss about 4 months from the first dose. This small observational study indicates the possible activity of topiramate in BTRE.

ZONISAMIDE

Zonisamide is also a newer generation AED with demonstrated efficacy for the treatment of partial seizures, including simple and partial seizures even with secondary generalization.[51] It has been approved by the FDA since 2000 as an adjunctive treatment in refractory partial seizures. The most common side effects of zonisamide are generally mild to moderate, manageable, and similar to other AEDs. CNS- and GI-related toxicities may be common, including somnolence, dizziness, agitation/irritability, fatigue, tiredness, ataxia, weight loss, and anorexia. The tolerability of zonisamide typically improves with duration of treatment and a slower drug titration often reduces the incidence of adverse effects. The pharmacokinetic profile of zonisamide is also favorable for the potential treatment of BTRE. Zonisamide is rapidly absorbed, with good oral bioavailability, a long serum half-life, and has no effects on cytochrome P450 (CYP). However, zonisamide is metabolized by CYP3A4 and therefore coadministration with CYP3A4 inducers or inhibitors may effect serum concentrations of zonisamide.[51,52]

Because of these favorable properties and the abundance of refractory seizures in patients with brain tumors, Maschio and colleagues evaluated the efficacy and tolerability in a small number of patients who received zonisamide at a single institution (see Table 13.3).[47] Six patients suffering from BTRE who had already been treated with other AEDs, and whose seizure control had been insufficient despite maximum tolerated doses of the other AEDs, were recruited consecutively to this study. Zonisamide was titrated according to the technical file with titration over 6 weeks, reaching a mean dose of 283.3 mg/day (range 100-400 mg/day). The approved titration for zonisamide is not faster than 100 mg/day every 2 weeks in order to reach steady state at each dose level (start at 100 mg/day, may be increased to 200 mg/day after

2 weeks; further dose increases to 300 and 400 mg/day can be made with minimum of 2 weeks between adjustments). In the month prior to the introduction of zonisamide patients were on polytherapy with lamotrigine, levetiracetam, oxcarbazepine, phenytoin, and pregabalin.

The mean seizure frequency prior to starting zonisamide had been 27.7 seizures per month. The mean duration of follow-up for these six patients was 8 months (range 1-18 months). At the last follow-up, the mean seizure number was reduced to 8.8 seizures per month. The responder rate for all patients available at last follow-up was 83.3%. Two patients experienced grade 3 side effects leading to discontinuation of zonisamide (one with sexual dysfunction and one with drowsiness). Despite the limited data, zonisamide may provide benefit as adjunctive treatment of BTRE in patients with continued seizures despite maximizing current AEDs. The high percentage of side effects (two of the six patients) in this study may limit its use compared to other newer generation AEDs.

LAMOTRIGINE

Lamotrigine was approved in 1994 and is indicated for the adjunctive treatment of partial as well as generalized tonic-clonic siezures and for monotherapy treatment of partial seizures.[53] Some favorable properties of lamotrigine include its lack of induction or inhibition of CYP3A4 enzymes, resulting in few drug interactions; a long half-life allows for once a day dosing; and mood-stabilizing effects may allow for treatment of dual indications in certain patients. However, one of the limitations of lamotrigine is the long initial titration in which clinical efficacy is not expected before 3-4 weeks of therapy.[54] This titration often requires $\geq$6 weeks to achieve target therapeutic doses. This long titration schedule is done to reduce the incidence of severe skin adverse events. In addition, lamotrigine may also cause bone marrow suppression, which may limit its use in patients on myelosuppression chemotherapy.[2]

There are no published trials specifically evaluating lamotrigine for treatment of BTRE. However, studies on other AEDs have reported the use of lamotrigine. Of 19 patients that received levetiracetam as adjunctive treatment for persistent seizures, two patients had been receiving treatment with lamotrigine.[25] In addition, van Breemen and colleagues evaluated various AEDs in patients with gliomas and seizures.[55] In this study, four types of AED therapy were distinguished: (1) VPA with levetiratcetam (LEV) $\pm$ other AEDs; (2) VPA with LEV $\pm$ other AEDs; (3) LEV without VPA $\pm$ other AEDs; (4) other AEDs without VPA/LEV. Lamotrigine was part of "other AEDs" and was typically added after VPA and LEV had failed to control seizures. Other AEDs used included carbamazepine, phenytoin, and oxcarbazepine. While lamotrigine was not specifically evaluated, the authors did note that the combination of levetiracetam plus VPA had better seizure control than VPA plus carbazmazepine or lamotrigine.

Despite the lack of data specifically in the brain tumor population, lamotrigine remains a viable option for treatment of BTRE if treatment with other AEDs has failed to adequately control seizure activity. The long initial titration and lack of benefit over other newer generation AEDs tends to limit its use in the brain tumor population.

CONCLUSION

Newer generation AEDs have introduced newer mechanisms of action and a reduced frequency of drug interactions in the treatment of BTRE. The majority of the data on AEDs in BTRE consists of either small prospective or retrospective reviews. Despite this lack of large randomized controlled trials, newer generation AEDs seem to be effective in the treatment of BTRE. While there is no clear first choice in the treatment of BTRE, prescribers have numerous options and therapy can be directed based on patients' comorbidities and concomitant medications. Levetiracetam is a common first choice due to the multiple small reports and favorable pharmacokinetic and pharmacodynamic properties of the medication. Unfortunately, refractory epilepsy is common in brain tumor patients and often necessitates multiple AEDs. More data is needed regarding optimal sequencing of AEDs.

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CHAPTER

14

Clinical Approach to Brain Tumor-Related Epilepsy

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CHAPTER CONTENTS

Seizure activity in a patient with brain tumor-related epilepsy (BTRE) can arise at the onset of symptoms, prior to the official diagnosis, or at a later time during the course of the illness. In those patients with delayed-onset seizure activity, the first event may coincide with surgical intervention (i.e., biopsy or resection), radiotherapy (RT), or chemotherapy. Thus, the clinician must make numerous decisions during the clinical evaluation and treatment of BTRE. These decision address commencement of treatment (i.e., at the onset of verified seizure activity versus prophylaxis at the time of surgical diagnosis), anticonvulsant selection, duration of anticonvulsant use, possible interactions between anticonvulsants and chemotherapy, optimization of anticonvulsant treatment, and recommendations regarding driving privileges for patients with BTRE. This chapter reviews all of these decision points.

SEIZURE PROPHYLAXIS IN PATIENTS WITH BTRE

Patients with brain tumors often have seizures as a presenting symptom of their disease (20-40% of cases).[1] For these patients, the established recommendation is to initiate antiepileptic therapy in a timely fashion, and the literature supports the continuation of antiepileptic therapy even after surgery. Many patients undergo neurosurgical interventions without first experiencing seizures, however, and for them, a number of unresolved questions remain regarding the proposed usefulness of prophylactic treatment with antiepileptic drugs (AEDs).

Seizures are known to be a complication of surgery for supratentorial tumors, with an incidence of 15-20%.[2–5] Postsurgical seizures are classified as either early or late and are distinct from other types of seizures. Such differentiation is key to the discussion of prophylactic treatment. Early seizures are those that occur within a week of the intervention,[5] and they are more associated with surgical procedures (provoked seizures), largely occurring within the first 48-72 hours after surgery.[5–7] Whether focal or generalized, early seizures represent dramatic and potentially dangerous events, not only with regard to the etiological diagnosis but also because they can have a potentially deleterious effect on a brain recovering from recent surgery, due to continuous epileptic activity.[5–8] Late seizures are those that appear more than 1 week after surgery, are often recurrent, and are more frequently seen in patients who have presurgical seizures. These events can either be due to the

gliosis as a consequence of the surgery, and residual tumor cells, or to the recurrence of neoplastic disease (unprovoked seizures). The risk of seizures after surgery can depend on a number of factors such as:

Type of tumor: Low-grade tumors grow slowly and are more epileptogenic than those that grow more quickly. Lesions with increased risk of bleeding are associated with a higher probability of seizure (e.g., melanoma metastases).

Localization of the tumor: The tumors most associated with seizures are supratentorial. On the contrary, seizures caused by infratentorial lesions only result from indirect causes such as increased intracranial pressure or edema. Tumors located in superficial cortical areas are most likely to produce seizures, particularly when the temporal or frontal lobes or the insula are involved.[9]

Type of surgical approach: Some aspects of the intervention may influence the onset of seizures, such as extension of cortical damage, the duration of surgery, complications (e.g., ischemia and infection), edema, postsurgical bleeding, and incomplete removal of the tumor. The incision through the cerebral cortex does not necessarily increase the risk for seizures, but there can be an increased risk from damage to the cortical surface from lobar retraction. This may explain why seizures are also frequent in the case of extra-axial tumors.

Presence of postoperative neurological deficits: Research has suggested that focal neurological deficits present in the immediate postoperative phase may give rise to a higher incidence of seizures, but these data have been conflicting.[8,10]

Previous history of seizures: Tumors that present with preoperative seizures appear more apt to give rise to postoperative seizures (20–40% of cases).

Role of EEG: The literature presents conflicting data on the role of EEG in predicting the appearance of seizures after brain surgery.[11–13]

For patients undergoing surgery, the postsurgical risk of epileptogenesis is closely related to the question of prophylaxis via AEDs. This issue is particularly complex for the management of brain-tumor patients who have not experienced seizures as a presenting symptom; when planning treatment, the clinician must consider whether to introduce an antiepileptic prophylaxis, the duration of prophylaxis, and its possible withdrawal.

The significant incidence of postoperative seizures has given rise to increased debate regarding the possible usefulness of prophylaxis. Published cases on the topic are extremely heterogeneous and present conflicting results; the studies that address these cases are not easily compared, due to differences in selection criteria (e.g., patients with seizures and seizure-free), variables studied, follow-up periods, and AEDs used. In addition, the studies consider the seizure-onset risk for postoperative patients who have different neurosurgical pathologies (trauma, tumors, bleeding).

To date, the published data has not supported the widespread practice of administering long-term prophylactic anticonvulsant therapy after neurosurgery.[14] The first meta-analysis to address this issue largely evaluated prospective and randomized studies, but there were too few studies and nearly all of them failed to demonstrate the efficacy of AEDs in preventing the onset of postoperative epilepsy.[7] The fact is that tumor epileptogenesis is an extremely complex phenomenon involving a number of different mechanisms, including changes in peritumoral amino acids, metabolic changes, expression of neuronal and glial enzymes, and localized immunological abnormalities.[15] Individual AEDs would not likely be able to act on the totality of these mechanisms. The possible role of prophylactic AEDs in the prevention of early postoperative seizures in brain-tumor patients has not been studied extensively, and the available data remains inconclusive and controversial.

Among all the AEDs, phenytoin (PHT) has been the drug most widely studied for use in prophylaxis. Although the efficacy of PHT in preventing early posttraumatic seizures has been demonstrated, its potential utility as a prophylaxis for early postsurgical seizures has yet to be substantiated.[16] A number of randomized trials with this drug each showed different results.[3,6,10,17,18] The varying results, most often associated with a lack of statistical significance, might well be due to different methodologies, such as timing and mode of administration of the drug in relation to the surgical procedure; heterogeneous indications for surgery (i.e., not all patients had a brain tumor; many were operated on for a brain injury); and the occasional absence of plasma-level monitoring, which is critical to the success of treatment, especially in patients treated with PHT.[15] However, one study conducted by De Santis *et al.* is of interest because it differs from the previously mentioned randomized studies in at least three areas: (1) inclusion was restricted to patients operated on for supratentorial tumors, thus eliminating the confounding factor of brain injury and reducing the heterogeneity in the underlying conditions that characterizes the majority of existing studies; (2) intensive monitoring of plasma levels of the drug; (3) the combination of PHT with other AEDs in most cases.[5] The ineffectiveness of PHT in the study by De Santis *et al.* cannot be explained by differences between patients and controls, because the two groups were balanced in terms of baseline clinical characteristics, neurosurgical procedures, and incidence of postoperative complications. Furthermore, the occurrence of seizures in the group of patients treated with PHT could not be attributed to an inadequate dose, because the patients who presented with seizures had drug concentrations in the therapeutic range when their

seizures had occurred. For these reasons, De Santis *et al.* concluded that PHT was ineffective as a monotherapy for protecting against early postoperative seizures.[5] Already in 1996, Kuijlen *et al.* had concluded that there were too few studies regarding prophylactic anticonvulsant therapy in patients undergoing neurosurgical procedures, especially prospective and randomized studies.[7] In addition, Kuijlen *et al.* documented that almost all of the existing studies failed to show evidence of the efficacy of AEDs in preventing postoperative epilepsy.[7] In 2000, members of the American Academy of Neurology (AAN) published practice parameters for the use of anticonvulsant prophylaxes in patients with primary and metastatic brain tumors.[1] Glantz *et al.* evaluated the efficacy of prophylactic anticonvulsants in preventing seizures in patients with brain tumors, taking into consideration a total of 12 studies, including randomized controlled studies and cohort studies.[10,17–27] According to the authors, none of these studies demonstrated the effectiveness of these drugs when given prophylactically. Four of the twelve studies provided evidence at Level 1. Glantz *et al.*[1] provided the following recommendations after analysis of these 12 studies:

> 1. In patients with newly diagnosed brain tumors, anticonvulsant medications are not effective in preventing first seizures. Because of their lack of efficacy and their potential side effects, prophylactic anticonvulsants should not be used routinely in patients with newly diagnosed brain tumors (standard).
> 2. In patients with brain tumors who have not had a seizure, tapering and discontinuing anticonvulsants after the first postoperative week is appropriate, particularly in those patients who are medically stable and who are experiencing anticonvulsant-related side effects (guideline).

Nancy Temkin conducted two meta-analyses of all studies published on the subject of antiepileptic prophylaxis, highlighting important differences in the methodological approaches and in the conclusions.[28,29] The objective of her first meta-analysis was to provide a synthesis of evidence for the effectiveness of AEDs in preventing seizures and to assess the specific effects of prophylaxis on early and late postoperative seizures. A total of 47 studies were analyzed using seven AEDs, in mono- or polytherapy. Temkin concluded the following: (a) more effective and/or promising results exist for early seizures (acute, symptomatic), (b) no AED demonstrated effectiveness on late seizures (unprovoked), thus confirming the absence of antiepileptogenic properties of AEDs.

In Temkin's second meta-analysis, six randomized controlled trials were considered: two studies specifically addressed patients with brain tumors, and four studies were conducted on patients with various pathological conditions. Two studies addressed early seizures, and four studies evaluated both early and late seizures. From this meta-analysis, the author deduces that treatment with AEDs, especially with PHT, reduces the risk of early seizures 40-50%, but the effects on the seizures that occur later are nonexistent or, in any case, less than 50%. Temkin concludes her review by stating, "the guidelines of professional organizations for subsets of neurosurgery cases consider prophylaxis, especially using PHT, to be an option for the first week after surgery, but consider the routine use of prophylactic anticonvulsants after the first week as not being warranted."[28] In 2004, the Mayo Clinic published an additional meta-analysis of the works that have been cited here, in order to assess the efficacy of prophylactic anticonvulsant therapy, specifically in patients operated on for a brain tumor who had not had seizures at onset.[30] From 474 potentially relevant articles, 17 were selected, and of those, only five met the following inclusion criteria: patients with tumors (primitive glial tumors, metastases, and meningiomas), no history of epilepsy, and randomization of AED (PHT, phenobarbitol [PB], valproic acid [VPA]) or placebo. The five studies analyzed a total of 403 adults with cancer, including primitive glial tumors ($n=151$), brain metastases ($n=156$), and meningiomas ($n=96$). The three AEDs studied were PB, PHT, and VPA. This meta-analysis confirmed the lack of benefit from AEDs at 1-week and 6-month follow-ups. In addition, AEDs were found to have no effect on the prevention of seizures, when evaluated for different pathologies (i.e., glial tumors, meningiomas, or metastases).

In 2008, the Cochrane Collaboration published a systematic review of prophylaxis in patients with brain tumors.[31] Five randomized controlled trials were evaluated for a total of 404 patients with brain tumors. Cochran concluded that, in this patient population, substantial differences existed in the prevention of a first seizure for the treated group and the control group. The study also demonstrated that treated patients had a higher risk of presenting with adverse events as compared to the group of untreated patients. The drugs evaluated were PHT, PB, and VPA. There were no studies of newer generation AEDs.

In 2010, Klimek Dammers performed a review of the literature regarding the use of perioperative antiepileptic therapy in different neurosurgical diseases.[32] Although there is a lack of evidence for the benefit of prophylactic anticonvulsant therapy, the authors noted that this therapeutic approach is commonly used during the perioperative course of neurosurgical patients. In particular, the authors concluded that AEDs for prophylaxis are still routinely prescribed, despite the fact that these drugs can cause collateral effects and that this practice has not yet been validated by clear evidence for patients with brain tumors. Also in 2010, Mikkelsen

conducted a review of the work published from 1990 to 2000, with the aim of verifying the role of antiepileptic prophylaxis in a specific population of adult patients with solid metastases who had not had seizures.[33] The rationale of the study was that intracranial metastases of systemic cancers tend to be less infiltrating than primary tumors of the brain and are associated with seizures less often than primary tumors. This study found no indication for AED prophylaxis (using PHT and PB) because of the reduced incidence of seizures and the lack of statistically significant differences in the seizure frequencies of treated and nontreated patients. This review concluded with a Level 3 recommendation to not introduce prophylactic therapy, citing the fact that anticonvulsants may have collateral effects.

For long-term use of anticonvulsant prophylaxis, the most current published data indicate that there is no clear proof of effectiveness. Opinions still differ regarding use during the perioperative period, however, and no strong position for one particular view has yet emerged. Therefore, in advising against prophylactic anticonvulsant therapy for patients with newly diagnosed brain tumors, published studies are in line with the recommendations of the AAN.[1] In addition to not being effective in preventing the onset of seizures, AEDs can also provoke multiple adverse events that should not be ignored in this specific patient population (e.g., skin rash, hematological toxicity, and encephalopathy). Also, drug interactions can be numerous and clinically relevant (i.e., reduced efficacy or increased toxicity of a specific drug), especially for individuals having received chemotherapy and corticosteroids, drugs that share the same metabolic pathways through the AED cytochrome P450.[34] Thus, in patients with brain tumors who have not had seizures, it is appropriate to suspend AEDs after the first postoperative week.

Information is limited regarding the new AEDs and their possible role in prophylaxis. Literature data is also limited for these drugs regarding the range of medications to choose from as well as their actual effectiveness. The following have not yet been tested in randomized controlled trials: oxcarbazepine (OXC), levetiracetam (LEV), topiramate (TPM), lamotrigine (LTG), and gabapentin (GBP). These drugs would likely present fewer adverse events and less chance of interaction with steroids and chemotherapy, which are usually taken by patients with brain tumors.[34,35] In addition, the newer AEDs possess characteristics that could also be better exploited in the perioperative period (linear kinetics, the possibility of faster titration, quick achievement of steady-state, no need for the monitoring of plasma levels).

In 2007, Mauro *et al.* documented these characteristics within the context of a clinical experience with OXC (a new AED) in the early postoperative phase.[36] However, this is a retrospective, uncontrolled study conducted on a population entirely comprised of patients who were seizure-free at the onset of illness. Therefore, future meta-analyses will need to include randomized trials and numerous controlled case studies (i.e., as homogeneous as possible), perhaps considering specific subgroups thought to be at higher risk (related to histology and tumor location, type of surgical procedure, patient's age, etc.) and evaluating potential antiepileptic and antiepileptogenic characteristics of the newer AEDs. In fact, Forsyth *et al.*[18] prematurely ended their study due to the high rate of mortality and the unexpectedly low percentage of seizures in the group that was not taking AEDs.[17] They calculated that the sample size must be 900 patients for a clinical study to provide clinically meaningful data with adequate statistical power. Concerning the evaluation of the efficacy of new AEDs as prophylactic therapy, the 2008 study by Milligan compares the prophylactic effectiveness and tolerability of LEV and PHT monotherapy in supratentorial neurosurgery for brain tumors and other pathologies.[37] One hundred and five patients treated with LEV monotherapy were compared to 210 patients treated with PHT monotherapy, with the aim of evaluating the appearance of seizures within 7 days after surgery, as well as the presence of adverse reactions and development of epilepsy after 12 months. The authors concluded that both LEV and PHT were associated with a low risk of early postoperative seizures and a moderate risk of developing epilepsy later. LEV was associated with a significantly reduced risk of early adverse reactions compared to PHT, as well as with a higher retention rate in patients with epilepsy after 1 year. Although the differences in the efficacy of the two drugs were not reported, treatment with LEV showed a better tolerability, and a greater number of patients continued treatment with LEV for 1 year after surgery. In the group treated with PHT, the number of patients with adverse events was higher than the number of patients who had seizures. A 2009 analysis of this article made by Fountain concludes that, despite the limitations of a retrospective study, it would be reasonable to use LEV in place of PHT for seizure prophylaxis after supratentorial craniotomy.[38] In 2009, Lim published a pilot study aimed at testing the safety and feasibility of switching from PHT to LEV monotherapy for preventing postoperative seizures in glioma patients.[39] The study involved 29 patients at follow-up, treated with PHT and then randomized in a 2:1 ratio to either switch to LEV within 24 hours after surgery or to continue with PHT. The study showed that it is safe to replace PHT with LEV monotherapy following craniotomy for supratentorial gliomas. Also, Lim highlights the need for extended randomized controlled, double-blind trials, just as the other authors have. Finally, a

recent retrospective study by Zachenhofer in 2011 evaluated the efficacy and tolerability of LEV as perioperative prophylaxis in supratentorial brain tumors.[40] They included 78 patients with supratentorial brain tumors treated with LEV perioperatively. Due to the fact that 38.5% had experienced preoperative seizures, a correct prophylaxis was only given to 61.5% of patients. At the end of the follow-up period (average duration of 10.5 months), 91% of patients were seizure-free, and 26% were not taking AEDs. In 6.4% of participants, side effects such as progressive drowsiness and reactive psychosis were observed, but these side effects resolved after reduction of the dose of LEV. The authors concluded that LEV proved to be effective perioperatively in patients with brain tumors, with reversible side effects in 6.4% of patients. A recent review of evidence-based support for the use of AEDs as prophylaxes in neurocritical treatments recently considered studies of patients who had undergone neurosurgery for brain tumors.[41] The great disparity of opinions and the lack of evidence of clear benefits for this patient population were cited. Published data to date clearly associates the older AEDs with increased adverse events and clinically relevant pharmacological interactions. These events appear to be much less frequent with new AEDs, such as LEV, but more randomized studies, as well as those with larger numbers of patients are needed, to fully support AED use for seizure prophylaxis in patients with brain tumors.

If the use of prophylactic AEDs in patients with brain tumors is a complex and problematic issue, it can be equally if not more difficult to establish if and when AED therapy should be suspended. Although it has been deemed appropriate to interrupt an AED 1 week following surgery, as reported in guidelines available in the literature, clinicians often hesitate to suspend therapy for patients who must be treated with RT, because published data suggests a possible increase of seizures during this procedure. Further studies are necessary to assess the value of continuing prophylactic antiepileptic therapy, at least until the end of RT sessions.

IS THERE A BEST PRACTICE FOR SEIZURE TREATMENT?

Introduction

Seizures are a common symptom of malignant gliomas. In fact, they are present in 30-60% of all gliomas and variable in malignant glioblastomas (GBM), ranging from 5% to 53.4% in various studies.[42–47] They represent the presenting symptom in 20-40% of patients with GBM, and in a further 20-30%, seizures will occur during the course of the disease.[48,49] Seizures are most commonly simple partial events. Small, malignant gliomas in the frontal lobe are more likely to induce postoperative seizures, and patients who have had seizures prior to and after surgery are probably more protected by AEDs than are patients who have only experienced postoperative seizures.[42] Seizures are a presenting symptom in 20-40% of patients with brain metastases, especially in those patients with multiple metastases.[22,46,50–55] Approximately 10% of patients who do not have seizures at onset develop them during the course of disease.[22] Seizures secondary to metastases occur in 67% of patients with melanoma, in 48% of those with lung cancer, in 33% of those with breast cancer, and in 55% of those with unknown primary tumors.[22,52,53] Despite recent therapeutic advances and improvements in both surgical techniques and RT, the median survival time for patients with brain metastases is only 1 month without treatment, 4-5 months with RT, and 6-12 months with surgery and RT; the percentage of surviving patients is 10% at 1 year, and only a few patients survive to 2 years.[52,56–58] Three prognostic groups were identified for patients with brain metastases based on performance status, the number of metastases (single and multiple), and the extent of extracranial disease. These factors are connected with significant differences in outcome (in median months of survival), and, therefore, they influence the choice of cancer treatment.[51] The maintenance or recovery of a good quality of life (QoL) remains a key therapeutic objective for patients with brain metastases, as is the case with patients who have primary tumors, and improved QoL can be achieved through the reduction of symptoms and neurological deficits, control of the intracranial disease, extension of survival, and, most importantly, the proper management of therapies.[52,53,57,59,60]

Drug Resistance and Epileptogenicity

Brain tumor-related epilepsy is often characterized by resistance to drug treatments. The definition of resistance to AEDs is defined by the ad hoc Task Force of the International League Against Epilepsy (ILAE) Commission on therapeutic strategies as: "the failure to respond to treatment with two tolerated AEDs selected and used appropriately for the purpose of achieving and maintaining seizure freedom".[61] Resistance is classified according to the following characteristics: primary, secondary, specific, and nonspecific. Primary resistance refers to an intrinsic component of the disease (i.e., the tumor itself), and secondary resistance refers to an undesirable consequence of the disease itself (e.g., limited efficacy of pharmacological therapies due to drug interactions). Specific refers to the patient's response to a particular drug, and nonspecific refers to the patient's response to various

drugs.[62–64] Taking into consideration this definition, tumor-related epilepsy can be considered a drug-resistant epilepsy with mixed characteristics (i.e., among those outlined in this paragraph). In fact, the pathophysiological mechanisms underlying seizures in patients with brain tumors are not clearly understood.[15] On an experimental level, the peritumoral area has shown changes in morphology, the types and concentrations of amino acids, pH, glutaminergic receptors (e.g., N-methyl-D-aspartate receptor - NMDA -; alfa-Amino-3-hydroxy-5-methyl-4-isoxazolepropioni acid - AMPA), and other enzymes and transporter proteins.[15,65–67] Regarding the pathogenesis of seizures in tumor-related epilepsy, the development of resistance is probably multifactorial and related to mechanisms that bypass the AEDs.[65] Insufficient seizure control may be due to the fact that the antiepileptic action of many AEDs is due to changes in excitability mediated by ion channels.[15,68] However, tumor mechanisms of epileptogenesis are multifactorial and not just related to the activity of ion channels (e.g., changes in pH, amino acids, proteins, etc.). Seizures could also result from tumor progression with further damage to surrounding brain tissue, and in this case, a previously used AED might not be effective.

Finally, the seeming ineffectiveness of prophylactic AEDs may result from insufficient concentrations of the drugs in the serum or at the site of action in the brain, possibly due to pharmacological interactions with cancer therapies or to tumor-specific genetic alterations and expression of proteins. In patients with drug-resistant epilepsy, evidence of poor intraparenchymal accumulation of AEDs has been documented. This phenomenon is due to the overexpression of genes and proteins that mediate nonspecific resistance to treatments. These proteins have also been found in neurons and glia of the epileptogenic zone. In patients with tumor-related epilepsy, the increase of these intracellular proteins could be caused by the tumor itself, which is very typical behavior in systemic tumors.

With regard to drug resistance, there are two current hypotheses called the target hypothesis and the transport hypothesis. The *target hypothesis* suggests that drug resistance might be due to modifications of the receptor sites targeted by the AEDs, thereby making it less sensitive to the anticonvulsant effect. The *transportation hypothesis* suggests that drug resistance may be due to the fact that the AEDs are unable to penetrate their sites of action in the brain. This phenomenon is closely related to the overexpression of drug transporter proteins in tumor cells and vasculature, which can restrict access of the AEDs to the brain tumor tissue. This overexpression can also occur in the neuronal and glial membranes, thus potentially reducing the effectiveness of drugs due to reduced access to intracellular sites of action. In 1970, Victor Ling discovered multidrug transporter proteins in tumor cells resistant to chemotherapy, and these substances became known as multidrug resistant proteins (MDRs) and P-glycoprotein (P-gp), with the P referring to permeability because they were responsible for reducing the concentrations of chemotherapy drugs in the target cells. Today, there are various multidrug transporters, such as P-gp, MRP1, MRP2, and breast cancer resistance protein. The primary, physiological function of such proteins is to pump lipophilic drugs and other xenobiotics out of the cells to avoid the accumulation of potentially toxic substances. Paradoxically, this process also decreases the effectiveness of these drugs by restricting access to the tissues in and around the brain tumor. Although there are many MRPs in the endothelial cells of brain tumors and the peritumoral region, P-gp is the most important in drug-resistant epilepsy because it is capable of transporting a large number of AEDs, including carbamazepine CBZ, falbamate FBM, gabapentin GBP, lamotrigine LTG, phenobarbital PB, phenytoine PHT, and topiramate TPM. Experimental results indicate that, in patients with refractory epilepsy, the transport proteins P-gp, MRP1, and MRP2 are over expressed in both the capillary endothelial cells of newly formed capillaries and in the tumor cells. The problem is that it is not always possible to transfer the results from experimental studies done on animals to human beings.[69,70] Indeed, a study by Baltes seems to indicate a likely role of P-gp in reducing the access of certain AEDs, such as PHT and LEV, in humans due to an overexpression of P-gp and MRP2 providing a barrier.[69] Even the concentration of intracerebral OXC is inversely proportional to the expression of MDR1 mRNA in patients with refractory epilepsy.

Use of Systemic Treatment for Seizure Control

To date, some studies in the literature show that RT in its various modes (brachytherapy, external beam RT, conventional stereotactic RT) can reduce the frequency of seizures, especially in patients with low-grade gliomas, with response rates ranging from 40% to 75% (seizure-free in 22-55 % of cases).[71–75] Reseachers have also observed that the reduction of seizure frequency can begin during the early stages of radiation treatment, and it is not necessarily associated with a significant reduction in the volume of the tumor, as indicated by magnetic resonance imaging. In recent years, an increasing number of studies addressed the possible role of chemotherapy in reducing seizures in patients with low-grade glioma. In particular, the use of PCV (procarbazine, CCNU, vincristine) or temozolomide significantly improved seizure control (>50% reduction in seizures, compared to baseline) in 50-65% of patients, of which 20-30% have become seizure-free.[76–87] The

patients with a reduction in seizure frequency did not necessarily have a reduction in the volume of the tumor, however, because the frequency drop was also observed during stable disease. In fact, the majority of these patients have non-enhancing lesions on MRI and show only modest reductions in T2/FLAIR high signal abnormality, or no modifications at all. Therefore, the possibility of seizure response to antineoplastic treatments should always be considered when evaluating the effectiveness of concomitant antiepileptic and antineoplastic treatments.[87]

This consideration (i.e., possible seizure response to systemic therapies) is particular to BTRE because it is a unique subtype of epilepsy, due to its presumably multifaceted pathogenetic mechanisms and resistance to common AEDs. These characteristics have led to many recent neuro-oncological studies that have discussed the possible use of CT or RT as therapy for epileptic seizures in patients with brain tumors.[9,74,79,83,88–93] For example, Chalifoux and Elisevich describe a significant reduction in seizure frequency for a small case series of patients with high-grade gliomas who had been treated with RT, with benefits extending beyond the early postradiation period.[88] Other published data cites positive effects on seizure frequency in patients with low-grade glioma after RT or CT with temozolomide. Rudà *et al.* have also demonstrated "a significant and durable benefit from radiotherapy in term of epilepsy control."[94]

The published research has yet to address a number of serious issues, however, regarding the use of systemic therapies for seizure control in BTRE patients, and some of these issues are mentioned below. For example, in studies on BTRE, the criteria for measuring seizure improvement represent a major concern. Some studies have suggested that CT can bring about "seizure improvement," without indicating how this "improvement" was measured.[79,83] The studies' authors do not seem to have considered the fact that seizures are extremely difficult for the patient or caregivers to evaluate. A seizure diary is usually given to epileptic patients, who are asked, along with their caregivers, to take note of seizure frequency and to report the number during check-ups. However, the number of seizures often tends to be underestimated, or seizures are missed altogether because medical personnel, patients, and caregivers have not been trained to specifically recognize these symptoms.[79] Also, most seizures in these patients tend to be simple and complex focal, and thus, they have clinical manifestations that are extremely difficult to interpret and evaluate.

Furthermore, reporting successful use of CT or RT as treatment for epileptic seizures can lead to increased risk for patients with stable neuro-oncological disease because such reporting could give rise to the perception that BTRE patients could be treated for seizures with CT and/or RT. In addition, many studies undertaken to demonstrate the efficacy of CT and RT for epileptic seizures were retrospective, meaning that the primary objective of the studies was not to verify and count epileptic seizures, but to evaluate the response of oncological disease to anticancer treatments.[79,83] The fact that these retrospective studies have a limited number of patients from oncology departments, often with charts that are years old, should not be overlooked.[74,88]

Lastly, clinicians should consider the doses of AEDs discussed in these studies. As stated, the difficult nature of recording seizure frequency plays a significant role here because the reported number of seizures largely determines the efficacy of the therapeutic treatment. Often, the doses of AEDs in these studies are not documented clearly, and no verification is made as to whether the drugs had been used properly (maximum possible dose for each patient, with add-ons clearly identified) prior to determining whether or not the therapy is efficacious.[79]

Future scientific research will undoubtedly arrive at a common therapeutic approach for both brain tumors and epilepsy,[66,91–93,95–102] especially considering recent experimental data indicating that epileptogenesis related to brain tumors is multifactorial with common pathways.[15,65,67,93,95–99,103–105] However, clinicians should exercise caution when making suggestions regarding the use of CT or RT to treat epileptic seizures in brain-tumor patients. More research needs to be done before these new discoveries can be put to clinical use. For this reason, as suggested by Englot *et al.*, adjuvant antineoplastic therapy should not be considered as a primary antiepileptic treatment.[9] At this time, the most substantiated position appears to be that CT and RT might act in synergy with AEDs for seizure control.[67] Thus, based on new experimental discoveries, we can only factually state that, at best, CT and RT should be used as a type of AED in add-on.[91–93,96,97,100,101,103]

Both patients and clinicians would benefit from an interdisciplinary approach through which each specialist could allow each patient to best utilize his or her professional competence. Hopefully, the considerations presented here can be appreciated within the context of the valuable collaborative framework offered by Rudà *et al.*: "an effective treatment of tumor-related epilepsy needs a multimodality approach including both AEDs and antineoplastic modalities (surgery, radiotherapy, chemotherapy), and probably a 'personalized' approach will offer the best results."[94]

Use of AEDs as Antineoplastic Treatment

The treatment of BTRE with AEDs is often associated with insufficient seizure control. This phenomenon (pharmacoresistance) is poorly understood and may result from different pathophysiological and pharmacologic mechanisms.[106] The role that P-gp and multidrug

resistance transporters (MRPs) play in the transport of lipophilic substances, such as AEDs, through the blood-brain barrier may be of critical importance. P-gp and MRPs are also involved in the explanation of human glioma chemoresistance against several anticancer drugs. *In vitro* and *in vivo* studies have provided evidence of the regulation of P-gp expression or function by AEDs.[107–109] The literature confirms this possible intrinsic antineoplastic effect for some AEDs.[110] In fact, experimental data indicate that some AEDs induce apoptosis, the main mode of action of anticancer drugs. Mechanisms involved include the upregulation of gene expression in the proapoptotic ERK-AP-1 pathway, inhibition of glycogen synthase kinase-3-b, downregulation of protein kinase C, activation of peroxisome proliferator-activated receptors-g and -d, and blocking of histone deacetylase (HDAC).

Of the first-generation AEDs, preclinical studies on cell lines have documented the antitumor action of VPA. Such action, mediated in part by inhibition of HDAC, leads to an arrest of cell growth through the promotion of apoptosis, the reduction of the capacity of invasion, and the induction of autophagy.[111–121] However, a clear antineoplastic activity has not yet been confirmed in clinical studies. The potential impact of VPA on the survival of GBM patients enrolled in the study EORTC 26981-22981 (i.e., Stupp protocol) has recently been retrospectively assessed.[122] The retrospective study identified three subgroups: patients not in treatment with AEDs, patients treated with inducing AEDs, and patients treated with VPA alone.[123] The median survival for the three subgroups in the arm RT + TMZ treatment of concomitant/adjuvant was 13, 14, and 17 months, respectively ($p = 0.0001$). These varying survival times could suggest an advantage for the group treated with VPA, indicating a possible synergy between VPA and chemotherapy. In any event, given the retrospective nature of the study, as well as the fact that it was not designed to evaluate the role of AEDs, these results should be considered with caution. Among the new AEDs, the literature indicates that TPM and the major metabolite of LEV, 2-pyrrolidinone-*n*-butyric acid, are also able to induce histone hyperacetylation in human cells.[124] In a recent paper, LEV *in vitro* seemed to be the most potent methyl guanine methyl transferase (MGMT) inhibitor among several AEDs with diverse MGMT regulatory actions. This observation suggests that LEV inhibits human malignant glioma cell proliferation and increases glioma cell sensitivity to the alkylating agent temozolomide.[125] Overcoming drug-resistance protein activity may improve the treatment and prognosis of BTRE. The use of AEDs is necessary for seizure control, and therefore, if these drugs could have a possible intrinsic antineoplastic effect in addition to reducing seizures, they could provide a double positive effect. Exploration of AED potential in this area represents an important direction for future research.

Efficacy of AEDs on BTRE: An Overview

In its guidelines for the treatment of partial seizures in adults, the International League Against Epilepsy outlined the following monotherapies of choice: CBZ or PHT (Level of evidence A) or VPA (Level of Evidence B).[126]

For the treatment of epilepsy in adults with symptomatic epilepsy, an expert opinion published in 2005 recommended the use of CBZ, OXC, or LTG as initial monotherapy and LEV, CBZ, and LTG as add-ons.[127] The AAN has also compiled guidelines for the treatment of newly diagnosed epilepsy, recommending that patients start with older-generation AEDs or with new AEDs (LTG, OXC, GBP, TMP), indicating that the choice would depend on individual patient characteristics (A Level of Evidence). OXC is considered equivalent to CBZ and PHT in terms of effectiveness, but it appears to be more tolerable.[128] Regarding the treatment of refractory partial epilepsy, AAN guidelines identify both OXC and TPM as drugs that may be used as monotherapy (Level of Evidence A). LTG can also be used as monotherapy for these forms, but it has a B level of evidence. As for GBP, LEV, tiagabine (TGB), and zonisamide (ZNS), there is insufficient evidence to support the use of the drugs for the monotherapy of refractory partial epilepsy, but TPM can reportedly be used for refractory generalized tonoclonal seizures. Regarding the use of AEDs in BTRE, to date there have been no studies comparing the efficacy of old and new AEDs in this patient population.

Regarding the effectiveness of new AEDs for the treatment of BTRE, to date, the only published studies use cases in which different histological types are included. Of these studies, in recent years, numerous works have investigated LEV in monotherapy or as an add-on; OXC and TPM in monotherapy; and GBP, pregabalin, TGB, and ZNS as add-ons.[1,65,129–146]

Adverse Events Specific to BTRE Patients

In patients with brain tumors treated with older AEDs, studies have detected a higher incidence of serious adverse events (23.8%), as well as an increased incidence of moderate-grade adverse events (20-40%).[1,49] Also, for both metastases and malignant gliomas, the evaluation of adverse events related to AEDs is crucial when choosing the AED therapy, because these affect the perception of the patients' QoL more than seizure frequency.[46] For example, patients with brain malignancies treated with PB experience increased risk of developing periarthritis.[46,49] The possibility of skin rash in

cancer patients undergoing RT is 5-10%. With the addition of PHT, it can be as high as 22%, and it is also higher than the average with CBZ or PB.[147] In particular, the combination of PHT or CBZ with RT may predispose a patient to Stevens-Johnson syndrome. Therefore, according to many authors, the use of PHT or CBZ during RT is not advisable in patients with glial neoplasms.[46,49,53,148–154] In addition, LTG may induce agranulocytosis with severe prolonged neutropenia; therefore, special precautions need to be taken when AEDs are prescribed for patients undergoing CT. In such cases, it is useful to monitor hematological parameters every 2-4 weeks for the first 6 months.[155] To date, the literature on new AEDs indicates an incidence of side effects of approximately 11.4% with OXC, 14.9% with TPM, 22-37% with LEV, 33.3% with ZNS, and 55.5 % with PGB.[42,45,63,132–134,136–144,156] Among the possible side effects that appear in patients with epilepsy secondary to brain tumors, the appearance of a rash needs to be seriously examined. To date, rashes have been described almost exclusively in patients during therapy with older AEDs. However, published case reports describe the onset of rash in four patients with tumor-related epilepsy in monotherapy with OXC during RT, indicating that the risk of serious skin reactions in patients treated with AEDs during RT should not be underestimated, even with the use of new AEDs.[153,157]

Potential Interactions with Systemic Treatments

The consistent risk of serious, significant interactions between AEDs and CT represent one of the key concerns involved in the choice of an AED: older-generation AEDs (CBZ, PHT, PB) are potent inducers of the cytochrome P450 and may increase the metabolism of chemotherapy and cortisone, metabolized by the same isoenzyme. Conversely, chemotherapy may increase the metabolism of these AEDs, reducing the plasma levels and, therefore, their effectiveness.[34,35,46,49,54,55,57,148,154,158–162] From the standpoint of inductive effects on other AEDs, CBZ, PHT, and PB, being strong enzyme inducers, can modify the kinetics of the other AEDs, but this does not occur with GBP, vigabatrin (VGB), LTG, LEV, TPM, TGB, and ZNS.[163–166] TPM, LTG, and OXC are very weak inducers, but VPA is an enzyme inhibitor and therefore is notable for accelerating the metabolism of CT and/or steroids. It can also lead to an increase in hematological toxicity, however.[34,54,167] GBP, PGB, TGB, and LEV do not induce the hepatic enzymes.[54,57,154,160] In a study comparing AED inducers and inductors, GBM patients treated with nitrosoureas (CCNU) and CBZ, PHT, or polypharmacy with enzyme-inducing AEDs had reduced survival compared to those treated with VPA, LTG, and LEV, while the latter group experienced a greater occurrence of hematological toxicity.[45] Other studies conducted using irinotecan in combination with AEDs showed that PHT, CBZ, and PB are capable of altering pharmacokinetics and pharmacodynamics, necessitating increased dosages of CT, whereas with GBP, VPA, LEV, TPM, LTG, TGB, and ZNS, the dosage of irinotecan could not be stabilized.[168–171]

Cloughesy conducted a study on patients with malignant gliomas treated with noninducing AEDs, and in the study, tipifarnib demonstrated a better biological effect on survival. On the other hand, in the study by Grossman, patients with malignant gliomas treated with 9-aminocamptothecan in association with PHT, CBZ, VPA, and PB had levels of CT that were lower at steady-state, thus requiring major adjustments in the dose of CT.[172,173] No current data addresses the possible interaction between bevacizumab (humanized monoclonal antibody directed against the vascular endothelial growth factor - VEGF-receptor) and AEDs. The metabolism type of this agent (not liver or kidney) makes the problem of interaction less relevant. In contrast, this aspect should be carefully considered when using agents in the category of small molecules (e.g., lapatinib, dasatinib, erlotinib, etc.) due to the fact that they have a metabolism at the level of hepatic cytochromes, and therefore, the use of an antiepileptic drug inducer is likely to impair their effectiveness.

Impact of AED Therapies on Cognition

Patients with gliomas using CBZ, PB, PHT, and VPA have worse performance on cognitive tests, compared to those who do not use them, with the exception of verbal memory. Such findings suggest that the AEDs may adversely affect cognitive abilities more than the onset of seizures.[102] According to some authors, new AEDs such as GBP, OXC, and LTG may have minor, negative neurocognitive effects.[174] Of all the AEDs, PB has the worst cognitive profile, so it is not recommended in patients with cognitive deficits and brain tumors.[46,49,175] AEDs with GABAergic mechanisms (PB, benzodiazepines, VGB, TGB, and TPM) can induce sedation and depression, and VPA, LTG, and OXC may have antidepressant effects.[46] In one study of nononcological epileptic patients, OXC was demonstrated to be more tolerable compared with CBZ and PHT, and it was also capable of improving QoL associated with the emotional and psychological aspects of epilepsy.[176] Regarding the impact of AEDs on the cognitive functions of general epilepsy patients (i.e., nononcological), some comparative studies have indicated a trend in favor of minor adverse effects in cognition with newer AEDs in comparison to older AEDs.[174] In cancer patients, the older AEDs, such as CBZ, PB, VPA, and PHT, induce decreased cognitive

functioning, depression, and irritability, but the newer AEDs seem to have minor, negative cognitive effects.[174] Furthermore, in a recent report, researchers noted a sharp decline in cognitive functions in patients with high-grade brain tumors during the course of the disease and at the stage of progression, which the authors attributed to the use of AEDs.[177] Though the specific type of AED was not indicated in this study, the results imply that the use of these drugs in such patients should be planned with care. All of the older AEDs produced negative cognitive effects when compared to the nondrug conditions. Although the cognitive effects of AEDs are generally modest, these effects can have clinical significance. The available data suggest that some of the newer AEDs (GBP, LEV, LTG, OXC, TGB) have fewer effects on cognition and memory than the older AEDs do and that these differences can have a significant clinical impact.[178]

Impact of AED Therapies on QoL

Cognitive impairment in patients with brain tumors depends on three factors: the location and size of the lesion, chemotherapy, and RT. In particular, CT and RT affect the speed of information processing, executive functions of the frontal lobe, memory, attention, and sustained motor coordination. Therefore, clinicians and patients should consider that existing therapies are more aggressive than in the past and, therefore, may lead to an increase in cognitive disorders due to CT and RT and, thus, a worsened QoL.[179] The QoL for patients with high-grade brain tumors, in particular, is affected by factors such as the specific therapies they undergo (i.e., chemotherapy, RT, surgery, and supportive care, including AEDs), the physical disability connected to the location of the lesion, and the associated neurocognitive dysfunction.[180] The cancer patient thus views metastases as a signal of the end of his/her life, leading him or her to reflect on the apparent uselessness of previous treatments (i.e., heavy to bear) and to think about an imminent end.[53,179] These patients face behavioral, emotional, and intellectual difficulties, and they are often unable to live independently and to carry out activities of daily living. Some authors also report a decline in cognitive function that can substantially influence their QoL as well as their choice of treatments; cognitive impairment often impacts functional independence more than the presence of a physical disability.[52]

In the literature on patients with all types of cancer, QoL is not always considered a priority. Controlling symptoms and the progression of the disease seem to take precedent. Brain tumors often affect young patients for whom satisfactory sexual performance is critical to emotional balance, and this aspect, a fundamental component of QoL, should not be overlooked. For this reason, the choice of the AED must take into account the possible effects on patient's sexual life.[181] In patients with epilepsy, sexual dysfunction occurs in 11-22% of those treated with PB, CBZ, PHT, and PRM. The negative effect of newer AEDs on sexual function has only been described in two cases, during use of TPM (reversible after suspension).[182,183] To date, no randomized or comparative trials have addressed the effects of AEDs (both old and new) on sexual performance in patients with brain tumors. The only case report in the literature relates to ZNS as add-on in a patient with an oligoastrocytoma who experienced reversible erectile disorder.[184] On the basis of these considerations, QoL must be recognized as a primary goal in patients with malignant gliomas or brain metastases. Epilepsy must also be seen as a symptom that can affect the long-term disability of the patient, and it should be evaluated carefully when AED therapy is selected.

How to Choose an AED?

Based on all of the data reported above and in Chapter 13, we conclude that the older, first-generation AED inducers (CBZ, PHT, PRM, and PB) must not be used to treat patients with BTRE.[55,57,74,75,158,159,168,170–174,179] Interference with CT can occur and induce important adverse events in this patient population, in particular drugs such as irinotecan.[168–171] Older AEDs should also be avoided for patients who need to undergo RT, due to the potential danger of synergistic adverse reactions.[151,152] In addition, we advise avoiding the use of VPA in the treatment of patients who are treated with nitrosoureas, cisplatin, etoposide, and methotrexate due to potential, serious adverse events.[45,167]

On the other hand, the treatment of seizures with newer generation AEDs (GBP, LEV, LTG, OXC, TGB, TPM, and ZNS) appears to be associated with less adverse events and fewer interactions with CT and RT, compared to the older AEDs.[45,102,132–146,156,158,161,162,168,170–173,175] Among the newer AEDs, the published data suggest that LEV, as monotherapy or as an add-on, seems to be as effective as the older AEDs, but it is better tolerated and appears to have no interactions with chemotherapy.[74,134,141,143,144,169,170] Of the new AEDs used only as add-on therapy, recent data suggests that GBP, lacosamide, and pregabalin appear to be good therapeutic choices.[45,133,145,146,185,186] When considering an AED for this patient population, other variables must also be taken into account, however, including mood and cognitive disturbances. For this reason, in BTRE patients with mood disturbances and cognitive dysfunction, AEDs such as LEV, LTG, OXC, and VPA should be preferred, and barbiturates are not

recommended, due to the frequency of adverse events such as cognitive disorders.

Is It Possible to Stop an AED in BTRE, and When?

The withdrawal of an AED should only be considered for patients who have had an isolated epileptic seizure. In all other cases, this consideration (i.e., suspension of AEDs) is not recommended, and careful choice of the appropriate AED therapy must be made, taking into consideration possible interference with systemic treatments, as well as collateral affects that could affect the patient's QoL. In any event, the duration of antiepileptic treatment in patients with an isolated seizure represents one unresolved issue; the clinician must guide the patient in making the decision only after he/she has been informed of the risks of having another seizure in the event that no therapy is taken. After a thorough explanation, the patient must weigh the risk of having another seizure against the burden of possible collateral effects. In any event, discontinuing the medication would only be appropriate in selected cases of stable oncological disease, with localization outside of critical brain areas (e.g., rolandic, mediotemporal), or after completion of radiation therapy.

CLINICAL APPROACH TO BTRE

As noted in Chapters 11-13, the efficacy of AEDs against seizure activity is fairly uniform, without any one drug having significantly superior performance.[187] With that in mind and because there are no large-scale, well-designed randomized trials in patients with BTRE to use for evidence-based guidelines, the decision on which drug to use for treatment has to be based on other factors, including relative efficacy in specific seizure types, tolerability profile, comorbidities, drug-interaction potential, and cost.[188–190] The majority of neuro-oncologists, epileptologists, and neurosurgeons caring for patients with BTRE would agree that starting antiseizure therapy with a non-enzyme-inducing AED is the best initial approach, due to the drugs' excellent tolerability profiles and reduced potential for drug-drug interactions. The drugs that are prescribed most often include LTG, LEV, OXC, TPM, and GBP, as well as VPA. ZNS is another option because it is now approved for initial monotherapy of focal seizures in adults. There is less accumulated experience with other second-generation AEDs for the initial treatment of patients with BTRE, such as TGB, PGB, and lacosamide, and thus far, they are mainly restricted to adjunctive therapy.[190] A recent Dutch study of GBM patients reported that the most common AEDs used for initial monotherapy were VPA and LEV.[191] Initial seizure freedom was achieved in 41 of 100 patients (41%) in the VPA group, in 16 of 37 patients (43.3%) in the LEV group, and in 89 of 116 (76.7%) patients subsequently placed on a combination of VPA and LEV. Some authors are now using VPA more often as the initial treatment choice in patients with GBM and BTRE, due to the recent description of its HDAC properties and potential improvement in overall survival.[97,123,188] However, this effect may be counterbalanced by an increased risk of hematological toxicity, in particular thrombocytopenia.

When initial AED treatment fails due to a tolerability problem (e.g., skin rash), a different drug from the list above should be substituted in its place, preferably one not likely to produce a similar toxicity.[188–190] If the initial drug results in a partial but incomplete reduction in seizure activity, despite aggressive and full dosing, then adding a second AED from the list above is warranted. Some of the common combinations that have been described include VPA + LEV, LEV + TPM, LTG + TPM, LEV + LTG, and VPA + TPM. However, the use of polytherapy with AEDs can result in a higher burden of side effects and toxicity. Patients receiving optimal therapy with multiple AEDs who are still having uncontrolled seizures should be evaluated for poor compliance.

DRIVING AND BTRE

Being able to drive a car is an essential aspect of modern society in the United States, Canada, Western Europe, and many other countries. Driving is often critical for employment opportunities, socialization, dating, raising a family with children, and self-esteem. Because it is so important for all aspects of modern life, the ability to drive is often listed as the top concern in surveys of epilepsy patients.[192,193] Due to the risk of having a seizure and causing a motor vehicle accident, which may result in property damage, injuries, and even death to the patient and others on the road, individuals with epilepsy have often had restrictions on their ability to drive. Such restrictions began in the late 1800s, soon after the introduction of the automobile, when physicians and legislators recognized that seizure activity could pose a risk for driving.[192] At first, most patients with seizure activity and epilepsy were not allowed to obtain drivers licenses. By the late 1940s, however, it became more apparent that some patients with epilepsy could improve over time, developing cessation of seizure activity, or they could achieve complete control of seizures with medication, therefore becoming potentially safe drivers.

Driving is a very complex sensorimotor skill that requires the driver to correctly identify threats and changes in the environment, interpret those changes very quickly, and then respond appropriately to avoid an accident.[194,195] The threats and traffic changes are quite variable depending on the local environment, traffic density, weather conditions, and physical condition of the driver. The ability to drive safely and respond appropriately require normal vision (including visual acuity and full visual fields), motor skills, reaction times, cognition, and judgment. Patients with BTRE may have impairment or compromise of one or more of these neurological spheres due to their condition (including the brain tumor and epilepsy-related issues). The use of AEDs might negatively impact a patient's ability to safely operate a car, through impaired cognition, reduced judgment, and slowing of motor reaction times. In addition, AEDs may also cause blurred or double vision, severe fatigue, and tremors, which could also impact driving safety. If the patient has a seizure that alters the level of consciousness or causes full-blown unconsciousness, including complex partial seizures or various forms of generalized seizure events, there is a significant risk of losing control of the vehicle and causing an accident. Seizures that do not alter awareness, but affect motor control to some degree, might also impact driving safety.

There is a general perception that drivers with epilepsy are at much higher risk for motor vehicle accidents, due to their potential for loss of consciousness, loss of motor control, and use of AEDs.[192,194] Drivers with epilepsy actually pose less of a crash risk than do drivers with cardiovascular disease, however, or healthy drivers less than 25 years of age. Over 40,000 drivers die in motor vehicle accidents each year in the United States, with roughly 30% of those fatal accidents being related to the use of alcohol.[195] In contrast, the driving fatalities related to epilepsy only comprise 0.2% of all fatal crashes and only 4.2% of all medically related crashes. In addition, the relative rate of risk for a motor vehicle accident in patients with epilepsy is only 1.33, which is much lower than the risk associated with many other medical conditions, including alcoholism (2.0), mental illness (1.72), and medication effects (1.58).

In order to maintain or regain driving privileges, a patient with epilepsy or BTRE must have been seizure-free for a seizure-free interval (SFI) of some mandated length of time.[192–196] The SFI is variable within the United States and around the world. In the United States, the range is quite wide and can be 3 months, 6 months, or even a year in some states (with a median of about 6 months). There is also variability in other westernized countries such as Canada, Japan, Australia, and the countries of Western Europe. However, in most countries around the world, the SFI is typically between 3 months and a year. In a consensus statement on driving restrictions for patients with seizures, the American Academy of Neurology, American Epilepsy Society, and Epilepsy Foundation of America included the following recommendations: a 3-month SFI, no mandatory reporting to driving authorities, special exemption for those with purely nocturnal seizures, simple partial seizures that will not affect driving, a consistent and prolonged aura, and an isolated event due to a change in medication/acute illness.[197] In Arizona, the SFI has been reduced from 12 to 3 months without a significantly increased number of seizure-related crashes or deaths.[198]

In spite of the risks associated with driving when ongoing seizure activity is not well controlled, many patients with epilepsy and BTRE continue to drive. Many issues seem to be involved in the decision to continue driving, but several studies suggest that needing to drive for work, being male, and being married are the dominant factors.[199,200] In one survey, roughly 36% of patients with uncontrolled seizures had driven a car in the previous year.[199] Some authors suggest the use of ambulatory EEG monitoring in patients with questionable seizure control, in order to determine a more accurate seizure rate and whether or not they should be allowed to drive.[201]

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CHAPTER

15

Neuropsychology of BTRE

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CHAPTER CONTENTS

INTRODUCTION

Clinical neuropsychology is an applied science concerned with the behavioral expression of brain dysfunctions.[1] A neuropsychological examination may have four different objectives: diagnosis, patient care, treatment, and research.

Diagnosis. A battery of neuropsychological tests can be useful in identifying neurological disorders, helping to distinguish between different neurological conditions; discriminating between psychiatric and neurological symptoms; and providing behavioral data useful for localizing the anatomical site of a lesion.

Patient care. Descriptive evaluations may be employed in many ways in the care and treatment of patients with brain damage. A precise neuropsychological diagnosis is essential for careful management of many neurological disorders. The relative sensitivity and precision of neuropsychological tests make them an important tool for following the course of neurological diseases. Regular evaluations repeated over time can provide reliable indications of whether the underlying disease is changing, how rapidly, and in what manner.

Treatment. Rehabilitation of cognitive deficits is a treatment strategy expanding rapidly. An accurate assessment of neuropsychological performances is necessary for the definition of the cognitive baseline profile of the patient and for designing a rehabilitative program. In this way, the rehabilitation therapist obtains a reliable appraisal of patients' mental capabilities. Repeating assessment during follow-up can demonstrate patients' improvement over time.

Research. Neuropsychological assessment can be used for research purposes to study the organization of brain activity and its translation into behavior as well as specific brain disorders and behavioral disabilities. Neuropsychological studies serve more than one purpose: diagnostic issues, vocational or family problems, patient care needs.[1]

Neuropsychological issues and assessment of them in patients with brain tumor-related epilepsy (BTRE) must take into consideration the simultaneous presence of two different illnesses: brain tumor (BT) and epilepsy. Both impact the neuropsychological profile of the patient in different ways. In the literature, neuropsychological issues have been amply discussed for either BT, or for

epilepsy, but there is little if any data on this topic as it relates to BTRE. The following sections address a range of neuropsychological issues ranging from cognitive impairment to neuropsychological assessments, and sexual dysfunction to the overall quality of life (QoL), and the majority of the data that is presented comes from published studies that treat the two pathologies separately. However, the intent of this chapter is to demonstrate that the studies that have been done on BT patients and on patients with epilepsy have significant implications for BTRE, which we discuss at the end of each section, with the limited data that exists for this pathology, when available.

OVERVIEW OF NEUROCOGNITIVE IMPAIRMENT IN BT, EPILEPSY, AND BTRE

Neurocognitive Impairment in BT

Most patients with BT experience cognitive impairments of attention, executive and intellectual functions, visual-spatial and constructional abilities, sensory perceptual functions, language and memory.[2] Histology and tumor site, disease progression, treatment-related neurotoxicity, neural reorganization, individual psychophysical conditions, and comorbidity such as epilepsy and cardiovascular failures contribute to the type and severity of cognitive impairment in BT patients.[3] More than half of long-term survivors of glioma develop serious cognitive deficits, especially in short-term memory.[4] Therefore, assessment of cognitive impairments has become increasingly important for clinical diagnosis and follow-up.[3] According to recent findings, BT causes alterations of brain connectivity.[5] Learning and memory deficits have been related to changes in amplitude and synchronization of low-frequency connectivity, involving different neural networks.[6] Together with toxic and metabolic insults, such alterations explain the nonfocal cognitive patterns of BT, suggesting whole-brain dysfunction.[3] In addition to cognitive dysfunctions, patients experience numerous other symptoms that negatively affect their ability to participate fully in work, social life, relationships and leisure activities, such as neurological problems, fatigue, mood disorders, and sexual dysfunctions. These can often be the presenting symptoms of the tumor itself and can persist after treatment is discontinued.

There are a number of determining factors that contribute to cognitive deficits in BT patients: the tumor itself, neuronal changes, radiotherapy (RT), surgery, chemotherapy (CT), and other drugs.

The anatomical site as well as the slow, insidious growth and infiltrative nature of many tumors produce variable deficits. In addition, the histology of the tumor appears to contribute to a range of cognitive profiles. In fact, low-grade glioma (LGG) patients showed mild cognitive deficits at disease onset, usually marked by epileptic seizures.[7] An important study that was significant for its presurgical investigation, involved 139 patients with BT[8] evaluated by means of psychometric testing procedures that measured various aspects of memory, attention, language, or executive functions. The results demonstrated that more than 90% of patients displayed impairments in at least one area of cognition: executive functions, memory, and attention. However, presurgical neuropsychological testing is not routine and for this reason, the effect of the tumor on cognitive impairment remains at this moment inconclusive. Other factors influencing cognitive deficits in BT patients are related to age and medical complications. Older patients are more at risk independently from the histopathology of the tumor, while adjuvant medications may cause cognitive and mood disturbances.[4]

Given the prolonged life expectancy of patients with high-grade gliomas (HGG) resulting from improvements in treatment/therapies, cognitive assessment has become increasingly important in these patients for two reasons: first, because they can assist in the identification of cognitive deficits/possible neurological disorders and in the subsequent support and rehabilitative therapies; second, because data has indicated that they might be a valuable instrument for predicting tumor recurrence.

One important study demonstrating the "predictive" value of neuropsychological tests results was conducted by Meyers *et al.*[9]: using a battery of tests widely used for assessing cognitive functions commonly affected by BT, their evaluation of 80 patients with HGG and GBM demonstrated that cognitive function was a unique prognostic factor in predicting survival in those patients. In particular, performance on a test of verbal memory was related to survival after accounting for age, KPS score, histology, extent of resection, number of recurrences, and time since diagnosis. This data was confirmed also by Armstrong *et al.*,[10] who demonstrated the value of longitudinal neuropsychological assessment in the early detection of BT recurrence.

Recently, another work conducted by Bosma *et al.*[11] confirmed these data in a study of 32 HGG patients that indicated cognitive decline as being more pronounced in patients with tumor recurrence or in those who were being treated with corticosteroids and antiepileptic drugs (AEDs). In line with this study, Brown *et al.*[12] showed that up to 2 years after surgery, the percentage of long-term survivors of HGG with cognitive impairment was stable in the absence of recurrence.

Research on cognitive functioning in patients with brain metastasis has been limited, but is an important area, considering brain metastases are one of the most common neurologic complications of cancer, with a

variable incidence of 9-17%, when taking into consideration all types of tumors.[13] Data has shown that individuals with multiple cerebral metastases who had either been treated with whole-brain RT, or who had not yet been treated, experienced deficits in motor speed, manual dexterity, memory, and executive functions.[14] A pilot study[15] in which neurocognitive function was prospectively measured for 15 patients with 1-3 newly diagnosed brain metastases, treated with initial stereotactic radiosurgery alone showed that at baseline, 67% of the patients had impairment on one or more neurocognitive tests. The domains most frequently impaired at baseline were executive function, motor dexterity, and learning/memory. At 1 month, declines in the learning/memory and motor dexterity domains were most common. In a subgroup of five patients still alive 200 days after enrollment, there was stable or improved neurocognitive performance across executive function, learning/memory, and motor dexterity. However, still today, neuropsychological evaluation of patients with cerebral metastases usually concentrates on possible effects of radiation therapy on cognition, whereas a novel study approach that develops a cognitive profile of the patient, independently of the therapy that he/she has received, could be more complete.

Regarding pathological mechanisms related to the appearance of cognitive deficits in BT, there are literature data that explore different hypothesis. Neurochemical changes can be involved; these changes in brain of glioma patients have been demonstrated with magnetic resonance spectroscopic imaging.[16] These studies show a loss of choline in areas with normal-appearing white matter, reflecting remote membrane damage, far from the tumor site and radiation site. However, the degree and manner in which these neurochemical changes—distant from the site of the tumor occur—is not yet understood.[4] Also studies in rodents have demonstrated that whole-brain irradiation leads to a significant decrease in the number of newborn mature and immature neurons in the dentate gyrus and has been associated with impairments in hippocampal-dependent spatial learning and memory.[17]

Many studies have been published on the effect of RT on cognitive deficits. Unfortunately, many of these studies are retrospective[3,11] and, in addition, there is great variability among them regarding the illnesses of the patients; the type of radiotherapies used; and the batteries of neuropsychological tests used. All of these factors make it difficult to ascertain the extent to which the tumor itself is of major importance in determining cognitive deficits, or whether these deficits may be due to the RT.[18] It has also been hypothesized that the cause of RT effects on cognitive functions can be the induction of inflammatory cytokines, disruption of the hypothalamic-pituitary-adrenal axis, and alteration of neurotransmitters.[4] The following represent some of the data that have emerged. RT may provoke a range of cognitive changes,[19,20] usually many months after disease onset.[21] RT is widely known to cause injury to white matter and results in cognitive impairment related to frontal-subcortical dysfunctions. A comparative study by Klein *et al.*,[22] evaluating the effect of RT on mid-term to long-term cognitive sequelae in LGG, demonstrated that cognitive decline was worse for irradiated than for nonirradiated patients. This study also showed that RT was associated with cognitive impairment, irrespective of disease duration, and total radiation dose, but higher fraction doses (greater than 2 Gy) resulted in more severe deficits. In another study, about 200 adults with supratentorial LGG were randomly assigned to a lower or a higher dose of localized RT and were screened for cognitive performance by the mini mental state examination (MMSE).[23] In this population, most patients maintained a stable neurocognitive status after focal RT as measured by the MMSE. Patients with an abnormal baseline MMSE were more likely to have an improvement in cognitive abilities than deterioration after receiving RT. Only a small percentage of patients had cognitive deterioration after RT. However, MMSE is not considered to be a complete enough instrument today for measuring cognitive impairment in BT patients; when used alone, it can lead to possibly dangerous conclusions that erroneously point to some drugs or treatments as having no cognitive side effects.[24]

Surgery for BTs leads to the histological diagnosis and assists in the alleviation of neurological symptoms through the reduction of tumor mass.[25] However, surgery can cause transient neurological deficits owing to damage of normal surrounding tissue.[25] As described by Scheibel and coworkers,[26] surgery in patients with glioma leads to focal cognitive deficits, but the extent of tumor removal has not been found to affect cognition.[27,28]

The role surgery may play in cognitive deficits is still open to debate: on one hand, previous studies have reported that surgery-related perioperative complications are the dominant cause of postoperative cognitive deficits, including shunt infection, bacterial meningitis, and neurological deficits.[29,30] On the other hand, other studies have indicated that cognitive deficits after surgery are not likely to be caused by surgery or perioperative factors.[31] Studies on surgery in patients with LGG in eloquent brain locations have shown a high percentage of postoperative cognitive deficits, especially speech deficits related to removal of temporal language areas and Broca's area.[18,32] However, most of these deficits resolved within 3 months, presumably owing to the plasticity of the normal brain.[18,32] In any event, there have not been many systematic reports on the immediate and long-term surgical effects on cognition.

Finally, there are literature data on possible negative effects of CT and steroids on cognition. The possible

negative effects of CT are hard to distinguish from those provoked by RT, because most patients treated with CT have already been treated with RT or are treated with radiation concomitantly. The characteristics of CT related cognitive deficits differ from those of RT because they tend to appear during, or soon after, CT.[33] Regarding chemotherapeutic agents routinely used in BT patients, one study on effects of concomitant RT and temozolomide (TMZ)[34] in GBM patients showed that the majority of the patients already had multiple cognitive deficits at baseline, preceding RT treatment. Their results highlighted that cognitive functioning remains rather stable during treatment; also indicating that the addition of TMZ to RT does not necessarily lead to an additional deterioration in cognitive functioning, during the first 6 months after diagnosis.

Recently, there has been growing interest in the effect on bevacizumab on cognitive functions. Bevacizumab is a humanized monoclonal antibody that has demonstrated promising results in patients with recurrent HGG.[35] A potentially positive impact of bevacizumab-based therapy on neurocognitive function, performance status, and/or QoL has also started to emerge from reports of clinical studies among GBM patients.[36,37] In a retrospective study of recurrent GBM patients treated with and without bevacizumab,[36] it was reported that bevacizumab-treated patients maintained their performance status longer with respect to nontreated patients. Another study[37] on 167 patients with GBM, at first or second relapse, showed that patients treated with bevacizumab who had an objective response or progression free survival >6 months, had improved or stable neurocognitive functions at the last follow-up. However, future data needs to include a control group to facilitate comparison and better data interpretation.

One of the causes of cognitive deficits in BT is brain edema, which is treated with corticosteroids, of which dexamethasone is the most common.[25] However, while corticosteroids can reduce edema, and therefore alleviate cognitive deficits, they can also induce mood dysfunction, and though rare, psychosis and dementia-like cognitive changes.[25,38] Corticosteroid-related dementia is characterized by deficits in memory, attention, concentration, mental speed and efficiency, and occupational performance. Therefore, to avoid further cognitive dysfunction, when brain edema is controlled, the use of steroids should be limited as much as possible.[38]

Neurocognitive Impairment in Epilepsy

Patients with epilepsy often present with cognitive complaints.[39] Cognitive disorders can be found in a wide range of seizure disorders including temporal and frontal lobe epilepsies, primary generalized idiopathic epilepsies and epileptic encephalopathies.[40] These cognitive deficits can be permanent when caused by structural lesions that lead to epilepsy (trauma, hypoxia-ischemia insults, etc.) or dynamic, when caused by the temporary disruption of neuronal activity patterns.[40] This second type of impairment is dynamic in the sense that the deficits are either happening in stages or transiently affecting the patients. These cognitive and behavioral deficits can occur as a result of the seizures themselves or interictal epileptiform abnormalities. First, seizures themselves can have negative effects on cognition[40,41] not only for the obvious inabilities during seizures, but also due to the postictal state that usually corresponds to a period of drastically decreased cognitive ability. Secondly, there is increasing evidence that interictal abnormalities can result in cognitive impairment, though much more short-lived than that of the postictal period. Epileptiform abnormalities, including interictal spikes or spike-and-wave discharges, represent an aberrant discharge of a large number of neurons near the recording site. These transient events can produce brief disturbances in neural processing, resulting in a phenomenon called transitory cognitive impairment. However, they rarely produce overt cognitive disturbances.[40,42]

Studies on the side effects of AEDs and on subjective complaints, in outpatients or community patients with well-controlled seizures, have revealed that about 70% of patients report problems in some cognitive area, the most common being memory, correlated to the assumption of AEDs.[39,43,44] The correlation between some AEDs and possible cognitive disturbances has been well documented in the literature and continues to be a strong area of interest among epileptologists and neurologists. Cognitive side effects are commonly seen in patients undergoing long-term AED therapy. For many patients, they may be more debilitating than the actual seizures themselves and, thus, contribute to a worse QoL.[45] In the reviews of the older AEDs (so-called first-generation AEDs—addressed in Chapter 11 of this volume), the four major drugs phenytoin, phenobarbital, carbamazepine, and valproic acid have been rated as follows: phenytoin and phenobarbital are indicated as the most detrimental to cognitive function, and carbamazepine and valproic acid the least. Some reviews have suggested that cognitive effects may differ, depending on the individual drug. For example: phenobarbital is associated with mental slowing, attention deficits, and memory problems; phenytoin with reduction in motor speed, problem-solving and attention deficits; and carbamazepine with impaired motor tasks.[46] Regarding new-generation AEDs (such as gabapentin, lacosamide, lamotrigine, levetiracetam (LEV), oxcarbazepine (OXC), pregabalin (PGB), tiagabine, topiramate vigabatrin, zonisamide) the available data suggest that some of them have fewer effects on

cognition and memory than the older AEDs, and that these differences can have clinical impact. It has been reported that gabapentin and lamotrigine have fewer cognitive side effects than carbamazepine,[47,48] while OXC, vigabatrin, and LEV seem not to have induced cognitive changes[46,49]; and tiagabine as add-on seems to induce a modest improvement in some cognitive domains (motor speed, speed of reading, attention, and verbal fluency).[49] A recent study showed that LEV used in monotherapy for over one year revealed significant improvements in verbal and visual attention, psychomotor speed, mental flexibility, executive function, verbal fluency, and word generation.[50]

The only new AEDs known to cause significant cognitive side effects are topiramate and zonisamide: both have diffuse cognitive effects as well as specific effects on language and memory.[45,51,52] In particular, zonisamide reduced performance on delayed word recall, attention, and verbal fluency, and this worsening was related to dose.[53] Topiramate's most intolerable adverse effects are seen in verbal fluency and reaction time, resulting in high discontinuation rates in patients taking it for epilepsy.[54] More recently, lacosamide has shown a cognitive profile that is quite safe, similar to that of lamotrigine and superior to topiramate.[55,56]

NEUROCOGNITIVE IMPAIRMENT IN BTRE

Up until this point, we have examined data regarding cognitive deficits in either BT or epilepsy. Few studies have been done to date on cognitive disturbances in BTRE. Therefore, little is known about this topic. The following section represents some of the data that have recently emerged.

The use of AEDs in the treatment of patients with BTRE, like in patients with non-oncological epilepsy, could alter cognitive performances. To date, there is only one paper that has focused on the impact of AEDs on cognitive functioning and QoL in glioma patients.[7] It evaluates possible deficits in the cognitive domains of information processing speed, psychomotor function, attentional functioning, verbal memory, working memory, and executive functioning. Results showed that working memory capacity and executive functioning were well below the levels attained by healthy controls. Moreover, the authors observed that the lower cognitive deficits of these glioma patients were due to AEDs. However, in this paper, only old AEDs were administered (phenobarbital, valproic acid, carbamazepine, and phenitoine), and the authors themselves stated that newer AEDs, including gabapentin, lamotrigine, and OXC, might control seizures as effectively as the established AEDs and possibly have fewer and less severe side effects.

SPECIFIC COGNITIVE DEFICITS IN BT, EPILEPSY, AND BTRE

Specific Cognitive Deficits in BT

Regarding the type of cognitive deficits in BT, a study by Sweet *et al.*[57] supported the notion that anatomical area is closely associated with cognitive deficits. Anterior cingulate cortex controls attention and conflict monitoring. Patients' response time for processing conflicts has been found to extend with anterior cingulated damage.[58] Tumors involving the pineal region have been found to be associated with impairment of memory, visuospatial function, attention, visuomotor function, problem solving, and affective disorders. Transient mutism and behavioral change have been associated with surgery affecting the vermis[59–61].With the growing consensus on the effect of lateralization, many studies have demonstrated that left-hemisphere tumors cause verbal deficits, including verbal intelligent quotient (IQ) and memory disorders, while right-hemisphere tumors tend to induce nonverbal memory disorders such as visuospatial and abstract reasoning abilities.[62–66] A systematic review on neurocognitive deficits in BT after treatment comparing literature from 2002 to 2012 showed that the most impaired domains are working memory, cognitive flexibility, cognitive processing speed, visual search, planning, and general attention.[67]

A recent paper by Mu *et al.*[68] showed that patients with left frontal glioma had deficits in verbal working memory and the ability to identify anger. Authors hypothesize that this may have resulted from damage to functional frontal cortex regions, in which roles in these two capabilities have not been confirmed. Table 15.1 shows specific cognitive deficits in BT.

Specific Cognitive Deficits in Epilepsy

In patients with non-oncological epilepsy, different types of cognitive deficits can be due to a number of invariant variables, such as genetics, basic brain lesion, site and side of structural brain lesion, and age at onset, together with the duration of epilepsy as well as dynamic variables including seizure frequency, ictal as well as interictal transient focal or long-lasting electroencephalographic epileptic discharges, adverse effects from antiepileptic medications or surgical intervention, and psychosocial variables.[69] Empirical work that focuses on the effects of seizures on cognition is relatively limited and has resulted in mixed findings.[70] Past research has found that patients with epileptic seizures result in poorer performance on psychometric tests (memory performances and IQ) compared with healthy individuals, especially in cases of generalized tonic-clonic seizures.[41] In mixed samples of newly diagnosed

TABLE 15.1 Cognitive Deficits in BT

Anatomical Area of the Tumor	Type of Deficit
Frontal	Working memory
	Inhibition of interference on ongoing actions
	Social cognition
	Risk assessment
	Decision making
	Use of external feedback
	Initiative
	Abstract reasoning
	Mental flexibility
	Expression
Temporal	Naming
	Verbal fluency
	Comprehension
	Memory
	Semantic competence
	Social cognition
Parietal	Visuospatial recognition
	Semantic competence
	Social cognition
Occipital	Visuospatial recognition
	Semantic competence
	Social cognition
Cerebellum	Capacity to modulate and check the mental operations implicated in a variety of activities (executive function, prosody, grammar, theory of mind, spatial memory)
Diencephalon/ corpus callosum	Memory

adult patients, deficits in visual motor tasks, mental flexibility, memory, reaction times, and attention were found.[71,72] Patients with mesial temporal lobe epilepsy and longer seizure duration display more severe cognitive deficits than those with other epilepsies irrespective of seizure onset laterality.[73] A retrospective analysis of neuropsychological data from 3193 patients with focal epilepsies at the Bonn Centre (1989-2006) in which the majority of patients (>70%) suffered from temporal lobe epilepsy, showed that memory functions are particularly susceptible to epilepsy-related neuropsychological disturbances.

Also AEDs can influence cognitive deficits. The older AED may result in impairments of attention and cognitive slowing, which can have secondary effects on memory by reducing the efficiency of encoding and retrieval.[74,75] Of the newer drugs, such as lamotrigine, LEV, and topiramate, data on cognitive side effects are growing in the last years.[25] Regarding the way in which AEDs can cause cognitive deficits, different mechanisms have been described in the literature.

Specific Cognitive Deficits in BTRE

In patients with BTRE, cognitive deficits can be due to the summation of all three factors: the tumor, epilepsy, and their respective treatments. As already mentioned, there has been only one work to date that evaluates the cognitive domains in BTRE,[7] and it was done 10 years ago, with AEDs that are no longer in use today; new-generation AEDs are now used that are better tolerated and have less impact on the neuropsychological profile of the patient. Therefore, future studies regarding cognitive deficits in BTRE patients are vitally important for a better understanding of their potential causes; only then can an effective rehabilitative program be designed.

OVERVIEW OF NEUROPSYCHOLOGICAL ASSESSMENT TECHNIQUES FOR BT, EPILEPSY, AND BTRE

Neuropsychological Assessment Techniques for BT

A correct and exhaustive neuropsychological evaluation is used to determine the level of patient awareness and to arrive at a general cognitive profile. Although neuropsychological evaluation has enormous utility for BT patients, it needs to be done in a manner that causes the least amount of distress for the patient; tests mustn't be too time-consuming and should be concise and "patient-friendly." According to studies described below, tests for attention, executive function, and memory can detect the main BT-related cognitive deficits and, among these, some measures also have clinical and prognostic significance. Tests for language functions are discussed separately.

Test Objectives. Regarding patients with BT, the objectives of neuropsychological testing vary in relation to the stage of disease and phase of treatment. For instance, in the early course of BT, the utility of neuropsychological assessment is to show the possible effects of BT in patients with otherwise normal neurologic status[76]; after diagnosis, neuropsychological assessments provide criteria for decision making[77] and yield indicators for monitoring postsurgical changes and the effects of treatment. Serial, longitudinal neuropsychological evaluations also support prognosis; test scores may predict survival in patients with HGG or brain metastase[9,14] and may anticipate tumor recurrence by weeks or months.[24] Finally,

neuropsychological testing may yield information for planning nonpharmacological treatment, for example cognitive rehabilitation or psychological support.

Types of Tests. A complex and changing pattern of cognitive functions such as those found in BT patients requires multidimensional testing; the use of more than one test is necessary because even if one test is sensitive to a particular cognitive domain, it cannot yield exhaustive information. General cognitive profile tests and prestructured tests for evaluation of IQ (e.g., WAIS and MMSE) are insensitive to specific changes common to patients with BT.[23,78] Thus, neuropsychological testing should have the following characteristics: standardized procedures, adequate psychometric properties (content, structure, convergent, and divergent validity; inter-rater and intertest reliability), and parallel forms.[3] For BT patients, the test measures should also be sensitive to the highest and lowest levels of performance, in different phases of disease and treatment, and be able to detect clinically significant changes (those with practical consequences or effects on everyday activity); may be different from statistically significant changes (observed at the group level). For example, Taphoorn and Klein[25] proposed a hierarchical model of assessment for patients with LGG or HGG, evaluating perception, information processing, attention, executive, memory, and intellectual abilities. Regarding LGG, Papagno *et al.*[79] described the Milano-Bicocca Battery. This battery investigates language, memory, apraxia, including visual-constructional abilities, and executive functions. The total time of administration in its long version is 1.5-2 h. A shortened version of this battery requires approximately 1 h, depending on the patient's cognitive abilities. Zarghi *et al.*[2] tried to determine the diagnostic role of a variety of cognitive tests in assessing neurocognitive impairments among patients with BT as compared to healthy participants, citing the Continuous Performance test (CPT), Stroop test, and Tower of London test (TOL). Regarding these tests, CPT generates quantitative data relating to the participant's ability to sustain attention for a period of time. The Stroop test is a quick and commonly used measure for assessing dysfunction in selective attention and cognitive flexibility[80] and may also be useful for investigating cognitive inhibitory processes. Finally, the TOL test can help detect unexpected impairments to the planning processes of frontal lobe.[81] Results of this study show that BT patients in comparison to healthy participants experienced more cognitive deficits on sustained, selective attention and planning.

Another area of impairment assessed by neurological tests is language; literature data indicate that there are three important steps for language assessment of patients with BT[82]: (1) Preoperative evaluation: to identify linguistic deficits and to provide a baseline for postoperative and follow-up evaluations. The diagnostic endpoint of this stage is to identify the functional damage to the language system in the greatest possible detail. (2) Postoperative evaluation: conducted repeatedly in the immediate postsurgery period (days to 2-3 weeks, depending on the medical condition), in order to monitor recovery. They should be started as soon as the patient is medically stable and can collaborate in neuropsychological testing. Critically, they should not take up too much time, so as not to exhaust the subject (no longer than 20-25 min). Another reason for keeping these batteries short is that in the days immediately following surgery, the cognitive status of the patient can change very rapidly, and therefore, batteries that must be administered in more than one session might yield results that are not reliable. Selection of the tasks to be included in postoperative evaluations should be guided by the changes observed intraoperatively and by knowledge of the linguistic/cognitive consequences that are most likely to follow tissue removal in a given region.[82] (3) Follow-up evaluation: should not be scheduled at too close intervals, in order to avoid fatigue, to prevent learning effects, and to permit a careful scrutiny of the effects of cognitive rehabilitation. At least 6 months should elapse between two consecutive evaluations. Since these evaluations are critical for mapping subject's recovery, it is also necessary that improvements of performance be distinguishable as clearly as possible from effects of learning.[82] Therefore, parallel versions of these tasks should be available.

However, it must be pointed out that there is great variability in the published studies regarding which tests are used, and consequently, the wide range of deficits and cognitive profiles that are reported. To date, published studies have not used the same batteries of tests and have highlighted a wide range of different deficits and cognitive profiles of patients.[21,23,83] This heterogeneity makes it difficult to have homogenous results, standardized instruments and comparable patient profiles (i.e., cognitive profiles).

Neuropsychological Assessment Techniques for Epilepsy

The batteries of tests used in epilepsy differ to those used in BT. Together with some neuropsychological measures (Rey auditory verbal learning test; Rey Complex Figure; Marching Test from the Reitan-Indiana Neuropsychological Test Battery for Young Children; Controlled Oral Word Association Test),[84,85] general, broad-spectrum batteries of tests are routinely used in epilepsy: Wechsler Adult Intelligence Scale-Revised (WAIS-R); Wide Range Achievement Test-Revised (WRAT-R); Neuropsychological Battery for Epilepsy.[86] All of these tests have been used in numerous studies in the literature and all have been utilized in the evaluation of both seizure effects[41,87,88] and AED effects.[89–91]

An overabundance of noncomputerized neuropsychological tests (i.e., paper-pencil) are used routinely in the field of epilepsy[92] (see Table 15.2). However, recently, computerized testing appears to offer an alternative that might be beneficial in terms of cost-effectiveness and time reduction to assess cognitive functions in patients with epilepsy.[56]

To date, only three tests, Computerized Cognitive Tests in Epilepsy (CCTE),[93] the "FePsy" (http://www.fepsy.com), and the Neurocog FX[56,94] have been explicitly devised for and validated for epilepsy. These tests showed sensitivity to clinical parameters, like focus lateralization, localization, or the presence/absence of epileptiform activity. To date, there is much less published evidence supporting the usefulness of these computerized tests in patients with epilepsy. Therefore, further studies should be encouraged.

Neuropsychological Assessment Techniques for BTRE

The neuropsychological assessment techniques for BTRE patients should integrate the knowledge of BT and of epilepsy. Particular attention should be given to evaluation of the cognitive domains that are most effected in BT and epilepsy, primarily memory, executive functions, and language.[8,73,95–97]

TABLE 15.2 Tests used to explore Cognitive Functions, Personality, Mood and Quality of Life in Epilepsy

Cognitive Functions	Tests
Abstract reasoning	Raven Progressive Matrices
Verbal and visuospatial reasoning	Wechsler Adult Intelligent Scale (adults and children), Stanford Binet
Attention	Digit span, Stroop test
Verbal memory	Wechsler Memory Scale (adults and children), Rey Auditory Verbal Learning Test
Visuospatial memory	Rey-Osterrieth Complex Figure, recall
Motor functions	Finger tapping test
Executive functions	Rey-Osterrieth Complex Figure, copy
	Wisconsin Card Sorting Test
	Tower of London
	Fluency test
Personality	Rorschach
	MMPI (Minnesota Multiphasic Personality Inventory)
Mood	Hamilton Anxiety Rating Scale
	Hamilton Depression Rating Scale, Beck Depression Inventory
Quality of life	QOLIE-31 (Quality of Life in Epilepsy), SF-36 (Short Form Health Survey)

Therefore, in BTRE patients, the use of a battery of cognitive tests that explores memory (short-term/long-term, auditory verbal/visual-spatial) as well as functions (attention, executive, fluency, and visual-perceptive) would be optimal; this could be quite intensive (i.e., requiring focus/attention) but care is taken to not require too much time—it can be administered in 50 min (see Table 15.3).

If patients with BTRE have had generalized seizures within 2 days prior to the scheduled test, it is important to postpone the neuropsychological evaluation, because lingering cognitive deficits may persist for minutes to days, depending on the type and severity of the seizure.[98]

PSYCHOLOGICAL ISSUES IN BT, EPILEPSY, AND BTRE

Psychological Issues in BT

Psychological symptoms in BT patients may include anxiety, depression, and fear of dying.[99] Patients may be unable to return to work after completion of

TABLE 15.3 Example of a Battery of Tests used for patients with BTRE

Neuropsychological Domain	Test Used
Global neurocognitive performances	Mini Mental State Examination
Abstract reasoning	Raven Progressive Matrices or Coloured Progressive Matrices
Attention/executive functions	Trail making test, Frontal Assessment Battery, Stroop test
Fluency	Phonetic and semantic fluency
Short-term auditory-verbal memory	Span forward and backward, Rey Auditory Verbal Learning test, immediate recall
Long-term auditory-verbal memory/episodic memory	Rey Auditory Verbal Learning test—immediate and delayed recall, story recall
Short and long-term visuospatial memory	Corsi Span, Rey-Osterrieth Complex Figure recall
Visuospatial abilities	Rey-Osterrieth Complex Figure copy
Mood	Hamilton Anxiety and Depression Rating Scale
	Zung Self Depression Rating Scale
	Neuropsychiatric Inventory (NPI)
QoL	EORTC-QLQ-C30
	QOLIE 31p (V2)
Side effects	Adverse Event Profile

treatment. For some patients, especially in advanced phase of the illness, constant supervision may become necessary.[100–102] Depression is the most common comorbidity in BT[103] and has been reported to be related to location of the tumor and extent of disease.[104] Over the past decade, studies have suggested that there is a relationship between depression and poor outcome in patients undergoing craniotomy for brain lesions as a whole.[105,106] BT patients who are depressed may have a variety of symptoms in addition to their neurological deficits such as dysphoric mood, helplessness, worthlessness, guilt, loss of self-esteem, and concentration difficulties.[103] Many of these symptoms are the same criteria used in the DSM-IV to make a diagnosis of depression.[107] In these patients it's important when exploring a diagnosis of depression to distinguish it from apathy. While depressed patients tend to feel an emotional pain, apathetic patients have a lack of feeling, emotion, interest, or concern.[103] This distinction is especially important in determining the incidence of depression, as well as in determining what types of treatments should best be considered. Patients with BT may initially present with psychiatric symptoms: personality change, abulia, apathy, either auditory or visual hallucinations, mania, panic attacks, and amnesia.[108] These symptoms may be indistinguishable from such symptoms in psychiatric patients without BTs. Obviously, the presence of any one of these particular symptoms does not mean that a psychiatric patient has a BT. It may be necessary to look for other clues that may be present. Psychiatric symptoms emerging after the age of 40 should increase the index of suspicion for the presence of a BT, especially if in addition to neurological symptoms or signs: headache, seizure, and memory loss. Patients who respond poorly to treatment and those with an absence of a family history of psychiatric illness should raise concerns about a BT. Any of these unusual features of psychiatric disease warrant investigation with neurodiagnostic imaging, preferably magnetic resonance imaging (MRI) of the brain with and without contrast.

Another important symptom to explore in these patients is distress. Distress is "a multidetermined, unpleasant emotional experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and spiritual crisis".[109] Relatively little is known about the frequency, longitudinal course, independent associations, and reported causes of emotional distress in adults with gliomas.[110] Intracranial tumors rank among those cancer sites that result in the highest emotional burden for the patient.[111,112] Knowledge of the intensity of stress, anxiety and depression as well as the coping strategies adopted by the patients is important for clinicians in their efforts to tailor care to patients' individual needs. Evaluation of depression[110,113] show that patients at the first occurrence of brain neoplasm wish to confront the situation and adopt optimistic coping strategies, seek support and take a constructive problem-solving approach. In the same fashion, patients with a recurrent neoplasm adopt the same strategy, as if it were a first-time diagnosis.[113] They also report the same likelihood of anxiety at a borderline level and at a clinically relevant level, as well as the same likelihood of depression at a borderline level. BT patients underestimate their psychological problems and the negative impact of any changes occurring since surgery/diagnosis when compared with their caregivers[114]. A recent study[114] showed that BT patients can also underestimate the negative impact of the tumor on their interpersonal relationships, emotional and cognitive functioning, and ability to cope by comparison with their caregivers and patients in the control group. Qualitative data supported these findings, showing a disagreement between BT patient and caregivers's interpretation of the prominent changes occurring since diagnosis/surgery that was not seen in the control group. The tendency of the BT group to underestimate their problems by comparison with their caregivers may be a consequence of reduced insight, specific to patients with brain impairment.[115,116] Alternatively, it may be in part a result of denial, a common coping mechanism used by oncology patients with a poor prognosis[117] or a combination of these factors. A recent paper[110] showed that at each time-point, one-third of patients reported significant emotional distress, evaluated by means of National Comprehensive Cancer Network Distress Thermometer and problem checklist. This distress persisted during follow-up among those initially highly distressed. Young, functionally impaired, and depressed glioma patients may particularly benefit from increased support.[110] During early treatment phase, a high number of patients with BT perceive elevated levels of distress. About half of patients studied in a paper by Goebel *et al.*[111] were classified as suffering from relevant distress.

Psychological Issues in Epilepsy

Regarding the psychological issues of patients with epilepsy, behavioral disorders are more frequent in people with epileptic seizures than individuals who do not have epilepsy.[118] However, interictal behavioral changes in epilepsy remain difficult to define, mainly because most epidemiological studies have been carried out in centers for epilepsy, in which many patients have

refractory epilepsy and a variety of pathological conditions. Behavioral disorders may precede, occur with, or follow a diagnosis of epilepsy. Comorbidities like depression and anxiety are present in patients with epilepsy. Most behavioral disturbances are observed more frequently in people with drug-resistant epilepsy, with frequent seizures, or with temporal lobe epilepsy.[118] Depression is the most frequent psychiatric disorder in patients with epilepsy. In a recent review,[119] the prevalence of interictal depression was quoted as being present in 25-55% of people with epilepsy. The occurrence of depression can have a major impact on the QoL of patients with epilepsy, even more so than the seizure frequency itself.[120] Among the potential neurobiological and psychosocial determinants, epilepsy variables such as seizure type (temporal lobe epilepsy and partial seizures), severity (the prevalence of depression increases with increased seizure severity),[121,122] modification of frequency (either increased or decreased), and AED treatment have been associated with depression.[123] However, there is some evidence that the following variables may be associated with the depressive symptoms that occur during AED therapy: enhanced GABA neurotransmission, folate deficiency, polytherapy, presence of hippocampal sclerosis, forced normalization and a past history of affective disorders.[124]

Anxiety disorders are present in 10-25% of patients with epilepsy.[125] Panic attacks and phobias are the most common psychiatric disorders during seizures. Literature data describe that an important cause of behavioral changes in epilepsy are AEDs.[49] AEDs can cause effects on mood, especially irritability, depression, and impaired cognition.[49] For these reasons, various tests have been created for evaluation of adverse effects, including psychological effects of AEDs in epilepsy. One of the most used is Adverse Event Profile.[126] Therefore, a correct evaluation of behavioral disturbances in patients with epilepsy should include evaluation of anxiety/depression with a focus on specific effects of AEDs on mood by means of Hospital Anxiety and Depression Scale, Beck Depression Inventory II, and State-Trait Anxiety Inventory.[127,128]

Psychological Issues in BTRE

Finally, regarding psychological issues in BTRE, there are limited data in the literature at this time. The few studies that have been published regarding the effects of AEDs on mood demonstrate that PGB and OXC can have positive effects on mood in patients with BTRE.[129,130] In particular, PGB improved anxiety in patients with BTRE and OXC did not modify the psychological profile of patients. Given the substantial data that exist regarding the psychological issues present in both BT and epilepsy patients, and taking into account the scarce data for BTRE patients, it has become evident that an appropriate battery of tests for the evaluation of psychological factors should become routine in the care of BTRE patients. A good approach to this problem appears to be screening by specific tests on mood (Hamilton Anxiety and Depression Rating Scale, Zung Self Depression Rating Scale)[129,130] and Neuropsychiatric Inventory.[131]

SEXUAL DISTURBANCES IN PATIENTS WITH BT, EPILEPSY AND BTRE

Sexual Disturbances in Patients with BT

Cancer and its treatments frequently affect sexual functioning and intimacy.[132] Across cancer types, estimates of sexual dysfunction after treatment range from 40% to 100% and involve many causes.[133–135] Common physical difficulties include achieving and sustaining intercourse (e.g., loss of sexual sensations, erectile dysfunction in men, pain with intercourse in women). Psychological effects can shape patients' feelings of desirability.[133–135] Patients' sexual functioning and sexual identity can be affected even when no outward change in appearance is visible and when the cancer does not directly affect sexual physiology.[132] Sexual problems may develop at any point during the disease course, including at diagnosis, during treatment, and after active treatment or during post-treatment follow-up[136] and are concerns for patients at all stages of disease progression.[132] Unlike many other side effects of cancer treatment, sexual problems commonly do not resolve in the first 2 years of disease-free survival but may remain constant and relatively severe.[137] Development of a comprehensive, self-reported measure of sexual functioning for use with cancer populations is important for several reasons. Measures developed and validated for use in noncancer populations may not be valid for cancer patients because some aspects of sexual difficulties may be unique to cancer populations, such as effects of particular chemotherapeutic agents or surgeries. A recent review of the literature on sexual function measures used in cancer populations found 257 articles that reported the administration of 31 psychometrically evaluated sexual function measures to individuals who were diagnosed with cancer, but most of these tests had not been used widely in cancer populations.[138] A recent qualitative study (not including BT patients)[139] showed that across all cancers, the most commonly discussed cancer- or treatment-related effects on sexual functioning and intimacy were fatigue, treatment-related hair loss, weight gain, and organ loss or scarring. Additional barriers were unique to particular diagnoses, such as

shortness of breath in lung cancer, gastrointestinal problems in colorectal cancers, and incontinence in prostate cancer. Sexual functioning and intimacy were considered important to QoL. While most effects of cancer were considered negative, many participants identified improvements to intimacy after cancer. Sexual concerns are often neglected in patients who suffer from brain cancer. Even in the face of severe, chronic, debilitating progressive disease, sexual functioning may be critical for establishing some sense of normalcy. There are only two papers on sexuality in BT, one is a case report[140] that showed how the patient benefited from education, encouragement, and supportive therapy. The other one is a review[141] on survivors from childhood BT and showed that in a cohort of 60 childhood cancer survivors, psychosexual problems were frequently reported.[142] A total of 20% of survivors felt a limitation in their sexual life because of their illness; older survivors felt "less experienced" than age-matched peers, and their overall appraisement of their sexual QoL was less positive. Survivors treated in adolescence were reported to have a delay in achieving psychosexual milestones, leading the authors to suggest that treatment in adolescence may be a risk factor for sexual problems in adult survivors of childhood cancer.

Sexual Disturbances in Patients with Epilepsy

In patients with epilepsy, the percentage of sexual dysfunction is 11-22% during treatment with phenobarbital, carbamazepine, phenitoine, or primidone. There have been only two studies published in which two cases of reversible sexual dysfunction are described using a newer AED, topiramate.[143,144] Recently, three cases of anorgasmia in patients with epilepsy in therapy with PGB as add-on were described.[145] For this reason, the choice of the AED should take into account the possible effects on sexuality.

Sexual Disturbances in Patients with BTRE

BTRE often affects young and older adults; individuals who in many cases may have a low life expectancy, and a constant fear of dying and/or sense of uncertainty due to the duplicity of their disease. For these reasons, a satisfactory sexual relationship can be a fundamental aspect of emotional well-being and a significant contribution to good QoL.[13]

For these reasons, the possible effects of AEDs on sexual sphere must be considered; and the choice of the drug should be made monitoring this aspect by means of interview and by instilling a climate of trust with the physician or team caring for the patient.

To date, there are no randomized trials or comparison on the effect of AEDs (both old and new) on sexual satisfaction in patients with BTRE. The only case report in the literature concerns an erectile dysfunction related to the assumption of add-on ZNS in a patient with oligoastrocytoma. This symptom completely disappeared upon suspension from this drug.[146]

A patient's sexual complaints during or following cancer treatment should be discussed by the oncology team, or patients should be referred to comprehensive sexual health programs for treatment, if available. Therefore, when caring for the patient, it is important to explore with him/her how BTRE is experienced physically and emotionally, including sexual dimensions and pleasure. In this case, a multidisciplinary team that addresses the possible neurological and psychological effects of AEDs can help a patient resolve any sexual dysfunction issues.

QoL ASSESSMENT AND MONITORING IN BT, EPILEPSY AND BTRE

QoL Assessment and Monitoring in BT

As life expectancy in HGG, and particularly in recurrent GBM, is so short, issues relating to QoL are immensely important to patients and their caregivers.[147] This is especially important in relation to new treatments in recurrent GBM. These new therapies do not yet have evidence supporting their contribution to extended survival, but may significantly delay the expected steep QoL deterioration occurring after progression following standard therapies.[148] Unfortunately, QoL data are difficult to collect in cancer patients because they may be unwilling to complete the questionnaire when they are not feeling well. Furthermore, repeated application of lengthy, formal QoL questionnaires can represent a major and impractical burden for patients.[149] Also, the analysis of QoL data is challenging due to the high rates of nonrandom missing QoL values that may be linked to patients' QoL status, and if ignored, may introduce bias to the interpretation of results.[149] Interpretation of the impact of standard and new therapies on QoL in GBM patients is consequently problematic, even when attempting to classify their effect into the three broad categories of negative, positive, or neutral. QoL in patients with HGG has recently been reviewed in detail[148]. Problems with interpretation of different studies and the paucity of robust QoL informations derived from well powered, randomized controlled trials were noted. Among the seven randomized controlled trials of new treatments published from 2002 to 2007, these authors identified that for HGG, there was little or no difference between treatment groups at baseline or follow-up evaluation. They suggested, therefore, that standard

multidimensional QoL questionnaires might contain too many items and consequently lack sensitivity to detect QoL changes in patients with HGG. Simpler, practical, and more sensitive instruments (such as cognitive function) are therefore needed to study QoL changes in relation to therapy in HGG. Thus, the factor of missing substantial follow-up data (primarily related to dropouts) needs to be addressed.

Many investigations have been undertaken to explore the multidimensional QoL of BT patients.[150] The instruments most commonly adopted by investigators are the FACT-BR (Functional Assessment of Cancer Therapy-Brain) and the QLQ-BN20.[151,152] The FACT-BR is a validated instrument and provides a comprehensive assessment of the emotional, social, psychological, and cognitive aspects of a BT patient's life. The QLQBN20 addresses symptoms that are specific to brain cancer or its treatment. However, the FACT-BR and QLQ-BN20 do not examine many other issues that patients and caregivers must struggle with, such as disease management, healthcare and daily living needs. A study conducted by the University of California, San Francisco (UCSF) neuro-oncology clinic[150] showed that many patients with BT and their caregiver need require additional resources and information, especially concerning coping strategies for addressing the emotional burden of the disease. These findings indicate that the information obtained during visits with health care providers is inadequate to satisfy these needs. Treating the caregivers' emotional needs can improve patient QoL and overall care. Since it is not feasible for most neuro-oncology providers to spend extensive time discussing the emotional impact of the disease with the patient and caregivers, a psychologist and possibly further psychiatric evaluation and counseling, may prove beneficial in helping families cope with a BT diagnosis. The unifying theme in all of the questions addressing the emotional domains the caregiver's need to share the experience with someone else; thus, distributing information on support groups as well as educational sessions at clinic visits may be effective methods to satisfy this need.

QoL Assessment and Monitoring in Epilepsy

Several reports from industrialized and developing countries indicate that QoL is significantly worse in people with epilepsy than it is in the general population[153] or with people who suffer from other chronic clinical conditions. Particular attention has been given in the past years to factors that might impact the QoL of patients with epilepsy: newly diagnosed seizures,[154] AEDs, and psychosocial and cognitive problems.[155] The recognition of the importance of cognitive performance to QoL led to the construction of new QoL instruments that cover this domain (e.g., ESI-55, QOLIEs). Vickrey *et al.*[156] for instance, reported that the Cognitive Function Scale from the ESI-55 (self-perception of functioning) correlated with Emotional Well-Being and General QoL in individuals with epilepsy. Nevertheless, Wilson and Goetz[157] recognizing the importance of the subjective assessment of cognitive functioning in QoL assessment, maintained that such assessment may be influenced by external factors (e.g., depression). Consequently, they also suggested the consideration of a direct measure of cognitive performance. Herman[158] cautioned that any QoL model that does not include the area of cognitive functioning is incomplete. In addition, he emphasized the need to view neuropsychological and QoL assessments as complementary, rather than as synonymous, and urged their integration. Leidy *et al.*[159] were the first to assess the performance of a QoL measure taking into consideration memory deficits. Those individuals with memory deficits had significantly worse QoL than the ones without memory deficits; the only area between the two groups that showed no differences was the Mental Health domain.

There are numerous instruments used to evaluate QoL in epilepsy.[160] The QOLIE-31[161] is used often. It is a 31-item self-administered questionnaire designed for completion by patients alone. It includes seven subscales (Seizure Worry, Overall QoL, Emotional Well-Being, Energy-Fatigue, Cognitive Functioning, Medication Effects, Social Function) and the Health Status item. Responses can be scored to provide subscale scores and a Total Score. The QOLIE-31-P (Patient-Weighted Quality of Life in Epilepsy Questionnaire) is an adaptation of the original QOLIE-31 instrument. An extra item was added to each of the seven subscales asking the patient to grade his or her overall "distress" related to the topic of each subscale. These ratings were converted to scores of 0-100 points, with higher converted scores reflecting higher distress.[162] In addition, an item asking about the relative importance of each subscale topic and an item asking about perception of change in overall QoL (since starting study medication) were added.

Side effects of AEDs can impact QoL, and therefore, an evaluation of side effects of AEDs is mandatory. Gilliam *et al.*[126] evaluated the clinical utility of a self-report instrument that could identify adverse AED effects and guide medication regimen changes that could reduce the toxicity. The instrument (Adverse Event Profile) contains 19 brief items that assess the frequency of a different adverse effect (dizziness, headache, confusion, hair loss, weight gain, memory loss, depression, etc.) using a Likert scale of 1-4, with 4 indicating more frequent occurrences. A score ranging from 19 to 76 may be calculated to measure total side effect burden of a medication regimen.

QoL Assessment and Monitoring in BTRE

The diagnosis of epilepsy in a patient with no oncological disease already implicates an important change in concept of QoL that involves three main factors:

1. Possible side effects from drugs.
2. The negative psychological impact caused by losing control of one's body and losing contact with the environment.
3. The rejection and marginalization that still occurs today due to a societal view of individuals with epilepsy as "strange."

These three factors become even heavier to bear in patients that must confront both pathologies: epilepsy and BT. Patients are subjected to systemic treatments for the neoplastic disease as well as antiepileptic therapies, and therefore are at even greater risk for side effects and drug interactions. The loss of control of one's body during a seizure and the frustration that accompanies such an experience represent for the patient a total lack of autonomy. The unpredictability of adverse events leads to an enormous sense of insecurity. In addition, seizures are a constant reminder to the patient of his/her illness and of being considered "different." Marginalization and rejection are especially felt by individuals who have a visible physical disability like hemiparesis or problems with speech (which may be due to the site of the tumor), and also by those whose physical aspect has been altered due to systemic therapies (hair loss from radiation, retention of liquids, or noticeable weight gain due to the assumption of steroids). All of these factors together with the label "epileptic" can cause the patient to feel extremely frustrated when attempting any type of social and/or interpersonal relationship.[13] Therefore QoL for patients with BTRE needs to be a primary objective. Together with the knowledge that epilepsy can significantly affect the long-term disability of the patient, the choice of AED must take into consideration the fact that in addition to controlling seizures, the drug could also have an effect on cognitive functioning, efficacy of systemic therapies, and the frequency of adverse events. For these reason, it is useful to perform a type of "screening" that assesses specific effects of seizures and AEDs on QoL, by means of specific questionnaires such as: QOLIE 32P (V2), and Adverse Event Profile[126,161] (see Table 15.3). Some recent studies demonstrated the positive effect of new AEDs, LEV, OXC, and PGB on social function, personal interaction, and mood.[129,130,163] In particular, LEV monotherapy in a group of 29 patients followed with 12 months of follow-up and evaluated by QoL and neuropsychological tests induced less worry about seizures and the effects of antiepileptic and improved the ability to maintain social functions.[163] OXC induced an improvement in Zung Self Depression Rating Scale in line with a recent study that showed that OXC has a positive effect on dysthymic symptoms in patients with epilepsy, compared with controls; which supports the hypothesis that OXC improves mood.[129] PGB as add-on in 25 patients with BTRE based on the QOLIE-31-P, induced a significant improvement of the subscale "seizure worry" of QOLIE-31-P (V2) and a significant decrease in distress scores related to AEDs and social life. A significant decrease in Hamilton Anxiety Rating Scale score was also documented confirming its effect on anxiety.[130]

CONCLUSIONS

Periodic neurological and neuropsychological check-ups are an important part of patient evaluation and of the patient-doctor feedback. They allow the monitoring of neurocognitive performances and possible side effects over time and thus enable the team of medical professionals to plan any necessary interventional strategies.[13,164] The neuropsychological profile of a patient with BTRE encompasses many challenges of living with both BT and epilepsy. For this reason, careful monitoring over time, at different phases is fundamental for following this pathology in a positive manner, in an attempt to reinforce all of the patient's capabilities that are present despite the pathology. The objectives are to provide an individual approach, as much as possible, and to maintain a good QoL for patients with BTRE.

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CHAPTER

16

Cognitive Rehabilitation in Patients with BTRE

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CHAPTER CONTENTS

INTRODUCTION

The efficacy of cognitive rehabilitation has become a focus of scrutiny in scientific literature. Several evidence-based reviews have been published supporting, greater or lesser, the efficacy of cognitive rehabilitation in stroke or traumatic brain injury.[1] While there has been increasing interest in cognitive rehabilitation for brain tumor (BT) patients and limited data are available for epilepsy patients, at present there are no data on the effects of cognitive rehabilitation for patients with brain tumor-related epilepsy (BTRE). This chapter focuses on the results of cognitive rehabilitation in either BT patients or patients with epilepsy in order to draw implications for future research on BTRE in this area.

Cognitive rehabilitation is defined as "a systematic, functionally oriented service of therapeutic activities that is based on assessment and understanding of the patient's brain-behavioral deficits".[2,56] Though little data are available for cognitive rehabilitation for patients with nontraumatic brain injuries such as BTs, the 1998 NIH Consensus Statement on Rehabilitation of Persons with Traumatic Brain Injury is a useful reference, in any event. It defines the goals of cognitive rehabilitation as follows: "The goals of cognitive and behavioral rehabilitation are to enhance the person's capacity to process and interpret information and to improve the person's ability to function in all aspects of family and community life. Restorative training focuses on improving a specific cognitive function, whereas compensatory training focuses on adapting to the presence of a cognitive deficit. Compensatory approaches may have restorative effects at certain times. Some cognitive-rehabilitation programs (CRPs) rely on a single strategy (such as computer-assisted cognitive training); others use an integrated or interdisciplinary approach. A single program can target either an isolated cognitive function or multiple functions concurrently."[3] Cognitive rehabilitation may help to recover impairments in many cognitive domains: attention, executive functions, perception, memory, language, reasoning, problem solving, planning, self-monitoring, and awareness. The primary objective of cognitive rehabilitation is to relieve acquired cognitive disturbances and disability. An intervention of cognitive rehabilitation may include psychological support to help patients and their next of kin to cope with difficulties

encountered during their daily lives due to cognitive deficits.[2]

Cicerone et al.[2] describe Multiple approaches of cognitive rehabilitation[2]: (1) reinforcing, strengthening, or reestablishing previously learned patterns of behavior; (2) establishing new patterns of cognitive activity through compensatory cognitive mechanisms for impaired neurologic systems; (3) establishing new patterns of activity through external compensatory mechanisms such as personal orthoses or environmental structuring and support; and (4) enabling persons to adapt to their cognitive disability, even though it may not be possible to directly modify or compensate for cognitive impairment, in order to improve their overall level of functioning and quality of life. Another approach includes the creation of a broad range of activities for patients and their families that combine education and other activities such as counseling and supportive intervention (psychoeducation) with regard to brain functioning, cognitive deficits, and their consequences for daily life.[4] Due to the scope of functional domains affected by cognitive disability, professionals from a range of disciplines provide cognitive-rehabilitation services, including clinical neuropsychologists and speech-language pathologists. For this reason, cognitive rehabilitation has been defined as a "collaborative service".[4,57]

Recently, cognitive rehabilitation has been more widely used among patients with BT.[5] Due to the fact that patients affected by BT are often of working age and, therefore, getting back to the job is a priority, the need to improve cognitive deficits following surgery is an urgent one. As described in more detail in Chapter 15, these patients often have difficulty multitasking and become easily overwhelmed when more than one thing is happening at a time.[6] They encounter problems in maintaining focused attention and miss points in conversations; every task may require increased effort. The impact of these symptoms is related to a number of individual factors, including age, work, family, and leisure activities.[6] Patients who are working may have many more problems than retired patients, while young individuals can recover more easily than older ones.[6]

Differently than for BT patients, use of cognitive rehabilitation for epilepsy patients is not widespread. It must take into consideration the fact that epilepsy is a chronic condition[7] and that cognitive deficits may depend on numerous factors (described in Chapter 15: antiepileptic drugs, seizure, and interictal epileptiform abnormalities). In any event, patients with epilepsy often have good awareness and insight and can be collaborative in programs of rehabilitation. Recently a program of virtual reality[8] has been applied in rehabilitation of a small sample of patients with epilepsy, showing a good effect of training on real-life cognitive abilities.

No study has been published on cognitive rehabilitation of patients with BTRE. Given that the overall objective of cognitive rehabilitation is to improve impairments of patients with only one pathology, it follows suit that it would be even more necessary in patients with multiple pathologies who assume numerous therapies. Creating a cognitive rehabilitative plan for a patient with BTRE must take into consideration the medical and psychological factors that are present in both pathologies, BT and epilepsy (as discussed in Chapter 15); each being complex. This necessitates the constant exchange of information among professionals from various disciplines.

GOALS OF COGNITIVE REHABILITATION

Cognitive rehabilitation may have different goals depending on the paradigm used. Two general paradigms are described in cognitive rehabilitation, the first, *traditional*, is focused on underlying neuropsychological impairment with the goal of restoring cognitive functions.[4] The methods of assessment are based on neuropsychological tests used for diagnosis, treatment planning, and outcome measures. The treatment modalities and methods used are cognitive exercises to restore impaired cognitive processes, together with other cognitive exercises to acquire compensatory cognitive behaviors. This approach is performed in a clinical setting using specialized equipment and programs, with the presence of cognitive retraining specialists. The primary treatment goal of this approach is to improve an individual's performance by eliminating or reducing underlying cognitive impairments.[9–11] For this reason, it can be seen as largely curative or restorative, focusing on the underlying deficit by directly changing the patient's impaired cognitive functions. In case of failure of restorative exercises, clinicians often attempt to help the individual acquire compensatory behaviors (e.g., internal mnemonics or organizational strategies, self-cueing) or assistive devices (e.g., memory books, pager reminder systems).[4] The second approach is a *contextualized* paradigm, defined as a context-sensitive framework.[4] This approach focuses on the body, activities, and the context with the primary goal to help patients with their real world activities. The methods of assessment are based on neuropsychological tests used for diagnosis, treatment planning, and outcome measures with possible dynamic manipulation of task variables to isolate underlying processes. Treatment modalities are more flexible than those of the traditional paradigm with environmental modifications.[4]

Cognitive rehabilitation within the contextualized paradigm is analogous to physical rehabilitation.[4] Clinicians usually make responsible decisions about

combinations of *body structure/function-oriented interventions* (e.g., surgery, pharmacology, physical exercises), *activity/participation-oriented interventions* (e.g., use of compensatory motor patterns) and *context-oriented interventions* (e.g., environmental modifications, specialized supports provided by others).[4] The work of the rehabilitation team may have a positive effect on a patient's success without necessarily changing the physical abilities profile. Similarly, cognitive rehabilitation may be efficacious in individual cases despite minimal change of cognitive deficits.[4]

TREATMENT MODALITIES IN BT

Cognitive rehabilitation for BT patients was first reported in 1983, in a case study of a patient who experienced cognitive deficits after right temporal lobectomy for an astrocytoma.[12] Two methods were used, the retraining of simple cognitive capacities at home as well as psychoeducational and compensation techniques. The researchers noted that the large improvements in some tests could probably be attributed to these interventions, although they concluded that other improvements were due to practice effects.[13] Ten years later, Meyers and Boake[14] published an overview of general strategies for cognitive, vocational, and psychological support that could be integrated in rehabilitation programs for patients with BT. Subsequently, Sherer *et al.*[15] studied 13 patients with malignant primary BT and cognitive deficits. Patients were selected for a rehabilitation program originally developed for survivors of traumatic brain injury; the program was used first in a clinical setting and later in a community-based setting. The results were described in terms of clinicians' ratings of independence and productivity.[12] In the last 5 years, literature on CRPs has increased.

Four papers have been published[16–19] on cognitive rehabilitation in BT patients in the last 5 years, all of which used a *traditional* rehabilitative approach.

One[16] pilot study, addressed the lack of knowledge about the potential quality of life (QoL) benefits of rehabilitative interventions for patients with BT, by means of a cognitive-rehabilitation and problem-solving therapy that had been used successfully with other populations. The intervention group received: six sessions of cognitive rehabilitation and six sessions of problem-solving therapy provided concurrently with radiation therapy over the course of 2 weeks. In brief, patients and caregivers were taught to use a time-table such as an external aid to compensate for cognitive symptoms. Patients and their caregivers completed six, 50-min sessions in a 2-week period (approximately). Specific goals for each session were provided by trained personnel with a master's level degrees in psychology. The portion of the intervention that included problem solving involved teaching the patient and caregiver a model of stress and a specific, positive problem-solving technique for its management. This intervention also involved six, 50-min sessions over a 2-week period featuring specific goals provided by a neuropsychologist. Cognitive-rehabilitation and problem-solving techniques were delivered concurrently. After receiving the intervention, 88% (7/8) of patients continued to use the study-specific strategies and would recommend the intervention to other patients with a BT diagnosis. Moreover, positive QoL benefits for patients and caregivers throughout the study were highlighted.

The training applied by Hassler *et al.*[17] consists of a method based on a *holistic form* of memory empowerment, using all senses, emotions, and intellectual capabilities of an individual. This method engages the whole spectrum of mental activities through exercises referring to skills useful in everyday life. The objective of the training is to promote mental capacity, preserve the functional potential for intellectual ability and memory, and to reactivate restricted capacities (i.e., deficits). Patients perform the training in a relaxed atmosphere without pressure to perform or time restrictions. The opportunity to perform the training in a small group allows the development of group dynamics and social skills. Each patient has the opportunity to watch and to listen to other attendees, to experience his/her proposed solutions to the exercises, and to learn to accept his/her contribution and personality. In each session, all aspects of mental activity are separately addressed, using exercises to train perception, concentration, attention, memory, retentiveness, verbal memory, and creativity. Special emphasis is put on training concentration skills, with exercises directed toward the enhancement of power of concentration. Another important task is to enhance short-term memory in order to facilitate the processes of learning new information, putting it into context and using mnemonics. The patients showed a great diversity in their performances, from worsening to improvement.

A recent paper by Gehring *et al.*[18] described a mixed rehabilitation program. It is composed of a *strategy* component for teaching of strategies for improving attention, executive functioning and memory, and a *retraining* component, that focuses on frequently practicing an attentional component involving exercises in a game-like computer program. Authors chose to use both techniques because the first is often used for mild cognitive impairment, while teaching of (compensating) strategies are frequently employed in patients with more severe deficits. Previously, the same group of researchers published a randomized controlled trial in which this program was used. The CRP consisted of six, weekly individual sessions of 2 h each. The intervention, carried out by one of seven neuropsychologists, incorporated

both cognitive retraining and compensation training. For the retraining component, a computer program (C-Car) was developed which consisted of a series of hierarchically graded tasks designed to strengthen various aspects of attention on the basis of patient needs. The program focused on attention, because attention deficits are frequently experienced by patients with gliomas and rehabilitation of attention deficits also may have a salutary effect on other cognitive domains.[20,21] The compensation training component consisted of six psychoeducation sessions that addressed attention, memory, and executive function. These sessions included both didactic and practical elements aimed at helping patients compensate for impaired cognitive functions. Additional weekly homework assignments consisted of computer-based attention retraining exercises and of logs kept about experiences where compensatory strategies were applied in daily life. Approximately 3 months after completion of the CRP, participants had a telephone-based booster session, during which key aspects of the compensation training were reemphasized.

The paper by Zucchella *et al.*[19] showed an in-patient, CRP used in the early post-surgery period in patients affected by BT. The training used is in line with the recent guidelines of Cicerone *et al.* on cognitive rehabilitation[22] and combines direct training of impaired functions and development of compensatory strategies and generalization to real life. During each session, patients performed 45 min of therapy-guided exercises with increasing difficulty level to stimulate different cognitive functions. Patients showed a significant improvement in all cognitive functions explored. The control group used in this paper (i.e., those who did not undertake cognitive training) showed a mild cognitive improvement after normal rehabilitation program (physiotherapy, medications), due to the natural recovery occurring after the removal of the intracranial space-occupying lesions and the relief of cerebral edema.[19] This paper seems to provide a foundation for the administration of early, in-patient cognitive rehabilitation to BT patients after neurosurgery. In this patient population, with poor prognosis and short life expectancy, an early intervention should improve the recovery process and reduce disability (see Table 16.1 for details of studies).

TREATMENT MODALITIES IN EPILEPSY

As described in Chapter 15, epilepsy comprises a set of disorders with divergent symptoms, all involving episodic abnormal electrical brain activity.[1] Different epilepsy types and foci may differentially affect brain and cognitive functions, as may the frequency, intensity, and chronicity of seizures. Antiepileptic drugs also affect cognition. Various cognitive disturbances are found in epilepsy, such as attention or concentration problems, mental slowing, language difficulties, deficits in executive functions, and memory problems. Memory deficits are most commonly observed during neuropsychological evaluation[7] (described in Chapter 15). A small sample of papers have studied the possible effects of cognitive rehabilitation in patients with epilepsy: three single case studies, a case series, and a Class II study on 44 patients with focal seizures and attention deficits.[23–27] Engelberts *et al.*[23] compared two training groups and waitlist control with pre-, post-, and 6-month follow-up testing in 44 patients with focal seizures and attention deficits. The conditions were as follows: retraining with repetition and rehearsal, training in compensatory strategy use, and no training. Measures of outcome were neuropsychological tests, neuropsychological self-report, and QoL tests. Both treatment groups showed improvement in training specific tests, had fewer cognitive complaints, and an increase in QoL report at post-test and 6-month follow-up.

Helmstaedter *et al.*[24] performed a case series of 112 patients, post-temporal lobe surgery (57 left side, 55 right side) with training using compensatory strategies; exercises in attention, problem solving, and memory; practical work-life exercises; individual counseling; and social/physical activities. Outcome measures were verbal memory, figural memory, psychomotor speed and attention. For individuals with right-sided surgery, the training effect was significant for verbal memory, with nontreated patients being four times more likely to show a decline in scores than treated patients.

The other three papers[25–27] included single patient studies, each with different clinical characteristics, different training approaches and evaluated with different outcome measures. However, in all three, the training improved cognitive functions.

TABLE 16.1 Cognitive Functions Improved in Patients with BT after Cognitive Rehabilitation

Paper	Population Studies	Cognitive Functions Improved
Locke *et al.*[16]	19 patients with primary BT/caregiver pairs	Speed of processing, executive functions
Gehring *et al.*[58]	140 patients with low and high-grade gliomas	Attention, verbal memory
Hassler *et al.*[17]	11 patients with high-grade gliomas	Verbal learning
Zucchella *et al.*[19]	62 patients mostly with high-grade gliomas	All cognitive functions examined (memory, reasoning, fluency, executive functions, attention, visuoconstructional abilities)

TREATMENT MODALITIES IN BTRE

As mentioned, there are no published studies on the efficacy of cognitive rehabilitation in BTRE patients. The rehabilitative approach for this patient population would need to take into consideration the cognitive deficits resulting from the neoplasm and epilepsy and their respective treatments (as discussed in Chapter 15). Together with specific problems related to BT, as far as cognitive rehabilitation for BTRE patients is considered, some factors strictly related to epilepsy have to be taken into account.[7] First, in contrast with patients with closed head injuries or cerebrovascular accidents, epilepsy, even in BT, is a chronic condition; the chronic aspect of epilepsy may cause memory problems to worsen over time. In addition, many patients and their relatives are convinced that epilepsy or the antiepileptic treatment will eventually cause a cognitive deterioration, in any event. Lastly, seizures that occur during a cognitive-rehabilitation treatment may interfere with progress, or may cause temporary discontinuation of the treatment.

After taking into consideration the various studies that have been published regarding cognitive rehabilitation for either BT or epilepsy patients, it could be assumed that for BTRE patients, a mixed therapeutic approach would be optimal: (1) a traditional approach with neuropsychological evaluation and cognitive rehabilitation and (2) a support intervention that would allow the positive results obtained in training to be applied to the social sphere, which is extremely important for these patients. In our center, a traditional protocol consists of a 10-week rehabilitation period, made up of one individual weekly session with a psychologist, of 1 h each. To evaluate the effects of this training, two successive assessments with neuropsychological tests (described in Table 15.2 of Chapter 15) are performed (soon after the training and after 6 months). The software used is TNP Tonetta software.[28,29] TNP is a multimedial software flexible and adaptable to people of different ages, different diseases, different social backgrounds, and different nationalities. TNP, originally introduced as an approach to aphasic patients, allows the treatment of almost all cognitive deficits from focal lesions. The multisectorial nature of the interventions makes it an ideal tool for the rehabilitation of cognitive dysfunctions.[28,29] The training is based on the assumption that the recovery of cognitive abilities is possible by stimulation of the plastic capacity of a modular system, which proposes stimulation of residual abilities ("healthy modules") whose reorganization will lead to as much autonomy as possible. The flexibility of the program is what makes it unique. The organization of open models allows the therapist to modify and adapt exercises and also build new ones, thus responding to the individual patient's needs.

PHARMACOLOGICAL APPROACHES FOR TREATMENT OF COGNITIVE DEFICITS

Together with the cognitive rehabilitation of patients with BT, a pharmacological approach has been proposed, using drugs to improve cognitive status whose efficacy in other neurological pathologies, such Alzheimer's disease and vascular dementia, is well documented.[12] The first report of a pharmacological approach to treatment of cognitive deficits in patients with BT was published in 1995.[30] Weitzner and colleagues described the effects of the methylphenidate (MPH) on three patients with BT and cognitive deficits. MPH was expected to act as an indirect agonist, causing release of catecholamines, that would control attention and memory. Arousal, attention, initiation speed of tasks, and mood were all improved. Meyers and colleagues[31] subsequently used MPH to treat patients who had primary BT and cognitive deficits. Mean test scores in several cognitive domains were significantly improved in the group of 26 patients, despite progressive disease and increasing radiation damage. There were also improvements in subjective cognitive functioning and mood. However, an important limitation of the study was the absence of a control group—thus, a placebo effect, or a practice effect due to repeated neuropsychological testing, might have accounted, at least in part, for the improvement in cognitive functioning and symptoms.

Modafinil (MOD), a drug in the same class as MPH, was tested in a small, randomized study that compared high doses with low doses[32]; cognitive functioning, fatigue, and mood were improved in 30 patients with primary BT, but unfortunately, potential differences between the different doses were not discussed.

Shaw and colleagues[33] investigated the effects of donepezil on cognitive function, mood, and QoL, in an uncontrolled study of patients with BT who had received radiotherapy. Donepezil is an acetylcholinesterase inhibitor that has shown efficacy in mild to severe Alzheimer's disease and vascular dementia. Because radiation-induced brain injury has features similar to Alzheimer's disease, Shaw and colleagues proposed that donepezil would decrease cognitive symptoms in brain-irradiated patients. After 24 weeks of treatment, there were significant improvements in tests of diverse cognitive domains in the 24 irradiated patients, most of whom had low-grade gliomas. Some aspects of mood and health-related QoL were also improved, and 10 of the 21 patients who completed the washout period chose to renew their use of donepezil. Shaw and colleagues stated that a practice effect was unlikely and they did not take into account the possible role of a placebo effect.

The same researchers also performed an uncontrolled study of ginkgo biloba, reported in a short summary in a review.[34] Cognitive function and QoL improved in the patients who completed the 24-week evaluation, but further details of the study have not been published.

Gehring *et al.*[35] in an open-label, randomized pilot trial examined both the general and differential efficacy of 4 weeks of MPH and MOD in 24 BT patients. Participants completed cognitive tests and self-report measures of fatigue, sleep disturbance, mood, and QoL at baseline and after 4 weeks. Following treatment, there was evidence of a positive effect on test results in speed of processing and executive function requiring divided attention. Patients with the greatest deficit in executive function at baseline had the greatest benefit following stimulant therapy. Inconsistent, differential effects were found on a measure of attention in favor of MPH and on a measure of processing speed in favor of MOD. A general beneficial effect on patient-reported measures of fatigue, mood, and QoL, was observed with no statistically significant differences between treatment arms in these measures over time. A recent multicenter, double-blind placebo-controlled crossover trial by Boele *et al.*[36] evaluated the effects of the psychostimulant MOD on fatigue, depression, health-related QoL, and cognitive functioning in BT patients. Patients randomly received either 6 weeks of treatment with MOD (up to 400 mg/day) or 6 weeks with placebo. After a 1-week washout period, the opposite treatment was provided. Assessments took place at baseline and immediately after the first and second condition. Patients completed self-report questionnaires on fatigue, depression, QoL, and self-perceived cognitive functioning and also underwent a complete battery of neuropsychological tests. Relative to baseline, patients reported lower fatigue severity and better motivation in both the MOD and placebo groups. The same held for physical health, working memory, and information processing capacity. Depressive symptoms remained unchanged. MOD did not exceed the effects of placebo with respect to symptom management. Many patients dropped out during the trial, due mostly to side effects. For these reasons, the authors state that other interventions, preferably nonpharmacologic, should be considered to improve symptom management of BT patients.[36]

A pharmacological approach for treatment of cognitive deficits could be considered for BTRE patients, but a number of concerns still need to be considered; for example, when to administer the drugs (i.e., only during the rehabilitation treatment or between treatments); the duration of the drug therapy (i.e., only during the rehabilitation treatment or for the entire course of the disease); elevated costs that must be justified by measurable benefits; and last but not least, possible side effects. For all of these reasons, in order to consider pharmacological support for cognitive deficits as a therapeutic option in patients with BTRE, research protocols, and multicenter studies would be necessary.

CAREGIVERS ISSUES

The psychological burden induced by BT is profound both for the patient and for his/her family. From the time of diagnosis, patients and their family members are in a situation characterized by many confounding feelings, such as uncertainty, fear, and hope.[37] Usually, a family member becomes the primary caregiver. The same is true for patients with epilepsy, where family members must face the unpredictable nature of seizures. This along with the fear of seizure occurrence can have a markedly negative effect, both direct and indirect, on QoL for caregivers or family.[38] This section on caregivers was included in this chapter because of recent attention in the literature to caregiver needs, specifically regarding the need to forge a caregiver-practitioner partnership, in order to guarantee the success of any rehabilitation program.

Definitions of *caregiver* vary greatly, but in the opinion of many, they must include two aspects: a measure of the work that is being accomplished and an indicator that the person receiving this help has a functional, cognitive, or mental limitation that prevents them from accomplishing those activities alone.[39,40] The variety of activities accomplished by caregivers covers all the work required to respond to the physical, psychological, and social needs of the person requiring support. In particular, caregiving for persons with diseases that affect cognitive functions, such as Alzheimer's disease, is associated with higher levels of loneliness, stress, and depression, and also results in high levels of unmet need.[41] Caregivers of BT patients face unique challenges among cancer caregiver populations. Schmer and colleagues[42] postulate that the diagnosis of a BT is particularly stressful for caregivers because the prognosis is unfavorable and life expectancy is short. These caregivers deal not only with cancer-related issues, but also with neuropsychological issues, such as alterations in functional status, cognitive status, and behavioral changes.[43] These changes demand family caregivers to give emotional support and provide assistance in everyday activities, health-related tasks, and management of economic resources.[44] Caregivers may experience both positive effects (increased sense of self-gratification), and negative effects (depression, anxiety, and physical illness). BTs also seriously reduce caregivers' QoL, increasing the degree of anxiety and depression.[45] Janda *et al.*[46] found that caregivers who took care of patients with high-grade malignancy, such as glioblastoma, were more likely to experience a lower QoL: this could reflect

the high burden that often accompanies caring for family members with such complicated care needs. On the other hand, physical health did not seem compromised: caregivers reacted by improving their capacity to tolerate physical efforts related to taking care of their loved one. This study also showed that living with a BT diagnosis can be devastating both for patients and their caregivers, independent of the malignancy of the disease. BT diagnosis impacts on the everyday life of a spouse or family member, resulting in the possible development of different crisis trajectories.[47] At the time of diagnosis, the relationship between the patient and the next of kin may be characterized by closeness, but later on, depending on how the disease medically and psychologically affects the patient, it may also be characterized by behavioral changes or greater distance. The next of kin may find themselves living with a person who, due to cognitive decline and personality change, is no longer the same.

It is often assumed that BT patients' significant others may face greater stress than those of patients with malignancies not involving the central nervous system, due to progressive changes in neurological and cognitive functioning. A recent paper by Boele *et al.*[48] demonstrates that significant others of patients with highly malignant central nervous system tumors in the acute phase are at increased risk of compromised QoL compared to those of patients with systemic tumors without central nervous system involvement and a comparable life expectancy.

Together with issues related to BT, seizures also affect QoL of caregivers of patients with BTRE. Attitudes of others toward seizures is an important variable influencing the QoL of patients with epilepsy, and caring for them can take a significant emotional toll on parents, siblings, and other family members. Caregivers of adults with epilepsy were more likely to report that epilepsy limited the ability of the persons in their care to participate in many social and daily activities.[49] Approximately half of the caregivers reported that epilepsy either somewhat or completely hindered the ability of the person with epilepsy to hold a full-time or part-time job or to drive. Caregivers also thought that epilepsy resulted in lowered expectations from others and reduced the chances of success at work.[49]

Given the burden experienced by those who care for either BT or epilepsy patients, it can be assumed that individuals who care for BTRE could have even a greater need for appropriate help, care, and support. They would benefit greatly from monitoring, and treatment, if necessary, for anxiety or depression, when it impacts their QoL, making them less able to handle the situation of disease and a caregiving situation.[37] This recognition of the unique needs of caregivers is based on the consideration of the role of caregiver as essential partner or "co-expert" in carrying out CRPs.

IMPLICATIONS FOR FUTURE RESEARCH IN BTRE

The reasons for the paucity of cognitive intervention studies in BT patients compared with other types of acquired brain injury may include the relatively low incidence of this disease, its progressive nature, and the relatively poor prognosis associated with it.[50] Gradually, as survival increased, interest expanded to include concern with long-term sequelae of the disease and its treatment, including cognitive impairment. Recently, evidence for the efficacy of cognitive rehabilitation in other patient populations has accumulated,[51] leading to a greater acceptance of this technique as a legitimate goal in the treatment of BT. Therefore, the inclusion of cognitive rehabilitation in the range of services offered to the BTRE patient population may have two primary aims:

1. improvement of patient discomfort and confidence in cognitive abilities due to the ability to return to work
2. reduction of overall health-care burden for the patient.

To date, there are only data about cost-effectiveness of CRPs in other neurological pathologies.[52,53] Neither BT nor BTRE patients have ever been included in studies of this nature. Given the elevated costs to health-care systems involved in the treatment of these pathologies, cost-benefit studies regarding human and material resources, which would provide some proof of efficacy, would need to be undertaken prior to inclusion of these cognitive rehabilitative services as part of the standard care model for this patient population. To this end, it would be necessary to have standardized protocols that would enable the comparison of different approaches to cognitive rehabilitation and different health-care facilities. Many of the published studies and those currently being carried out on the treatment of cognitive deficits in patients with BT have methodological limitations. Often these limitations can impact the quality of the research and the ability to draw consistent conclusions. Perhaps the most important limitation is the failure to employ an appropriate control group in order to rule out practice effects (i.e., improved neuropsychological test performance due to repeated testing over time), and other effects such as regression to the mean or spontaneous recovery. In studies where the use of a control group is not possible, Gehring *et al.*[4,50] suggest two choices:

- variety of baseline assessments, as practice effects are most likely to occur between the first and second testing sessions;
- parallel neuropsychological tests (alternate forms) that are alternately administered to the different groups.

In addition, problems with patient accrual and attrition over time have been reported in many trials.[50] In some cases, this may be due to logistical barriers, such as timing and duration of neuropsychological testing, or the patient having to move to a hospital to undergo cognitive rehabilitation and/or evaluation. Arranging for the training and assessments to take place at the patient's home may be an effective means of limiting both problems with accrual and drop-out rate.[50] On the other hand, training and assessment at home presents other issues: travel expenses and the need for more flexibility of researchers, patients, and their families to create optimal circumstances for performing assessments and training. Recently, Internet-based programs have been developed and may help to overcome these impediments; however, data are lacking.[50]

Another issue that is commonly encountered in studies of cognitive functioning in chronically ill patients is the discrepancy observed between the subjective (self-report) and objective (neuropsychological testing) measures of cognitive functioning.[54,55] For this reason, it may be appropriate to screen and recruit patients where both objectively determined and self-reported cognitive complaints exist.[50] In particular, the experience of cognitive symptoms may be crucial in motivating patients to undergo CRPs.

Future CRPs for BTRE patients can draw upon the literature that exists for BT patients, but researchers will have to carefully consider the characteristics that epilepsy contributes to the therapeutic plan for this unique patient population: the presence of seizures (another clinical factor which can influence cognitive performances), antiepileptic drugs that can also alter some cognitive performances (as described in Chapter 15), and the psychological factors related to the chronicity of epilepsy itself.

CASE STUDY-1

Male, 46 years

In 2009, followed by a sudden loss of consciousness with vomiting at work, a brain contrast-enhanced MRI with gadolinium revealed a right frontal meningioma near the falx cerebri with perilesional edema and compression of lateral ventricle. Following this diagnosis, gross total resection surgery was performed in June 2009. Following surgery, antiepileptic therapy was started, with oxcarbazepine (OXC) 900 mg/day. Despite the fact that this therapy continued without interruption for a period of 4 years, the patient continued to have nocturnal focal motor seizures, with elementary clonic motor signs in the right arm, with undefined frequency. In addition, patient also reported continuous frontal headache several times a week and sleep disturbances, specifically, insomnia. For this reason, in 2011, the patient came to our center and during an initial intake interview, reported memory problems. During neuropsychological assessment at the patient's first visit, he mentioned that some cognitive difficulties (especially regarding attention and memory) had also been present before the diagnosis of meningioma. His profile included the following: completion only of elementary school; minimal curiosity; little or no intellectual activities (e.g., reading only sports page of newspaper regarding favorite team); no hobbies; and clerk-level employment, such as storekeeper (last position held prior to neurosurgical intervention). With the exception of the neurosurgical intervention for the removal of the BT, patient declared that no other events had occurred in the past or recently, which may have had a significant emotional impact on his life.

The following were performed:

- Neurological Physical Examination

  There were no cranial nerve deficits, with slight weakness in the right limbs. Weakness on the right emisoma. Tendon reflexes were present, with slight prevalence on the right upper limb. Sporadic urinary incontinence during the day was reported.

  Due to insufficient seizure control with OXC therapy, we decided to change antiepileptic therapy to lamotrigine 400 mg/day.

- Neuropsychological Assessment

Patient demonstrated: slow thinking, low concentration and attention, and mild disorientation. Spontaneous, fluent speech, that was quantitatively limited, poorly articulated with poor communication effectiveness. There were no errors in production or difficulty in comprehension. The content of thoughts expressed was appropriate to the context and there were no apparent disorders. Patient conduct was adequate and appropriate for the tests. In addition, the patient seemed to be slightly anosognosic about his difficulties and the impact that these have on everyday life. In describing his cognitive impairment, the patient reported only minor memory deficits ("sometimes I forget things, dates, days . . ."). The attention level was stable and sufficient enough to endure the entire neuropsychological assessment. The patient also presented a collaborative attitude and sufficient motivation. Finally, the emotional state of the patient demonstrated a moderate decline in mood and apathy, though not evident from performance anxiety.

At baseline, performance on neuropsychological tests was as follows:

Test	Result
Mini-mental state examination	*Lower than normal*
Digit span forward	Within limits
Digit span backward	Within limits
Recall of bisyllabic word	Within limits

Rey Auditory Verbal Learning test, immediate recall	Lower limits
Rey Auditory Verbal Learning test, delayed recall	Lower limits
Logic memory	*Lower than normal*
Rey-Osterrieth complex figure, copy	*Lower than normal*
Rey-Osterrieth complex figure, recall	*Lower than normal*
Clock drawing test	*Lower than normal*
Trail Making Test Part-A	Normal
Trail Making Test Part-B	Lower limits
Frontal Assessment Battery	*Lower than normal*
Phonetic fluency	Lower limits
Semantic fluency	*Lower than normal*
Raven Progressive Matrices	Lower limits

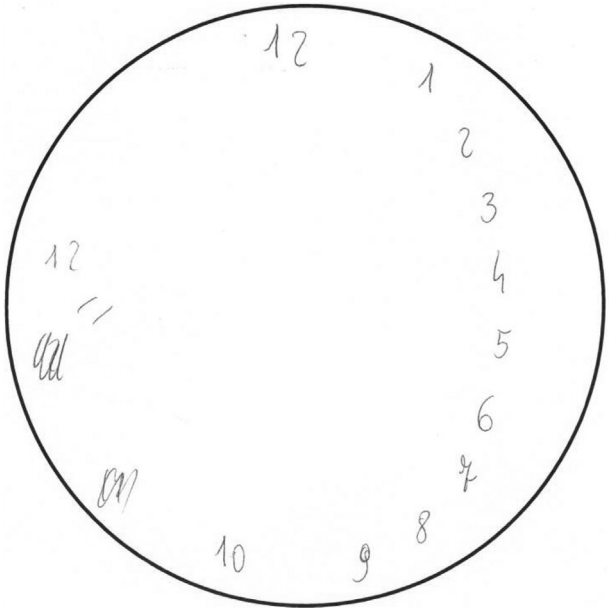

FIGURE 16.1 Clock drawing test at baseline showing visuospatial disorganization.

Results

General Cognitive Efficiency

The performance on mini-mental state examination demonstrated lower than normal results, and scores on Raven's Progressive Matrices were at the lower limit of normal. These results are indicative of a reduction of general cognitive efficiency

Memory

The patient's performance on span forward and backward tasks were in the normal range. In addition, the scores on the recall of bisillabic word were within limits. These scores are indicative of sufficient short-term memory and auditory-verbal ability in the process of coding in short-term verbal information. The scores obtained in the Rey Auditory Verbal Learning test, both in immediate recall and delayed, were lower than normal, while the performance in logic memory test prose were below the normal ranges. These results indicate the presence of difficulties in verbal long-term memory, whose nature is due to deficiency frontal/executive difficulties, both in encoding and information retrieval. Finally, there is also a deficit in the long-term visuospatial memory (Rey-Osterrieth complex figure, recall). The performance on this figure also supports the assumption that the memory difficulties are attributable to a deficit in the frontal processes of recovery.

Visuospatial and Constructive Functions

Praxic and constructive functions were insufficient when measured by simple tasks (copy design of the mini-mental state examination) and when measured by tests that require complex organization and planning and execution (Clock drawing test and Rey-Osterrieth complex figure, copy). In the clock drawing test, there was a severe level of visuospatial disorganization, which made it impossible to position the elements correctly (see Figure 16.1). There are omissions and perseverations. This showed a lack of planning that was more evident in the copy of the complex figure.

Abstract Reasoning

Abstract reasoning skills were at lower limits. During Raven Progressive Matrices we observed inadequate use of problem-solving strategies and numerous perseverations. Even this figure can be interpreted as indicative of a frontal-executive deficit.

Attention

The scores on the Trail Making Test, Part-A, were fully normal, indicating good attention span.

Executive Functions

Scores on the Frontal Assessment Battery were lower than normal, with lower limit of normal performance in Part B of the Trail Making Test. These data suggest a weakness of the regulatory processes and a reduction in attentional control. Finally, the patient scores were at the lower limit of normal in tests of verbal fluency by letter, and lower than normal results in semantic fluency tests. These results are indicative of a difficulty in the ability to search words using phonemic and semantic criteria and of a scarce cognitive flexibility (shifting).

Rehabilitation Training

A training of 10 weeks with one session/week (duration 1 h) was scheduled with the following objectives:

- recovery of mnesic and attentional functions through the creation of compensation and reinforcement strategies of intact cognitive functions;
- training of lexical skills;
- training of logic and abstract reasoning.

The following domains were targeted weekly with the software TNP Tonetta[27,28]: attention, memory, reasoning.

Starting from the fifth week of training, we proposed the reading of short stories with the aim of facilitating conceptualization, memorization of logic-casual relations, and the elaboration of significant elements.

To help the patient develop alternative strategies of reasoning and flexibility, the Tower of Hanoi was utilized.

Exercises with paper and pencil were performed to improve lexical skills (phonologic and semantic).

Description of Instruments and Procedures

TNP Tonetta Software The TNP is a multimedial software, flexible and adaptable to people of different ages, different diseases, different social backgrounds, and different nationalities.[27,28] The TNP, originally introduced as an approach to aphasic patient, allows the treatment of almost all the cognitive deficits from focal lesions. The multisectorial nature of the interventions makes it an ideal tool for the rehabilitation of cognitive dysfunctions.[27,28] The training is based on the assumption that the recovery of cognitive abilities is possible by stimulation of the plastic capacity of a modular system, which proposes the stimulation of residual abilities ("healthy modules") whose reorganization will lead to greater autonomy as much as possible. The most important peculiarity of the program, and what perhaps makes it really unique, is its flexibility. The organization of open models allows the therapist to modify and adapt the exercises and build new ones, thus responding to the individual patient's needs.

The exercises administered were exercises for logic-inductive reasoning; attention (divided, diffuse attention); and memory (short term, long term). For all the exercises, these variables were adapted to the patient characteristics: duration of exercise; delay of response and time of presentation of stimuli.

Tower of Hanoi The standard Tower of Hanoi is composed of three pegs: A–C. On peg A, there are differently sized disks, the largest at the bottom and the smallest at the top, forming a type of cone shape. The goal is to move all disks to peg C, with the following two constraints: first, only one disk at a time can be moved; second, a larger disk cannot be placed on top of a smaller disk. The task is a good illustration of means-ends analysis.

A computerized version of this test was used with varying levels of difficulty, ranging from 3 to 15 disks.

Paper and Pencil Exercises to Improve Lexical Skills The exercises for phonologic fluency ask the patient to say all of the words that come into mind for each letter (three letters with 5 min per letter assigned), concentrating on nouns, verbs, and adjectives, without proper nouns of people or names of cities. This time-frame can be diminished over time if there is improvement.

The exercises for categorical fluency, on the other hand, ask the patient to say all of the words that come into mind for a given category (three categories with 5 min per category assigned). Here, too, 5 min are allowed for each category, but this time frame can be diminished over time if there is improvement.

These exams were administered in paper and pencil mode.

The patient underwent neuropsychological evaluation post cognitive training.

Test	Result
Mini-mental state examination	Normal
Digit span forward	Within limits
Digit span backward	Within limits
Recall of bisillabic word	Within limits
Rey Auditory Verbal Learning test, immediate recall	Within limits
Rey Auditory Verbal Learning test, delayed recall	Within limits
Logic memory	*Lower than normal*
Rey-Osterrieth complex figure, copy	*Lower than normal*
Rey-Osterrieth complex figure, recall	*Lower than normal*
Clock drawing test	*Lower than normal*
Trail Making Test Part-A	Normal
Trail Making Test Part-B	Normal
Frontal Assessment Battery	Normal
Phonetic fluency	Within limits
Semantic fluency	Within limits
Raven Progressive Matrices	Within limits

Results

General Cognitive Efficiency

Results obtained at MMSE and Raven Progressive Matrices, slightly improved with respect to baseline and this indicates a sufficient cognitive efficiency.

Memory

At follow-up short-term memory was normal, indicating sufficient processing of codification of verbal information.

Rey Auditory Verbal Learning test (immediate and delayed recall) was slightly improved. The results on the logic memory tests again indicate deficits (lower than the norm). These results indicate difficulties in organizing structural information (logic memory test). However, there were also deficits in long-term visual spatial memory (Complex Figure Rey-Osterrieth, recall). These results

demonstrated deficits in recovery of information due to frontal deficits.

Visuospatial and Constructive Functions

The constructive functioning deficit was stable, while a planning deficit due to frontal deficit was confirmed.

Abstract Reasoning

There was improvement in abstract reasoning with the use of better problem-solving strategies.

Attention

The points on the Trail Making Test, Part-A, showed results in the normal range, indicating a good attention capacity.

Executive Functions

Tests scores of executive functions were improved, indicating an improvement of regulation and control of attention. Fluency was improved as well.

Conclusion

During the training the patient was seizure free. The results of this neurocognitive rehabilitation program indicated overall improvement of cognitive function, despite the persistence of frontal deficits. For the patient, this meant an opportunity to begin again with various family and social activities. Future rehabilitation for this patient could be to retrain in areas where deficits were still present and to reinforce overall patient potential.

CASE STUDY-2

The 27-year-old male patient was diagnosed with testicular cancer in 2002. In 2003, a focal sensory seizure occurred with elementary sensory symptoms, characterized by paresthaesie on the right half of the face and right arm that lasted about 20 min. A repetitive frontoparietal left lesion was diagnosed and the patient subsequently underwent a surgical intervention. Starting in 2003 (see Figures 16.2–16.4), after surgery, he took OXC 1500 mg/day with good seizure control. While the oncological disease had stabilized, in 2010, a seizure reappeared. His oncologist increased OXC to 1800 mg/day and sent him to our center. At first visit he underwent:

(1) Neurological visit: KPS 100 Barthel index 100 MMSE 30; mild right sensori-motor hemisyndrome. Seizure frequency was 8/month. The EEG was normal.
(2) Psychological interview

During the psychological intake interview, the patient described a moderately anxious state that he had felt at the same time that seizures had occurred. This state interfered with his ability to calmly live his daily life or to

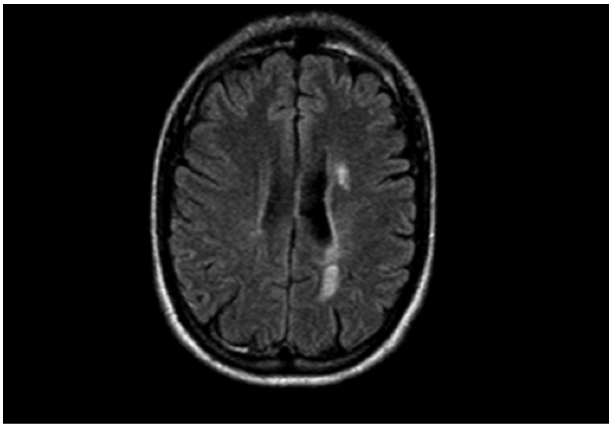

FIGURE 16.2 FLAIR sequences in axial planes.
MR shows an alteration area correlated with postsurgical and postradiotherapy injury in the left frontoparietal lobe.
Another area of altered signal intensity that does not show enhancement after gadolinium infusion is near the body of the lateral ventricle.
Courtesy of Dr Antonello Vidiri, Department of Radiology, Regina Elena National Cancer Institute.

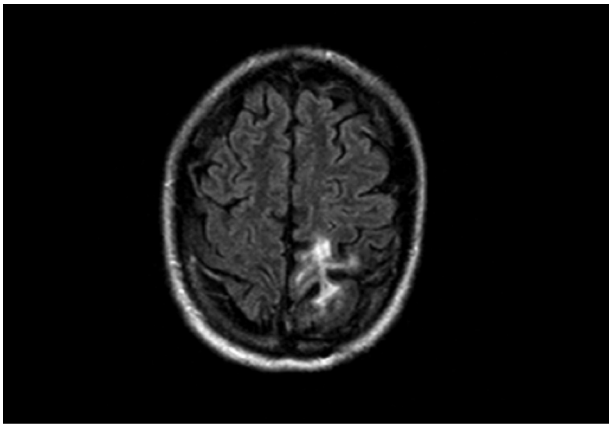

FIGURE 16.3 FLAIR sequences in axial planes.

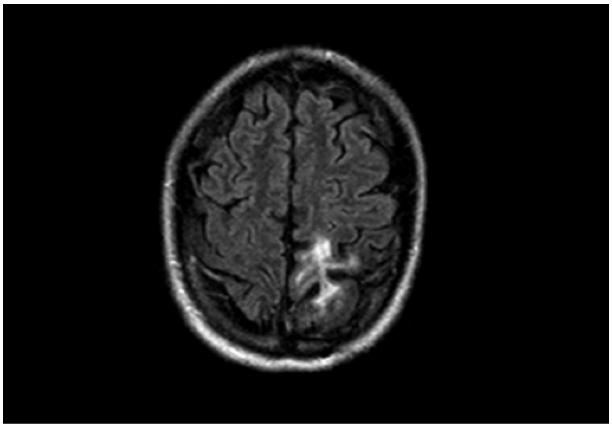

FIGURE 16.4 SE T1 weighted sequences after gadolinium infusion.
Courtesy of Dr Antonello Vidiri, Department of Radiology, Regina Elena National Cancer Institute.

face the demands of his professional life (as electrician); his social life was affected as well. The profound concern over the return of his illness and fear of seizure reoccurrence kept him from doing anything alone. The patient was constantly focused on his body, especially on his right arm and leg, and was always on guard and worried about possible seizure reoccurrence. In addition, the patient was worried about cognitive problems that he had noticed for some years, in particular memory and fluency deficits.

(3) Neuropsychological evaluation:
- Battery of tests to evaluate cognitive functions
- QoL tests (EORTC QLQ C30; QOLIE 31 P)
- Adverse events test (Adverse Event Profile)
- Hamilton Anxiety Rating Scale (HAM-A)
- Hamilton Depression Rating Scale (HAM-D)

Neuropsychological Tests

Test	Result
Digit span forward	*Lower than normal*
Digit span backward	Lower limits
Rey Auditory Verbal Learning test, immediate recall	Normal
Rey Auditory Verbal Learning test, delayed recall	Normal
Rey-Osterrieth complex figure, copy	Normal
Rey-Osterrieth complex figure, recall	Normal
Clock drawing test	Normal
Trail Making Test Part-A	*Lower than normal*
Trail Making Test Part-B	Lower limits
Frontal Assessment Battery	Lower limits
Phonetic fluency	*Lower than normal*
Semantic fluency	Normal
Raven Progressive Matrices	Normal

Neuropsychological diagnosis was: mild attentional and fluency deficit in patient with a moderate anxiety (HAM-A = 29) and a light depression (HAM-D = 12).

Therapy

For the persistence of seizures the neurologist added lacosamide 400 mg/day. Alprazolam 0.25 mg was added twice a day to control anxiety.

A reevaluation of anxiety, depression, and quality of live was scheduled at a distance of one and a half months (see Figures 16.5–16.8).

Neuropsychological and Psychological Schedules

The patient started cognitive rehabilitation and a weekly session of psychological counseling, for learning coping strategies regarding seizures.

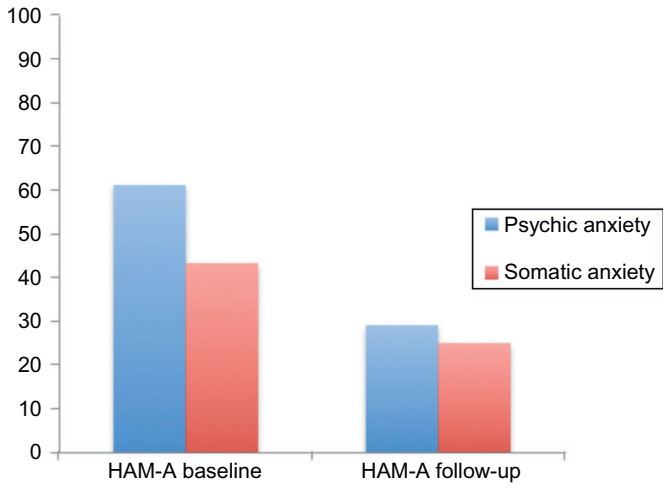

FIGURE 16.5 Scores obtained at Hamilton Anxiety Rating Scale (HAM-A) show an improvement at follow-up in psychic and somatic anxiety (overall score at baseline = 29; overall score at follow-up = 15, cut off ≥14).

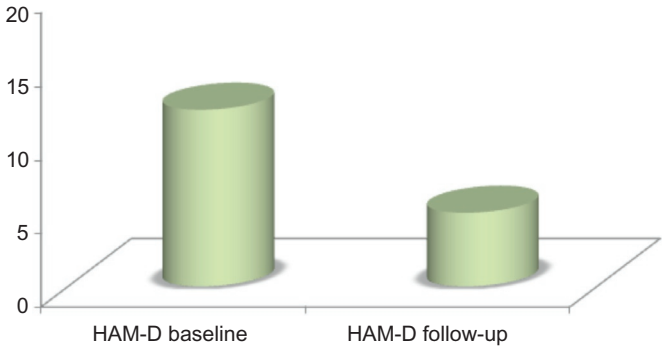

FIGURE 16.6 Scores obtained at Hamilton Depression Rating Scale (HAM-D) show an improvement at follow-up (overall score at baseline = 12, mild depression; overall score at follow-up = 6, absence of depression).

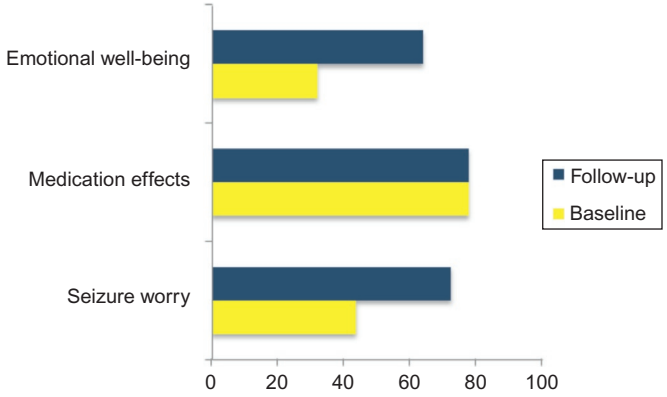

FIGURE 16.7 QOLIE 31P-V2 subscales. Scores obtained at seizure worry, medication effects, emotional well-being.

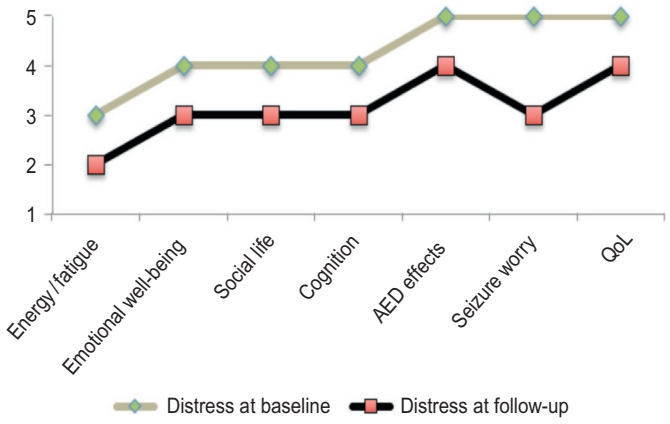

FIGURE 16.8 QOLIE 31P-V2 subscales. Scores obtained at scales of distress for each subscale show an improvement at follow-up.

Rehabilitation Training

A training of 10 weeks with one session/week (duration 1 h) was scheduled with the following objectives:

- recovery of mnesic and attentional functions by the creation compensation strategies and reinforcement of intact cognitive functions;
- training of lexical skills.

The following domains were addressed weekly with the software TNP Tonetta[27,28]: attention, memory.

Exercises with paper and pencil were performed to improve the lexical skills (phonologic and semantic).

Results (After 10 Sessions of Training)

All tests of cognitive functions were in the normal ranges.
Neurological status: unchanged
Seizure frequency: only two seizures in 6 months
No side effects
Oncological disease: stable
Ongoing psychological counseling with a good participation and motivation.

Conclusion

The results of this neurocognitive rehabilitation program indicated overall improvement of cognitive function. The weekly psychological counseling improved levels of anxiety and depression and enabled the patient to be sufficiently integrated in social and work life.

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CHAPTER

17

Social Cost of Brain Tumor-Related Epilepsy

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CHAPTER CONTENTS

INTRODUCTION

Health promotion as defined by the World Health Organization (WHO) is the process of enabling people to increase control over, and to improve, their health. It moves beyond a focus on individual behavior toward a wide range of social and environmental interventions. As is evident by such a broad definition, a population's health is the concern of many stakeholders who each represent a particular perspective and/or priority: from government institutions and policy makers, researchers and clinicians to health-care professionals and economists, to name only a few. Life is our highest value, and as health is fundamental to life, it leads to the creation of wealth.[1] Current policy agendas are faced with a complex health-care landscape that is changing due to people living longer, with costs that are escalating and resources that are diminishing. For this reason, today more than ever, professionals across disciplines are either preparing, participating in, or consulting studies pertaining to economic and societal costs related to health, health services, and illnesses themselves. Cost reduction will be a primary focus of all health-care systems regardless of political or geographical orientation. It will need to be structured by redefining health-care packages made available by public funds, which will mark the level of society's commitment to the well-being of its citizens. Patients will ultimately be made aware of these funds and the private sector will cover any additional costs not covered. For this reason, private interests will gain more importance. Within this context, it will be essential to create and foster sustainable clinical leadership: there can be no sustainable reform in the future without a solid core of medical professionals.[1,2] While health-care costs have continued to be a primary concern of policy makers, there has also been a significant paradigm shift that sees the patient as the focal point. In fact, today's patient is increasingly well informed and motivated and is at the center of all efforts and all health-care provisions. There has been increased interest in monitoring the effectiveness of health-care provisions, quality-control, and measuring the effectiveness of therapies by means of health technology assessment (HTA) and outcome indicators. Assessment can be done by a range of stakeholders: patients, patients groups, clinicians, health care organizations and providers of finance.[1,2]

This chapter on social costs was included in this volume on brain tumor-related epilepsy (BTRE) for a number of important reasons: first, because health-care professionals everywhere have understood the necessity of placing illness in general (i.e., rather than a specific

disease), treatment alternatives, and most importantly patients' well-being, in a political, economic, and social context. Governments across the globe with different national market conditions, environments, and types of health systems all have in common the fact that their policy makers must reach compromises and deal with powerful interest groups/strong political constituencies[3]; second, because the numerous difficulties in evaluating the economic factors related to a single illness category (i.e., a particular disease) have been amply documented in the literature, but there is not yet a model for evaluating the economic issues related to a pathology that involves two serious illnesses simultaneously, as is the case with BTRE; third, and most importantly, cost studies that have been published, while representing important steps forward in certain areas of brain-related diseases, exist either for brain tumor or for epilepsy; however, there is not one health economic study to date (to our knowledge) that takes BTRE into consideration.

The political, economic, and social contexts of health and health services are inescapable. This can be seen within countries and between continents.[1] Take for example the two very different scenarios regarding funding (or lack of) for neuroscience that unfolded as the first chapters of this book were being planned. Here are some highlights from those two contrasting realities:

In May, 2013, representatives from three of Europe's most prominent neuroscience societies, the European Brain Council (EBC), European Science Foundation (ESF), and Federation of European Neuroscience Societies (FENS), convened in Brussels to discuss possible drastic program cuts in European funding for brain research. The focus of the meeting was the European Unions's (EU) Horizon 2020 program (http://ec.europa.eu/programmes/horizon2020/), Europe's most significant funding scheme for research and innovation, planned for the period 2014-2020, with a budget of about €70 billion (http://ec.europa.eu/programmes/horizon2020/). A report of the meeting was published (see Annex). The report, *The Prospects of Brain Research within Horizon 2020: Responding Efficiently to Europe's Societal Needs*, stated that "totally unexpectedly, in the H2020 program, no dedicated financial resources for brain research have yet been decided" (the definitive funding program was finalized in December 2013, with no dedicated funds for neuroscience having been allocated as had been done in the previous EU funding cycle). The Executive Summary continued to note that the apparent decrease in neuroscience funding came as a surprise to these organizations and to the European scientific community as a whole, seeing as the EU funding scheme that had preceded H2020 had recognized brain research as a priority that warranted the necessary financial resources. Comprehensive support of more than €1.9 billion was awarded since 2007, with a yearly allocation of more than €300 million and a total of 1268 projects. The report concluded with a communication of disappointment and regret that the structure from past programs would in any event be discontinued, which would seriously dilute resources available for brain research (see Appendix).

In sharp contrast to the above, a press release dated September 16, 2013, announced that the United States National Institutes of Health (NIH) director, Francis S. Collins, M.D., Ph.D., had approved initial areas of high-priority brain research to guide $40 million dollars of NIH fiscal year 2014 funding within the BRAIN initiative (Brain Research through Advancing Innovative Neurotechnologies) that was eventually announced by U.S. President Obama. While the BRAIN initiative has a heavy technological focus, it was explained that a key component of the program will be input sought broadly from the scientific community, patient advocates, and the general public. The published report from the Brussels meeting mentioned above did not lose the opportunity to point out that the U.S. NIH spent $5548 billion dollars on neuroscience and nervous disorders in 2011—18% of its total budget—with those 2 areas plus behavioral science and mental health making the top 20 list of the NIH's 235 health categories earmarked for R&D spending; referring to these numbers, the authors of the report commented that Europe, with its rich traditions and stellar history in dedicating resources to neurosciences "should do no less." These two very different realities and many others represented in the scientific literature in these past years are perfect examples of the kinds of issues that are addressed by health economics, which is a subbranch of the discipline of economics.

HEALTH ECONOMIC REPORTING: TERMINOLOGY AND AIMS

As a point of reference, it is helpful to think of standard economics as the study of how individuals/societies must eventually choose to allocate scarce resources among competing, alternative uses and then, how they distribute products resulting from those uses, among members of society.[1,4–8] For the purposes of this volume (i.e., intended for medical professionals), a simple definition of health economics would be the application of economic principles as defined above, to analyze health and health-care resource use, with the ultimate objective of maximizing social benefits obtained from constrained resources (i.e., health producing).[9]

Within the context of health economics, there are different types of evaluations. Some of these identify the costs, consequences, and benefits of competing resources (i.e., health programs, services, or treatments) and others use cost analyses that are not comparative in

nature. In addition to these, there is yet another type of evaluation that looks at single illness categories. The first type (i.e., comparative) facilitates decisions regarding how resources will be best used. The second type (i.e., noncomparative and/or regarding single illnesses) helps identify areas that might need more resources, without addressing how to allocate them. The third type, called cost of illness studies (COI) or disease burden studies, are used to estimate the economic impact of an illness; they measure the economic burden of a disease or diseases in an attempt to estimate the amount that could potentially be saved or gained if the disease were eradicated.[1,10] They are typically divided into two major categories: (1) core costs resulting directly from the illness and (2) other related costs including non-health costs of the illness.[11] These are perhaps the most common of all health economic studies and have been at the center of much controversy regarding methodological limitations and overall usefulness.[1,5]

It is not the focus of this chapter to comment on the validity of one type of economic evaluation over another. Shortcomings or drawbacks of any given method or approach to economic analysis will be discussed only for terms of clarifying the use of a given approach and for highlighting the differences between the options. For our purposes here, it is important to point out that COIs, not being comparative in nature—that is, they are not used to assess the costs and benefits of alternative interventions or programs[12]—can assist policy makers in identifying where resources should be directed (i.e., which diseases need to be addressed), but cannot, by themselves, speak to how resources must be distributed. For this reason, they are often used together with the other types of economic studies cited, or provide important data, upon which those other types of evaluations are based. Within this chapter, the term *economic evaluation* implies *health economic evaluation*, unless otherwise specified. Each type of economic evaluation has its own set of terms and definitions, and specific audiences for whom the evaluation is being done. However, independently of these, economic reports usually facilitate analyses regarding effectiveness and efficiency, but can also address equity concerns (i.e., equal access to care). Unfortunately, what is efficient is often not equitable.[13] The first part of this Chapter will provide a brief overview of basic health economic concepts and will offer examples of the most prevalent types of issues that influence policy and funding decisions. The second part of the Chapter will address Health Technology Assessment which includes an analysis of the costs related to pharmacological therapies and will also include issues related more specifically to the focus of this volume: social and economic costs related to neurological disorders, epilepsy, and brain tumor (no data specifically relating to BTRE is available yet).

There are entire courses and workshops in health policy departments and government offices dedicated to nomenclature because there is not yet full consensus on health economic terminology. However, there has been an attempt to standardize terminology, to some extent. This has lead to the differentiation between "partial" and "full" studies. It is important to point out that there is no hierarchical scale of validity or significance assigned to these terms, whereby "partial" means less important/significant than "full." It is simply a matter of scope, which depends on the purpose of the research and the audience for whom it is being performed. In order to understand this distinction, it is helpful to consider the following: cost in this context means the value of all of the resources used to produce a service, while outcomes can be seen from either the patient or intervention perspective—the first having to do with the measure of the consequence or end result of the patient's encounter(s) with the health-care system[14] and the latter concerning the end results that are assessed for groups of patients with certain trends being identified regarding clinical outcomes and effectiveness (i.e., medical interventions).[14] Partial studies are narrower in focus, and each type has a particular function. They look at either costs or consequences/outcomes of one intervention/program, while full economic evaluations take into consideration both (i.e., costs and consequences), and a number of other factors, in most cases. An essential feature of the "full" study is that it is comparative in nature: it compares two or more alternative interventions/programs. There are numerous studies that perform cost analysis and describe outcomes, efficacy, or effectiveness of only one program/intervention that claim to be economic evaluations. However, according to the most recent criteria, they are not considered to be such.

Whether a *partial* or *full* economic evaluation is undertaken depends on several factors that are determined in the first phase of any health-care study, a phase which is called "framing." It is during this phase that the decisions are made as to which costs and outcomes are relevant. In addition to those decisions, a methodological approach is decided upon based on the answers to two fundamental questions: (1) "What do we need to know?" and (2) "How are we going to find out?"[15] The first question identifies the type of problem to be addressed—which can be very narrow in focus—for example, an illness that affects a small, specific segment of the population. From there, a number of other concerns are addressed, such as audience (i.e., who will be using the data/how will they use them); perspective (i.e., what costs are relevant/who will bear the costs and who will gain from the intervention); and time frame.[16]

As mentioned earlier, the focus of an economic evaluation is divided between two main areas: on the one

hand, there is the specific illness or health problem, and all of the costs related to it. These are the COI studies (burden of illness) mentioned and are typically used for a given population, region, or country. On the other hand, there is the focus on interventions themselves. Some evaluations of interventions look only at components and cost analyses for one given program, while others look more completely at a comparison between alternative programs and their costs and benefits.

The main types of health-care cost analyses can be summarized as follows: (1) cost description: describes only costs of a single health program with no examination of outcomes; (2) outcome description: examines only outcomes of a single health program with no examination of costs; (3) cost-outcome description: examines costs and outcomes of a single health program; (4) efficacy or effectiveness evaluation: examines cost and consequences of two or more health programs in order to determine technical efficiency within a given budget; (5) cost analysis: examines only cost of two or more health programs with no examination of outcomes; (6) cost-minimization analysis: only costs are examined for alternatives that are assumed to have equivalent impact; (7) full economic evaluation (explained below in more detail).

The full economic evaluation is made up of three major types of analyses: (1) *cost-benefit analysis*: all costs and consequences of a program are expressed in the same units, usually money; used to determine allocative efficiency; i.e., comparison of costs and benefits across programs serving different patient groups[17]; (2) *cost-effectiveness analysis*: costs and consequences of alternative interventions are expressed by cost per unit of health outcome; used to determine technical efficiency; i.e., comparison of costs and consequences of competing interventions for a given patient group within a given budget[17]; and (3) *cost-utility analysis*: an economic study design in which interventions that produce different consequences, in terms of both quantity and quality of life, are expressed as "utilities."[1,4–8] These are measures that comprise both length of life and subjective levels of well-being. The best-known utility measure is the "quality adjusted life year" or QALY. In this case, competing interventions are compared in terms of cost per utility (cost per QALY).[16–19] Simply put, the ultimate objective of health economic reporting is to help decision makers evaluate (within the context of scarce resources) whether programs/interventions are producing health outcomes that justify the amount of resources that are being dedicated to produce them.

All health economic reporting, regardless of the specific type of report, should be aimed at supporting well-informed decisions concerning health services/systems. There should be an interest in creating a wider knowledge base for evaluating the costs and benefits of interventions to enable better targeting of financial resources in the health sector[3]; primary objectives should be to improve the health of all groups within a society to the maximum extent.[20] To meet these objectives, there must be some understanding of how existing, limited health resources are being used; only then can more efficient and effective future uses be planned. Governments are recognizing that they have a central role in leading to this understanding, especially in identifying areas that require intervention. The amount of national resources that are dedicated to health care varies significantly throughout the world, with goals and priorities tailored to each country and a range of factors specific to a nation. Regardless of the specific amount that any given nation spends, it always represents a substantial investment. Therefore, the sheer size of expenditures on health makes it critical to grasp the impact of government policies on people's health.[3] With this in mind, decision makers must look not only at how to reduce costs of disease and how to improve resource use, but must also establish priorities; this is one of the limitations of COI studies, in that they cannot be used alone for setting priorities and allocating health resources—for which data on effectiveness is needed.[1,4–8] Reports examining the economic impact of specific diseases must go beyond the information provided by clinical and epidemiological studies, in order to assist health policy decision making. The data produced must address or target a policy area, and there must be a clearly defined scope, purpose, and perspective established at the onset.[1,4–8]

HEALTH ECONOMICS: FUNDING PRIORITIES

Which health programs/illnesses receive government resources and priority setting is always central to the health economic sector. Responsiveness to disease burden,[21,22] as it has been called, has come under a great deal of public scrutiny over the years, especially in the United States, regarding the U.S. NIH, the largest single funder of biomedical research in the world.[20,21] The first report by Sampat[21] looks at the correlation between a major government funding agency's budget decisions and specific disease categories; more specifically, this study examines NIH funding 13 years after a controversial article by Johnson[23] and explores whether the allocations are "appropriate"; in other words, whether particular diseases command too much or too little funding—a common debate in health policy circles. The too much or too little concept, according to the authors of the study, should be linked to the overall disease burden and not to an illness being in the spotlight for other reasons, as Johnson had suggested.[23] Though there are many factors that contribute to disease burden, the study

looked at two measures, deaths and hospitalizations, because data for these two factors were systematically available across all disease categories examined. Perhaps the most valuable information to come out of this report was the suggestion that future studies focus less on the nature of the data itself and more on gathering detailed information about the decision-making process, such as: specific criteria used, the weight assigned to it, as well as where in the decision-making process it was used.[21,22]

William D. Savedoff, in his paper, *What Should a Country Spend on Health Care?*[24] looks at what underlying factors influence a governmental approach to determining its per capita health spending. This report was prompted by a startling truth emphatically highlighted in discussions of U.S. health-care spending throughout the health economic literature—and that is the fact that health outcomes across nations are not strongly related to the level of spending on health services (once other factors and other kinds of spending are considered).[24]

The focus of Savedoff's article, stated clearly in its title, is the decision-making process across nations regarding their respective per capita health spending. The article is, in part, a response to the remarkable range in health-care spending across countries, not all easily explained by a country's overall wealth or level of development. Savedoff's proposed four classifications, summed up here, are extremely useful for demonstrating the factors that can influence any national government's health policy: (1) the peer approach compares how one country fares relative to similar countries, not far from the concept of benchmarking in the business world; (2) the political economy approach is also known as a social science perspective, because it looks at the social actors who tend to influence the political decision-making process; (3) the production approach uses aggregate data to examine the impact that health spending, socioeconomic characteristics, demographics, and other factors have on a population's health conditions; a desired health status is then chosen and predictions are made as to the change in health spending that would be necessary to attain that level of health; and finally; (4) the budget approach takes into account current/desired health status, prices, effectiveness and trade-offs, but it lacks explicit attention to measures of effectiveness that address how services influence health outcomes. While there is no formal recommendation for how much a country should spend on health care, Savedoff's short, but thought-provoking article mentions that the answer to the question (posed by the article's title) depends on whether a public budget, as opposed to total health spending (i.e., which includes out of pocket spending) is being considered. Savedoff concludes with a preference for the budget approach, seeing it as both feasible and quantifiable, as well as the most complete.[24] Just as there is no one approach or standard formula that applies to national health-care spending, there is no one type of health economic evaluation that satisfies all stakeholders.

The fact of the matter is that costs cannot be examined in a vacuum. They must always be seen within a larger, social context. How a health economic report should be structured is important, but the "why" at the center of health-care reform, is equally as important. What determines which illness or treatment program receives more resources? Of course, from a patient as well as from an overall humanistic standpoint, all illnesses are equal. Health economic studies are one vehicle by which policy makers are made more aware of an illness or intervention; ongoing research and published studies in a disease area help raise the visibility for that area.

At present, there are no published data concerning the social and economic impact of BTRE. If this pathology received more visibility vis-à-vis cost reports, might major international funding bodies (private and public) appropriate more funds to this illness, which to the best of our knowledge has received little or none to date? Effective campaigns that increase public/policy maker awareness are no guarantee that research funding will increase, however. Take non-oncological epilepsy for example, a disease which has seen a significant increase in awareness campaigns (i.e., public and private) over the past years such as the Global Campaign Against Epilepsy sponsored by WHO, International League against Epilepsy (ILAE), and the International Bureau of Epilepsy (IBE); but which, unfortunately, has not resulted in a corresponding increase in research funding.

What gets funded or *who* receives the benefit of more government investments is also tied to a nation's specific challenges and epidemiological profile. For example, the appropriate amount of spending in a country with a malnourished population facing endemic malaria and an epidemic of HIV/AIDS is likely to be different from one with limited infectious disease and a high incidence of cancer and chronic conditions.[24] It is clear though, that policy makers do not decide which diseases to fund based only on epidemiological data. There are many factors that impact policy and funding decisions, and while health comprises a large part of public spending for all nations, it must compete with many other critical areas. In effect, health economics addresses how to make the right choices about competing programs and resources when all are necessary; the fact is that for all governments, a host of pressing social demands such as housing, education, public infrastructure, and safety/security as well as the arts must also be considered.[24] A range of government institutions participate in appropriating budgets; however, in addition to the epidemiological and social contexts mentioned, appropriation of funds in many cases represents prevalent cultural attitudes within a country.

Health Technology Assessment

To counteract possible overspending without justifiable evidence of patient benefits, there is a strong international movement toward better monitoring of the use of new drugs and medical devices, both for safety and cost-containment purposes. Health technology is defined as the application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures and systems developed to solve a health problem and improve quality of lives.[25,26] The sector dedicated to this monitoring of medical technology costs is known as Health Technology Assessment (HTA). The potential role and importance of a new health technology must be evaluated with a clearly defined process that identifies which technology necessitates more detailed assessment (e.g. technology assessment).[27] HTA has been included in this chapter because pharmaceuticals and medical devices, included in the definition of health technology, are seen as the most important drivers of the health-spending trend. New technologies with claims of improving the health of populations are continuously being developed; however, often the benefits that have been proposed by these developments have not been easy to measure. Even if there were methodologies for evaluating and clearly demonstrating a cost benefit, the time factor alone for being able to do so poses many problems.

While still relatively new, HTA has shown remarkable growth over the past decade. Having begun in the United States, it spread to Europe, and has now become an integral part of health-care decision making throughout the world.[25–30] It has similarities to evidence-based health care and evidence-based policy making in that it couples decision making with sound evidence. HTA was focused initially on providing a useful framework for health policy makers, primarily within national governments. However, more recently, efforts have been increasingly devoted to more effective dissemination and implementation in order to influence administrators and clinicians.[25,26] While early assessments tended to focus on large, expensive, machine-based technologies, smaller technologies and "softer" technologies (such as counseling) as well as health-care needs are now included. Broader issues, such as organizational, social, and ethical implications have received increasing attention. Variability exists in the methods for priority setting of HTA across HTA agencies.[28] In this area, research priorities must be identified if high quality and cost-effective health care is to be achieved in Europe.[25–30] Relative effectiveness and individualized treatments are other areas of growing interest.

BTRE: Economic Burden Within the Context of Neurological Disease

The general issues related to health economic studies addressed up to this point were presented as a background with which to approach the more specific discussion to follow, concerning the social and economic burden of BTRE within the context of neurological disease.

In terms of the health economic burden, disorders of the brain likely constitute the number one economic challenge for European health care.[7,31–34] In a landmark study sponsored by the European Brain Council,[33] annual costs pertaining to neurological and mental disorders throughout Europe were examined in an attempt to understand and estimate their overall cost burden. These disorders were found to have a high prevalence as well as short- and long-term impairments and disabilities, contributing to an emotional, financial, and social burden for patients and their families. That study was updated and expanded (i.e. including more countries and more disorders), the total cost of 19 disorders of the brain was estimated at €798 billion in 2010 for 30 European countries.[7] Direct costs constituted the majority of costs (37% direct health-care costs and 23% direct nonmedical costs) whereas the remaining 40% were indirect costs associated with patients' production losses. Within this study, the costs (in billion € Purchasing Power Parity - PPP for the year 2010) for brain tumors and epilepsy were as follows: brain tumor: €5.2; epilepsy: €13.8. Though the authors acknowledge serious limitations in the accuracy of the costs estimates due to lack of data in many areas, they caution that their findings should be considered conservative, in any event. The study declares that the cost model utilized clearly reveals that "brain disorders overall are much more costly than previously estimated constituting a major health economic challenge for Europe".[7]

EPILEPSY

Of all of the chronic neurological disorders, epilepsy is one that has an enormous socio-economic impact; not only due to its chronicity, but also because still today, the mere mention of the illness brings with it a negative label that impacts the quality of life of the individuals with epilepsy and that of caregivers.[35,37] In addition to the disability that many patients can experience due to possible severe medical and physical complications, there can be numerous neuropsychological and behavioral factors that compromise the personal and professional sphere of individuals with the disease.[36] For all of these reasons, the costs of epilepsy cannot be measured only in economic terms, because the costs of the condition must also be seen within a psychosocial context.[35,37] Despite the social stigma and challenges that are experienced by individuals with epilepsy in their social and work environment, there still remains a tendency in the literature to represent patients' views about their illness through the perspective of the health care providers. The health care professionals' point of view

regarding epilepsy are obviously different than those of patients, however, they must merge for the provision of optimal epilepsy care.[37] Another critical point for moving towards a care model that is more inclusive (i.e., of the patient), is the need to involve the community at large; negative cultural and social beliefs are still pervasive in 2014, and are major obstacles that must be overcome.[37]

Individuals with epilepsy are forced to address not only the physical burden that can result from seizures, but they must also assume a relevant social burden that exists independently of the clinical prognosis.[38,40]

All of the social and cultural problems culminate in one term that has been and still is applicable to epilepsy – *stigma*. The literature data on the negative impact of the stigma on social function and quality of life of people with epilepsy has been amply treated in the literature.[39–42]

Whether for social or clinical reasons, many individuals with epilepsy have limited employment and regarding disability benefits, epilepsy is often left off the lists of illnesses for which individuals may receive disability benefits. Even if some benefits do exist, rarely do the patients and their families receive proper information about how to access them. This is one area that could improve greatly, from a health policy, legislative and public information standpoint.[37]

The gold standard for measuring the global disease burden is "Disability-adjusted life years" (DALYs). The World Health Organization (WHO) utilizing this metric, whereby a DALY represented one lost year of healthy life, calculated the global burden of disease and injury that is attributable to different causes or risk factors. The gap between current health status and an ideal situation where everyone lives into old age, free of disease and disability, is assessed in order to arrive at the measure of burden. In 2000, literature data estimated that epilepsy contributed more than 7 million DALYs (0.5%) to the global burden of disease.[37,43–44] On national scales, disease burden studies for individual nations have been conducted primarily for high-income countries[45–47] and have indicated the significant economic implications of epilepsy with regard to utilization of health-care service, premature mortality and lost work productivity.[37]

The attributable burden of epilepsy has been established, which leads to two subsequent questions for decision-making and priority setting, avertable burden and resource efficiency.[37] The first makes reference to the proportion of attributable burden that is averted currently or that could be avoided through the use of proven efficacious treatments and the second refers to the identification of the most cost-effective means to reduce the burden.

Discovering the optimal technical response to the attributable burden of epilepsy depends on a detailed analysis of these two issues: avertable burden and resource efficiency[48–49] and allows us to differentiate the various components of the epilepsy burden: disease burden already averted, using strategies already in place; disease burden that could be averted, by improvement of available, cost-effective interventions; and finally disease burden that, at this moment, is not able to be averted with existing resources.

The overall impact of epilepsy on health/health care must also be taken into consideration. In both epidemiological and economic studies,[37] a population-level approach has highlighted the negative impact that epilepsy has had on the present levels of these areas.

Patients with epilepsy were found to have significantly higher rates of contact with all sectors of the health care system (general practice, outpatient clinics, and hospital inpatient services) and have higher rates of medication use.[35] Compared with age and gender-matched control subjects, total expenses were higher in those with epilepsy. With specific reference to employment, patients with epilepsy also had lower employment rates and tended to receive more welfare payments. In addition, employed patients tended to have lower incomes than employed control subjects. Taking all of these factors into consideration, it is clear that epilepsy has a significant socioeconomic impact, especially for those patients who experience onset in childhood, adolescence or younger adulthood; a pronounced effect on direct and indirect costs has been seen by age at onset, as well as by gender.[35] Epilepsy is a chronic neurologic disorder that in addition to having an influence on patients' social competence and family relationships, has a considerable negative economic impact.[35,50–52]

The vast range of clinical severity and responses to treatment among epilepsy patients must also be taken into consideration; these factors make understanding costs of the disease difficult to understand – even within a single country.[31,36,53] Despite the fact that a clinical classification is recommended for any kind of cost analysis study, many studies on the costs related to epilepsy have not done this and have analyzed epilepsy as a whole.[54–56] In fact, in newly diagnosed patients – costs related to diagnostic procedures represented the predominant expenditures, while for all other patients (i.e., those with persistent seizures), costs increased in direct relationship to the severity of the disease.[45,46,57–60] In the paper of Beghi *et al.*,[36] the authors' results are in line with other Italian studies of similar design, pointing to a six- to eightfold difference in the costs incurred by patients with inactive epilepsy and those with frequent seizures (i.e., drug resistant).[61] This is particularly relevant to the discussion of costs related to BTRE, seeing that it is a sub-type of epilepsy characterized by its drug resistance. In future health economic studies regarding BTRE, the impact that inadequately treated seizures (i.e., in terms of frequency and/or severity) may have on clinical, psychological, social, and economic issues

must be evaluated.[62] Costs impact both the individual and societal level in different ways, depending on a number of national, cultural, and structural factors. This makes a comparison between different nations extremely challenging. Among the few studies that have been undertaken to evaluate epilepsy related costs,[36] results were difficult to compare within different nations due to a range of both monetary and clinical issues, the first having to do with exchange rates and purchasing power of different currencies, and the second resulting from different health care systems.[31,41,46,63,64] Even within the European Union, prices of medical services and drugs vary greatly.[65]

The serious lack of methodological standardization for health economic evaluation must not be overlooked as a priority area for improvement. In fact, methodological issues are the most common explanation for the different cost estimates in published reports[54,66] and significantly affect the results of any health economic studies. The study of Levy *et al.* (2002)[67] reviewed the literature to identify and discuss methodological concerns. The authors included all studies devoted to cost-based evaluation in epilepsy, published in English from 1989 to 2001, and identified via a Medline search. They identified a series of methodological problems existing in the various types of studies: problems related to study design and choice of an outcome measure, heterogeneity of concepts and estimating methods, many unconstrained choices left open, the failure to incorporate patient's point of view in outcome measurement.

Of all the costs incurred by individuals with epilepsy, the most significant are generated by drugs, with the newer generation AEDs having a major impact. Particular attention must be given to the role AEDs play in efficiently/effectively meeting patients needs; higher costs have been seen when patient needs are more efficiently met. Health care providers and purchasers have met with increased pressure due to the significantly higher costs of the new AEDs.[68–69] The increasing number of these new antiepileptic drugs have fostered the development of economic studies in epilepsy.[67] If selected with specific criteria, the newer AEDs may be more cost effective for some patients: those who have contraindications for the older AEDs, who have experienced adverse events or who have failed to respond to the older drugs altogether, may be treated more cost effectively with the newer AEDs used as monotherapy.[70] This can be particularly true in BTRE where literature data indicate a higher risk of side effects with old AEDs.[71–72] In any event, quality data from clinical trials that could demonstrate clear benefits of using newer monotherapy/adjunctive therapy AEDs over older drugs is still lacking in the literature, and the few studies that have investigated the use of one newer AED in preference to another have produced little evidence.[70]

With the exception of comparisons between newer adjunctive AEDs and placebo, where significant differences favored newer AEDs, data in the literature pertaining to clinical effectiveness, safety, and tolerability have failed to demonstrate consistent and statistically significant differences between the drugs. In addition, data from trials cited in the literature have often had limited applicability due to study design: relatively short-term treatment durations and failure to limit recruitment to either partial or generalized onset seizures.[70]

Given the range of pharmacological choices that the clinician has, it will be increasingly important to include cost data in this choice. From a cost perspective, the relationship between costs, patient needs, and efficiency of treatment, is best evaluated with cost-effectiveness, cost-utility, and cost-minimization studies. While studies using these approaches have been done, the true impact that this research has had on treatment decisions has yet to be established.[73] The fact remains that few economic appraisals have been done in the field of epilepsy. Therefore, at this moment, it is difficult for health care practitioners to make rational decisions regarding new treatments, on the basis of cost; there is simply too little information available.[73]

The way that an individual is affected by a disease influences treatment options and their related costs; this must be taken into consideration when choosing one treatment over another. Over the last 20 years, there has been increasing evidence that clinicians accept the need to consider the financial implications of the treatments they prescribe. Some economic evaluations regarding epilepsy treatment have been done to assess the financial impact of physicians' choices in: newly diagnosed epilepsy, chronic active epilepsy, epilepsy surgery, and childhood epilepsy.[55,73] While the several new AEDs that have been introduced over the last 10 years are more expensive than their predecessors, cost should not be the only criterion, given that evidence indicates that they may offer some advantages in terms of clinical efficacy. Thus, treatment decisions in the future will need to take into consideration a host of issues, including comparative risks, benefits, and costs of alternative AEDs.[74] With regard to scarce health care resources, it is becoming increasingly important that treatments that are offered are effective. There is now an increased focus on the relationship between cost and outcome – yet there are still few economic appraisals. Even when studies have been performed, outcome is often defined in non-monetary terms, and therefore, the studies do not adequately address issues concerning absolute spending levels and the willingness of society to pay. Despite the increasing socio-economic importance of including information pertaining to costs in treatment decisions, many physicians are still unaware of medication costs.[74] The aim of economic

appraisal of any intervention is to improve allocation of scarce health care resources to improve health. Given that the cost of AEDs represents a significant proportion of the total amount spent on medical services for epilepsy, their evaluation within a pharmacoeconomics context is of vital importance.[68] The advantages of some new AEDs which include GBP, LTG, TGB, TPM, VGB, ZSM, all of which were initially licensed as add-on treatments for refractory partial epilepsy, have been cited in the literature as: improved seizure control; fewer drug interactions; and a superior side-effect profile when compared with the more established therapies such as PB, PHT, CBZ, and VPA. For all these reasons, the new AEDs are being prescribed more frequently, and therefore, the relative and absolute amount spent on these drugs will probably increase and will present a challenge to health care providers.[68]

Health care costs for the management of patients with epilepsy have been impacted by new neuroradiologic techniques and surgical approaches, in addition to increasing drug costs.[36] Hospital admissions have also been found to be a significant source of expenditure.[36] Beghi *et al.* noted that, with the exception of surgical candidates who may require hospitalization for diagnostic purposes, there has been no evidence that patients with more severe epilepsy have been hospitalized more. Though they suggest that this could be indirect evidence of a greater treatment efficacy (i.e., in these patients), they also note that well designed prospective, cost-effectiveness studies, which use hospital admissions as a surrogate end point of treatment efficacy, are required to confirm this assumption.[36] This study emphasizes the need to address the costs of epilepsy by separating patients into different disease categories. For all of these reasons, physicians must balance risks and costs of a given treatment with its potential benefits. This is true for both non-oncological epilepsy as well as for BTRE, and this type of consideration represents an area where quality health economic reporting will be most valuable in the future.

For future treatment of all pathologies, including epilepsy, physicians will need to consider the cost as well as the efficacy (e.g., clinical) of the treatments they prescribe.[62] Within this context, the ethical implications of cost containments must be considered and for this reason the cost-effectiveness of treatments must be documented with appropriately designed studies.

In BTRE, however, the evaluations of the costs of new AEDs assume a different role in this context (i.e., cost-containment). In this particular patient population, the higher costs of the newer drugs must be weighed against a host of potentially serious problems associated with the older AEDs, especially those related to CT and RT. Here, increased side effects due to either the AEDs themselves (i.e., the older ones) or CT/RT, impact costs significantly; the medical treatment of these side effects can lead to added costs, brought about by: unprogrammed hospital admission for reasons not associated with the oncological illness; possible reduction of efficacy of CT in association with the older AEDs; and possible decreased life expectancy of the patient.[74–79] To date, there are no studies in the literature that take into account these issues, but future studies will need to take them into consideration.

BRAIN TUMOR

A brain tumor, even more than other cancers, often brings about a significant reduction in income and productivity. The Kaiser Family Foundation report, *Nobody asks if you can afford a brain tumor, you just go where you are led, then your whole world just implodes on itself, and nothing is ever the same* (—brain tumor patient 2006), was undertaken because it was hypothesized that problems seen in the general cancer population would be even greater among brain tumor patients. These tumors and their treatments often limit working, driving, socializing, and more. Household income can be significantly reduced due to cognitive changes from the tumor or from various treatments, which individuals might have to take for up to a year, or longer, in some cases, preventing them from returning to work altogether. In addition to income levels being affected by reduction in work load or cessation of work, MRI scans that are part of patient follow-up and done at regular intervals tend to be very expensive, if not covered by national health care programs. (Nobody can afford brain tumor National Brain Tumor Foundation 2007 http://www.sehn.org/tccpdf/brain tumor financial impact.pdf.)

Of course, the types of costs incurred by cancer patients vary according to national healthcare coverage. Some studies in the general oncology population have shown that medical costs related to prescription drugs and insurance coverage may be problematic for all types of cancer patients.[80,81] A recent oncology study (i.e., regarding the U.S.) also indicated that work interruptions and resulting income changes occur across cancer types, but offered no information about brain tumor patients (Kaiser Family Foundation, *Nobody asks if you can afford a brain tumor, you just go where you are led, then your whole world just implodes on itself, and nothing is ever the same.* (—brain tumor patient 2006). Other studies have shown that in many areas across the globe, medical debt, whether from cancer or ongoing chronic illnesses, may have severe negative impacts on individuals' whole lives, not just during the treatment period but well into the future (www.theaccessproject.com). In countries without a nationally, subsidized health care system, individuals may incur credit card debt or go through

their retirement savings to pay for treatment, placing the long-term financial health of the entire family at risk (Nobody can afford brain tumor National Brain Tumor Foundation 2007 http://www.sehn.org/tccpdf/brain tumor financial impact.pdf.)

In past years, many studies were conducted in different European countries, each focusing on a particular aspect of the economic costs of brain tumors. Therefore, the national characteristics and the context of the national health care system of each country drove the perspective of each study.

For example, a Swedish study by Blomquist *et al.* estimated the costs of brain tumor in Sweden (i.e., direct and indirect) in 1996.[82] Tumor sub-types were also taken into consideration. The direct costs of brain tumors examined were hospitalizations, out-patient and long-term care, and pharmaceuticals, while the indirect costs included were employment-related costs (e.g., sick leave and early retirement) and premature mortality. The authors were able to conduct a thorough study of this kind, thanks to Sweden's comprehensive national databases, from which their data was collected. The results showed that indirect costs, of which premature mortality constituted the majority, represented 75% of the total cost. Of the direct costs, hospital care was the largest cost item. Utilizing a purchasing power parity adjusted to 2003 prices and taking into account the prevalence of brain tumors, they found the cost per patient to be €35,450. Regarding tumor subtypes, 42% of the direct costs were represented by astrocytomas III–IV, while meningiomas accounted for 30%. The authors came to the conclusion that the prior studies that had been done on health care utilization and costs for brain tumors had for the most part focused on new treatments and had been limited due to patient selection (i.e., utilizing only certain subgroups of patients) and the fact that they were based on a single case series from a local hospital.[86]

A Swiss study by Wellis *et al.* (2003)[84] analyzed the direct costs related to treatment costs, specifically microsurgical treatment, of individuals with brain tumors. In addition to examining costs related to microsurgical treatment of brain tumors, the study also examined these treatment costs for a range of other brain pathologies, including arteriovenous malformation, acoustic neuroma, and brain metastasis. The treatment costs pertaining to a total of 127 patients were analyzed. No indirect costs were included in their analysis.[86] The study indicated a mean total direct cost of €12,562 per patient, calculated utilizing a purchase power parity of 2004 prices.[85]

Finally, a British study, conducted by Latif *et al.* (1998) examined the direct hospital costs resulting from the treatment of patients who had had biopsy proven malignant glioma (glioblastoma and anaplastic astrocytoma).[83] The authors did not include community-based care in the study.[83] Also in this study, the indirect costs were not examined. Using price power parity adjusted to 2003 prices, the mean total costs were cited as €26,052 per patient. Of those costs, radiotherapy represented 56%, while neurosurgical bed days and neurosurgery were 15% and 13% respectively. However, the authors caution that determining costs related to microsurgery is quite difficult due to numerous and interrelated sub-procedures.[83]

As clearly stated in the 2005 landmark study, Cost of Disorders of the Brain in Europe, "the most obvious limitation of the economic data for the brain tumor population is that there is so little of it."[33] The study by Blomqvist *et al.*[82] was for the most part a prevalence study, however incidence and prevalence approaches were used to calculate indirect costs that resulted from production losses (i.e., due to premature mortality).[86] As for the accessibility of epidemiological data pertaining to brain tumors, the International Agency for Research on Cancer (IARC) database appears to be the best source; however it contains only data regarding primary malignant tumors (i.e., excluding benign primary and metastatic secondary tumors).[86]

CONCLUSION

To date, there are few cost studies relating to either epilepsy or brain tumor and no cost data pertaining to BTRE.

This book views BTRE not as comorbid pathologies, but as a unique pathology that embraces two serious diseases. Given the increased number of clinical and experimental studies for BTRE that have appeared in the literature, it seems that the time is ripe for economic evaluations and COIs for BTRE. As this chapter has pointed out, these types of studies will present numerous challenges; future BTRE cost studies will need to include different treatment sequences, within both monotherapy and adjunctive therapy; length of follow-up; recruitment of patients with either partial or generalized seizures; investigation of effectiveness and cost-effectiveness in patients with generalized onset seizures; investigation of effectiveness in specific populations of epilepsy patients; studies evaluating cognitive outcomes; and the correct assessment of quality of life, using preference-based measures of outcomes.

In addition, international collaboration for data gathering, research, and reporting are of utmost importance—so that future health policies can be evidence-based and informed by solid, reliable data. Increased cross-national, BTRE-related datasets and initiatives could offer comparable demographic indicators that would help international organizations and governments, planners, and businesses make informed decisions.

The findings highlighted throughout this chapter underscore the value of cross-national data for research and policy. International and multicountry data will help governments and policy makers better understand the broader implications and consequences of BTRE, which could facilitate the crafting of appropriate policies.

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The Prospects of Brain Research within Horizon 2020: Responding Efficiently to Europe's Societal Needs European Parliament, Brussels May 30th, 2013

SUMMARY

Brain research in Europe is a rapidly evolving field, and in the last decade it has constantly been at the forefront of science.

In addition, in our aging society, one of the major societal challenges is the treatment of diseases of the brain: it is important to understand/remind ourselves that, to date, we do not have any therapy for the majority of these diseases and that at present more than 500 million European citizens are living with a brain disease. Finding new treatments for these disorders is a priority for all the developed countries and this will only be achieved by a coordinated program to increase support for the research efforts in the field. Traditionally, Europe has been and remains at the forefront of neurology and neuroscience: thus a major innovation in the treatment of neural diseases can be expected to stem from this continent.

In line with the above, the European Commission provided a comprehensive support for brain research in FP7, as brain research was rightly considered a priority to be endowed with the necessary, dedicated financial resources: more than EUR 1.9 billion has been dedicated to brain-related research since 2007 (a yearly allocation of more than EUR 300 million) funding 1,268 projects.

This has supported the foundation of a community dedicated to brain research: a novel community, which has drawn together the unsurpassed multidisciplinarity which is particularly important and needed for this research. It is also enhanced by the involvement of the patient advocacy community, which is now growing in professionalism and credibility and actively working in our partnerships to produce innovation. Cures are closer but have not yet arrived. Thus at this stage of development in the research advances toward real solutions, it is a major surprise to hear that all the structure from past framework programs will be discontinued with the Horizon 2020 program. Even more disappointing and incomprehensible is the fact that this new approach will seriously dilute the resources available for brain research in favor of other areas which are undoubtedly important, but do not always address a major societal challenge such as the urgent challenge of brain diseases.

In fact, totally unexpectedly in the H2020 program, **no dedicated financial resources** for brain research generally have yet been decided. This is extremely disappointing and difficult to understand, considering that brain research sits within the three main pillars of H2020.

Given this situation, for one key aspect of H2020—to tackle societal challenges by helping to bridge the gap between research and the market—the need to reinforce innovation and use-directed research is not fulfilled.

Globally, the current proposals for the H2020 program raise the threat that the overall broad and inclusive

approach of H2020 will be compromised by an excessive focus on perceived short-term market requirements in the definition of its outcomes.

The stakeholders at the May 30th meeting agreed that a continued, strong funding for neuroscience is essential within H2020, and the following considerations and recommendations focused on brain research arose from the discussions:

- Tackling societal challenges and making breakthrough discoveries is not a linear process and what is needed is a strong support for science and innovation as a holistic system. This is particularly true for brain research because basic brain physiology is still poorly understood due to the past difficulties in the study of such a complex system. Such difficulties, however, can be overcome with a highly multidisciplinary approach requiring strategies of intervention, which favor the development and continuation of a novel research community with unsurpassed levels of collaboration and knowledge across discipline borders.
- Keeping a fair balance between basic research and societal challenges is seen as a priority and basic research, in all disciplines, should be supported within all three pillars of Horizon 2020.
- Research excellence needs to be well balanced by a complementary focus on innovation (application of the results of creative research), policy priorities, societal challenges, and emerging new technologies.
- Research excellence in a long-term perspective requires the continuous fostering of the research community; creating and maintaining its attractiveness to younger researchers is indispensable. Thus, a continuous supply of excellent training for young researchers is a necessity. The crucial importance of these long-term goals for society as a whole cannot be allowed to be swept aside by short-term market needs.
- A key to scientific breakthrough lies in interdisciplinary research, particularly when addressing societal challenges. Horizon 2020 has to strike a balance in supporting research in all scientific disciplines. The success of H2020 will be measured by how it encourages and improves education, dialogue, and collaboration among different competences and disciplines related to brain functioning and diseases. Specific support must therefore be given to actions aimed at broadening collaboration among disciplines focused at understanding brain functions and pathologies. This type of approach is bound to provide creative research and innovation.
- The alignment of National research agendas on brain research should be favored—maintain a pragmatic organization of research. The complexity of brain research requires a global approach where all national research agendas are aligned and research infrastructures, models, and human cohorts are open to all researchers in the field.
- Patient organizations are very important for the development of the field, as improvement in the quality of life of the citizens they represent is the focus of our work. They should be properly informed on the results of research projects, and involved from the beginning in all aspects of the research decision policies. Without knowing what the patients' real needs are, how can we develop our research to achieve the best results?
- Interaction and collaboration between all areas of brain research is necessary to reach the final aim, thus effort should be made to maintain the competence in all fields including those of neglected technical areas.

The huge and increasing societal cost of brain illness has been clearly shown by the EBC study published in 2011. At almost €800Bn each year, this is a burden which must be lessened by real action now. Without focused leadership from Horizon 2020, which will encourage and support the efforts of science and society to collaborate on brain research, the European Union member states will face dire consequences in terms of budgetary crises and severe social distress in the years ahead.

Prof. Monica di Luca
President Elect, FENS

Mary Baker
Past President, EBC

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