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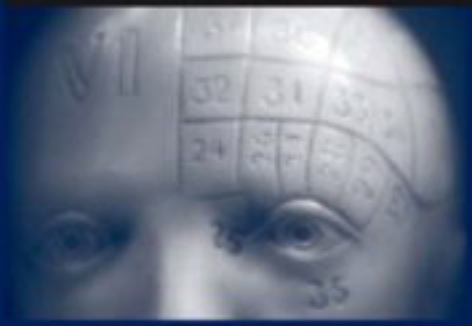

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NEUROLOGIC CLINICS OF NORTH AMERICA

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Preface

Pediatric Neurology, Part I

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Guest Editors

Faced with editing an issue of *Neurologic Clinics* on Pediatric Neurology and charged with the task of covering topics in which there have been significant advances since the last *Clinics* issue on Pediatric Neurology (1990), we quickly realized that the advances in Pediatric Neurology have been so substantial that there were few areas that could be excluded. With this in mind we approached the publisher with the concept of preparing either a two-part issue or two separate issues devoted to Pediatric Neurology. Fortunately, it was apparent to all that this was the only reasonable approach, and permission was given to produce two issues, one in 2002 and a second in 2003. Even so, we had to carefully select the topics to be presented. As a result we have attempted to limit the contributions to those in which there have been the greatest or most important changes over the last decade.

The first of our issues includes topics in which there have been revolutionary changes in our understanding. Foremost among these are the genetics of brain development, the neurocutaneous syndromes, and Rett syndrome. Also included in the first issue are articles describing infections of the nervous system. These consist of AIDS in children, a topic which has changed remarkably in the last decade, meningitis and encephalitis in the post HiB immunization era, and an expanded view of congenital infections.

Neuroradiology has continued to advance in the last decade, and the newer technologies have changed the ways we evaluate and manage our patients. Advanced MRI techniques, a significant part of the new developments in pediatric neuroradiology, represent important additions, not only improving our ability to evaluate our patients clinically but also providing an unique set of techniques that enhance our understanding of basic pathogenetic mechanisms.

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The first volume also includes updates regarding childhood stroke and epilepsy. Cerebral vascular disease in children is remarkably common particularly when one considers that most cerebral palsy results from cerebral vascular disease in one form or another. Our understanding of the causes and prevention of childhood stroke has changed considerably in the last decade. Equally important advances have occurred in the evaluation and management of childhood epilepsy. New anticonvulsants, non-medicinal therapies, and surgical management of intractable seizures have revolutionized the approaches to children with epilepsy.

The final articles in this issue address movement disorders in children and a new class of conditions called neurotransmitter disorders. Movement disorders continue to cause concern. We do not know basic pathogenetic mechanisms, our therapies have limitations, and the co-morbid conditions can be difficult to address, as well. The influence of streptococcal infection is a fascinating, novel aspect of the pathogenesis of movement disorders as well as a variety of psychiatric conditions. Knowledge regarding neurotransmitter disorders, a group of rare but important disorders, has evolved in the last decade and reflects a new way of viewing these enigmatic conditions.

Topics that will be included in the second volume include neuromuscular disease, autism, learning disabilities, ADHD, neuro-oncology, neurorehabilitation, sleep disorders in childhood, depression in children, neuroimmunology, headache, and selected neurometabolic conditions. Due to space limitations an the desire to "update areas with new developments," there will be many topics that cannot be included. We believe, however, that two volumes are better than one; having two volumes allows us to cover many areas in which the new developments have most important implications for the practice of neurology and pediatric neurology. We hope the readers will find these articles as entertaining and informative as we have.

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Brain development and the genetics of brain development

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The brain is a seemingly nonsegmented organ that is, however, formed in a segmented fashion by the overlap of genes that define anatomic and probably functional components of the brain. Other genes and their encoded proteins regulate the processes of cell proliferation and migration; many of these genes have been identified based upon discoveries of human and mouse disease-causing genes.

Human brain developmental disorders represent clinical challenges for the diagnosing clinician as well as for the treating physician. Some disorders represent well-defined clinical and genetic entities for which there are specific tests; others have ill-defined genetic causes, while others can have both genetic and destructive causes. In most cases the recognition of a disorder of brain development portends certain developmental disabilities and often seizure disorders that can be very difficult to treat. In addition, it now bears upon the treating physician to recognize the genetic causes, and to properly advise patients and their families of the risks of recurrence or refer them to the proper specialist who can do so. The genetics of some of these disorders are not all well defined at present, and the recognition of some disorders is variable; what is known is presented herein.

The genetics and signaling utilized in brain development is briefly reviewed to provide the framework for the understanding of human brain developmental disorders. The well-defined genetic disorders of brain development are discussed, and a brief suggested algorithm for evaluation and for counseling of patients is provided.

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Brain development

Overview

General mechanisms tend to recur in all phases of brain development, and these include induction, cell proliferation, cell fate determination (differentiation), cell process formation and targeting (synapse formation), and cell movement (migration). *Induction* is the process by which one group of cells or tissue determines the fate of another by the release of soluble factors or inducers. *Cell fate* or *differentiation* is dependent upon this process of induction, and probably can best be understood as the initiation of a genetic program by the recognition of an inducing molecule and/or expression of a transcriptional regulator. In general, it is rare that a cell in the nervous system is born and differentiates in the same location that it finally resides. Rather, cells *migrate* over long distances to reach their final locations. Similarly, cells in the nervous system must extend processes over long distances to reach their synaptic targets.

Neural tube formation

The human brain is formed from the *neuroectoderm*, a placode of cells that are induced to differentiate from the surrounding ectoderm by the presence of the notochord at about 18 days gestation. Candidate inducing factors include the retinoids, follistatin, and Noggin [1–4]. The neuroectoderm develops folds in the lateral aspects that begin to approximate in the region of the future medulla and fuse at 22 days gestation. This closure is known as *neurulation*, and results in the formation of a tube termed the *neural tube* [5]. The anterior neural tube closes by about 24 days gestation and serves as the foundation for further brain development; the posterior neural tube closes by about 26 days gestation and serves as the foundation for further spinal cord development. Defects in the closure of the neural tube lead to encephaloceles or myelomeningoceles.

Nervous system segmentation

At the rostral end of the newly closed neural tube flexures delineate the primary vesicles, which are designated as the hindbrain (rhombencephalon), mesencephalon, and forebrain (prosencephalon). The primary vesicles can be further subdivided into secondary vesicles that will form adult brain structures. The hindbrain can be divided into the metencephalon and myelencephalon, which will become the pons, cerebellum, and medulla oblongata of the adult. The mesencephalon will be the midbrain, and the prosencephalon divides into the telencephalon (two telencephalic vesicles) and diencephalon. The telencephalic vesicles will become the cerebral hemispheres; the diencephalon will become the thalamus and hypothalamus.

Regional specification of the developing telencephalon is an important step in brain development, and is likely under control of a number of genes

that encode transcription regulators. In the fruit fly, *Drosophila*, these genes are involved in segmentation of this animal and define structures such as hair-like spiracles. Not surprisingly, the role of these genes in human brain development differs, yet it appears that the general role of these proteins is that of regional specification of clones of cells destined to form specific brain structures. Homeobox and other transcription genes encode some of these transcriptional regulators and these "turn on" genes by binding to specific DNA sequences, and in so doing initiate genetic programs that lead to cell and tissue differentiation. *EMX2*, a transcriptional regulator, has a homolog in *Drosophila* that defines the hair spiracles and has been implicated in human brain malformations.

Disorders of segmentation

Schizencephaly (cleft in brain) has been regarded by many as a migration abnormality; however, it is best understood as a disorder of segmentation because one of the genes that is abnormal in the more severe and familial forms is *EMX2* [6,7]. Thus, this developmental disorder, at least in the more severe cases, appears to the result of failure of regional specification of a clone of cells that are destined to be part of the cortex.

Clinically, these patients vary depending upon the size of the defect and upon whether bilateral disease is present [8]. The clefts extend from the pia to the ventricle and are lined with a polymicrogyric gray matter (see the discussion in Polymicrogyria) [9]. The pia and ependyma are usually in apposition, especially in severe cases. The defect is termed *open-lipped* if the cleft walls are separated by cerebrospinal fluid, and *closed-lipped* if the walls are in contact with one another. Bilateral schizencephaly is associated with mental retardation and spastic cerebral palsy; affected patients often are microcephalic. Seizures almost always accompany severe lesions, especially the open-lipped and bilateral schizencephalies. The exact frequency of seizures in patients with the less severe lesions is uncertain. Most patients in whom schizencephaly is diagnosed undergo neuroimaging because of seizures. Therefore, a bias in favor of a universal occurrence of seizures in this disorder is noted. Hence, patients with schizencephaly who do not have epilepsy might exist, but the malformation remains undetected because no imaging is performed.

Seizure type and onset may also vary in this disorder. Patients may experience focal or generalized seizures, and some will present with infantile spasms. The onset varies from infancy to the early adult years. Seizures may be easily controlled or may be recalcitrant to standard anticonvulsant therapy.

Improvements in neuroimaging have enhanced the recognition of schizencephalic lesions [9–13]. The lesions may occur in isolation or may be associated with other anomalies of brain development such as septo-optic dysplasia (see Disorders of prosencephalic cleavage; Fig. 2) [14].

Disorders of segmentation likely represent a heterogeneous set of abnormalities of varying etiologies. One theory holds that an early (first-trimester)

destructive event disturbs subsequent formation of the cortex. Another theory is that segmental failure occurs in the formation of a portion of the germinal matrix or in the migration of primitive neuroblasts. Certainly, the finding of mutations of the *EMX2* gene in some patients with the open-lipped form of schizencephaly supports the latter hypothesis.

Prosencephalon cleavage

At about 42 days of gestation, the prosencephalon undergoes a division into two telencephalic vesicles that are destined to become the cerebral hemispheres. The anterior portion of this cleavage is induced by midline facial structures and the presence of the notochord. Abnormalities of this process are thought to result in holoprosencephaly, septo-optic dysplasia, and agenesis of the corpus callosum [15]. One of the important molecules responsible for the induction of this cleavage is Sonic hedgehog [16]. This protein is produced by the notochord, ventral forebrain, and the floor plate of the neural tube [17]. It interacts through at least one receptor, PTCH—a human homolog of patched, and alters the expression of transcription factors [18,19]. Furthermore, in an interesting link between these ventral inductive events and segmentation, Sonic hedgehog can alter the expression of the transcriptional regulating genes when applied to proliferating cells at critical times in development [21]. This ties the inductive proteins to the expression of transcriptional regulating genes and gives a hint as to the mechanisms involved in inductive processes.

Other molecules of interest in this inductive process are the retinoids, which are lipids capable of crossing membranes and that have been shown to exist in posterior to anterior gradients across embryos [3,20]. Retinoic acid can alter the pattern of transcriptional factors in neuroepithelial cells [3] and can downregulate Sonic hedgehog, perhaps explaining some of the head defects seen in retinoid embryopathy [17,22].

Disorders of prosencephalon cleavage

Holoprosencephaly

Holoprosencephaly is a heterogeneous disorder of prosencephalon cleavage that results from a failure of the prosencephalic vesicle to cleave normally. Three forms of this disorder have been described: alobar, semilobar, and lobar [23,24]. In the alobar form, the telencephalic vesicle completely fails to divide, producing a single horseshoe-shaped ventricle, sometimes with a dorsal cyst, fused thalami, and a malformed cortex (Fig. 1C). In the semilobar form, the interhemispheric fissure is present posteriorly, but the frontal and, sometimes, parietal lobes, continue across the midline [25]; in some cases just ventral fusion is noted (Fig. 1A and B). In the lobar form, only minor changes may be seen: the anterior falx and the septum pellucidum usually are absent, the frontal lobes and horns are hypoplastic, and the genu of the corpus callosum may be abnormal.

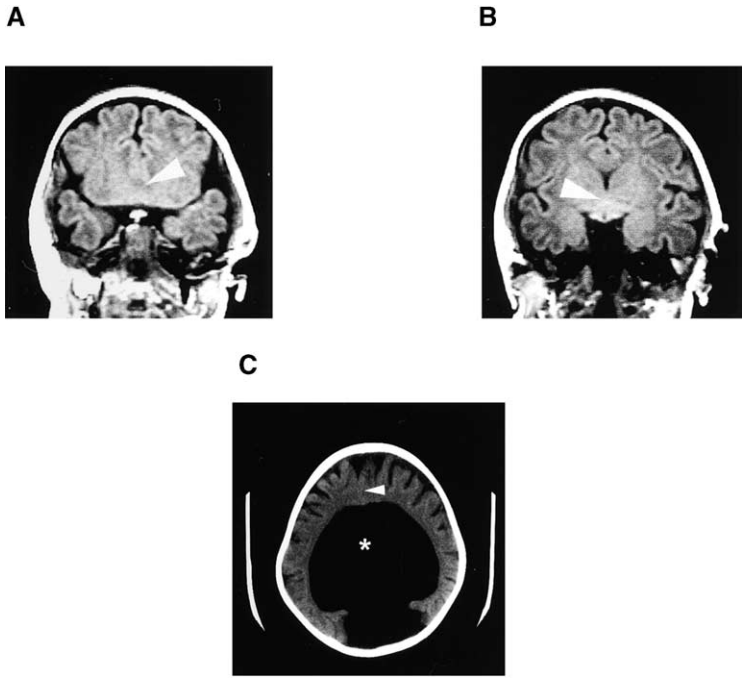

Fig. 1. Holoprosencephaly. (A, B) Images from the same patient with semilobar holoprosencephaly. *Arrowheads* point to lack of ventral interhemispheric cleavage in (A) and to fused thalami in (B). Note in (B) that the septum pellucidum is absent. (C) Alobar holoprosencephaly. Note the horseshoe or mushroom-shaped single ventricle designated by *. The *arrowhead* points to the anterior midline where no interhemispheric fissure is noted.

Holoprosencephaly is associated with a spectrum of midline facial defects. These include cyclopia, a supraorbital proboscis, ethmocephali, in which the nose is replaced by a proboscis located above hypoteloric eyes; cebocephaly, in which hypotelorism and a nose with a single nostril are seen; and premaxillary agenesis, with hypotelorism, a flat nose, and a midline cleft lip [26].

Only children who have the lobar and semilobar forms are known to survive for more than a few months. An infant affected with the severe form is microcephalic, hypotonic, and visually inattentive [25]. In infants with the less severe forms of holoprosencephaly, myoclonic seizures frequently develop and, if the infant survives, autonomic dysfunction, failure to thrive, psychomotor retardation, and atonic or spastic cerebral palsy often are present. Some infants with the lobar form may be only mildly affected and, for example, present as a relatively mild spastic diplegia. Pituitary defects may be associated with these malformations, and may result in neuroendocrine dysfunction [27]. One, therefore, has to wonder how much

genetic overlap exists between this condition and septo-optic dysplasia to be described below.

Holoprosencephaly has been associated with maternal diabetes [28], retinoic acid exposure, cytomegalovirus, and rubella [29]. Chromosome abnormalities associated with this disorder include trisomies 13 and 18; duplications of 3p, 13q, and 18q; and deletions in 2p, 7q, 13q, and 18q [30]. Of particular concern to the clinician is the existence of an autosomal dominant form in which mutations in *Sonic Hedgehog* lead to variable expression of holoprosencephaly. In the mildest form of this genetic disorder, patients may have a single central incisor, a choroid fissure coloboma, or simply attention deficit disorder; a parent of a child with holoprosencephaly manifesting these features should be considered to be at high risk for recurrence of holoprosencephaly in their children (up to 50% risk) [31,32]. A number of other genes (*HPE1* (21q22.3), *HPE2* (2p21), *HPE3* (7q36), *HPE4* (18p), *ZIC2*, *SIX3* (2p21), and *PATCHED*) have been associated with holoprosencephaly, and although potentially inherited in an autosomal recessive fashion, most occurrence seems to be random [33,34].

Septo-optic dysplasia

Septo-optic dysplasia (de Morsier syndrome) is a disorder characterized by the absence of the septum pellucidum, optic nerve hypoplasia, and hypothalamic dysfunction (Fig. 2A, B). It may be associated with agenesis of the corpus callosum. This disorder should be considered in any patient who exhibits at least two of the above abnormalities and perhaps even solely hypothalamic dysfunction [35]. Septo-optic dysplasia also appears to involve prosencephalic cleavage and development of anterior telencephalic structures [36]. About 50% of patients with septo-optic dysplasia have schizencephaly [14] (Fig. 2C, D).

Patients may present with visual disturbance, seizures, mental retardation, hemiparesis (especially if associated with schizencephaly), quadriparesis, or hypothalamic dysfunction. Endocrine abnormalities may include growth hormone, thyroid hormone, or antidiuretic hormone function or levels. The consideration of septo-optic dysplasia necessitates an evaluation of the hypothalamic–pituitary axis because as many as 60% of the children with this disorder might exhibit evidence of a disturbance of endocrine function [37]. This evaluation can include thyroid function studies and electrolytes; these patients are at high risk for growth retardation.

The recent identification of patients with this condition that harbor mutations in the transcriptional regulator gene *HESX1*, suggest that the mechanism of this disorder is likely genetic and a patterning or segmental abnormality [38]. Even though the genetic abnormality has been identified for a minority of patients, there exists the possibility that this may not represent an entirely genetic disorder because associations have been made with young maternal age, diabetes, the use of anticonvulsants, phencyclidine, cocaine, and alcohol [39].

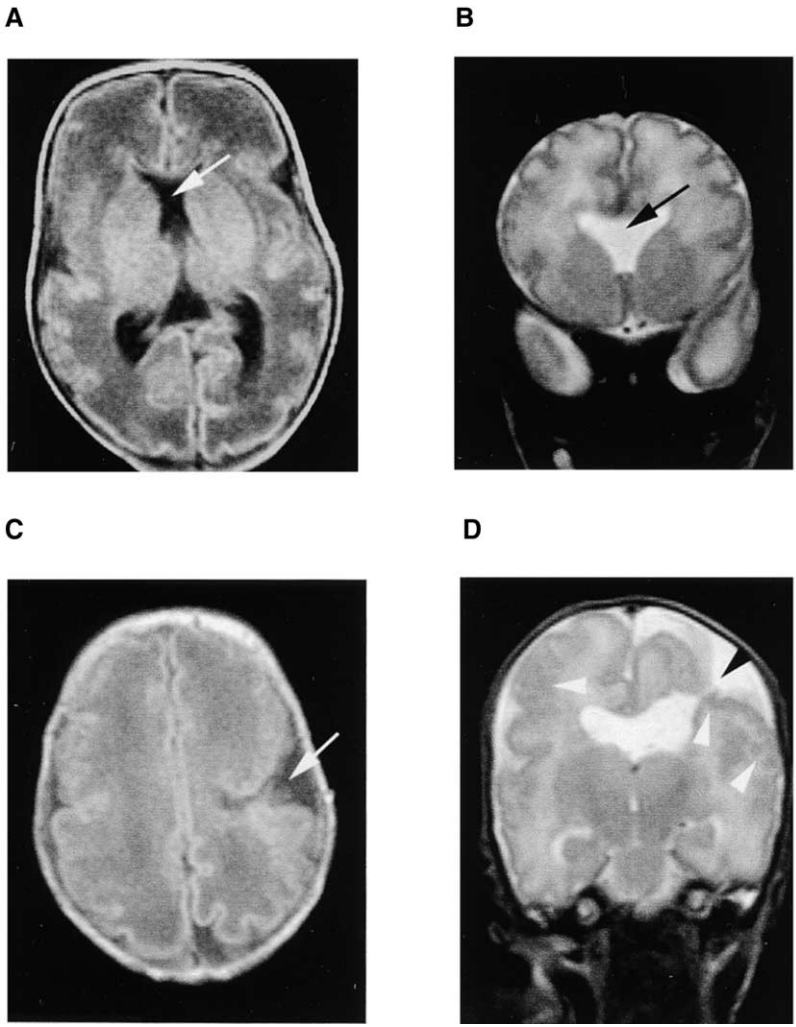

Fig. 2. Septo-optic dysplasia with associated schizencephaly. All images are from the same patient. (A, B) Axial and coronal images, respectively, with *arrows* pointing the midline where a septum pellucidum should be present, but is not. In (C) and (D) axial and coronal images show a superior open lipped schizencephaly designated by the *arrow* in (C) and by the *black arrowhead* in (D). Additionally, areas of polymicrogyria are noted and are designated by *white arrowheads*.

Cell proliferation

Following telencephalic cleavage, a layer of proliferative pseudostratified neuroepithelium lines the ventricles of the telencephalic vesicles. These cells will give rise to the neurons and glia of the mature brain. The generation of the proper complement of cells is a highly ordered process that results in the

generation of billions of neurons and glia. Neuroepithelial processes extend from the ventricular surface to the pial surface, and the nuclei of the primitive neuroepithelial cells move from the cortical surface in a premitotic phase to a mitotic phase near the ventricle. Cells divide at the most ventricular aspects of the developing telencephalon, and after division move back toward the pial surface. The pial processes of neuroepithelial cells near the ventricle often will detach from the cortical surface before a new cycle begins.

Neuroepithelial cells divide in so-called proliferative units such that each unit will undergo a specific number of divisions resulting in the appropriate number of cells for the future cortex. Abnormalities in the number of proliferative units or in the total number of divisions can lead to disorders of the brain manifested by abnormal brain size and, therefore, an unusually small or large head circumference. Two such disorders resulting in small head size—radial microbrain and microcephaly vera—are believed to result from abnormalities of this phase of neurodevelopment [40]. Disorders in which too many cells are generated in the proliferative phase result in megalencephaly (large brain) or, if proliferative events go awry on only one side of the developing cortex, hemimegalencephaly.

The genes and molecules involved in regulating the proliferative cycles in human brain formation are likely similar to those involved in other species. This cell cycle in the brain can be divided into a number of distinct phases: mitosis (M), first gap (G_1), deoxyribonucleic acid synthesis (S), and second gap (G_2) [41]. These phases appear to be regulated by key molecules to check the advancement of proliferation. Some cells enter a resting state (G_0) that they maintain throughout life. Others temporarily enter this phase to await a specific signal to proliferate later. Probably the G_1–S transition regulation determines the number of cell cycles and, therefore, the complement of cells that will make brain [40]. Cyclins are proteins that appear to be involved in cell cycle control. These proteins are activating subunits of cyclin-dependent kinases. Cyclins Dl, D2, D3, C, and E seem to control the key transition of a cell to the G_1–S interface; this transition is regarded as important because it commits a cell to division [42–44]. Cyclin E seems to be the gatekeeper for this transition, and is essential for movement from the G_1 to the S phase [42,45].

The number of cells that finally make up the mature nervous system is less than that generated during proliferation. Cells appear not only to be programmed to proliferate during development but to contain programs that lead to cell death [46,47]. The term *apoptosis* (from the Greek, meaning "a falling off") has been applied to this programmed loss of cells [48].

Disorders of neuronal and glial proliferation

Microcephaly

Although primary microcephaly may be a normal variant, in the classic symptomatic form, clinical and radiologic examinations reveal a receding

forehead, flat occiput, early closure of fontanelles, and hair anomalies such as multiple hair whirls and an anterior cowlick. Neuroimaging may show small frontal and occipital lobes, open opercula, and a small cerebellum [24]. The cortex may appear thickened and the white matter reduced. Histologic examination may show a reduction of cell layers in some areas and an increase in others [49].

Neurologic findings also vary. Only mild psychomotor retardation may be noted, sometimes associated with pyramidal signs, or more severe retardation, seizures, and an atonic cerebral palsy might be evidenced. Primary microcephaly is seen in many genetic syndromes and, in its isolated form, may be autosomal recessive, autosomal dominant, or X-linked [50–52]. *Microcephaly vera* is the term most often applied to this genetic form of microcephaly. Affected children present with a head circumference that is usually more than 4 standard deviations below the mean, hypotonia, and psychomotor retardation. They later show mental retardation, dyspraxias, motor incoordination and, sometimes, seizures. On histologic examination, neurons in layers II and III are depleted [53].

Destructive lesions of the forming brain, such as those caused by teratogens and by infectious agents, also may result in microcephaly. Teratogens of note are alcohol, cocaine, and hyperphenylalaninemia (maternal phenylketonuria) [54]. Intense radiation exposure (such as that from a nuclear explosion) in the first trimester, can cause microcephaly [55]. Microcephaly and intracranial calcifications are likely due to well-recognized in utero infections caused by cytomegalovirus, toxoplasmosis, or the human immunodeficiency virus.

Megalencephaly and hemimegalencephaly

The terms *megalencephaly* and *hemimegalencephaly* refer to disorders in which the brain volume is greater than normal (not owing to the abnormal storage of material); usually, the enlarged brain is accompanied by macrocephaly, or a large head. Although considered by some to be a migration disorder, the increase in brain size in these disorders appears to be attributable to errors in neuroepithelial proliferation, as the microscopic appearance of the brain is that of an increase in number of cells (both neurons and glia) and in cell size [56–59].

Typically, patients are noted to have large heads at birth, and may manifest an accelerated head growth in the first few months of life [60,61]. Children with megalencephaly or hemimegalencephaly may come to medical attention when presenting with seizures, a developmental disorder (mental retardation), hemihypertrophy, or a hemiparesis (opposite the affected hemisphere). Seizures vary both in onset and in type, and usually are the most problematic symptom, sometimes necessitating hemispherectomy or callosotomy [58].

Approximately 50% of patients with linear sebaceous nevus syndrome have hemimegalencephaly [62,63]. Many patients with hypomelanosis of Ito also

have hemimegalencephaly [64]. The neuropathologic and clinical pictures of these associations appear to be identical to the isolated hemimegalencephalies.

Neuronal differentiation

Normal differentiation

At the time of neuronal differentiation the neural tube consists of four consecutive layers: (1) the ventricular zone, the innermost layer, which gives rise to neurons and all of the glia of the central nervous system; (2) the subventricular zone, which is the adjacent, more superficial layer and is the staging area from which postmitotic neurons begin to differentiate and to migrate; (3) the intermediate zone, which is the contiguous, more superficial zone, and which is destined to become the cortical plate and the future cerebral cortex; and (4) the marginal zone, which is the outermost zone and is composed of the cytoplasmic extensions of ventricular neuroblasts, corticopetal fibers, and the terminal processes of radial glia (which, at this time, are completely spanning the neural tube).

Differentiation of neuroepithelial cells begins in the subventricular layer at approximately gestational day 26. The older, larger pyramidal cells are the first cells to be born and probably differentiate early to act as targets in the migration of the nervous system.

Disorders of differentiation

Disorders such as tuberous sclerosis, in which both tumor development and areas of cortical dysplasia are seen, might be a differentiation disorder. The brain manifestations of this disorder include hamartomas of the subependymal layer, areas of cortical migration abnormalities (tubers, cortical dysgenesis), and the development of giant-cell astrocytomas in upwards of 5% of affected patients. Two genes for tuberous sclerosis have been identified: *TSC1* (encodes for Hamartin) has been localized to 9q34 [65], and *TSC2* (encodes for Tuberin) has been localized to l6pl3.3 [65].

Neuronal migration

Normal migration

At the most rostral end of the neural tube in the 40- to 41-day-old fetus, the first mature neurons, *Cajal-Retzius cells*, begin the complex trip to the cortical surface. Cajal-Retzius cells, subplate neurons, and corticopetal nerve fibers form a preplate [66]. The neurons generated in the proliferative phase of neurodevelopment represent billions of cells poised to begin the trip to the cortical surface and to form the cortical plate. These neurons accomplish this task by attaching to and migrating along radial glial in a process known as *radial migration* or by somal translocation in a neuronal process [67]. The radial glia extend from the ventricle to the cortical surface. In the process of migration, the deepest layer of the cortical plate migrates and

deposits before the other layers. Therefore, the first neurons to arrive at the future cortex are layer VI neurons. More superficial layers of cortex then are formed—the neurons of layer V migrate and pass the neurons of layer VI; the same process occurs for layers IV, III, and II. The cortex therefore is formed in an inside-out fashion [67–69].

A possible mode of movement in neuronal migration on glia would be the attachment of the neuroblast to a matrix secreted by either the glia or the neurons. The attachment of the neuron would be through *integrin* receptors, cytoskeletal-linking membrane-bound recognition sites for adhesion molecules. That attachment serves as a stronghold for the leading process and soma of the migrating neuron. Neuron movement on radial glia involves an extension of a leading process, a neural outgrowth having an orderly arrangement of microtubules. Shortening of the leading process owing to depolymerization or shifts of microtubules may result in movement of the soma relative to the attachment points. This theory of movement of neurons also must include a phase of detachment from the matrix at certain sites, so that the neuron can navigate successfully along as much as 6 cm of developing cortex (the maximum estimated distance of radial migration of a neuron in the human). Finally, the movement of cells must stop at the appropriate location, the boundary between layer I and the forming cortical plate. Therefore, some stop signal must be given for the migrating neuron to detach from the radial glia and begin to differentiate into a cortical neuron. Perhaps that signal is REELIN, a protein that is disrupted in the mouse mutant Reeler and is expressed solely in the Cajal Retizius cells at this phase of development [66,70–73].

Migration disorders

Advanced neuroimaging techniques, particularly magnetic resonance imaging, have allowed the recognition of major migration disorders and of the frequency of more subtle disorders of migration. Some of these disorders are associated with typical clinical features that might alert the clinician to the presence of such malformations even before imaging is obtained. In other disorders, the clinical features are so varied that a strong correlation between imaging and the clinical presentation points to a specific genetic syndrome.

Lissencephaly

Lissencephaly (smooth brain) refers to the external appearance of the cerebral cortex in those disorders in which a neuronal migration aberration leads to a relatively smooth cortical surface. One should not consider only agyria in making this diagnosis, rather, the full spectrum includes agyria and pachygyria. Gyri and sulci do not form in this disorder because the lack of cortical–cortical attractive forces owing to improper axon pathways. At least two types have been identified: classic lissencephaly, and cobblestone

lissencephaly. The distinction is based upon the external appearance and upon the underlying histology, and can be made with neuroimaging.

Classic lissencephaly

Classic lissencephaly may occur in isolation, owing to *LIS1* or *Doublecortin* aberrations or in combination with somatic features and *LIS1* deletions in the Miller-Dieker syndrome. The hallmarks on imaging are a lack of opercularization (covering of the sylvian fissure), large ventricles or colpocephaly (dilated posterior horns), and agyria or pachygyria (Fig. 3). The corpus callosum is almost always present, and the posterior fossa is usually normal, although a form of lissencephaly does exist that includes cerebellar hypoplasia.

LIS1 genetic syndromes

The Miller-Dieker phenotype consists of distinct facial features that include bitemporal hallowing, upturned nares, and a peculiar burying of the

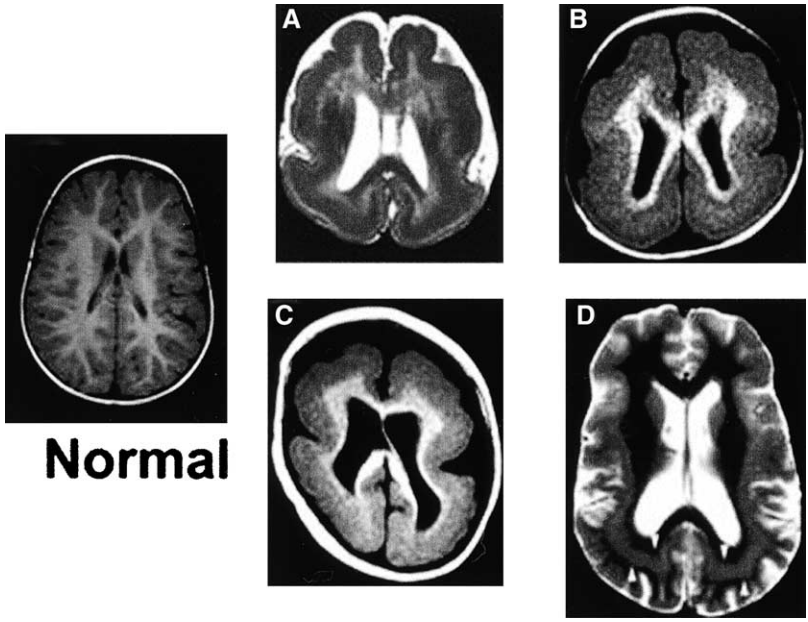

Fig. 3. Neuronal migration disorders: classic lissencephaly spectrum. A normal T1-weighted axial image is shown for comparison. Images (A) ILS 176, (B) ILS165, and (D) LP94-051 are gifts from William Dobyns and the Lissencephaly Project. ILS176 and ILS165 are images from patients with deletions of the *LIS1* gene. (C) ILS087 and (D) ILS94-051 are images from patients with point mutations detected in sequencing of the *LIS1* gene. ILS176, ILS165, and ILS087 represent grade 2 or 3 lissencephaly with the typical thickened cortex, heterotopic cells below surface, and an abnormally smooth cortical surface. LP94-051 represents a patient with band heterotopia who had a mutation in *LIS1*; the band is worse posteriorly.

upper lip by the lower lip at the corners of the mouth. The lissencephaly is usually more severe than isolated lissencephaly, and the prognosis is worse. Most affected patients die in the first few years of life.

By both molecular and cytogenetic techniques, deletions in the terminal portion of one arm of chromosome 17 can be found in approximately 90% of Miller-Dicker lissencephalv cases [74]. The deletions of the terminal part of chromosome 17 in these cases have included microdeletions [74], ring 17 chromosome [75], pericentric inversions [76], and a partial monosomy of 17p13.3 [77]. The most appropriate genetic test is a fluorescent in situ hybridization (FISH) for *LIS1*; this test involves marking chromosome 17 at the centromere and *LIS1* with fluorescent probes.

The greatest risk to future offspring exists when a parent harbors a balanced translocation involving this region of chromosome 17. In families that are affected in this manner, screening by amniocentesis can be performed in subsequent pregnancies. Therefore, it is recommended that both parents have screening for chromosome 17 rearrangements by FISH for *LIS1*. Should a translocation be present in a parent, then the *LIS1* fluorescence will be on another chromosome.

Isolated lissencephaly

Classic lissencephaly without somatic or facial features represents a distinct genetic syndrome from Miller-Dieker, but it involves the same gene *LIS1*. Approximately 40% of patients with isolated lissencephaly have FISH detectable deletions of *LIS1*, and about 20% of additional patients harbor mutations of this gene [78–80]. The remaining patients may have mutations involving promoter regions of *LIS1* or abnormalities of other genes such as *Doublecortin* or the involvement of other genes that have not been recognized.

The genetic risk of recurrence is highest when rearrangements of chromosome 17 exist in one parent. This is rare in isolated lissencephaly, but could occur. Therefore, it would be prudent to perform FISH for *LIS1* in the parents of children with isolated lissencephaly who have FISH proven deletions for the *LIS1* region.

The prognosis for this disorder is better than that for Miller-Dieker syndrome, but it is not consistent with long-term survival. These patients typically present in the first few months of life with hypotonia, lack of visual fixation, and often seizures. Patients with lissencephaly will uniformly have seizures and profound mental retardation. Often, seizures are very difficult to control and require multiple anticonvulsant drugs.

X-linked lissencephaly

The imaging of *X-linked lissencephaly* looks nearly identical to the images of lissencephaly involving *LISI*. Patients have classic lissencephaly, and the neurologic presentation described above. However, the skeletal and other

anomalies seen in the Miller-Dieker are not noted in this form of lissencephaly. When viewing the images from patients with lissencephaly owing to abnormalities of *LIS1* and of *Doublecortin* it is apparent that differences in an anterior to posterior gradient of severity exists [81–83] (Fig. 4). *Doublecortin* mutations result in anterior greater than posterior severity, whereas *LIS1* mutations result in posterior greater than anterior severity [84].

In addition, X-linked lissencephaly occurs mostly in boys; girls who are heterozygous for *Doublecortin* mutations have band heterotopia [80,81,85] (Fig. 4). Women with band heterotopia have been known to give birth to boys with lissencephaly. In female patients, the less severe phenotype probably is attributed to random lyonization of the X chromosome, such that in a variable number of cells, normal gene expression is seen and, in the remaining cells, the *Doublecortin* mutation-containing X chromosome is expressed. It is presumed that those cells expressing the abnormal X chromosome will be arrested in the migration to the surface of the brain and reside in a subcortical band.

When viewing images from patients with this disorder, a thick band of tissue that is isointense with cerebral gray matter is seen within what should be the white matter of the hemispheres (Fig. 4). The overlying gyral appearance may vary from normal cortex to a pachygyria. A brain biopsy performed in a patient demonstrated well-preserved lamination in cortical layers I–IV [86]. Layers V–VI were not clearly separated and merged with underlying white matter. Beneath the white matter was a coalescent cluster of large, well-differentiated neurons.

Lissencephaly with cerebellar hypoplasia

The association of lissencephaly with cerebellar hypoplasia represents a distinct malformation from both a genetic and clinical standpoint to those described above. The cerebellar hypoplasia is usually extreme, and the brainstem may be small. Patients may or may not have an associated micro-

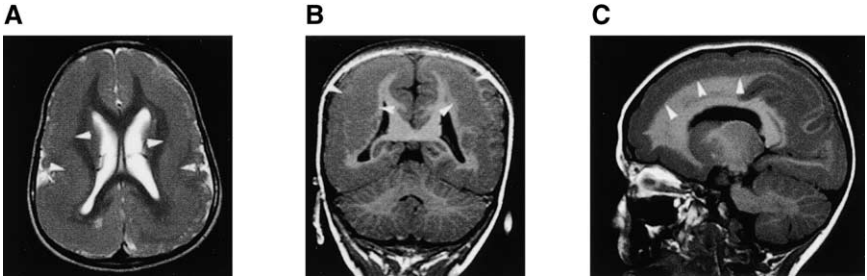

Fig. 4. Subcortical band heterotopia. (A, B, C) Images from the same patient showing different views of extensive subcortical band heterotopia owing to a *Doublecortin* mutation. *Arrowheads* point to subcortical band in axial (A), coronal (B), and lateral saggital (C) views. The subcortical bands have the same signal intensity of overlying gray matter.

cephaly. This disorder is often inherited in an autosomal recessive fashion and may be due to mutations in *REELIN* in some families [87].

Cobblestone lissencephaly

Cobblestone lissencephalies are disorders in which a smooth configuration of cortex is noted, but the distinction from classic lissencephaly is made based upon the clinical association of eye abnormalities, muscle disease, and progressive hydrocephalus (Fig. 5). The term ''cobblestone'' refers to the appearance of the cortical surface upon pathologic examination. In these disorders, cells pass their stopping point and erupt over the surface of the cortex into the subarachnoid spaces. This results in a cobblestone street appearance to the surface, and therefore, the name.

The Walker-Warburg, muscle–eye–brain, and HARD ± E syndromes are likely all varying degrees of the same entity. Abnormalities that may or may not be seen in these disorders include muscular dystrophy, ocular anterior chamber abnormalities, retinal dysplasias (evidenced by abnormal electroretinogram and visual evoked responses), hydrocephalus (usually of an obstructive type), and encephaloceles. The Walker-Warburg syndrome might be diagnosed even if the ocular examination and muscle biopsies are normal if on MRI, an abnormal white matter signal and a thickened falx suggest the diagnosis. Neuroimaging of the muscle–eye–brain disorders often reveals focal white matter abnormalities.

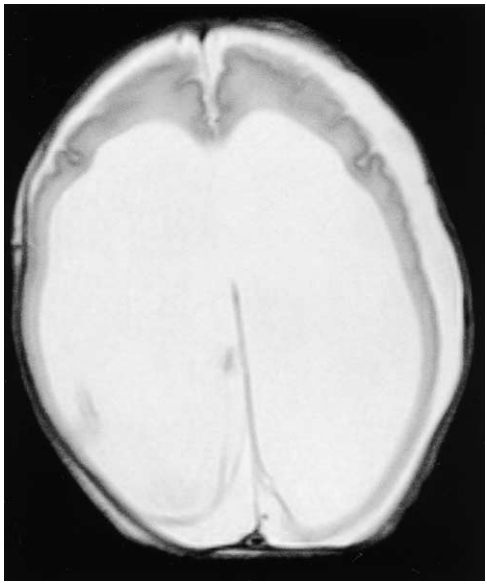

Fig. 5. Cobblestone lissencephaly. Note extensive hydrocephalus, abnormal white matter, and relatively smooth cortical surface.

Fukuyama muscular dystrophy is distinguished from the WalkerWarburg-like syndromes by the severity of the muscular dystrophy [88–91]. This disorder is seen more often in Japan than in the Western hemisphere, probably because it is the result of a founder mutation. Patients typically present with evidence of a neuronal migration defect, hypotonia, and depressed reflexes. Recent identification of *Fukutin* as the causative gene in this disorder should provide insight into the pathogenesis of the cobblestone lissencephalies [92]. This disorder is inherited as an autosomal recessive disorder.

The cobblestone lissencephalies often have an associated cerebellar and brainstem hypoplasia, and therefore may be difficult to distinguish from lissencephaly with cerebellar hypoplasia described above. The presence of eye abnormalities, elevated CPK, or other evidence for the presence of muscle disease and progressive hydrocephalus distinguish this disorder. These disorders may be inherited in an autosomal recessive manner.

Polymicrogyria

Polymicrogyria (many small gyri) is a disorder often considered to be a neuronal migration disorder, but alternate theories exist regarding its pathogenesis. The microscopic appearance of the lesion is that of too many small abnormal gyri. The gyri may be shallow and separated by shallow sulci, which may be associated with an apparent increased cortical thickness on neuroimaging (Fig. 6). The multiple small convolutions may not have intervening sulci, or the sulci may be bridged by fusion of overlying molecular layer, which may give a smooth appearance to the brain's surface. The interface of white matter with gray matter is not distinct and often this observation serves as the confirmation of the presence of polymicrogyria.

Polymicrogyria has also been associated with genetic and chromosomal disorders. It is found in disorders of peroxisomal metabolism such as Zellweger syndrome and neonatal adrenal leukodystrophy. Familial bilateral frontal polymicrogyria and bilateral perisylvian polymicrogyria have been reported. Therefore, if no identifiable cause of the polymicrogyric malformation is found, the recurrence risk may be that of an autosomal recessive disorder. A bilateral parasagittal parieto-occipital polymicrogyria has also been described.

The clinical picture varies depending on the location, extent, and cause of the abnormality. Microcephaly with severe developmental delay and hypertonia may result when polymicrogyria is diffuse. When polymicrogyria is unilateral, focal deficits might be seen. Epilepsy often is present, characterized by partial complex seizures or partial seizures that secondarily generalize. The age at presentation and severity of seizures depends on the extent of the associated pathology.

Bilateral perisylvian dysplasia is a disorder of perisylvian polymicrogyria resulting in an uncovered sylvian fissure on neuroimaging and on saggital imaging an extension of the sylvian fissure to the top of the convexity

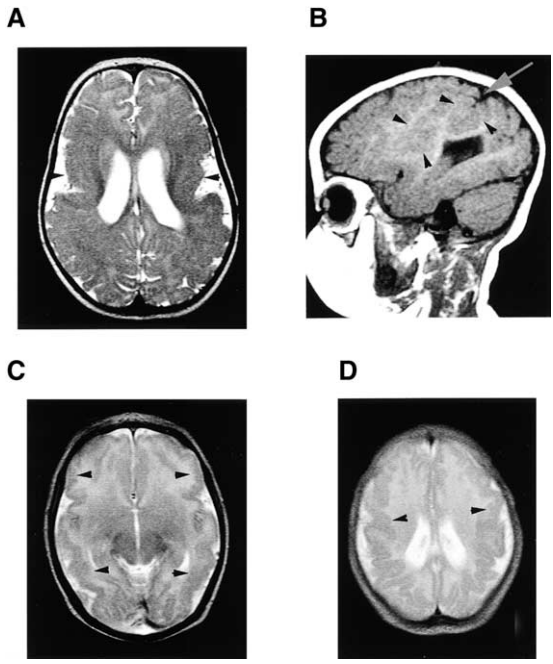

Fig. 6. Polymicrogyria. (A, B) Axial and saggital images from the same patient that demonstrate the findings typical of bilateral perisylvian dysplasia. *Black arrowheads* in (A) point to uncovered sylvian fissures (lack of opercularization) and in (B) to areas of polymicrogyria lining the sylvian fissure. *Gray arrow* in (B) points to an extension of the sylvian fissure to the top of the convexity. (C) Imaging from a patient with extensive polymicrogyria designated by *black arrowheads*. (D) Imaging from a patient with frontal and perisylvian polymicrogyria (*black arrowheads*).

(Fig. 6A, B). Patients with bilateral perisylvian dysplasia have a pseudobulbar palsy, and often dysphagia can impair proper nutrition. The majority of patients have epilepsy with early onset; infantile spasms are common.

The cause of this syndrome remains unknown, although hints of a genetic mechanism exist. Detailed chromosomal analyses have revealed deletions of chromosomes 1, 2, 6, 21, and 22 [93], and an X-linked form has been also described [94,95]. Monozygotic twins and siblings with this disorder have been described, suggesting a possible autosomal recessive mechanism. Some speculate that this is a disorder of regional specification, given the bilateral, symmetric nature of the lesions.

Heterotopias

Heterotopias are collections of normal-appearing neurons in an abnormal location, presumably secondary to a disturbance in migration. The exact mechanism of the migration aberration has not been established, although various hypotheses have been proposed. These include damage to the radial glial fibers, premature transformation of radial glial cells into

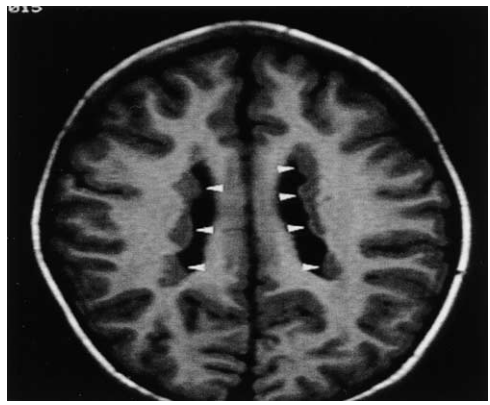

Fig. 7. Bilateral periventricular nodular heterotopia. *Arrowheads* point to nodules with MR signaling characteristics that are similar to gray matter lining the lateral aspects of the lateral ventricles.

astrocytes, or a deficiency of specific molecules on the surface of neuroblasts or of the radial glial cells (or the receptors for those molecules) that results in disruption of the normal migration process [96]. Heterotopias often occur as isolated defects that may result in only epilepsy. However, when they are multiple, heterotopias might also be associated with a developmental disorder and cerebral palsy (usually spastic). In addition, if other migration defects such as gyral abnormalities are present, the clinical syndrome may be more profound. Usually, no cause is apparent. Occasionally, heterotopias may be found in a variety of syndromes, including neonatal adrenal leukodystrophy, glutaric aciduria type 2, GM1 gangliosidosis, neurocutaneous syndromes, multiple congenital anomaly syndromes, chromosomal abnormalities, and fetal toxic exposures.

Heterotopias may be classified by their location: subpial, within the cerebral white matter, and in the subependymal region. When subependymal, one must consider the X-linked dominant disorder associated with Filamin mutations (Xq28) (Fig. 7). Leptomeningeal heterotopias often contain astrocytes mixed with ectopic neurons and may resemble a gliotic scar. They may be related to discontinuities in the external limiting membrane and often are associated with cobblestone lissencephaly. These *subarachnoid heterotopias* are responsible for the pebbled appearance of the surface of the brain. *White matter heterotopias* may be focal, subcortical, or diffuse. They may cause distortion of the ventricles and may be associated with diminished white matter in the surrounding area.

Summary

The progress made in the understanding of the genetics of human brain malformations has lead to insight into the formation of brain and into

mechanisms of disease affecting brain. It bears upon neurologists and geneticists to recognize the patterns of diseases of brain formation, to properly diagnose such disorders, to assess the recurrence risk of these malformations, and to guide families with appropriate expectations for outcomes. This article may serve as a guide to neurologists in their approach to these disorders. Because this area is one of rapid progress, the clinician is advised to seek more current information that may be available through on-line databases and other sources.

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Tuberous sclerosis complex and neurofibromatosis type 1: the two most common neurocutaneous diseases

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Tuberous sclerosis complex (TSC) and neurofibromatosis type 1 (NF1) are autosomal dominant disorders. They are the prototypes of the neurocutaneous diseases. The involvement of multiple tissues and organs, the similar locations of the macular skin lesions of TSC and NF1, the variable clinical expressivity, and similarities in their biochemical pathologic findings cause these two disorders to be considered more closely related than the other neurocutaneous syndromes. Clinically, however, the two disorders are easily differentiated. Other disorders classically considered as neurocutaneous diseases include neurofibromatosis type 2 (NF2) [1], ataxia telangiectasia, von Hippel Lindau syndrome, and Sturge-Weber syndrome. This article focuses on TSC and NF1, particularly with regard to salient clinical aspects of childhood presentation and genetic aspects.

Tuberous sclerosis complex

TSC is an autosomal dominant disorder that involves multiple organs and tissues. The major impact of the disorder is on the brain, skin, and kidneys, but it also affects the eyes and heart. The prevalence of TSC is 1:10,000. Lesions are caused by hamartomas and hamartias [2]. A major point regarding symptoms and signs of TSC is the variable clinical expression of the disorder, even among patients from families with multiple affected generations. The major manifestations of TSC include skin lesions in more than 95%, mental retardation in approximately 50%, autism, seizures in approximately 85%, kidney disease in approximately 60% or more, and uncommon cerebral

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giant cell astrocytomas, but the severity ranges from asymptomatic patients to severe disability. Although the neurologic symptoms most often raise suspicion for the diagnosis of TSC, the relatively unique skin lesions and cranial MRI characteristics are the most helpful for confirming the diagnosis. Diagnosis requires the presence of two or more hamartomas.

Neurologic symptoms of tuberous sclerosis complex

The neurologic symptoms of TSC are the ones that often call attention to the diagnosis but are not adequate to confirm the diagnosis. TSC patients may have epilepsy, mental retardation, and autism as well as learning disorders. Although neurologic symptoms provide much of the morbidity, TSC patients do not demonstrate unique manifestations of these neurologic problems. For example, even though TSC is one of the major diagnosable causes of infantile spasms, there are many other causes. By contrast, cutaneous symptoms are more helpful for diagnosis but cause no significant morbidity, with the exception of occasional disfigurement.

Seizures

Typical absence seizures do not occur more frequently in TSC patients than in the general population, but all other seizure types are more common in TSC patients. The most common seizure types are infantile spasms or partial seizures, often with rapid secondary generalization. Seizures are the most common neurologic symptom of TSC, occurring in approximately 85% of patients [2]. The prevalence of seizures and mental retardation is not related to subependymal nodules, but the prevalence of both is higher in patients with more cortical tubers.

The most serious seizures for TSC patients are infantile spasms [3], which peak between 4 and 6 months of age. Neonatal onset of seizures in TSC is uncommon. The diagnosis of TSC should be considered in all infants who have infantile spasms. The more common features that raise suspicion for TSC in patients who have infantile spasms include hypomelanotic macules of the skin, cortical tubers on cranial MRI, and cardiac rhabdomyomas by echocardiography. For older children who have seizures, the suspicion for TSC is raised by additional dermatologic manifestations. If there is no family history for TSC and no cranial MRI or skin findings for TSC, further evaluation for TSC in an epileptic patient is usually unnecessary.

Seizures are evaluated and treated medically in TSC patients in the same manner as in other patients with epilepsy; that is, electroencephalograms (EEGs) are performed as part of seizure diagnosis and are repeated as indicated by the course of the seizures. Some antiepileptic agents have been specifically tested in TSC and found to have similar utility as in non-TSC patients. For example, lamotrigine is a useful antiepileptic medication for TSC patients and is more likely to decrease seizures in those TSC patients who have partial seizures only and no history of infantile spasms [4]. Infantile spasms are

typically treated with corticotropin or prednisone. In general, antiepileptic medications for TSC patients are chosen based on seizure type [4].

Still controversial is the use of vigabatrin for the treatment of infantile spasms in TSC [5]. Evidence has indicated that vigabatrin is especially effective for the infantile spasms of TSC, leading to rapid cessation of infantile spasms in 95% of TSC patients [6]. This is a success rate that is arguably not achieved by the more standard treatments of corticotropin or prednisone or by alternative antiepileptic agents, such as topiramate, zonisamide, lamotrigine, divalproex sodium, or others. As yet, no randomized trial has confirmed the superiority of vigabatrin. Evidence of side effects of vigabatrin, such as constriction of visual fields in human beings and vacuolation of cerebral white matter in animals, has derailed efforts for US Food and Drug Administration (FDA) approval of vigabatrin in the United States and has raised serious concerns regarding the safety of vigabatrin [5,7]. Therefore, if parents in the United States desire that their infants receive vigabatrin treatment for infantile spasms, they must obtain it from foreign countries.

Surgical treatment of intractable seizures in TSC is receiving more attention. Previously, it was argued that the multiple cortical tubers of TSC rendered futile the surgical excision of epileptic foci; that is, removal of one epileptic tuber would probably uncover the epileptogenic activity of another tuber. However, several series have demonstrated the utility of tuberectomy in selected TSC patients whose major seizure activity arises from a single tuber [8,9]. Localization of epileptogenic tubers can be improved with multimodality imaging, including combinations of positron emission tomography (PET) scanning, single photon emission computed tomography (SPECT) scans, and MRI [10]. When seizures remain medically intractable and tuber resection is not tenable, the ketogenic diet, corpus callosotomy, or vagus nerve stimulation is a viable alternative treatment [8].

Mental retardation

The second most common neurologic symptom of TSC is mental retardation, which occurs in approximately 50% of patients. When generalized seizures, including infantile spasms, start in the first 2 years of life, most TSC patients are mentally retarded, autistic, or both. All mentally retarded children with TSC have seizures. TSC patients who have normal intelligence may or may not have seizures, but the seizures are usually not as severe and usually have later onset (Fig. 1). TSC patients who have the most tubers are more likely to have both mental retardation and seizures [2]. The most disabled are those TSC patients who have both infantile spasms and severe to profound mental retardation. Behavior problems, such as hyperkinesis, attention problems, and aggression, are often associated with mental retardation or autism.

Autism

Among patients who have autism, the cause is unknown for many. Nevertheless, there are several recognizable causes of infantile autism that

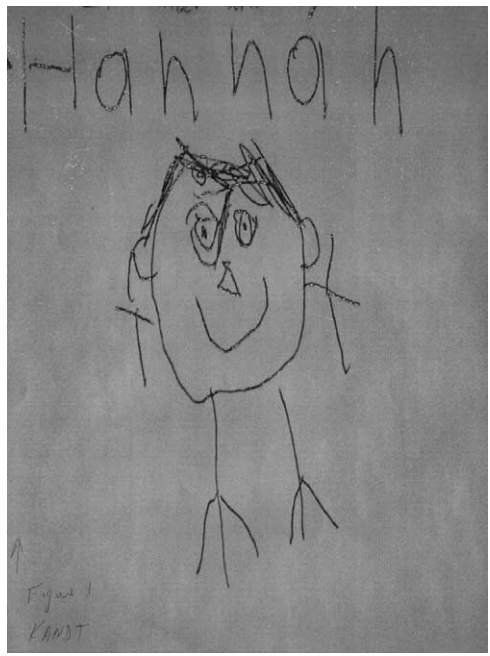

Fig. 1. A human figure drawing and printed name by a 5-year-old normally intelligent girl with tuberous sclerosis complex.

stand out, including TSC, Rett syndrome, and fragile X syndrome. As many as 50% to 60% of TSC patients may have autism, but the true prevalence is probably lower. Autism may be more prevalent in TSC patients whose tubers predominate in the temporal lobes or cerebellum. Although autism may occur in TSC patients who have neither seizures or mental retardation, the presence of seizures in an autistic patient increases the likelihood of TSC. Therefore, as with patients who have infantile spasms, it is important to consider and evaluate for the diagnosis of TSC for autism, particularly for autistic patients who have seizures.

Autism is a communication disorder that constitutes a syndrome composed of a triad of features: impairment of reciprocal social interaction, impairment in verbal and nonverbal communication, and a markedly restricted repertoire of activities and interests that may manifest as stereotypic activities. It is important to note that all these features are common in patients who have mental retardation and that they become more common as IQ decreases. Therefore, to make a diagnosis of autism, the impairments must be out of proportion to those that are appropriate for the patient's intellectual level.

In a study using PET scans, compared with TSC patients who were retarded or had normal intelligence, autistic TSC patients were more likely to show glucose hypometabolism in the lateral temporal cortices,

increased uptake of α-methyl-tryptophan in caudate nuclei, and glucose hypermetabolism in deep cerebellar nuclei [11]. Either a prior history of infantile spasms or the presence of temporal lobe hypometabolism in TSC patients was associated with a communication disorder [11]. The overall number of cortical tubers does not correlate with a greater likelihood of autism, but an increased number of cerebellar tubers does [12].

Increased intracranial pressure

Increased intracranial pressure in TSC is caused by the subependymal giant cell astrocytoma, a lesion relatively unique to TSC [13] and typically finishing its growth by the end of the second decade. The giant cell astrocytoma of the brain characteristically arises at either foramen of Monro from a subependymal nodule and typically enhances after intravenous contrast on CT or MRI [14]. If it grows large enough to obstruct one or both foramina of Monro, the astrocytoma may cause hydrocephalus, which is often unilateral. Baseline cranial MRI is useful to determine if the ventricle was abnormally shaped or enlarged before the giant cell astrocytoma. Indications for surgical removal of this relatively benign mass include progressive enlargement of the giant cell astrocytoma, progressive ventricular enlargement, or symptoms of elevated intracranial pressure. If the giant cell tumor is first diagnosed in an individual near or older than 20 years of age who has hydrocephalus that is not progressive, the risk of surgery may outweigh the benefit. Early symptoms of hydrocephalus typically include morning headache and vomiting, and sometimes sixth cranial nerve palsy. The giant cell astrocytoma can be surgically removed with a minimal chance of recurrence. Chemotherapy or radiation therapy is unnecessary and is not administered.

Dermatologic signs of tuberous sclerosis complex

The skin lesions are most helpful in recognizing TSC. There are multiple skin lesions that are characteristic of TSC. The most common skin lesions are hypomelanotic macules (also called hypopigmented macules or ash-leaf spots).

Hypomelanotic macules

Probably 90% or more of TSC patients have hypomelanotic macules, often 0.5 to 2 cm but sometimes larger, occurring on the face, trunk, and extremities (Fig. 2). The macules do not disturb the contour of the skin; they cannot be detected by an examiner with closed eyes. They are pale but do not totally lack pigment as opposed to vitiligo. Frequently, they have an ash-leaf shape, but equally as often in my experience, they have the shape of a thumb print. Occasionally, the hypomelanosis manifests on the scalp as white hair-poliosis. On sun-exposed skin, particularly in older individuals who have tanned their skin repeatedly, areas of skin atrophy may show a similar decrease of pigment as the hypopigmented macules. These areas should

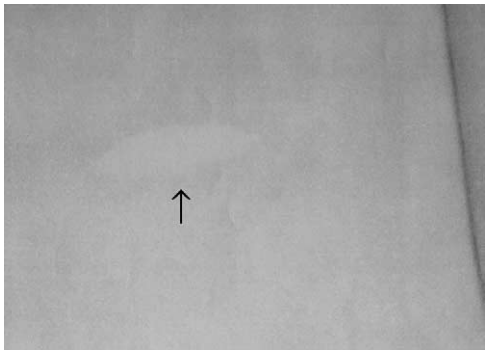

Fig. 2. A hypomelanotic macule of tuberous sclerosis complex.

be discounted as providing diagnostic evidence for TSC. Of particular difficulty is the differentiation between small areas of skin atrophy and the confetti lesions of TSC in these sun-exposed individuals; the confetti lesions, as the name suggests, manifest as numerous small hypopigmented spots. Hypomelanotic macules rarely may occur in individuals without TSC, but usually are single or few in number. In TSC, hypomelanotic macules are valuable to suggest the diagnosis because they are usually present at birth, a time when there may be few other manifestations. Because the macules are pale, they can be difficult to detect, especially in pale-skinned individuals. Skin examination with the ultraviolet Wood's light makes the macules easy to detect but is not always necessary in patients with dark complexions.

Angiofibromas

Facial angiofibromas are the classic skin lesions of TSC. Perhaps 50% of TSC patients have facial angiofibromas; in the past, they were misnamed as adenoma sebaceum. The angiofibromas typically do not occur until near puberty, a time when the facial bumps can easily be confused with acne. Angiofibromas do not have comedones (whiteheads or blackheads), however. The facial angiofibromas may occur in a limited distribution when first developing, and there may only be three or four, most often on the cheeks and quite close to the nose or in the depression between the lower lip and chin (Fig. 3), and they may progress near and after puberty. In older people, facial angiofibromas can be misdiagnosed as acne rosacea. In people with lighter complexions, the facial angiofibromas are often flesh colored, but the red angiomatous component may show through, giving the impression of a red papular rash. In younger children destined to develop angiofibromas, a fever may cause excessive reddening of the cheeks. Angiofibromas, even when not numerous, may cause facial disfigurement because of their redness or prominence. They may also be prone to easy bleeding even from such minor trauma as contact with a pillow case, as occurred with the teenager in Figure 4.

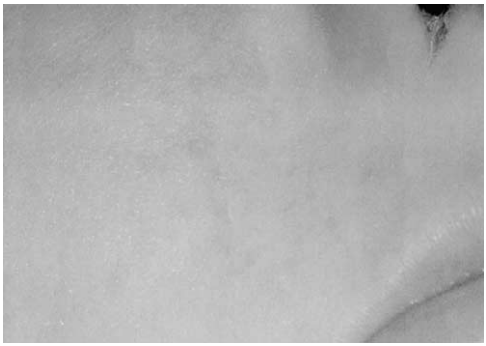

Fig. 3. A small number of flesh-colored tuberous sclerosis complex angiofibromas on the cheek near the nose and a small number in the depression between the lip and chin.

Other skin lesions: forehead plaques, shagreen patches, ungual fibromas, and gingival fibromas

The forehead plaques and shagreen patches have the same angiofibromatous pathologic appearance as facial angiofibromas but appear less vascular and are most common in other areas. Forehead plaques are often darker than surrounding skin, and their location is implicit in the name.

Fig. 4. More extensive tuberous sclerosis complex angiofibromas. These may bleed with mild trauma. In this boy, the angiofibromas are bright red. Note the gingival fibromas.

Identical-appearing lesions may be present on the scalp or cheeks, however. The shagreen patches are often in the region of the lower back, either close to the midline or on the sides of the back. Sometimes they are in groups of small papules that are only several millimeters large, or they can give the appearance of the surface of an orange peel, but they are usually flesh colored or slightly darker or redder than surrounding skin. One of my patients had multiple large shagreen patches, including one on his forearm (forearm shagreen). Several patients have had shagreen patches on their thighs or buttocks. In most cases, no treatment is necessary for shagreen patches.

The ungual fibromas have the same pathologic characteristics as the facial angiofibromas and are generally flesh colored. Some have a red core from the angiomatous component (Fig. 5). Rarely, trauma to the nail can cause an ungual fibroma (Fig. 6), or the chronic trauma from tight shoes can cause the appearance of an ungual fibroma, especially on the lateral side of the fifth toe. Gingival fibromas between the teeth are less common (see Fig. 4).

Other clinical findings in tuberous sclerosis complex

Renal involvement is relatively common in TSC and includes renal cysts, angiomyolipomas, and, rarely, renal carcinoma (<2%). The original localization of the TSC2 gene was facilitated by the occurrence of polycystic kidneys in TSC, because it led to the use of DNA probes related to autosomal dominant polycystic kidney disease [15,16]. A contiguous gene syndrome in which there are deletions of both the TSC2 gene and the adjacent PKD1 gene manifests both TSC and massively enlarged polycystic kidneys at birth [17]. Significant cystic renal disease in TSC more often occurs with the TSC2 gene. Renal cysts occur in approximately 10% to 20% of individuals with TSC. Of patients with angiomyolipomas, approximately 10% have TSC [18]. By contrast, as many as 75% of TSC patients develop angiomyolipomas [19]. Angiomyolipomas are more common in women and are a common cause of morbidity in TSC. Angiomyolipomas have fat–easily seen on CT,

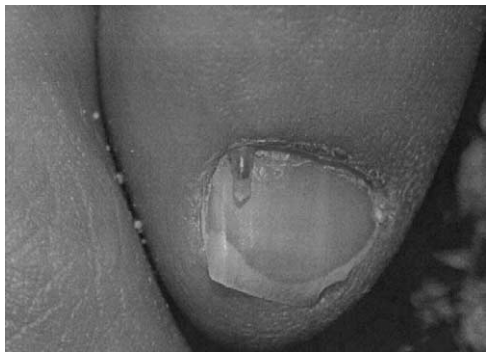

Fig. 5. A flesh-colored ungual fibroma with a central red core.

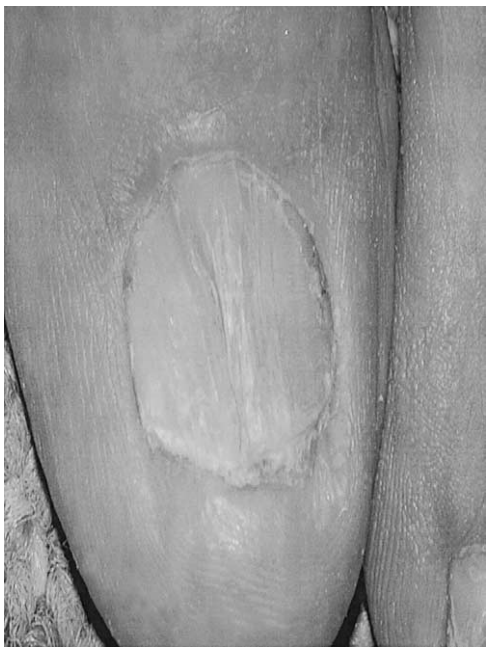

Fig. 6. A traumatic ungual fibroma on the great toe of a patient with back pain and no clinical features of tuberous sclerosis complex. His toe was traumatized with a hammer when he was 6 years old, and it was traumatized again years later with a cast iron skillet that removed the nail.

a feature that differentiates them from renal cell carcinomas. Renal insufficiency can occur with both cysts and angiomyolipomas, and serious hemorrhage may occur with larger angiomyolipomas (>3.5 cm). Renal disease is a leading cause of death in TSC [18].

Cardiac rhabdomyomas are usually asymptomatic but may cause obstruction of flow through the heart; congestive heart failure; cardiac arrhythmias, including Wolff-Parkinson-White syndrome; and sudden death. Rarely, they are associated with stroke, which is more likely related to associated thrombotic material than to tumor fragments [20]. Although TSC pulmonary disease is rare, it can cause severe lung problems. It occurs in adult women (<1%). Aneurysms of cerebral and other vessels rarely occur, but most have been reported in children or young adults [2]. Retinal hamartomas rarely cause visual dysfunction but may be useful to confirm the diagnosis. Other findings are numerous [2] and sometimes helpful for diagnosis, but unless symptomatic, they rarely require clinical attention.

Neuroimaging of tuberous sclerosis complex

Radiologic signs in the brain, such as by MRI, most commonly include cortical tubers in the cerebrum or cerebellum. Other findings include

subependymal nodules, dysplastic heterotopic neurons that are seen as "migration lines", and subependymal giant cell astrocytomas.

In infants, the cortical tubers show different signal characteristics; that is, tubers have high T1 signal in infants, whereas the tubers do not begin to show high T2 signal until the child reaches the age of 12 months. Because MRI T2-weighted sequences show the contrast between the hypomyelination often associated with tubers and normal myelination, tubers are more readily imaged by MRI after myelination has matured to a greater extent (ie, from 12–18 months and older). Typical MRI T2-weighted sequences detect many tubers, but MRI more readily detects tubers using fluid-attenuated inversion recovery (FLAIR) sequences. Tubers are typically seen at the gray-white junction in the cerebral cortex (Fig. 7).

Subependymal nodules are present in more than 80% of TSC patients and are commonly calcified. On MRI, they have relatively high T1 signal (isointense to white matter) and are found throughout the outer walls of the lateral ventricles (Fig. 8), often adjacent to caudate nuclei. On T2-weighted images, subependymal nodules are sometimes isointense to white matter but are often hypointense, particularly if they are calcified (Fig. 9). Calcified subependymal nodules are easy to see on CT, but they are now readily recognized by MRI;

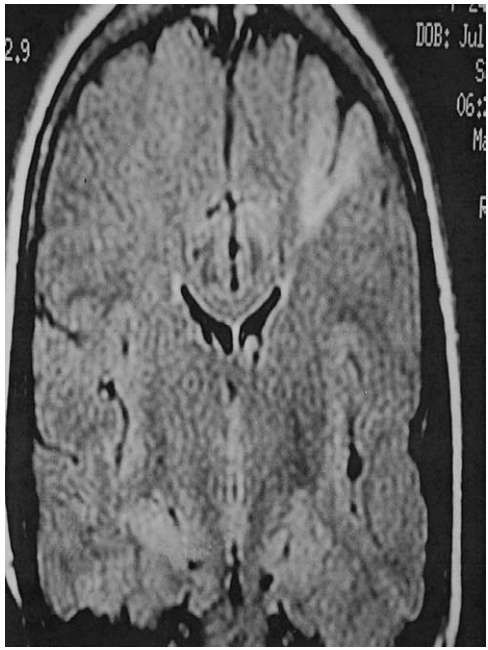

Fig. 7. Coronal fluid-attenuated inversion recovery MRI demonstrating a cortical tuber with a migration line extending to the edge of the ventricle.

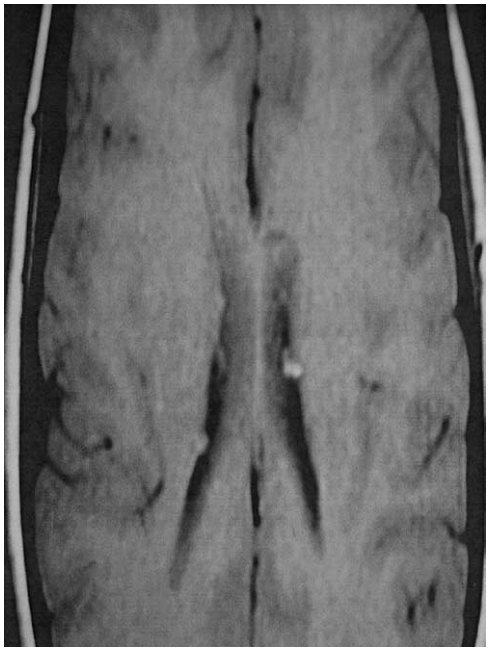

Fig. 8. Axial T1-weighted MRI demonstrating subependymal nodules.

therefore, MRI is more commonly used for cranial imaging in TSC because it is superior to CT for detection of cortical tubers and migration lines.

Genetic aspects of tuberous sclerosis complex

Unique to neurocutaneous diseases, inactivating mutations in either of two distinct TSC genes (TSC1 and TSC2) cause one basic syndrome. Before DNA linkage studies, it was not suspected that TSC could be caused by

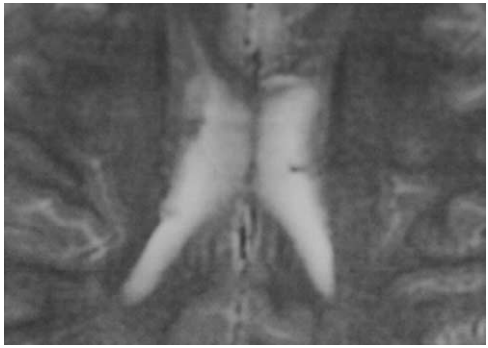

Fig. 9. Axial T2-weighted MRI demonstrating the same subependymal nodules as in Figure 8.

more than one gene [15,21]. This contrasts with the situation in neurofibromatosis. Although NF1 and NF2 are caused by two different genes, the two genes cause two distinct disorders, and they were recognized as such before the genes were discovered.

Of the two TSC genes, the TSC1 gene was the first to be localized (in 1987) to chromosome 9, but the gene was not sequenced until 1997 [22]. By contrast, after TSC2 was mapped to chromosome 16 in 1992 [16], the gene was sequenced the next year [23]. Although a third TSC locus is possible, it is unlikely [23]. The product of the TSC1 gene is called hamartin, and that of the TSC2 gene is called tuberin [24].

Autosomal dominant inheritance occurs with TSC. In TSC families, the cause is almost evenly divided between TSC1 and TSC2 mutations. As many as two thirds of TSC cases occur as a result of sporadic (not inherited) mutations, however, and most sporadic TSC cases are caused by mutations in TSC2. Because of gonadal mosaicism in TSC, a recurrence risk of 2% is quoted to parents who are themselves unaffected but have a child with TSC.

Clinical differences between TSC1 and TSC2 are now being recognized, but they are typically differences of degree and not of character. For example, in one series of 224 patients, the clinical syndrome caused by TSC2 was more severe and more often associated with mental retardation [25]. By contrast, another large series of 225 patients found no phenotypic differences between TSC1 and TSC2 [26]. Although differences between TSC1 and TSC2 families are recognized, the symptoms of TSC are still highly variable in onset and severity. Even in a TSC1 or TSC2 family in which multiple members have TSC, there may be great variability—one patient may have skin lesions, seizures, and mental retardation, whereas others may have skin lesions or seizures but no other problems. The kidney may have cysts, benign tumors, or, rarely, renal cell carcinoma (<2%).

Part of the variability of TSC manifestations stems from the mode in which the defective genes have their deleterious effect. Although their cellular functions remain to be elucidated, several facts have been discovered. Tuberin and hamartin interact in a protein complex [27], which perhaps explains why a deficiency of either one can produce essentially the same clinical syndrome. Both hamartin from TSC1 and tuberin from TSC2 are thought to function, at least in part, as tumor suppressor genes, by which they regulate cell growth and development. It is thought that both alleles of a TSC gene must be defective for the development of a hamartoma or hamartia. This model seems valid for most manifestations of TSC but has not been proven for cortical tubers. As an example of this model, the TSC2 allele on one member of the chromosome 16 pair may harbor a mutation inherited from one of the parents (ie, germline mutation). At the TSC2 allele on the other chromosome 16, a somatic mutation (eg, deletion) may occur. The absence of both normal alleles produces a lack of tuberin, culminating in one of the manifestations of TSC, such as a renal angiomyolipoma [28].

Diagnosis of tuberous sclerosis complex

Blood tests based on gene analysis are available but have a high false-negative rate. No single sign is present in all patients. The diagnostic features constituting hamartomas or hamartias have been divided into major and minor categories [29]. For diagnosis as definite TSC, the patient should have 2 of 11 major features or 1 major feature plus 2 of 9 minor features. Genetic blood tests for TSC1 and TSC2 are available, but perhaps 30% of patients with TSC have negative results.

Major diagnostic features include the following:

Facial angiofibromas or forehead plaque
Nontraumatic ungual fibroma
Three or more hypomelanotic macules
Shagreen patch
Multiple retinal nodular hamartomas
Cortical tuber (dysplasia plus migration tracts count as one feature)
Subependymal nodule
Subependymal giant cell astrocytoma
Cardiac rhabdomyoma (single or multiple)
Lymphangiomyomatosis
Renal angiomyolipoma (when both lymphangiomyomatosis and renal angiomyolipomas are present, they count as one feature)

Minor diagnostic features include the following:

Multiple dental pits
Hamartomatous rectal polyps (histologic confirmation is suggested)
Bone cysts (radiographic diagnosis is sufficient)
Cerebral white matter radial migration lines
Gingival fibromas
Nonrenal hamartoma
Retinal achromic patch
"Confetti" skin lesions
Multiple renal cysts

Additional diagnostic categories include probable TSC with one major plus one minor feature and possible TSC with one major or two or more minor features.

When performing the diagnostic workup, a careful history and skin examination are the first steps. If infantile spasms or autism is present, further workup to diagnose TSC includes MRI of the brain. If either skin lesions or brain MRI findings are present but inadequate for a diagnosis of TSC, ophthalmologic examination for retinal hamartomas or renal ultrasonography may provide confirmatory evidence. Echocardiography is usually not helpful past the age of 2 years, because cardiac rhabdomyomas regress with advancing age [30]. When TSC is diagnosed, the following

studies are performed if not already completed: neurodevelopmental testing, ophthalmologic examination, electrocardiography, renal ultrasonography, and MRI of the brain [31].

Recommendations for follow-up testing after diagnosis focus on treatment or prevention of problems [31]. If there are no seizures, EEG is not needed. Neurodevelopmental testing is repeated at school entrance. Giant cell astrocytomas of the brain typically do not grow after the second decade, whereas renal angiomyolipomas often enlarge during early adulthood. Therefore, MRI of the brain is repeated every 1 to 3 years during childhood and adolescence, and renal ultrasonography is repeated every 1 to 3 years. For either brain MRI or renal ultrasonography, symptoms may require more scans. Chest CT is performed at adulthood in women for the rare complication of pulmonary lymphangiomyomatosis and is repeated if pulmonary dysfunction occurs. Other tests, such as EEG, ophthalmologic examination, electrocardiography, and echocardiography, are repeated only if clinical findings suggest the need [31].

Treatment of tuberous sclerosis complex

After diagnosis, TSC patients require treatment of seizures, educational treatment for mental retardation and autism, and pharmacologic treatment for behavioral disorders related to mental retardation and autism. The major symptom that can be treated is the epilepsy. Various antiepileptic medications, and sometimes surgical approaches, are used as discussed previously. Facial lesions are treated with laser therapy, and bothersome ungual fibromas can be surgically removed. For patients with learning problems, mental retardation, or autism, educational intervention is helpful, but medications can also be useful, including dextroamphetamine and other psychostimulants for hyperactivity and inattention, fluoxetine for autistic symptoms, clonidine for hyperarousal, and risperidone for aggression. Giant cell astrocytomas of the brain are treated surgically as discussed previously. Renal angiomyolipomas, particularly those larger than 3.5 cm, can often be treated with nephron-sparing surgery. For renal failure, TSC patients may undergo kidney transplantation and do not have excessive risk from immunosuppression.

Neurofibromatosis type 1

NF1 is an autosomal dominant disorder with variable expressivity; patients who have the abnormal NF1 gene may manifest (express) different numbers or intensities of features, even within NF1 families. The prevalence is approximately 1 per 4000, the same order of magnitude as Duchenne muscular dystrophy. In contrast to TSC, mental retardation or seizures are relatively uncommon, but nerve sheath and central nervous system tumors

cause the major morbidity. The diagnostic suspicion is usually raised by the presence of multiple café au lait spots. Less commonly, in infants, the diagnosis is suspected because of facial malformations caused by bone dysplasia. Occasionally, children present with impaired vision from optic nerve glioma. Onset with other types of neurologic dysfunction is uncommon. Diagnosis requires two or more of the diagnostic features.

Diagnostic criteria for neurofibromatosis type 1

Two or more of the following criteria are required for diagnosis:

Six or more café au lait spots 1.5 cm or larger in postpubertal individuals and 0.5 cm or larger in prepubertal children
Two or more neurofibromas of any type or one or more plexiform neurofibromas
Freckling in the axillary or inguinal regions
Optic nerve glioma (optic pathway tumor)
Two or more Lisch nodules (iris hamartomas)
A distinctive osseous lesion, such as dysplasia of the sphenoid bone and dysplasia or thinning of long bone cortex (pseudoarthrosis)
A first-degree relative with NF1 according to the preceding criteria

Of note, the absence of café au lait spots, axillary freckling, cutaneous neurofibromas, and Lisch nodules by the age of 5 years excludes the diagnosis of NF1 with greater than 95% certainty. Blood tests based on gene analysis are available but have a high false-negative rate.

Dermatologic features of neurofibromatosis type 1

Café au lait spots and skinfold freckling

The hallmark sign of NF1 is the café au lait spot (Fig. 10), named because of its color, similar to coffee with milk. Most children with NF1 have café au lait spots and axillary freckling, and most adults also have cutaneous

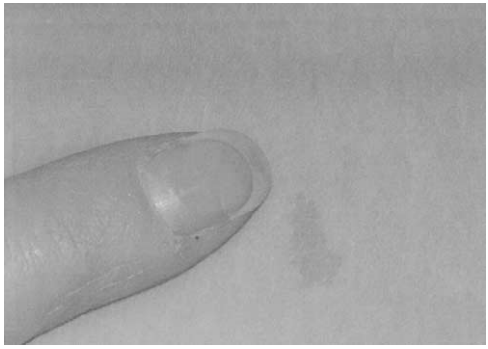

Fig. 10. Café au lait spot.

neurofibromas and Lisch nodules of the iris. Other than cosmesis, café au lait spots have no clinical consequences and no need for treatment. One or two café au lait spots are common in individuals without NF1, but six or more café au lait spots, occurring in more than 95% of people with NF1, rarely occur in people without NF1. Café au lait spots are macular; are distributed on the trunk, face, and extremities; and are darker in sun-exposed areas. A regular border differentiates café au lait spots of NF1 from the café au lait spots of McCune-Albright syndrome (polyostotic fibrous dysplasia with precocious puberty). Rarely, a child may have isolated autosomal dominant café au lait spots. Café au lait spots are typically present by 2 years of age, but other manifestations of NF1 often do not develop until later. Among children with six or more typical café au lait spots, most (73%) develop other findings for NF1 or segmental NF1 by the age of 5 years [32].

Axillary freckling occurs in most children with NF1 but may not have developed by the time the café au lait spots are first diagnosed. By 5 years of age, however, as many as 84% of the children with NF1 have axillary freckling, with a smaller proportion (~50%) having inguinal freckling. Submammary freckling in women with NF1 occurs less commonly. Skinfold freckling is diagnostically helpful because freckling in individuals without NF1 is rare in areas that are not sun exposed.

Neurofibromas

Cutaneous (dermal) neurofibromas. Neurofibromas arise from the peripheral nerve sheath. Neurofibromas of the skin are rare in young children but may develop in preadolescence in up to 14% of children less than 10 years old. When they first appear, the neurofibromas often have a slight irregularity of skin with a combined small elevation and depression, sometimes with reddening of skin caused by dilated or proliferated capillaries. Larger neurofibromas protrude from the skin, are often pink or violaceous, and frequently have an appearance that suggests a hard surface, but they are typically soft, and some even feel velvety. Cutaneous neurofibromas typically enlarge and increase in number at certain times of hormonal change (puberty in boys and girls and pregnancy in girls and women). Although 95% of adults with NF1 who are more than 30 years old have neurofibromas, less than half of adolescents with NF1 have neurofibromas. Typically, an early age at the time of appearance of neurofibromas portends larger and more numerous neurofibromas in adulthood. Some neurofibromas, particularly subcutaneous neurofibromas or nodular neurofibromas on nerve trunks, may be painful or pruritic, and they can be removed surgically.

Plexiform neurofibromas. Compared with dermal neurofibromas, these skin tumors have ill-defined borders and are more diffuse and highly vascular and do not follow tissue planes. The skin overlying the tumor is typically hyperpigmented and often hairy. Associated structures can be hypertrophied. Some feel nodular with palpable nerve trunks. Plexiform neurofibromas that occur

in deep structures (eg, mediastinum and retroperitoneal compartment) may be difficult to diagnose and may cause various complications relating to the structures involved. Plexiform neurofibromas occur in approximately 25% of NF1 patients and are present at birth or detected in early childhood; however, they may enlarge, especially near adolescence. They may be disfiguring, particularly when they involve the head (eg, eyelids) or neck. The plexiform neurofibromas are difficult to treat surgically, regrow if not completely removed, and do not respond to radiation therapy. If they are disfiguring or located in areas that cause significant morbidity, they should be removed. The best results occur with early removal, but because of their nature, the surgical morbidity may be substantial, making the decision for surgery difficult.

In contrast to dermal neurofibromas, which have no malignant potential, plexiform neurofibromas may transform in 1% to 4% of individuals into neurofibrosarcomas, rarely before the age of 10 years. Areas of abrasion (eg, the belt line) are more susceptible to malignant transformation. Rapid growth is an indication for biopsy [33].

Lisch nodules of the iris

Lisch nodules are benign iris hamartomas, often visible only by slit-lamp examination. They cause no clinical problems but are useful for diagnosis. They are uncommon in young children (22% by 5 years of age), but if only café au lait spots are present, the discovery of Lisch nodules can confirm the diagnosis of NF1. They occur in 70% of children by 10 years of age [34] and are present in almost all adults (96%) with NF1.

Neurologic features of neurofibromatosis type 1

Tumors

The most common tumors of the central nervous system in NF1 occur in the optic pathways, and are mostly slow-growing low-grade astrocytomas. Rarely, meningiomas occur in the same location in NF1 patients and may show identical findings. Although imaging studies demonstrate that approximately 15% to 20% of NF1 patients have optic pathway tumors, no more than half of the tumors become symptomatic. In general, the presence of an optic nerve glioma in a child should raise the suspicion for NF1; at least 50% of children with optic nerve gliomas have NF1. Because chiasmatic tumors may involve the hypothalamus, the occurrence of precocious puberty in NF1 children should signal the likelihood of an optic glioma. Most children with symptomatic gliomas develop decreased visual acuity and optic pallor/atrophy, but depending on the location of the tumor in the visual pathways, they may present with visual field defects, restricted eye movements, proptosis, headache, or hypothalamic dysfunction. Tumors that cause symptoms are typically diagnosed by the age of 6 years, and more than 90% show no progression of symptoms after diagnosis. A more recent study of 1893 NF1 patients less than 21 years old found that symptomatic

optic gliomas are usually diagnosed by the age of 3 years [34]. Therefore, imaging as a screen for optic pathway tumors in the absence of symptoms has limited value. Treatment for progressive tumors usually includes surgery and chemotherapy [35] or radiation therapy. Nevertheless, treatment of lesions that are questionably progressive should be tempered by reports of spontaneous regression [36] as well as by treatment complications, such as radiation-induced vasculopathy [37], cognitive problems, endocrine dysfunction, and the possibility, particularly after radiation therapy, of transformation of low-grade tumors into more malignant tumors. Whether treated initially or not, patients with visual pathway tumors are followed closely for any deterioration of vision or endocrinologic dysfunction.

Symptomatic parenchymal brain tumors occur infrequently in NF1 (~1%–2% of patients), and they are usually low-grade astrocytomas. Brain tumors in NF1 generally become symptomatic by the time the patient reaches the age of 20 years. With the exception of brainstem gliomas, the outcome of these tumors is typically the same as in children without NF1. Brainstem gliomas, however, show slower progression or even regression in NF1 and may not need treatment [38]. Hydrocephalus, which may occur with brainstem tumors (eg, tectal gliomas), may require ventriculoperitoneal shunting. Other tumor types are much less common, including ependymomas, meningiomas, medulloblastomas, and primitive neuroectodermal tumors, and these tumor types are treated as they would be in children without NF1.

If brain tumors are symptomatic and they are low-grade hemispheric or cerebellar astrocytomas, they are often removed surgically, particularly if they are not in areas that are critical for nervous system function. Those that are recurrent or not surgically accessible are treated with chemotherapy [35] or radiation therapy. In young children, the morbidity from radiation therapy is high. Similar to optic nerve gliomas in NF1, parenchymal brain tumors are not treated on discovery. They should be monitored before treatment for either lack of progression or the possibility of spontaneous regression [36,38].

Spinal nerve root neurofibromas and, less commonly, spinal cord gliomas may cause symptoms and are typically treated surgically. Spinal meningoceles, often thoracic, are caused by dural ectasia and can be confused with neurofibromas. Spinal meningiomas are probably no more common in NF1 than in the normal population; rather, they more commonly complicate NF2.

Cognitive problems

Mental retardation occurs only slightly more commonly in NF1 (4%–8%) than in the normal population (3%). Specific learning disabilities have a major impact, however, and occur in 30% to 60% of children with NF1. Psychologic testing shows visual-spatial problems, language disorders, and memory dysfunction. Some of the children have attention-deficit hyperactivity disorder. It remains unsettled as to whether cranial MRI T2

hyperintensities are correlated significantly with the learning problems of NF1. Awareness of the possibility of learning problems in NF1 children can lead to proper educational treatment.

Other complications of neurofibromatosis type 1

NF1 may cause problems with almost every organ system because it affects both neural crest–derived cells and mesodermal tissues. There is only a slight increase in the prevalence of epilepsy, perhaps 2% to 5%. Somewhat less than half of NF1 children have macrocephaly without hydrocephalus or any definite abnormality. Short stature occurs in approximately one third of such children.

Scoliosis is frequent in NF1 (~15%). Scoliosis occurs earlier, and it more commonly needs surgical correction than does idiopathic scoliosis. Although it may have a long length similar to idiopathic scoliosis, vertebral dysplasia is often related to the NF1 scoliosis and then may show an acute angulation. Causes of scoliosis include spinal meningoceles and nerve root neurofibromas (often with a dumbbell configuration). Sphenoid wing dysplasia occurs congenitally in less than 1% of children with NF1 but is relatively unique for NF1. Thinning of long bones, especially with medial bowing of the tibia, may predispose to fractures and pseudoarthrosis.

Glaucoma occurs rarely and is usually congenital. It is associated with photophobia and enlargement of the corneal diameter. Neurofibromas can occur in multiple areas, leading to unexpected complications, including constipation and prostate involvement [39]. Some tissues may be enlarged, leading to clitoral enlargement, macrodactyly (with or without a plexiform neurofibroma), and macroglossia. Hypertension may occur in childhood but is more common in adults with NF1. A neurofibroma may compress the renal artery, or the vascular dysplasia of NF1 may cause renovascular hypertension. NF1 may be the most common cause of renovascular hypertension in children [40]. Hypertension may also be caused by a pheochromocytoma. In addition to pheochromocytoma, NF1 is rarely associated with other neoplasms, such as carcinoid of the duodenum, nonlymphocytic leukemia, adenocarcinoma of the ampulla of Vater, and possibly rhabdomyosarcoma.

The vascular dysplasia of NF1 is also associated with stroke in childhood, usually caused by the moyamoya phenomenon associated with occlusion of the supraclinoid carotid artery or proximal vessels of the circle of Willis [41].

Neuroimaging in neurofibromatosis type 1

Compared with TSC, neuroimaging in NF1 does not have as much importance for diagnosis of the disorder but is more important for monitoring complications. There are no neuroimaging findings included in the

diagnostic criteria for NF1. When the consensus criteria for diagnosis of NF1 were formulated in 1987, there was not much experience with MRI, especially in children. MRI T2 hyperintensities may have diagnostic significance, however. In NF1, most young patients have unidentified bright objects (UBOs) on cranial MRI (Fig. 11), whereas the prevalence of UBOs goes down in older children. The nature of the UBOs remains unclear, and they are postulated to represent hamartomas, dysmyelinated areas, or spongiosis. Most adults with NF1 either do not have UBOs typical for NF1 or have confounding lesions caused by vascular or other disease. DeBella et al [42] used cranial MRI to examine 19 children with NF1 and 19 controls. Of the 19 control children, 11 had UBOs. Of note, the control children all had neurologic disorders. When only the UBOs typical for NF1 were considered (ie, those located in the basal ganglia, cerebellum, and brainstem), their presence was correlated with NF1 to a high degree, yielding a diagnostic sensitivity of 97% and a specificity of 79%. In terms of diagnosis, UBOs are more helpful in young children who have only one criterion for diagnosis (usually multiple café au lait spots). They are less helpful later, because by the age of 5 years, diagnosis can usually be made based on other criteria. Further studies are necessary before typical UBOs can be considered a diagnostic criterion.

Because of the morbidity of tumors in NF1, the follow-up of optic nerve gliomas, brain tumors, and spinal lesions is the most important use of neuroimaging in NF1. On T2-weighted MRI, optic nerve gliomas either demonstrate an enlarged optic nerve with a core of low signal surrounded by high

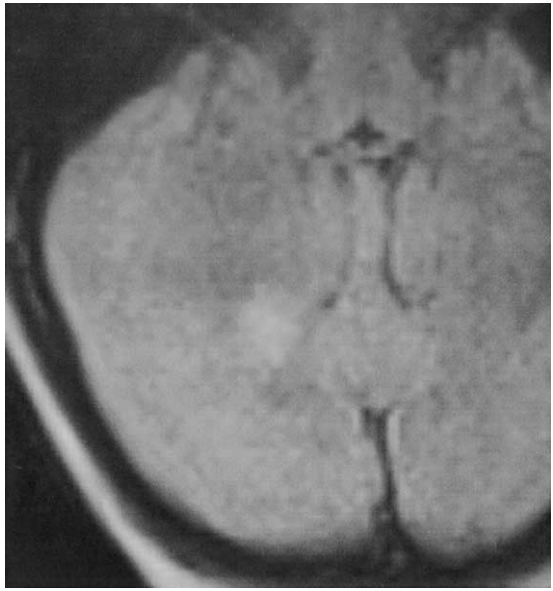

Fig. 11. Axial T2-weighted MRI of unidentified bright object in the cerebellar white matter.

signal, or there is a tubular enlargement of affected optic nerves. Optic nerve sheath dysplasia occasionally is mistaken for an optic nerve tumor.

As discussed previously, imaging of asymptomatic patients to screen for optic nerve gliomas or brain tumors is rarely useful. Most clinicians obtain a baseline cranial MRI. If asymptomatic lesions are discovered that might represent tumors, they are commonly monitored every year or so. Cranial MRI T2 hyperintensities in the visual pathways, brainstem, or cerebellum often represent benign UBOs. After discovery of MRI T2 hyperintensities, however, it is helpful to perform a study with contrast. An enhancing lesion is more likely to represent an astrocytoma or other tumor. Although lack of enhancement is reassuring, some astrocytomas do not enhance. A follow-up scan is usually indicated to confirm lack of progression.

Genetic aspects of neurofibromatosis type 1

NF1 is an autosomal dominant disorder. For an affected parent, the risk of affected offspring is 50% with each pregnancy. The spontaneous mutation rate is high; thus, perhaps 50% of affected patients represent sporadic cases. Those with a new sporadic mutation then transmit NF1 as an autosomal dominant disorder. The gene for NF1 was initially localized to chromosome 17 in 1987, the same year that TSC1 was localized to chromosome 9. The NF1 gene is large and was described in 1990. There is only one gene that causes NF1. Most NF1 mutations cause premature truncation of the neurofibromin protein. Similar to the TSC1 and TSC2 gene products, the normal NF1 gene product, neurofibromin, is thought to function as a tumor suppressor [24]. Neurofibromas are composed of multiple cellular elements, but the Schwann cell seems to be the target for NF1 gene inactivation. An individual with NF1 inherits an inactivating mutation of one of the NF1 alleles. This mutation is present in all cells. When a somatic inactivating mutation of the NF1 gene occurs in the other allele, a neurofibroma or other tumor may develop. The prevalence of learning problems and other symptoms unrelated to tumor formation has led to the speculation that this large gene may have additional functions that may play a role in the heterozygous state.

Germline mosaicism, documented in only one clinically normal father of two offspring with NF1, is thought to be rare enough that it is not important for genetic counseling [43]. By contrast, some patients have segmental or anatomically limited signs of NF1 consistent with somatic mosaicism. If patients with segmental NF1 have mosaicism of germ cells, they transmit NF1 as an autosomal dominant disorder.

Management of neurofibromatosis type 1

Patients with NF1 have multiple possible complications and need access to multiple specialists. A clinician who has a broad familiarity with NF1, often a neurologist or geneticist, coordinates the care. Patients are seen yearly and are evaluated for complications, such as focal neurologic dysfunction,

abnormal puberty, optic pathway tumor, scoliosis, cognitive/learning problems, and hypertension. Counseling includes supportive information, genetic aspects, surveillance of plexiform neurofibromas for malignant transformation, and reassurance that less than half of NF1 patients (40%) develop medical problems from NF1. The similarity of a small portion of the neurofibromin molecule to the GTPase-activating proteins raises the possibility of pharmacologic treatment (eg, farnesyl transferase inhibitors), which might prevent or ameliorate the neoplastic complications of NF1.

Summary

TSC and NF1 are the most common of the neurocutaneous diseases, and both are autosomal dominant with a high spontaneous mutation rate. For diagnosis, two features are necessary for each disease. Skin findings for each are especially helpful for diagnosis, as is neuroimaging in TSC. For NF1, neuroimaging is not yet reliable for diagnosis. In children, brain symptoms cause most of the morbidity in TSC, and nerve sheath and nervous system tumors as well as learning disabilities cause major morbidity in NF1. Renal disease becomes a serious problem for adults with TSC. The TSC1, TSC2, and NF1 genes function as tumor suppressor genes and have other functions that are being investigated. Blood tests for diagnosis have a high false-negative rate. Therapies for TSC and for NF1 are both medical and surgical.

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Neuroradiology of the central nervous system in childhood

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The introduction of clinical magnetic resonance scanners in the late 1970s provided a new window into understanding the CNS. Subsequent refinements in computer hardware, software, and gradient coils led to improved image quality, faster scan times, and advanced capabilities, such as magnetic resonance angiography (MRA), magnetic resonance venography (MRV), magnetic resonance spectroscopy (MRS), diffusion and perfusion imaging, and cortical activation.

Although MRI and advanced magnetic resonance applications provide the backbone for CNS imaging, other techniques such as CT angiography, cranial sonography, and catheter angiography have important roles in the diagnosis and treatment of pediatric CNS disease. In the child with seizures refractory to medical management, nuclear medicine single photon emission computed tomography (SPECT) and positron emission tomography (PET) scans are integral in evaluation and preoperative planning.

The purpose of this article is to familiarize readers with new imaging applications, describe the strengths and weaknesses of medical imaging technology, and emphasize the practical aspects of imaging the pediatric CNS. Because of the advances in MRI, most of this article is devoted to the role of MRI in evaluating children with diseases of the CNS.

Advanced applications of magnetic resonance imaging

Diffusion-weighted magnetic resonance imaging

Diffusion-weighted magnetic resonance imaging (MRI) is a powerful tool for noninvasive neuroimaging. The signal intensity in a diffusion-weighted

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image is a function of the random translational motion of water molecules (Brownian motion). Neurologic conditions that produce cell membrane depolarization, such as acute ischemic stroke, result in cytotoxic edema,one of the underlying mechanisms responsible for diffusion-weighted changes in the brain [1,2]. In cytotoxic edema, the apparent diffusion coefficient (ADC) of water in ischemic tissue is reduced relative to that of normal brain water and allows the ischemic territory to be visualized as a hyperintense region. Water ADC values are also affected by the presence and orientation of biologic barriers to translational water motion, such as cell membranes and myelin fibers [3]. Because diffusion-weighted imaging is mapped to a T2-weighted image, any lesion with a prolonged T2 value may appear hyperintense on diffusion-weighted images. ADC maps reveal an initial restrictive diffusion coefficient within minutes of infarction, and the ADC remains abnormally low for approximately 4 to 6 days. ADC values normalize at 7 to 10 days, but become high after approximately 10 to 14 days [3,4].

Diffusion-weighted imaging has an essential role in the management of acute clinical stroke. Cerebral ischemia arises from a reduction in the brain tissue blood supply because of an obstruction of inflowing arterial blood. When cerebral blood flow falls below a critical threshold, metabolic energy failure disrupts water and electrolyte homeostasis and leads to cytotoxic edema (Fig. 1). A similar perfusion-deficit threshold has been shown to coincide with the onset of ADC changes, and a correlation exists between ADC reduction and cerebral cytotoxic edema [3–5]. Because diffusion-weighted imaging normalizes by 10 to 14 days after infarction, this technique has proven useful for distinguishing recent stroke from remote infarction. The utilization of diffusion-weighted imaging in the neonate, infant, and child provides important insights into such pathologic processes as anoxic ischemic encephalopathy, clinically significant hypoglycemia, status epilepticus, and

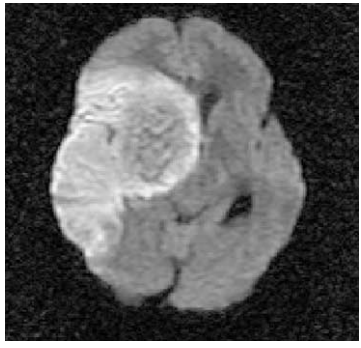

Fig. 1. Diffusion-weighted MRI in a 15-year-old girl with acute lymphocytic leukemia receiving L-asparaginase, who suffered a devastating clinical stroke 10 hours before this scan. Cytotoxic edema is seen as bright signal within the right hemisphere.

neuronal necrosis secondary to encephalitis. In large part, T2-weighted images and fluid attenuated inversion recovery (FLAIR) images have proven to be relatively insensitive in the early detection of these pathologic states. Diffusion-weighted imaging has become an integral part of brain imaging when evaluating the possibility of early infarction and in differentiating early infarction from chronic infarction in children with sickle cell disease, congenital heart disease, bacterial endocarditis, hypercoagulable states, vasculitides, arterial dissection, near drowning, hypoglycemia, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), and other disorders predisposing to stroke [1].

In children with traumatic brain injuries, diffusion-weighted imaging may reveal areas of restricted diffusion secondary to cellular injury. Diffusion restriction may be observed in contusional, hemorrhagic, and penetrating injuries of the brain. Diffusion-weighted imaging has become a particularly powerful tool in detecting superimposed posttraumatic infarction that may be silent on early CT and standard MRI scans of the abused child. Explanations for these diffusion changes after abuse include profound or prolonged hypoxia, hypotension, hypoventilation, seizures, suffocation, strangulation, and cerebral edema [1,2].

Encephalitis, meningitis, vasculitis, and demyelinating diseases may have overlapping clinical and MRI findings. In bacterial meningitis, diffusion-weighted imaging has a role in differentiating reversible processes, such as inflammatory vasogenic edema, from cytotoxic edema, and brain infarctions. In acute disseminated encephalomyelitis (ADEM), most lesions appear isointense to normal brain on diffusion-weighted images, suggesting that the demyelinating process has not caused permanent cell injury [1,2].

In addition to the low ADC values observed in acute stroke and severe hypoglycemia, low ADC values can reflect the presence of viscous material, such as the contents of a brain abscess. Therefore, diffusion-weighted imaging can play a role in the evaluation of a cavitary ring-enhancing lesion, distinguishing abscess from CNS tumor.

Some chemotherapy and transplant-associated medications, such as cyclosporin, are associated with CNS toxicity manifested by T2 hyperintensity on brain MRI (the reversible posterior leukoencephalopathy syndrome). Diffusion-weighted imaging has been helpful in differentiating irreversible or cytotoxic-associated abnormalities from those changes that are likely to be reversible.

Several technical factors and artifacts can compromise diffusion-weighted imaging. Fat has a low ADC value and therefore is bright on diffusion-weighted imaging. Magnetic susceptibility effects, such as those seen with shunt connectors, surgical clips, and dental metallic hardware, can create obstacles to performing clinical diffusion-weighted imaging. Additionally, motion artifacts, such as patient head motion, breathing, and cardiac driven cerebrospinal fluid (CSF) pulsation, can compromise diagnostic information.

Noninvasive vascular imaging: magnetic resonance angiography and magnetic resonance venography

In the diagnostic evaluation of pediatric CNS disease, MRA and MRV represent valuable alternatives to catheter angiography and venography. From a practical standpoint, MRA adds no more than 5 to 7 minutes to the MRI examination. MRA yields information regarding signal from protons in flowing blood. Flow direction, volume, and velocity affect the flow signal and apparent size of the vessel being studied. The MRA techniques most commonly used in the clinical setting of pediatric neuroradiology are time-of-flight (TOF) MRA and phase contrast angiography (PCA) (Fig. 2). TOF techniques take advantage of the differences in signal amplitude between stationary tissue and flowing blood (flow-related enhancement), whereas PCA exploits differences in signal phase between flowing and stationary spins [6].

Physiologic and anatomic factors influence the image quality and interpretation of MRA/MRV studies. Relevant factors include blood flow direction relative to the imaging plane, geometry of the vessel, velocity of flow, complex patterns of flow, and T1 relaxation times of stationary tissue (eg, parenchymal hemorrhage). Maximum flow-related enhancement occurs in

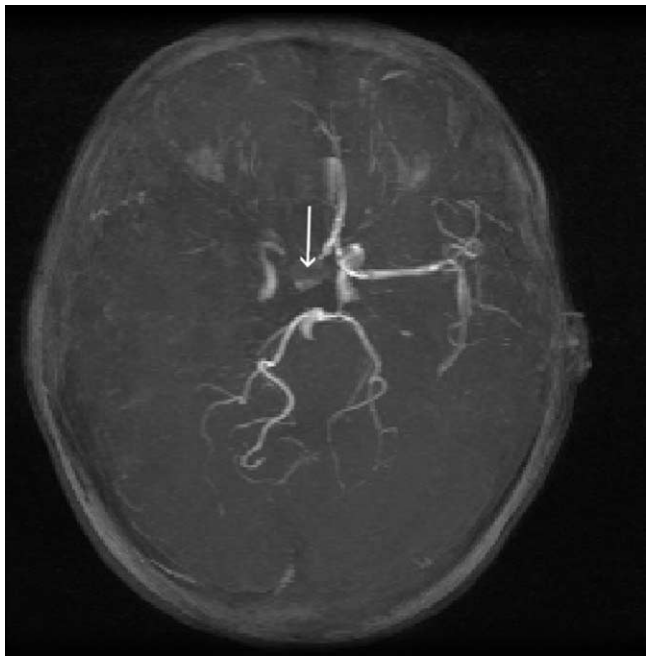

Fig. 2. Three-dimensional time-of-flight magnetic resonance angiography shows occlusion of the right supraclinoid carotid artery (*arrow*).

TOF MRA when blood is flowing perpendicular to the plane of section. An example would be flow within the sagittal sinus detected with coronal MRV. Flow appearing obliquely or parallel to the plane of section results in loss of signal and can suggest vessel narrowing or thrombosis. Vessels that have complex geometry or turbulent flow are subject to areas of signal loss. Another potential pitfall in the interpretation of TOF MRA is the presence of fat or methemoglobin in the region of interest. This can lead to short T1 relaxation times and "shine through" that may mimic pathologic changes. We avoid this pitfall by close scrutiny of the source images or by implementing a phase contrast technique. Because PCA is a true background subtraction technique, it should be used in cases of suspected vessel thrombosis, such as subacute dural venous sinus thrombosis or subacute parenchymal hemorrhage [6].

Both two-dimensional (2D) and three-dimensional (3D) techniques can be applied to TOF and PCA. The 3D techniques are best for high-resolution imaging of small vessels having complex geometry, allowing the arteries to be viewed in multiple oblique projections without a loss in spatial resolution. In 3D techniques, thin nonoverlapping slices (1 mm in thickness) are also used. In 2D TOF and 2D PCA, the slice thickness ranges from 2 to 5 mm and slices are overlapped by approximately 20% to 30%. Using these thicker slices allows coverage of larger anatomic regions, such as the pediatric neck for carotid and vertebral artery assessment [6].

Clinical applications of MRA include investigation of suspected anatomic arterial variants (eg, embryonic basilar-carotid connections), evaluation of unusual vessel turns that may mimic an aneurysm, intracranial vessel relation to tumor (displacement versus encasement), and suspected arteriovenous malformations (Fig. 3). Studying the venous side of the intracranial circulation using MRV is useful in evaluating children with suspected intracranial dural venous thrombosis, evaluation of pseudotumor cerebri, preoperative evaluation of encephalocele, and evaluation of tumors that are juxtaposed to venous structures (Figs. 4 and 5).

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) offers the capability to study brain metabolism in vivo. The relatively short acquisition times make it possible to perform MRS in conjunction with conventional MRI studies even in young sedated children. MRS is proving to be helpful in the diagnostic evaluation and management of pediatric patients with brain tumors, metabolic and heritable disorders, epilepsy, demyelinating disease, hypoxic-ischemic encephalopathy, head trauma, developmental delay, and hypotonia as well as in the evaluation of T2 signal abnormalities in patients with symmetric basal ganglia signal alterations [7,8].

The primary choice in parameters with conventional MRS software is between short and long echo times (TEs). Long TE acquisitions produce

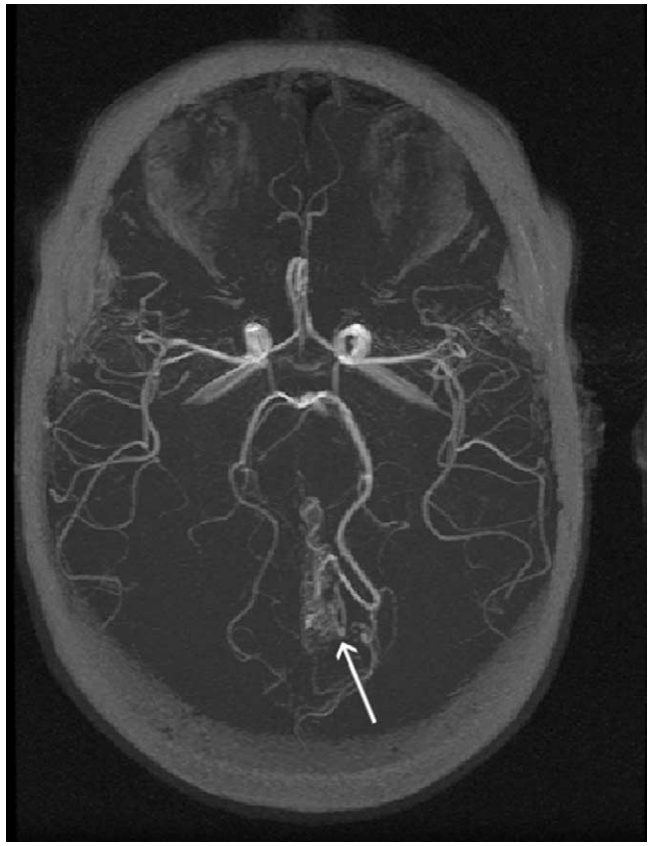

Fig. 3. Three-dimensional time-of-flight magnetic resonance angiography in a 12-year-old girl with headache shows an arteriovenous malformation fed by the left posterior cerebral artery (*arrow*).

spectra that include *N*-acetyl aspartate (NAA), choline (Cho), creatine/phosphocreatine (Cre), and possibly lactate (Lac) peaks. Short TE acquisitions include these same neurometabolites, myoinositol (mI), glutamate (Glu), glutamine (Glx), and possibly alanine (Ala) as well as proteins and lipids.

NAA, which is present in relatively large quantities in the brain, is the largest peak in the normal spectra found at 2.02 ppm. NAA, generally believed to be a neuron-specific metabolite, has also been found in immature oligodendrocytes and astrocyte progenitor cells. Reduced NAA is found early in disorders that cause a decline in the number of neurons, impairment in neuronal metabolism, or replacement of normal neurons. In normal brain development, there is a progressive increase in NAA, particularly in the cerebral gray matter, from a ventral to dorsal direction and from the cerebral hemispheres to the level of the spinal cord (Fig. 6) [9,10].

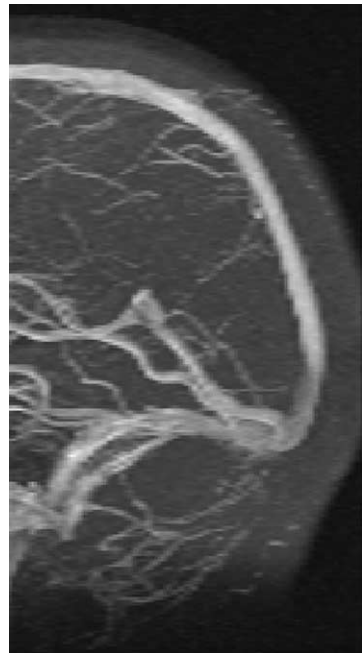

Fig. 4. Normal phase contrast magnetic resonance venography in sagittal projection shows normal flow signal within the sagittal sinus.

Cho, found at 3.2 ppm, primarily represents phospho-/glycerophospho-/phosphatidyl-choline. An elevation in total Cho may reflect increased membrane turnover, such as one might see with cell proliferation secondary to gliosis, cerebral neoplasm, or in the normal actively myelinating infant brain. Cho can also rise with increased membrane breakdown in demyelinating and dysmyelinating disorders. Regional variation in Cho is found between white matter and gray matter [7].

Creatine (Cre) is found at two locations, 3.0 ppm and 3.9 ppm. These peaks, indicate energy stores of the brain, reflecting a combination of Cre and phosphocreatine. There is a relatively high concentration of Cre in the brain with a progressive increase from white matter to gray matter and an increase from the cerebral hemispheres to the cerebellum. The Cre peak is generally accepted as an internal standard of reference [7,9,10].

Lactate is undetectable in the normal spectra. The lactate peak can be visualized, however, in any condition that causes anaerobic glycolysis. This includes energy metabolism disorders, hypoxia, stroke, neoplasms, or seizures. Lactate can be detected in macrophages and therefore may be seen with acute inflammation. Lactate also accumulates in necrotic and infarcted tissue. When present, we note it as a doublet at 1.3 ppm [11,12].

Myoinositol (mI) (at 3.56 ppm) is not present in neurons and may be glia specific, because variations are often linked to myelin formation and myelin

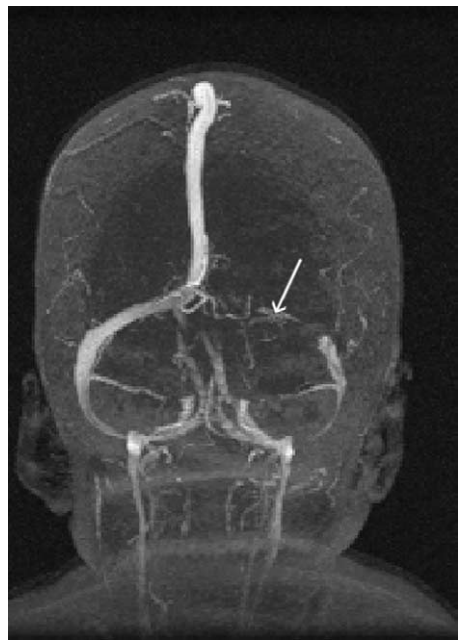

Fig. 5. Coronal phase contrast magnetic resonance venography shows thrombus within the left transverse sinus (*arrow*).

breakdown. This is not surprising, because mI represents a component of the membrane phospholipid. mI, an important osmotic regulator, serves a reserve pool for inositol diphosphate, which acts as a second messenger [13].

Glutamate (Glu), glutamine (Gln), and gamma-amino glutaric acid (GABA), which are generally inseparable at 1.5 T, result in a complex peak seen just to be the left of the NAA peak (between 2.1 and 2.5 ppm). Glu, an excitatory amino acid found in neurons, participates in the regulation of fatty acid synthesis and in the Krebs cycle. Glu also has a role in ammonia regulation but is restricted to the cerebral astrocytes. GABA, a product of Glu, functions as an inhibitory neurotransmitter [12].

Lipids produce peaks at 0.9 to 2.0 ppm, reflecting methyl protons of lipids (macromolecules, methylene protons of neutral lipids, lactate, and cytosolic protein macromolecules). Lipid peaks may be found in the setting of a necrosis, high-grade tumors, meningiomas, myelin breakdown, and certain inborn errors of metabolism.

The developing brain displays variations in the content of certain neurometabolites. The NAA content, low at birth, increases rapidly for the first 2 years of life. Because most neurons form during gestation, the postnatal changes presumably reflect changes in the number and size of neuronal dendrites, the number and complexity of dendritic/axonal connections, and the organization and differentiation of neurons and their connections. Choline

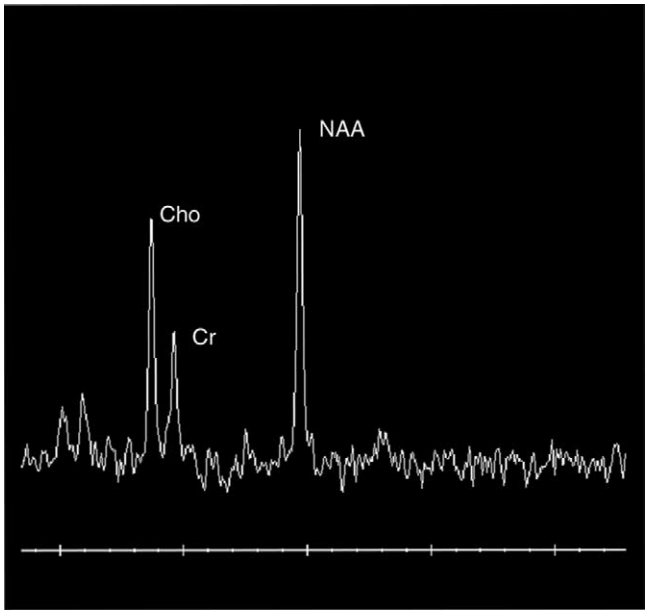

Fig. 6. Normal white matter spectra (magnetic resonance spectroscopy) (echo time = 288) in a 2-year-old boy being evaluated for developmental delay. NAA = *N*-acetyl aspartate; Cr = creatine and phosphocreatine; Cho = choline compounds. X axis = parts per million (ppm).

shows a relative decline in amplitude in the first 2 to 3 years of life, reflecting progressive myelination. Creatine rises to adolescent or young adult levels by approximately 4 months of age. A prominent myoinositol peak is seen at birth but rapidly declines in the first 3 to 4 months, reaching adult levels by the end of the first year [7].

Clinical applications of magnetic resonance spectroscopy

Neoplasms

Considerable interest has been generated regarding the utilization of MRS in the evaluation of intracranial neoplasms. Most studies suggest certain trends, a low NAA/Cre ratio, and an elevated Cho/Cre ratio. Some tumors show elevated lactate and lipids as well. The NAA content is reduced, because the tumor replaces normal neurons or the tumor cells produce lower amounts of NAA than normal neurons. Cre can be reduced if energy stores are reduced by the high metabolic demand of tumor. The Cho content, elevated secondary to increased membrane turnover, rapid tumor cell growth, and proliferation of the tumor, tends to be more prominent in aggressive or anaplastic tumors.

Although lactate can be observed in the setting of cerebral neoplasms, its presence is not predictive of tumor grade. The presence of lactate depends on the level of glycolytic activity. Elevated lipid levels in the context of elevated

lactate are more suggestive of an anaplastic or aggressive tumor. Additional clinical questions that are raised in the context of a cerebral neoplasm include distinguishing residual tumor from postoperative changes, assessing tumor progression from radiation necrosis, determining the nature of an unknown mass (a primary/secondary tumor, infectious lesion, or tumefactive demyelinating disease), and assessing if a lesion is benign or malignant.

MRS can be used to evaluate a cystic brain mass when the considerations include abscess or necrotic tumor. Not only can lactate and lipids be present, but abscesses usually contain products of fermentation and leukocyte lysis, such as acetate and succinate, and amino acids, such as valine and leucine, and products of proteolysis. A number of unknown marker peaks for infection have been described at 2.2, 2.9, 3.2, 3.4, and 3.8 ppm [14,15].

Epilepsy

The preoperative evaluation of children with epilepsy includes analysis of seizure semiology, neuropsychologic testing, video electroencephalographic (EEG) monitoring, MRI, and occasionally SPECT or PET. Accurate localization of a structural abnormality by MRI and MRI results that are concordant with other clinical information increase the likelihood that the child will be seizure-free after epilepsy surgery [16]. PET serves as an alternative screening procedure in patients who have discordant clinical data [34]. PET has a high sensitivity and specificity for identifying seizure foci. The cost, regional localization, and limited availability, however, make PET a somewhat less attractive modality [17,18].

MRS has been shown to be helpful in the lateralization of epileptogenicity in children with suspected mesiotemporal lobe seizures. The MRI features in children with mesiotemporal sclerosis consist of more subtle volume loss and/or signal abnormalities in the hippocampal formations than might be seen in adults. At least one study has shown an advantage in sensitivity in MRS compared with PET, presumably reflecting the enhanced capability of MRS to detect subtle neuronal dysfunction [16,19].

Metabolic diseases and white matter diseases

The MRS findings in leukodystrophies and metabolic disorders are variable. Many of these conditions are associated with a reduction in NAA as a result of neuronal/axonal degeneration and loss of brain parenchyma. Metachromatic leukodystrophy (MLD), a dysmyelinating disorder, has a nonspecific CT and MRI appearance. In addition to showing reductions in NAA, the spectra of children with MLD identify mild increases in lactate, large reductions in Glu, and striking elevations in mI. Myoinositol, a distinguishing finding on MRS in MLD, may actually play a role in the pathophysiology (myelin membrane instability) of the disorder [20]. MRS plays an important role in confirming the diagnosis of Canavan disease; the underlying deficiency in aspartoacylase, and resultant accumulation of NAA leads to striking elevations in the NAA/Cho and NAA/Cre ratios [21].

MRS has been shown to be more sensitive than MRI for detection of abnormal white matter in children with adrenoleukodystrophy (ALD). Consequently, MRS can be used to monitor the progression and efficacy of therapy in these patients. In ALD, MRS shows a reduction in the NAA/Cre ratio; a reduced NAA/Cho ratio; an elevation in the Cho/Cre ratio; and an increase in Glx, mI, and lipids. Lactate may be present as well [8,12].

MRS frequently identifies elevated lactate content in patients with disorders of energy metabolism. Lactate is thought to be an indicator of impaired mitochondrial oxidative metabolism. Some of the disorders in which MRS has been used in this regard include mitochondrial myopathy, MELAS, myoclonus, epilepsy with ragged red fibers (MERFF), Leigh syndrome, and Kearns-Sayre syndrome.

MRS can also be used to detect certain amino acidopathies and to monitor disease activity. The enzyme deficiency in children with maple syrup urine disease causes an accumulation of branch chain amino acids and their 2-oxyacids. The latter can be recognized as a small inverted peak at 0.9 ppm and additional pathologic peaks at 2.4 and 4.2 ppm. In nonketotic hyperglycinemia, a glycine (Gly) peak is detected at 3.55 ppm [8].

Global cerebral insult

There is considerable interest in the application of MRS in the evaluation of neonatal asphyxia, near drowning, and traumatic brain injuries. Although CT answers urgent management questions and MRI provides additional imaging details, neither CT or MRI detects extensive cellular damage that may be evolving. In traumatic brain injuries, the spectrum of MRS findings includes reduced NAA/Cre ratios reflecting neuroaxonal injury; elevated Cho content indicating diffuse axonal injury and membrane turnover; low NAA, Cho, and mI in the setting of inappropriate diuretic hormone secretion (SIADH); and increased Cho, Cre, mI, or NAA in hyperosmolar states after trauma.

The presence of lactate correlates with poor neurologic outcome in children who have experienced perinatal asphyxia or near drowning. Lactate appears in the first 24 hours and persists for at least 48 hours in the setting of asphyxia. If the child or infant is not studied within the first 2 or 3 days after the event, a reduction in the NAA may be a more useful predictor of poor outcome (Fig. 7) [11,22].

Cortical activation (functional MRI) imaging in children

The ability to combine brain function with detailed anatomy is a powerful tool that can be used to understand physiologic changes in the pediatric patient. Activation functional MRI (fMRI) utilizes the blood oxygenation level–dependent (BOLD) technique to examine changes in the oxy-/deoxyhemoglobin ratio after activities designed to stimulate a particular area of the brain. fMRI in children is more challenging than in adults owing to a

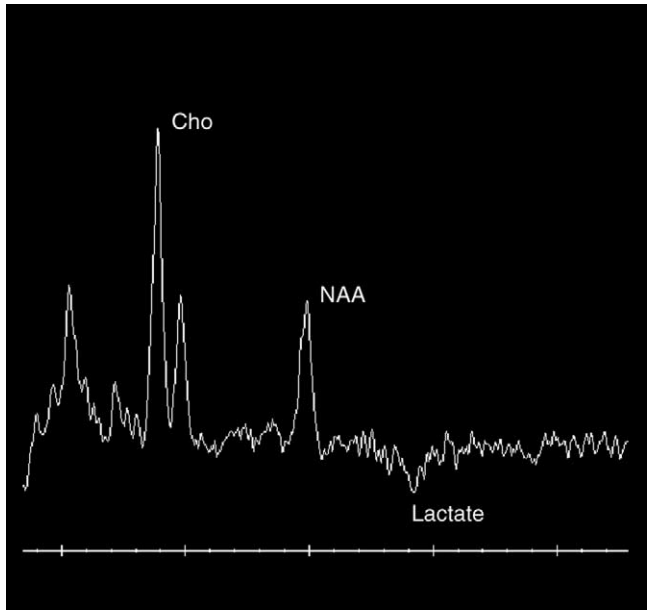

Fig. 7. Intermediate echo time (144) magnetic resonance spectroscopy of the occipital cortex in a 4-year-old boy 4 days out from drowning. There is reduction of *N*-acetyl aspartate, elevation of choline, and the presence of lactate. X axis = parts per million (ppm).

need for cooperation in performing tasks, such as motor and language paradigms. Most of the current paradigms do not allow for sedation, although there are novel techniques to perform fMRI in sedated infants and children [23].

A common indication for fMRI is to noninvasively map functional brain tissue in localized areas of eloquence with respect to pathologic areas of the brain. This has tremendous utility in surgical planning. Finger-thumb opposition can be used to outline the sensorimotor cortex and define displacement of the central sulcus in relation to space-occupying lesions. The utilization of liquid crystal display (LCD) goggles stimulates the visual cortex. Utilization of covert letter and word generation paradigms identifies hemispheric dominance for language before temporal lobectomy in children with intractable complex partial seizures. In selected patients, utilization of a covert word generation technique permits the determination of hemispheric dominance for language; when combined with a memory paradigm, this technique may eliminate the need for more invasive Wada testing in some children before surgery [23,24].

Advanced computerized tomography applications

Conventional CT remains an important clinical tool in the assessment of acute head injury, acute neurologic decline, cranial-facial and cerebral

malformations, investigation of infectious intracranial processes, and the follow-up of patients with CSF diversionary shunts.

Computerized tomography angiography

CT angiography (CTA) is a less invasive alternative to conventional radiographic angiography. There is a wide clinical application of CTA in the adult population for the investigation of head and neck vessels, the aorta, and retroperitoneal arteries and veins. Overall, there is more limited experience with the use of CTA in young children. CTA of the head and neck has an advantage compared with other body locations in that it is not limited by respiratory artifacts; therefore, high-resolution images can be obtained [25].

Indications for CTA in the pediatric population include patients who are not candidates for the MRI environment, such as children with pacemakers or patients who have aneurysms and/or other surgical clips juxtaposed to areas of vascular interest. CTA can also rapidly provide highly detailed information regarding vascular anatomy before surgery, such as in the case of a patient with acute neurologic decline, suspected arterial dissection, or cerebral hematoma, in whom CTA provides a useful presurgical map of vascular anomalies or an aneurysm nidus (Fig. 8) [25].

Advanced ultrasound techniques for pediatric cranial imaging

Transcranial Doppler sonography in children

Transcranial Doppler (TCD) sonography is a noninvasive technique that uses a 2- to 2.5-MHz Doppler transducer to measure the velocity and pulsatility of blood flow within the intracranial arteries of the circle of Willis and the vertebrobasilar system. The clinical indications for TCD in children include evaluating children with various vasculopathies, such as sickle cell disease and moya moya syndrome; evaluating arteriovenous malformations; confirmation of clinical brain death; evaluating children with asphyxia and cerebral edema; monitoring children with hydrocephalus and subdural effusions; evaluating and following patients with vasospasm, especially after subarachnoid hemorrhage; monitoring children during cerebrovascular and cardiovascular interventional and surgical procedures; and investigating migraine headaches [26–28].

Nuclear medicine single photon emission computed tomography/positron emission tomography brain imaging

Functional brain imaging refers to a set of techniques used to derive images reflecting biochemical, physiologic, or electrical properties of the CNS. The most practical of these nuclear medicine techniques are SPECT and PET. Of these two, SPECT may be the more widely available technique.

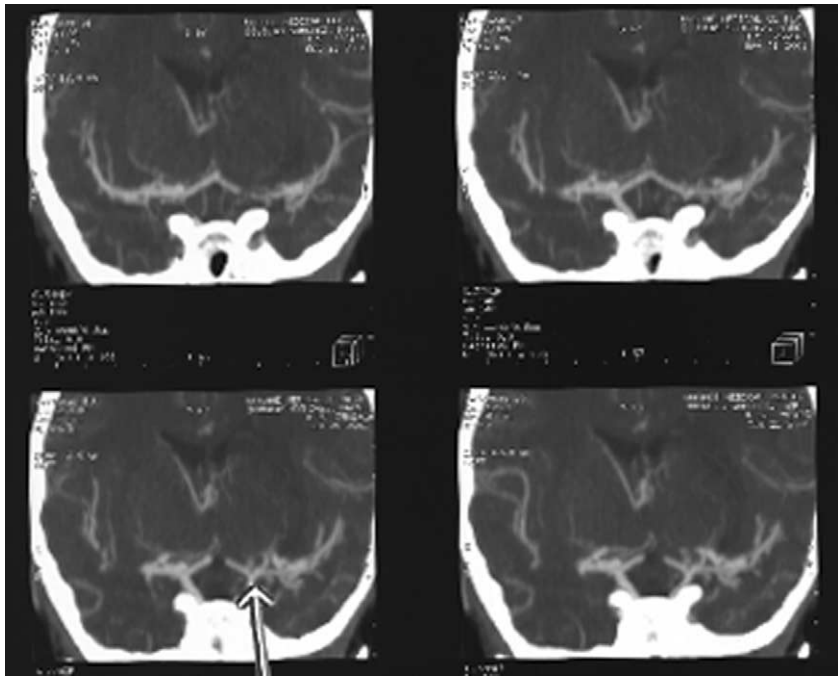

Fig. 8. Coronal CT angiography in a 15-year-old boy with acute onset right hemiplegia after a neck injury shows diminished caliber of the left supraclinoid carotid consistent with nonocclusive dissection (*arrow*).

Although the diversity of radiopharmaceuticals available for brain SPECT is not as great as those for PET, the variety of SPECT tracers is expanding rapidly [29,34].

SPECT tracers, such as Technetium-99m hexamethylpropylene amine oxime (99m Tc-HMPAO), is extracted by brain tissues on the first arterial pass after intravenous injection and is retained within the brain for several hours. Typically, there is symmetric distribution of the radiotracer within both hemispheres. The basal ganglia, occipital cortex, and cerebellum often seem to have slightly increased normal uptake compared with other regions of the brain. Reduced tracer uptake may be seen in association with cerebral ischemia. Conversely, regions of increased radiotracer uptake reflect a hypermetabolic focus, such as one might see with seizure activity or luxury perfusion of the brain [29–31].

PET imaging requires a cyclotron in which an isotope target is bombarded with a beam of protons (hydrogen nuclei stripped of electrons). The most commonly administered PET radionuclide, ^{18}F, is used for the production of ^{18}F-2-deoxy-2-fluor-D-glucose (^{18}FDG). PET imaging has been limited by the availability of cyclotron facilities, cost of instrumentation, and short half-lives of the radioisotope [34].

Both SPECT and PET have become indispensable in evaluation of medically intractable epilepsy. Essential to the success of seizure surgery is the accurate localization of the seizure focus. SPECT/PET imaging can be performed at a seizure-free baseline (interictal) or be performed during a seizure (ictal) (Fig. 9). The choice of options in imaging procedures (SPECT or PET) depends, in part, on the institutional logistics in performing the studies and the stability of the available radiotracers. Tracers that do not have good stability over time or have short half-lives are difficult to prepare and deliver to a convulsing child. During the interictal period, the seizure focus is identified as an area of reduced perfusion/metabolism. Baseline interictal scans can have a normal appearance, however. During a seizure, there is an area of increased perfusion/metabolism identifying the seizure focus [17,18,30–33].

Catheter angiography

Although vascular imaging, such as MRA and MRV, has often supplanted the necessity for catheter angiography in the infant or child with CNS disease, there remain several important indications for catheter angiography. These include the diagnosis, characterization, and follow-up of arteriovenous malformations; the evaluation of nonocclusive arterial dissection

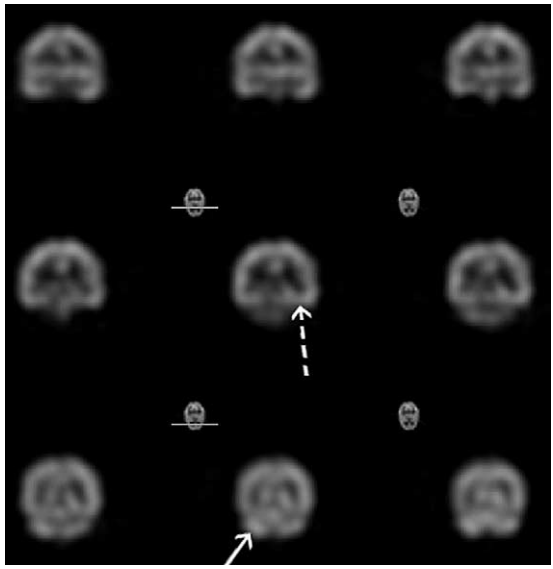

Fig. 9. Ictal Tc-HMPAO (Technetium-99m hexamethylpropylene amine oxime—99m Tc-HMPAO) single photon emission computed tomography scan (coronal images) shows increased tracer uptake in the left temporal lobe (*dashed arrow*) and right cerebellar hemisphere (*solid arrow*) (crossed cerebellar diaschisis).

in the patient with stroke; preoperative evaluation of certain cerebral tumors (eg, meningioma); Wada testing; and inferior petrosal venous sampling in patients with Cushing syndrome and normal pituitary imaging. Major therapeutic applications of CNS catheter angiography/venography include embolization of tumors and clot removal in children with intracranial venous sinus thrombosis. Advances in spiral and 3D angiography have diminished contrast requirements and examination times for catheter cerebral angiography, which, in turn, diminishes the complications of catheter angiography in the pediatric patient.

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HIV-1 infection and AIDS

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The clinical and immunologic features of pediatric AIDS were described in 1983 within a short time after the disease was recognized in adults (homosexual men, injecting drug users [IDUs], and women whose only risk factors were sexual relations with men who were bisexual or IDUs or both) [1–4]. The following year, neurologic involvement was reported in children. A progressive encephalopathy (PE) syndrome was described, as was a more stable neurologic impairment [5,6,47]. It was recognized that by the time HIV-1 had advanced to AIDS, neurologic complications were frequent [6,8–13]. Over the next 10 years, the numbers of persons with AIDS escalated. By the end of the decade, AIDS had reached epidemic proportions. AIDS had become one of the leading causes of childhood morbidity and mortality in this country and worldwide [4].

Since then, much has been learned about the biology of HIV-1 and the cells it infects. Much has been learned about viral transmission and the natural history of HIV-1 infection. Key studies led to a better understanding of maternal-infant transmission and strategies for interrupting transmission, resulting in a significant reduction in vertically transmitted disease. More proficient diagnostic techniques made early diagnosis and identification of HIV-1–infected infants possible during asymptomatic or mildly symptomatic disease stages. Major advances in treatment of primary HIV-1 infection with highly active antiretroviral therapy (HAART) and immunomodulating therapies along with successful prophylaxis for life threatening opportunistic infections (OIs), and more aggressive and successful medical management of HIV-1/AIDS–associated conditions have resulted in prolonged survival of HIV-1–infected persons [14].

In developed countries (and in countries where these therapies are readily available), there has been a dramatic decline in the numbers of infants born

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HIV-1 infected and markedly improved length of survival of those infected [15–20], Children with HIV-1/AIDS are living longer. A significant and increasing percentage of children are surviving into adolescence and young adulthood [15,19,20]. Pediatric HIV-1/AIDS has become a chronic disease. Unfortunately, this is not the case worldwide, where the complexity of medical care required and expensive drug therapies are limited [4,20,21].

The clinical, virologic, and immunologic features of pediatric HIV-1 infection and AIDS have recently been reviewed in the *Pediatric Clinics of North America* [14]. This article covers neurologic disorders. Salient features of pediatric HIV/AIDS (Tables 1–3) (Box 1) and its epidemiology are briefly summarized, because neurologic aspects need to be viewed in the context of this complex and progressive illness, whose epidemiology is diverse and changing, as is the availability of treatment. A list of diagnoses that indicate AIDS is included in the box on this page.

Epidemiology

Now into the third decade of the epidemic, more than 60 million people worldwide are estimated to have been infected with HIV-1. By the end of 1999, 18.8 million people had died of AIDS; and of these persons, 3.8 million were children. HIV/AIDS is now the fourth leading cause of death worldwide [21,22].

A changing epidemic

At the end of 2001, an estimated 40 million persons worldwide were living with HIV/AIDS. Of these persons, 37.2 million were adults and 2.7 million

Table 1
Centers for Disease Control and Prevention pediatric HIV classification (1994)[a]

	Clinical signs/symptoms			
Immunological	N: No	A: Mild	B: Moderate	C: Severe
No evidence of suppression	N1	A1	B1	C1
Evidence of moderate suppression	N2	A2	B2	C2
Severe suppression	N3	A3	B3	C3

[a] Centers for Disease Control and Prevention (CDC) revised classification system for HIV infection of children less than 13 years of age. Initially developed for surveillance purposes, the CDC classification for pediatric AIDS is based on three parameters: (1) infection status, (2) immunological status, and (3) clinical status. Clinical conditions are specified (see Table 3 and Box 1) and pediatric age-related definitions of immune suppression (see Table 2), and more recently, HIV-1 RNA copy numbers (viral markers) are delineated. The scheme reflects the child's disease stage, establishes mutually exclusive categories and is useful for monitoring therapy and assessing disease progression. *From* Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age; official authorized addenda—human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9-CM. MMWR weekly 1994;43: 1–10 [122].

Table 2
Immunological categories[a,b]

	No/μL (%)		
Immune category	<12 months of age	1–5 years	6–12 years
Category 1 No suppression (N1)	≥1500 (≥25%)	≥1000 (≥25%)	≤500 (≥25%)
Category 2 No suppression (N2)	750–1499 (15%–24%)	500 (15%–24%)–999	200–499 (15%–24%)
Category 3 No suppression (N3)	<750 (<15%)	<500 (<15%)	<200 (<15%)

[a] CD4+ T-Lymphocyte Counts: The CD4+ absolute number that identifies a specific level of immunosuppression changes with age. Generally, healthy non HIV-1 infected infants have considerably higher counts than do non-infected adults. The counts slowly decline to adult values by approximately age 6 years. CD4+ T-lymphocyte counts or percentages are used in conjunction with HIV-1 RNA copy numbers [122].

[b] HIV-1 RNA copy numbers: HIV-1 RNA copy numbers in infants and young children differ form those of infected adults. Infants have a prolonged period of high HIV-1 RNA copy numbers, perhaps as a result of the lower efficiency of an immature but developing immune system in containing viral replication, or a greater number of HIV-1–susceptible cells, or both. RNA copy number slowly declines during the first several years after birth, with the most rapid decline occurring during the first year of life. A slower decline continues until about 4 to 5 years of age. High HIV-1 RNA levels [>299,000 copies per milliliter] in infants younger than the age of 12 months appear to correlate with rapid disease progression and death [30]. HIV-1 RNA copy number is used as a guide to initiate, monitor, and change therapy.

were children. During 2001, 3 million HIV-1–infected persons died; approximately 580,000 were children [21]. Of the 5 million people newly infected with HIV-1 during 2001, 1.8 million were women and 800,000 were children; approximately 2000 HIV-1–infected infants were born per day [22]. As grim as these statistics are, the World Health Organization (WHO) indicates that they still underestimate the enormity of the pandemic.

In many parts of the world, most new infections occurred in young adults, with young women of childbearing age being especially vulnerable. The WHO reports a striking diversity of HIV's spread. For example, Eastern Europe and Central Asia are experiencing a fast-growing epidemic, with the number of new HIV infections rising steeply because of IDUs and sexually transmitted infection in young people. An overall adult HIV prevalence of 10% is reported in some sub-Saharan African countries. In contrast, 119 countries of the world have an adult prevalence of less than 1% [22].

Heterosexual HIV-1 transmission predominates in some regions (sub-Saharan Africa, Asia, and the Caribbean) where the male-to-female ratio of infection is approximately 1:1. In Southeast Asia, India, and South Africa, the number of persons infected continues to escalate. The increase in the number of HIV-1–infected women of childbearing age is paralleled by the potential increase in infants born HIV-1 infected [4,22].

Table 3
Pediatric HIV classification: clinical categories[a]

Category N: not symptomatic	Children who have no signs or symptoms considered to be the result of HIV infection or who only have one of the conditions listed in category A
Category A: mild symptomatic	Children with 2 of the following conditions but none of the conditions listed in categories B and C Lymphadenopathy (0.5 cm at more than two sites; bilateral = one site) Hepatomegaly Splenomegaly Dermatitis Parotitis Recurrent or persistent upper respiratory infection, sinusitis, or otitis media
Category B: moderately symptomatic	Children who have symptomatic conditions other than those listed for category A or C that are attributed to HIV infection. Conditions in clinical category B include but are not limited to Anemia (<8 g/dL), neutropenia (<1000/mm), or thrombocytopenia (<100,000/mm) persisting for 30 days Bacterial meningitis, pneumonia, or sepsis (single episode) Candidiasis, oropharyngeal (ie, thrush) persisting for >2 months Cardiomyopathy Cytomegalovirus infection with onset before the age of 1 month Diarrhea, recurrent or chronic Hepatitis HSV stomatitis, recurrent (ie, >2 episodes within 1 year) HSV bronchitis, pneumonitis, or esophagitis with onset before the age of 1 month Herpes zoster (ie, shingles) involving at least two distinct episodes or more than one dermatome Leiomyosarcoma LIP or pulmonary lymphoid hoperplasia complex Nephropathy Nocardiosis Fever lasting >1 month Toxoplasmosis with onset before the age of 1 month Varicella, disseminated (ie, complicated chicken pox)
Category C: severely symptomatic	Children who have any condition listed in the 1987 surveillance case definition for AIDS, with the exception of the LIP (which is a category B condition).

[a] *Modified from* Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR Weekly 1994;43:1–10 [122].

AIDS orphans

The number of infected and uninfected children born to mothers with HIV-1/AIDS who have already or will become ''AIDS orphans'' continues to rise. In the United States alone, there are more than 80,000 uninfected AIDS orphans. Worldwide, an estimated 13 million children less than 15

Box 1. Diagnoses that indicate AIDS

Serious bacterial infections[c], multiple or recurrent
Candidiasis of the trachea, bronchi, or lungs[a]
Candidiasis of the esophagus[a,b]
Coccidioidomycosis, disseminated or extrapulmonary[c]
Cryptococcosis, extrapulmonary[a]
Cryptosporidiosis, chronic intestinal[a]
CMV (other than liver, spleen, nodes) onset at age >1 month[a]
CMV retinitis (with loss of vision)[a,b]
HIV encephalopathy[c]
Chronic herpes simplex virus ulcer (>1 month duration) or pneumonitis or esophagitis onset at >1 month of age[a]
Histoplasmosis, disseminated or extrapulmonary[a]
Isosporiasis, chronic intestinal (>1 month duration)[c]
Kaposi sarcoma[a,b]
Lymphoid interstitial pneumonitis[a,b]
Lymphoma, primary brain[a]
Lymphoma (Burkitt or immunoblastic sarcoma)[c]
Mycobacterium avium complex or *M. kansasii*, disseminated or extrapulmonary[a]
M. tuberculosis or acid-fast infection (species not identified), disseminated or extrapulmonaryc or pulmonary[d]
Pneumonia, recurrent[d]
Pneumocystis carinii pneumonia[a,b]
Progressive multifocal leukoencephalopathy[a]
Toxoplasmosis of brain, onset at age >1 month[a,b]
Wasting syndrome caused by HIV[c]

[a] If indicator disease is diagnosed definitively (eg, biopsy, culture) and there is no other cause of immunodeficiency, laboratory documentation of HIV infection is not required.

[b] Presumptive diagnosis of indicator disease is accepted if there is laboratory evidence of HIV infection (1987 addition).

[c] Requires laboratory evidence of HIV infection (1987 addition).

[d] Requires laboratory evidence of HIV infection (1993 addition; adults and adolescents).

Modified from 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR; Recommendations and reports 1994/43(RR-12).

years of age have lost their mother or both parents to AIDS. Most of these children live in a sub-Saharan African country. The total number of children orphaned by the epidemic is forecasted to more than double by the year 2010 [4,22].

HIV-1 transmission

Mother-to-infant transmission

Mother-to-infant infection (in utero, intrapartum, or postpartum via breast-feeding) accounts for 90% or more of childhood HIV-1 infection, with most perinatal transmission occurring close to the time of or during birth. A 25% rate (range: 16%–45%) of mother-to-infant transmission is estimated from studies conducted in the United States, Europe, Asia, and Africa. Increased transmission risks include low maternal CD4+ counts, high viral loads, advanced HIV-1 disease [AIDS], low vitamin A, placental membrane inflammation, premature rupture of membranes, increased infant exposure to maternal blood, premature delivery, and breast-feeding [16,23,24].

In 1994, zidovudine (ZDV) chemoprophylaxis was documented to reduce perinatal HIV-1 transmission by almost 70% [25]. Antiretroviral therapy was then recommended for HIV-1–infected pregnant women [20]. In developed countries, this resulted in a dramatic decline in the rate of mother-to-infant transmission. The estimated number of pediatric AIDS cases diagnosed each year among children in the United States declined consistently, from a peak of 949 in 1992 to 105 in 2000 [26]. Different antiretroviral agents and combinations continue to be studied in clinical trials.

Worldwide, unfortunately, this has not been the case, and it is worldwide where the epidemic predominates. Heretofore, access to these medications has been limited [4,16,22]. Trials of shorter courses of orally administered antiretroviral agents, now in progress, in developing countries are promising, and continued clinical trials are ongoing.

HIV-1 transmission infection through breast-feeding continues to be a significant concern, because the rates of infection from breast-feeding (estimated at $\sim$15%) may offset the benefits of treatment during pregnancy and the perinatal period [16,21]. This is a major problem in some developing countries, where safe alternatives to breast-feeding (access to formula milk powder, clean water, and sanitation) are lacking.

Blood/blood product transfusion or contaminated injection equipment

Iatrogenic viral transmission through blood/blood product transfusion or reuse of contaminated injection equipment occurred in the early years of the epidemic before HIV-1 blood donor screening and is no longer a major problem [21]. Viral transmission in IDUs who are adolescents, however, remains a major concern in this country and worldwide [22,27].

Sexual transmission

Of the 5 million new HIV-1 infections in 2001, 50% were in the 15- to 24-year-old age group. HIV-1/AIDS prevalence among this age group is 11.8 million (7.3 million girls, 4.5 million boys). Injection drug use and sexual

exposure were the most common risk factors [22]. Behavioral and educational interventions continue to be explored and instituted [28].

A recently acknowledged and major issue is sexual abuse of children and adolescents (in the home and community and commercial sexual exploitation) [21]. Most sex industry children are 13- to 18-year-old girls. It is unknown how many child sex workers there are in the world because of the clandestine nature of this multibillion dollar world industry. In India, for example, approximately 20% of the 2 million sex workers are less than 15 years of age and 50% are less than 18 years of age. In Cambodia, 30% of sex workers ranging from 13 to 19 years of age are HIV-1 infected [22].

Pediatric HIV-1/AIDS

Natural history

Vertically acquired HIV-1 infection occurs at a time when the immune and nervous systems are immature. The viral load of untreated infants is high and persistent, estimated at a median of 700,000 copies, and can stay this high for approximately 2 years [29,30]. In contrast, the initial viral load in untreated initially infected adults is approximately 600,000 copies; by 8 to 12 weeks after the initial infection, this decreases significantly as a result of the host immune response [31]. The adverse effects of the virus on the developing nervous and immune systems often result in more rapid onset of clinical symptoms and progression to death. Before the widespread use of antiretroviral agents, a bimodal evolution of symptomatic HIV-1 disease and rate of survival was observed [14,33,34]. Approximately 20% of infants developed clinical and immunologic manifestations of AIDS within the first years of life (rapid progressors). These infants often had high levels of detectable virus at birth and died of AIDS-related complications between 1 and 4 years of age. Not infrequently ''HIV/AIDS'' encephalopathy was the presenting AIDS indicator condition, estimated in up to 67% of infants with AIDS [34–36,134]. The second group of children had a less rapid form of the disease (slow progressors). Approximately 75% of these children survived to the age of 5 years, with 40% to 50% progressing to AIDS or death by the age of 6 years and a mean survival time of 9 to 10 years of age [36]. Higher mortality rates of HIV-1–infected children were reported from developing geographic areas such as Africa (45%–50% of infected children died by the age of 2 years, and 62% to 66% died by the age of 3 years) [20,23,37]. In reality, a trimodal evolution exists, with the third ''hump'' (albeit the smallest) occurring in the preadolescent and adolescent years [33,38–41]. As in adults, latency to onset of moderately symptomatic disease in this group may be 10 years or more. What factors underlie the difference between these groups remains unclear but may relate to timing of HIV-1 infection (gestation versus parturition), stage of maternal HIV-1 disease during pregnancy and delivery (maternal viremia), neonate viral load, virulence of the infecting virus, and as yet undefined host-related factors [29].

Pediatric HIV-1 infection in the highly active antiretroviral therapy era

HIV-1 infection can now be diagnosed by the polymerase chain reaction (PCR) in most infants by the age of 1 month and in almost all infants by the age of 6 months [42,43]. Early identification enables early institution of prophylactic therapy for OIs (namely, *Pneumocystis carinii* pneumonia [PCP]) and early antiretroviral treatment of primary infection [42,44]. Clinical studies charting the course of children born after 1995 are in progress. Results to date show AIDS-free survival to be significantly longer for these children than for those born before 1995. For those children born before 1994 who survived to that time, HAART therapy has been shown to stabilize disease and delay progression to AIDS [15,18–20,30].

Neurologic disorders

Neurologic disorders associated with HIV-1 infection can occur during every disease stage. Certain complications and syndromes characteristically occur with greater frequency during certain disease stages. HIV-1/AIDS neurologic disorders can be classified as those caused by (1) primary HIV-1 infection (eg, HIV-1/AIDS encephalopathy), (2) secondarily by complications of immunosuppression (infections, neoplasms, and strokes), (3) complications of systemic HIV-1 disease (metabolic and endocrinologic derangements associated with systemic HIV-1–related disorders and its therapies), and (4) toxic/metabolic complications of antiretroviral and antimicrobial therapies [9,45,46]. These conditions are not mutually exclusive; coexisting pathologic conditions can exist.

The diagnosis of an HIV-1 neurologic disorder requires the skill of a neurologist, a careful medical and developmental history, an HIV-1 systemic disease history, assessment of current immunologic and virologic status, a medication history, neurologic examination, neuroimaging studies, and neuropsychologic assessment [47]. Neuropsychologic evaluation determines the child's cognitive abilities, characterizes domains of strengths and weaknesses, and tracks progressive dysfunction (should this occur) as well as response to therapy.

In the era of HAART therapy, HIV-1/AIDS encephalopathy is an infrequent and often treatable complication that seems to respond well to effective antiretroviral control (see section on changing neuroepidemiology). Central nervous system (CNS) complications of immunodeficiency and AIDS-related conditions are also less frequent because therapy has effectively delayed advanced HIV-1 disease, profound immunodeficiency, and AIDS-related systemic conditions [44].

It is not known whether HIV-1/AIDS–associated CNS disease manifestations differ, should they develop, in children exposed perinatally to antire troviral agents and subsequently treated with HAART regimens. It is possible that early signs may be subtle; may not at first be apparent on

motor examination; and may present as changes in behavior, mood, or cognition.

HIV-1/AIDS–associated central nervous system disease

Progressive encephalopathy

HIV-1/AIDS–associated PE childhood, like its adult counterpart (AIDS dementia complex [ADC]) [48,85], is a syndrome complex with cognitive, motor, and behavioral features linked to primary HIV-1 CNS infection [48]. Cognitive impairment, acquired microcephaly, and progressive corticospinal tract (CST) signs are the hallmark manifestations [5,6,8,9,11,48]. Rigidity (superimposed on spasticity) and cerebellar signs may also develop [8,10]. Mood and behavioral problems are common [8,10,49]. Associated neuroimaging features are listed in Table 4. PE usually develops in children with advanced HIV-1 disease and is associated with a poor long-term outcome [35,36,49–53].

The neurologic course is variable from individual to individual [5,9,10]. Progression in some infants is rapid, resulting in quadriparesis and severe cognitive impairment within months of onset, whereas other children have a stepwise course with periods of decline followed by relatively stable periods, which may or may not be followed by further deterioration. Cognitive and motor impairment can also be discordant. Some young children develop disabling motor deficits yet maintain relatively stable (albeit impaired) cognitive function, whereas other children have more impaired cognitive than motor function [5–10,13,45,47,49,50].

Table 4
Neuroimaging features and findings

Magnetic resonance imaging computerized tomography (MRI CT)
Cerebral atrophy
Serial studies often show progressive atrophy
Basal ganglia calcification
Serial CT studies may show progressive calcification ± frontal white matter calcification
White matter
Serial studies often show progressive patchy or diffuse periventricular white matter changes
CT: hypodensity-rarefaction
MRI: abnormal high signal on T2-weighted images
A correlation appears to exist between progressive changes and severity of "encephalopathy," cognitive dysfunction and behavioral changes [5,8–11,32,45,50,123–126].
MR spectroscopy (MRS)
Basal Ganglia/White Matter (Centrum Semiovale)
Decreased N-acetyl aspartate, (NAA)
Increased choline (cho) and myo–inositol
MRS offers a potentially valuable *in vivo* approach to study dynamic metabolic changes at different stages of HIV-1 associated CNS disease and may be useful in evaluation of disease progression and response to therapy [127–131,137,138].

Signs of CNS disease manifest according to age of onset [47]. Motor involvement is usually more prominent in younger children than in school-aged children. Newborns are usually well at birth with no recognizable neurologic features of HIV-1–associated CNS disease, although a slightly smaller than anticipated head circumference may be seen [55]. It is during infancy, however, that the most easily recognized and devastating PE syndrome occurs. Characteristic features are (1) progressive CST signs with loss of previously acquired motor milestones or a markedly deviant rate of attaining motor skills, (2) decline in mental development or marked "delays" in cognitive development, and (3) acquired microcephaly. A less severe CNS syndrome occurring within the first 2 years of life manifests as hypotonia with delays in attainment of motor milestones associated frequently with delays in acquisition of language [10,13,54].

A change of gait is often the first sign of HIV-1 CNS disease in toddlers and young children. They begin to toe walk, are hyperreflexic, and develop spasticity. The rate of progression is variable. Some children are wheelchair bound within months, others require orthotics, and others maintain independent ambulation, although they have a spastic gait. Impairment of fine motor skills and dexterity is common as are cognitive deficits ranging from mild mental retardation to low average or "borderline" intelligence [5,8–10,45,47,50].

Behavioral changes, loss of interest in school performance, decreased attention, declining cognitive abilities, psychomotor slowing, decreased verbal output, emotional lability, social withdrawal, and, more rarely, psychotic manifestations are reported in school-aged children. Hyperreflexia, clumsiness, and poor fine motor ability and dexterity usually ensue. Progressive CST signs, movement disorders, cerebellar signs, and myelopathy may arise as disease advances, as does cognitive decline. At end stage, the child is apathetic and abulic [8–10,45,47,49].

Neurodevelopmental status

The frequency of developmental problems is high, as noted in the initial descriptions of children with HIV/AIDS and subsequently corroborated by other studies [10,13,47,50,51,54–58]. Almost half of the antiretroviral-naive symptomatic children entered in one study had deviant development (involving motor function [23%], reflexes [21%], and behavior [13%]). Almost 50% of the children in the youngest age group had motor dysfunction, and 21% of the cohort had cognitive deficiencies, again, with the highest percentages in the youngest age groups (3–12 months [33.7%], >12–30 months [19%], >30 months to 6 years [21%]) [59]. At follow-up, those children with the lowest IQ scores and those with motor dysfunction had the highest risk for disease progression [52].

It also must be kept in mind that neurodevelopmental status can be affected by non-HIV-1–related comorbid conditions, which, unfortunately, occur with significant frequency in this population (eg, those related to

maternal high-risk factors during pregnancy, premature birth, complications in the neonatal period, and innumerable postnatal psychosocial stressors) [10,45,50,51,54–58].

HIV-1–associated minor motor and cognitive impairment

Minor motor impairment, with or without cognitive deficits, remains a frequent finding in school-aged children, many of whom had delays in motor and language development as infants [13,47,49]. The term denotes minor degrees of cognitive and motor impairment that are not sufficient for the diagnosis of PE. Manifestations include mild clumsiness and learning disabilities. Although composite IQ scores range from average, low average, and borderline to mild mental retardation, selective deficits in visual-spatial and organizational skills, cognitive flexibility, and expressive language problems are reported [49,58,60–67]. This suggests that HIV-1 may compromise many aspects of cognitive and motor development and results in a mild but stable encephalopathy [9,10].

Neuropsychiatric problems

Psychosis. Acute psychosis, confusion, agitation, delirium, mania, and catatonia can occur in advanced HIV-1 disease. Changes in mental status may be caused by HIV-1 CNS disease, complications of CNS OIs (eg, cytomegalovirus [CMV] encephalitis), nutritional deficiencies, or toxic effects of antiretroviral and other therapies [49].

Mood, affect, and depression. Emotional lability, mood swings, agitation, new onset of extreme impulsiveness, and attention problems can occur [8,9,49]. Other children may show flattened affect, lack of social responsiveness, withdrawal, and declining interest in the environment. HIV-1–associated CNS disease can cause or contribute to an ''organic'' depression, as can coexisting HIV-1/AIDS conditions (eg, endocrinologic and metabolic disturbances). Chronic disease, frequent hospitalizations, illness and death of family members, changing caretakers, psychosocial stressors, and stigmata attached to HIV disease itself may also lead to major depression and other behavioral or affective changes.

Changing neuroepidemiology

The incidence and prevalence of pediatric HIV-1/AIDS PE has significantly decreased in the past several years. Whereas a 16% to 30% incidence of pediatric HIV-1/AIDS PE had been reported from various cohort studies conducted in the first decades of the epidemic [47], a recent report estimated a yearly incidence (January 2000–January 2001) of 4% and an overall prevalence of 10% [68].

Neuroepidemiologic changes can be attributed to (1) an overall decline in the numbers of infants born HIV-1 infected, and thus in the actual numbers of infants with potentially rapidly progressive disease and PE; (2) early identification and treatment of those infants born HIV-1 infected, resulting in delay of advanced disease; and (3) HAART therapy for those children who have survived, with stabilization of disease, delay of disease progression, and reduced risk of developing PE [16,18–20,24,30,43,53,65].

Neuropathology of HIV-1–associated central nervous system disease

HIV-1

The etiologic agent was isolated in 1983 [69,70], demonstrated in the CNS shortly thereafter [72–76], and named human immunodeficiency virus in 1986 [77]. HIV-1 belongs to the Lentivirinae subfamily of nononcogenic cytopathic retroviruses [77,78]. A subfamily well recognized to cause neurologic disease, lentiviruses are species specific, have long periods of clinical latency and mechanisms to evade immune clearance, cause persistent infection and multisystem disease, and characteristically invade the CNS soon after primary infection [78].

Retroviruses are enveloped RNA viruses that use reverse transcriptase (RT) to transcribe virion RNA into linear double-stranded DNA with subsequent integration into the host genome. They are approximately 100 nm in diameter and have two single strands of RNA, which permits recombination between the strands (and potential for great genetic diversity). The genome is 10 kilobases in size and contains three major structural genes, *gag, pol, and env*, as well as extra genes that are essential to viral replication. The retroviral life cycle involves two forms, a DNA provirus and an RNA-containing infectious virion. Retroviruses have the advantage of latency because they have a DNA intermediate in their replication cycle and because the DNA provirus is integrated into the chromosomal DNA. Additionally, HIV-1 is a CD4+ T-cell and macrophage-tropic virus and has the advantage of reducing the effectiveness of host immune attacks [46].

Neuropathologic findings

Neuropathologic features of HIV-1/AIDS encephalopathy are listed in the Box 2. HIV-1 is localized in macrophages, microglia, and multinucleated giant cells found predominantly in the basal ganglia, subthalamic nucleus, substantia nigra, dentate nucleus, and white matter (HIV-1 is highly neurotropic but not neuronotropic) [46,75,79–82,136,139]. These cells express both CD4+ and β-chemokine receptors (eg, CCR5 and CXCR4), which permit HIV-1 entry and mediate fusion with macrophage tropic strains. It is these cells that support productive retroviral infection. HIV-1 has also been demonstrated in endothelial cells and glial cells (although glial cell infection is thought to be a nonproductive infection) [7]. In adults, high levels of HIV-1 mRNA and expression of viral proteins in microglia and macrophages seem to correlate with the severity of clinical disease [46,67,83,84].

Box 2. Neuropathological features and findings

Gross brain studies
- Cerebral atrophy
  - Ventricular enlargement; widening of sulci; attenuation of deep cerebral white matter

Microscopic studies
- HIV-1 encephalitis
  - Foci of inflammatory cells, microglia, macrophages, multinucleated giant cells
- HIV-1 leukoencephalopathy
  - Diffuse staining pallor of myelin; diffuse damage to white matter; myelin loss, reactive astrogliosis; multinucleated giant cells, macrophages
- HIV-1 poliodystrophy
- Calcific vasculopathy
  - Mineralization detected in walls of vessels, basal ganglia, and white matter
    - white matter changes and gliosis are common
    - may have associated HIV encephalitis
    - most characteristic neuropathologic finding in infants and children

Spinal cord studies
- Corticospinal tract pathologic findings: striking myelin pallor restricted to the corticospinal tracts
  - ''Axonopathy type''
  - ''Myelinopathy type''
- Myelitis
- Vacuolar myelopathy: older children

Data from [5,8,9,12,79,94–97,102,132,133,135].

Neuropathophysiologic mechanisms

The mechanisms underlying HIV-1–associated CNS disease are not fully understood and are the focus of ongoing research. Processes possibly contributing to the pathophysiology include toxicity of HIV proteins; macrophage factors; locally synthesized cytokines; and viral- and host-related factors [83].

HIV-1–infected macrophages/monocytes in blood are thought to be recruited to the brain by upregulation of chemoattractant chemokines and adhesion molecules on endothelial cells, enabling transendothelial migration of these cells into the CNS compartment. Activated macrophages release multiple proinflammatory cytokines as well as other factors that may impair

Box 3. Possible factors in the pathogenesis of HIV-1–associated central nervous system disease

Viral proteins
- Blocking of transmitters
- Interference with neurotrophic factors and cell function
- Toxicity of viral polypeptide

Cytokines
- Direct toxicity
- Neuroimmune-mediated central nervous system dysfunction and injury
- Stimulation of astrocytes

Excitotoxin

Toxicity of other soluble factors

Autoimmunity
- Molecular mimicry
- Immune response to HIV-1 antigens
- T-cell deregulation

Increased HIV-1 viral load in central nervous system
- Transactivation
- Cytokine induced
- Emergence of neurovirulent strains

Host factors

Data from Johnson RT, McArthur JC, Narayan O. The neurobiology of human immunodeficiency virus infections. FASEB J 1988;2:2970–2981, [78].

neuronal and glial function, interfere with the release of neurotransmitters, and alter synaptic transmission [46]. The current consensus is of a cytokine-mediated cascade leading to neuronal dysfunction [21] and ultimately to a neurodegenerative pathway [83]. Excitotoxicity (chronic hyperactivation of excitatory amino acid pathways) may also contribute to neuronal injury via *N*-methyl-D-aspartate receptor activation and calcium influx [84].

Neuropathologic findings and the developing brain

In adults, HIV-1 infection occurs in a fully developed organism. In contrast, vertically transmitted HIV-1 infection occurs in an immature developing organism. HIV-1–associated dementia (formally referred to as ADC-AIDS dementia complex) arises in a mature and completely myelinated nervous system and in a fully developed CNS immune system [48]. Although HIV-1 invades the CNS soon after primary infection in both adults [71,73] and children [86–89], signs of CNS disease in adults, adolescents, and older children usually do not occur until the disease is in an advanced stage, when the patient is severely immunosuppressed. In contrast, in some infants

and young children, AIDS encephalopathy is frequently the AIDS-defining illness, even at a time when the infant is not severely immunosuppressed [35,36]. The late fetal and postnatal periods of brain development are a dynamic time characterized by elaboration of dendritic and axonal ramifications, establishment of synaptic contacts, selective elimination of neuronal processes and synapses, programmed cell death, and proliferation of glia and myelination [90]. Astrocytes perform a myriad of complex and vital functions, including neuroendocrine, nutritive, and supportive functions in relation to neuronal homeostasis as well as in the reaction to metabolic and structural insults [90]. Many of these developmental events are controlled, in part, by amino acid transmitters (as well as other trophic factors), which are reflected in receptor ontogeny. In the early postnatal period, there is overexpression of receptors in some regions (eg, glutamate receptors in the basal ganglia and thalamus). In the immature brain, it is these regions that seem to be especially vulnerable to various perturbations and insults [90,91]. Perturbations in these and other developmental processes may lead to disturbances in proliferation, myelination, neuronal function, and even cell death [90,91]. The maturational stage of the nervous and immune systems at the time of viral exposure may explain differences in the effects of HIV-1 in infants versus adults, may account for age-specific vulnerabilities, and may contribute to age-of-onset differences in clinical manifestations and progression [10,92,93].

Impaired brain growth, manifested as acquired microcephaly, is a characteristic finding. A significant reduction in brain weight and volume of cortical regions, subcortical gray matter, and cerebral white matter is seen at autopsy [94–97]. There are no gross or microscopic malformations, evidence of impaired neurogenesis, or disordered neuronal migration (although as in adult neuropathologic studies [98], neuronal loss and damage to the dendritic arbor are observed in some cases) [95]. HIV-1 infection of the immature brain may affect brain cell proliferation and account, in part, for acquired microcephaly [53,94]. It is also tempting to speculate that interference with synaptogenesis could partly explain developmental delays and cognitive impairment. Factors like CNS viral load, viral strain differences, and evolution of neurotropic and neurovirulent strains as well as mechanisms underlying viral protein and cytokine-mediated effects and toxicities and as yet undefined viral–host interactions may affect the disease course and outcome, however [47]. These issues are the focus of continued investigations.

Secondary central nervous system complications

As the name of the disease implies, AIDS ultimately culminates in the development of profound immunosuppression [14]. The child becomes susceptible to infections, neoplasms, and cerebrovascular complications. Manifestations include the new onset of mental status changes, headache, seizures, or focal neurologic deficits [10].

CNS infections

CNS infections caused by common pathogens and OIs develop the latter especially in advanced disease when the child is immunosuppressed (Box 3). Before HAART therapy, CMV encephalitis and *Candida albican*s meningitis and microabscesses were the most commonly identified organisms. Congenital CNS infections (eg, toxoplasmosis, CMV) were described infrequently, as was measles encephalitis. Reactivation of previously acquired infection (eg, toxoplasmosis, herpes simplex virus [HSV], varicella zoster virus [VZV]), as in adults, did occur in children with advanced disease, as did progressive multifocal leukoencephalopathy (PML), an almost unheard of complication of immunosuppressed children before the HIV/AIDS epidemic [9,94,99–109].

Neoplasms

Primary CNS lymphoma (PCNSL) and systemic lymphoma metastatic to the CNS were the most frequently reported neoplasms and occurred in immunodeficient children with advanced disease [9,94,110–112]. PCNSL, an aggressive B-cell tumor considered to be part of the spectrum of B-cell proliferative disorders associated with pediatric HIV-1/AIDS, is related to Epstein-Barr virus. PCNSL, the most frequent cause of mass lesions in pediatric AIDS, can occur as a single mass lesion or as multicentric lesions [9,110,111]. CT characteristics include hyperdense or isodense mass lesions with variable contrast enhancement; diffusely infiltrating contrast-enhancing lesions; or periventricular contrasting lesions. The basal ganglia, corpus callosum, and periventricular white matter are the most common locations. Definitive diagnosis is made by biopsy, although magnetic resonance spectroscopy (MRS) studies may be able to differentiate lymphoma from other lesions. Reduction in tumor size is achievable with radiation therapy [112]; however, long-term survival rates are grim because of tumor recurrence as well as advancing HIV-1 disease. Patients most often succumb to other AIDS-related illnesses, OIs, or both.

Cerebrovascular complications

Cerebrovascular complications include intracerebral hemorrhage and infarction. Clinical presentation is variable, reflecting the severity and location of the hemorrhage. Strokes may be catastrophic and fatal or clinically silent [9,113].

Intracerebral hemorrhage occurs in the setting of immune-mediated thrombocytopenia, as subarachnoid hemorrhage associated with aneurysmal arteriopathy of major cerebral arteries, or as hemorrhage into tumor [113].

Infarctions are associated with pathologic changes of cerebral blood vessels, meningeal infections, or cardiomyopathy or coagulopathies [94,113]. Cerebral vascular ectasia and aneurysmal arteriopathy of major cerebral arteries and thrombosis of these arteries or of small cortical vessels are

reported [9,81,94,113–115]. Fusiform aneurysmal dilation of the branch vessels of the circle of Willis (diffuse and fusiform or focal and saccular) is an increasingly recognized complication of pediatric AIDS (and has occurred in children who were not severely immunosuppressed) [114,115]. The mechanism by which HIV-1 causes CNS arterial damage is unclear. Gp41-positive cells in arterial walls and positive macrophage markers of leukocyte common antigen (but not endothelial markers) have been demonstrated with immunohistochemical staining, suggesting that HIV-1 may be directly involved in vascular pathologic changes (possible direct HIV endothelial invasion and exposure to toxic cytokines) [81]. An underlying VZV vasculitis is also hypothesized, however. A fibrosing inflammatory vasculopathy is described as well and thought to be related to primary HIV-1 CNS infection [94,113]. Pathologic examination shows sclerotic vessels with obliterated or markedly stenosed lumens. A subacute necrotizing encephalopathy with cystic encephalomalacia seems to be associated with dilated cardiomyopathy and may be related to an acquired mitochondrial cytopathy or hypoxic-ischemic damage [94]. Multiple ischemic infarcts may also result from leptomeningitis associated with infectious etiologies such as VZV, *Mycobacterium tuberculosis*, and *Treponema pallidum*) [47,101,116].

Peripheral nervous system involvement

Distal sensory or sensorimotor axonal neuropathy (DSP) described by children as pain and burning in the feet and legs, demyelinating neuropathy, lumbosacral polyneuropathy, mononeuritis multiplex, inflammatory polyneuropathy, median nerve compression at the carpal tunnel, and neuropathy related to antiretroviral therapy are described, although far less frequently than in adults. Similar to the case in adults, however, DSP and CMV polyneuropathy occur in the setting of advanced HIV-1 disease (and HIV-1 CNS disease) and peripheral neuropathy occurs as a toxicity of antiretroviral therapy [42,117,118].

Management and therapy

Management of the HIV-infected child continues to evolve and is increasingly complex [14,42,44]. Greater understanding of the biology of HIV-1, factors related to viral entry, viral–host interaction, rates of viral production, associated fluctuations and progressive T-cell depletion, emergence of viral variants, viral distribution in different cellular compartments, and issues of latency have led to changes in therapeutic strategies, and these studies are ongoing [29]. Therapeutic strategies have expanded greatly from treatment with a single drug to combination therapy that includes up to three different classes of antiretroviral agents [29,30,42,44]. Early initiation of this combination therapy to target specific components unique to the

virus is currently recommended to suppress HIV-1 replication without disruption of normal cellular function, preserve immune function, and reduce the development of resistant organisms [30].

Whenever possible, a team approach supervised by an expert in this field is recommended [44]. The mainstays of HIV-1 management include early identification of the HIV-1–infected infant, antiretroviral therapy targeted to the retrovirus, prophylaxis and treatment of OIs, and management of HIV/AIDS–related conditions. Guidelines for management and therapy, with updates, are provided by the US Department of Health and Human Services Panel of Clinical Practices for Treatment of HIV Infection (USDPH) [42]. In parallel are habilitation/rehabilitation programs as well as attention to pain management, psychosocial stressors, and quality of life.

Antiretroviral agents

As of February 2001, there were 11 antiretroviral drugs approved for use in HIV-1–infected children and 15 approved for use in adolescents. These drugs fall into three major classes, nucleoside analogue reverse transcriptase inhibitors (NRTIs), nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (Table 5). NRTIs and NNRTIs act at the early stage of viral replication, and inhibitors of viral protease work in the later stage after viral integration [30,42].

Some potential neurologic complications are listed in Box 4. Detailed pediatric antiretroviral drug information, mechanisms of action, and toxicities are detailed and updated by the USDPH [42]. Nucleoside analogue drugs can induce mitochondrial dysfunction because of their affinity for mitochondrial gamma DNS polymerase and interfere with mitochondrial replication. This can result in mitochondrial DNA depletion and dysfunction. In vitro studies show the relative potency is highest for didoxycytidine (ddC), followed by didanosine (ddI), stavudine (d4T), lamivudine (3TC), ZVD, and Abacavir (ABC). Toxicity related to mitochondrial dysfunction is reported in patients receiving long-term treatment with these agents. In general, resolution occurs with discontinuation of the drug(s). A possible genetic susceptibility to these toxicities is suggested [42].

New classes of antiretroviral drugs are being studied (eg, fusion inhibitors that inhibit viral binding or fusion to host target cells). In addition to antiretroviral drugs, cytokine blockers, calcium channel blockers, antioxidants, and immunomodulating agents are being evaluated [42]. Vaccine development is ongoing [119].

The time to initiate therapy for asymptomatic children, the time to consider a ''drug holiday'' for children with undetectable viral titers, and when to change therapy and to which regimen for symptomatic children who have evidence of virologic, immunologic, or clinical disease progression or toxicity or intolerance or adherence to their current drug regimen continue to be investigated [42].

Management for HIV-1/AIDS–associated neurologic disorders

HIV-1–associated progressive encephalopathy

HIV-1/AIDS PE should be treated with at least one antiretroviral agent with substantial CNS penetration (CSF-to-plasma ratios >0.2 [eg, ZVD or Neverapine (NVP)]). HAART therapy has been shown to stabilize disease and to reverse HIV-1–associated CNS signs in some children when treated in the early stage [42,44].

Neurobehavioral complications

Psychosis

Acute psychotic episodes respond to neuroleptic medications. Children with HIV-1 CNS disease may require lower than normal doses. Psychotherapy should be a component of treatment [44].

Depression

Antidepressant medications in conjunction with psychotherapy can be beneficial. Interactions between protease inhibitors and psychotropic medications may occur, and dosages may need to be adjusted [44].

Short-term individual psychotherapy helps the child to cope with issues like death in the family. A children's group (longer term therapy) helps to enable children to deal with the issues of chronic illness, death, and social stigmata associated with HIV-1 infection.

Attention-deficit disorder/attention-deficit hyperactivity disorder

Methylphenidate is of benefit for some HIV-1–infected children with attention-deficit disorder/attention-deficit hyperactivity disorder (ADD/ADHD). Appetite suppression with stimulants can be an undesirable side effect in HIV-1–infected children and needs to be monitored. Behavioral modification techniques are also strongly recommended and should be instituted before and in conjunction with a medication trial when possible [44].

Pain syndromes

Children with HIV-1/AIDS (like children with other chronic diseases) encounter painful medical procedures; many have pain related to their underlying condition. A combination of pharmacologic and nonpharmacologic therapies is recommended, as is an aggressive approach to pain management, including management of painful procedures [120].

Analgesic therapy should be initiated after a thorough clinical assessment, which includes assessment of pain severity as well as identification and treatment of the underlying cause of pain. The WHO analgesic ladder provides a useful guideline for treatment strategies [121].

Table 5
Antiretroviral agents and potential neurological toxicities[a]

Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI)	
Zidovudine (ZVD) (Retrovir; AZT; ZVD)	Headache; less commonly myopathy, myositis ZVD concentration may increase with valproate Phenytoin concentrations may increase or decrease
Didanosine (Videx; ddI)	Peripheral neuropathy (dose related)
Stavudine (Zerit; d4T)	Headache; less commonly peripheral neuropathy
Lamivudine (Epivir; 3TC)	Headache; less commonly peripheral neuropathy
Zalcitabine (Hivid; ddC)	Headache; peripheral neuropathy Not recommended with concomitant use of DD1 because of increased risk of neuropathy
Abacavir (Ziagen ABC)	Headache
Nonnucleoside reverse transcriptase inhibitors (NNRTI)	
Neverapine (Viramune; NVP)	Headache; less commonly myalgias or arthralgias Serum concentrations of antiepileptic drugs and psychotropics should be monitored
Delavirdine (Rescriptor; DLV)	Headache Decreases metabolism of certain drugs, resulting in increased drug levels Not recommended for concurrent use with antihistamines, sedative-hyponotics, calcium channel blockers, amphetamines
Efavirenz (Sustiva; EFV)	Mental status changes: Scomnolence, insomnia, confusion, abnormal dreams, abnormal thoughts, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria (reported more frequently in adults) EFV highly plasma bound; Potential for drug interactions with other highly protein bound drugs (phenobarbital, phenytoin)
Protease inhibitors (PI)	
Saquinavir (Fortovase; Zavirase; Invirase; SQV)	Headache, paresthesias Not recommended for concurrent use with antihistamine, sedative-hypnotics May decrease metabolism of drugs resulting in increased drug levels
Indinavir (Crixivan; IDV)	Headache; dizziness Not recommended for concurrent use with antihistamine, sedative-hypnotics May decrease metabolism of drugs resulting in increased drug levels
Ritonavir (Norvir; RTV)	Headache; less commonly circumoral paresthesias Not recommended for concurrent use with analgesics (eg, meperidine, piroxicam, proposcyphene, antihistamines, sedative-hypnotics, psychotropic drugs; bupropion hydrochloride, clozapine pimozide) Antiepileptic drugs (carbamazepine, phenytoin, phenobarbital) should be monitored; antiepileptic drugs may lower levels of RTV

Table 5 (*continued*)

Kaletra (Lopinavir)	Headache Not recommended for concurrent use with antihistamine, sedative-hypnotics; neuroleptics, St. John's wort Antiepileptic drugs (carbamazepine, phenytoin, phenobarbital) may lower levels of lopinavir antiepileptic drugs levels should be monitored
Nelfinavir (Viracept; NFV)	Not recommended for concurrent use with antihistamine, sedative-hypnotics May decrease metabolism of drugs, resulting in increased drug levels
Amprenavir (Agenerase; APV, VIX478)	Paresthesias Inhibitor of cytochrome P450 isoenzyme CYP3A4; drug reaction possible with tricyclic antidepressants

[a] Toxicities listed are not all-inclusive. More complete and detailed prescribing and toxicity information is available [42] and from the drug companies. These should be reviewed before prescribing these drugs. Nucleoside analogue drugs can induce mitochondrial dysfunction (see text).

Neurologic and neurodevelopmental deficits

Habilitation/rehabilitation services are required by many HIV-1–infected children. As noted previously, the rate of neurodevelopmental, motor, and cognitive deficiencies is high. HIV-1–infected children (like non-HIV-1–infected children) benefit from habilitation/rehabilitation services, including early intervention, therapeutic nursery schools, physical and occupational programs, and special educational classes and services. When indicated, habilitation/rehabilitation programs should be an integral part of the child's clinical regimen and should be individualized to the needs of the child. The child with a stable diplegia syndrome often benefits from gait analysis, orthotics, and, when indicated, Botox therapy and/or orthopedic procedures [47,61].

Summary

Since the initial descriptions of AIDS in the late 1970s, much has been learned about the biology of HIV-1 and the cells it infects. Much has also been learned about mother-to-infant viral transmission and the natural history of HIV-1 infection. Key studies led to strategies for interrupting mother-to-infant transmission, resulting in a significant decline in neonatal HIV-1 infection. More proficient diagnostic techniques made early diagnosis of HIV-1–infected neonates and infants possible during asymptomatic or mildly symptomatic disease stages. Major advances in treatment led to the control of viral replication and thereby altered the course of disease progression. HIV-1/AIDS–associated neurologic disorders declined in parallel. In countries where these therapies are readily available, a dramatic decline in

Box 4. Treatment of HIV-1/AIDS–associated neurologic disorders

HIV-1 associated progressive encephalopathy
- One or more central nervous system penetrating antiretroviral agent having cerebrospinal fluid/plasma ratios >0.2 (eg, zidovudine or Neverapine (NVP))

Neurobehavioral complications
- Psychosis
  - Neuroleptics*
  - Psychotherapy
- Depression
  - Antidepressants
  - Psychotherapy
    - Individual*
    - Group*
- Attention-deficit hyperactivity disorder/Attention-deficit disorder
  - Psychostimulants
    - Methylphenidate*
    - Behavioral modification

Pain management
- Painful medical procedures
- Pain related to HIV-1 related conditions
  - Combination of pharmacologic and nonpharmacologic therapies
  - Analgesic therapy should be initiated after a thorough clinical assessment
    - Assessment of pain severity
    - Identification and treatment of the underlying cause of pain
  - WHO analgesic ladder provides a useful guideline for treatment strategies

Habilitation/rehabilitation
- Therapeutic nursery schools
- Special education classes
- Physical and occupational therapy

* See text.

Data from Committee on Pediatric AIDS. (1) Antiretroviral therapy and medical management of pediatric HIV infection. (2) A report on the prevention of opportunistic infections in persons infected with human immunodeficiency virus. Pediatric 1998;102:1005–86 [44].

the number of infants born HIV-1 infected has been realized as has a markedly improved survival rate of those infected.

Many questions remain, however. The long-term effects of prenatal exposure to antiretroviral agents are not yet known and continue to be studied. Just exactly how HAART therapy may affect early signs of pediatric HIV-1/AIDS–associated CNS disease, should they develop, is unclear. As new antiretroviral agents are developed and new combination drug regimens are instituted, the potential for neurologic complications, toxicities, and adverse drug interactions (eg, with antiepileptic drugs (AEDS)) exists and needs to be identified and monitored.

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Meningitis and encephalitis in children An update

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A discussion of meningitis and encephalitis requires the use of superlatives. The clinical presentation of these diseases can be among the most dramatic in all of pediatrics. The disorders, among the most devastating in all of neurology and pediatrics, can strike and kill rapidly. Immunizations aimed at preventing these diseases and antibiotics used to treat them represent some of the most spectacular successes of modern medicine. At the same time, the infectious agents responsible for many cases of these disorders are ones against which modern medicine struggles but remains virtually helpless. Meningitis and encephalitis lack nothing for drama.

Definitions and overview

Meningitis is inflammation of the two meningeal membranes (arachnoid and pia mater) that surround the brain and spinal cord. The space between these membranes is the subarachnoid space, which contains cerebrospinal fluid (CSF). In the process of meningitis, inflammatory cells spill into the CSF from the meninges, producing an increased cell count and a diagnostic hallmark of the disease. The classic signs and symptoms of meningitis are headache, fever, and nuchal rigidity.

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Encephalitis is inflammation of brain parenchyma. Evidence of this inflammation may be gained from clinical history, patient examination, and laboratory testing. The clinical hallmarks of encephalitis include fever, headache, and brain dysfunction, which may manifest as a diminished level of consciousness, focal neurologic deficits, or focal or generalized seizure activity.

Although meningitis and encephalitis are considered separate entities, in reality, inflammation of the meninges often spreads to involve adjacent brain parenchyma, and inflammation of the brain parenchyma often involves the meninges. It is probably because of this spread of inflammation that patients with meningitis often also have seizures and encephalopathy, whereas patients with encephalitis often have a CSF pleocytosis. In this sense, most cases of meningitis and encephalitis are actually cases of "meningoencephalitis." Nevertheless, despite this neuropathologic reality, it remains useful to consider meningitis and encephalitis separately. The signs and symptoms of either meningitis or encephalitis usually predominate in any given case, and the agents responsible for the diseases overlap only minimally.

Both meningitis and encephalitis can be acute, subacute, or chronic disorders, and both can be either infectious or noninfectious in etiology. Within the pediatric population, however, most of these cases are acute and caused by infectious agents. Therefore, this article focuses on the infectious causes of acute meningitis and encephalitis in children. New information regarding the pathophysiology, etiology, treatment, and prevention of infectious meningitis and encephalitis is discussed. Subacute and chronic meningitis and encephalitis and the noninfectious causes of these disorders have recently been reviewed elsewhere [1,2].

Meningitis

Pathophysiology of bacterial meningitis

Until recently, it was assumed that damage to the central nervous system (CNS) accompanying bacterial meningitis was directly induced by the infecting pathogens. Within the past decade, much has been discovered regarding the pathogenesis of bacterial meningitis, including the key fact that much of the brain injury accompanying bacterial meningitis is inflammation mediated.

Outside the neonatal period, most bacteria that cause meningitis initially colonize the nasopharynx by attaching to nasopharyngeal epithelial cells [3]. (In the neonate, colonization of the nasopharynx probably occurs only rarely, and the infection is blood borne from an unknown initial site.) To facilitate attachment to the nasopharyngeal mucosal epithelial cells, bacteria secrete IgA proteases that break down the mucus barrier and extend cellular processes (pili) that adhere to host cell surface receptors.

Once the bacteria have successfully attached to the nasopharyngeal mucosa, they travel across the epithelial membrane to invade the adjacent

intravascular space. The bacteria traverse the epithelial membrane either within intracellular vacuoles or by creating separations in the apical tight junctions of the columnar epithelial cells [3].

Bacterial invasion of the intravascular space induces a bacteremia and triggers the host's initial complement-mediated defense. Some bacteria evade the complement pathway and avoid neutrophilic phagocytosis via the presence of a polysaccharide capsule. Most bacterial strains that cause meningitis have a capsular polysaccharide and are referred to as "encapsulated" bacteria [4].

Bacteria that survive in the circulation may then enter the CSF. The mechanism and site at which bacteria invade the CSF are not known for certain, but transmission across the choroid plexus and cerebral capillaries is most likely. Cells of the choroid plexus and cerebral capillaries possess surface molecules that bacteria use as receptors for adherence to specific bacterial structures, thus allowing for attachment and invasion [5].

Once pathogens reach the CSF, they have an excellent chance of continuing to survive, principally because the subarachnoid space is a region of impaired host defense. Before infection, the CSF contains insufficient immunoglobulin concentrations, neutrophils, and complement components to inhibit the rapid multiplication of bacteria [6,7].

Eventually, the host does generate an immune response to the bacteria in the CSF. This immune response may effectively kill bacteria, but the killing process releases bacterial cell wall components that trigger an inflammatory cascade which often culminates in severe brain injury. Liberation of subcapsular surface components, including the bacterial cell wall and lipopolysaccharide, stimulate endothelial cells and CNS macrophages to produce numerous proinflammatory molecules, including tumor necrosis factor (TNF), interleukin (IL)-1, platelet activating factor, and IL-6 [8,9]. In addition, the complement cascade is activated, triggering further inflammation and the activation of granulocytes and platelets.

A key event in the inflammatory cascade accompanying bacterial meningitis is the migration of neutrophils into the CSF and a subsequent breakdown of the blood–brain barrier. A three-phase model has been proposed to explain these events [3]. The first phase begins with the release of inflammatory cytokines within the CSF in response to bacterial replication and lysis. These inflammatory cytokines bind to receptors on the surfaces of endothelial cells, generating the local production of thrombin, which induces the surface expression of selectin molecules (CD62 and endothelial leukocyte adhesion molecule-1). These selectin molecules enhance the binding of neutrophils to the endothelial surface. The prolonged inflammatory cytokine stimulation triggers the second phase, in which vascular endothelium releases IL-8. Release of this cytokine induces the binding of neutrophils to endothelial intercellular adhesion molecules (ICAMs), which leads to neutrophil diapedesis and entry into the CSF. In the third phase, cytokines within the CSF degranulate and release vasoactive lipid autocoids, including

leukotrienes and prostaglandins, along with toxic oxygen intermediates. These agents impair the blood–brain barrier, thus allowing the leakage of albumin into the CSF. The migration of neutrophils into the CSF in bacterial meningitis may produce a thick exudate that encases the brain and spinal cord in pus.

Bacterial infection of the meninges and the immune response to the infection can lead to brain injury through at least three broad mechanisms. First, chemical agents released by the bacteria or by cells of the immune system may be directly toxic to neurons. For example, lipopolysaccharide, TNF, platelet activating factor, and nitric oxide are all present in high concentrations in bacterial meningitis and can all damage or kill neurons [10–14].

Second, brain injury in bacterial meningitis can be induced through vascular mechanisms. Meningitis, sepsis, and the proinflammatory cytokines accompanying them may induce septic shock and global cerebral hypoperfusion [15]. The purulent exudate through which arteries and veins pass in the subarachnoid space may lead to vasospasm and vasculitis with secondary thrombosis, ischemia, and infarction [16]. Bacterial meningitis can also cause loss of cerebral autoregulation with subsequent inability of the vasculature to respond to tissue blood flow demands [17]. Occasionally, necrotizing arteritis may induce subarachnoid hemorrhage [18].

The third mechanism by which bacterial meningitis induces brain dysfunction and injury is through increased intracranial pressure. The toxic, metabolic, and vascular changes accompanying meningitis induce a combination of vasogenic, cytotoxic, and interstitial edema. Endotoxin and fragments of the cell wall of gram-positive organisms induce the release of IL-1 and TNF from macrophages and other sources [19]. These agents act on endothelial cells to increase the permeability of cerebral vasculature [20]. The intercellular junctions, which are normally tightly closed, are opened, thus increasing permeability to circulating albumin and inducing vasogenic edema [21]. Interstitial edema is principally caused by a diminished resorption of CSF. The accumulation of inflammatory cells, protein, and other material within the CSF interferes with functioning of the arachnoid villi and blocks the resorption of CSF from the subarachnoid space [22]. Similarly, the ventriculitis that often accompanies meningitis may occlude the cerebral aqueduct and lead to hydrocephalus, further exacerbating interstitial edema and elevating intracranial pressure. Early and common findings on CT in children with bacterial meningitis are ventriculomegaly and enlargement of subarachnoid spaces [23,24].

Increased intracranial pressure in meningitis induces brain pathologic changes via at least two mechanisms. First, elevation of intracranial pressure reduces cerebral perfusion pressure and can lead to cerebral ischemia [25,26]. Second, if the intracranial pressure rises substantially, as it often does in bacterial meningitis, cerebral herniation may occur. Cerebral herniation is commonly the ultimate cause of death in fatal cases of bacterial meningitis in children [27,28].

The use of corticosteroids in bacterial meningitis

In the preantibiotic era, more than 90% of children with bacterial meningitis died from the disease. The introduction of antibiotics and the development of pediatric intensive care have reduced the mortality rate to approximately 5% (although the mortality rate remains higher for some pathogens). Despite the reduction in mortality, substantial morbidity remains. As many as 20% to 30% of the survivors have long-term neurologic sequelae, the most common of which is hearing impairment [29,30].

The discovery that much of the brain injury accompanying bacterial meningitis is inflammation mediated sparked the hypothesis that modulation of the immune response may ameliorate the brain damage. Studies employing animal models of bacterial meningitis provided strong evidence supporting this hypothesis. The anti-inflammatory steroid dexamethasone substantially reduced levels of the cytokines IL-1 and TNF as well as prostaglandin E_2 within the CSF of infected animals [31,32]. These reductions in the chemical mediators of inflammation were accompanied by reductions in intracranial pressure, brain edema, and CSF lactate concentrations [33,34]. As these laboratory values were improved by the dexamethasone therapy, so were the outcomes for the experimental animals. Administration of dexamethasone decreased mortality and clinically evident neurologic sequelae in the animals with experimental bacterial meningitis [31].

These positive findings in animal studies led to clinical studies of dexamethasone in human patients with bacterial meningitis. Since 1988, reports of a dozen randomized and controlled trials of dexamethasone therapy in childhood meningitis have been published [35–38]. The results of most of these studies have suggested that dexamethasone can diminish meningeal inflammation and decrease the incidence and severity of brain injury in bacterial meningitis. Nevertheless, the issue of whether to use dexamethasone in the treatment of bacterial meningitis remains controversial.

Numerous findings from the clinical studies support the use of dexamethasone in bacterial meningitis. Dexamethasone can improve CSF profiles in meningitis by reducing CSF levels of the proinflammatory cytokines TNF, IL-1, and platelet-activating factor; can reduce CSF lactate and protein levels; and can increase CSF glucose concentrations [37,38]. Although the steroid reduces CSF inflammation, it does not delay CSF sterilization [39]. In the initial hours and days after the administration of dexamethasone for bacterial meningitis, the steroid can reduce intracranial pressure, improve cerebral perfusion pressure and the acute clinical condition of the patient, and reduce the number of days of fever and the number of seizures while the patient is hospitalized [37,38,40]. Most importantly, administration of dexamethasone to children with bacterial meningitis can reduce fatality as well as the frequency and severity of both acute and long-term neurologic and audiologic sequelae [37–40].

Despite these positive findings, the enthusiasm of many experts for the use of dexamethasone in bacterial meningitis is dampened by several facts.

First, the effect of dexamethasone seems to be pathogen specific. Dexamethasone may improve outcome in pneumococcal meningitis and *Haemophilus influenzae* meningitis; however, in meningitis caused by other pathogens, there is no compelling evidence that dexamethasone is of any benefit. Second, *H. influenzae* was the predominant pathogen in most of the clinical studies; however, as discussed below, this pathogen is now responsible for only a small portion of bacterial meningitis.

Third, most of the studies were performed before the widespread problem of penicillin-resistant *Streptococcus pneumoniae* emerged. Thus, the effectiveness of dexamethasone in the treatment of this critically important pathogen is unclear. Fourth, although adverse effects of dexamethasone in the treatment of meningitis have not been common, several patients have developed gastrointestinal bleeding requiring blood transfusions [39,41]. Finally, the anti-inflammatory property for which dexamethasone is employed may have its own negative effects by decreasing CSF penetration of some antimicrobials, such as vancomycin, and by interfering with the ability to interpret clinical response, such as resolution of fever [42–44]. This latter problem necessitates that all infants and children treated with dexamethasone for meningitis undergo a repeat lumbar puncture after 24 to 48 hours of therapy so as to verify CSF sterilization.

The role of corticosteroids in the treatment of bacterial meningitis remains controversial. The strength of the animal research and clinical studies persuaded the American Academy of Pediatrics to recommend the use of dexamethasone for the treatment of meningitis caused by *H. influenzae* [45] and to consider dexamethasone if the meningitis is caused by *S. pneumoniae* [46]. At the time of the initial diagnosis of meningitis, however, the etiologic organism is unknown, and many experts in the treatment of meningitis do not necessarily agree with or follow the American Academy of Pediatrics' recommendations [47–49].

Despite the controversy, three principles regarding the use of dexamethasone enjoy wide agreement. First, if dexamethasone is used, the first dose ought to be administered before or with the first dose of antibiotics and not after antibiotics have already been started [50]. The biologic role of the corticosteroid is to block the upregulation of the inflammatory mediators induced by the products of bacterial lysis [51]. Administration of antibiotics before the corticosteroid would lyse the bacteria, trigger the inflammatory cascade, and render the corticosteroid less effective. Second, if dexamethasone is used, the dose should be 0.6 mg/kg/d in four divided doses given intravenously for the first 4 days of antibiotic treatment [140]. Lower doses are less effective, and higher doses have not been studied systematically. Third, dexamethasone in the treatment of meningitis should be considered only for patients who are 6 weeks of age or older. The efficacy of dexamethasone has not been studied in younger infants, where the etiologic organisms and pathophysiology of meningitis are different than in older children.

The changing etiology and epidemiology of bacterial meningitis in children

Impact of Haemophilus influenzae *vaccination*. Until recent times, bacterial meningitis was a disease primarily of children, and the main causative organism was *H. influenzae*. During the recent past, *H. influenzae* meningitis or invasive disease developed in nearly 1 in 200 children by the time they were 5 years of age [52]. An epidemiologic study in 1986 revealed that the median age of children with bacterial meningitis was 15 months and that H. influenzae was responsible for 45% of all cases of bacterial meningitis and for 70% of the cases in children between 1 month and 5 years of age [53]. Just 9 years later, however, another epidemiologic study showed that the median age of persons with bacterial meningitis had risen to 25 years and that *H. influenzae* was a relatively rare cause of bacterial meningitis in any age group, including children [54].

With the decline in *H. influenzae*, pneumococci and meningococci are now the principal causes of bacterial meningitis in children from 1 month to 18 years of age. In neonates, group B streptococcus, *Escherichia coli*, and *Listeria monocytogenes* remain the primary culprits [55,56]. Development and administration of effective vaccines for these pathogens could make bacterial meningitis in childhood largely a relic of the past.

This dramatic change in the epidemiology of bacterial meningitis was a result of the introduction in 1988 of the conjugated *H. influenzae* type b vaccine for children more than 2 years of age and in 1990 for infants 2 months of age and older. Routine administration of this vaccine to infants and children has decreased the incidence of bacterial meningitis in children between 1 month and 5 years of age by 87%. Because this age group previously represented almost two thirds of the cases of bacterial meningitis, protection of children against *H. influenzae* meningitis has resulted in a 55% decline in all cases of bacterial meningitis [54]. Unquestionably, development of the conjugated *H. influenzae* vaccine represents one of the most important events in the history of pediatric infectious disease.

Impact of penicillin-resistant Streptococcus pneumoniae. The second recent development of great importance in the etiology of bacterial meningitis is the emergence of penicillin-resistant *S. pneumoniae*. Antibiotic resistance is of particular concern because of the prevalence of this pathogen as a cause of meningitis. *S. pneumoniae*, the leading cause of bacterial meningitis in the 1-month to 2-year-old age group and in adults, is second only to *Neisseria meningitidis* in the 2- to 18-year-old age group [54]. Indeed, *S. pneumoniae* is the principal etiologic cause of bacterial meningitis in human beings.

In the microbiology laboratory, penicillin susceptibility testing classifies *S. pneumoniae* isolates as either susceptible (minimal inhibitory concentration [MIC] < 0.06 μg/mL), intermediate resistant (MIC $= 0.1$–1.0 μg/mL), or highly resistant (MIC > 2.0 μg/mL) [57]. Until recently, virtually all isolates of *S. pneumoniae* were susceptible to penicillin and to the cephalosporins.

This susceptibility allowed for the simple and effective use of monotherapy with a single antibiotic (usually a third-generation cephalosporin or a penicillin derivative) for the empiric and specific treatment of most children with bacterial meningitis outside the neonatal period.

National studies in the United States have revealed that the prevalence of both intermediate-resistant and highly resistant clinical isolates of *S. pneumoniae* have increased at alarming rates for the past decade. A study conducted in 1999 through 2000 revealed that 34.2% of *S. pneumoniae* clinical isolates were penicillin resistant and that 21.5% were highly resistant [58]. The authors of this study had conducted an earlier national study in 1994 through 1995. When they compared the earlier and latter studies, the authors found that the prevalence of penicillin resistance in *S. pneumoniae* isolates in 1999 through 2000 had increased by 10.6% in 5 years.

The molecular basis of penicillin resistance is mutation in the bacterial genes encoding for high-molecular-weight penicillin-binding proteins. These proteins normally function as enzymes that play important roles in the synthesis and modification of bacterial cell walls [59,60]. Amino acid substitutions within these proteins diminish the affinity of the proteins for penicillin. The more substantial the change in these proteins, the greater is the resistance to penicillin. Because all β-lactam antibiotics interact with penicillin-binding proteins, modification of the proteins can lead to cross-resistance among penicillins, cephalosporins, and carbapenems [57]. Luckily, alteration in the penicillin-binding proteins does not confer resistance to vancomycin. Resistance of *S. pneumoniae* to vancomycin has not yet been reported.

The emergence of penicillin resistance may have been caused, in part, by genetic drift, but the actions of physicians have undoubtedly played an important role. The overuse of antibiotics, particularly the administration of antibiotics to children with fever, has led to an environment in which mutations encoding penicillin resistance have been naturally selected.

A newly transformed pneumococcus may be as viable as the original non-transformed strain and demonstrates a selective advantage in an environment containing penicillin. The transformed organism may proliferate and colonize the original host and the host's contacts. In this way, penicillin-resistant clones have emerged at focal locations in the world and have subsequently disseminated across the globe. Within the United States, day care centers seem to serve as major sites of pneumococcal spread. One study documented the extensive spread of a particular penicillin-resistant pneumococcal serotype within a day care center [61]. After a child is colonized with *S. pneumoniae* in a day care setting, the pathogen is often introduced into the household and subsequently spreads to others within the household and beyond [62].

In the very recent past, these obstacles to development of an effective pneumococcal vaccine have been overcome. The issue of inadequate immunogenicity was resolved by conjugation of the polysaccharide antigens

to a protein carrier. The problem of multiple pneumococcal serotypes was largely overcome by taking advantage of the fact that seven serotypes are responsible for the vast majority of invasive disease in children.

The increased prevalence of penicillin-resistant *S. pneumoniae* has dictated important changes in laboratory testing and in antibiotic therapy whenever meningitis caused by *S. pneumoniae* is suspected. No longer can it be assumed that penicillin or a third-generation cephalosporin alone can adequately treat the infection. All *S. pneumoniae* isolates from CSF and all other normally sterile body fluids should be tested for in vitro antimicrobial susceptibility to determine the MIC to penicillin, cefotaxime, and ceftriaxone. Isolates found to have intermediate or high resistance should have additional susceptibility testing to vancomycin, rifampin, and meropenem.

Children 1 month of age and older with definite or suspected bacterial meningitis should initially receive combination therapy with vancomycin and ceftriaxone or cefotaxime. This empiric therapy is particularly indicated if the Gram stain of CSF reveals gram-positive diplococci, a finding strongly suggestive of pneumococcal meningitis. If a child has a severe allergy to the β-lactam antibiotics, treatment should initially consist of combination therapy with vancomycin and rifampin. Antibiotic susceptibility results should guide subsequent treatment. If the pneumococcal isolate is susceptible to penicillin, cefotaxime, or ceftriaxone, one of these three antibiotics should be continued and vancomycin should be promptly discontinued. Discontinuation of vancomycin minimizes the risk of vancomycin toxicity in the patient and vancomycin resistance in *S. pneumoniae*.

If the isolate has intermediate- or high-level resistance to penicillins and to the cephalosporins, vancomycin should be continued along with ceftriaxone or cefotaxime. In vitro experiments and animal studies of penicillin- and cephalosporin-resistant meningitis have demonstrated that the combination of vancomycin and ceftriaxone has greater antimicrobial activity than either agent used alone [63]. Vancomycin as a single agent for the treatment of bacterial meningitis is not recommended because of its relatively poor penetration into the CSF. Attempts to treat pneumococcal meningitis with vancomycin alone have resulted in clinical failure [64]. If the isolate has an unusually high level of resistance to cephalosporins (MIC >4 μg/mL) or if the clinical course or repeat lumbar puncture suggests that cephalosporin and vancomycin are not adequately effective, addition of rifampin or meropenem to vancomycin should be considered [65].

The increasing prominence of pneumococcal infections and antimicrobial resistance provided a strong impetus for development of an effective vaccine to reduce the risk of pneumococcal disease in children. Development of a pneumococcal vaccine was complicated by the existence of more than 90 different serotypes of pneumococcus, many of which cause invasive disease. Serotyping of *S. pneumoniae* is based on antigenic differences of the capsular polysaccharides [66]. Pneumococcal vaccine development was further complicated by the fact that purified capsular polysaccharide antigens do not

generate an adequate immune response in young children. Thus, the 23-valent pneumococcal vaccine, which was composed of purified capsular polysaccharide antigens of 23 pneumococcal serotypes, was ineffective in preventing invasive pneumococcal infections in young children [67].

The heptavalent pneumococcal conjugate vaccine (PCV7) was evaluated for efficacy, immunogenicity, and safety in a large trial in northern California between 1995 and 1999 [68]. The results were spectacularly positive. The trial demonstrated a vaccine efficacy of 97.4% and reduced the total invasive pneumococcal disease burden in children by 89.1%. The vaccine induced a substantial immunologic response to pneumococcal polysaccharide of all seven serotypes included in the conjugate. Safety monitoring revealed no severe adverse events related to vaccination. In 2000, the PCV7 vaccine was approved by the US Food and Drug Administration and recommended by the American Academy of Pediatrics for all children from 2 to 23 months of age and for children from 24 to 59 months of age who are at increased risk of developing invasive pneumococcal disease [50]. Since then, shortages of PCV7 have necessitated revision of recommendations for use of this vaccine [69].

It is anticipated that the incidence of disease caused by the serotypes included in the vaccine will be greatly diminished. In addition, the vaccine seems to induce cross-protection among related serotypes and may reduce the incidence of infections caused by serotypes not included in the vaccine [68]. Furthermore, because the strains included in the PCV7 vaccine are the same strains that have developed resistance to penicillin and other antibiotics [57], the reduction in disease induced by these strains may reduce the use of broad-spectrum antibiotics and slow the development of antibiotic resistance.

Lymphocytic choriomeningitis virus

Lymphocytic choriomeningitis virus (LCMV), first isolated in 1933 from a patient with meningoencephalitis, was named for the intense lymphocytic infiltration that it induced in the choroid plexus and meninges of infected patients and laboratory animals [70]. LCMV is a member of the Arenaviridae family of viruses, and like all arenaviruses, it utilizes rodents as its principal reservoir. The common house mouse, *Mus musculus*, is both the natural host and reservoir for the virus, which is vertically transferred from one generation of mice to the next via intrauterine infection. Mice that acquire the virus transplacentally often remain asymptomatic despite heavy infection, because LCMV is not cytolytic and because congenital infection in rodents provides them with immunologic tolerance for the virus. Throughout their lives, mice congenitally infected with LCMV shed large quantities of the virus in urine, saliva, and other bodily secretions [71]. A substantial proportion of wild mice harbor the virus, and large numbers of people become infected [72–75].

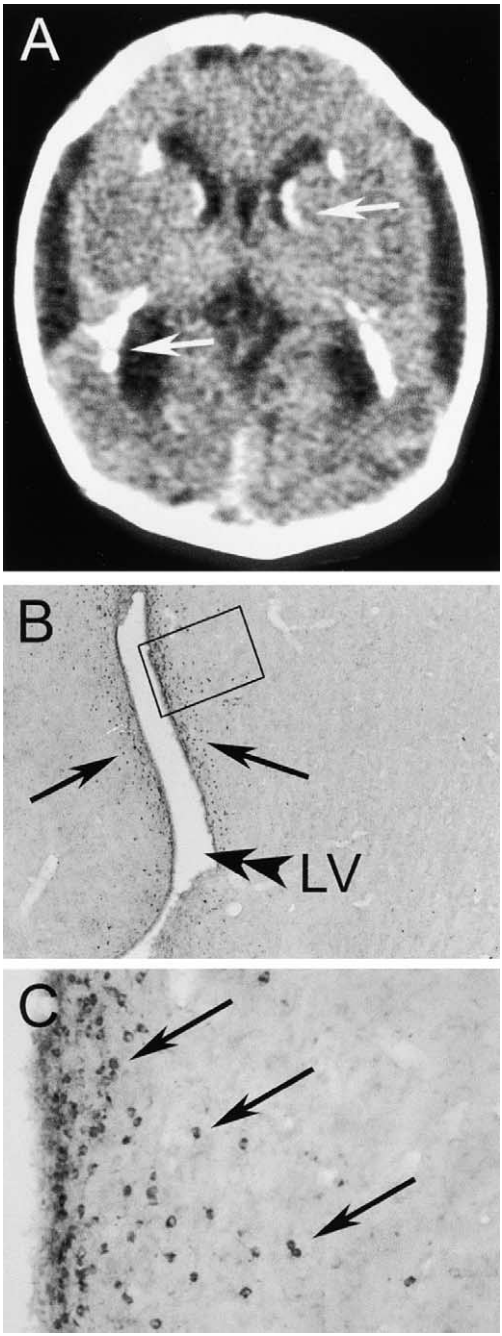
Children and adults acquire LCMV by inhalation of aerosolized virus or by direct contact with the contaminated fomites. Most commonly, infection of people occurs during the autumn and winter months, when mice cohabit with human beings. Congenital infection with LCMV occurs when a pregnant woman acquires the virus and transmits LCMV to the fetus, presumably during maternal viremia. The virus can also be acquired during the intrapartum period, probably by exposure to maternal blood or vaginal secretions during maternal viremia [76]. During the past decade, LCMV was identified as an important and underrecognized cause of neurologic birth defects in the United States [77–80].

The clinical spectrum of postnatal LCMV infection is broad; in as many as one third of acquired infections, infection is asymptomatic. When disease occurs, infection typically manifests as a self-limited febrile illness. Because the symptoms are usually sufficiently mild, many patients with acquired LCMV infection do not seek medical attention, and most cases are never formally diagnosed. Patients occasionally have an aseptic meningitis with headache, nuchal rigidity, vomiting, fever, photophobia, and malaise. The duration of the illness is usually only 1 to 3 weeks, and patients recover fully [81]. LCMV infection can sometimes be more severe and produce transverse myelitis, hydrocephalus, and encephalitis. Rarely, an acquired LCMV infection is fatal [82].

The hallmark laboratory abnormality of LCMV infection is a CSF pleocytosis. The CSF may contain hundreds or thousands of white blood cells per cubic millimeter, most of which are lymphocytes. CSF eosinophilia has also been reported [83]. Hypoglycorrhachia and mild elevations of CSF protein are commonly observed.

Whereas most postnatal LCMV infections in children and adults are self-limited and benign, LCMV infection in utero can be devastating. Infection of the human fetus can induce spontaneous abortion and fetal death [84]. Among those fetuses that survive, hallmarks of congenital LCMV infection are vision impairment and brain dysfunction [85,141]. Vision impairment is caused principally by chorioretinitis and the formation of chorioretinal scars [86] that may mimic those of congenital toxoplasmosis [87]. Other ocular abnormalities associated with intrauterine infections include optic atrophy, nystagmus, vitreitis, strabismus, micro-ophthalmia, and cataracts [78].

Intrauterine infection with LCMV often leads to either macrocephaly or microcephaly. When macrocephaly develops, it is almost invariably caused by noncommunicating hydrocephalus. Microcephaly accompanying congenital LCMV infection is caused by a virus-induced failure of brain growth. In addition to hydrocephalus and microencephaly, other abnormalities of brain structure commonly induced by congenital LCMV infection include periventricular mineralizations, cortical dysplasia, and cerebellar hypoplasia (Figs. 1 and 2) [77,79,80,86]. (The reader is referred to additional discussion of congenital LCMV virus infection elsewhere in this issue).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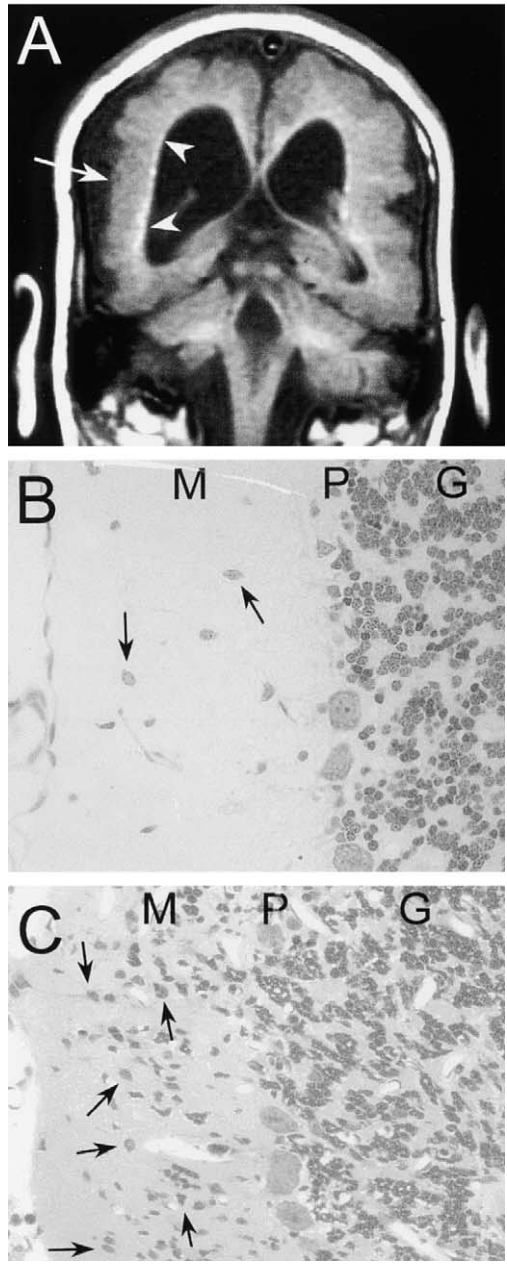
The cellular and molecular mechanisms underlying LCMV-induced damage to the developing human brain are unknown. LCMV is not cytolytic in most cell types, including glia and neurons [71]. Thus, unlike herpes simplex virus and several other pathogens that induce brain damage by directly killing host cells, LCMV teratogenesis must have some other underlying pathogenesis. Studies in our laboratory using a developing rat model indicate that LCMV produces neuropathologic changes closely mimicking those found in human beings (see Figs. 1 and 2) [88,89]. These pathologic changes include microcephaly, cerebellar hypoplasia, chorioretinitis, neuronal loss, and neuronal migrational disturbances [90–92]. Developing rats infected with LCMV have learning deficits, ataxia, movement disturbances, and seizure disorders, as do children with congenital LCMV infection [93,94].

Within the developing rat brain, glial cells play a critical role in the pathogenesis of the disease [88]. Glial cells, including astrocytes and radial glia, are the initial targets of the virus within the brain parenchyma. In addition, glial cells are the principal cell types in which the virus replicates and are the conduit through which the virus reaches susceptible neurons. Because radial glia cells constitute the scaffolding along which neurons migrate to reach their final destinations, it is likely that infection of these radial glia and disruption of their function underlie the neuronal migration disturbances evident in congenital LCMV infection (see Fig. 2).

Mitotically active cells, such as the periventricular cells that give rise to neurons and glia (see Fig. 1), are particularly vulnerable to LCMV infection [89,95–97]. Periventricular calcifications observed in human patients with congenital LCMV infection are a reflection of the preferential infection and subsequent death of the neuronal precursors residing there. The noncommunicating hydrocephalus commonly observed in children with congenital LCMV is likely caused by ependymal inflammation within the ventricular system, particularly at the cerebral aqueduct, producing blockage of CSF egress.

Acute LCMV infections in children and adults can be diagnosed by isolating the virus from CSF. By the time of birth, however, infants infected with LCMV prenatally may no longer harbor the virus. Thus, congenital

Fig. 1. Periventricular pathologic findings in congenital lymphocytic choriomeningitis virus (LCMV) infection. (A) Head CT scan from a 3-day-old baby with congenital LCMV infection demonstrates periventricular mineralization (*arrows*) adjacent to the lateral ventricles. Mineralization in this location is common in congenital LCMV infection and likely reflects the preferential infection of mitotically active neuronal precursors within the subependymal zone. (B) Horizontal section through the forebrain of a 25-day-old rat infected as a neonate with LCMV. The section is stained with a polyclonal antibody for LCMV. LV, lateral ventricle. Note the specific infection of cells (*arrows*) adjacent to the lateral ventricle (magnification ×15). (C) Inset from part B. The infected cells (*arrows*) have the morphology of neurons. Thus, within the developing human and rat brains, the periventricular neurons are particularly susceptible to LCMV infection (magnification ×70).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LCMV infection is usually diagnosed serologically. The immunofluorescent antibody test detects both IgM and IgG and has greater sensitivity than the more widely available complement fixation method [74]. An LCMV-specific ELISA, which measures titers of LCMV IgG and IgM, is performed at the Centers for Disease Control and Prevention. The polymerase chain reaction (PCR) has also been used to detect LCMV RNA sequences in an infected infant [79]; however, because LCMV does not induce persistent infections in human beings, PCR may have low sensitivity in detecting intrauterine infections.

Encephalitis

West Nile virus encephalitis

West Nile virus (WNV) first appeared in the Americas in the summer of 1999 when it caused an epidemic of human neurologic disease in and around New York City [98]. Since then, the virus has become enzootic within reservoir and vector species in the United States, has spread geographically, and has continued to cause neurologic disease in human beings. Although the frequency and severity of disease induced by the virus tend to be greater in the elderly, children are vulnerable to the infection and its consequences.

WNV, an arbovirus (arthropod-borne virus) in the Flaviviridae family, was initially isolated in 1937 from a woman with a febrile illness in the West Nile district of Uganda. Since then, the virus has been found throughout much of the African continent and in the Middle East and Europe along major bird migration flyways [99]. The geographic distribution of the virus correlates with the migratory patterns of birds in that part of the world, because birds are the main reservoir of the virus [100].

Mosquitoes of the Culex family, the principal vectors of WNV, transmit the virus between the natural bird hosts. Culex mosquitoes feed primarily on birds but bite human beings and other mammals. Unlike birds, people do not develop a viremia sufficient to continue the transmission cycle if bitten

Fig. 2. Lymphocytic choriomeningitis virus (LCMV) induces a neuronal migrational disturbance in the developing brain. (A) MRI scan from a 3-year-old child with congenital LCMV infection. Note the abnormal gyral pattern (*arrow*) and paucity of underlying white matter (*arrowheads*), which are strongly suggestive of disrupted neuronal migration. (B) Normal cerebellar cortex from a control (uninfected) adult rat consists of a molecular layer (M), Purkinje cell layer (P), and granule cell layer (G). Within the molecular layer, a few basket cells and stellate cells (*arrows*) are normally present. Granule cells have migrated through the molecular layer but no longer reside there (magnification ×100). (C) Cerebellar cortex from an adult rat infected as a neonate with LCMV. Many granule cells (*arrows*) remain abnormally placed within the molecular layer. As a result of infection with LCMV, these ectopic neurons have failed to migrate properly to their normal location within the granule cell layer (magnification ×100).

by another mosquito. Thus, although people may become infected and ill, they are a dead-end host for the virus. Other mammals, including horses, may also develop symptomatic infections from the bite of an infected mosquito, but they are also dead-end hosts [99].

In the summer of 1999, all human WNV cases were localized to the metropolitan area of New York City [101]. Since then, the infection has been diagnosed in residents of many other states along the Atlantic seaboard. Avian surveillance has indicated a substantial northward and southward expansion of epizootic activity, a pattern consistent with viral spread by migrating birds. Furthermore, WNV has been detected in an increasing number of mosquito species, some of which more readily feed on human beings and other mammals than do Culex mosquitos. These epidemiologic findings indicate amplification of the virus in the United States and suggest that the importance of WNV as a cause of disease in North America is likely to continue to increase [102].

Most WNV infections in human beings are clinically silent, with 120 to 160 asymptomatic infections for every overt infection [103,104]. Among those individuals who do develop disease, many have only mild signs and symptoms, including fever, malaise, periocular pain, lymphadenopathy, and myalgia. A fine maculopapular rash may be present and occurs more often in children than in adults [105].

Unfortunately, some individuals infected with WNV become critically ill, virtually always with neurologic signs and symptoms. Of patients hospitalized with WNV infection, approximately two thirds have encephalitis and approximately one third have meningitis without encephalitis [101]. The signs and symptoms in WNV encephalitis—fever, nausea, vomiting, headache, altered mental status and stiff neck—generally mimic those observed in meningitis or encephalitis caused by other pathogens. By contrast, encephalitis caused by WNV only rarely manifests with seizures but commonly includes cranial nerve dysfunction. These findings suggest that the brain stem may be a principal target of WNV. Many patients with WNV develop an erythematous rash, an unusual feature in other forms of viral encephalitis.

Many patients with WNV develop patterns of weakness that are unusual in other forms of encephalitis or meningitis. This weakness may manifest as pronounced proximal muscle weakness or as flaccid paralysis of the extremities. Many patients with weakness have evidence of transverse myelitis or Guillain-Barré syndrome [106]. Among patients hospitalized with WNV, the infection has a mortality rate of 10% to 15%. Patients with encephalitis and weakness have a mortality rate of 30%. The risk of death from WNV infection is much greater in the elderly than in children or young adults.

The CSF findings of WNV encephalitis typically include a pleocytosis and a moderately elevated protein concentration. CT of the brain typically shows no abnormalities, whereas MRI may show enhancement of the meninges and periventricular regions [101]. Among patients with weakness, electrophysiologic testing often reveals evidence of either an axonal

polyneuropathy, demyelinating polyneuropathy, or both. Decreased nerve conduction velocity and diminished compound muscle action potentials and fibrillation potentials are common findings on electromyography of weak patients infected with WNV [101,107].

The diagnostic test of choice is the WNV ELISA. This assay, the most sensitive of the available tests, yields useful results from blood or CSF. A problem with serologic diagnosis of WNV is the potential for cross-reactivity among the flaviviruses. False-positive results for WNV may arise when the infecting virus is St. Louis encephalitis or dengue fever or when the patient has been immunized with yellow fever or Japanese encephalitis vaccines. If positive, the ELISA results should be verified by the more specific plaque reduction neutralization test [108]. Separate ELISA tests can be performed for IgG and IgM antibodies [109]. Another potential problem is that IgM antibodies for WNV can persist for up to 1 year, thus causing confusion as to whether the antibodies reflect an acute or prior infection.

Infection with WNV can also be demonstrated by isolating the virus in cell culture. Molecular techniques using real-time PCR have recently been developed as an assay for WNV [110]. The advantage of real-time PCR lies in the rapidity with which an etiologic diagnosis can be made. An important disadvantage of this technique, however, lies in its relatively low sensitivity [111]. If specific therapy for WNV encephalitis becomes available, there should be an increased impetus for sensitive molecular diagnosis. Because no specific effective therapy exists for WNV encephalitis, treatment is supportive. Ribavirin inhibits WNV replication and the cytopathic effect of the virus on cultured neural cells but has not been studied in controlled trials [112].

Because the bite of a WNV-infected mosquito is a crucial step in the development of WNV encephalitis, personal and community protective measures can be taken to reduce the risk of infection by reducing the risk of mosquito bites. One community measure may include surveillance to monitor the prevalence of infection in mosquitoes, birds, and horses [113]. When human-biting mosquitoes are infected and present in sufficient numbers, the mosquito populations may be effectively reduced, under proper conditions, by the application of insecticides [114]. Individuals can reduce their own risks by minimizing exposure to mosquito vectors, by covering exposed skin with repellants, and by eliminating mosquito breeding grounds by removing containers capable of holding water.

Human herpesvirus-6 infection, febrile seizures, and encephalitis

Another recent important development has been the identification of human herpesvirus-6 (HHV-6) and the elucidation of its role in human disease. HHV-6, a member of the Herpesviridae family of viruses, was discovered in 1986. Although biologically similar to cytomegalovirus (CMV), the virus was recognized as serologically and genetically distinct from other human herpes viruses [115]. Soon thereafter, HHV-6 was noted to be

ubiquitous and a principal cause of the common childhood disease exanthem subitum (also referred to as roseola or sixth disease) [116]. From the neurologic perspective, HHV-6 is of importance because of its linkage to febrile seizures and encephalitis.

Exanthem subitum typically occurs between 6 months and 2 years of age and is characterized by an abrupt rise in temperature, often to approximately 40°C, followed several days later by a rapid defervescence that coincides with the emergence of an erythematous maculopapular rash that can persist for several days. Fever is a prominent component of the disease, and it has been recognized for many years that febrile seizures occur commonly during the early (febrile) stage of exanthem subitum.

The linkage of exanthem subitum to febrile seizures, along with the identification of HHV-6 as the causative pathogen for exanthem subitum, led naturally to the hypothesis that HHV-6 infection may underlie many cases of febrile seizures. This has proven to be true. Multiple studies have demonstrated that a substantial proportion of febrile seizures occur in children with a primary HHV-6 infection [117–119]. The risk of febrile seizures is high during primary infection with HHV-6, whether or not the child develops the rash of exanthem subitum.

In addition to increasing the risk of febrile seizures, a primary infection with HHV-6 may increase the severity of the febrile convulsion. Partial seizures, prolonged seizures, and repeated seizures are more common when the febrile seizures are associated with HHV-6 infection than when the seizures are caused by other pathogens [119]. Furthermore, reports have suggested that HHV-6 may persist within the CNS [120] and that reactivation of HHV-6 may be associated with recurrent febrile seizures [118]. This remains controversial, however, and at least one study has found that children with an initial febrile seizure induced by HHV-6 infection have a lower risk of febrile seizure recurrence than do children whose febrile seizures were triggered by other pathogens [121].

Although the association of HHV-6 infection with febrile seizures is well documented, the mechanism underlying this association remains unclear. One possibility is that HHV-6 directly invades brain parenchyma during a primary infection and that the febrile convulsion is triggered by brain infection. This hypothesis is supported by the findings that HHV-6 is a neurotropic virus that can replicate in glial cells and in brain endothelial cells [122–125]. Identification of HHV-6 DNA in CSF of patients with febrile seizures further supports the notion that the brain is invaded during HHV-6 infection [118,123]. Other studies have not found HHV-6 DNA in the CSF of patients with febrile seizures [126,127], however, and the question of brain invasion in typical cases of HHV-6 infection remains controversial.

A second possibility is that the seizures are triggered not by direct viral invasion of the CNS but by the production of a toxin or inflammatory molecule liberated as part of the viral infection. Cytokines, for example, are

produced at high levels by circulating monocytes during HHV-6 infection and can act on neurons to lower the seizure threshold [128–130].

A third possibility is that the febrile convulsions are not directly related to the HHV-6 infection per se but to a characteristic of the fever induced by the infection. Febrile seizures occur almost exclusively in children, presumably because the immature brain has a lower seizure threshold to the destabilizing effects of temperature elevation. A hallmark of exanthem subitum is a rapid onset of high fever. Thus, children infected with HHV-6 may be at greater risk for seizures than children with other infections because of the rapidity of high fever onset with HHV-6. Arguing against this possibility, however, are the findings that neither the maximal temperature nor the duration of fever before the seizure differed between febrile children who developed seizures and those who did not [117,131].

In a few patients, HHV-6 produces encephalitis. Encephalitis caused by HHV-6 has been observed both in immunocompromised patients and in children whose immune function was apparently normal [132,133]. As might have been anticipated from the association of HHV-6 with convulsions, seizures, and status epilepticus are common presenting signs of HHV-6 encephalitis [119,134]. Confusion and headache, common symptoms of encephalitis in general, are also commonly observed in encephalitis caused by HHV-6. When a patient develops encephalitis in association with exanthem subitum, the signs of encephalitis usually arise during the febrile phase of the illness before the onset of rash [119,134].

Whether invasion of the brain by HHV-6 is necessary to produce encephalitis is unresolved. In some cases of HHV-6 encephalitis, viral antigen has been detected within brain astrocytes and neurons [132], the location of viral antigen has been correlated with the sites of neuropathologic changes [135], and HHV-6 DNA has been detected in CSF. These findings strongly suggest that viral invasion occurs and that the presence HHV-6 within the brain plays a key role in the pathophysiology. Nevertheless, other studies have noted the distinct absence of viral antigen from the brain [136] and of viral DNA from the CSF [134] in cases of HHV-6 encephalitis. These results suggest that in at least some cases of HHV-6 encephalitis, the brain dysfunction may be caused by an extrainfectious process.

Most children who develop HHV-6 encephalitis have a good outcome with no neurologic sequelae. Some children are left with serious permanent neurologic problems, however, including mental retardation, hemiplegia, and epilepsy [137–139]. Occasional cases of HHV-6 encephalitis have been fatal [125,132,136].

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Congenital infections

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Women encounter many infectious pathogens during their pregnancies, but few of these pathogens possess the ability to infect the placenta and damage the developing fetus. Nonetheless, these pathogens, grouped traditionally as toxoplasmosis, others, rubella, cytomegalovirus (CMV), and herpes (TORCH) infections [1], remain important causes of deafness, vision loss, and behavioral or neurologic disorders among children throughout the world. A list of infectious agents potentially associated with intrauterine central nervous system (CNS) infections is displayed in the box.

Although the introduction of the rubella vaccine in the late 1960s led to a dramatic reduction in the incidence of the congenital rubella syndrome (CRS), the past decade has seen only modest changes in the epidemiology of congenital infections. Immunization programs are likely to reduce the risk of congenital varicella syndrome, but there are currently no effective strategies to prevent intrauterine CMV infection or congenital toxoplasmosis, which are important causes of permanent neurologic disability among children worldwide. This article describes the major pathogens causing intrauterine infections and summarizes the current status of treatment and prevention.

Cytomegalovirus

Epidemiology

In the United States, 0.4% to 2.5% of newborns shed CMV at birth, and most human beings become infected with the virus thereafter, usually without recognizable symptoms [2–4]. Acutely infected persons have viremia that lasts up to 3 months, and CMV is then shed in their urine, saliva, semen (if

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Infectious agents potentially associated with intrauterine central nervous system infections

Viruses
- Rubella
- Cytomegalovirus
- Herpes simplex virus type 2
- Varicella zoster virus
- Lymphocytic choriomeningitis virus
- Western equine encephalitis virus

Protozoa
- *Toxoplasma gondii*
- *Plasmodium* sp.
- *Trypanosoma cruzi*

Other
- *Treponema pallidum*

male), and cervical fluids (if female) for a year or more. Seropositive breast-feeding women shed infectious virus in breast milk within 1 month of lactation as a consequence of reactivated CMV infection [2,4]. Congenitally infected infants shed CMV in urine for several years [2].

The incidence of acquired CMV infection among children and adults, including women of childbearing age, averages 1% to 2% annually. By adulthood, 40% to 100% of the population has been infected with CMV [2–4]. Infants acquire CMV from their breast-feeding mothers, and young children become infected through direct contact with CMV-excreting playmates. Group child care in the United States plays a major role in the transmission of CMV among young children, their parents, and their care providers [5–8]. Adults acquire CMV via blood transfusion, sexual contact, organ transplantation, or contact with young children. Adults with multiple sexual partners have increased rates of CMV acquisition [4].

Seronegative women have the greatest risk of transmitting CMV to their unborn infants. Approximately 40% of women who acquire primary CMV infection during pregnancy transmit CMV to their fetuses, and approximately 10% of the infected infants have CMV disease [9]. Reinfection with new CMV strains occurs, particularly among young children in child care environments [10]. CMV-seropositive women can also be reinfected with new CMV strains, and these new strains can cause disease in their offspring [11].

Clinical manifestations

Most acquired CMV infections in healthy children or adults do not produce recognizable symptoms. Some infected persons experience a

self-limited infectious mononucleosis syndrome that resembles infection with the Epstein-Barr virus, a closely related member of the herpesvirus family. By contrast, symptomatic and potentially life-threatening CMV infections can occur in children or adults who are immunocompromised by AIDS, chemotherapy, organ transplantation, or other disorders affecting cell-mediated immunity. Potential complications of CMV infection in such persons include pneumonitis, hepatitis, gastroenteritis, retinitis, and meningoencephalitis [12].

Most CMV-infected neonates have no apparent signs of CMV infection at birth. Approximately 10% of the infected newborns have systemic signs (Table 1), which consist of jaundice, hepatomegaly, splenomegaly, petechial or purpuric rash, intrauterine growth retardation, or respiratory distress [13,14]. Neurologic signs of intrauterine CMV infection include microcephaly, chorioretinitis, seizures, sensorineural hearing loss, and hypo- or hypertonia.

Diagnosis

The diagnosis of intrauterine infection is established best by detecting the virus in urine or saliva in clinical samples obtained during the first 3 weeks of life [2–4]. Because congenitally infected infants shed enormous quantities

Table 1
Neonatal clinical features in infants with proven intrauterine cytomegalovirus, *Toxoplasma gondii*, or rubella infections

	Approximate prevalence		
Feature	Cytomegalovirus[a]	*T. gondii*[b]	Rubella[c]
Petechiae	50%	20%	35%
Microcephaly	50%	15%	25%
Hydrocephalus	5%	40%	—
Intrauterine growth retardation	50%	10%	60%
Hepatomegaly	45%	50%	35%
Splenomegaly	45%	50%	35%
Jaundice at birth	40%	65%	15%
Sensorineural hearing loss	40%	—	60%
Abnormal tone	25%	30%	ND
Chorioretinitis	10%	75%	10%
Seizures	10%	15%	ND
Death	5%	5%	ND
Pneumonitis	5%	10%	ND
Congenital heart disease	—	—	70%

Data from
[a] National Congenital Cytomegalovirus Disease Registry [13].
[b] Koskiniemi et al [28], Couvreur and Desmonts [36], and Roizen et al [37].
[c] Schluter et al [85].
[d] ND = no data.

of CMV in their urine, culturing urine using the shell vial assay is the gold standard for the diagnosis of intrauterine CMV infection. The polymerase chain reaction (PCR) can detect CMV DNA in several body fluids, including urine, but the sensitivity of this approach does not exceed that of the shell vial assay. Measuring CMV-specific IgG or IgM in the infant's serum has much lower sensitivity than culturing the infant's urine for CMV, and the CMV antigenemia assay has no role in the diagnosis of congenital CMV infection.

Intrauterine CMV infection can be diagnosed prenatally by performing amniocentesis and fetal blood sampling [15–17]. CMV can be detected in amniotic fluid by cell culture, shell vial assay, or PCR, and CMV-specific IgM can be detected in the serum of infected fetuses. Ultrasonography can be used to identify CMV-induced organ damage, particularly of the developing fetal brain. A normal ultrasound scan early in gestation does not preclude organ damage during the subsequent stages of intrauterine development, however.

Neuroimaging studies provide useful information regarding the effects of CMV infection on the developing brain and the likelihood of neurodevelopmental sequelae [18,19]. Approximately 50% of infants with intrauterine CMV infection have periventricular calcifications (Fig. 1), a hallmark of intrauterine infection, and infants with calcifications have higher rates of permanent neurodevelopmental disabilities [18,19]. Neuroimaging studies in infants with intrauterine CMV infection may also show periventricular leukomalacia, polymicrogyria, pachygyria, or lissencephaly. Because CT detects small calcifications more effectively than MRI, CT is the preferable initial imaging study. After the age of 2 years, MRI provides accurate information regarding cortical dysplasia, polymicrogyria, and other disorders of neuronal migration associated with congenital CMV infection.

Prevention, treatment, and prognosis

Pregnant women can reduce their risk of CMV infection by avoiding direct contact with the urine and saliva of toddler-aged children [20]. Should inadvertent skin contact occur, hand washing with soap and water eliminates the virus from the skin.

Because the CNS damage associated with CMV largely occurs in utero, postnatal antiviral therapy has only a modest effect on neurodevelopmental outcomes. Sequelae of intrauterine CMV infection include cerebral palsy, mental retardation, and seizures [21]. The available data suggest that postnatal therapy with ganciclovir may reduce the severity of sensorineural hearing loss and may treat CMV-induced pneumonia in congenitally infected infants [22,23]. In the National Institute of Allergy and Infectious Diseases Children's Antiviral Study Group–sponsored treatment trial, infants received 6 mg/kg intravenously every 12 hours for 6 weeks [22,24].

CMV vaccines, including subunit vaccines based on glycoprotein B, a CMV protein that induces robust immunologic responses, and vaccines

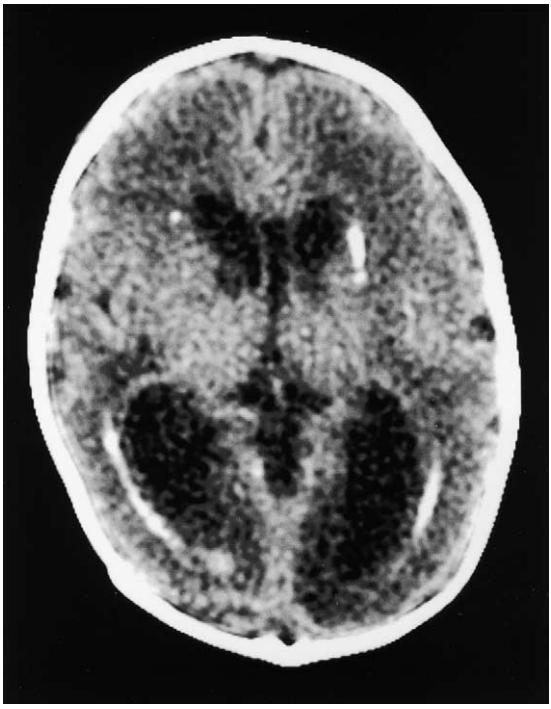

Fig. 1. An unenhanced head CT scan of an infant with congenital cytomegalovirus (CMV) infection shows dense periventricular calcifications. The white matter appears hypodense, suggesting periventricular leukomalacia. The cortical and white matter features of congenital CMV infection are imaged better by MRI, but MRI can miss small calcifications, which are the most common central nervous system features of intrauterine CMV infection.

using attenuated live CMV, have been investigated in phase 1 and 2 trials [25,26]. These vaccines seem safe, but no data exist regarding their efficacy to prevent maternal or fetal infection. Recent observations indicating that reinfection with new CMV strains can cause intrauterine infection in seropositive women suggest that prevention of CMV is likely to remain a complex problem even when safe and effective vaccines are developed [11].

Most infants with silent CMV infections escape neurodevelopmental sequelae. Approximately 15% of these children later manifest varying degrees of sensorineural hearing loss. Because of the high incidence of intrauterine CMV infection, this disorder represents the most common cause of nongenetic deafness in many regions of the world [27]. By contrast, infants with CMV disease have high rates (>90%) of neurodevelopmental sequelae, consisting of cerebral palsy, seizures, sensorineural hearing loss, mental retardation, behavioral disorders, and vision loss [2,3,18,19,21]. Approximately 9000 infants annually in the United States have audiologic or neurologic sequelae of intrauterine CMV infections [2].

Toxoplasma gondii

Epidemiology

Toxoplasma gondii, an obligate intracellular protozoan, infects birds and many mammals, especially cats, worldwide [28]. Human beings acquire infection by ingesting undercooked meat that contains bradyzoites, the encysted form of *T. gondii* found in tissues, or by ingesting fruits, vegetables, and other foodstuffs that are contaminated by oocysts, the highly infectious form of the organism [29]. Infected cats, important contributors to human infection, excrete vast quantities of oocysts, and these oocysts can remain viable in warm moist soils for a year or more.

Wide variations reflecting dietary habits, feline exposure, contact with soil, and other variables exist in the seroprevalence rates against *T. gondii* infection among human populations. Recent epidemiologic data from the Centers for Disease Control and Prevention (CDC) indicate that 15% of young women have serologic evidence of prior *T. gondii* infection [30], confirming that most women in the United States remain susceptible to *T. gondii*. By contrast, studies in France, a highly endemic region, show that 50% to 80% of women of childbearing age possess antitoxoplasma antibodies [31].

Approximately 0.1% to 2% of the adult population, depending on the geographic region and risk variables, acquire *T. gondii* annually [30–32]; like CMV, fetal infections complicate approximately 40% of the infections in pregnant women [33]. Rates of congenital infection vary from 0.8 per 10,000 live births to as high as 1 per 1000 live birth [32–35]. These data suggest that as many as 3000 to 4000 infants with congenital toxoplasmosis are born in the United States each year.

Clinical manifestations

The risk of experiencing symptoms during acquired toxoplasmosis, like that of CMV infection, depends largely on the immune status of the infected host. Although persons with AIDS and other immunocompromising disorders have high rates of invasive infections, healthy pregnant women who become infected with *T. gondii* rarely have recognizable symptoms. Occasionally, an acute mononucleosis-like illness with prominent lymphadenopathy develops [28].

As the TORCH acronym implies, infants with congenital toxoplasmosis resemble those with intrauterine CMV infection [28,36–38]. A substantial number infants lack identifiable symptoms of *T. gondii* infection at birth, but unlike CMV, most of these infants later have ophthalmologic or neurologic sequelae of intrauterine infection with *T. gondii* [36]. Symptomatic neonates commonly exhibit jaundice, splenomegaly, hepatomegaly, fever, anemia, chorioretinitis, hydrocephalus or microcephaly, and petechiae secondary to thrombocytopenia (see Table 1). Infants with congenital toxoplas-

mosis frequently have hydrocephalus and chorioretinitis, whereas intrauterine growth retardation and sensorineural hearing loss are more likely in CMV-infected infants. Intrauterine coinfections with *T. gondii* and HIV or CMV have been described elsewhere [39].

Diagnosis

The diagnosis of intrauterine infection with *T. gondii* is usually established postnatally using serologic methods [40,41], although inoculation of fresh placental tissues into laboratory mice can confirm the diagnosis of congenital toxoplasmosis. The PCR can be used to detect *T. gondii* in clinical specimens [42]. Antitoxoplasma antibodies of several classes (IgM, IgG, IgA, and IgE) can be detected in the infant's serum. Because as many as 25% of infected infants lack antitoxoplasma IgM and detection of antitoxoplasma IgG does not distinguish intrauterine infection from passive transmission of maternal antibody, serologic studies of infants and their mothers should be sent to a laboratory, such as the Palo Alto Laboratories (telephone number: 650-853-4828), that performs a panel of serologic studies for *T. gondii* [40].

Imaging studies in infants with congenital toxoplasmosis often reveal intracranial calcifications and ventriculomegaly caused by either hydrocephalus or passive ventricular enlargement secondary to loss of brain parenchyma [38]. In contrast to the calcifications observed in infants with congenital CMV infection, calcifications in congenital toxoplasmosis tend to be scattered throughout the brain parenchyma rather than being predominantly periventricular (Fig. 2). Hydrocephalus results from periventricular inflammation of the aqueduct of Sylvius or foramina of Monro.

Prevention, treatment, and prognosis

There are currently no effective vaccine strategies to prevent congenital toxoplasmosis. Pregnant women can reduce their risk of exposure to *T. gondii* by avoiding cats and consumption of undercooked meats (Table 2). In endemic regions, such as France and Italy, treating infected mothers with spiramycin or pyrimethamine-sulfadiazine has been advocated to reduce the risk of congenital toxoplasmosis [43–46]. Treatment within 4 weeks of maternal seroconversion seems to be more effective than delayed therapy [47]. Therapeutic abortion has also been used when the diagnosis of intrauterine toxoplasmosis has been confirmed by amniocentesis or cordocentesis and evidence of CNS disease has been detected by fetal ultrasonography.

Studies performed during the early 1990s indicated that the prognosis of infants with congenital toxoplasmosis can be improved by early shunting of obstructive hydrocephalus and prolonged postnatal therapy with sulfadiazine and pyrimethamine [37,48,49]. Currently, infants with proven congenital toxoplasmosis should be treated with 100 mg/kg/d of sulfadiazine and 1 mg/kg/d of pyrimethamine for 6 months followed by the same dose three

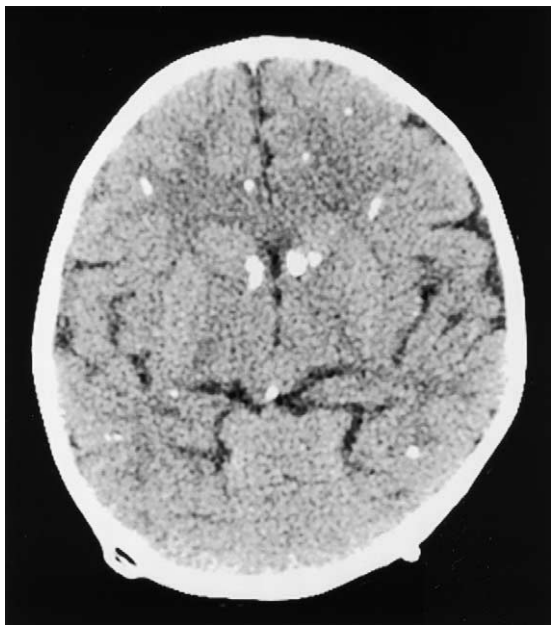

Fig. 2. An unenhanced head CT scan of an infant with congenital toxoplasmosis shows scattered and dense parenchymal calcifications. The infant underwent ventriculoperitoneal shunt placement in the perinatal period as indicated by the valves present on the surface of the calvarium bilaterally.

times per week for an additional 6 months. Infants require 5 to 10 mg of folinic acid three times weekly.

Previous studies of untreated infants with congenital toxoplasmosis indicated that 80% of surviving infants have epilepsy, 70% have cerebral palsy, 60% have visual impairment, and nearly 60% have IQs below 70 [36]. By contrast, infants receiving prolonged courses of antitoxoplasma therapy with sulfadiazine and pyrimethamine have much lower rates of these complications [48,49].

Herpes simplex virus type 2

Epidemiology

Herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) have approximately 50% nucleotide homology but display considerable differences in their epidemiology and clinical manifestations [50]. HSV-1, typically transmitted by oral routes, causes stomatitis, keratitis, and meningitis or encephalitis in children or adults. By contrast, HSV-2, typically transmitted sexually, causes genital infection, myelitis, aseptic

Table 2
Strategies for the prevention and treatment of intrauterine infections

Infectious disorder	Preventive measures	Therapy
Cytomegalovirus	Avoiding contact with young children during pregnancy, practicing monogamy	Ganciclovir[a]
Herpes simplex virus	None established	Acyclovir[b]
Varicella zoster virus	Avoiding contact with persons with chickenpox immunization[c]	None
Rubella	Immunization in childhood	None
Lymphocytic choriomeningitis virus	Avoiding contact with mice and hamsters during pregnancy	None
Toxoplasma gondii	Avoiding contact with cats and avoiding consumption of poorly cooked meats, prenatal therapy with spiramycin or sulfadiazine-pyrimethamine	Sulfadiazine and pyrimethamine
Syphilis	Avoiding contact with infected persons, maternal penicillin therapy	Penicillin

[a] Experimental (see text).
[b] Acyclovir therapy diminishes viral shedding but does not affect neurologic outcome in congenitally infected infants.
[c] Presumptive benefit of childhood immunization.

meningitis, and infections in newborn infants. Intrauterine HSV disease, a rare disorder, results from HSV-2 infection.

The incidence of HSV-2 infection is highest among young women, of whom approximately 2% acquire the virus each year [51]. Primary infection usually occurs without recognizable symptoms. Epidemiologic studies from several regions of the world, including the United States, indicate that approximately 30% of 30-year-old women have serologic evidence of prior HSV-2 infection [52–55]. The seroprevalence of HSV-2 infection among women in the United States has risen steadily during the past three decades [51]. The risk of HSV-2 seropositivity among women in the United States is associated with several sociodemographic factors, including African-American race, lower income, greater number of lifetime sexual partners, earlier age of sexual intercourse, and drug use [54,56].

As many as 2% of pregnant women become infected with HSV during pregnancy, but most of these infections do not produce fetal or neonatal disease [57]. Neonatal disease is more likely when mothers have genital HSV infection near the time of delivery. The risk of intrauterine transmission of HSV-2 to the fetus seems to be low, and the factors that determine the pathogenesis of congenital HSV infection have not been determined. Fewer than 50 cases of intrauterine HSV infection have been described.

Clinical manifestations

Approximately 5% of the infants with neonatal HSV-2 infections acquire the virus in utero [58]. Within 24 to 48 hours of birth, these congenitally infected infants have signs of HSV disease consisting of skin vesicles or scarring, chorioretinitis, microcephaly, and micro-ophthalmia [59–61]. Intrauterine growth retardation can also be present. Of 13 such infants identified by the National Institutes of Health–Collaborative Antiviral Study Group (NIH-CASG) [59], 12 had skin lesions, 8 had chorioretinitis, 7 had microcephaly, and 5 had hydranencephaly, evidence of severe brain necrosis. Less severe congenital HSV-2 infections likely occur, albeit infrequently.

Diagnosis

The diagnosis of congenital HSV-2 infection can be established best by detecting the virus in skin lesions or body fluids using either cell culture or PCR [62,63]. Samples for virus detection should include skin vesicle fluid; cerebrospinal fluid (CSF); and swabs of the conjunctiva, rectum, and oropharynx. Serologic studies may reveal evidence of HSV-2–specific antibody, but serologic diagnosis can be confounded by passive transmission of maternal antibody. Tzank preparation has low sensitivity. Ophthalmologic examination may reveal chorioretinitis and micro-ophthalmia, and imaging studies usually detect evidence of severe brain destruction. Infants with intrauterine HSV infections frequently have dense calcifications of the basal

ganglia and thalami, diffuse hemispheric cystic lesions, and a lissencephalic-like appearance of the cerebral cortex (Fig. 3) [64].

Prevention, treatment, and prognosis

Preventing neonatal HSV-2 infection, including intrauterine infection, remains problematic. In the NIH-CASG study described previously, 4 of the 13 mothers reported primary HSV-2 infections and 1 had recurrent genital herpes, but the remainder (8 of 13) had no known history of genital HSV infection [59]. These data are similar to those of other epidemiologic studies indicating that most women with genital HSV are either unaware of their infection or have asymptomatic shedding of HSV-2 [52,57].

Although infants with neonatal HSV infections require prolonged high-dose therapy with acyclovir (60 mg/kg/d for 21 days) [65], acyclovir has little or no beneficial effect on the severe CNS damage that accompanies intrauterine HSV-2 infection. Infants with congenital HSV-2 infections often die in infancy, and most of the infants who survive have neurologic sequelae consisting of cerebral palsy, epilepsy, and mental retardation [59–61].

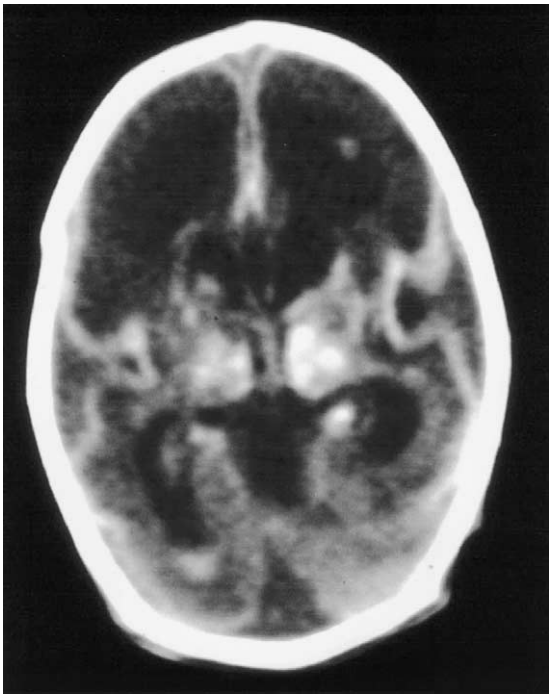

Fig. 3. An unenhanced head CT scan of a neonate with intrauterine herpes simplex virus (HSV) infection shows dense calcifications of the deep nuclei, diffuse white matter hypodensity, and cortical dysplasia resembling lissencephaly.

Varicella zoster virus

Epidemiology

The varicella zoster virus (VZV) causes chickenpox (varicella) and shingles (herpes zoster). Chickenpox, reflecting primary VZV infection, typically affects children less than 10 years of age, with a peak incidence between 5 and 9 years of age among unimmunized children in temperate climates [66]. Chickenpox, common during the winter and spring months, results from respiratory droplet transmission. Children with chickenpox are contagious for approximately 4 days before and 5 days after the onset of the rash.

Chickenpox develops in approximately 0.05% of pregnant women [67]. Women who acquire VZV before the twentieth week of gestation have a 2% risk of delivering an infant with the fetal varicella syndrome [68,69]. This risk is greatest in first-trimester infections, whereas the fetal varicella syndrome is highly unlikely in women who have chickenpox during the second half of pregnancy. Maternal VZV reactivation (ie, shingles) poses little or no risk to the developing fetus.

Clinical manifestations

Clinical manifestations of the congenital varicella syndrome consist of limb hypoplasia, chorioretinitis, cataracts, micro-ophthalmia, cutaneous scaring (cicatrix), and neurologic abnormalities [61,69–71]. The latter can include microcephaly, hydrocephalus, seizures, extremity paralysis, Horner syndrome, and cranial neuropathies. Intrauterine growth retardation can be an additional feature. In general, earlier maternal infections are associated with more severe intrauterine disease.

Diagnosis

Although the diagnosis can be suspected on the basis of the maternal history, virologic confirmation of intrauterine varicella infection can be difficult. Infection can be established by detecting the virus in fetal tissues with cell culture or PCR and by detecting VZV-specific IgM in fetal blood samples obtained by cordocentesis [72,73]. Ultrasonography frequently reveals fetal anomalies compatible with varicella infection. At birth, infants with the fetal varicella virus syndrome no longer shed VZV, and VZV-specific IgM can be undetectable [72]. Imaging studies may show intracranial calcifications, cortical dysplasia, or hydranencephaly [61,64].

Prevention, treatment, and prognosis

Susceptible women can reduce their risk of contracting chickenpox by avoiding children during their pregnancies. Although the efficacy of varicella zoster immune globulin (VZIG) in preventing the fetal varicella syndrome is

unproven, VZIG should be considered when susceptible pregnant women have significant exposures to persons with chickenpox. VZIG should be given within 96 hours of the exposure [74].

Postnatal therapy with acyclovir or other antiviral medications provides no benefit for infants with the congenital varicella syndrome. A substantial number of infants with the fetal varicella syndrome die during infancy. Many of the surviving infants have permanent sequelae affecting their vision or neurologic development [61,71].

Lymphocytic choriomeningitis virus

Epidemiology

Lymphocytic choriomeningitis (LCM) virus, first identified as a cause of human infection in the 1930s, naturally infects the feral house mouse (*Mus musculus*) but can also infect hamsters [75]. Infected mice and hamsters chronically excrete LCM virus in urine, feces, and respiratory secretions. Human infection results from inhalation of infected aerosols, direct contact with infected animals, or ingestion of material contaminated by infected excreta. Occasional outbreaks have been associated with the purchase of pet hamsters or occupational contact with infected laboratory mice [76,77]. Most recognized human infections develop during the winter months, although infections can be observed throughout the year.

Seroprevalence studies suggest that the incidence of LCM virus infection is low among the general population. Approximately 5% of the adults attending a sexually transmitted disease clinic in Baltimore had serologic evidence of prior LCM virus infection [78]. Trapping of mice from urban sites in Baltimore disclosed considerable variation in LCM virus infection rates among mouse colonies [79]. A seroepidemiologic study performed in Birmingham, Alabama indicated that persons older than 30 years of age were more likely to have serologic evidence of prior LCM virus infection (5.4% seroprevalence among persons >30 years of age versus 0.3% among persons <30 years of age) [80]. Seroprevalence rates of 2.4% and 4% were observed among adults in Argentina and Nova Scotia [81,82]. Intrauterine LCM virus infection is presumed to be a rare condition, but no surveillance studies have been performed to establish the incidence of the disorder [75].

Clinical manifestations

The clinical features of congenital LCM virus infection mimic those of intrauterine CMV disease and congenital toxoplasmosis [75,83,84]. Among 26 reported cases reviewed by Wright and colleagues [84] in 1997, 88% had chorioretinopathy, 43% had macrocephaly at birth, and 13% were microcephalic. Virtually all infants were born at term and had normal birth weights. Occasional infants have vesicular or bullous skin lesions.

Approximately 50% of mothers who give birth to infants with congenital LCM virus infection recalled influenza-like illness during pregnancy, and one fourth reported contact with rodents, usually mice, during their pregnancies.

Diagnosis

Currently, the diagnosis of congenital LCM virus infection is established by serologic studies of the mother and infant [75,84]. Antibodies against LCM virus can be detected in the infant's serum or CSF. Because of the low seroprevalence of LCM virus infection in the general population, detection of LCM virus–specific antibodies, particularly LCM virus–specific IgM, strongly supports the diagnosis. The virus can be detected by PCR, but this method does not yet have diagnostic utility in human infections. Imaging studies in infants with congenital LCM virus infections may show hydrocephalus, intracranial calcifications, and cortical dysplasia [84].

Prevention, treatment, and prognosis

No vaccine exists to prevent infection with LCM virus, but pregnant women can reduce their risk of LCM virus infection by avoiding mice and pet hamsters during their pregnancies. Effective postnatal antiviral therapy of LCM virus infections has not been described.

Approximately 35% of infants die from complications of congenital LCM virus infection [84]. Most surviving infants have neurodevelopmental sequelae consisting of cerebral palsy, epilepsy, vision loss, and mental retardation. Because the virus causes an intense inflammatory reaction within CSF pathways, infants can experience progressive hydrocephalus and require shunt placement (see additional discussions of LCM virus infections elsewhere in this issue).

Rubella

Epidemiology

The epidemiology of CRS, the consequence of maternal rubella (German measles) infection, has changed considerably since Gregg's initial description of the syndrome [85]. In the prevaccine era, epidemics of rubella appeared at 6- to 9-year intervals, causing thousands of cases of CRS, but after licensure of the rubella vaccine in 1969 and aggressive immunization programs targeting adolescents and adults in the 1980s, the incidence of the CRS in the United States and other nations declined dramatically [85]. In the United States, only one to three cases of CRS were reported to the CDC annually during the mid- to late 1980s, an incidence of less than 0.1 case of CRS per 100,000 live births [86,87]. In recent years, cases of CRS in the United States have occurred primarily among immigrants from regions without compulsory immunization [85,88].

Clinical manifestations

In 1941, Gregg [89] linked maternal rubella virus infection to cataracts, hearing loss, and heart disease in young infants. Later reports, especially those describing infants born during the rubella pandemic of the early 1960s, expanded the clinical features of the disorder [90–92]. Neonates with CRS have a spectrum of abnormalities that includes cataracts, retinopathy, micro-ophthalmia, microcephaly, and sensorineural hearing loss as well as meningoencephalitis, osteopathy, pneumonitis, hepatitis, hepatosplenomegaly, thrombocytopenia, and jaundice (see Table 1). The propensity of the rubella virus to infect the heart causes myocarditis, patent ductus arteriosus, valvular stenosis, or septal defects at the atrial or ventricular level [91].

The fetal consequences of rubella relate directly to the gestational timing of infection [90,91]. Maternal rubella during the initial 8 weeks of gestation produces cataracts and congenital heart lesions, whereas hearing loss correlates with infection during the first 16 weeks. Stillbirth or spontaneous abortion can also occur during this time. By contrast, infections after the sixteenth week of gestation usually leave no sequelae, although silently infected infants can have sensorineural hearing loss.

Diagnosis

The diagnosis of CRS can be confirmed by detecting infectious virus in body fluids (nasal secretions, urine, or CSF) or rubella virus–specific IgM in the infant's serum [93]. Postnatal persistence of rubella-specific IgG supports the diagnosis of CRS. Imaging studies can show periventricular calcifications, periventricular leukomalacia, or subependymal cystic lesions.

Prevention, treatment, and prognosis

Because CRS cannot be treated effectively by postnatal antiviral therapy, infection must be prevented by vaccination. Serologic screening of women can determine the risk of fetal infection and should be performed before pregnancy and in pregnant women exposed to rubella [94]. The presence of maternal antibody before conception or at the time of rubella exposure indicates that the fetus is not at risk.

The Committee on Infectious Diseases of the American Academy of Pediatrics recommends that serologic studies in women who are exposed to rubella be repeated in 3 to 4 weeks and once again 6 weeks after exposure if the second sample was also negative [94]. Persistently negative samples indicate that maternal infection did not occur, whereas seroconversion indicates infection and potential risk to the fetus. Termination of pregnancy is considered in confirmed primary rubella infections early in gestation. When termination is not an option, immune globulin can be considered, although the efficacy of this approach is unproven [94].

Progressive sensorineural hearing loss can develop in children who survive CRS, indicating the need for serial audiometry, and children with CRS also have an increased risk of growth failure or diabetes mellitus beginning in the second or third decade of life [95,96]. Neurologic sequelae include microcephaly, language delay, autistic features, and developmental or mental retardation.

Syphilis

Epidemiology

Although the overall incidence of congenital syphilis, the consequence of maternal infection with *Treponema pallidum*, is low in the United States, syphilis remains a threat in urban areas and the rural South [97–99]. In virtually all other developed countries, syphilis is rare. The resurgence of congenital syphilis in the United States during the late 1980s and early 1990s was associated with maternal use of illicit drugs, especially cocaine [99]. Untreated maternal infection causes perinatal death, stillbirth, or miscarriage in approximately 40% of pregnancies, and rates of fetal infections during secondary-stage maternal infections range from 60% to 100%.

Clinical manifestations

Early signs of congenital syphilis can be evident at birth or appear during the first 2 years of life [100,101]. These consist of intrauterine growth retardation, rash, hepatosplenomegaly, jaundice, lymphadenopathy, pseudoparalysis, and bony abnormalities. Hemolytic anemia, thrombocytopenia, leukocytosis, or leukopenia can be present, and radiographic studies during the perinatal period may show signs of osteochondritis [101]. Late signs of congenital syphilis, features evident after 2 years of age, include sensorineural deafness, dental abnormalities, saddle nose, saber shins, hydrocephalus, and developmental delay.

Diagnosis

Infants with suspected congenital syphilis require (1) quantitative treponemal and nontreponemal assays of serum, (2) VDRL and routine studies of CSF, (3) complete blood cell and platelet counts, and (4) long bone radiographs. Definitive diagnosis is made by demonstrating spirochetes in exudates or tissues using darkfield or direct immunofluorescence microscopy [102]. Serologic tests consist of nontreponemal tests, such as the VDRL slide test or rapid plasmin reagin (RPR) test, and treponemal tests, such as the fluorescent treponemal antibody absorption (FTA-ABS) test or microhemagglutination test for *T. pallidum* (MHA-TP). Infants likely have congenital syphilis when spirochetes are present in tissues or when they have

reactive CSF VDRL test results or serum quantitative treponemal test results four times higher than those of the mother [102].

Prevention and treatment

Women with acquired syphilis require penicillin treatment using two doses of benzathine penicillin (2.4 million U administered intramuscularly) given 1 week apart, regardless of the timing of pregnancy [102,103]. No effective alternatives exist for penicillin-allergic persons, so desensitization should be performed.

Neonates with proven or highly suspected symptomatic congenital syphilis require 50,000 U/kg of aqueous crystalline penicillin G given intravenously every 12 hours during the first week of life and every 8 hours thereafter for a total of 10 days [103]. Alternatively, procaine penicillin G can be given intramuscularly at a dose of 50,000 U/kg once a day for 10 days. Infectious disease experts should be consulted regarding current treatment strategies for infants whose mothers received inadequate treatment, infants with asymptomatic infections, or infants older than 4 weeks with possible syphilis and neurologic involvement. Should penicillin G not be available, alternative treatment recommendations can be found at www.cdc.gov/nchstp/dstd/penicillinG.htm/.

Other agents

Intrauterine transmission of *Plasmodium* sp produces congenital malaria, a neonatal disorder with fever, jaundice, hepatosplenomegaly, thrombocytopenia, and hemolytic anemia [104]. The diagnosis can be suspected on the basis of sociodemographic data and confirmed by detecting parasites in Wright- or Giemsa-stained blood smears. Treatment consists of chloroquine administered orally for sensitive plasmodia or quinine plus a second antimalarial agent for chloroquine-insensitive organisms [105].

Infants with congenital Chagas disease, which is caused by intrauterine infection with *Trypanosoma cruzi*, have hepatosplenomegaly, petechiae, jaundice, anemia, and seizures. The diagnosis can be established by detecting serologic responses or parasitemia [106]. *T. cruzi* remains endemic in most of Latin America. Intrauterine infection with Venezuelan equine encephalitis (VEE) virus, another pathogen endemic to Latin America, causes severe fetal disease with stillbirth and hydranencephaly [107].

Conditions that mimic congenital viral infections

Several noninfectious disorders produce clinical features that can resemble those of intrauterine infections [108]. Aicardi syndrome, Warburg syndrome, incontinentia pigmenti, and neonatal Graves disease are among the noninfectious disorders that occasionally may be confused with an intrauterine infection.

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Cerebral venous thrombosis and venous malformations in children

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Cerebral venous thrombosis (CVT) usually involves the cerebral venous sinuses such as the sagittal and transverse sinuses, and may extend to involve the cerebral veins. The earliest description of the neuropathology of CVT in children is by Bailey and Hass in 1931 [1]. CVT has been considered a rare disorder with poor prognosis. It is now clear that CVT is more common than once believed and there is increasing awareness of the variety of clinical presentations [2]. It is estimated that CVT constitutes 25% of ischemic cerebrovascular disease in children with an annual incidence of 0.29 per 100,000 [3,4]. Outlook for CVT has also changed dramatically, owing to earlier diagnosis and effective treatment; however, with variable and subtle clinical presentation, it remains a diagnostic challenge.

Venous anatomy

The venous drainage of the cerebral hemispheres can be subdivided into a superficial and a deep one. The intra-axial veins collect capillary blood and drain into the superficial and deep venous systems that empty into the dural sinuses, themselves drained mostly by internal jugular veins [5,6]. This network of vessels runs independent of the arteries, and anastomosis freely, and is unresponsive to changes in the systemic blood pressure.

The superficial venous system is composed mainly of the superior and inferior superficial veins that drain into the superior sagittal sinus (SSS) and cavernous sinus, respectively. The middle cerebral veins are connected to the SSS by the great anastomotic vein of Trolard and to the transverse sinus by

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the vein of Labbè. The SSS empties into the right lateral sinus (transverse and sigmoid sinuses) and the right jugular veins in most cases.

The deep venous system consists of the galenic system and variable basal veins. The galenic system is formed by the vein of Galen and its major tributaries, the basal vein of Rosenthal, and the internal cerebral veins. This system empties into the straight sinuses and ultimately into the left lateral sinus and the left jugular vein in most cases.

Anteriorly, the paired cavernous sinuses drain blood from the orbits through the ophthalmic veins and from the anterior part of the base of the brain by the sphenoparietal sinuses and the middle cerebral veins. This system communicates with the jugular system by way of the superior and inferior petrosal sinuses [5].

The cerebellum is drained by the superior, inferior, and lateral sets of veins. The superior cerebellar veins drain into the straight sinus and the vein of Galen. The inferior cerebellar veins drain into the lateral, superior petrosal, and occipital sinuses.

Pathophysiology

Thrombosis of the venous system can occur because of venous stasis, prothrombotic states, involvement of the vessel wall, and less frequently, embolization [5]. The slower blood flow favors the formation and propagation of thrombus in the venous system. There is also a relative absence of thrombomodulin in the lining of cerebral sinuses that may further increase the tendency to thrombosis [7]. Impairment of venous drainage results in congestion and swelling of the underlying white matter with subsequent ischemia. Platelets play a minimal role in venous thrombosis. In neonates, the venous sinuses are located along the suture line and are prone to mechanical distortion during calvarial molding in the birth process that can predispose to cerebral venous thrombosis [8].

Superior sagittal sinus thrombosis usually results in bilateral cortical infarcts, often hemorrhagic. Deep venous thrombosis may produce thalamic or cerebellar infarcts. Recanalization of the occluded sinus may occur over several days and weeks. The site of the thrombosis and the area of infarction do not clearly correlate with the neurologic deficit when compared with arterial strokes [9].

Clinical presentation

The presenting clinical features of venous sinus thrombosis in children are age-dependent and can vary from minimal and nonspecific symptoms such as decreased oral intake and irritability to more ominous signs such as lethargy and coma. Neonates and younger children seem to be at greater risk for CVT. In our series of 31 patients with CVT, 19 patients (61.2%) were

neonates with a median age of 14 days [2]. In another series 41% of the patients were neonates [10]. Seizures, fever, lethargy, or irritability and respiratory distress are common signs of CVT in neonates [2,11]. Older children commonly present with fever and lethargy often associated with the classic signs of intracranial hypertension such as vomiting, headache, papilledema, and abducens nerve palsy [2,10–13]. Diagnosis of CVT in children is challenging because of the variable and nonspecific presentation and therefore a high index of suspicion is required [12].

Radiographic features

Widespread availability of computerized tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance venography (MRV), has resulted in increased and earlier diagnosis of CVT in children and neonates. Head CT (HCT) with or without contrast may be suggestive of CVT but can miss the diagnosis in 10%–40% of patients and may underestimate the extent of the thrombosis [5,11]. Three abnormalities on HCT are considered "direct" signs of CVT: the cord sign, the dense triangle sign, and the empty delta sign (Box 1) [14–16]. HCT may be false positive, particularly in neonates; the higher hematocrit and slower venous blood flow in this age group produce a high-density triangle in the torcula, mimicking sinus thrombosis [15]. MRI and MRV show details of the area of infarct and visualize the absence of flow and the presence of the thrombus and clot progression [17]. MRV shows decreased venous flow. The clot appears as increased signal on T1-weighted and T2-weighted images in a venous sinus or cerebral vein (Figs. 1 and 2). Four-vessel angiography (conventional or digital) shows in detail the partial or complete lack of filling of the cerebral veins or venous sinuses, enlarged collateral veins, delayed venous emptying, and reversal of normal venous flow direction. At present MRI and MRV that

Box 1. Direct signs of CVT visualized in CT of the head (HCT)

1. Cord sign (HCT without contrast): a linear area of increased density related to the thrombus in veins or sinuses. This sign is rare and its diagnostic value is debated [3].
2. Dense triangle sign (HCT without contrast): opacification of torcula by freshly thrombosed blood [16].
3. Empty delta sign (HCT with contrast): the "delta sign" is the area of hypodensity in the torcula correlating with the thrombus in the sinus surrounded with contrast. It is the most common sign, present in approximately 30 percent of the published cases [16].

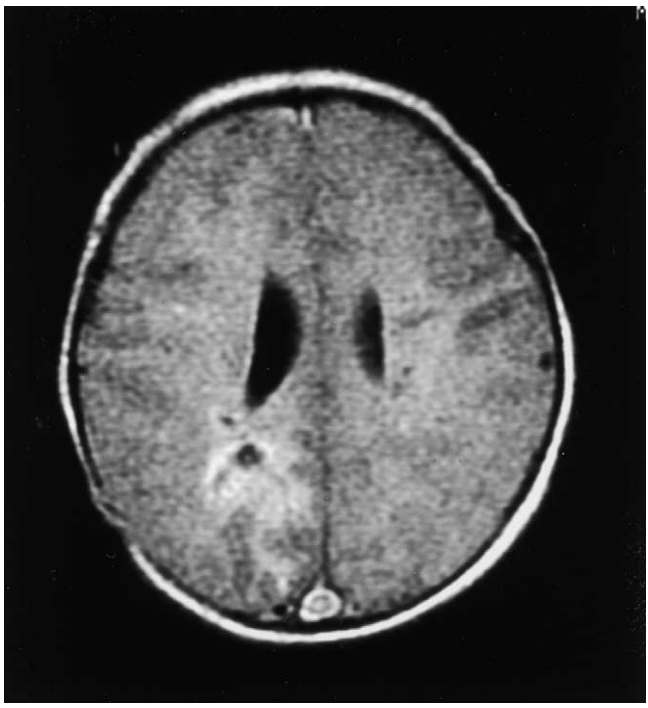

Fig. 1. Magnetic resonance imaging (MRI) scan of a 17-day-old boy showing occlusion of the superior sagittal sinus with a right occipital hemorrhagic stroke. FLAIR TR 10002, TE 148.

are more sensitive than CT are the methods of choice for diagnosis and follow-up of CVT, with angiography required only in difficult or doubtful cases [5].

Risk factors for cerebral venous thrombosis

Cerebral venous thrombosis may be associated with a variety of local or systemic conditions. In approximately 25% of patients, no risk factor can be identified despite extensive search. The investigators found a predisposing risk factor in 24 of 31 (77%) patients [2]. In one prospective population-based study, 65% of children with CVT had multiple risk factors and 40% had more than three [10]. Caution must be exercised when diagnosing idiopathic CVT, as continued surveillance may uncover causes that require treatment. Common risk factors for venous sinus thrombosis in children and adolescents are shown in Box 2.

CVT is associated with states of altered cerebral hemodynamics such as dehydration, shock, and congestive heart failure [1,2,18]. Systemic sepsis and local infection such as mastoiditis remain important causes of CVT. The

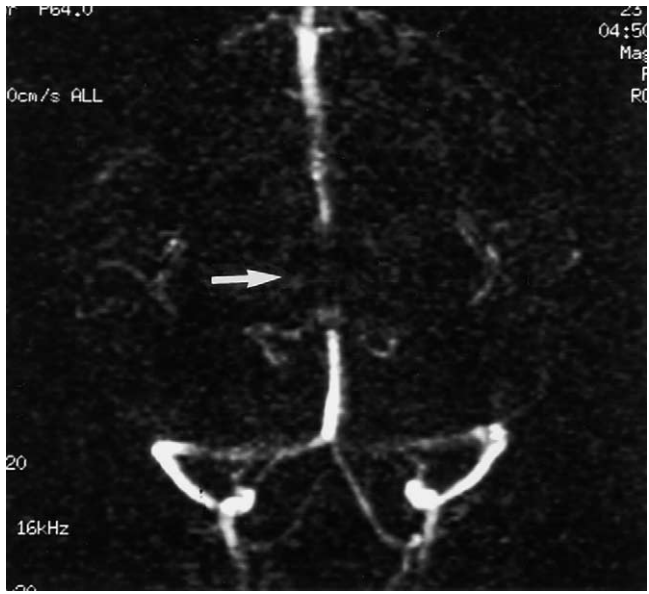

Fig. 2. Venogram of a 14-day-old boy showing partial sagittal sinus thrombosis (arrow).

investigators found mastoiditis in 7 of 12 children older than 1 month of age with CVT [2]. Other paranasal sinus infections and perioral and periorbital infections may also be associated with CVT.

A hypercoagulable state, whether acquired or inherited, is important in the pathogenesis of CVT in children [2]. Inherited hypercoagulable disorders were present in 31% of children in one study [10]. Common causes of prothrombotic states are listed in Box 3. Patients with malignant tumor may have a variety of coagulation abnormalities leading to a prothrombotic state (Trosseau syndrome: malignancy-associated hypercoagulable state) [19]. Chemotherapy, particularly L-asparaginase, may also be associated with CVT. CVT has been described in children with non-Hodgkin lymphoma, leukemia, and neuroblastoma [20].

Connective tissue diseases including systemic lupus erythematosus and rheumatoid arthritis have been reported as rare causes of CVT in older children [21,22]. CVT may be seen in patients with nephrotic syndrome and is commonly attributed to renal loss of coagulation factors. Certain drugs including oral contraceptives, increasingly used by adolescent girls, predispose to CVT [23].

The prevalence of hereditary thrombophilia is estimated at 1:2500 to 1:5000 [24]. Newborns and infants less than 1 year of age are at the greatest risk for thromboembolic complications, and the incidence decreases significantly following the first year of life [24,25]. Protein C, protein S, and antithrombin III deficiency, congenital or acquired because of renal loss,

Box 2. Risk factors for cerebral venous thrombosis

Septic Thrombosis

Otitis Media and mastoiditis
Paranasal sinusitis, scalp and face infections
Purulent meningitis
Sepsis in neonates

Aseptic Thrombosis

Dehydration
Trauma
Congenital heart disease, Congestive heart failure
Leukemia and myeloproliferative disease
Hemoglobinopathies
Inherited prothrombotic disorders
Iron deficiency anemia
Drugs: L-asparaginase, oral contraceptives
Renal disease: nephrotic syndrome, Liver disease
Disseminated intravascular coagulation
Autoimmune disease: SLE, ulcerative colitis, Behçet's disease
Malignancy
Surgery
Pregnancy

See text for details

hepatic failure, or disseminated intravascular coagulation have been associated with CVT [26].

Factor V Leiden gene mutation resulting in resistance to activated protein C (APCR) is an important cause of venous thrombosis [2,27,28]. Factor V Leiden gene mutation occurs in 5%–12% of the general pediatric population [24] and accounts for 90%–95% of all activated protein C resistance [29]. Heterozygous carriers have a sevenfold increased risk for thrombosis, whereas the risk for homozygous individuals is increased 80-fold [29]. The impact of Factor V Leiden mutation in children with CVT seems to be highest in newborns and young infants, reflecting the different physiology of hemostasis, with proportionately lower levels of protein C and protein S frequently observed in this age group [24]. Inherited abnormalities of fibrinolysis including plasminogen deficiency, plasminogen activator deficiency, dysfibrinogenemia, and Factor XII deficiency have been linked to venous strokes in young adults [30,31].

Presence of antiphospholipid antibodies (aPL) has been related to venous thrombosis in children [32]. In the absence of connective tissue diseases, the

Box 3. Prothrombotic abnormalities associated with CVT in children

Protein C deficiency
Protein S deficiency
Antithrombin III deficiency
Activated protein C resistance
Factor V Leiden gene mutation
Prothrombin G20210A gene mutation
Hereditary thrombophilia
Antiphospholipid antibody syndrome
Homocystinuria

association of aPL and stroke is known as primary antiphospholipid antibody syndrome, characterized by chronic headaches, livedo reticularis, pulmonary hypertension, recurrent episodes of deep venous thrombosis, and arterial and venous strokes [33]. In a prospective blood bank survey, antiphospholipid antibodies were detected in 6.5% of normal subjects with prevalence increasing with age [34]. The presence of aPL conveys a stroke risk 10 times that seen in patients without aPL [35]. Children with antiphospholipid antibodies have a significantly increased risk for arterial and venous thrombosis, 50% of these occur in the central nervous system [32].

Arterial and venous thrombosis is a frequent complication in homocystinuria; however, cerebral venous thrombosis is rare [36]. Patients with this disorder have marfanoid body type, ectopic lentis, and mental retardation, and one third of these patients have thromboembolic events. The proposed mechanism is caused by abnormal collagen cross-links with consequent abnormalities in vessel walls and increased platelet adhesion [35].

The high incidence of inherited hypercoagulable disorders in children with venous sinus thrombosis suggests that a thorough hematologic evaluation should be done regardless of the presence of other risk factors or lack of family history of thrombotic events [2]. Plasma concentration of many coagulation proteins reaches adult ranges by several months of age and age-corrected values should be used [37]. Box 4 lists suggested investigations for hypercoagulable disorders in children with venous sinus thrombosis.

Treatment

Conservative general medical care and neurologic supportive care is the mainstay of treatment. Adequate hydration is paramount. Aggressive antibiotic therapy and antiepileptic medications should be used when appropriate. Surgical debridement is recommended for the treatment of mastoiditis [38]. The role of internal jugular vein ligation in patients with mastoiditis

Box 4. Prothrombotic disorders laboratory studies for patients with CVT

Complete Blood Cell Count
Platelets count
PT, INR, and aPTT
Protein C activity, protein C Antigen
Protein S clottable, protein S total Antigen
Antithrombin III functional, antithrombin III Antigen
Activated protein C resistance (APCR)
Factor V Leiden mutation
Prothrombin G20210A mutation
Homocysteine level
MTHFR polymorphism
Lipid profile
Lipoprotein (a)
Antiphospholipid antibody panel
dRVVT/Lupus anticoagulant assay
Fibrinogen activity
Fibrinogen Antigen
Factor VIII assay

PT = prothrombin time, INR = international normalized ratio, aPTT = activated partial thromboplastin time, dRVVT = dilute Russell viper venom time, MTHFR = Methylenetetrahydrofolate reductase.

is controversial and should be reserved for those cases in which thrombophlebitic or embolic spread beyond the sinus is suspected [39].

Some investigators have been more enthusiastic about systemic fibrinolysis and anticoagulation therapy. There is limited data regarding the efficacy and safety of systemic anticoagulation in a pediatric population. Low molecular weight heparin (LMWH) was found to be safe when used in children with CVT. This study did not evaluate the efficacy of anticoagulation in mortality and long-term neurologic morbidity [40]. Isolated case reports have shown improvement in patients with extensive thrombosis and low incidence of complications [41,42]. The role of thrombolytic therapy in children remains controversial.

Outcome

Some investigators have suggested that the outcome of cerebral venous thrombosis is age-related, with neonates and young children having unfavorable outcomes [2]. Barron et al reported 10 neonates with cerebral venous thrombosis with only 2 being entirely normal at subsequent exami-

nations [11]. Other investigators have reported similar unfavorable results [43,44]. In our study of 19 neonates with CVT, 11 had developmental delays and only 5 had no neurologic deficit. Fifty percent of the older children were neurologically intact [2]. Others have reported complete resolution of neurologic deficits in 95% of cases [11]. Shevell et al reported normal outcomes in 88% of neonates with dural venous thrombosis [13]. The reason for the discrepancy in results is not clear and might represent selection bias. Outcome may also be related to localization of the thrombus and the presence of infarct or hemorrhage. Barron et al found that infants and children with infarction caused by deep venous thrombosis had persistent neurologic disability [11]. The investigator's experience suggests that multiple sinus thrombosis is associated with higher morbidity [2].

In a large case series of 77 adult patients by Preter et al, 9 patients (11%) had recurrent sinus thrombosis, all in the first year [45]. Recurrent thrombosis has not been reported in pediatric series [2,11–13,44].

Vascular malformations

The vascular malformations of the central nervous system are an important cause of hemorrhagic strokes in children. Arteriovenous malformations are characterized by direct anastomosis of arterial and venous channels without an intervening capillary bed [46]. These are discussed elsewhere. Here we discuss common venous malformations of childhood.

Vein of Galen aneurysmal malformation

The vein of Galen aneurysmal malformation (VGAM) accounts for approximately 10% of the vascular malformation in childhood [47]. VGAM corresponds to 60% of the lesions that present before 6 months of age, however [48].

Clinical features

The clinical presentation of VGAM is age-dependent. Forty to fifty percent of all VGAM presents in the neonatal period, usually with high output congestive heart failure [49]. Persistent pulmonary hypertension and heart murmur may be present [49]. In late infancy, patients usually present with hydrocephalus and seizures. Spontaneous intracranial hemorrhage is especially common. Dilated scalp veins and a loud bruit over the head are important diagnostic clues. Older children and adolescents usually present with seizures and intracranial hemorrhage. Signs of brainstem and cerebellar involvement are frequent. Once these lesions become symptomatic, the mortality is approximately 50%. Stroke in venous distribution can occur secondary to shunting of blood through the malformation and away from the

brain parenchyma or "steal phenomenon" [50]. There is an interesting association between congenital cardiac defects, especially aortic coarctation and sinus venosus atrial septal defect, and VGAM [51]. Echocardiogram with attention to the aortic arch and pulmonary veins is imperative in the evaluation of children with VGAM [51].

Diagnostic studies

Doppler ultrasound is critical for the prenatal diagnosis of VGAM, and shows an intracerebral hypoechoic cyst [52]. Intrauterine MRI and MRA usually confirm the diagnosis [53]. Three-dimensional power Doppler ultrasonography (3D-CPA) may assist in the diagnosis and provides a three-dimensional visualization of the vasculature [54]. MRI is mandatory before treatment to assess the condition of the brain parenchyma [55]. Conventional angiography is essential for pretreatment evaluation.

Treatment and outcome

A few cases have been reported with spontaneous thromboses of VGAM after diagnostic angiography [56,57]. The approach is influenced greatly by age, clinical symptoms, and the angiographic architecture of the malformation. Therapeutic options are primarily based on whether a true arteriovenous malformation (AVM) is present or if the malformation represents an arteriovenous fistula involving the vein of Galen. Arterial endovascular approaches, microneurosurgery, or radiosurgery are preferred for the management of the former, whereas the transvenous endovascular approach has become the cornerstone for the treatment of the latter [58]. Endovascular embolization remains the treatment of choice in most cases, offering a high rate of cure with low morbidity [59], with multiple stage embolizations sometimes being necessary [60]. Some of the complications of endovascular treatment include perforation of the thin-walled aneurysm or the feeding vessels, cerebral infarction, or other neurologic sequelae [61]. Gamma knife surgery is a viable option in clinically stable patients, especially after failure of multiple embolizations [62].

Before the era of sophisticated imaging technologies and endovascular treatment, vein of Galen malformations were fatal in 90% of symptomatic patients less than 1 month of age and in half of those patients between 1 month and 1 year of age [63]. Treatment of VGAM has been revolutionized by transcatheter embolization techniques, with 70%–80% survival among neonates and young infants, and cure rates of approximately 50% [64]. Neonates with VGAM presenting with early cardiac failure continue to have high morbidity and mortality, and outcomes are significantly better in those presenting in later childhood [60]. Neurologic outcomes in survivors are generally poor. In one study of 22 children, there was a 37% incidence of mental retardation, and 82% had seizure disorder [65].

Cavernous malformations

Cavernous malformations (CM) are congenital vascular malformations characterized by irregular sinusoidal vessels lined by thin walls surrounded by normal brain tissue with no obvious feeding arteries or venous drainage. Estimated prevalence of CM ranges from 0.47–0.9% [66–68]. Multiple CMs are common and they often coexist with other vascular anomalies [69].

CM may be sporadic or familial. They are inherited as an autosomal dominant trait. The familial cases have a higher incidence of multiple cavernous malformations and are more likely to be symptomatic [70]. Seventy-five percent of patients who have multiple lesions and who present as sporadic cases in fact have a hereditary form of the disorder [70]. It has been estimated that the familial cases make up approximately half of the reported cases [69]. Dubovsky et al in 1995 mapped a gene (CCM1) associated with familial CMs to chromosome 7q11-q22 [71]. Additional genes have been found on chromosomes 7q, 7p, and 3q (KRIT1, CCM2, and CCM3) [72,73].

Clinical features

Most patients with CMs are asymptomatic. CMs are more commonly identified in adults than in children. They may cause hemorrhage and focal neurologic deficits [74]. Seizures are the presenting symptom in two thirds of the cases [75,76]; 40% of these may have refractory epilepsy [77]. CMs associated with venous angiomas are more likely to present with symptomatic hemorrhage [78]. Familial cases may also have retinal lesions and present with progressive visual loss [79].

Diagnostic studies

CT of the head shows calcification in 50% of the patients. A low-density lesion with faint nonhomogenous enhancement is visualized on contrasted CT. MRI is more sensitive and shows a well-defined lesion with a central focus of mixed signal intensity surrounded by a rim of signal void caused by the paramagnetic effect of haemosiderin (Fig. 3) [76,80,81]. Angiography is normal in most of the cases or reveals an avascular mass [82].

Treatment and outcome

The significant risk for bleeding from CM is approximately 0.25% per person-year and many physicians reserve surgery for patients with intractable seizures or bleeding [66,83]. Management strategy for CM is complex and controversial. The general consensus is that microsurgical resection of the lesion is the best treatment in patients with intractable epilepsy. The success rate following surgical excision in patients with intractable seizures varies from 20%–80% [77,84–87]. The management of asymptomatic CM

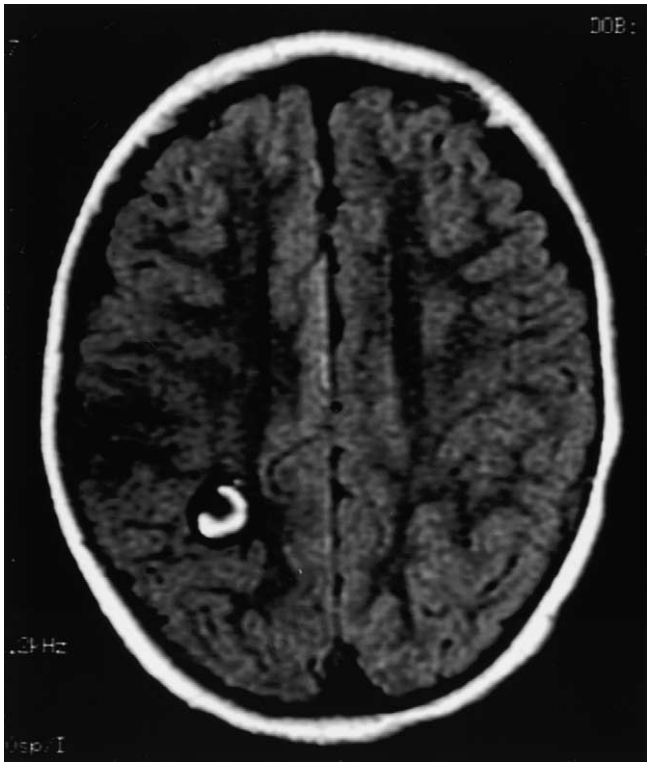

Fig. 3. T1-weighted magnetic resonance imaging (MRI) scan of a 5-year-old boy showing a right parietal cavernous angioma.

is conservative because of the low risk for bleeding. Radiosurgery may be an option for the treatment of epilepsy when the CM is located in an eloquent area.

Venous angiomas

Venous angiomas are neither true malformations nor tumors. They should properly be called developmental venous anomalies and represent anomalous but normal venous drainage [88]. They represent the most common type of intracranial ''vascular malformations'' documented by brain imaging and by autopsy, with prevalence as high as 3% [89].

Clinical features

Venous angiomas are rarely symptomatic unless associated with another vascular malformation [78]. Rare cases presenting with seizures, headache, and intracerebral hemorrhage have been reported [90]. These patients often have mixed lesions with features of CM, venous angiomas, and AVM [66,90,91].

Imaging studies

Venous angiomas are often missed on CT without contrast. Contrast-enhanced CT shows a hyperdense linear lesion perpendicular to the cerebral cortex. A hypodense lesion on T1-weighted sequences that enhances with gadolinium is seen on MRI [92]. The characteristic caput medusae pattern, corresponding to a large venous trunk fed by tributary veins is visualized in the late venous phase of conventional angiography [93].

Treatment and outcome

Unless there is an associated CM or AVM, observation is indicated [66,92]. In cases of hemorrhage caused by mixed CM/venous angiomas, removal of the CM with preservation of the venous angioma may be necessary [88]. The venous angioma is a functional venous channel that drains normal parenchyma and the risk for venous infarction after surgery or radiosurgery is high. Radiosurgery has no role in the treatment of venous angiomas [88].

Summary

Venous strokes are not as common as arterial strokes in the pediatric population, but may be associated with significant mortality and morbidity. Cerebral vein thrombosis and venous sinus thrombosis are responsible for most venous strokes. Vein of Galen malformation is a rare but important cause of mortality in neonates and infants. Awareness of these potential causes of stroke in the pediatric population, early diagnosis, and appropriate therapeutic strategies are paramount to reduce mortality and improve neurologic outcome.

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Arterial strokes in children

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Stroke in children is more common than once suspected. Stroke is a catastrophic event in any individual's life and is especially tragic in children, with potential long-term disability and burden for the victims, families, and the community. The loss of full earning potential is incalculable for the individual and cumulatively enormous for society. The World Health Organization's MONICA Project defines stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death with no apparent cause other than of vascular origin" [1]. The definition includes ischemic and hemorrhagic infarction and intracerebral and subarachnoid hemorrhage. In adults, 80%–85% of strokes are ischemic, whereas the remaining 15%–20% are hemorrhagic. In children, 55% are believed to be ischemic, and the remainder hemorrhagic [2,3].

Strokes in adults are often caused by atherosclerosis; the etiology of stroke in children is diverse and challenging. Although many different causes and potential risk factors for childhood stroke have been described, ischemic stroke in children frequently results from cardiac embolism, nonatherosclerotic vasculopathies, or prothrombotic states. The main causes of nontraumatic hemorrhagic strokes are ruptured vascular malformations, bleeding diathesis, sympathomimetic drug abuse, or intracranial tumoral bleeding [4].

Epidemiology

There is limited information regarding stroke epidemiology in children. Retrospective studies have generally reported stroke incidence of approximately 2.5 to 3.1 cases per 100,000 children per year [5,6]. The reported incidence of 0.2 strokes per 100,000 children per year among Japanese children

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was low not only because of the low rates of congenital heart disease but also because strokes caused by Moyamoya disease, a leading cause of stroke in Japan, were excluded [7]. The higher rate of approximately 13 cases of stroke per 100,000 children per year, in the prospective French study, probably reflected the general availability of CT scan [8]. Hemorrhagic strokes account for approximately half of all strokes in the pediatric population (Table 1). Recurrence is estimated to occur in 20% of the children [9].

Ischemic cerebral infarction

Several factors increase the risk for ischemic stroke in children. Congenital heart disease remains an important risk factor. Other risk factors include atherosclerotic and nonatherosclerotic vasculopathies, hemoglobinopathies such as sickle cell disease, cerebral, and meningeal infections, prothrombotic states, and trauma (Box 1). A variety of genetic disorders have been implicated in stroke in children [10]. Some inherited diseases, such as the hereditary dyslipoproteinemias, predispose to accelerated atherosclerosis. Deficiencies of protein C and S, antithrombin-III deficiency, prothrombin G20210A mutant genotype, and activated protein C resistance are examples of inherited hematologic abnormalities associated with ischemic stroke [11,12]. Other inherited metabolic disorders such as the syndrome of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), Fabry disease, Menkes disease, Tangier disease, and homocystinuria may be associated with strokes. Some children may have multiple risk factors.

Congenital heart disease

Cardioembolic stroke presumably accounts for nearly a fifth to a third of all ischemic strokes with congenital heart disease being an important risk factor in children (Fig. 1) [13]. Congenital heart disease is reported to occur

Table 1
Age-specific incidence rates of cerebral infarctions in children per 100,000 per year

Population	Years	Age group	Rate	Ischemic	Hemorrhagic
Rochester, MN[a]	1965–74	0–14 yrs	2.5	0.63	1.89
Linköping, Sweden	1970–79	<15 yrs	2.1	NA	NA
Tohoku, Japan[b]	1974–89	<16 yrs	NA	0.2	NA
Cincinnati, OH[c]	1988–89	<15 yrs	2.7	1.2	1.5
Dijon, France[d]	1985–93	<16 yrs	13.0	7.9	5.1

[a] Stroke related to birth, intracranial infection, or trauma excluded.
[b] Ischemic cerebral infarctions only. Excluded cases of Moyamoya.
[c] Traumatic brain hemorrhage and germinal matrix hemorrhage excluded.
[d] Prospective study.
NA, Not available or not reported.

Box 1. Risk factors for ischemic strokes in children

Cardioembolic
Congenital cardiac diseases
Cardiac surgery
Myocarditis
Infection
Central nervous system infection
Sepsis/septic embolism
Hemoglobinopathies
Sickle cell disease
Vascular abnormalities
Moyamoya disease
Fibromuscular dysplasia
Vasculitis
Isolated CNS angiitis
SLE vasculatilis
Arterial dissection
Spontaneous
Trauma
Antiphospholipid antibodies
Antithrombin III deficiency
Prothrombin gene 20210A mutation
Dysfibrinogenemia
Factor V Leiden mutation
Protein S deficiency
Protein C deficiency
Hyperhomocysteinemia/MTHFR gene mutation
Elevated lipoprotein A
Polycythemia
Hyperlipidemia
Extrinsic arterial compression
Mitochondrial diseases
Drugs
Cocaine
Methylphenidate
Phenylpropanolamine

in approximately 5–10 per 1000 live births [14]. Heart disease may be implicated in cerebral infarction in one of four ways: there may be (1) a right-to-left shunt, (2) valvular disease, (3) endocardial disease, or (4) thrombus or tumor in the left heart. Cardiac embolization also may occur during cardiac surgery using cardiopulmonary bypass. Finally, presumed cardioembolic

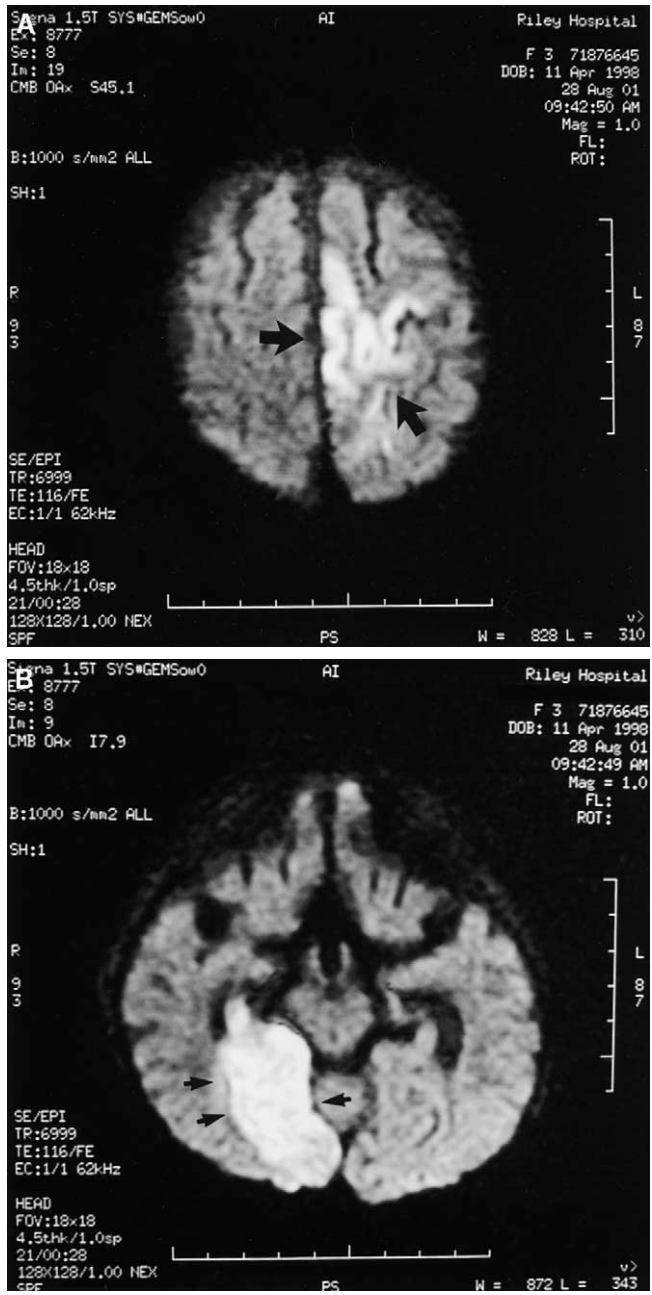

Fig. 1. A 3-year-old girl with history of congenital heart disease (transposition of great vessel and ventricular septal defect) presented with a right-sided hemiparesis, seizures, and decreased mental status. Top, weighted-diffusion MR scan shows left anterior cerebral artery (*arrows*) and, bottom, right posterior cerebral artery (*arrowheads*) distribution ischemic infarcts.

stroke in fact may be caused by pulmonary arteriovenous fistula. Children with congenital heart disease and anemia are at high risk for cerebral infarction whereas sinovenous thrombosis is more likely in children who have polycythemia and high hematocrit.

A right-to-left shunt may occur across the ventricles as in ventricular septal defect or Tetralogy of Fallot or across the atria as in atrial septal defect (ASD) or patent foramen ovale (PFO). Under normal circumstances the left heart pressures are greater than the right heart pressures and shunting of blood if any is from left to right. In some situations, however, there may be a reversal of this gradient as may occur during a Valsalva maneuver or when there is obstruction to the right ventricular outflow, as may be the case in Tetralogy of Fallot caused by pulmonary stenosis and in some patients with pulmonary hypertension. A thrombus may therefore pass from the venous system to the arterial system by way of this defect in the heart, resulting in a cardioembolic stroke.

ASD/PFO is an important consideration in cerebral infarcts and is often uncovered during investigations following a stroke. PFO may be a common occurrence; it has been found in 35% of people between the ages of 1 and 29 years [15]. PFO was present in 40% of patients with stroke compared with 10% in the control group [16]. Closure of PFO has been advocated in such patients. The PFO may close spontaneously in the first few years of life and hence it may be appropriate to watch children with early onset stroke when a small PFO is presumed to be the only risk factor.

Valvular disease may be congenital, as in a bicuspid aortic valve, or it may be acquired. Acquired valvular heart disease may be rheumatic, prosthetic, infective, inflammatory, marantic, myxomatous, degenerative, or traumatic. Rheumatic heart disease is the most common cause of acquired valvular heart disease and mitral valve is the most commonly affected valve, followed by aortic and pulmonary valves. Presence of atrial fibrillation increases the risk for thromboembolism [101]. Infective endocarditis is an important cause of thromboembolism in patients with congenital and acquired cardiac valvular disease. Strokes can result from septic embolization, mycotic aneurysm formation, and vasculitis. Infective endocarditis involving the left side and larger vegetations are associated with a higher risk for embolism. Intravenous drug users are at an increased risk for developing infective endocarditis. Development of mycotic aneurysm is an important complication. Arteriography may be necessary to exclude a mycotic aneurysm in patients who develop focal signs. Patients with prosthetic heart valves have an increased risk for thromboembolism. Prosthetic heart valves may be mechanical or biologic. Mechanical valves have a higher risk for thromboembolism compared with biologic valves and they require lifetime anticoagulation. The risk for systemic thromboembolism in patients receiving anticoagulation is 4% with mitral and 2% with aortic position mechanical heart valves [17]. Infective endocarditis should be a strong consideration in any febrile stroke patient. Endocarditis such as Libman-Sacks endocarditis

may be associated with strokes. Patients with antiphospholipid antibody syndrome have been reported with findings resembling verrucous endocarditis of the mitral and aortic valves [18].

Cardiomyopathies secondary to valvular, ischemic, hypertensive, or inflammatory heart disease are uncommon in children. Primary cardiomyopathies may be dilated, restrictive, hypertrophic, or obliterative. Cardiomyopathies may also be seen in a variety of metabolic and genetic childhood neurologic diseases such as Duchenne and Becker muscular dystrophy, myotonic dystrophy, Friedreich ataxia, infantile acid maltase deficiency (Pompe disease), carnitine-palmitoyl transferase II deficiency, Refsum disease, and neonatal and infantile mitochondrial disorders. Complete heart block is frequently seen in patients with Kearns-Sayre syndrome [19].

Thrombus in the left atrium or the left ventricle may result in cardioembolic stroke. Patients with rheumatic heart disease with mitral valve involvement and dilated left atrium are at risk for developing a thrombus in the left atrium and appendage. Risk is increased when this is complicated by the presence of atrial fibrillation. Thrombus in the left ventricle may follow myocardial infarction causing a dyskinetic-hypokinetic ventricular musculature. Kawasaki disease, polyarteritis nodosa, rheumatic carditis with coronary artery involvement, and congenital anomalies of the origin of the coronary arteries may place some children at risk for myocardial infarction. Risk for cerebral embolism is 1%–3% in acute myocardial infarction [19]. Atrial myxoma is the most common primary cardiac tumor and may be familial. Rhabdomyomas are most often associated with tuberous sclerosis and are rarely associated with strokes.

The Fontan operation is one of the most common cardiac operations for children with congenital heart disease after the first year of age and essentially consists of an anastomosis of the right atrium to the pulmonary artery. In a series of 645 patients who underwent the Fontan procedure over a 15-year period, 17 patients (2.6%) suffered a stroke following surgery. The risk period for stroke extended from the first postoperative day to 32 months following the Fontan procedure [20]. In another review of 68 patients who underwent the Fontan procedure, 6 of the 64 surviving patients had stroke. They all had normal hematologic and coagulation parameters at the onset of the neurologic symptoms. Two patients were on platelet antiaggregants, and one patient was on warfarin [21].

Congenital abnormalities of the aortic arch and aortic valve may be associated with cerebrovascular disease such as Moyamoya disease, arterial dissection, and aneurysms [22,23]. Strokes have been reported in patients with Williams syndrome [24].

Anticoagulant therapy is recommended for stroke patients with acute myocardial infarction, prosthetic and rheumatic valvular heart disease, and for those patients who have stroke from other noninfective cardiac sources of emboli. Prolonged parenteral antibiotic therapy is the mainstay of treatment for infective endocarditis. Selective surgical or transcatheter repair

may be indicated for ASD. Optimal treatment of paradoxic embolism associated with PFO or ASA is currently unknown. Prompt surgical resection is indicated for patients with atrial myxomas [25–28].

Cervicocephalic arterial dissection

Cervicocephalic arterial dissection is an important risk factor for stroke in children. Dissection of the extracranial and intracranial portions of the carotid and vertebrobasilar arteries may occur spontaneously or may be secondary to trauma or other underlying vascular risk factors. Among 263 consecutive patients with spontaneous cervicocephalic arterial dissections evaluated at the Mayo Clinic, 18 (6.8%) were 18 years of age or younger [29]. In another study of 59 children who underwent conventional arteriography, 12 patients (20%) were found to have dissection of cervicocephalic arteries [30]. Initial symptoms may be nonspecific, with patients complaining of headache or neck pain followed by focal neurologic signs. There seems to be a male predominance; dissections affecting the carotid circulation have been reported more often than those involving the vertebrobasilar system [31]. History of trauma often is not forthcoming or trauma may be trivial such as a fall [32]. Advances in neuroimaging, particularly in noninvasive techniques such as MR angiography (MRA), have improved our ability to diagnose dissections of the cerebral arteries. MRA may miss the vascular abnormality, particularly in dissections involving the posterior circulation. Particular attention should be paid to the C1-C2 region, as that is the most common site of vertebral artery dissection [33]. Four-vessel conventional angiography remains the gold standard [34]. The risk for recurrent dissection in a study spanning 10 years in children and adults was 12% and seems to be particularly high in the few months immediately following presentation [29].

Anticoagulation may be helpful in appropriate cases though data are too limited to make firm recommendations. Mortality seems to be higher among patients with anterior circulation dissection, particularly intracranial dissections [35].

Moyamoya disease

Moyamoya disease (MMD) is a nonatherosclerotic, noninflammatory, vasculopathy characterized by chronic progressive stenosis or occlusion of the terminal internal carotid arteries and the proximal portions of the anterior cerebral arteries and middle cerebral arteries. MMD, more common among the Japanese, Korean, and Chinese populations, occurs in patients of all races and ethnic groups. It may be familial [36]. Some investigators have suggested that MMD is most likely inherited in a polygenic mode or in an autosomal dominant fashion with a low penetrance [37]. Recent studies have mapped the locus for familial MMD to chromosomes 3, 6, and 17 [37–39]. MMD has been reported in association with a variety of conditions

such as neonatal anoxia, trauma, basilar meningitis, tuberculous meningitis, leptospirosis, cranial irradiation therapy for optic pathway gliomas, neurofibromatosis, tuberous sclerosis, brain tumors, fibromuscular dysplasia, polyarteritis nodosa, Marfan syndrome, pseudoxanthoma elasticum, hypomelanosis of Ito, Williams syndrome, cerebral dissecting and saccular aneurysms, sickle cell anemia, β thalassemia, Fanconi anemia, Apert syndrome, factor XII deficiency, type I glycogenosis, NADH-coenzyme Q reductase deficiency, renal artery stenosis, Down syndrome, and coarctation of the aorta [40]. Aneurysms and arteriovenous malformations have been detected in up to 11% of patients [41]. Presenting symptoms of MMD include headaches, progressive cognitive decline, seizures, and strokes. Nearly half of the patients present before 10 years of age.

MRI shows infarcts in multiple arterial distributions. MRI with contrast shows the collateral developed secondary to stenosis of the major arterial branches (Fig. 2). The angiographic features of MMD include (1) bilateral stenosis or occlusion of the supraclinoid portion of the internal carotid

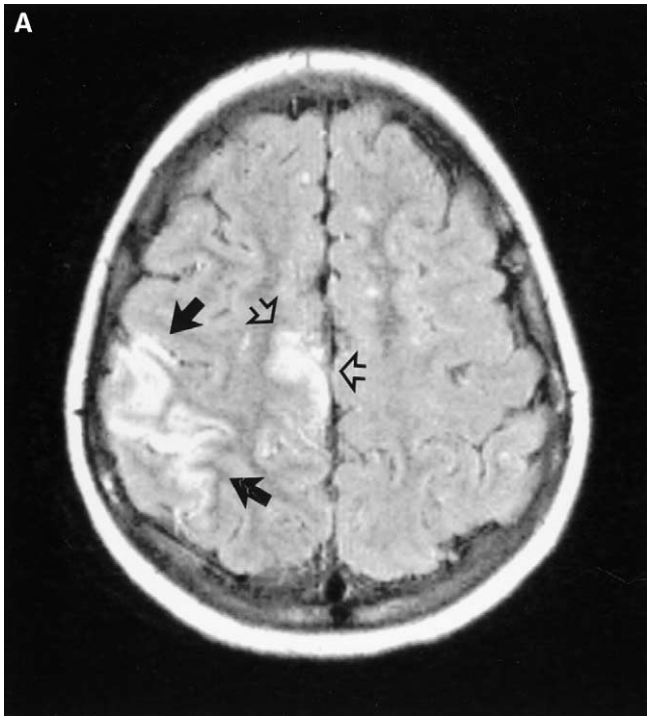

Fig. 2. (A) A 10-year-old girl with history of chronic headaches and developmental delay presented with sudden onset left-sided weakness. FLAIR MRI scan demonstrates right middle cerebral artery (*large arrows*) and right anterior cerebral artery (*open arrows*) distribution ischemic infarcts. (B) Axial contrast enhanced T1-weighted MR scan shows enlarged collateral vessels (*arrowheads*).

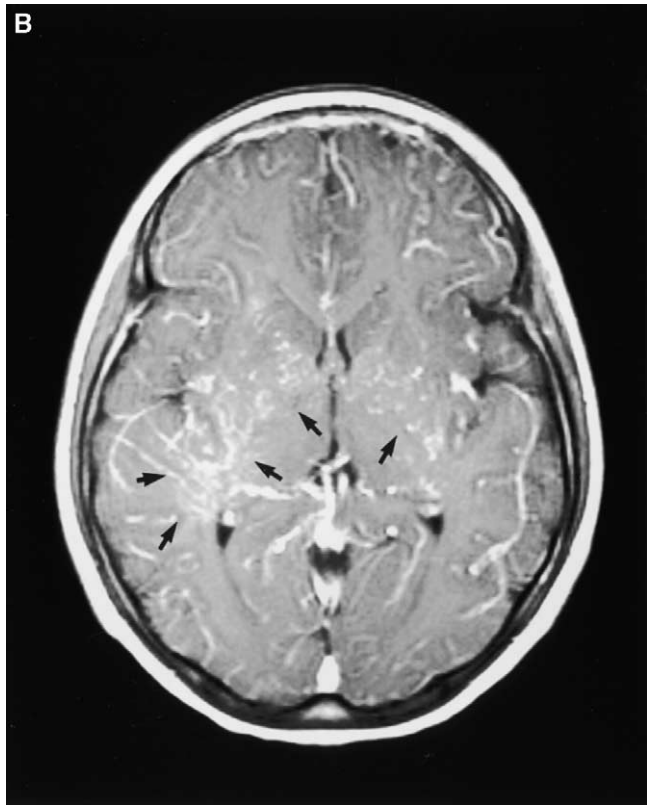

Fig. 2 (*continued*)

artery (ICA) that extends to the proximal portions of the anterior cerebral artery (ACA) and the middle cerebral artery (MCA), and (2) the presence of parenchymal collateral vessels, or Moyamoya vessels (MMVs), from the suprasellar cistern to the cerebral base [42]. MR angiography is an important diagnostic modality for the screening and longitudinal follow-up of MMD [43]. Four-vessel conventional angiography remains the gold standard for the diagnosis of Moyamoya disease. Positron emission tomography and SPECT are useful in the evaluation of perfusion reserve and help guide therapeutic approach [44].

Antiplatelet agents such as aspirin and ticlopidine and calcium channel antagonists (nimodipine and nicardipine) have been used for the medical treatment of MMD [45]. Multiple surgical procedures including encephalomyoarteriosynangiosis (EMAS), encephaloduro-arteriosynangiosis (EDAS), and encephalomyosynangiosis (EMS) have been advocated. Strict maintenance of normotension, euvolemia, and normocapnia, and possibly the use of nimodipine perioperatively, are important measures [40,44,46]. Early

surgical intervention may be beneficial, delaying a decline in cognitive performance and activities of daily living score [47,48].

Cerebral vasculitis

Cerebral vasculitis is an uncommon cause of stroke in children. The authors found that 4% of strokes were attributable to vasculitis in children [49]. Schoenberg et al did not find any cause of vasculitis in children younger than 14 years of age with cerebrovascular disease [6].

Cerebral vasculitis may be infectious or noninfectious. Varicella, bacterial and tuberculous meningitis, and human immunodeficiency virus (HIV) are associated with stroke (Fig. 3) [35,50–54]. Noninfectious cerebral vasculitis may be idiopathic or secondary to a variety of systemic illnesses such as Behçet disease, sarcoidosis, Sjögren syndrome, ulcerative colitis, Kawasaki disease, and Henoch-Schonlein Purpura (HSP), among others [55,56].

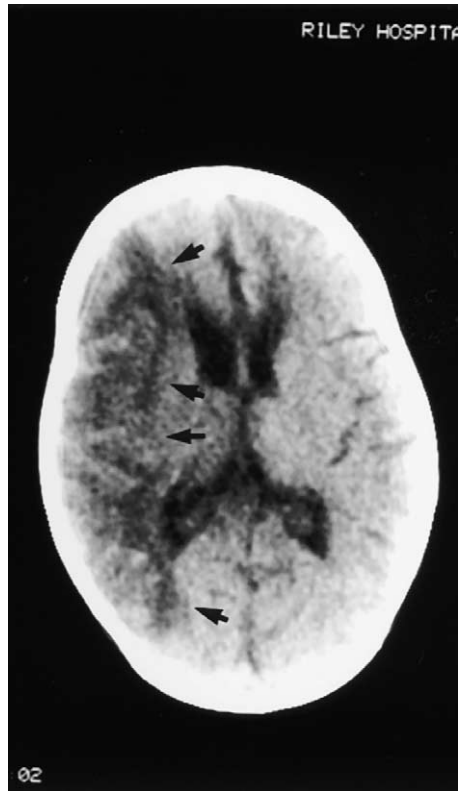

Fig. 3. An 8-month-old girl with bacterial meningitis and sudden-onset left-sided hemiparesis and seizures. Axial head CT without contrast shows a large right middle cerebral artery territory ischemic infarct (*arrows*).

Cerebral vasculitis should be considered when the stroke is associated with systemic manifestations such as persistent fever, weight loss, myalgias, arthralgias, renal disease, and skin lesions. It may present with encephalopathy, meningeal signs, and multiple focal neurologic deficits. Stroke and other neurologic symptoms might be the initial manifestation of vasculitis or complicate the course of a previously diagnosed systemic illness.

Primary angiitis of the central nervous system (PACNS) is an idiopathic vasculitis confined to the CNS. PACNS most commonly involves small vessels, although involvement of medium and large cerebral vessels has been reported [57].

Clinical course is gradual and variable, with headaches, focal seizures, multifocal neurologic deficits, and neurobehavioral impairment, reflecting multifocal or diffuse brain damage. Neuroimaging reveals multiple cerebral ischemic lesions. Cerebral spinal fluid might show elevated protein and mild pleocytosis but is nonspecific. Cerebral angiogram may show multiple vessel involvement or may be normal. Meningeal and brain biopsy may be diagnostic in some cases. Corticosteroids and cyclophosphomide are mainstays of treatment. Outcome is variable [55].

Radiation vasculopathy

Radiation-induced vasculopathy may involve large or small vessels and is confined to the area of irradiation. Delayed capillary endothelial damage leads to breakdown of the blood–brain barrier, vasogenic edema, endothelial hyperplasia, and fibrinoid necrosis of penetrating arterioles in the white matter of the CNS [58]. Large vessels show vessel wall fibrosis and evidence of accelerated atherosclerosis. Foulardi et al found that 25 of 421 consecutive children with CNS tumors treated with radiation therapy developed clinically silent lacunar strokes [59]. A Moyamoya-like picture following radiation therapy of optic pathway gliomas has been reported [60].

Drugs

Illicit drugs are a rare but increasingly recognized cause of stroke in teenagers and young adults. In one case-control study of patients aged 15–44 years, after controlling for identifiable risk factors such as cardiac disease, diabetes mellitus, hypertension, smoking, alcohol use, and pregnancy, and excluding cases caused by endocarditis, the estimated overall relative risk for stroke among young adult illicit drug users was 6.5. The relative risk was even higher at 11.2 in patients younger than 35 years [61]. Cerebral infarcts and hemorrhage have been reported in patients abusing drugs such as amphetamines, ecstasy, cocaine, phencyclidine (PCP), and glue sniffing, among others. Suggested mechanisms include transient cerebral vasoconstriction, unmasking of a pre-existing cardiovascular disease, toxic vasculitis, and prothrombotic tendencies [62].

Sickle cell disease

Sickle cell disease (SCD) is common in the African American population with an estimated incidence of 1 in 400. Strokes occur in nearly 10% of patients with SCD and almost half of these will have a second stroke [63]. There is a high incidence of first-time stroke among younger children, with most strokes occurring before 10 years of age [64]. Cerebral infarction is caused primarily by an occlusive arteriopathy involving the distal intracranial segments of the internal carotid artery, and proximal anterior and middle cerebral arteries.

Transcranial Doppler (TCD) is valuable in detecting arterial stenosis in patients with SCD with velocities of 200 cm/sec or higher associated with a high risk for cerebral infarction [65,66]. There is a drastic reduction in the risk for a first stroke in children with SCD who had abnormal results on TCD and are placed in a transfusion program [67]. Long-term transfusion therapy was associated with a reduced risk for stroke recurrence to as low as 10% and has become routine after stroke in children with SCD [68]. It is unclear how long transfusion should be continued as a means of preventing stroke in children with sickle cell anemia.

Allogenic bone marrow transplantation (BMT) has been used in children with SCD [69]. There are substantial barriers to BMT, however, that include transplant-related toxicity and lack of a suitable human leukocyte antigen (HLA)-matched family donor that preclude its widespread application to patients with SCD [70].

Genetic and metabolic causes

A variety of genetic and metabolic disorders may be associated with strokes in children. Conditions associated with cardioembolic strokes include mitral valve prolapse, Marfan syndrome, tuberous sclerosis complex when cardiac rhabdomyoma is present, hereditary cardiac conduction defects, and hereditary cardiomyopathies [71]. A variety of hereditary coagulation disorders may also predispose children to strokes, as discussed later. Occipital lobes are the most common site of ''stroke'' in MELAS. The strokes in MELAS often do not conform to a vascular territory. Several other metabolic disorders including Leigh disease, organic and amino-acidemias, Sneddon syndrome, carbohydrate-deficiency glycoprotein syndrome, and carnitine deficiency have been reported to have ''stroke-like symptoms'' [72–74].

Homocystinuria is an autosomal-recessive disorder characterized by multiple abnormalities including mental retardation, lens dislocation, and predisposition to cerebrovascular disease. Classic homocystinuria results from deficiency of cystathionine β-synthase enzyme activity. Combined homocystinuria and methylmalonic acidemia and a variant form caused by deficiency of methylenetetrahydrofolate reductase enzyme also are believed to increase the risk for strokes [75]. Hyperhomocysteinemia may also result from nutritional deficiency of folic acid or vitamin B12.

Prothrombotic disorders

Prothrombotic disorders are an important risk factor for stroke in children. A prothrombotic state is an impairment of the normal hemostatic system in which the balance has shifted toward thrombosis. It is most commonly caused by an abnormality or impairment of the vascular endothelium, the coagulation cascade, the fibrinolytic system, or the platelets.

Cerebral infarction has been reported in children who have deficiency of protein C, protein S, antithrombin III, and plasminogen, or the presence of activated protein C resistance (APCR). Presence of mutations such as Factor V Leiden mutation, prothrombin G20210A mutation, homozygous methylenetetrahydrofolate dehydrogenase (MTHFR) polymorphism and antiphospholipid antibodies, hyperhomocysteinemia, and elevated lipoprotein (a) are other risk factors [76,77]. Protein C, protein S, and antithrombin III deficiency may be inherited or acquired. Infection, medications such L-asparaginase, or hepatic and renal disease are the most common causes of acquired deficiency.

Factor V Leiden mutation occurs in 5%–12% of the general pediatric population. Heterozygous carriers have a sevenfold increased risk for thrombosis, whereas the risk for homozygous individuals is increased 80-fold [78]. In a prospective blood bank survey, antiphospholipid antibodies were detected in approximately 6.5% of normal subjects [79]. Children with antiphospholipid antibodies have a significantly increased risk for arterial and venous thrombosis, of which 50% occur in the central nervous system [80]. Lipoprotein (a) is an LDL-like lipoprotein that is usually associated with hypercholesterolemia and is an independent risk factor [81]. Lipoprotein (a) levels are increased in children with arterial strokes when compared with control subjects [82].

The overall incidence of prothrombotic states in children with ischemic strokes is reported to be 10%–50% [80,82,83].

All children with cerebral infarction should be evaluated for the presence of a prothrombotic state. A suggested workup is outlined in Box 2.

Atherosclerotic cerebrovascular disease

Atherosclerotic cerebrovascular disease is rare in children. Dyslipidemic states may hasten this process. In a large retrospective study, lipid abnormalities including elevated triglycerides and low-density lipoprotein cholesterol, and a depressed high-density lipoprotein cholesterol were seen in one third of 42 children with ischemic stroke [84]. More studies are needed to investigate the significance of increased levels of lipoprotein (a) in childhood stroke.

Other risk factors such as hypertension, hyperinsulinemia or insulin resistance, and obesity often coexist [85]. Hypertension is an important and independent risk factor [86]. Diabetes mellitus is another important risk

Box 2. Coagulation work up in children with stroke

Complete blood count including platelets count
Prothrombin time and activated partial thromboplastin time
Plasminogen level
Fibrinogen level
Protein C activity
Protein S activity
Activated protein C resistance
Antithrombin III activity
Antiphospholipid antibodies panel
Homocysteine level, folate level, vitamin B12 level as indicated
Factor V Leiden gene mutation
Prothrombin 20210A gene mutation
Methylene tetrahydrofolate reductase (MTHFR) polymorphism
Lipoprotein a level
Fasting lipid profile

factor in adults but is rarely associated with strokes in children. There has not been a systematic study of the effect of glucose-tolerance abnormalities in childhood stroke [87].

Treatment and outcome in children with arterial ischemic stroke

Determination of the etiology of cerebral infarction in childhood is important because it strongly influences outcome, recurrence risk, and treatment of choice [30]. There are no multicenter controlled clinical trials addressing the efficacy and safety of primary and secondary prevention of stroke in children except those associated with sickle cell disease. This paucity of clinical studies is attributable to a variety of factors: (1) cerebrovascular disorders in children are rare, (2) the diversity and overlapping of risk factors create a heterogeneous patient population, and (3) children tend to present to medical attention with stroke later than adults, making difficult the use of acute treatment such as thrombolytics [88]. Intervention in children with stroke usually follows extrapolation from randomized trial in adults, but the efficacy and safety of applying adult population data in children is not established [89].

When feasible, surgical correction of a cardiac defect is important to prevent recurrence. Anticoagulation is necessary in patients with a demonstrable thrombus either in the heart or in the vessels, as may be seen in a cervicocephalic dissection, because of the high risk for embolic stroke. Some children with a prothrombotic state may also require anticoagulation. Heparin, low

molecular weight heparins, and warfarin are the most commonly used drugs for anticoagulation. Systemic anticoagulation has been controversial and efficacy has not been established in prospective pediatric studies.

Intravascular thrombolysis is controversial and efficacy has not been established in pediatric patients. Thrombolytic agents such as urokinase and streptokinase promote clot lysis by converting plasminogen to plasmin, but also stimulate plasmin-mediated proteolysis of blood coagulation factors [90]. The use of these agents results in a high risk for catastrophic hemorrhage. The tissue plasminogen activator (t-PA) is clot-selective, has a shorter half-life, and produces lower levels of fibrinogen degradation products, but no trial has demonstrated acceptable safety in the pediatric stroke population. The delay in diagnosis that so often occurs in children with ischemic stroke reduces the likelihood that a child with an ischemic stroke will be seen early enough to benefit from thrombolytic agents [91].

Repeated blood transfusions to keep the sickle cell level low are important in the primary and secondary prevention of stroke in children with SCD [67]. Moyamoya disease is best treated surgically, though others and the authors have also used calcium channel blocking drugs in some patients. Corticosteroids are often the mainstay of treatment in noninfectious vasculitis. Supplementation with folic acid and vitamin B12 and the use of cholesterol lowering agents may be appropriate in some children. Aspirin has been used in children despite lack of data supporting its efficacy in preventing stroke in the pediatric population.

Hemorrhagic strokes

Germinal matrix hemorrhage is the most common intracranial hemorrhage in premature infants. Nontraumatic intracranial hemorrhage and that caused by coagulation factor defects has been described in term infants [92,93]. Trauma is the most common cause of intracranial hemorrhage in children. Thrombocytopenia also is an important risk factor for intracranial hemorrhage [94]. Structural vascular lesions are an important risk factor in children with spontaneous intraparenchymal hemorrhage [5,6]. Arteriovenous malformations are the most common cause of nontraumatic intracranial hemorrhage and should always be suspected in children with unexplained parenchymal hematoma. Aneurysms are a common cause of hemorrhage in adults but are rare in children. Other risk factors include hereditary or acquired hematologic disorders, drugs, and neoplastic disease.

Arteriovenous malformations

Arteriovenous malformations (AVMs) of the brain are congenital high-flow vascular lesions. AVMs are characterized by a direct fistulous connection between the arteries and veins without an intervening capillary bed.

An AVM was found to be the cause of hemorrhage in one third of 68 children studied by Al-Jarallah et al [94]. Patients most commonly present with hemorrhage or seizures (Fig. 4); less often headache, mass effect, or focal neurologic deficits are the presenting symptoms. Natural history studies suggest that the average risk for bleeding is 2%–4% per year. The risk for death with an initial rupture of the brain AVM is 10% and the risk increases with each subsequent hemorrhage. Complete surgical resection is the ideal treatment and eliminates the risk for recurrent hemorrhage. This is not always possible, however, because of the size or location of the AVM. Patients may be treated by endovascular and stereotactic radiosurgery that sometimes may be followed by surgical extirpation [95].

Hereditary and acquired coagulation disorders

Factor VII and factor VIII deficiency have been associated with intracranial hemorrhage in children [92,96]. Intracranial hemorrhage may affect 2.6%–13.8% of hemophiliacs and is one of the major causes of death among hemophiliacs. Diagnosis of hemophilia is often overlooked in children presenting with intracranial hemorrhage, particularly if there is a history of head trauma [92].

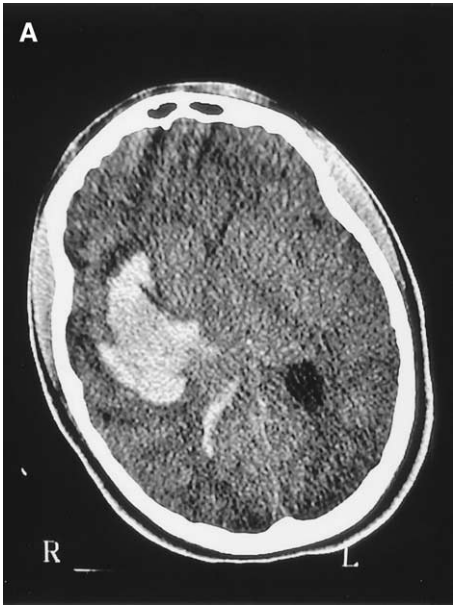

Fig. 4. (A) An 8-year-old boy presented with an acute left hemiparesis, severe headache, and nuchal rigidity. Axial head CT without contrast shows a right frontoparietal hemorrhage. (B) Right internal carotid angiogram, midarterial phase, lateral view, disclosed an arteriovenous malformation (arrow).

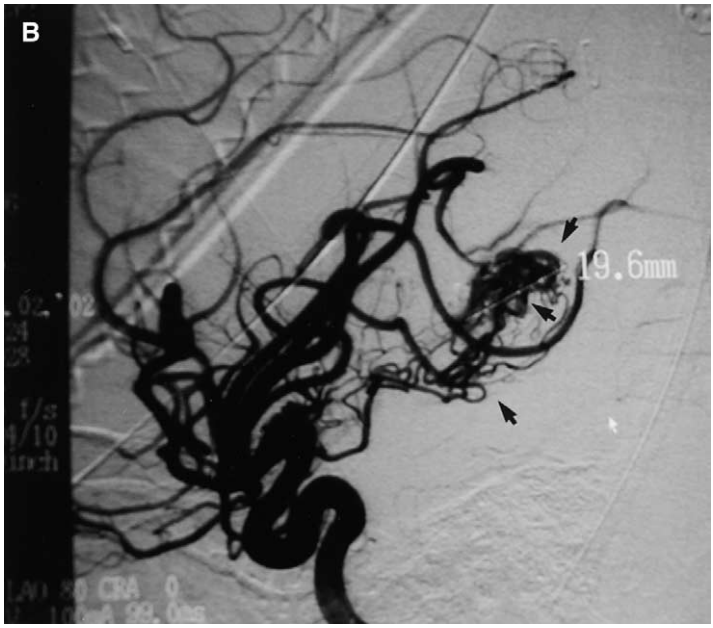

Fig. 4 (*continued*)

Congenital afibrinogenemia is a rare autosomal recessive disorder with an estimated incidence of two per one million births. The condition is characterized by a complete absence of fibrinogen (coagulation factor I), thus impairing fibrin clot formation. The incidence of spontaneous intracerebral bleeding in patients with afibrinogenemia is unknown. Recurrent hemorrhage in patients with afibrinogenemia may be fatal. Fibrinogen level must be checked in children presenting with spontaneous or traumatic intracranial hemorrhage [97]. Intracranial hemorrhage also has been reported with a variety of other hereditary and acquired coagulopathies including Factor V Leiden mutation, Vitamin K deficiency, and renal or liver failure resulting in secondary coagulation factor deficiency [98–100].

Miscellaneous

Hypertension is a common cause of intracranial hemorrhage in adults but not in children. In a series of 68 patients, intracranial hemorrhage could not be attributed to systemic arterial hypertension in any patient [94]. Intracranial hemorrhage may complicate an intracranial tumor. Intracranial hemorrhage may also occur during treatment of childhood malignancies. Intracranial hemorrhage may be the presentation of Moyamoya disease especially in young adults [40]. Hemorrhagic transformation of an ischemic stroke may occur, and broadens the differential diagnosis of brain hemorrhage to include all of the risk factors for ischemic infarction [94].

Diagnostic approach in children with arterial hemorrhagic stroke

A complete medical history including detailed family history is important to identify inherited risk factors for intracranial hemorrhages. A comprehensive coagulation workup should be performed, particularly in the presence of family history of recurrent thrombosis or hemorrhage. CT of the head is the best imaging study to identify acute hemorrhage. Workup also should include MRI, magnetic resonance angiography, and conventional four-vessel angiography in selected cases, especially when a clear risk factor for hemorrhage cannot be established or for patients in whom there is a reason to suspect multiple risk factors. The best time to obtain conventional angiography is unclear, because it might be normal in the acute phase owing to the tamponade effect with the hematoma occluding the blood vessels. In this case angiography should be repeated in a few weeks.

Medical treatment is mainly supportive with adequate oxygenation, ventilation, and hydration. Hypertension should be aggressively treated and secondary hypoxia avoided. Mannitol and steroids are used to decrease intracranial pressure. Surgical hematoma removal might be required, particularly if significant mass effect is present. AVMs usually require surgical intervention. Outcome is variable depending on the cause, localization, and size of the hemorrhage.

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Movement disorders in children and adolescents

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Tourette syndrome (TS) and Sydenham chorea (SC) are prototypical movement disorders that have onset in children. Once considered distinct in etiology and clinical presentation, TS and SC may have overlapping pathophysiology involving common neural, genetic, infectious, and immune factors. Obsessions and compulsions co-occur with both, adding cognitive symptoms to these two disorders of movement. Moreover, the boundary between the two conditions has become blurred by the description of a putative new clinical entity known as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). All three of these conditions seem to involve the circuitry of the basal ganglia, and all may be associated with abnormal regulation of dopamine and/or serotonin. A fourth type of movement disorder, drug-induced dyskinesia, is rare in children but may become more germane as dopamine agonists and antagonists are increasingly prescribed for children. This article reviews current knowledge regarding TS, SC, PANDAS, and drug-induced dyskinesia in children.

Children and adolescents may experience other movement disorders, such as neuroacanthocytosis, Wilson disease, Huntington disease, benign familial chorea, myoclonus, and a number of disorders associated with

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tremor. These have been subjects of recent reports [1,2] and are outside the scope of this review.

Tics and Tourette syndrome

Tics are sudden, stereotyped, coordinated, and involuntary movements or sounds. They may be simple, such as a blink or sniff. Alternatively, tics may be complex, such as gesticulating or uttering words, phrases, or sentences. Although more commonly rapid and brief, tics may also present as sustained expressions, movements, or postures that may be referred to as dystonic tics. Tics may be preceded by premonitory sensations of tension that build until the tic occurs, with a feeling of relief accompanying the occurrence of the tic. Tics may be suppressible for brief periods of time, leading parents, teachers, or others to erroneously believe that the tics are willful or that a child can eliminate tics by "trying hard." Tics may sometimes cause self-injury by hitting, biting, poking, or other complex actions. They may also result in pain or injury to muscles or joints because of repetitive or violent movements. Once thought common, coprolalia (the involuntary utterance of forbidden or insulting words, phrases, or sentences) is rare and is sometimes difficult to distinguish from a psychogenic or pseudo tic.

The major problems caused specifically by tics are usually psychologic and social, resulting from social intolerance and an erosion of the child's sense of self. Tics resulting in injury, pain, or disruption of normal activities deserve pharmacotherapy. Treatment of the child or adolescent with TS must often target symptoms secondary to other neuropsychiatric disorders, including obsessive-compulsive disorder (OCD) or attention-deficit/hyperactivity disorder (ADHD).

Tourette syndrome and the Tourette spectrum disorders

In 1885, a French neurologist published a description of nine cases with a syndrome characterized by multiple motor and vocal tics, echolalia, and coprolalia [3]. The neurologist was Gilles de la Tourette, a student of Charcot at the Salpetriere Hospital. Tourette emphasized the childhood onset, waxing and waning course, and hereditary nature of TS. He also considered the syndrome to be rare and lifelong in duration, concepts that have recently been shown to be incorrect.

Two overlapping systems of classification of tic disorders have recently been published: the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision* (DSM-IV-TR) [4] and the Tourette Syndrome Classification Study Group's system [5]. Both systems treat tic disorders as spectrum disorders with TS at the most severe end of the spectrum. The specific classes of tic disorders in both systems differ from each other on clinical grounds (eg, presence of motor

or vocal tics, duration and course of tics). The Tourette Syndrome Study Group makes a further distinction between tic disorders based only on reported history versus tic disorders based on combined history and observation of tics by an examiner. Evidence supporting distinctions between classes of tic disorders is sparse, but the arbitrary distinctions seem to have utility for clinical and research purposes.

In the DSM-IV-TR, the transient tic of childhood is defined by a duration of less than 12 months, duration of at least 4 weeks, and inclusion of either single or multiple motor and/or vocal tics. Chronic motor or vocal tics may also be single or multiple but are confined to one class (motor or vocal). Duration must be at least 1 year, with no tic-free period of more than 3 consecutive months. The DSM-IV-TR [4] definition of Tourette disorder requires the combination of motor and vocal tics, duration of at least 1 year with no tic-free interval longer that 4 months, onset before the age of 18 years, and exclusion of other causes (direct physiologic effects of a substance [eg, stimulant drugs] or a general medical condition [eg, Huntington disease or postviral encephalitis]). In contrast to the DSM-IV [6], however, the newer definition does not require "marked distress or significant impairment." "Tic disorder not otherwise specified" is the category for cases not fulfilling the required duration or age at onset criteria.

Epidemiology of tics and tic disorders

Gilles de la Tourette estimated the population prevalence of TS as one case per million. Modern studies all agree that the rate is much higher, but differences in methodology give a wide range in prevalence estimates. Scahill et al [7] recently summarized 10 published studies of TS prevalence, estimating the true rate to be 10 to 30 cases per 10,000 children. In general, higher rates have been found in younger age groups, supporting the notion that many cases remit partially or completely by adulthood. Chronic tic disorders are more common than TS, occurring in 2% to 5% of school-aged children [7]. Transient tics seem to be at least as common as chronic tics and may be underestimated because of their transient and perhaps more subtle nature [7].

TS is more common in males than females, with male/female ratio ranging from a high of 10:1 [8] to a low of 2:1 [9,10]. TS also seems to be more common in children than in adults. A study of children and adults with TS in North Dakota resulted in estimates of 9.3 per 10,000 for boys and 0.77 per 10,000 for men, giving boys a prevalence 10 times greater than that of men [11]. Similarly, the rate for North Dakota girls, 1 per 10,000, was higher than the rate for women, 0.22 per 10,000. Tic onset is more common before 7 years of age, and tic severity usually peaks between the ages of 7 and 15 years [12,13]. The temporal clustering of tics within bursts seems to be a fractal pattern that is apparent at different time scales (eg, seconds, hours, days, months) [14].

Causes of tics and Tourette syndrome

Jankovic [15] recently reviewed the causes of tics, subgrouping them into primary and secondary tic disorders. Although the transient tics of childhood and chronic single tics may occur sporadically, they also seem to be alternative expressions of genes conferring risk for the Tourette spectrum. Multiple genes on different chromosomes operating singly or in combination with other genes and/or environmental factors likely contribute to differences in the onset and severity of TS spectrum disorders. Molecular linkage studies suggest that loci on chromosomes 4, 8, and 11 are involved [16,17]. More recently, a reanalysis of the Tourette Syndrome Association (TSA) sib pair sample using OCD symptom factors and a recursive partitioning analytic technique found evidence for hoarding symptoms on chromosomes 4, 5, and 17 [18].

Other idiopathic or hereditary disorders may manifest tics, including Huntington disease, primary dystonia, neuroacanthocytosis, Hallervorden-Spatz disease, Wilson disease, and tuberous sclerosis. Tics may also be secondary to a long list of infections, drugs, toxins, or developmental disorders. SC and drug-induced tics, discussed in detail below, are examples of secondary disorders, although genetic vulnerability still seems to be an important factor.

Perturbation of corticostriatothalamocortical (CSTC) circuits, basal ganglia, and dopaminergic overactivity seem to be common neuropathogenic factors that result in tics [19]. Both pathologic tics and adaptive habits that link sensory cues with motor action apparently arise from the complex parallel CSTC circuits [20]. Autopsy studies have implicated an array of neurochemicals, including decreased 5-hydroxytryptamine, glutamate, cyclic AMP, dopamine reuptake sites, and dynorphin-like immunoreactivity [21–24]. Overall, neuroimaging studies of adults consistently implicate the basal ganglia. Much of the current literature may not be applicable to children, however, and may reflect effects of drug treatment, development, and neuropsychiatric comorbidity [25].

A recent volumetric MRI study of children and adults with TS implicates larger volumes in dorsal prefrontal and parieto-occipital regions and smaller inferior occipital volumes compared with controls [26]. Peterson and colleagues [26] hypothesize that tics result from inhibitory deficits in a broadly distributed action-attentional system involving these brain regions. Smaller volumes in the orbitofrontal and parieto-occipital regions were associated with worse symptoms, possibly resulting in insufficient ability to inhibit tics. In contrast, the larger prefrontal volumes were hypothesized to be caused by an activity-dependent structural plasticity reflecting active tic suppression. Fredericksen and colleagues [27] identified an increase in right frontal white matter, which may suggest a failure of axonal pruning.

Functional imaging studies (positron emission tomography [PET], single photon emission computed tomography [SPECT], and functional MRI [fMRI]) have detected decreased blood flow in the basal ganglia, especially

in the ventral striatum [28–34]. Decreased blood flow of the frontostriatal pathway has been associated with symptom severity [27]. The most consistent differences between groups have been found in the temporolimbic system, which includes the anterior cingulate, parahippocampal, and possibly insular cortices and could be involved with such behavioral functions as impulse control, reward contingency, and executive functions [33,35]. Brain regions involved in attentional functioning (frontal, temporal, and superior temporal association cortices) have also demonstrated significant differences between TS and normal control samples [35]. Radioligand studies have provided modest, although less conclusive, evidence for abnormal dopaminergic activity in the basal ganglia [36–39]. Most findings are sex specific to males and suggestive that females have a different phenotypic morphology [40,41]. This may reflect neurodevelopmental differences between the sexes [42–47].

Treatment of Tourette syndrome

There are three basic principles when considering treatment of TS or another tic disorder. First, the tics require treatment. Parental education, reassurance, and advocacy may be all that is required with less severe tic disorders, which often disappear by young adulthood. For mild to moderate cases of TS, education of the child and family about tics should be the first treatment goal. Increasing tolerance of tics by the child, parents, teachers, coaches, and peers may be the only treatment needed.

Tic-suppressing medication (Table 1) is indicated when tics interfere with activities, lead to ostracism or avoidance of social settings, or cause self-injury. Tics that require pharmacologic intervention should be sufficiently severe that they overwhelm the ability to cope and affect the patient's social or emotional functioning. The decision to begin tic-suppressing medication requires a thorough assessment of the child's tics, including the family and social context. A discussion of the target symptoms is helpful so that the child and parents realize what symptoms are likely to improve. Equally important is an explicit explanation of the limitations and risks for the medication chosen. For example, haloperidol or pimozide, when given alone, is unlikely to improve OCD or ADHD. Furthermore, the patient and the parents should understand that the goal of treating tics with tic-suppressing medication is to make tics tolerable and not to eliminate them. Therefore, improved coping is always a treatment goal.

Second, use the least amount of medication that works. Although this is a good axiom to apply to all patients, it is particularly important for the young TS patient who may require potent medications with serious side effects. The corollary of this approach is to use enough medication to make a difference. Insufficient amounts of a "good" medication may be worse than no medication at all. The patient receives all the risks without compensatory benefits. Thus, drug treatment requires repeated assessment, particularly as the severity of the disorder waxes and wanes.

Table 1
Medical Management of Tics

Medication	Primary indication	Dose	Common side effects
Haloperidol	Suppression of tics	0.25 mg to 3–5 mg/day, qd to tid	Weight gain, lethargy, anhedonia, depression, EPS
Pimozide	Suppression of tics	0.5 mg to 6–8 mg/day, qd to tid	Weight gain, lethargy, anhedonia, depression, EPS, prolonged QT
Risperidone	Suppression of tics, calming of behavior	0.25 mg to 6 mg/day, qhs, bid to tid	Sedation, fatigue, weight gain, tremor, milder EPS
Clonidine	Suppression of tics, calming of behavior	0.025 mg to 0.1 mg tid	Sedation, postural hypotension rare
Clonidine patch	Same as clonidine	TTS-1 patch weekly; increase to TTS-2 or TTS-3 patch as needed	Same as clonidine sedation usually less with patch
Guanfacine	Calming of behavior; possibly suppression of tics	0.5 mg to 1 mg tid	Same as clonidine
Imipramine	Attentional difficulties in person with tics	10 to 75 mg/day qhs or bid to tid	Sedation, tremor, fatigue, irritability
Clonazepam	Suppression of tics	0.25 mg qd to tid to 1 mg tid	Sedation, irritability, behavior change
Tetrabenazine[a]	Suppression of tics	12.5 mg to 75 mg/day	Depression, sedation, anxiety, insomnia, akathisia
Pergolide	Suppression of tics	25 mcg qhs, increase to 50 mcg tid as needed	Minimal dizzyness, sedation, nausea

qd, each day; tid, three times daily; qhs, at bedtime; bid, twice daily; TTS, Transdermal Therapeutic System; EPS, extrapyramidal movement syndromes.

Local botulinum toxin injection has been utilized as an alternative treatment for motor tics.

[a] Not marketed in the US.

Third, comorbid disorders may seriously interfere in the patient's life, although the tics themselves have little impact. A parent may enter the physician's office with the goal of eradicating the newly discovered tics in a child, although the associated OCD, ADHD, or behavioral problems are the major causes of dysfunction. Physicians must assess the whole patient to recognize or exclude other disorders or psychosocial factors that contribute to distress and dysfunction. ADHD frequently co-occurs with TS, as does OCD [48,49]. Anxiety disorders, mood disorders, pervasive developmental disorders, mental retardation, and specific learning disorders have all been reported as comorbid, although such co-occurrence could represent an ascertainment bias rather than true comorbidity. Substance abuse (eg, cocaine, amphetamines) or the use of anabolic steroids can exacerbate tics.

Haloperidol, first reported to be an effective tic-suppressing medicine in the 1960s, is still a mainstay of therapy [50–53]. Shapiro et al [54] argued

that the possibility of effective treatment using haloperidol gave rise to increasing awareness of the disorder among patients and physicians. Pimozide, a dopamine (D_2)-receptor antagonist, is currently the only US Food and Drug Administration (FDA)–approved drug for the treatment of TS in children and adolescents. Both haloperidol and pimozide are widely used. Studies comparing haloperidol and pimozide have provided conflicting results [55,56].

Fluphenazine has also been used with reported benefit [57]. This medication can cause dystonias and dyskinesias. Newer antipsychotics have been tried with some reported success, but controlled studies are rare. A controlled study of clozapine (Clozaril) resulted in an exacerbation of tics at low doses and a lack of efficacy in reducing tics [58]. A comparative, double-blind, parallel-group study of risperidone and pimozide has recently shown efficacy for both drugs in treating patients with TS [59]. Patients receiving risperidone had fewer extrapyramidal side effects. Ziprasidone was effective and tolerable in a randomized controlled trial of children and adolescents with TS [55].

Clonidine (Catapress) has been used frequently in children with TS. Mixed results indicate that this α-adrenergic receptor agonist has less tic-suppressing potency than the neuroleptics. It may be helpful for improving impulse control in comorbid ADHD, but the frequent sedation and short half-life can be problematic for the pill form, and contact dermatitis often limits use of the skin patch form of clonidine. Guanfacine, an α_2-adrenergic cousin to clonidine that offers a longer half-life with fewer side effects, produced improvement in one controlled trial [60].

Pergolide is an ergot alkaloid derivative used in the management of Parkinson disease. Pergolide is a potent dopaminergic agonist at both D_1 and D_2 dopamine receptors. In a recent randomized, double-blind, crossover study, pergolide was shown to be an effective treatment for TS in children [61]. The medication was well tolerated with no serious side effects.

Botulinum toxin (Botox) has been used to treat motor and vocal tics, and a recent double-blind, controlled, clinical trial demonstrated efficacy [62]. Both the frequency of the tic and its associated urge were decreased. Remarkably, patients did not report an overall benefit from the treatment in this study, and the authors urged careful consideration when deciding whether a tic should be treated with Botox. In an earlier clinical trial, a baclofen/botulinum toxin type A preparation was used and found to be effective in treating TS [63]. Baclofen alone may benefit children with TS, as suggested by the results of a recent double-blind, placebo-controlled, crossover trial [64].

Clinical management of Tourette syndrome

Because of the variety of cognitive, behavioral, and emotional difficulties associated with TS, clinicians play an important role in assisting parents and

school professionals to support the child's academic, social, and developmental functioning. In mild to moderately severe cases, support and patience from teachers and parents may be all that is necessary. Educating teachers about classroom accommodations, such as allowing the child to leave the classroom to relieve tics or to take tests privately so as to decrease anxiety can be helpful. Many children with TS have visuomotor difficulties that could be helped by allowing the use of a computer for written assignments, providing photocopies of classroom notes and daily assignments, and permitting oral tests.

Clinical suspicion of a possible specific learning disability should lead to referral to a school psychologist for further academic assessment. Furthermore, collaboration with school professionals is recommended to determine the child's baseline functioning and to monitor response to any intervention [65]. Finally, the Tourette Syndrome Association has an excellent Internet site (http://www.tsa-usa.org) that provides parents, teachers, and professionals with information on educational materials, support services, and related web pages.

Sydenham chorea

Generally considered a monophasic illness in most affected individuals, SC is characterized by the subacute onset of a movement disorder that generally remits over a period of weeks to months [66–71]. Generalized chorea of variable severity is typical. The face, tongue, and upper extremities are usually affected, more or less symmetrically in 80% to 90% of cases. So-called paralytic chorea, prominent hypotonia, and motor impairment simulating muscle weakness occur rarely (<10% of cases), whereas predominant unilateral involvement is evident in up to 40% of the recent Utah cases.

The clinical features of SC include the typical movement disorder, hypotonia, dysarthria, apparent muscle weakness, motor impersistence, and restlessness or hyperkinesis [67–70]. There are often associated emotional and behavioral disturbances [70,72], and writing difficulties in school are common. Onset of SC, as with rheumatic fever (RF) in general, typically occurs between 8 and 12 years of age. There is a female predominance [67–70].

Specific manifestations of the movement disorder and the associated motor impersistence include the "milk-maid's grip" (inability to sustain continuous even hand grip pressure on the fingers of the examiner) and a "darting tongue" (erratic retraction, protrusion, and deviation of the tongue caused by chorea of affected muscles). The movement disorder disappears in sleep and is often intensified on intention. Children often unconsciously attempt to control the movements of the affected limbs (by constraining their movement using body position or other limbs [eg, sitting on their hands]) or consciously disguise the choreiform movements in semivoluntary acts.

The emotional disturbance accompanying SC has long been recognized and classically has been said to include emotional lability, distractibility, and inattention as well as nightmares and night terrors. Obsessive-compulsive symptoms or clinical OCD may accompany SC. Swedo and her colleagues [70,73] reported that 82% of patients with SC had concomitant onset of obsessions and compulsions and that one third met requirements for OCD. More recently, Brazilian children with either SC (n = 20) or RF without SC (n = 22) were found to have increased rates of OCD (13.6% and 10%, respectively) compared with control children (n = 20 [0%]) [74]. This Brazilian study also found increased rates of ADHD and major depressive disorder (MDD) in both SC and RF cases compared with controls. Interestingly, the ADHD and MDD rates were even significantly higher in SC compared with RF. Furthermore, the frequency of tics or TS was also increased in both RF and SC, with the rate in SC being even higher than in RF. A mail survey of 65 Utah SC cases and 35 non-SC RF cases found evidence for OCD in 25% of SC cases compared with 9% of non-SC RF cases (unpublished data). These reports support the hypothesis that similar or related basal ganglia circuitry may be involved in SC, OCD, and other childhood neuropsychiatric disorders.

Virtually all cases of SC resolve spontaneously with time over weeks to months. Recurrences may occur in up to 20%, and more than one recurrence is possible in a given individual [75,76]. The overlap between SC and related immune-mediated causes of chorea (eg, the primary antiphospholipid antibody syndrome or systemic lupus erythematosus) may account for some of these unusual recurrences or relapsing and remitting cases in individuals properly treated with prophylactic antibiotics [77,78]. In addition, pregnancy and oral contraceptive use may result in the re-emergence of chorea in previously affected women (eg, chorea gravidarum). Alterations in cerebral dopamine and other neurotransmitter receptors by sex steroids may provide one mechanism whereby this transient reappearance of chorea may be mediated.

Relation to rheumatic fever

SC is one of the major manifestations of rheumatic fever according to the original and modified Jones criteria (along with carditis, erythema marginatum, arthritis, and subcutaneous nodules) [79,80]. Unlike these other major features, however, SC generally follows streptococcal pharyngitis by a prolonged interval of weeks to 9 months [67]. In addition, in recent outbreaks in the United States, SC has occurred as a solitary manifestation of RF in up to 40% of instances [81–83]. The long interval between streptococcal infection and appearance of chorea also results in a lower rate of positive serologic test results using antistreptolysin O titer (ASO) titer. This makes identification of rheumatic chorea difficult in many cases. Reliance on the ASO titer alone for serologic confirmation of prior infection is suboptimal,

because the anti-DNase B titer persists for a longer interval after group A streptococcal pharyngitis and thus provides more reliable serologic evidence of previous streptococcal infection [84].

In recent outbreaks in Utah, clinically evident carditis was identified in approximately 30% of individuals with SC [82,83]. Other major manifestations of RF were more rare. Prior streptococcal infection had often passed unrecognized and therefore had gone untreated. Veasy and his colleagues [82,83] identified what they considered to be significant subclinical mitral regurgitation on echocardiography in most children with chorea believed to be otherwise consistent with SC (ie, with other proximate causes excluded). If this "silent regurgitation" is accepted as a reliable indicator of rheumatic mitral valve involvement [85–90], most individuals with putative SC in the recent Utah outbreak have carditis. The addition of silent regurgitation as a criterion for RF has facilitated the diagnosis of SC in Utah children with serologic evidence of streptococcal disease and absence of other major manifestations of RF [91].

Laboratory evaluation

The differential diagnosis of SC includes systemic lupus erythematosus [92–94], the primary antiphospholipid antibody syndrome [95–100], Wilson disease, neuroacanthocytosis, Huntington disease, benign familial chorea, other paroxysmal movement disorders, encephalitis [101], acute disseminated encephalomyelitis (ADEM), drug intoxication, and focal basal ganglia lesions caused by stroke, tumor, or even mitochondrial cytopathies.

The first step in diagnosis is a careful history and physical examination seeking to establish the occurrence of other major manifestations of RF and a history of prior streptococcal infection (recent culture or current ASO/anti-DNase B assays). Secondary evaluation in some children with chorea and suspected SC includes the following: serum electrolytes, calcium, glucose, thyroid function tests, complete blood cell count, sedimentation rate, serum copper and ceruloplasmin, antinuclear antibodies, and anticardiolipin antibodies (IgG and IgM). The latter are often elevated in the setting of SC [78] but may also be elevated in the so-called primary antiphospholipid antibody syndrome [96] or in systemic lupus erythematosus (which may present with chorea before the appearance of other systemic disease) [93]. MRI of the brain is generally indicated and is usually normal (see comments below). Identification of serum antineuronal antibodies has been used as a research tool (see comments below), but such assays have limited clinical roles currently. The same applies to detection of the D8/17 antigen (discussed below).

Immunopathogenesis of Sydenham chorea: new developments

The last two decades have witnessed a burgeoning of interest in the immunopathogenesis of RF, SC, and potentially related conditions. Most

new developments have arisen from studies of the putative immunopathogenetic mechanisms of disease combined with novel neuroimaging methods. Following the hypothesis that "molecular mimicry" [102] may account for the occurrence of tissue injury in RF, Husby and colleagues [103] first identified "antineuronal antibodies" directed against human cerebral tissue in the serum taken from children with SC [104–106].

Little subsequent progress was made, however, until the recent resurgence of RF and SC in the United States [81,83] and the emergence of the PANDAS hypothesis [107]. Several subsequent studies have identified autoantibodies directed against human basal ganglia in children with SC [70,108–110], but neither the sensitivity nor the specificity of the assay seems to be particularly high in many of these studies. Furthermore, similar rates of antineuronal antibodies have been identified in a variety of clinical settings (subsumed under the acronym PANDAS), including children with OCD [111–113], children with tic disorders [114,115], and particularly children with ADHD and tics [109]. Likewise, a recent study describes and even better characterizes autoantibodies directed against cerebral tissue antigens in children with ADEM believed to be secondary to acute streptococcal infections (so-called PSADEM) [101]. Thus, the presence of autoantibodies directed against cerebral tissue antigens (particularly against basal ganglia) seems not to be specific to SC. These findings suggest that similar mechanisms of molecular mimicry may underlie a variety of immune-mediated poststreptococcal neurologic disorders [110,116].

The effect of putative immune-mediated targeting of basal ganglia structures has been recently investigated using MRI morphometry and functional imaging (SPECT). Several limited case series have suggested transient T2 signal abnormalities within the caudate and putamen of some children with SC [117–122]. This seems to be a rare finding in our experience and one that might be difficult to replicate. Quantitative studies, however, have identified subtle but statistically significant transient increases in the volume of the basal ganglia during symptomatic SC, followed by a decrement in volume after resolution of the clinical illness [123]. These findings have been proposed to reflect subtle inflammation or edema of these structures, presumably secondary to immune-mediated injury.

Similar findings have been reported in OCD and the PANDAS subgroups [124,125] but not in TS [126]. Likewise, transient hypermetabolism in the contralateral basal ganglia has been clearly demonstrated in several children with rheumatic hemichorea, with resolution of the hypermetabolism after clinical remission [66,69,119,127–129]. Thus, a neurophysiologic correlate to the observed movement disorder may be demonstrable using functional neuroimaging techniques, indicating dysfunction of the extrapyramidal system in SC. No volumetric changes were found in the total cerebral, prefrontal, midfrontal, or thalamic cortices.

Treatment of Sydenham chorea

No report on a controlled treatment trial has been published regarding the management of SC. Approaches to treatment can be either symptomatic or immunomodulatory [67,68,130]. The most important strategy is to prevent recurrence by prophylactic antibiotic management. Some controversy exists regarding the optimal interval for administration of intramuscular benzathine penicillin, with some investigators promoting a 3-week interval rather than the standard 4-week interval [131]. Consensus on this issue remains to be reached [75,80]. The reader is referred to the *2000 Red Book* published by the American Academy of Pediatrics [132] for current recommendations regarding antibiotic prophylaxis.

Because SC remits spontaneously in most patients, treatment should be reserved for more severely affected children. Children who fall frequently or cannot feed themselves are candidates for drug treatment. Symptomatic treatment includes most medications used for the treatment of chorea and other hyperkinetic movement disorders in other circumstances, including neuroleptics (primarily haloperidol), benzodiazepines (clonazepam and clorazepate), valproic acid, depleters of synaptic dopamine (eg, reserpine and tetrabenazine), and perhaps baclofen. This wide array of options underscores the often unsatisfactory clinical response to such agents. The risk of tardive dyskinesia from haloperidol, although present, is probably remote.

Immunomodulatory therapy may include oral steroids, intravenous immunoglobulin, and plasmapheresis, although the latter two are expensive and are not endorsed for general clinical application even by the investigators reporting on their use [133]. Benefit from plasmapheresis and intravenous immunoglobulin in SC has been reported [130], and this response lends credence to the immunopathogenic hypothesis of SC. Since the resurgence of SC in the intermountain western United States in 1985, pediatric neurologists at the University of Utah have considered prednisone to be the drug of first choice in SC of sufficient severity to warrant treatment [134]. The drug is given at a dose of 1 to 2 mg/kg/d for 7 to 10 days, followed by a gradual taper over a similar period. Most children respond well, although the natural history of the disease makes assessment of efficacy difficult without a controlled trial. Occasional patients have seemed to relapse during or after reduction in the prednisone dose but have improved again with a second course. No serious complications have been encountered.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

The acronym PANDAS is based on cases of OCD and tics studied at the National Institute of Mental Health (NIMH) [73,135–137]. The conceptual model postulates that antibodies against basal ganglia are triggered by

streptococcal infection in a manner analogous to SC. The NIMH working definition requires the abrupt onset of tics or OCD after infection with group A β-hemolytic streptococcus (GAS) in prepubertal children, with motoric hyperactivity and adventitious movements but not frank chorea [136]. The explosive onset of symptoms is said to distinguish PANDAS from the typical case of TS or OCD, which usually begins gradually.

By this definition, PANDAS differs from RF and represents a subset of the TS spectrum disorders (tics, TS, and OCD). The precise boundaries of PANDAS, SC, and the TS spectrum have not been established [138–141]. It seems possible that there may be multiple shared risk factors across these conditions, including genetic vulnerabilities in families, pathogenic features of particular GAS strains, seasonal exposure modulated by crowding, and age-specific brain or immune vulnerabilities.

Unfortunately, proof of a GAS-triggered autoimmune pathogenesis is likely to be challenging because of the hypothesized extended duration from exposure GAS and onset of PANDAS, the high incidence of GAS infections in children, and the absence of laboratory or neuroimaging tests specific for either SC or PANDAS. On the positive side, several preliminary studies offer exciting and provocative results that support extensive follow-up studies. These early results include D8/17 assays, family studies, neuroimaging, treatment, and immune studies.

D8/17 is a monoclonal antibody that reacts with antigens on B-lymphocytes (reviewed by Murphy and Goodman [142]). Originally developed in the context of RF research, greater D8/17 reactivity occurs in RF cases and perhaps in individuals at greater genetic risk for RF [143–145]. Thus, D8/17 may be a marker for genetic susceptibility to RF and a marker for PANDAS. In Swedo et al's (1997) study [137], 23 of 27 (85%) PANDAS patients, 8 of 9 (89%) SC patients, and 4 of 24 (17%) healthy children were D8/17-positive. The results of this study seem to be consistent with Murphy et al's study of children with TS and OCD [146]. Both studies raise the exciting possibility that D8/17 reactivity may help to clarify the relation between SC, PANDAS, and the genetic subtypes of TS and OCD. The reliability, sensitivity, specificity, and methodology of D8/17 have not been adequately documented, however [142]. Studies in Utah and elsewhere are underway, but assay of D8/17 has not been established as a clinical test at this point.

Family studies support the PANDAS concept. The relation of PANDAS in probands to TS and other psychiatric disorders in family members has been studied by the NIMH group [147]. First-degree relatives of PANDAS probands had high rates of tics and/or OCD. This suggests that genetic factors probably contribute to the risk of PANDAS, although it can also be argued that family members share environmental exposures, especially to GAS. Preliminary data from a mail survey of 100 Utah RF cases support the NIMH observations but raise questions about the boundary between PANDAS and SC. In 14 of 65 (22%) individuals with SC in Utah, at least one first-degree relative had a history of tics, TS, or OCD. Curiously, only

2 of 35 (6%) of those RF patients without SC had a first-degree relative with tics and/or OCD. The difference in reported TS spectrum disorders between SC and non-SC RF families is statistically significant ($z = 2.08$; $P = 0.02$). This preliminary result suggests that SC and TS spectrum disorders may share genetic susceptibility factors. It also raises the question as to whether PANDAS and SC are truly separate entities.

Immune studies

Besides D8/17, immunologic support for the PANDAS model comes from other antibody studies of subjects with tics and OCD, from a provocative animal model, and from treatment studies (described below). Several groups have detected elevated antineuronal antibodies in patient sera [109,110,115,148–150]. Morshed and colleagues [110] reported elevated antinuclear antibodies in TS compared with controls. Serum ASO and anti-DNase B titers were not found to be associated with tics or OCD, but higher titers were associated with ADHD [151]. Furthermore, higher titers were also associated with an increased volume of basal ganglia on MRI [152]. Finally, Hallett and colleagues [153] have reported that serum taken from TS patients causes motor and phonic stereotypies reminiscent of tics when microinfused into rat striatum. If replicated, this animal model may provide an important methodologic advance.

Treatment of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

PANDAS cases have been treated at the NIMH with total plasma exchange, intravenous immunoglobulin, and antibiotic prophylaxis [139]. Plasma exchange and immunoglobulin produced significant improvement, but prophylaxis did not. Tucker and colleagues [150] at Yale University treated a single case of PANDAS with total plasma exchange, resulting in clinical improvement and a concomitant decreased volume of basal ganglia on MRI. Although these research studies lend support to the PANDAS concept, further research is needed before a clinical standard of care can be formulated. Currently, clinicians are advised to assess abrupt onset or treatment-resistant cases of TS and/or OCD for evidence of GAS pharyngitis and to treat children suffering from pharyngitis with penicillin or an appropriate alternative [139]. Total plasma exchange and intravenous immunoglobulin should not be administered outside of a research protocol.

Drug-induced movement disorders

Numerous medications can induce movement disorders. In children, the most common relevant medication exposures include stimulants, neuroleptics, and antidopaminergic antihistamines. Stimulants, whether prescribed

to treat comorbid ADHD or used as substances of abuse, have been reported to provoke tic onset or severity. Recent prospective studies of stimulant treatment of children with concurrent tics and ADHD found that such treatment was relatively safe, particularly if dosage changes are small and gradual [154,155]. Long-term risks for stimulant exposure on the natural history of tics are not known, however [156].

Movement disorders have been attributed to many other drugs, but the literature describing such associations comes largely from adult populations [157]. Dopamine antagonist activity provides a model mechanism for the prototypical neuroleptics and antihistamines. Other drugs reported to cause movement disorders in children include phenytoin, carbamazepine, chloroquine, and vincristine. Acute dystonia, parkinsonism, akathisia, treatment emergent dyskinesia, and withdrawal emergent dyskinesia are all potential complications of neuroleptic treatment. Unfortunately, the literature on these disorders in children is sparse [157].

The term *tardive dyskinesia* (TD) was originally applied to a specific pattern of continuous orobuccal dyskinesia emerging during the chronic treatment of schizophrenic adults with neuroleptic medications. With time, variations of this condition have been recognized and discussed, including tardive dystonia, withdrawal dyskinesias, and tardive TS. The pathophysiology of these conditions remains to be clarified, but dopamine receptor upregulation and other pharmacologically induced alterations in neural circuitry have been proposed as potential causes. Recent investigations suggest that specific inherited genetic polymorphisms of the dopamine type 3 (DRD3) receptor (a ser-to-gly substitution in exon 1 of DRD3) and/or of the serotonin type 2C (5-HT2C) receptor (cys-to-ser substitution) may predispose to the emergence of TD [158–160].

Given the widespread use of typical and atypical antipsychotic medications in children with schizophrenia, autism, aggressive behavior disorders, mood disorders like bipolar disease, and tic disorders [161–164], drug-induced tardive movement disorders are a potential concern. Although studies of TD in pediatric patients have been largely retrospective, they suggest that such treatment is not benign, with TD or related tardive or withdrawal emergent dyskinesias occurring in up 10% to 20% of patients [162–167]. The risk seems to be increased in girls, in children with a strong family history of movement disorders, during longer duration of neuroleptic administration at higher doses, and possibly in association with on-off use of these medications [168].

Extrapolating from studies in adults, it is likely that TD occurs more frequently in the setting of schizophrenia than in other neuropsychiatric conditions [168,169]. In fact, there is considerable evidence that orobuccal dyskinesias may represent an inherent feature of schizophrenia rather than a consequence its treatment [168,169]. In this respect, it is interesting to note that the risk of TD in the treatment of TS and tic disorders may be low. Although several experts have reported cases of TD in their TS patients

treated with neuroleptics [170,171], pediatric TS clinics in Utah have not identified a single case of persistent TD in the cumulative experience of nearly 40 years (>300 pediatric patients treated up to early adulthood). Likewise, no cases of TD occurred among 65 children treated with pimozide by Regeur and colleagues [172]. Therefore, the risk of TD in children treated for TS and tic disorders must be quite low during childhood and adolescence [173]. It is likely that the risk of TD is higher with the increased exposure required by decades of treatment in severe lifelong TS.

Finally, it is hoped that the use of atypical neuroleptics reduces the occurrence of TD in at-risk populations [161,174,175]. The development of these agents has in large part been directed toward identifying agents effective for the "negative symptoms" of schizophrenia but with lower risks of extrapyramidal symptoms. Although cases of TD have apparently been identified after treatment with risperidone, for example [174,176,177], studies to date suggest that the risk of TD and other tardive movement disorders is likely to be much lower with these atypical neuroleptic agents than with conventional higher potency dopamine antagonists [161].

No single treatment is recognized to be superior for the treatment of tardive movement disorders [1,2]. In children, discontinuation of the offending agent is usually followed by gradual disappearance of the dyskinesia. Various interim treatments have been proposed, including tetrabenazine, baclofen, valproic acid, benzodiazepines, and atypical neuroleptics [1,2].

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Rett syndrome
Current status and new vistas

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Imagine that you encounter a puzzling condition affecting young girls and, despite repeated attempts, are unable to convince other clinicians that they represent a unique and previously unrecognized syndrome. Then, fast forward 35 years and find that not only has this syndrome been associated with mutations in a specific gene but that a myriad of other clinical presentations may result from mutations in this gene. Such is the history of Rett syndrome (RS). Unfortunately, Andreas Rett did not live to realize the fruits of these findings. Nevertheless, his initial observations and his persistence in pursuing the underlying basis of RS have opened important new vistas in neurodevelopmental disorders and, more broadly, in neurobiology.

In the early 1960s, Rett, a developmental pediatrician in Vienna, recognized this syndrome as a neurodevelopmental disorder predominantly affecting young girls [1]. His early accounts of RS were, however, brief and not widely circulated. Bengt Hagberg noted girls in Sweden with similar clinical features about the same time. Nevertheless, not until 1983 did Hagberg and colleagues [2] report their experiences with RS in Sweden, France, and Portugal in the first widely circulated English language publication on the disorder. In short order, RS was identified in the United States, Japan, and throughout Western Europe [3–6]. Several epidemiologic studies (Table 1) were conducted, producing prevalence rates ranging from 1:10,000 in Sweden [7] to 1:22,000 in Texas [8]. As such, it is now clear that RS occurs throughout the world and is the leading cause of profound cognitive impairment in girls and women.

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Table 1
Prevalence of Rett syndrome

Location	Year	Number	Prevalence
Western Scotland	1982	19	1:15,000
Switzerland	1982	27	1:24,600
Western Sweden	1982	12	1:13,000
Japan	1988	24	1:25,000
Texas	1990	103	1:22,800
Australia	1995	79	1:22,000
Sweden	1996	69	1:13,000

Clinical characteristics

RS (Fig. 1) is characterized by profound cognitive impairment, communication dysfunction, stereotypic movements, and pervasive growth failure, which follow a period of apparently normal development for the first 6 to 18 months of life [9]. All attempts to find a biologic marker were unsuccessful until the recent identification of a gene for RS [10]. The diagnosis of RS, however, is based on clinical criteria (Table 2) [11,12], because not all girls with the RS phenotype have mutations in this gene (see below). These include normal pre- and perinatal periods and apparently normal development for the first several months of life. Thereafter, purposeful hand skills are lost along with regression of psychomotor and communication functions. These changes may occur as early as 6 months of age or as late as 2.5 years. Some girls may have features of the autistic spectrum disorders in the sense that eye contact is poor and attempts at socialization and

Fig. 1. Six-year-old girl with typical features of Rett syndrome and mutation in *MECP2*.

Table 2
Diagnostic criteria for Rett syndrome

Criteria	Onset
Apparently normal prenatal and perinatal periods	—
Psychomotor development may seem normal through 6 months or may be delayed from birth	6–8 months
Postnatal deceleration of head growth rate in most children	3 months–4 years
Decrease of purposeful hand skills	6 months–2.5 years
Communication dysfunction and social withdrawal	9 months–2.5 years
Severely impaired expressive and receptive language and psychomotor impairment	
Stereotypic movements	1–3 years
Hand washing/wringing	
Hand clapping/patting	
Hand mouthing	
Impaired or absent locomotion	1–4 years
Absence of other disease process	
Organomegaly	
Optic atrophy	
Retinal changes	
Intrauterine growth retardation	

communication are severely limited. Profound irritability without apparent explanation is often noted in these early years. Rett noted deceleration in the rate of head growth [1]. This finding may appear as early as 3 months of age and may represent the first clinical sign of RS. It may also be profound, leading to microcephaly in some girls [13]. Stereotypic hand movements emerge between the ages of 1 and 3 years and are characterized by hand-washing, hand-wringing, or hand-clapping/hand-patting movements. Hand stereotypies occur typically but not exclusively in the midline. Occasionally, hand mouthing or picking at the hair or clothes is the predominant stereotypy. Most girls with RS are able to walk; however, gait is apraxic, broad based, wandering, and purposeless in character. Walking is often initiated by first stepping backward (retropulsion). Side-to-side rocking is common.

The diagnosis of RS requires a careful history and neurologic evaluation to include growth and developmental parameters. Ancillary evaluations should include audiologic and ophthalmologic assessments, chromosome analysis with high-resolution banding, and the molecular probe for Angelman syndrome (AS). Many behavioral features associated with RS resemble clinical seizures. Thus, video-electroencephalography (EEG) monitoring, if available, is recommended. An extensive investigation for inherited metabolic disorders is not warranted. Despite intensive investigations of amino and organic acids, mitochondrial function, and urea cycle metabolism, no consistent metabolic abnormality has been identified.

Definitive diagnosis is accomplished by mutation analysis on leukocyte DNA for the gene *MECP2*, which encodes the methyl–cytosine-guanosine (CpG)–binding protein 2 (MeCP2).

Clinical staging

RS has been characterized in four clinical stages [14], providing a format for plotting clinical progression. The transition from one stage to the next is generally along a continuum rather than an abrupt change. The first stage is the early-onset stagnation period, which occurs from the age of 6 to 18 months. Usually, this stage lasts weeks to months and consists of delay in developmental progress but no clear evidence of regression. The second stage is that of rapid developmental regression with an onset from the age of 1 to 3 or 4 years. This stage may be relatively brief, lasting days to weeks or as long as a year. Acquired skills in motor and communication function are lost and impairment of cognitive performance becomes apparent. At this stage, RS must be differentiated from autistic spectrum disorders, infantile neuronal ceroid lipofuscinosis, AS, or an acute toxic or infectious encephalopathy. Infantile neuronal ceroid lipofuscinosis and AS feature deceleration in the rate of head growth, seizures, and stereotypic movements resembling RS. The natural history of these two disorders is quite different from that of RS, however, and both can now be diagnosed by appropriate molecular genetic or biochemical testing. The third or pseudostationary stage, which may last for several decades, is reserved for those girls with preserved ability to walk. During this stage, communication functions such as socialization and eye contact may improve remarkably. Conversely, motor function may slowly decline such that ambulation and stereotypic hand movements diminish in speed and frequency. Ambulation often continues into middle age. In stage 3, RS must be differentiated from the ataxic static encephalopathies, spinocerebellar degeneration, AS, and neuronal ceroid lipofuscinosis as well as idiopathic psychomotor retardation. The fourth or late motor deterioration stage is achieved with the loss of ambulation, that is, when wheelchair dependency is complete. For those girls who never walk, staging moves directly from stage 2 to stage 4. Thus, stage 4 is now subdivided into girls who lose ambulation (4A) and those who never ambulate (4B). Girls in stage 4B are remarkably hypotonic and develop severe motor disability with muscle wasting and skeletal deformities. Despite transition to stage 4, eye contact and socialization may be quite intense even into adulthood.

Variant phenotypic expression

Variant phenotypic expressions of RS are well described. The so-called forme fruste is the most common, consisting of delay in onset until the age of 8 to 10 years [15]. Other atypical forms include a preserved speech variant [16], a congenital form in which no period of developmental progress is noted, and an early-onset seizure form [17]. The relatively severe epileptic encephalopathy of the early-onset seizure form results in little or no normal early development.

Hagberg and Skjeldal [18] developed criteria for delineating the variant phenotypes (Table 3). In a Swedish cohort, Hagberg [9] noted that of 130 girls, 82% of cases fulfilled the classic criteria, 12% were forme fruste, and the remainder included preserved speech or congenital forms.

Rett syndrome in boys and men

Convincing descriptions of boys and men with RS are limited. RS has been described in boys with more than one X chromosome (Klinefelter syndrome [XXY]) [19–22]. Alternatively, mutations in *MECP2* have been identified in male patients with features quite different from those of RS. These include individuals with a rapidly progressive encephalopathy [19,23–25], severe developmental delay [26–28], spastic paraparesis [29], and nonspecific mental retardation [30,31].

Specific clinical issues

Several specific clinical issues should be noted. These include longevity, cognitive impairment, seizures, breathing irregularities, scoliosis, ambulation, growth failure, gastrointestinal function, and self-abuse. In general, survival is quite prolonged, and growth failure is pervasive.

Longevity

Survival into middle age is typical. In the only systematic study, survival in RS followed that of all girls up to the age of 10 years. Survival to the age of 35 years was approximately 70% compared with 98% for all women and 27% for women with profound cognitive psychomotor impairments. These

Table 3
Diagnostic criteria for Rett syndrome variants

Main criteria	Supportive criteria
Loss of finger skills	Irregular breathing
Loss of babble/speech	Teeth grinding
Loss of communication skills	Scoliosis/kyphosis
Deceleration of head growth	Lower limb amyotrophy
Hand stereotypies	Cold purplish feet
RS disease profile	Laughing/screaming spells
	Bloating
	Gait dyspraxia
	RS electroencephalographic pattern
	RS eye pointing
	Pain indifference

RS, Rett syndrome.

Inclusion criteria: patient must meet at least 3 of 6 main criteria and 5 of 11 supportive criteria.

data have important implications for counseling parents about long-term care and future planning, because these women may well outlive their parents.

Cognitive impairment

Cognitive function is difficult to assess in RS. Without effective fine motor and communication skills, available standardized tests are problematic. Test results indicate a mental age at the 8- to 10-month level and gross motor function at the 12- to 18-month level. Assessments, which depend only on visual response, also yield cognitive levels in the severely impaired range. Adaptive skills (feeding, dressing, and toileting) are never acquired effectively, again presenting important implications for long-term care. To maximize their functional level, girls with RS should receive appropriate educational and habilitation service in physical, occupational, and speech therapy, including augmentative communication [32].

Seizures

Reports of seizure frequency yield variable rates ranging from 30% to 80% [33–36]. After the age of 2 years, EEG findings are invariably abnormal, featuring slowing in background activity, reduction or loss of posterior dominant rhythm, and recurrent spike and slow spike and wave activity. Clinical seizures may be infrequent or absent in most girls. Differentiating behavioral patterns from seizures may be difficult without video-EEG monitoring.

Seizure control with carbamazepine or sodium valproate is typically not difficult. Lamotrigine has also proved effective [37,38]. Although generally well tolerated, carbamazepine may produce agitation or self-abusive behavior. Caution is recommended regarding the use of sodium valproate because it has been shown recently to inhibit the activity of histone deacetylase (HDAC), a key component in transcription regulation [39]. As such, inhibition of HDAC could exacerbate the effect of a mutation in *MECP2* (see below).

Breathing irregularities

Irregular breathing during wakefulness, consisting of hyperventilation or breath holding, was first recognized by Rett [40–42]. In some instances, both may occur. Breath holding may be prolonged and alarming, occasionally exceeding 1 minute. In other girls, it may be quite subtle and hence underreported. Air swallowing (aerophagia) is common and may produce striking abdominal distention. Distention subsides during sleep.

Typically, irregular breathing has its onset in early childhood (3–5 years) and is maximal during early school age (5–10 years). It may dominate much of the waking activities. Thereafter, breathing irregularities diminish in

frequency and intensity. Efforts to modify breath holding or hyperventilation have generally been unsuccessful. The opiate antagonist naltrexone may provide benefit, but this response is not uniform and may simply reflect its sedating properties [43].

Irregular breathing during sleep is not typical of RS and should be assessed for causes of obstructive apnea.

Scoliosis

The incidence and severity of scoliosis increases with age, being present in approximately 8% of affected girls before school age and in more than 80% over 16 years of age [44–48]. The overall incidence is approximately 50%. Onset is typically noted at the age of 8 years or somewhat before. Progression, which is much more common in those girls who do not walk, may become clinically significant and require medical or surgical attention. Bracing is considered with a 25° curvature, but evidence of effectiveness is lacking. Surgery is recommended strongly when curvature exceeds 40°. In general, this procedure is tolerated well.

Ambulation

Ambulation occurs in 80% of girls with RS, but one quarter of these girls lose their ability to walk during or after the period of regression. Overall, approximately 60% of girls with RS remain ambulatory. Ambulation is encouraged as long as possible; failing this, weight bearing, including the use of standing frames, is encouraged. Bones tend to be undermineralized, and weight bearing may aid this problem.

Growth failure

Growth failure is pervasive, with the first evidence being deceleration in the rate of head growth as early as 3 months of age [13,49]. Median head circumference values fall to the second percentile for the normal population by the age of 4 to 5 years. Weight begins to decline from normal near the end of the first year of life, with the median value falling below the fifth percentile for the normal population by the age of approximately 7 years. Height or length falls off around 15 months of age. The median values again reach the fifth percentile for the normal population around the age of 7 years. Hand and foot growth is also involved, with the feet affected more than the hands. The reduction in the rate of foot growth parallels that of height [50].

Gastrointestinal function

Nutrition can be a major problem in RS. Girls with RS seem to have increased protein requirements [51–53]. Gastrostomy feeding may be

necessary in some girls to preserve growth as such. The guidance of a nutritionist with regard to dietary supplementation may be required.

Gastroesophageal reflux and esophagitis are common and help to account for recurrent periods of irritability or apparent distress. Constipation is another significant problem. Various strategies, including high-fiber foods, enemas, mineral oil, and milk of magnesia, have been variably successful. The frequent use of enemas may lead to dependency on this mode of treatment, and prolonged use of mineral oil may interfere with proper absorption of the fat-soluble vitamins. Despite the availability of flavored milk of magnesia, many girls resist taking it. Most recently, polyethylene glycol (Miralax) has proved particularly effective. It is tasteless and odorless and may be dissolved in juice, making it more palatable and much better tolerated.

Gallbladder dysfunction has also been recognized as a significant problem. Systematic study has not been conducted, but the occurrence of this problem, especially in younger children, seems to exceed that in the general population.

Self-abuse

Self-abusive behavior, such as hair pulling; biting of the fingers, hands, or other parts of the upper extremities; and hitting themselves about the face, is seen occasionally. Aggressive behavior toward others (hitting, biting, or hair pulling) may also occur. Before considering pharmacologic intervention, care should be taken to exclude other medical problems, particularly gastrointestinal dysfunction (gastroesophageal (G-E) reflux, constipation, gallbladder dysfunction) as noted previously or as a side effect of medications already in use. After excluding such problems, low-dose risperidone (0.5 mg twice daily) may be effective.

Other associated features

Bruxism (teeth grinding), interrupted sleep patterns, and vasomotor disturbances comprising cold feet and hands are common. Bruxism tends to be most prominent during early childhood and is resistant to medical management. Sleep is often fragmented [40], in some instances, for many nights in succession. This may result in disrupted sleep for the parents. Girls with RS may awaken in the night and be found playing quietly or laughing for no apparent reason. As such, chloral hydrate, diphenhydramine, or hydroxyzine may be required.

Vasomotor disturbances seem to represent autonomic nervous system dysfunction. Sympathectomy occurring during surgery for scoliosis has been noted to reverse these findings on the operated side. No effective treatment is available.

Long-term management

Presently, long-term management of girls with RS involves appropriate physical and occupational therapy, speech therapy, nutritional support, orthopedic intervention, and seizure control [9,32]. As noted previously, the potential longevity of women with RS requires long-term planning, because the parents may not be able to manage these needs as they age.

Neuropathology

The characteristic neuropathologic findings in RS consist of reduced brain weight, reduced volume of frontal cortex and deep gray nuclei, reduced melanin deposition in the substantia nigra, smaller neurons, reduced dendritic arborizations, and the absence of any recognizable disease process, particularly a progressive neurodegenerative disorder [54–58]. As such, the fundamental neurobiologic mechanism seems to be an arrest in normal neuronal maturation, giving RS the profile of a neurodevelopmental and not a neurodegenerative disorder.

The brain has a normal appearance but is approximately 60% to 70% of expected weight for age. Brain weights are uniformly low across the age spectrum with no pattern of progressive reduction with increasing age. Neuronal migration is normal, but the neurons are too small, too close together, and have too few processes. Dendritic arbors are markedly shortened and relatively primitive, resulting in increased cell packing density. These findings suggest a failure in the proper development or maintenance of synaptic connections. Several other neurodevelopmental disorders have similar neuropathologic features. In Down syndrome, dendritic branches are already deficient by 4 months of age, remaining so into adulthood [59]; in AS and fragile X syndrome, dendritic arborizations and spines are reduced [60–62]; and in autistic spectrum disorder, increased cell packing density and decreased cell size are typical [63].

The involvement of multiple neurotransmitter systems and the abnormalities in dendrite formation suggest that the impact of cellular dysfunction begins in the last third of gestation or early in infancy. The facts that neuronal proliferation and migration proceed appropriately and that deceleration in the rate of head growth is already present by 3 months of life suggest this temporal boundary.

Genetic basis of Rett syndrome

RS is a genetic disorder predominantly affecting girls and women and is transmitted in an X-linked dominant fashion with presumed lethality in boys and men. RS is sporadic in more than 99% of affected girls and women; that is, recurrence within families is less than 1%. Thus, for the most part, RS represents new mutations.

Despite the small number of familial cases, linkage studies were able to focus attention to Xq28, a gene-rich region [64,65]. As a result, mutations were identified in the gene *MECP2*, which encodes MeCP2 [10]. MeCP2 is expressed throughout the body but is highly expressed in brain. An array of *MECP2* mutations has been defined in girls or women with RS, but about two thirds of those with a molecular diagnosis are represented by eight specific mutations [10,19,25,66–82].

At present, mutations in *MECP2* have been identified in 80% to 85% of girls and women with classic RS, a figure which is likely to increase as the gene is sequenced more completely. In the case of variant forms of RS, the proportion with mutations in *MECP2* is less than 50%. Girls or women with RS demonstrate a broad range of functional capabilities presumably related to differences in the specific *MECP2* mutation. In terms of phenotype-genotype correlations in girls with classic RS, the most important determinant of clinical severity seems to be variability in X chromosome inactivation (XCI) [83], although the position and type of mutation are also important [19,72,74,83].

Family studies have demonstrated an unexpected spectrum of phenotypic abnormalities. In one family, these ranged from a mild learning disability in the mother and RS in her sister and daughter, to a severe and fatal encephalopathy in her son [23,25]. A similar pattern was noted subsequently in another family [24] and in a boy whose mother was asymptomatic [19]. The transmitting woman in each family had skewed XCI such that most cells expressed the X chromosome with normal *MECP2*.

The range of disorders associated with *MECP2* mutations now involves girls and women and well as boys and men (Table 4). Among girls and women, mutations have been identified most often in association with RS and its variants, including those with preserved speech [31,84–86], but also in the Angelman phenotype [87], in autistic spectrum disorder [19,30], and in normal women as well as those with a mild learning disability. Other than Klinefelter syndrome [19,20,88], *MECP2* mutations have been found in karyotypically normal boys with various forms of mental retardation as well as rapidly progressive encephalopathy as noted previously. *MECP2* mutations

Table 4
Phenotypes related to *MECP2* mutations

Girls/women	Boys/men
Rett syndrome	Fatal encephalopathy
Forme fruste	Rett/Klinefelter syndrome
Preserved speech variant	X-linked mental retardation/progressive spasticity
Delayed-onset variant	X-linked mental retardation
Angelman syndrome	Somatic mosaicism/neurodevelopmental delay
Autistic spectrum disorder	
Mild learning disability	
Normal carriers	

were found in two 46, XY boys with severe cognitive impairment, macrocephaly, chronic diarrhea, and progressive spasticity [29]. Both mothers and the two boys share a common mutation in *MECP2*. One mother was normal, but the other had borderline intelligence. In contrast, a more Rett-like phenotype in two boys is explained by somatic mosaicism for the *MECP2* gene; that is, some cells express a mutation in *MECP2*, although other cells have a normal copy of this gene [26,27]. To add further complexity, *MECP2* mutations were detected in 4 of 185 boys and men with nonspecific mental retardation [89], a frequency similar to that of fragile X syndrome as the basis for mental retardation in male patients. Karyotypically normal boys and men carrying *MECP2* mutations lack all the clinical features of RS, and regression in skills is not noted generally, but one common feature has been the absence of language.

MeCP2 function in developmental neurobiology

MeCP2 plays an important role in transcriptional silencing, yet its precise relation to developmental neurobiology is largely unknown [90]. The association of the gene encoding MeCP2 with RS has provided new impetus for such studies. MeCP2 functions in transcriptional silencing by binding to methylated CpG dinucleotides in gene promoter regions. In the mammalian genome, 60% to 90% of the cytosine residues in CpG dinucleotides are methylated, a process established during early embryonic differentiation [91]. Gene silencing via methylation is operative in such cellular processes as XCI, imprinting, silencing of endogenous retroviruses, and regulation of transcription. Transcriptional silencing in postmitotic cells, such as neurons, may promote efficient cellular function by preventing excess transcriptional noise [90,92].

The linkage between MeCP2 and transcriptional repression involves a corepressor protein, Sin3A, and HDAC. In this model (Fig. 2), MeCP2 mediates gene silencing by attracting HDAC to methylated DNA [93]. The target genes of MeCP2-mediated silencing and the specific role of this process in developmental neurobiology are unknown at present.

Mutations in *MECP2* such as those seen in RS do interfere with MeCP2 binding to methylated DNA [94]. The common MeCP2 missense mutations R106W and R133C and a third missense mutation result in a 100-fold reduction in affinity for methylated DNA, whereas another common missense mutation (T158M) has only a twofold reduction in binding affinity.

Based on the neuropathology of RS, *MECP2* seems to affect neuronal maturation and synaptic development [54,55]. Fragile X syndrome provides an interesting comparison with respect to dendritic arborizations [60,61] and transcriptional silencing [90]. The fragile X syndrome gene, *FMR1*, has an expansion of the CGG trinucleotide in the 5′-untranslated region. This would be predicted to result in excessive methylation of *FMR1* and

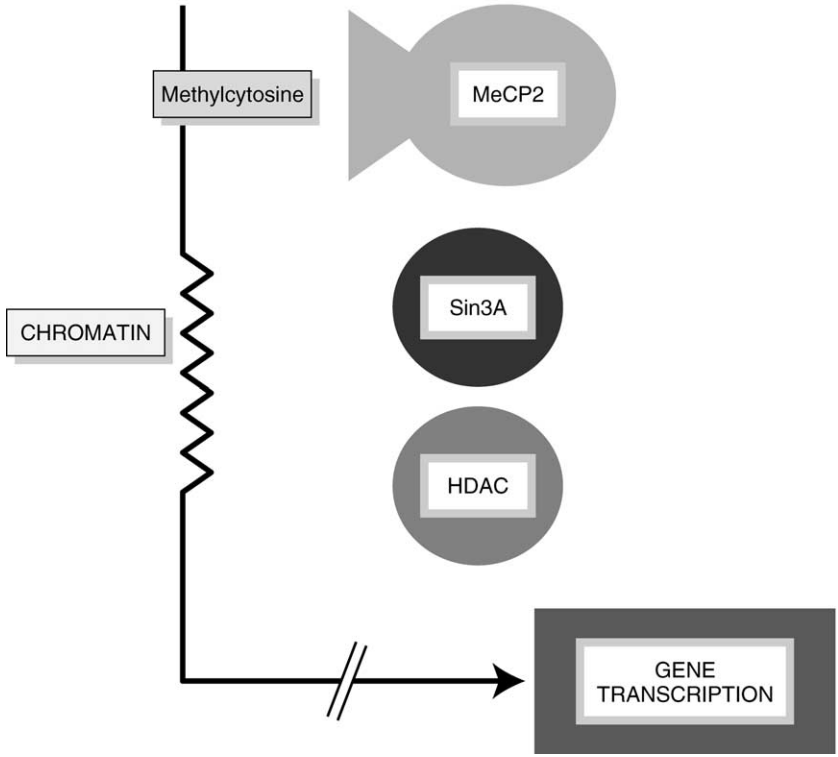

Fig. 2. Interplay between the methyl–cytosine-guanosine–binding protein 2 (MeCP2), the corepressor protein Sin3A, and histone deacetylase (HDAC) in transcriptional regulation through the compaction of chromatin. In this model, MeCP2 would bind to methylcytosine. This would mobilize the corepressor protein Sin3A and HDAC. HDAC would then deacetylate histone acetate groups, leading to compaction of chromatin, which would, in turn, downregulate or inhibit transcription of as yet undefined genes responsible for RS.

repression of its transcription through histone deacetylation as described previously [95–97]. The FMR1 protein (Fmrp) is abundant in neurons and seems to be critical for protein synthesis [98,99]. Thus, in fragile X syndrome, excessive transcriptional silencing leads to a loss of function. In RS, the lack of transcriptional silencing seems to lead to a gain of function in that the downstream genes typically repressed by MeCP2 are no longer regulated properly.

The enhanced interest in *MECP2* arising from RS opens new vistas regarding specific neurobiologic events and the downstream genes underlying RS on the one hand and normal neurodevelopment on the other. The unfolding panorama of ongoing investigations in RS, including the elaboration of mouse models, should certainly provide important new insights for both [100,101].

Summary

RS, the most common cause of profound cognitive impairment in girls and women, is composed of characteristic clinical features, including communication dysfunction, stereotypic movements, and pervasive growth failure. Neuropathologic findings indicate a failure of neuronal maturation with too small neurons and too few dendritic arbors and no evidence of a progressive neurodegenerative process. The combination of clinical and neuropathologic characteristics presents the profile of a neurodevelopmental disorder. Mutations in the gene *MECP2*, which encodes MeCP2, have been identified in 80% to 85% of girls and women with RS. Furthermore, the panorama of phenotypes with *MECP2* mutations now extends far beyond RS to include normal girls and women, mild learning disability, autistic spectrum disorders, and X-linked mental retardation. These rapid advances in our understanding of RS over the past three decades have opened new avenues of study in developmental neurobiology.

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Diagnosis and treatment of neurotransmitter-related disorders

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The term "neurotransmitter disorders" constitutes a broad spectrum of neurologic conditions that share certain clinical features depending on the severity and pattern of neurotransmitter deficiency or excess. Isolated exercise-induced dystonia, a gait disorder, or parkinsonian symptoms including oculogyric crises, hypokinesia, hypophonia, and tremor are more common in disorders associated with dopamine deficiency. If more than one neurotransmitter is involved, or if an associated tetrahydrobiopterin (BH4) deficiency is present, neurologic symptoms are typically more severe and include limb hypertonia or dystonia, axial and truncal hypotonia, abnormal eye movements, global developmental impairment, and autonomic symptoms. Less well recognized phenotypes include those characterized predominantly by encephalopathy, ataxia, and seizures.

Screening for this group of disorders has been underused. This is unfortunate in that many patients can benefit from directed treatment of their specific neurotransmitter deficiency states or associated BH4 deficiency, even before reaching a specific diagnosis. Cerebrospinal fluid (CSF) neurotransmitter metabolite analysis is necessary to confirm the diagnosis in many of these disorders, but some can be identified by characteristic clinical features, results of phenylalanine loading studies, urine pterin and catecholamine studies, plasma catecholamine studies, or specific enzyme testing in blood cells or skin fibroblasts to confirm the diagnosis. For ease of classification, these disorders can be divided into four groups:

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(1) neurotransmitter deficiency states with hyperphenylalaninemia, (2) neurotransmitter deficiency states without hyperphenylalaninemia, (3) secondary neurotransmitter deficiency states, and (4) disorders of neurotransmitter metabolism (Table 1).

Table 1
Primary neurotransmitter deficiency disorders

	Typical phenotype	Locus	Inheritance
Elevated plasma phenylalanine			
PTS deficiency	Encephalopathy, dystonia, spasticity, axial hypotonia, autonomic symptoms, oculogyric crises, seizures	11q22.3-23.3	AR
DHPR deficiency		4p15.31	AR
GTPCH deficiency		14q22.1-22.2	AR
Primapterinuria	Benign hyperphenylalaninemia	10q22	AR
Normal plasma phenylalanine			
GTPCH deficiency	Exercise-induced dystonia, gait disorder	14q22.1-22.2	AD
ALAAD deficiency	Dystonia, spasticity, axial hypotonia, autonomic symptoms, psychomotor retardation, oculogyric crises	7p11	AR
SPR deficiency	Parkinsonian symptoms, psychomotor retardation, behavioral disturbances	2p14-p12	AR
TH deficiency	Gait disturbance, infantile parkinsonism	11p15.5	AR, ? AD
TPH deficiency	Ataxia, speech delay, hypotonia, psychomotor retardation	11p15.3-p14	AR
DBH deficiency	Orthostatic hypotension, lethargy, ptosis	9q34	
MAOA deficiency	Mild mental retardation, tendency for violent or aggressive behavior	Xp11.23	XR
SSADH deficiency	Psychomotor retardation, ataxia, seizures	6p22	AR

PTS, 6-Pyruvoyltetrahydrobiopterin; DHPR, dihydropteridine reductase; GTPCH, GTP cyclohydrolase; ALAAD, aromatic L-amino acid decarboxylase; SPR, sepiapterin reductase; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase; DBH, dopamine beta-hydroxylase; MAOA, monoamine oxidase A; SSADH, succinic semialdehyde dehydrogenase.

Neurotransmitter deficiency states with hyperphenylalaninemia

The neurotransmitter deficiency and hyperphenylalaninemia in infants in this group arise as a result of defects in BH4 metabolism (Fig. 1). Patients are usually identified by way of elevated phenylalanine levels on newborn screening, as BH4 is required for phenylalanine hydroxylation in the liver. The neurotransmitter deficiency results from the lack of BH4, an obligatory cofactor required for the synthesis of the catecholamines and serotonin. Although most academic center-based biochemical genetics clinics that follow children with phenylketonuria (PKU) systematically perform the additional studies required to diagnose this group of disorders, occasionally children are not identified until they have progressive neurologic symptoms or clear evidence of developmental delay despite a phenylalanine-restricted diet. In the past, these patients were referred to as ''atypical phenylketonurics''. In some cases they were missed because they were discharged before an adequate interval to detect elevated phenylalanine levels.

Approximately 1%–3% of patients with hyperphenylalaninemia have an associated BH4 deficiency state; thus it is imperative to identify such children so that BH4 and neurotransmitter precursors can be supplemented as early as possible. The two most commonly identified disorders in these children are 6-pyruvoyltetrahydropterin synthase or PTS deficiency (that results in inadequate BH4 synthesis) and dihydropteridine reductase (DHPR) deficiency (that results in decreased regeneration of BH4 from dihydrobiopterin). Both are autosomal recessive disorders in which hyperphenylalaninemia results from a deficiency of BH4. Because of the involvement of BH4 in catecholamine and serotonin synthesis, such infants also have a manifest deficiency of neurotransmitter metabolites in addition to hyperphenylalaninemia. Other conditions in this category include autosomal recessive GTP cyclohydrolase deficiency and primapterinuria.

6-Pyruvoyltetrahydropterin synthase (6-PTS or 6-PTPS) deficiency

6-pyruvoyl tetrahydropterin synthase (6-PTPS, 6-PTS, or PTS) catalyzes the elimination of inorganic triphosphate from dihydroneopterin triphosphate to form 6-pyruvoyltetrahydropterin. Thus, patients have elevated neopterin to biopterin ratios in urine and plasma. Reduced PTS activity can be documented in red blood cells. In the classic form of the disorder, patients have reduced catecholamine and serotonin metabolites, and an increased neopterin to biopterin level in CSF. These patients are usually picked up on newborn screening as phenylketonurics, and show progressive signs of neurologic involvement in the first few months of life, including extrapyramidal signs, axial and truncal hypotonia, hypokinesia, feeding difficulties, choreoathetotic or dystonic limb movements, and autonomic symptoms. Many of these patients, despite early diagnosis and supplementation with

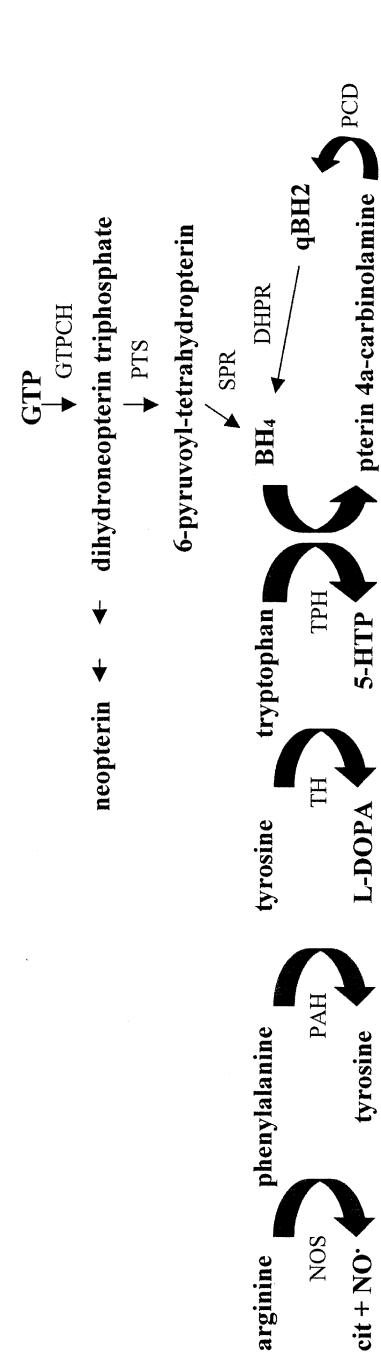

Fig. 1. Synthesis and catabolism of catecholamine and indoleamine neurotransmitters. GTPCH-GTP cyclohydrolase, PTS-6-pyruvoyl-tetrahydropterin synthase, SPR-sepiapterin reductase, DHPR-dihydropteridine reductase, PCD-pterin 4a-carbinolamine dehydratase, PAH-phenylalanine hydroxylase, TH-tyrosine hydroxylase, TPH-tryptophan hydroxylase, NOS-nitric oxide synthase, AADC-aromatic L-amino acid decarboxylase, B6-pyridoxine COMT-catechol-o-methyltransferase, MAO-monoamine oxidase, DBH-dopamine hydroxylase.

BH4 and neurotransmitter precursors, continue to manifest delays in development [1]. A ''peripheral'' form of the disorder is characterized by normal central neurotransmitter levels, and less significant or transient hyperphenylalaninemia [2]. Patients with the peripheral form have an excellent prognosis for normal neurologic development, provided the hyperphenylalaninemia is corrected by diet or BH4 administration.

Dihydropteridine reductase deficiency

Dihydropteridine reductase (DHPR) deficiency manifests in a variety of phenotypes, all with hyperphenylalaninemia. The clinical presentation is similar to that observed with PTS deficiency. Without folinic acid to restore methyltetrahydrofolate status in the CNS, these patients can have progressive calcification of the basal ganglia and subcortical regions, despite treatment with BH4 and neurotransmitter precursors [3]. A juvenile variant has been reported in which siblings were developmentally normal until 6 years of age, at which time they developed progressive encephalopathy, epilepsy, and pyramidal, cerebellar, and extrapyramidal features on clinical examination [4]. Diagnosis can be confirmed by the pattern of urine pterins, and documentation of abnormal DHPR activity in skin fibroblasts [5]. Phenylalanine loading tests are abnormal, and phenylalanine status improves or normalizes with BH4 supplementation. CSF neurotransmitter and pterin analysis reveals reduced HVA, 5-HIAA, decreased or normal BH4, and elevated dihydrobiopterin levels.

Autosomal recessive guanosine triphosphate cyclohydrolase deficiency

Although most mutations in guanosine triphosphate (GTP) cyclohydrolase to date have been documented in association with autosomal dominant dopa-responsive dystonia, or Segawa's disease, these patients do not have hyperphenylalaninemia on routine plasma screening studies. Patients with the autosomal recessive form of GTP cyclohydrolase deficiency, however, present in a similar fashion to patients with DHPR and PTS deficiency. Such patients have severe global developmental impairment, marked hypotonia of the trunk and axial muscles, limb hypertonia, convulsions, and autonomic symptoms including temperature dysregulation, excessive diaphoresis, and blood pressure lability caused by the associated catecholamine deficiency. They typically have absent GTP cyclohydrolase activity in blood cells, liver, and skin fibroblasts. By contrast, patients with autosomal dominant dopa-responsive dystonia are believed to have preservation of some GTP cyclohydrolase activity in liver because of their heterozygous state, enough to maintain normal phenylalanine levels under usual circumstances. CSF neurotransmitter analysis reveals low levels of HVA and 5-HIAA, and low neopterin and biopterin levels.

Pterin-4-alpha-carbinolamine dehydratase deficiency (primapterinuria)

Pterin-4-alpha-carbinolamine dehydratase deficiency, or primapterinuria, is a cause of mild hyperphenylalaninemia [6,7]. These infants are usually identified on newborn screening, but generally have a benign course with normal development. Phenylalanine hydroxylase catalyzes the conversion of phenylalanine to tyrosine during which BH4 is converted to the unstable carbinolamine, 4α-hydroxytetrahydrobiopterin [8]. Carbinolamine dehydratase catalyzes the dehydration of carbinolamine to quinonoid dihydropterin qBH2. The decreased rate of dehydration is responsible for the production of 7-biopterin in some mildly hyperphenylalaninemic individuals [9]. Urine studies reveal an excess of 7-substituted pterins and reduced biopterin levels, and an increased neopterin to biopterin ratio.

Role of BH4 in the central nervous system

Because BH4 is required for the hydroxylation of aromatic amino acids, its importance to the central nervous system (CNS) becomes immediately apparent. Tyrosine and tryptophan are required for the synthesis of catecholamines and serotonin. A BH4-dependent process can be strongly suspected when normalization of plasma phenylalanine levels occurs following BH4 supplementation. A dose of 5 mg/kg BH4 is the usual recommended dose for correcting peripheral hyperphenylalaninemia. Because BH4 crosses the blood–brain barrier poorly, however, lifelong supplementation with the neurotransmitter precursors L-dopa and 5-HTP, along with carbidopa to enhance CNS delivery, is necessary in most of the disorders mentioned earlier. A much higher dose of BH4, approximately 20 mg/kg, can normalize CSF BH4 levels, but is prohibitively expensive, and no studies exist as to the possible additional benefit of such a regimen. The higher requirement of tyrosine hydroxylase for BH4 in comparison with tryptophan hydroxylase may explain the more severe impairment in the catecholaminergic system compared with the serotonergic system.

The enzyme nitric oxide synthase also has an absolute requirement for BH4 for the oxidation of arginine to nitric oxide. The inability to replete normal levels of BH4 in the CNS with oral administration in its currently used doses may be one reason many children with BH4 deficient disorders develop lifelong cognitive and developmental impairments despite other treatments. Nitric oxide is believed to play a critical role of neuroprotection in the CNS, and reduced efficiency of this enzyme in the CNS may result in additional ongoing neuronal injury or cell death and vascular dysregulation and injury.

Neurotransmitter deficiency states without hyperphenylalaninemia

Neurotransmitter deficiency disorders not associated with hyperphenylalaninemia possess an increasingly complex spectrum of clinical phenotypes,

ranging from ataxia and mental retardation to spastic diplegia to exercise-induced dystonia. The lack of ascertainment by way of newborn screening and wide variance in phenotypes makes these disorders as a group much more challenging to recognize. Other than autosomal dominant dopa-responsive dystonia, the remaining disorders in this category are all inherited in an autosomal recessive fashion with the exception of MAO-A deficiency, a rare X-linked recessive disorder. Generally, heterozygous carriers for mutations in this latter group do not have a discernable phenotype, with rare exceptions in tyrosine hydroxylase deficiency and combined MAO-A and -B deficiency.

Segawa's disease, or autosomal dominant dopa-responsive dystonia

The most well described and widely identified entity among this group of disorders is autosomal dominant dopa-responsive dystonia caused by GTP cyclohydrolase deficiency, or Segawa's disease [10]. Identification and treatment of this disorder can be extremely rewarding because patients often benefit greatly with low dose L-dopa/carbidopa or even an anticholinergic agent [11; personal observations]. Patients with the classic presentation of exercise-induced dystonia are not difficult to recognize. This diagnosis should also be considered in patients with spastic diplegia, however, especially when significant fluctuation in gait or worsening gait at the end of the day is noted, and in patients with more atypical presentations, including writer's cramp or asymmetric limb dystonia. In patients with classic presentations, the clinician frequently makes the diagnosis on a presumptive basis, after observing remission of symptoms with a trial of L-dopa/carbidopa.

Although inheritance is autosomal dominant, penetrance is incomplete, and many reports exist about variable expressivity in different members of the same family [12]. In a family we have had the opportunity to follow for several years, the mother had spastic diplegia, one son had torticollis, and another son manifested a more typical exercise-induced dystonia phenotype. The female-to-male ratio in sporadic cases is 4:1, and investigators have confirmed increased penetrance of GTPCH I mutations in females [13,14].

Recently, we diagnosed a 55-year-old woman with a life-long history of a gait disorder and excessive fatigue with exertion. Her gait was suggestive of a hysterical gait disorder, strongly supported by her depressed, anxious affect. CSF analysis revealed, however, markedly decreased HVA, 5-HIAA, and BH4 levels; her phenylalanine loading test was consistent with heterozygote status for GTP cyclohydrolase activity, and skin fibroblast analysis revealed no enzyme activity. Her son has a similar history of gait disorder and depression and has attempted suicide on several occasions. There may be an increased burden of attentional difficulties, dysphoria, or depression in some families, although this has not been systemically evaluated.

CSF neurotransmitter metabolite and pterin studies are helpful in confirming the diagnosis in these patients, although they are not mandatory

because GTPCH activity can be measured directly from patient fibroblasts. If one intends to perform CSF analysis, it should be obtained before institution of a treatment trial of L-dopa/carbidopa, because treatment results in increased levels of HVA and 3-O-methyldopa. It is most important to perform these studies in patients with cognitive impairment or atypical presentation, because they may well have an alternative neurotransmitter deficiency disorder. The typical pattern in CSF in dopa-responsive dystonia is a low HVA level, normal or low 5-HIAA level, and reduced BH4 levels in CSF. Patients who are heterozygous for a GTPCH mutation, despite their normal blood phenylalanine levels on routine screening, can be shown to have abnormal phenylalanine metabolism if stressed by administration of an oral phenylalanine load (100 mg/kg). Therefore, if cytokine stimulated fibroblast enzyme analysis of biopterin metabolism is not feasible or patients decline a CSF examination and have an otherwise typical presentation, an oral phenylalanine load, with serial serum phenylalanine levels over the following 4 to 6 hours, can help confirm the clinical diagnosis.

Aromatic L-amino acid decarboxylase, or dopa-decarboxylase deficiency

Aromatic L-amino acid decarboxylase is a pyridoxine dependent enzyme that decarboxylates L-dopa and 5-HTP to make dopamine and serotonin respectively. Patients with this disorder typically present in the first few months of life with dystonia or intermittent limb spasticity, axial and truncal hypotonia, oculogyric crises, autonomic symptoms, ptosis, and psychomotor retardation [15]. As they get older, ataxia and expressive speech impairment are prominent features. CSF neurotransmitter metabolites show a characteristic pattern with low HVA and 5-HIAA, markedly elevated 3-O-methyldopa, 5-hydroxytryptophan and L-dopa, and normal biopterin and neopterin levels. Plasma L-dopa is markedly elevated. Urine catecholamines may be reduced or elevated [16,17]. These patients respond variably to treatment, with reported benefit in some patients with monoamine oxidase inhibitors, dopamine receptor agonists, L-dopa, and pyridoxine [18]. All patients reported to date have had some degree of cognitive impairment, however. Most children with this disorder are not identified until at least 4 to 6 months of age.

Sepiapterin reductase (SPR) deficiency

Sepiapterin reductase catalyzes the NADPH-dependent reduction of carbonyl derivatives, including pteridines, and plays an important role in BH4 biosynthesis. Somewhat surprisingly, the first identified cases had normal plasma phenylalanine and urine pterin levels [19]. Blau et al have hypothesized that peripheral tissues can use alternative carbonyl, aldose, and dihydrofolate reductases to perform the last two steps in BH4 biosynthesis.

Therefore, BH4 levels in the liver are likely to be normal, probably explaining the absence of hyperphenylalaninemia in these patients. In addition, it is likely that low dihydrofolate reductase activity in the brain allows accumulation of dihydrobiopterin that inhibits tyrosine and tryptophan hydroxylases, and uncouples nitric oxide synthase (nNOS), leading to neurotransmitter deficiency and neuronal cell death. Thus, identification of low CSF neurotransmitter levels and the presence of elevated CSF dihyrobiopterin is crucial for making the diagnosis in these patients.

Few patients have been reported to date [20,21]. Dystonic posturing, oculogyric crises, spasticity, tremor, and ataxia with recurrent falls were reported in one 9-year-old boy. He also had a depressed affect, aggressive behavior, and psychomotor retardation. Another child had psychomotor retardation, microcephaly, growth deficiency, spasticity, and dystonia. Blau et al recently confirmed this diagnosis in a 22-year-old woman with "cerebral palsy" and lifelong cognitive impairment and a gait disorder, who had been having increasing difficulties with head control, excessive fatigue and dystonia, with associated parkinsonian features including gait instability, hypophonia, and pallilalia. She had significant diurnal variation of symptoms, with symptoms much worse in the evenings. She benefited greatly with supplemental 5-hydroxytryptophan (HTP) and L-dopa/carbidopa, but later discontinued the 5-HTP because of side effects. CSF neurotransmitter metabolite and pterin analysis reveals low levels of HVA and 5-HIAA, and high levels of biopterin and dihydrobiopterin. Diagnosis can be confirmed by documenting low SPR activity in skin fibroblast cultures.

Tyrosine hydroxylase deficiency, infantile parkinsonism, or autosomal recessive dopa-responsive dystonia

Tyrosine hydroxylase deficiency, sometimes referred to as "autosomal recessive Segawa's disease," displays a diverse phenotype, ranging from exercise-induced dystonia to progressive gait disturbance and tremor in childhood to severe infantile parkinsonism [22–24]. An aberrant mRNA splice form is also over represented in progressive supranuclear palsy patients [22]. Low tyrosine hydroxylase activity results in significant CSF catecholamine deficiency as demonstrated by low HVA concentrations; CSF concentrations of S-HIAA, neopterin, and biopterin are normal. The children reported to date seem to have a paucity of autonomic features, suggesting a compensatory peripheral mechanism. In four patients whom the authors have tested, including one patient with the severe infantile variant of parkinsonism, peripheral plasma catecholamine levels have been normal, although reduced urine HVA levels have been noted.

Patients variably respond to L-dopa/carbidopa, and some have complete reversal of symptoms. The exception to this is the patient with the severe infantile parkinsonism form. These patients sometimes tolerate L-dopa poorly, with excessive dyskinesia, irritability, and reflux [25,26] personal

observations. Slow institution of small doses of L-dopa/carbidopa, along with selegiline (MAO-B inhibitor) and an anticholinergic agent such as trihexyphenidyl, may be more beneficial than L-dopa/carbidopa alone [27; personal observations]. When diagnosis occurs late in such patients, motor development must be recapitulated, and continued slow improvement over months is to be expected. One such patient whom we diagnosed at approximately 2 years of age had rigidity, tremor, bradykinesia, oculogyric crises, and severe psychomotor delay. Treatment with L-dopa/carbidopa alone caused severe dyskinesias with marked on-off effects. Addition of selegiline and then trihexyphenidyl provided significant benefit and led to attainment of motor skills and ability to ambulate independently over the next 3 years. Patients with a mild form of the disorder, such as an isolated gait disorder or exercise-induced dystonia, respond well to monotherapy with L-dopa/carbide and rarely develop dyskinesia. Although inheritance to date in most families seems to be recessive, at least one family has been described in which the father of the affected proband had mild exercise-induced dystonia responsive to therapy, raising the possibility that tyrosine hydroxylase deficiency could present in an autosomal dominant fashion in some families with a milder phenotype [28].

Tryptophan hydroxylase deficiency

Tryptophan hydroxylase (TPH) catalyzes the BH4-dependent hydroxylation of tryptophan to 5-HTP, which is then decarboxylated to form serotonin. TPH expression is limited to certain cells in the CNS and periphery, including raphe neurons, pinealocytes, mast cells, mononuclear leukocytes, beta cells of the islets of Langerhans, and enterochromaffin cells of the gut. Patients with presumed TPH deficiency have recently been reported, although it is not yet certain that their symptoms result from TPH deficiency [29]. Clinical features, consisting of ataxia, speech delay, mild psychomotor retardation, and hypotonia, are nonspecific. CSF neurotransmitter metabolite and pterin studies demonstrate the expected low 5-HIAA with normal HVA, neopterin, and biopterin levels. Mutations in the TPH gene have not yet been identified.

Dopamine beta-hydroxylase deficiency

Dopamine beta-hydroxylase (DBH) is the enzyme that converts dopamine to norepinephrine. Presenting symptoms of this disorder have been largely attributed to the importance of this enzyme in postganglionic sympathetic neurons [30]. Patients with severe deficiency of this enzyme, however, cannot synthesize norepinephrine, epinephrine, and octopamine in either the CNS or the peripheral autonomic neurons. Dopamine acts as a false neurotransmitter for noradrenergic neurons. Neonates with DBH deficiency can have episodic hypothermia, hypoglycemia, and hypotension, but survivors then

do fairly well until late childhood when overwhelming orthostatic hypotension profoundly limits their activities. The hypotension can be so severe as to lead to convulsive syncope with recurrent clonic seizures [31].

Most patients reported to date have been identified as young adults. Observation of severe orthostatic hypotension in a patient whose plasma norepinephrine/dopamine ratio is much less than one supports the diagnosis. Orthostatic hypotension, particularly after exercise, and ptosis are constant features. General lethargy and lassitude improve dramatically and blood pressure normalizes with treatment with d-l-threo-dihydroxyphenylserine, a synthetic amino acid that is converted to norepinephrine by aromatic L-amino acid decarboxylase. Whether or not these patients suffer from attention problems or other subtle cognitive deficits has not been adequately studied. Patients may undergo personality change, becoming more "aggressive" with treatment.

Monoamine oxidase deficiency

Monoamine oxidase is a mitochondrial enzyme involved in the catabolism of biogenic amines. Monoamine oxidase A (MAO-A), the primary type in fibroblasts, preferentially degrades serotonin and norepinephrine. Monoamine oxidase B (MAO-B), the primary type in platelets and in the brain, preferentially degrades phenylethylamine and benzylamine. These enzymes are critical in the neuronal metabolism of catecholamine and indoleamine neurotransmitters. The genes are closely linked on the X-chromosome, near the Norrie disease locus, and only affected boys have been identified to date [32]. Comparisons of the neurochemical characteristics of previously described patients with combined MAO-A and MAO-B deficiency and selective MAO-A deficiency have led to an improved understanding of the roles of MAO-A and MAO-B in the metabolic degradation of catecholamines and other biogenic amines, including serotonin and the trace amines.

Monoamine oxidase A deficiency

Brunner reported a family with an X-linked nondysmorphic mild mental retardation and a tendency to aggressive or violent behavior including arson, attempted rape, exhibitionism, and attempted suicide [33]. Urine studies revealed marked disturbance of monoamine metabolism. Normal platelet MAO-B activity suggested that the unusual behavior pattern in this family might be caused by isolated MAO-A deficiency, which was later confirmed by identification in all affected males of a point mutation leading to premature termination of the protein [34].

Measurement of MHPG (3-methoxy, 4-hydroxyphenolglycol, a metabolite of norepinephrine) in plasma is the most sensitive index of MAO-A activity in humans, and can be used to screen potential cases. MAO-A enzyme activity can be measured directly from fibroblasts, however. The

inability to identify additional patients despite screening in at-risk males with a mental retardation or behavioral phenotype makes it likely this disorder is rare [10]. Interestingly, a high activity MAO-A promoter allele has been found with increased frequency in women with panic disorder [35]. A possible association of decreased enzyme activity in women with bipolar disorder has also been reported [36].

Monoamine oxidase B deficiency

Isolated MAO-B deficiency has not yet been reported in a patient. Two brothers with a microdeletion including the Norrie locus and MAO-B, however, had features consistent with Norrie disease alone, with congenital blindness and progressive hearing loss caused by cochlear degeneration in adolescence. These patients had neither abnormal behavior nor mental retardation, leading the authors to conclude that MAO-A plays a more significant role than MAO-B in the metabolism of biogenic amines, and MAO-B deficiency alone may have a primarily neurochemical phenotype: that of increased phenylethylamine in urine [37].

Monoamine oxidase A and B deficiency

Conclusions regarding the phenotype of individuals with combined deficiency of MAO-A and MAO-B come primarily from a study of a single boy with a microdeletion at Xp14 involving the Norrie locus and documented severe deficiency of MAO-A and MAO-B activity [38]. He was severely mentally retarded, blind, and had other neurologic features including myoclonus and tendency for motor stereotypies. Because Norrie disease is an X-linked recessive disorder, obligate carriers would not be expected to have symptoms. In this family, two obligate carriers had normal IQ testing. The proband's mother had psychiatric symptoms characterized by ''chronic hypomania and schizotypal features,'' however, and both carriers had low MAO activity.

Succinic semialdehyde dehydrogenase deficiency

Succinic semialdehyde dehydrogenase (SSADH) deficiency is an autosomal recessive inborn error of metabolism associated with a defect in the metabolism of 4-gamma-aminobutyric acid or GABA [39]. Phenotypic features range from nonspecific global developmental delay and hypotonia to ataxia, severe mental retardation, visual impairment, and seizures. Urine organic acid screening to detect elevated 4-hydroxybutyric acid is the most easily available screening strategy, but GABA levels in CSF and urine are also elevated. Recently, improvement of seizures in a mouse model of the disorder was demonstrated with treatment with vigabatrin or a GABA B

receptor antagonist [40]. The relevance of these findings to treatment of patients, if any, is not yet known.

Secondary neurotransmitter deficiency states

Menkes disease is an X-linked recessive disorder in which affected males have progressive encephalopathy, spasticity, seizures, and sparse, brittle hair. The primary defect is reduced or absent function of the copper transporting ATPase, ATP7A. Multiple copper-dependent enzymes can be secondarily affected, including DBH, leading to secondary autonomic involvement and norepinephrine deficiency.

Hyperekplexia, or "startle disease" is a heterogeneous disorder caused by defects in the alpha-1 subunit of the glycine receptor [41]. The disorder occurs in autosomal dominant and recessive forms, and is characterized predominantly by stimulus-sensitive myoclonus. Transient hypertonia and hypokinesia in infancy in some families with the disorder has led to the designation "stiff baby syndrome." Dubowitz and colleagues reported an infant with classic startle disease in whom the CSF concentrations of gamma-aminobutyric acid (GABA) were substantially lower than normal during the first weeks of life [42]. Infants with hyperekplexia have higher than expected rates of sudden infant death syndrome.

Later in life patients develop involuntary myoclonus, markedly hyperactive brain-stem reflexes, and a momentary generalized jerking on falling asleep. An exaggerated startle response persists throughout life; sudden, unexpected acoustic or tactile stimuli can precipitate a brief attack of intense rigidity with falling. Congenital dislocation of the hip and inguinal and abdominal hernias, presumably caused by increased intra-abdominal pressure, are more frequent in affected families. Dramatic improvement of symptoms occurs in most patients with clonazepam.

Neurodegenerative disorders associated with ongoing cell loss are sometimes associated with reductions in neurotransmitter metabolites. We have seen such abnormalities in patients with leukodystrophy and progressive encephalopathy phenotypes in which we have been unable to identify a primary defect in neurotransmitter or pterin metabolism. Certain patients may still benefit from directed treatment of the underlying neurotransmitter deficiency. For example, in one young patient with an otherwise undefined leukodystrophy, supplementation with L-dopa/carbidopa markedly ameliorated his lower limb spasticity. Nonetheless, he continued to show progressive neurologic involvement with time, as expected.

Periods of hypoxia or ischemia can lead to secondary deficiencies of serotonin and dopamine as demonstrated by low levels of HVA and 5HIAA in CSF. In addition, BH4 levels are low and neopterin levels can be elevated. This presents a confusing pattern that mimics the metabolite profile observed in 6PTPS deficiency. The absence of hyperphenylalaninemia and the presence of signal abnormalities in the basal ganglia, thalamus,

and cortex consistent with hypoxic-ischemic encephalopathy allows differentiation.

Undefined neurotransmitter deficiency states

Several patients with documented neurotransmitter deficiency states do not fit easily into any of the above diagnostic categories, and the nature of their underlying defects remains unknown. One such example was a 21-year-old woman with mild global encephalopathy and stimulus-sensitive myoclonus, with low CSF HVA and 5-HIAA levels, but normal biopterin, neopterin, L-dopa, 5-HTP, and 3-O-methyldopa levels. She had a normal phenylalanine loading study. Another example is a 45-year-old man with apparent congenital cerebellar hypoplasia and stimulus-sensitive myoclonus. CSF studies revealed low HVA levels and biopterin levels, but he had a normal phenylalanine loading study. He has responded clinically to treatment with L-dopa/carbidopa.

Additional studies are needed to determine the precise defects affecting neurotransmitter levels and to ascertain whether they are primary or secondary. In addition to neurotransmitter deficiency, we have also seen excess levels of neurotransmitter metabolites in some cases. The etiology in these patients remains uncertain at this time, but may imply an underlying receptor defect, with secondary up-regulation. We've identified one young boy with microcephaly, mental retardation, and progressive spastic paraparesis. CSF neurotransmitter metabolites and urine catecholamines were elevated, but the exact etiology of his disorder is unknown.

A careful history of medications or herbal supplements is important, because some agents, such as serotonin reuptake inhibitors, could theoretically increase serotonin metabolite levels. Overall, CSF neurotransmitter metabolite and pterin assays provide powerful tools to help better characterize patients with otherwise undefined or poorly defined neurologic disorders.

Approach to treatment in patients with neurotransmitter deficiency states

Because patients with neurotransmitter deficiency disorders caused by tyrosine hydroxylase or BH4 deficiency have been deficient for prolonged periods before treatment, they can be extremely sensitive to initiation of neurotransmitter precursors. Starting with extremely conservative dosages, increasing the dosage slowly over weeks or months, and ensuring that peripheral aromatic L-amino acid decarboxylase is fully blocked by providing ample carbidopa can make the transition to treatment much easier. The rate or degree to which children respond depends on a variety of factors including age of diagnosis, specific disorder and mutation, presence or absence of associated hyperphenylalaninemia, and presence or absence of central BH4 deficiency. In general, optimism regarding improvement is warranted.

Institution of neurotransmitter precursor treatment may lead to new problems, such as intermittent dyskinesia related to a peak dose effect, changes in appetite, gastroesophageal reflux, diarrhea, or constipation. These problems, greatest in the first few weeks of institution of treatment, tend to improve with time. With regard to replacement of L-dopa, for instance, we have found that many children respond best to use of a slow release form of the medication, but such formulations were not created for use in children, rather for use in adults with Parkinson's disease. Support for parents and children during this often difficult period of transition from initiation of treatment to adjustment of medications is critical, because these patients will likely require neurotransmitter precursor replacement throughout their lifetimes.

In a disorder such as ALAAD, in which direct receptor agonists may be indicated, only adult formulations of these often potent medications are available, making the use of compounding necessary. Thus, giving more frequent and lower doses throughout the day may be necessary in some children. Although patients with primary neurotransmitter deficiency states are more likely to respond optimally to treatment, patients with secondary neurotransmitter deficiency may have some symptomatic benefit from directed treatment of their underlying neurotransmitter deficiency state.

Neurologic disorders characterized by excess neurotransmitter levels: nonketotic hyperglycinemia and leukoencephalopathy with vanishing white matter

Nonketotic hyperglycinemia (NKH) or "glycine encephalopathy" is a heterogeneous disorder associated with insufficient activity of various components of the mitochondrial glycine cleavage system. The enzyme system for cleavage of glycine is composed of four protein components: P protein, a pyridoxal phosphate-dependent glycine decarboxylase, H protein, a lipoic acid-containing protein, T protein, a tetrahydrofolate-requiring enzyme; and L protein, a lipoamide dehydrogenase. NKH may be caused by a defect in any one of these enzymes. It is an autosomal recessive disorder with several reported phenotypes, including the classic severe neonatal form, an infantile variant, a mild-episodic childhood variant, a late-onset form, and a benign reversible form [43].

Most patients described to date have the neonatal and most severe phenotype, likely because it is the most distinctive phenotype. These patients present shortly after birth with lethargy, encephalopathy, hypotonia, myoclonic jerks, and apnea. EEG generally shows a burst suppression pattern. Those who survive the neonatal period generally develop intractable seizures and profound mental retardation. Patients with the infantile form have seizures and variable cognitive impairment following a short period of apparently normal development. In the mild-episodic form, patients typically present sometime after infancy with mild psychomotor retardation and may

manifest episodes of delirium, chorea, and vertical gaze palsy during febrile illness. In the late-onset form, children present with progressive spastic diplegia and optic atrophy. They generally do not have seizures, and intellectual function is preserved.

Diagnosis is best made by documenting an increased CSF to plasma glycine ratio [44]. In the neonatal form of NKH, CSF glycine can be 30 times normal levels. Plasma glycine is also typically high, but can be in the normal range. A CSF/plasma ratio of >0.08 is usually considered diagnostic, but mildly affected cases can have ratios of 0.04 to 0.1 [44]. (In rare cases, CSF to plasma ratios are normal and only elevations in plasma glycine occur [51].) Confirmation of diagnosis requires enzyme analysis in liver or transformed lymphoblasts [45]. Treatment with dextromethorphan and sodium benzoate treatment have led to variable improvement in improving seizure control and behavioral problems in some patients [46,47].

Leukoencephalopathy with vanishing white matter (also known as childhood ataxia with central white matter hypomyelinization) is a recently identified leukodystrophy [48]. This is a heterogeneous autosomal recessive disorder characterized by progressive ataxia and motor impairment and encephalopathy in which episodic deterioration is associated with infection or minor head trauma. A wide range of onset has been reported in the dozen patients reported to date. CSF glycine is elevated, and can be helpful in confirming the diagnosis [49]. At least two genes have been recently noted to have mutations in patients with this disorder, EIF2B5 and EIF2B2, the first translation initiation factors implicated in human disease [50].

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New antiepileptic drug therapies

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The goal of seizure management is control of seizures with no or minimal adverse effects. This is achieved less frequently than one would hope, despite that many new antiepileptic medications have been licensed in the past decade. In a study of recently diagnosed patients with epilepsy, 47% were seizure-free with the first antiepileptic drug, 13% after the second drug, and 1% after the third drug [1]. Only 3% were seizure-free with two concomitant antiepileptic drugs and none with three antiepileptic drugs. The most frequently prescribed medications in this study were carbamazepine, valproate, and lamotrigine. Other studies suggest that less than 50% of patients respond to the first antiepileptic drug [2–4]. Thus, approximately 60% of patients become seizure-free on monotherapy, usually with the first or second antiepileptic drug. Thirty to forty percent of patients have seizures that are difficult to control. The role of the newer antiepileptic drugs in this group of patients seems modest to date. In this article we review the new antiepileptic drugs available and discuss what is known about their mechanisms of action, indications, adverse effects, interactions, and other relevant data.

Topiramate

Topiramate (Topamax), a novel antiepileptic medication derived from a naturally occurring monosaccharide, is approved in more than 65 countries. It has several mechanisms of action, including modulation of voltage-dependent sodium conductance, enhancement of gamma aminobutyric acid (GABA) activity at GABA-A receptors, reduction in glutamate release, and

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carbonic anhydrase inhibition [5–7]. It is well absorbed following oral ingestion with a time to maximum concentration of 2–4 hours. The rate of absorption may be slowed by food, and it is 15% bound to plasma protein. It has linear pharmacokinetics and is excreted unchanged in the urine with an elimination half-life of 19–23 hours. It should be administered twice daily. Concomitant carbamazepine and phenytoin reduce plasma concentrations and half-life. Topiramate has no effect on the plasma concentration of carbamazepine [8].

Efficacy has been demonstrated for the treatment of all seizure types [9–15]. In a recent randomized, multicenter, double-blind study of 252 adults and children with newly or recently diagnosed partial epilepsy, low-dose (25–50 mg/day) topiramate was compared with high-dose 200 or 500 mg/day [13]. Time to first seizure was longer in the high- than in the low-dose group (median 317 versus 108 days). Fifty-four percent in the high-dose group and 39% in the low-dose group became seizure-free. It is also effective in patients with the Lennox-Gastaut syndrome and infantile spasms [16–18].

Evidence of topiramate tolerability is based on data from more than 800,000 patients. Topiramate shows a good safety record with no evidence to date of serious or potentially life-threatening adverse effects, or idiosyncratic organ toxicity. The dose should be reduced by 50% in the presence of impaired renal function. Blood levels of phenytoin may be increased in combination with topiramate, and the efficacy of oral contraceptives is reduced. The most frequent adverse effect is decreased appetite and weight loss. Renal stones occur in 1.5% of patients. The risk for renal stones is increased with concomitant acetazolamide or the ketogenic diet. Cognitive slowing and behavioral changes are well described and are the most common reason for discontinuing the medication [19]. There are reports of efficacy of topiramate in bipolar disorder, migraine, neuropathic pain, and essential tremor, but this is not discussed here. Glaucoma has recently been described in association with topiramate [20,21].

Topiramate is available as 25-, 100-, and 200-mg tablets and 15- and 25-mgs sprinkles. In adults, the recommended starting dose is 25–50 mg daily, increasing by 25 mg weekly as tolerated. The maximum dose depends on adverse effects and seizure control; doses as high as 1600 mg daily have been used but are not recommended. If there is impaired renal function, the dose should be reduced. In children, the initial recommended dose is 1–3 mg/kg/day, increasing weekly by 1–3 mg/kg/day to a maximum dose of 5–9 mg/kg/day. In our experience, an initial dose of 15–25 mg/day, increasing by 15–25 mg weekly, is better tolerated than a more rapid titration in dose.

Vigabatrin

Since vigabatrin (Sabril), was initially licensed in 1989, it has been approved for use in 69 countries but not in the United States. Vigabatrin (gamma-vinyl GABA; MDL 71,754) was designed to achieve irreversible

inhibition of the enzyme gamma aminobutyric acid alpha-oxo-glutarate transaminase (GABA-T), the enzyme responsible for the catabolism of the inhibitory amino acid GABA. Vigabatrin increases the concentration of GABA in the brain, thus increasing inhibitory neurotransmission. Vigabatrin differs from GABA structurally by the presence of a vinyl moiety on the amine-bearing carbon.

Vigabatrin is rapidly absorbed, and peak plasma concentrations are reached within 2 hours. The plasma half-life is 5–11 hours and kinetics are linear. It is not protein bound, and excretion is primarily unchanged in the urine. The drug may lower serum levels of phenytoin, phenobarbital, and primidone.

Vigabatrin is an effective add-on treatment for patients with refractory partial epilepsy [22–26]. It is also indicated for the treatment of infantile spasms, and many neurologists regard it as the treatment of choice, especially in light of the potential for greater toxicity with other medications such as ACTH (Adrenocorticotropic hormone) or sodium valproate. It is an effective treatment for infantile spasms [27–30]. In the treatment of infantile spasms it has been demonstrated to be as effective as ACTH, particularly in the setting of tuberous sclerosis [31,32]. In a study of infantile spasms, assessing the efficacy of vigabatrin as initial monotherapy, with ACTH or sodium valproate as a second drug in nonresponders, 11 (26%) of 46 infants responded to vigabatrin, 82% within the first week [29]. Of the 31 infants who did not respond to vigabatrin, 21 were tried on ACTH and 11 of the 31 responded to ACTH. ACTH was associated with more adverse effects in this study. Six of the vigabatrin nonresponders were treated with sodium valproate and one responded to treatment. Vigabatrin is not effective in the treatment of myoclonic or absence seizures and may exacerbate such seizures [33].

The greatest concern with vigabatrin at present is the risk for persistent visual field defects [34,35]. Many patients are asymptomatic and for this reason, this adverse defect did not emerge in early studies. In a study of 32 patients on long-term vigabatrin, 13 (40%) were found to have a visual field constriction [36]. In a prospective study of patients evaluated for epilepsy surgery, 20 of 118 patients (17%) who had received vigabatrin had concentric visual field defects, compared with 0 of 39 patients (0%) who never received vigabatrin [37]. Of 99 patients treated with vigabatrin for 2.7–6.7 years, 29 (29%) had visual field defects [38]. Age, body weight, and daily or cumulative dose of vigabatrin were not associated with an increased risk for visual field defect. The pattern of vigabatrin-induced visual field defects is believed to be unique, typically affecting nasal aspects of the visual fields [38]. In infants and young children perimetric visual field testing is impossible or extremely difficult, and this raises special concerns in using vigabatrin in children. It would seem prudent, in infantile spasms, to try to withdraw vigabatrin after a few months of seizure control and to discontinue treatment when it is ineffective. Visual field defects associated with vigabatrin are considered irreversible, but rare reports suggest that reversal may occur with early withdrawal [39–41].

In a review of double-blind placebo-controlled trials of add-on vigabatrin in 717 patients with refractory partial epilepsy, there was a significantly higher incidence of depression and psychosis in the vigabatrin treated group versus placebo group [42], but no increase in aggressive behavior, agitation, manic behavior, anxiety, emotional lability, or suicide attempt was observed.

Vigabatrin, supplied as 500-mg tablets and 500-mg powder sachet, is not available in the United States. The recommended starting dose in adults is 2 g/day administered twice daily. The daily dose may be increased in increments of 0.5–1 g, depending on response and tolerability, to a maximum of 4 g/day. In children, the recommended starting dose is 40 mg/day, increasing to 80–100 mg/day. In infantile spasms, the initial dose is 40–50 mg/kg/day, increasing by 50 mg/kg/day until the spasms are controlled or to 150–200 mg/kg/day. Thus, efficacy in infantile spasms may be determined in a few days.

Oxcarbazepine

Oxcarbazepine (Trileptal), first introduced in Denmark in 1990, has been registered in more than 50 countries, including the United States, for use as monotherapy and as add-on treatment of partial epilepsy with or without secondary generalization. Oxcarbazepine and its active metabolite, the 10-monohydroxy derivative (MHD), limit high frequency repetitive neuronal firing by blocking voltage-dependent sodium channels [43]. MHD reduces the frequency of epileptiform spike discharges induced in hippocampal slices by penicillin, produces a reversible decrease in high voltage activated calcium currents, and reduces transmission of glutamate. Oxcarbazepine and MHD are similar to carbamazepine in their spectrum of antiseizure activity in animal models.

Oxcarbazepine is rapidly absorbed from the gastrointestinal tract and rapidly reduced to MHD by cytosolic ketoreductases. MHD is then glucuronidated by UDP-glucuronosyltransferase. The plasma half-life of oxcarbazepine is 1–2.7 hours and the plasma half-life of MHD is 8–10 hours [44]. Steady state is reached after 4 doses of oxcarbazepine, administered twice daily. Forty percent of MHD is bound to plasma proteins. There is little competitive interaction with other drugs for protein binding sites. Unlike carbamazepine there is no autoinduction of metabolism. Pharmacokinetics of oxcarbazepine or MHD are not affected by hepatic dysfunction, but impaired renal function may result in delayed clearance of MHD [45].

Neither oxcarbazepine nor MHD inhibit most human cytochrome P450 enzymes in vitro [46]. It is possible, however, that high doses of oxcarbazepine, in conjunction with other medications metabolized by CYP2C19, could affect the metabolism or serum concentrations of other medications such as phenytoin or lamotrigine. Oxcarbazepine induces a subgroup of

cytochrome 450 3A isoenzymes that are responsible for the metabolism of oral contraceptives.

In early double-blind studies, the efficacy of oxcarbazepine monotherapy was comparable with phenytoin, carbamazepine, and sodium valproate, in patients with newly diagnosed partial onset or generalized tonic clonic seizures [47]. Recent placebo and active-controlled studies confirm the efficacy of oxcarbazepine monotherapy in patients with partial epilepsy [48,49]. Studies of oxcarbazepine in children and adults with refractory partial epilepsy have demonstrated efficacy [50,51].

Skin reactions occur less frequently than they do with carbamazepine: 68 of 2436 oxcarbazepine treated patients (2.8%), versus 18 of 277 carbamazepine treated patients (6.5%), according to the manufacturer's database. Seventy-five percent of patients who experience skin reactions to carbamazepine do not react to oxcarbazepine. Nonetheless caution is recommended in using oxcarbazepine in patients who had severe reactions to carbamazepine. Hyponatraemia occurs more frequently with oxcarbazepine than with carbamazepine but is usually not clinically significant [52]. No clinically significant fluctuations in white blood cell counts or elevations of liver enzymes occurred in clinical studies. There is limited information on the safety of oxcarbazepine and MHD on the developing fetus. Oxcarbazepine and MHD cross the placenta and the placenta may metabolize oxcarbazepine to MHD. Oxcarbazepine may be effective in trigeminal neuralgia [53,54].

Oxcarbazepine is supplied as 150-mg, 300-mg, and 600-mg tablets and a suspension of 300 mg/5ml. The starting dose is 300–600 mg daily, increasing by 300 mg/day at 3–7 day intervals to a maximum of 2400 mg daily. If there is renal impairment, the initial dose should be lower and the rate of titration slower. In children, the initial dose is 8–10 mg/kg/day (maximum initial dose 600 mg daily), increasing by 8–10 mg/kg/day as tolerated at 3–7day intervals.

Gabapentin

Gabapentin (Neurontin) is approved in 34 countries for the treatment of partial epilepsy and neuropathic pain. Although structurally similar to GABA, the mechanism of gabapentin's action is not understood. Gabapentin is absorbed from the gastrointestinal tract through an active transport system. There is no protein binding. It is eliminated unchanged by the renal system, indicating that the dose should be reduced in patients with impaired renal function. It does not interact with hepatic enzymes, and thus there is minimal potential to interact with other drugs [55].

In a study of patients with newly diagnosed partial epilepsy, gabapentin 300, 900, and 1800 mg daily was compared with carbamazepine 600 mg daily [56]. Gabapentin was effective, and doses of 1800 mg were well tolerated as monotherapy. Retention rates were similar to carbamazepine. Another double blind, multicenter study compared the efficacy and tolerability of gabapentin and lamotrigine in 309 patients with partial or generalized

tonic-clonic seizures. The endpoint in this study was time to an exit event signaled by lack of efficacy, occurrence of status epilepticus, addition of another antiepileptic medication, or withdrawal because of a drug-related adverse event. Gabapentin (1200–3600 mg daily) was as effective as lamotrigine (100–300 mg daily) in seizure control and tolerability. Of those patients who completed the study (69.6% of the gabapentin-treated patients and 66.2% of the lamotrigine-treated patients), 76% were seizure-free for the final 12 weeks of treatment.

Studies of gabapentin add-on treatment for partial epilepsy in children aged 3–12 years showed that gabapentin was effective and well tolerated in children [57]. In a systematic review, the efficacy of gabapentin as add-on treatment was short term. Doses of gabapentin used in regulatory trials in adults were modest (900–1800 mg daily), but doses of 3600 mg daily or even up to 6000 mg daily have been used [58]. Gabapentin is effective in the management of neuropathic pain and social phobia, and it may have a role in movement disorders, migraine prophylaxis, and cocaine dependence [59].

Gabapentin's efficacy and tolerability have been observed across 2 million exposures [60]. No life threatening or serious adverse events have been described. The absence of interactions with other medications is advantageous in patients with complex medical problems and those patients who receive other medications.

Gabapentin is supplied as 100-, 300-, 400-, 600-, and 800-mg tablets. The initial dose is 300 mg daily, increasing by 300 mg per day or more slowly as tolerated. The maximum dose is not well established, but doses of 3.6 g daily may be used, administered three times daily. For children, doses of up to 50 mg/kg/day have been used safely, starting at 10 mg/kg/day.

Levetiracetam

Levetiracetam (Keppra) is a pyrrolidone, a group of compounds investigated for their cognition-enhancing effects. Piracetam was the first member of this group to have clinical application. Levetiracetam, a novel anticonvulsant drug, has an unknown mechanism of action in epilepsy. A selective binding site for levetiracetam in the brain has been postulated [61], and there is evidence of selective inhibition of N-type calcium channels in hippocampus CA1 cells [62]. Levetiracetam has a unique profile of anticonvulsant effect in animal studies, lacking effect in maximal electroshock and pentylenetetrazole models, but effective in suppressing seizures and spike wave activity in rat models of genetic absence epilepsy, and possibly preventing kindling [63,64].

Levetiracetam is well absorbed with oral bioavailability of nearly 100%. Mean time to peak concentration is 1.3 hours, with an elimination half-life of 6–8 hours in healthy children and adults. Half-life is prolonged to 10–11 hours in elderly patients because of reduction in renal function. There is no

protein binding. There is no hepatic metabolism, and the drug does not interact with or inhibit the hepatic CYP450 enzyme system. Most of the drug is excreted unchanged in the urine, with 24% hydrolyzed to an inactive metabolite. Reduction of dosage is recommended in the setting of renal impairment. There are no known significant drug interactions [65].

Levetiracetam was shown to be effective as add-on therapy in 324 patients with refractory partial epilepsy at doses of 1000 mg/day and 2000 mg/day [66]. A subsequent crossover trial comparing these two dosage levels with placebo indicated a significantly greater responder rate at the higher levetiracetam dose [67]. In the United States, another add-on study of 294 patients with refractory partial epilepsy revealed a significant difference in responder rate (>50% reduction in seizures) between placebo group (7.4%), 1000 mg/day group (37.1%), and 3000 mg/day group (39.6%) [68]. A study of later monotherapy among 86 responders in a conventional add-on study (3000 mg/day) indicated efficacy and tolerability in a subgroup of 36 patients who completed the monotherapy evaluation period. Nine patients in this group were seizure-free throughout the monotherapy evaluation period [69].

There are few reports of experience with levetiracetam treatment in children. In an open-label study, 12 of 24 children aged 6–12 years treated with levetiracetam (40 mg/kg/day) as add-on therapy for refractory partial complex seizures had a >50% reduction in seizures. Two patients were seizure-free [70]. Another open-label study of 65 children with highly refractory partial or generalized epilepsy revealed efficacy and tolerability in focal onset and primarily generalized convulsive seizures [71].

The adverse effects occurring more commonly in the levetiracetam than in the placebo treated group were: somnolence (14.8% versus 8.4%), asthenia (14.7% versus 9.1%), infection (primarily common cold) (13.4% versus 7.5%), and dizziness (8.8% versus 4.1%). There was no relationship to dosage [72]. Coordination difficulties were reported more commonly in levetiracetam-treated patients (3.4% versus 1.6%). Behavioral abnormalities occurred in 13.3% on active drug versus 6.2% of placebo-treated patients. Symptoms included agitation, hostility, anxiety, apathy, and depression. Psychotic symptoms (0.7% for levetiracetam versus 0.2% for placebo) and suicidal behavior (0.5% versus 0%) were also reported. These effects were reported early in therapy and led to treatment withdrawal. Other symptoms requiring treatment withdrawal were somnolence, dizziness, and asthenia. There were statistically but not clinically significant reductions in red blood cell count, hemoglobin, and hematocrit, and leukocyte count values for levetiracetam compared with placebo. Occurrence of infection was unrelated to white blood cell count. None of these changes required alteration of dosage.

Four children (ages 4, 13, 16, and 17 years) treated at one center experienced rapidly reversible psychotic symptoms on doses of 15–33 mg/kg/day for 2–90 days. All had prior cognitive deficits, and the three adolescents had

a history of mild behavioral problems [73]. Little is known regarding developmental effects of levetiracetam in humans. In pregnant rats, treatment is associated with minor fetal skeletal abnormalities and growth retardation.

Levetiracetam is supplied as 250-, 500-, and 750-mg tablets. Treatment initiation at 500 mg twice daily has been tolerated and this dose has been shown to have anticonvulsant effect. Dosage increments of 500–1000 mg/day may be introduced at 2 week intervals to the recommended maximum of 3000 mg/day. In elderly patients, initiation at 500 mg/day may prevent adverse effects. There are no recommended dosage guidelines for pediatric patients. Clinical trials in children have initiated treatment at 10 mg/kg/day, and increased to 40–60 mg/kg/day.

Zonisamide

Zonisamide (Zonegran), a sulfonamide derivative, has anticonvulsant properties in animal studies similar to phenytoin and valproate. It blocks sustained firing of neurons mediated by voltage-sensitive Na^+ channels and also reduces voltage-dependent T-type Ca^{++} current [74]. Although the drug has carbonic anhydrase activity, it is much less potent than acetazolamide and is not believed to exert significant anticonvulsant effect by way of this mechanism.

Bioavailability of zonisamide is estimated to be greater than 50% after oral administration. Time to peak plasma level is approximately 3 hours, with an elimination half-life of 50–70 hours. It is approximately 50% protein bound [75]. Most zonisamide is excreted unchanged in urine, with most of the remaining drug excreted as a reductive metabolite of the benzisoxazole ring. CYP450-3A isoenzyme is responsible for metabolism. Enzyme-inducing anticonvulsants increase the metabolism of zonisamide, lower plasma levels, and reduce its half-life (30 hours). Lamotrigine may inhibit clearance of zonisamide [76]. Zonisamide has no effect on hepatic microsomal enzymes, and apart from decreasing the metabolism of carbamazepine to its epoxide [77], it does not alter other anticonvulsant drug levels to a clinically significant degree [78].

Zonisamide has been shown to be effective for control of refractory localization-related epilepsies in several placebo-controlled, blinded studies [79,80]. It has been at least equivalent to carbamazepine in that setting [81]. A recent multicenter, double-blinded, placebo-controlled trial in 203 patients older than 12 years of age with refractory partial-onset seizures revealed efficacy at all doses tested (100, 200, and 400 mg/day) with best response at 400 mg/day [82]. Zonisamide has been reported to be effective in generalized epilepsy but there are no robust clinical trials in this area. In an open-label study of zonisamide monotherapy for pediatric epilepsy, 5 out of 5 patients (100%) with idiopathic generalized epilepsy achieved control, and the seizures of 7 out of 8 patients (88%) with symptomatic generalized epilepsy were controlled [83]. Eleven of 54 infants treated for infantile

spasms refractory to vitamin B6 achieved seizure control, but three subsequently relapsed [84]. Several reports suggest efficacy of zonisamide in progressive myoclonic epilepsies [78,85,86].

Adverse effects occurring significantly more commonly in patients treated with zonisamide during early studies were dizziness, somnolence, anorexia, ataxia, confusion, and abnormal thinking. In the most recent placebo-controlled add-on study, a lower incidence of adverse effects was attributed to a slower titration rate. Only weight loss was significantly more common in zonisamide-treated patients, although anorexia and ataxia were also reported more frequently in the zonisamide group. Cognitive effects are believed to be more likely to occur at zonisamide levels >30 mcg/ml [87]; reversible psychotic symptoms [88] and drug-induced behavior abnormalities in children [89] have been reported. Renal calculi developed in 2.6% of 505 patients treated in the United States and Europe, compared with 0.2% of 1008 patients in Japan. Most were small and did not require specific treatment [78]. A case of renal tubular acidosis in association with zonisamide treatment has been reported [90].

Serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been observed in patients receiving zonisamide, and seven deaths occurred in the first 11 years of marketing in Japan. Rash resulting in discontinuation of the drug occurred in 1.4% of patients during drug development in the United States and Europe. No cases of SJS or TEN were seen. Hyperpyrexia caused by oligohydrosis in children, particularly during hot weather, has also been reported, perhaps caused by inhibition of cholinergic innervation of sweat glands [91]. Leukopenia and agranulocytosis have been reported rarely. Elevation of hepatic transaminases may also occur. Zonisamide crosses the placenta and is present in breast milk at levels similar to those of plasma. Anencephaly was detected in one exposed pregnancy and atrial septal defect in another, in a review of 26 exposed offspring [92]. Both mothers were taking additional anticonvulsant drugs.

Zonisamide is available as a 100-mg powder-containing capsule. Treatment may be initiated in adults with 100 mg/day, with 100-mg increments at 2-week intervals to usual maximum of 400–600 mg/day, divided twice daily to minimize fluctuations in plasma levels. Levels of 20–30 mcg/ml have been associated with efficacy. In children, the recommended initial dose is 2–4 mg/kg/day divided twice daily, with increments at 2-week intervals to 6–8 mg/kg/day and a possible maximum of 12 mg/kg/day.

Lamotrigine

Lamotrigine (Lamictal), a phenyltriazine compound, inhibits voltage-sensitive Na^+ currents by interaction with the slow inactivated Na^+ channel, a mechanism similar to that of phenytoin and carbamazepine [93]. Unlike these two drugs, however, lamotrigine is active against partial onset and

generalized seizures. Other as yet unidentified molecular effects may be responsible for lamotrigine's broader anticonvulsant spectrum.

Oral bioavailability of lamotrigine is virtually 100%. Time to peak serum level is 1–3 hours [94]. Lamotrigine is 55% protein bound, a fraction that remains stable in the presence of other protein-bound anticonvulsants (eg, phenytoin, valproate). Lamotrigine does not alter the protein binding of other drugs. It is metabolized by glucuronosyl-transferases, and only 10% of the drug is excreted unchanged. None of the metabolites, all excreted in urine, have anticonvulsant properties. The glucuronidation step is rate limiting in the elimination of lamotrigine. The drug's half-life is approximately 30 hours in monotherapy, 14 hours in patients taking enzyme-inducing drugs, and up to 80 hours in patients taking valproate. Lamotrigine increases clearance of valproate by approximately 25%, but has no significant effect on carbamazepine. It has little effect on oral contraceptive levels [95].

Lamotrigine has been shown to be effective as add-on therapy for refractory partial onset seizures in adults [96–98] and children [99], and in refractory generalized epilepsy in adults [100] and children [101], including Lennox-Gastaut syndrome [102]. Monotherapy trials in newly diagnosed epilepsy have included a comparison with carbamazepine in which lamotrigine was shown to be as effective but better tolerated than carbamazepine [3], and a comparison with phenytoin in which there was equal efficacy between the drugs. Lamotrigine was better tolerated overall, with fewer central nervous system side effects, but had a higher incidence of rash [103].

A study comparing lamotrigine with valproate in patients previously treated with either phenytoin or carbamazepine monotherapy for partial seizures and weaned to monotherapy with one of the study drugs revealed significantly better maintenance of monotherapy on lamotrigine [104]. A placebo-controlled trial of monotherapy in typical absence seizures in children revealed significant benefit over placebo [105]. Franz et al reported seizure freedom in 24 out of 57 patients (42%) with tuberous sclerosis and epilepsy, and a further 21 (37%) who had >50% reduction in seizures without becoming seizure-free [106]. Efficacy in a heterogeneous group with refractory infantile spasms has been reported—asymmetrical spasms and postnatal brain injury were associated with response [107]. There are several reports suggesting a beneficial pharmacodynamic interaction between lamotrigine and depakote [108–110]. A synergistic effect of lamotrigine and topiramate has also been reported [111].

Common adverse effects of lamotrigine in monotherapy include headache (22%), asthenia (16%), nausea (10%), dizziness (8%), and somnolence (8%). Lamotrigine compares favorably with many antiepileptic drugs with regard to sedative side effects. Several studies have reported fewer cognitive effects in lamotrigine therapy when compared with other drugs [112], and a mental activating effect has been postulated by Meadoretal in 1997.

The occurrence of potentially life-threatening skin rash, however, is the greatest concern during lamotrigine therapy. The overall incidence of rash

on lamotrigine therapy is 10%–12%. Severe, potentially life-threatening rash such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) occurs in an estimated 1:1000 adults, and 1:100–200 children [113]. Although most cases occur within 8 weeks of treatment initiation, there have been occasional reports of SJS or TEN later in therapy. The incidence of serious rash, but not overall rash incidence, has declined following reduction in rate of initial dose escalation [114]. Rash may be slightly more common when lamotrigine is added to valproate therapy.

It is recommended that treatment be discontinued with the onset of rash. In children, when a rash characteristic of a viral syndrome occurs in a clinical context suggestive of that syndrome, it may be possible to continue lamotrigine therapy. Other rare but potentially fatal adverse effects include hepatic failure [115], agranulocytosis, and aplastic anemia. Causal relationship with lamotrigine is unclear. Lamotrigine has also been reported to induce tic disorder [116] and to exacerbate some cases of juvenile myoclonic epilepsy [96].

Lamotrigine is available as 25-, 100-, 150-, and 200- tablets, and 5-mg and 25-mg chewable/dispersible tablets. Dosing regimen varies depending on whether the depakote is being used concomitantly. In adults not receiving valproate, treatment can be initiated with 50 mg/day for 2 weeks, followed by 50 mg twice daily for 2 weeks, thereafter increasing by 100 mg every 1–2 weeks to 300–500 mg/day. In those patients receiving valproate, initial dose is 25 mg on alternate days for 2 weeks, then 25 mg/day for 2 weeks, thereafter increasing by 25–50 mg every 1–2 weeks to 100–400 mg/day.

Children starting on Lamictal monotherapy may take 0.3 mg/kg/day for 2 weeks, then 0.6 mg/kg/day for 2 weeks, gradually increasing to 2–8 mg/kg/day later. Children already on valproate should start on 0.15 mg/kg/day for 2 weeks, then 0.3 mg/kg/day for 2 weeks with further gradual increments to 1–5 mg/kg/day. Children already taking enzyme-inducing antiepileptic drugs may start at 0.6 mg/kg/day, increasing after 2 weeks to 1.2 mg/kg/day, with further increments at 1–2 weekly intervals to 5–15 mg/kg/day. When sodium valproate is added to a regimen already including lamotrigine, lamotrigine dosage should be reduced by 25%–50%.

Tiagabine

Tiagabine (Gabitril), a molecule designed specifically to block reuptake of GABA, inhibits the GAT 1-25 transportation system, thus increasing intrasynaptic GABA concentrations. Tiagabine has been effective in a variety of animal models for convulsive epilepsy, but in some models of absence epilepsy, the proportion of time that the EEG shows spike and wave discharges is increased [117,118].

Bioavailability of tiagabine approaches 100%. Absorption is slowed by administration with food. Time to peak activity is 30–90 minutes. It is 96% protein bound. Metabolism is extensive, and only 2% of the drug is

excreted unchanged in urine. Hepatic metabolism by the microsomal enzyme CYP450-3A is inducible. Elimination half-life is 7–9 hours in non-induced patients, and 2–4 hours in those patients taking inducing agents [119]. Tiagabine neither induces nor inhibits hepatic microsomal enzymes. The metabolism of tiagabine is slightly inhibited by valproate [94].

Tiagabine has been shown to be effective as add-on therapy for refractory partial seizures in adults [120]. This study and subsequent dose-frequency studies indicate that 32 mg/day is the minimum effective dose, and that either twice daily or four times a day dosing was effective [121]. Given that many of the study patients were taking enzyme-inducing antiepileptic agents, this suggests the therapeutic half-life exceeds the elimination half-life. When compared with phenytoin as add-on therapy to prior carbamazepine treatment, tiagabine efficacy was comparable to that of phenytoin, and tiagabine was better tolerated [122]. There have been some studies of monotherapy with tiagabine, usually in the setting of refractory partial epilepsy, that have been promising. Although pilot studies of tiagabine in pediatric patients have been mostly promising, no definitive study has been completed [123].

Adverse effects of tiagabine, usually mild or moderate and transient, most often involve the central nervous system. Dizziness, tremor, and difficulty concentrating were among the common side effects in controlled studies. Adverse effects are more common in polytherapy. In long-term, open label studies the most commonly reported unwanted effects were dizziness, somnolence, accidental injury, asthenia, and headache. Fifteen percent of patients in long-term studies discontinued tiagabine because of adverse effects [123]. There have been several reports of nonconvulsive status in patients treated with tiagabine. Review of these reports suggests that tiagabine does not cause nonconvulsive status, but may be associated with confusional states [124]. There also may be worsening of spike-wave discharges in individual patients at certain doses that resolves with dose adjustment and may not prohibit continued use of tiagabine [123]. Unlike vigabatrin, tiagabine does not seem to cause peripheral visual field loss [125].

Tiagabine is available as 4-, 12-, 16-, and 20-mg tablets. In adult patients, treatment should be initiated at 4 mg/day. The dose may be increased at weekly intervals by increments of 4–8 mg, to a maximum of 56 mg/day. The daily dose may be divided twice daily to four times daily. There are no dosing guidelines as yet for children younger than 12 years. Studies in younger children have used an initiating dose varying from 0.25–0.5 mg/kg/day, with increments of 0.25–0.5 mg at 2–4 week intervals, to maximum doses ranging from 1–2 mg/kg/day [126].

Felbamate

Felbamate (Felbatol), an effective broad-spectrum anticonvulsant drug, was first introduced in the United States in 1993 [127]. Initially believed to be free of serious toxicity, the drug was virtually withdrawn from the

market 1 year later, because of severe bone marrow and liver toxicity in several cases, leading to fatality in some. The American Academy of Neurology issued a practice advisory providing recommendations for its use based on quality of evidence for benefit, and understanding of attendant risks [128]. Situations considered to support use of felbamate are: (1) patients with Lennox-Gastaut syndrome older than age 4 years and unresponsive to primary antiepileptic drugs, (2) intractable partial seizures in patients older than age 18 years and unresponsive to standard antiepileptic agents (monotherapy with felbamate providing better risk/benefit ratio than polytherapy), (3) patients already on felbamate for 18 months at time of withdrawal of the drug. It is believed that the idiosyncratic responses to felbamate may be because of a specific metabolite that certain individuals are unable to clear effectively [126,129]. A urine screening test has been developed but not yet validated that may allow determination of individuals at lower risk for such responses [130]. Milder adverse effects include anorexia, weight loss, insomnia, and somnolence.

Oral bioavailability of felbamate is approximately 90%. Time to peak serum concentration is 1–4 hours. It is 20% – 25% protein bound and has an elimination half-life of 20 hours. Felbamate is excreted unchanged in urine (50%), but also undergoes hepatic metabolism by a variety of enzymes, including the cytochrome P450 enzymes. Felbamate is a potent inhibitor of hepatic microsomal enzymes [94]. This complicates addition of felbamate to existing regimens. Doses of concurrently administered drugs subject to hepatic metabolism, particularly valproate, should be reduced by 20%–30% when felbamate is initiated. A further reduction of up to one third the original dose is recommended as felbamate doses are escalated. Further adjustments may be needed [126]. Unlike phenytoin and valproate, levels of carbamazepine decrease slightly, but the proportion of the drug converted to the epoxide derivative increases.

Felbamate is available as 400- and 600-mg tablets, and 600-mg/5ml suspension. Initial dose in adults in 400 mg three times daily, increasing at 2-week intervals by an increment of 600 mg/day, to a maximum of 3600 mg/day. In children, initial doses of 15 mg/kg/day, increasing at 2-week intervals to 45 mg/kg/day have been used. Higher doses may be tolerated in children.

Fosphenytoin

Fosphenytoin (Cerebyx), which has no anticonvulsant activity of its own, is a prodrug of phenytoin. It was developed to avoid local complications of parenteral administration of phenytoin. It is rapidly and completely converted to phenytoin. It has been studied in adults and children of all ages. It was well tolerated intravenously and intramuscularly. After intravenous fosphenytoin administration there was a 9% incidence of pain or burning at the infusion site, compared with 90% after phenytoin administration.

Systemic adverse effects, such as cardiovascular complications (arrhythmia, hypotension) are infrequent. Fosphenytoin dosage is expressed as phenytoin sodium equivalents (PE). Dose is 15–20 mg PE/kg for loading dose, usually administered at 0.5–2.0 mg PE/kg/min, with a maximum rate of 3 mg PE/kg/min [131].

Sulthiame

Sulthiame (Ospolot), a sulfonamide derivative available in Europe for many years, is a carbonic anhydrase inhibitor that also blocks sodium channels [132]. It is effective in benign and atypical Rolandic epilepsy [133,134]. In a recent study of 66 children with benign partial epilepsy with central temporal spikes (BECTS), sulthiame 5 mg/kg/day was compared with placebo [133]. Eighty-one percent of the sulthiame treated group and 29% of the placebo treated group completed the study without any treatment failure events. Sulthiame was well tolerated and no patient stopped sulthiame because of adverse effects. Alterations of acid–base equilibrium, hyperventilation, and paresthesiae have been described with sulthiame. This drug is not available in the United States.

Stiripentol

Stiripentol, a new antiepileptic drug, has been studied in a limited way to date. It inhibits synaptosomal uptake of GABA in rodents and indirectly inhibits several P450 enzymes in humans. The drug's precise mechanism of action is poorly understood. If used in combination with other drugs metabolized by the cytochrome P450 system, it causes elevated levels of these medications, including carbamazepine and valproate. Stiripentol is effective in severe myoclonic epilepsy of infancy when used in combination with valproate and clobazam [135,136]. In a double-blind study comparing stiripentol with placebo in 41 children with severe myoclonic epilepsy of infancy, 71% of the stiripentol treated group had a greater than 50% reduction in frequency of generalized tonic-clonic or clonic seizures, and 9 of 21 in this group were seizure-free. Side effects such as drowsiness, loss of appetite, and hematologic abnormalities were common, and were often caused by elevations in the blood levels of coadministered drugs.

Stiripentol is available as 250-mg tablets. In adults, the recommended starting dose is 250–500 mg daily, increasing as tolerated to 1500 mg/day. In children, the starting dose is 50 mg/kg/day, increasing as tolerated to 100 mg/kg/day. This drug is not available in the United States.

Summary

The introduction of these new antiepileptic drugs, from felbamate to levetiracetam, raised hope of control of epilepsy with fewer adverse effects and

improved quality of life. Unfortunately, many patients continue to experience refractory epilepsy despite the use of these new agents, and dose-related adverse effects and idiosyncratic reactions continue to be problematic. A recent report describes six new compounds in preclinical development, and five in clinical trials [131]. As the number of available, effective, but imperfect antiepileptic drugs increases, many challenges remain. These include: choosing the drug appropriate for the epileptic syndrome, assessing accurately the range of a drug's adverse effects in an individual patient, and considering carefully the drug's interactions in combination drug therapy. In considering drug combinations, differing mechanisms of drug action and favorable pharmacodynamic interactions (an area requiring additional studies) are of importance. Clinicians caring for children who have epilepsy anticipate further advances in the pharmacogenetics and molecular pathophysiology of epilepsy, leading to individually tailored, effective, and safe therapy.

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Intractable pediatric epilepsy: Vagal nerve stimulation and the ketogenic diet

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Of the approximately 25% of patients with intractable seizures, more than half are not candidates for resective surgery. In adults, intractable epilepsy is generally defined as the persistence of seizures despite at least two appropriately chosen antiepileptic drugs (AEDs) that have been progressively increased until toxicity has been experienced. As shown recently, intractability can often be identified early in the course of epilepsy [1]. The probability of achieving control of seizures after failure of the second AED is approximately 3% [1].

The definition of medical intractability should take into account the natural history of seizures in childhood and the tendency for seizures to become less frequent and severe with passing age [2]. Nevertheless, the approach to intractability in childhood seems to be similar to that in adults. Despite the availability of newer AEDs, the rates of intractability do not seem to have decreased [3]. The likelihood of controlling seizures after two appropriately chosen AEDs fail is low [4]. In most children, at least three AEDs should be tried before a child is said to have intractable epilepsy [5].

An additional factor that should be considered in children is the cognitive decline children experience when having frequent seizures. This latter factor is particularly apparent when there is reversal of cognitive decline after successful control of seizures with epilepsy surgery [6,7]. Surgery is not an option for more than half of children with intractable epilepsy, however. The consequences of epilepsy beyond the occurrence of seizures is considerable. Patients with uncontrolled seizures experience a poorer quality of life, including poor self-esteem, higher levels of depression, and other limitations [8].

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The ketogenic diet and vagal nerve stimulation (VNS) offer adjunctive options to AED therapy for children with intractable epilepsy.

Evaluation and patient selection for vagal nerve stimulation and the ketogenic diet

Patients should be selected for either therapeutic option only after a comprehensive evaluation. The patient's seizures should be carefully characterized, and nonepileptic events should be excluded. The latter is particularly important in children with developmental delay and behavioral problems. Many of these patients have movements and behaviors that are mischaracterized as epileptic seizures [9–11]. Video-electroencephalographic (EEG) monitoring often results in the diagnosis of events that are either pure psychogenic events in isolation or associated with epileptic seizures or, in the younger child, represent physiologic events that mimic seizures [12–15]. A diagnosis of nonepileptic events should be considered in all children who do not seem to be responding to multiple medications or have variable and erratic response to therapy. Abnormal findings on routine (interictal) EEG may actually confound the diagnosis, because many children with static encephalopathy have epileptiform discharges. Such patients should be considered for video-EEG recording, which can help to distinguish nonepileptic from epileptic seizures [16].

Vagal nerve stimulation

In the mid-1980s, Zabara [17] first proposed VNS as a method of desynchronization of electrocerebral activity, thereby relieving seizures. The first patient with VNS who became seizure-free was reported in 1988 [18,19]. (The NeuroCybernetic Prosthesis (NCP) Houston, Texas) system was developed commercially and consists of (1) an encased pulse generator/battery, (2) bipolar stimulating leads, (3) a handheld programming wand, and (4) a magnet with which to activate the device externally. The pulse generator is typically implanted below the left clavicle in the subcutaneous tissue of the upper chest and is connected to the left vagus nerve in the neck via the bipolar lead. Placement of the pulse generator varies; in young children, the pulse generator may be implanted in the abdomen (for technical reasons), and it may be implanted in the lower anterior axilla beside the pectoral muscle in women (for cosmetic reasons).

VNS is the only nonpharmacologic intervention that has been approved by the US Food and Drug Administration for the treatment of epilepsy in adults and adolescents older than the age of 12 years; since 1997, more than 10,000 patients have received implants. Although there is a well-developed literature on its use in adults and older adolescents, there is also an emerging literature on the role of VNS in childhood [20].

Mechanism of action

Partial and generalized seizures are both reduced by chronic intermittent stimulation of the left vagus nerve. The left vagus nerve projects on both nuclei of the tractus solitarius as well as on the brainstem reticular formation and has projection on other medullary nuclei. Postsynaptic projections from the medulla occur in the pons, thalamus, amygdala, and insula. The reticular activating system and the limbic system feature prominently in the activation of the vagus nerve. Despite widespread synaptic projections beyond the medulla, the exact mechanism by which VNS reduces seizures is unknown.

VNS reduces penicillin-induced cortical interictal spiking rates by one third in rats. In animals, the stimulation effect may increase or decrease EEG synchronization depending on the rate of stimulation. This mechanism does not seem to be the primary factor underlying efficacy, however, and it has not been demonstrated in human patients. VNS does not seem to exert its effect by changes in the EEG. Changes in cerebrospinal fluid (CSF) inhibitory amino acids have been noted with chronic VNS, although these changes were observed in both responders and nonresponders to VNS. An interesting clinical observation is the increase in antiseizure effect that occurs with time. This increased seizure control, which occurs 6 to 12 months after stimulation, is also unexplained.

Efficacy, tolerability, and safety

After the first implantation in 1988, Penry and Dean [18] reported that 4 of 11 patients with intractable epilepsy became seizure-free after VNS. Early studies demonstrated that one third of patients experienced a greater than 50% reduction in seizure frequency. Randomized high versus low stimulation showed similar rates of seizure control, with this rate increasing to 52% at 18 months after VNS [21–25].

Pediatric studies have demonstrated highly variable efficacy rates of control compared with the adult series discussed previously [26]. Of 309 children between the ages of 3 and 18 years who received implants at various centers across the United States, favorable response rates (>50% seizure reduction) were seen in 19% to 53% of patients followed between 3 and 24 months [20].

Surgical considerations and complications

The midcervical portion of left vagus nerve chosen for electrical attachment is relatively free of branches and lies within the carotid sheath. It carries afferents from the cardiac atrioventricular node. The recurrent laryngeal nerve travels with the midcervical portion of the left vagus nerve. Stimulation of the midcervical portion therefore causes hoarseness, which occurs each time the device is stimulated. Typically, implantation takes 2 hours; patients may be observed overnight after implantation and are administered antibiotics for 24 hours.

The overall infection rate is 3%. Many patients were successfully treated with antibiotics, although 1% needed the device removed. Vocal cord paralysis is the most common surgical complication, occurring in approximately 1% of patients in the E05 study. Vocal cord dysfunction is suspected if the patient presents with persistent hoarseness dysphagia. Vocal cord dysfunction can be minimized when care is taken to avoid nerve retraction and damage to the vascular supply to the nerve. Avoidance of high-stimulation intensities may help to reduce the degree of vocal cord dysfunction. Other less frequently occurring complications include Horner syndrome, facial weakness, breakage of the leads, and bradycardia [23–25].

Initiation and maintenance parameters

After implantation, the device is typically turned on in the operating room to deliver a stimulation of 0.25 mA. Thereafter, 0.25-mA increments are adjusted to seizure response, or intolerable side effects may appear. Concomitant AED therapy is kept stable for 12 weeks while the device is being ramped up before a reduction in the dosage or number of AEDs is considered. Current generator batteries are expected to last 10 years, although this is dependent on stimulation parameters [22].

Other considerations with vagal nerve stimulation

The cost of the device and its implantation is a major disadvantage of this form of treatment. One third of patients experience no benefit after VNS. Unfortunately, there is no way to identify which patients are most likely to benefit from the device. Furthermore, only a few patients experience freedom from seizures. Advantages of VNS include absence of the cognitive side effects that are so common with AED treatment. In some patients, a reduction in the number or dosage of concomitant AEDs is possible. The availability of a relatively straightforward alternative therapy in patients who are not surgical candidates is an added advantage.

The ketogenic diet

The ketogenic diet (KD) is a high-fat, low-carbohydrate, adequate-protein regimen that has been used for more than 80 years for the treatment of intractable epilepsy. By now, the KD is familiar to most physicians caring for children with epilepsy. It is important for neurologists to understand some basic aspects of the KD and how it is used so as to select patients who are most likely to benefit from it.

The KD was originated in 1920 by Wilder [27]. It was devised to mimic fasting, which has been known for centuries to improve seizure control in persons with epilepsy. With the advent of multiple anticonvulsant medications in the middle and late twentieth century, the KD was relinquished

to the back closet of most epilepsy clinics. In the 1990s, however, the diet witnessed a resurgence, and it is now a common adjunctive therapy to standard AEDs.

Here, we briefly review the scientific basis for the KD, describe recent studies of its efficacy, and discuss cautionary measures that need to be taken when embarking on KD therapy. Details about other aspects of the KD are available in recent publications, including its history [28–30], possible mechanisms of action [31–34], details of administration [21,30], and complications [29,35,36].

Efficacy of the ketogenic diet

Numerous reports from the 1930s attest to the effectiveness of the KD in small uncontrolled series of patients [37–39]. In most of these older reports, there is a paucity of clinical details, and the seizures are not classified according to our modern schema. Nevertheless, these anecdotal reports document the effectiveness of the diet. Although a meta-analysis of those reports is not possible, roughly one third to one half of treated children had a "good" or "excellent" response to the diet, variously defined as at least 50% fewer seizures. In the modern era, the effectiveness of the KD has been confirmed. Interestingly, despite advances in epilepsy diagnosis and other aspects of modern medical care, the clinical response rate to the KD has been similar over many decades [40].

A multicenter study of KD efficacy that involved seven comprehensive epilepsy centers and included 51 children showed that more than 40% of children had at least a 50% decrease in seizure frequency when evaluated after 1 year on the diet [41]. The study found no relation between KD efficacy and patient age at diet initiation, seizure type, or EEG findings. Although this study was neither randomized nor blind, it showed that the KD could be successfully applied across a wide variety of clinical scenarios and in geographically diverse medical centers.

A large prospective study of KD efficacy was performed by the Pediatric Epilepsy Group at John Hopkins Hospital, which has been a leader in KD use. They prospectively followed 150 children (mean age = 5.3 years) with intractable epilepsy of different types [42]. These patients were extremely refractory, averaging 410 seizures per month and having been treated with an average of 6.2 medications before the KD. Overall, 75 of the 150 children had a persistent decrease in seizure frequency of greater than 50%. Thirty children had a greater than 90% seizure reduction, and an additional 7 children became seizure-free. Therefore, the KD has excellent efficacy across a wide variety of seizure types, ages, and etiologies. Children who remained on the diet longer tended to be those who responded well; those who discontinued the diet at less than 1 year tended to have a poorer response.

The same population has now been followed for up to 6 years, and the results remain impressive [43]. Twenty children remain seizure-free; only

1 is still on the KD, and the other 19 have been able to discontinue it and remain seizure-free. An additional 21 children had a greater than 90% reduction in seizure frequency (8 remain on the diet). Those who discontinued the diet had a lack of response, considered it too restrictive, or had complications at times of intercurrent illnesses. In addition to seizure control, many children were able to reduce or discontinue their standard anticonvulsants, with concomitant improvement in alertness and cognitive function and fewer anticonvulsant-related side effects [44].

Despite the theoretic and practical difficulties of designing a blind crossover study of KD efficacy, such a study is underway. Freeman [45] has enrolled children with frequent atonic seizures (most have Lennox-Gastaut syndrome). After 24 hours of video-EEG to quantify baseline seizure frequency, the children are randomly assigned either to the KD or to an identical KD with glucose added (to negate the ketosis). In the KD treatment arm, placebo (artificial sweetener) is added; this does not counteract the ketosis but makes the diet as "sweet" as that in the glucose-added arm. After 1 week on the respective diets, the groups are fasted briefly and then crossed over to the other treatment. Video-EEG data are also collected before and after the 1-week crossover phase. The data from this study, which is still ongoing, should provide important information regarding the short-term role of the KD (and ketosis) in atonic seizure control.

The beneficial effects of the KD on seizure control, cognitive function, and neurodevelopment have also been documented in other studies both in the United States and abroad [46–50]. It has been shown to be effective across the age spectrum from infants to adults [51,52], although it has been thought to work best in young and school-aged children for theoretic reasons related to efficiency of ketone extraction by the brain [53]. Finally, all types of seizures and epilepsy may be amenable to KD treatment [30,54].

Mechanism of action

Although it is reasonable to suspect that ketosis, a result of the ingestion of ketogenic foods, plays some role in anticonvulsant protection, it is not known exactly how the KD works. Overall, human and animal studies support the notion that ketosis is necessary but probably not sufficient for KD effectiveness. Other mechanisms that have been considered in the past include acidosis, dehydration, elevated lipid levels, and electrolyte derangement [55]. None of these hypotheses has stood the test of time. At present, there is an intense laboratory effort to uncover the mechanism of action of the KD [31,56–59]. Hopefully, such information will allow optimization of the administration, formulation, and composition of the KD.

The basis of the KD lies in the brain's use of fats rather than glucose as the primary cerebral energy source. Under conditions in which glucose is not available, such as fasting or the ketogenic diet, fatty acids are oxidized in the

liver to ketones (β-hydroxybutyrate, acetoacetic acid, and acetone) (Fig. 1). The liver lacks the enzymes to degrade these ketone bodies, so they enter the bloodstream and circulate to tissues (eg, brain, muscle), where they may be broken down for energy. The brain can extract and break down ketone bodies, which are funneled into the tricarboxylic acid cycle and then to the electron transport chain, with resultant energy production.

Ordinarily, the brain is an obligate user of glucose for its energy. There is a small arterial-venous gradient for ketones under ordinary dietary circumstances. During fasting or KD feeding, however, this gradient increases, and ketones cross the blood–brain barrier via a monocarboxylic acid transport system. Therefore, during ketosis, the brain uses ketones as its energy source [60]. Exactly how this metabolic transformation from carbohydrates to ketones for energy leads to an antiepileptic effect is currently unknown. Possibilities include alteration of the brain's energy charge (energy reserve) [61], a direct effect of ketones on the excitability and synaptic function of neurons [62], enhancement of gamma-aminobutyric acid (GABA) synthesis or function [59], or some other mechanism [33].

Clinical use of the ketogenic diet

The first question might be which patients are most likely to benefit from the KD. To date, children have been placed on the diet when all else has failed. It might be possible to achieve seizure control at an earlier stage in the course of the child's epilepsy, however, before exhausting all standard AEDs. Although exact criteria for trying the KD have not been elucidated, any child with intractable epilepsy should be considered a candidate.

There are a few conditions under which KD treatment is essential. DeVivo et al [63] described the syndrome of glucose transporter defect. This genetic disorder is characterized by a lack of the protein that transports glucose from the blood into the central nervous system. Therefore, affected children cannot use glucose properly for cerebral energy. The clinical presentation of this syndrome usually involves developmental delays and seizures. Affected children require the KD to provide sufficient energy for cerebral function.

There are certain conditions under which the KD could lead to neurologic deterioration, including pyruvate carboxylase deficiency, fatty acid oxidation disorders, mitochondrial disorders, and carnitine deficiency [36]. In all these disorders, switching to fats as the primary energy source could stress the body's metabolic regulatory systems and lead to energy failure.

Ketogenic diet formulation

There are several alternative KD formulations, but the classic diet consists of a 4:1 ratio (by weight) of fat/[protein + carbohydrates]. Obviously, a dietitian familiar with the KD is essential to teach the family meal plans

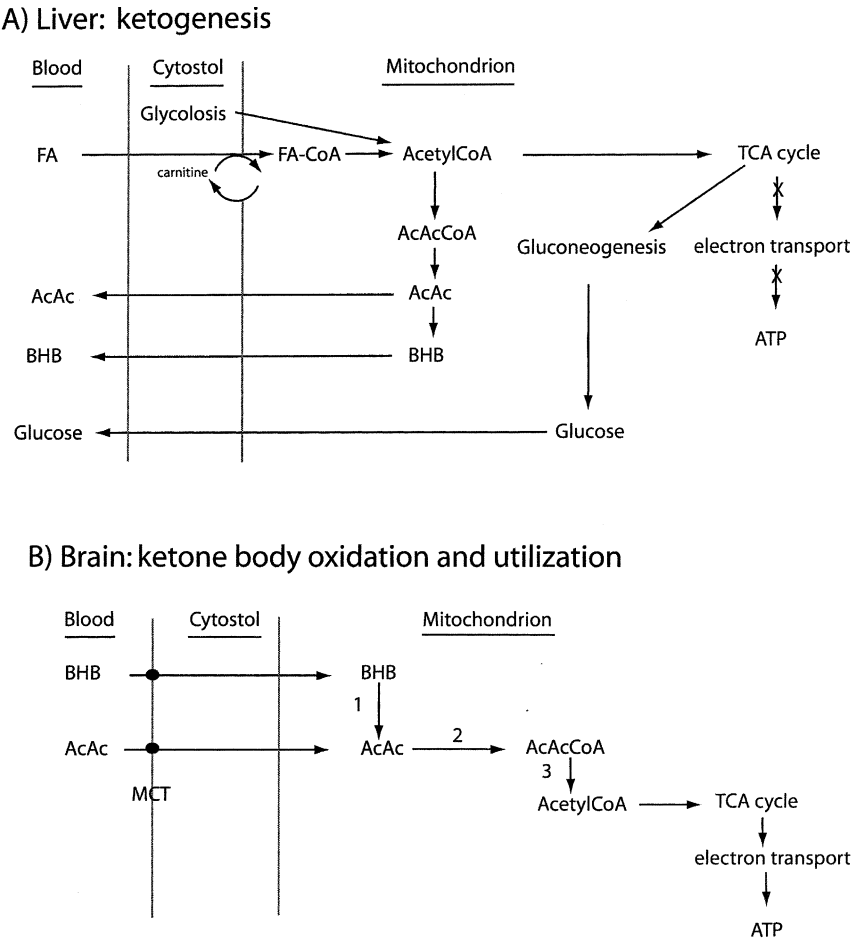

Fig. 1. Summary of ketogenesis and ketone body utilization. (A) Ketogenesis in the liver. FAs from the circulation enter hepatocytes. They cross into the inner mitochondrial membrane either by diffusion (short- and medium-chain FAs) or via carnitine (long-chain FAs). Under conditions of fasting or the high-fat low-carbohydrate ketogenic diet, carbohydrate substrate is lacking; thus, FAs are metabolized. Because oxaloacetate (a TCA cycle intermediate) is being diverted to gluconeogenesis, the TCA is not actively involved in energy generation. Acetyl CoA molecules are therefore not funneled into the TCA but are used for ketone body synthesis (AcAc, BHB). The ketones are exported into the circulation, because the liver lacks the enzymes required to catabolize AcAc and BHB. (B) Ketone body oxidation and utilization in the brain. BHB and AcAc enter neurons via the monocarboxylic acid transport system. In mitochondria, BHB and AcAc are broken down (by enzymes 1 and 2) into acetyl-CoA molecules that can then enter the TCA cycle for energy production. FA, fatty acid; CoA, coenzyme A; TCA, tricarboxylic acid; AcAc, acetoacetate; BHB, β-hydroxybutyrate; ATP, adenosine triphosphate; MCT, monocarboxylic acid transporter; 1, BHB dehydrogenase; 2, succinyl–CoA transferase (3-ketoacid CoA transferase); 3, acetoacetyl CoA thiolase.

and to calculate appropriate dietary needs for each child. Attention must be paid to total calories, sufficient protein for growth, and appropriate vitamins and minerals in addition to maintaining the rigid ratio of dietary components. Detailed guidelines for KD formulation are available [30].

An alternative formulation involving medium chain triglycerides (MCTs), which produces an equivalent degree of ketosis with a less restrictive fat-to-carbohydrate ratio, was popular in the 1980s [64]. Although the MCT formulation allows a greater amount of carbohydrates and is thus more palatable, it often resulted in severe diarrhea and is used only occasionally today.

The KD is most commonly initiated during a 3- to 5-day hospitalization. The diet begins with an initial fast, with modest fluid restriction to approximately 75% of maintenance. Once urinary ketones reach 3+ to 4+ as measured by urine dipsticks (correlating to approximately 80–160 mmol), the diet is started at a 4:1 ratio, with one third of the total calories as a ketogenic eggnog on day 1, two thirds on day 2, and, finally, the full-calorie diet on day 3. After that, ketogenic meals are started. Hospitalizing children has been considered important because of potential side effects during the period of fasting and initial KD administration, including dehydration, hypoglycemia, and other metabolic problems.

Complications of ketogenic diet use

The KD is a form of medical therapy rather than a fad diet. Although relatively safe in experienced medical hands, there are many potential side effects that might occur. Renal stones develop in approximately in 10% of children on the KD [65]. Some children on the KD develop reduced bone mass, and growth must be monitored carefully. Recently reported adverse effects include bruising as a result of altered platelet function [66], pancreatitis [67], and cardiomyopathy [68]. Interestingly, one might expect that long-term atherogenic complications would occur in children treated with this high-fat diet, but this has not been reported. It must be stressed that with close monitoring, the KD is safe in most children [30].

Some serious adverse events have been reported in children on the KD. In one study, such events occurred in 5 of 52 children on the KD and included hypoproteinemia, lipemia, hemolytic anemia, renal tubular acidosis, and elevated liver transaminases [35]. Many of these side effects were associated with concurrent valproic acid use; this anticonvulsant must be used with caution with the KD.

For optimal administration of the KD, an interdisciplinary program is suggested. This involves the coordinated care of a child by a team of health care professionals, including a neurologist, dietitian, nurse, and social worker [69]. Before initiating the KD in a child, it must be ensured that the parents are fully invested in this complicated approach.

Summary

The KD has been proven an effective alternative epilepsy treatment in children refractory to standard anticonvulsants. Children to be placed on the diet must be carefully selected, monitored, and followed. The diet is to be regarded as a strict medical regimen and requires a comprehensive medical team approach in concert with intensive parental involvement. With better understanding of the scientific principles underlying brain ketosis, we should be able to optimize the KD to achieve even better results.

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Epilepsy surgery Presurgical evaluation

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Approximately 5% of all children experience a seizure with a further 1%–2% having recurrent unprovoked seizures [1]. Major advances in the management and consequences of epilepsy have emerged in the last decade. Improved classification of seizures and epilepsy syndromes and the availability of new antiepileptic drugs (AEDs) account for a large portion of the advances. Despite these improvements, approximately 25% of children treated with appropriately chosen AED polytherapy have intractable epilepsy [1]. In many of these patients the intractability is established as early as following the first 2 years of initiation of treatment, or if seizures persist after a trial with two AEDs [2–4]. Although in the long term many of these children may eventually become seizure-free as adults, they will have sustained substantial social and educational burdens. Patients whose epilepsy does not remit also have an increased risk for death [5]. Many of these patients may benefit from epilepsy surgery performed early in the course of their epilepsy. Despite the possibility for becoming free from seizures, there is considerable delay in considering surgery for the treatment of seizures [6].

Several reasons seem to underlie this delay in consideration of epilepsy surgery. Older outcome figures for pediatric epilepsy surgery are in the range of a seizure-free rate of 20%–30%, a rate similar to that obtained with a new AED trial [7]. These data, however, originate from series collected between 1950 and 1980, before the availability of modern structural and functional neuroimaging and EEG techniques. Extra-temporal epilepsy is much more common than temporal lobe epilepsy in childhood. Approximately 80% of adults considered for epilepsy surgery have temporal lobe epilepsy, often of mesial temporal onset. The natural history of temporal lobe epilepsy is now well defined and the results of surgery are largely predictable [8]. Adults

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undergoing an anterior temporal lobectomy for complex partial seizures have seizure-free rates of 60%, with a further 26% experiencing only rare seizures. The known natural history of temporal lobe epilepsy and the results of contemporary epilepsy surgery have recently prompted a multicenter randomized trial to examine the role of early surgery when a patient has failed their first AED! Only 20% of intractable childhood epilepsy is of temporal lobe origin. Accordingly, pediatric neurologists have been reluctant to consider surgery as an option for their intractable patients. Familiarity with febrile seizures and the benign childhood epilepsies have resulted in a prevailing belief that seizures may not be of much consequence in children. Some of the "benign" partial epilepsy syndromes, however, have been increasingly associated with cognitive consequences [9].

Early observations of improvement in development following successful epilepsy surgery suggest that seizures may have serious consequence for the developing brain [10]. Contemporary clinical surgical series support these initial observations that behavior and cognition improves following successful surgery [11]. Furthermore, accumulating animal data suggests that intense neural activity, such as occurs in a seizure, may be of significant consequence in the developing brain [12–18].

Recently, pediatric surgical outcomes have become available for more than 200 children with intractable epilepsy. Seizure-free rates of 59%–67% were across all pediatric age groups [19], with a further 11%–20% experiencing only rare seizures. These outcomes match or closely approximate those reported for adults. Surprisingly, such results are seen across all age groups. Even in infancy, with careful patient selection, seizure-free rates of 50%–65% and rare seizures in a further 13%–25% were reported in more than 50 infants undergoing epilepsy surgery.

Medical intractability epilepsy

Seizure frequency is an important component of the definition of intractability. Seizure severity and seizure persistence despite therapeutic compliance and optimal therapy and the behavioral/educational impact of ongoing seizures, however, are important considerations [1]. Patients should be considered for epilepsy surgery only after careful demonstration of medical intractability [6]. Intractable epilepsy can be defined as seizures that are not brought under control despite 2 years of treatment with appropriately chosen AEDs. It assumes that AEDs have been tried in a methodical fashion, and adequate serum AED concentrations have been documented or clinical signs of toxicity have been demonstrated [11,20].

Surgical outcomes

The decision to consider surgery requires definition of an outcome measure. Freedom from seizures is the most favorable outcome, although in

patients continuing to have seizures the reduction in severity and frequency may improve overall quality of life [21,22]. The latter factor should be considered on an individual basis.

Epilepsy surgery in children who have been carefully chosen can result in either seizure freedom or a marked (>90%) reduction in seizures in approximately two thirds of children with intractable seizures [2,23,24]. These results are comparable to outcomes obtained in adults. Furthermore, the result are far superior to those obtained for pediatric epilepsy surgery performed in the pre-MRI era between 1940 and the late 1970s [7]. Eighty-five percent of parents surveyed following epilepsy surgery viewed the surgical outcome favorably [20], suggesting that there was a perceived improvement in the quality of life [25]. Favorable factors include the presence of disabling epilepsy, a localized epileptogenic zone, and a low risk for postoperative deficits [20].

Careful patient selection can reduce this rate in infants [19,26]. Mortality rates in infants undergoing surgery (particularly when associated with extensive resection), however, are approximately 2% and not surprisingly higher than in other age groups.

Presurgical evaluation

The primary determinant of successful outcome following epilepsy surgery is accurate identification of the site of seizure onset. The primary aim of the presurgical evaluation is the identification of the epileptogenic zone that is defined as the area "necessary and sufficient for initiating seizures and whose removal or disconnection is necessary for abolition of seizures." In practical terms this refers to the minimum amount of tissue that needs to be resected to ensure seizure freedom [27].

Seizure semiology

The manner in which a seizure evolves (seizure semiology) offers important clues to location of seizure onset. Every attempt should be made to understand the number of seizure types that a patient experiences and the precise semiology of each type [28]. Often multiple partial seizure types are a manifestation of differing degrees of evolution and differing propagation pathways from a single focus. Precise semiology that is confirmed following successful epilepsy surgery offers the best confirmation of seizures that originate from a particular lobe. Such evidence is now available in adults, although it is still lacking in children. Seizure classification in the young child and infant are inherently problematic because alterations in mental status cannot be confirmed [29–32]. In the older child, however, seizure semiology often has features resembling localization related seizures in adults [33]. The discussion that follows examines seizure semiology originating within a cerebral lobe as described in adults and the noninfant child.

Frontal lobe onset

Frontal lobe seizures are generally of short duration, typically unassociated with postictal confusion, and frequently nocturnal [34]. Differentiating nocturnal seizures from nocturnal parasomnias can be made on clinical grounds, although video-EEG may be required [35]. The presence of paroxysmal arousals with motor behaviors usually indicates epileptic seizure rather than parasomnias [36]. Nocturnal frontal lobe epilepsy is more common in boys than girls, with a typical onset in childhood [37]. Tonic or postural features are common in frontal lobe seizures and are suggestive of onset in the contralateral hemisphere. Furthermore, complex partial seizures of frontal lobe onset are more likely to be associated with thrashing, pedaling, and kicking the lower extremities [35]. Not surprisingly, once seizures have propagated from the frontal lobe to the temporal lobe it is not possible to determine region of onset. Complex gestural automatisms are frequently present and help differentiate frontal lobe seizures from those of temporal lobe onset in which simple orobucal or hand automatisms are common. Leg movements are prominent in frontal lobe seizures that do not propagate to other areas, whereas hand posturing is common in seizures that remain restricted to the temporal lobe [35,38]. When present, these features collectively support a finding of frontal lobe onset for seizures. Seizures originating from various regions within the frontal lobes often have unique differentiating features that help in localization [39,40]. Supplementary motor seizures are associated with preservation of consciousness, tonic posturing of the extremities (often bilaterally), and are often mistaken for psychogenic seizures [40]. The diagnosis can almost always be verified with prolonged video-EEG recording [40].

Temporal lobe onset

Temporal lobe seizures are often preceded by simple partial seizures that are reported as an epigastric rising sensation and may have autonomic accompaniments [41,42]. The semiology of temporal lobe seizures [43] is not clearly defined in childhood, although children older than age 6 years seem to demonstrate a semiology similar to adults. In younger children, it may be difficult to separate typical semiology of temporal lobe onset from seizures of frontal lobe onset [43]. Furthermore, automatisms tend to be simpler in younger children, typically limited to lip smacking and fumbling hand gestures [43]. Behavioral arrest, orofacial automatism, and convulsive activity are much more commonly seen in the young child [44]. These differences may stem from differences in seizure etiology. Younger children are unlikely to have mesial temporal sclerosis and are much more likely to have tumors or dysplasia underlying temporal lobe epilepsy [45–47]. Unlike frontal lobe epilepsy, postictal confusion is prominent particularly in patients with atrophy restricted to the amygdala. Children, like adults with temporal lobe epilepsy, may have a history of prolonged febrile seizures [48].

Occipital lobe onset

Occipital lobe seizures are usually characterized by simple visual auras (sparks, flashes, scotoma, or amaurosis) followed by contraversion of eyes and head or forced eyelid closure [49]. Children often report a sensation of ocular oscillation [50,51]. In adult patients who had undergone successful epilepsy surgery for occipital lobe seizures, clinical features alone suggested an occipital onset in more than two thirds of the patients [52]. Visual auras, most commonly elementary hallucinations and ictal blindness, occurred in 73% of patients. Contralateral eye deviation, blinking, a sensation of eye movement, and nystagmoid eye movements are also seen [53,54]. A third of patients exhibited another seizure type, suggesting ictal spread, with 50% having temporal lobe automatism and 38% having focal motor seizures [52]. Similar findings have been reported by other investigators [55–57]; therefore, video-EEG monitoring is frequently required to identify region of seizure onset.

Parietal lobe onset

Parietal lobe epilepsy is less common than seizures originating from other lobes. Prominent sensory changes that spread in a Jacksonian march are often present [58]. Clinical manifestations of parietal lobe epilepsy confirmed by tumoral surgery in 34 patients [59] suggest that auras are present in 79% of patients. Somatosensory (62%), visual (12%), and aphasia were the most common auras [59]. Localized ictal pain is a rare phenomena that when present is a strong predictor of parietal lobe seizures [60].

Synthesis of seizure semiology

Generating a hypothesis about region of seizure origin based on seizure semiology is the initial step in the strategy to localize seizures. It forms the basis for planning the remainder of the presurgical evaluation. There are several limitations with localization based on seizure semiology alone. As pointed out earlier, infants and young children often do not demonstrate localization-specific semiology [31]. Multiple seizure types that are suggestive of multiorigin and localization areas provide important information that may suggest that surgery is not a good option for the patient being evaluated. Propagated seizures may mislead as to site of origin and also require video-EEG. Alternatively, in patients with true multifocal seizures it may help delineate the most disabling target seizure to tackle.

Physical examination

The physical examination provides important clues in the evaluation of seizures and is particularly important in the presurgical evaluation [61].

Particular attention should be placed on the identification of skin lesions associated with tuberous sclerosis, neurofibromatosis, Sturge-Weber syndrome, and linear sebaceous nevus syndrome [61,62]. Identification of a tuberous sclerosis would help identify a cerebral tuber that underlies the patient's particular seizure [63]. The presence of hemiparesis and visual field deficits offers important clues to seizure localization and helps define the approach for seizures originating from or close to eloquent cerebral cortex. Children with hemiparesis or limb deformity without evidence of an acquired lesion should prompt a search for focal cortical dysplasia [64], an important finding indicating a lesion that could be amenable to epilepsy surgery.

Interictal electroencephalogram

The area of cortex that generates epileptiform discharges is referred to as the irritative zone. In approximately 50% of patients, scalp interictal EEG determines the approximate site of seizure onset [65], although in many patients epileptiform discharges extend far beyond the region that underlies the epileptogenic zone. At best, the interictal EEG offers important information allowing planning for further noninvasive and invasive studies. The epileptogenic zone can also be approximated by the region of polymorphic focal slow activity with focal attenuation of background activity. Interictal EEG also allows identification of unsuspected generalized epilepsy.

In temporal lobe epilepsy, the interictal EEG may also provide clues to the nature of the epileptogenic lesion. Similar to adults [66], anterior and inferiorly distributed temporal interictal sharp waves suggest mesial temporal sclerosis, whereas lateral or poorly localized epileptiform discharges are more often seen in children with low-grade temporal tumors [67].

Video-electroencephalogram monitoring

Video-EEG monitoring gives the clinician an opportunity to carefully analyze the clinical seizure, corroborate the historical description of the seizure, and attempt localization based on semiology [68–75]. It also allows the exclusion of nonepileptic seizures and the identification of all the seizure types that the patient experiences. The presence of multiple seizure types may indicate that surgery is not a good option or that in a particular clinical context one of the seizure types that is the most bothersome should be targeted.

The ictal onset zone is the cerebral parenchyma that underlies the onset of seizures. The ictal onset zone can usually be identified with ictal video-EEG, although it suffers from some of the same limitations as the interictal EEG described earlier [76]. Ictal onset in deep structures or regions not represented on the convexity often is seen only as slow activity occurring many seconds after the onset of clinical manifestations. Most patients in the presurgical evaluation require video-EEG study, although video-EEG evaluation may not be required in all patients undergoing epilepsy surgery [77].

Video-electroencephalogram monitoring and antiepileptic drug withdrawal

Video-EEG and intracranial EEG monitoring need to be performed in a timely and cost-efficient manner. To facilitate this, AEDs may need to be withdrawn either completely or partially so that seizures can be captured. Abrupt AED withdrawal leads to concern about provoking status epilepticus and on seizure localization and semiology. Furthermore, the order of individual AED withdrawal must also be addressed.

Not surprisingly, AED withdrawal in general results in an increased seizure frequency. Seizure semiology and EEG characteristics following AED withdrawal, however, are similar to prewithdrawal characteristics [78]. These findings have been shown for AED withdrawal in general and specifically for withdrawal of carbamazepine and phenytoin [79,80]. Rapid withdrawal of the barbiturates or benzodiazepines, however, may result in generalized seizures. The precipitation of previously not experienced seizures has been specifically shown for withdrawal of clonazepam [79]. Furthermore, new types of partial seizures uncovered by discontinuation of these agents may be evidence of previously quiescent multifocal epilepsy [80].

In summary, currently available literature suggests that nonbenzodiazepine and nonbarbiturate AED withdrawal is not likely to result in false ictal localization or atypical seizure presentation. Furthermore, withdrawal of phenytoin, carbamazepine, or valproic acid may increase the quantity of interictal EEG epileptiform discharges [81,82].

The rate of AED withdrawal that increases seizure frequency varies by individual AED. For carbamazepine or phenytoin withdrawal, absent or subtherapeutic serum concentration rather than the rate of serum concentration decline was most likely to be associated with an increase in seizure frequency [79]. Furthermore, seizure rates do seem to be significantly related to the rate of carbamazepine withdrawal, with secondarily generalized tonic-clonic seizures occurring more frequently when this agent is withdrawn over 4 days versus 10 days [83,84]. Theodore et al [85] observed that seizure frequency is related to declining serum concentrations, with the frequency of complex partial seizures increasing as phenobarbital levels decrease through the range of 15–20 mcg/ml and generalized convulsions occurring as serum levels decline to less than 10 mcg/ml. Initial serum concentration and rate of concentration decline do not seem to be related to increased seizure frequency.

Reduction of nonbarbiturate AED dosage should be done one drug at a time over 2–3 days. Recognizing that the desired increase in seizures may be most closely associated with absolute serum concentration, the extent of dosage reduction therefore depends on factors such as baseline drug concentration and baseline seizure frequency and severity. Efforts to reduce barbiturate or benzodiazepine medications should be done cautiously and grad ually and may begin well before hospital admission. If generalized tonic-clonic seizures do occur during withdrawal, reintroduction of small ''subtherapeutic'' doses of the withdrawn AED is reasonable.

Magnetoencephalography (MEG)

MEG is a new epilepsy evaluation technique in which the electromagnetic waves of the brain are detected and localized. Because epileptic discharges are fundamentally electrical phenomena, their origin establishes the functional location of the epileptogenic zone. Standard electroencephalography cannot always accurately localize the original tissue source of the electrical disturbance because signal reaching the recording electrodes can be distorted by craniotomy defects or overlying tissues. In contrast, the magnetic counterpart of the electromagnetic wave passes through the calvarium unimpeded, allowing a more precise anatomic localization. To measure the tiny magnetic signals of the brain, a large array of specialized superconducting amplifiers (SQUIDs) is placed over the head, and spontaneous electromagnetic activity is recorded. By coregistering the MEG data to the patient's MRI, a composite image reflecting electromagnetic function and associated structure can be seen. This combination of MEG with MRI has been termed magnetic source imaging (MSI). Early studies have shown the ability of MSI to localize epileptogenic zones in a group of medically refractory epilepsy patients. It seems to have particular usefulness in patients with neocortical sources, an area that is traditionally difficult to localize by EEG methods. In patients with multiple or widespread cortical lesions, the MEG localizations may allow direct visualization of the relation of the MEG seizure spike to the MRI lesion. In this same presurgical epilepsy population, MEG affords the opportunity to perform mapping of the auditory, visual, and somatosensory regions noninvasively before any planned resection.

Neuroimaging: magnetic resonance imaging, magnetic resonance spectroscopy, functional magnetic resonance imaging, and positron emission tomography

Magnetic resonance imaging (MRI)

MRI is the imaging modality of choice [86], although the specific techniques need to be specifically tailored to the patient [87–89]. Cranial computed tomography may be complementary in some cases to detect calcification, which might help explain the presence of low signal intensity in MRI images or help confirm a diagnosis of cysticercosis. MRI angiography or conventional angiography may be indicated if MRI findings suggest a vascular malformation. Intravenous contrast medium, although not required routinely in the evaluation of chronic seizures, may be useful in cases in which tumors or actively pathologic processes are suspected [90,91]. Improvement in imaging techniques has increased the percentage of cases in which lesions are detected. In the group of patients with complex partial seizures, mesial temporal sclerosis may be found in one third of patients. The use of surface coils and techniques with high spatial and contrast resolution have increased the accuracy of MRI for subtle cortical dysplasia [92–94].

The MRI examination of patients being evaluated for epilepsy surgery includes a sequence of T1-weighted images in the sagittal plane and images with T2 weighting. These may be obtained in axial or coronal plane with fast spine echo (FSE). These techniques include fluid attenuating inversion recovery (FLAIR), which uses an inversion time that cancels the signal from CSF. This sequence has the advantage that the signal from CSF does not obscure lesions near the CSF. A second advantage is the greater dynamic range in the image for the normal and pathologic cerebral tissues. Disadvantages of the technique are artifacts related to CSF pulsations and artifacts near the border of CSF and brain. Another technique used to defeat the signal intensity from CSF is inversion recovery prepared fast spin echo.

Although tailored protocols are critical to the detection of MTS [47,95], the pediatric magnetic resonance examination must also adequately cover the whole brain to assess general brain morphology and myelination status [96]. Evaluation of the cortex can be particularly challenging in the incompletely myelinated infant brain, because gray-white tissue contrast is suboptimal. In the first 2 years of life, heavy T1 and T2 weighting is required (TR is typically increased to approximately 3000 msec for T2 series). Phakomatoses such as tuberous sclerosis may be clinically unsuspected and first suggested by specific magnetic resonance findings.

The use of high-resolution volumetric techniques and phased-array MRI surface coils has improved the detection of subtle abnormalities of the cerebral cortex in patients with cortical dysplasia. The presence of a cortical dysplasia may be suspected because of a cortical dimple, an anomalous vessel, or abnormally small or large gyri. With additional images acquired by way of the surface coil or thin slice technique, the indistinctness of the gray–white junction characteristic of a cortical dysplasia can be detected. The proton-density images are often particularly useful in showing a funnel-shaped region of abnormal signal tapering downward from the cortex toward the ventricular margin. Longstanding dysplasias may have areas of gliosis that show hyperintense signal by T2 or FLAIR, making distinction from low-grade tumor difficult at times (by MRI and pathologic analysis). Dysplasia is favored over tumor when there is tissue loss, absence of mass effect, and presence of dysplastic cortical veins overlying the region. In the absence of imaging clues to the localization of a suspected cortical dysplasia, knowledge of the semiology or EEG localization may be useful to help direct surface coil placement for more detailed MR analysis. Diffusion-weighted imaging (DWI) has a role in the evaluation of some patients with chronic epilepsy [97]. In diffusion-weighted proton MRI, regions with limited diffusion or cytotoxic edema are characterized by higher signal intensity, whereas vasogenic edema shows low signal [98]. DWI is sensitive to a shift of water into the intracellular compartment that results from the loss of ATP. Although its more conventional use is in patients with stroke, DWI has been shown to reveal reversible changes in association with electrical brain activity in animals and in association with status epilepticus, either

convulsive or nonconvulsive, in humans. Following a seizure, imaging with DWI may demonstrate a region of diminished diffusion that appears as a region of increased signal intensity [95,99]. A region of abnormal diffusion in DWI in early reports seems to localize to the epileptogenic focus, although it is not confined to the focus.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) resolves the signal received from the region of interest into separate resonant frequency peaks for specific metabolites [100,101]. Proton MRS can be performed as a single voxel study in which the relative concentrations of choline, creatine, N-acetyl-aspartate (NAA), lactate, and other metabolites can be measured in a region of interest. It can be performed also as a two-dimensional or three-dimensional study in which the relative concentrations of these metabolites can be measure pixel by pixel in a large region of interest. It requires less than 15 minutes in conjunction with an imaging study. The concentration of NAA in the mesial temporal lobe is a sensitive measure of neuronal dropout and sclerosis. The addition of MRS to the imaging study can improve the detection of mesial temporal sclerosis, particularly in cases with questionable or borderline morphologic findings. The concentration of NAA in the temporal lobe contralateral to the temporal lobe targeted for resection is a good predictor of outcome from tailored temporal lobectomy.

Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) may be used in selected patients before epilepsy surgery to estimate the risk for a postoperative neurologic deficit [102,103]. With fMRI, the proximity of eloquent brain to the proposed resection can be determined noninvasively. fMRI allows for hemispheric dominance for language to be assessed accurately, obviating the invasive Wada test in some patients. The localization of memory functions by fMRI is under study. If fMRI localized memory accurately, it would likely replace Wada testing in patients with epilepsy. The ability of fMRI to show dynamic regional changes in cerebral blood flow and oxygenation can pinpoint anatomic sites of activation correlated to simultaneously acquired ictal or interictal EEG.

Positron emission tomography

Positron emission tomography (PET) and SPECT methods are usually reserved for the difficult epilepsy patient who is under consideration for seizure surgery [104]. Both techniques use injected radioactive tracers to produce functional brain images. The rationale behind their use is that epileptogenic zones tend to be hypermetabolic during a seizure, and may

become hypometabolic in the interictal period. Most of the commonly used radioligands are distributed according to blood flow and metabolism, with an uptake curve time course on the order of minutes. Recent advances in SPECT and PET instrumentation have improved resolution such that high quality sublobar localization data can now be expected from these techniques. In SPECT studies, we generally use Tc-99–labeled ECD or HMPAO; for PET studies, F-18 deoxyglucose is most commonly used. Advanced techniques that probe receptor kinetics or distinguish blood flow from metabolic changes also can be performed with other radio tracers. Ictal SPECT can be accomplished during inpatient hospitalizations for epilepsy monitoring and has a high sensitivity (80%–90%) for localizing the epileptogenic zone. Hypometabolic areas shown by interictal PET correlate highly with ultimate clinical lateralization of mesial and neocortical epilepsies.

Neuropsychologic evaluation

The neuropsychologic evaluation in epilepsy consists of psychometric assessment of mental status, evaluation of behavioral and emotional function, and determination of laterality of language and memory by way of the intracarotid sodium amobarbital procedure (Wada test). Anterior temporal lobectomy for surgical treatment of complex partial epilepsy is the most widely studied neuropsychologic area of epilepsy surgery. The role of the neuropsychologic evaluation in the young child with extratemporal epilepsy is still evolving.

The neuropsychologic assessment provides a baseline assessment of mental status against which the effects of epilepsy surgery can be assessed. It can also provide prognostic information regarding cognitive outcome and may help with localizing and lateralizing information [105–110]. Rausch [111] found considerable diversity across epilepsy centers regarding the depth, sophistication, and characteristics of neuropsychologic assessments.

The Wada test is a nonspecific moniker for a series of procedures that assess language dominance and memory patency in each cerebral hemisphere. The diversity of procedures used has been collectively called the Wada test. Although there have been several calls for standardization of the procedure, only recently has this been undertaken in a meaningful way [112].

The Loring protocol entails presentation of a standard set of eight to-be-remembered objects to the patient's intact visual field for approximately 5–10 seconds each. Following recovery from the neurologic effects of the perfusion (typically approximately 10 minutes post-drug administration), return of the patient's mental status to baseline condition, and cessation of unilateral EEG slowing, recognition memory testing is undertaken. The eight target stimuli are randomly intermixed with 16 foils and the subject is to indicate whether the presented item was or was not part of the initial target set. A net correct score for each hemisphere is derived. Left versus right hemisphere memory asymmetry scores have been shown to be associated with the presence or

absence of hippocampal sclerosis in the to-be-resected mesial temporal lobe region and to be predictive of favorable surgical outcome [113].

In younger children, the Wada test is often ineffective in helping determine the functional integrity of the ipsilateral medial temporal lobe and hippocampus. The ability to make confident predictions concerning postsurgical cognitive outcome in young children is weaker than in adolescents and adults. Little systematic research has been published on the effects of epilepsy surgery in postoperative memory functioning in children and on the rate of cognitive development in children undergoing surgery at a young age.

Freedom from seizures is the primary predictor of future employment and social integration [114,115]. Hence, careful objective assessment of cognitive, behavioral, and functional status of surgical candidates gives a sense of the prognosis for change in these areas of function, helps in the derivation of reasonable expectations for what may be achieved by epilepsy surgery, and facilitates determination of what rehabilitation or assistance the patient may need postoperatively.

Intracranial electroencephalograph

In my opinion, factors favoring an intracranial electroencephalograph (EEG) pattern being ictal include the following: (1) a sudden change in ongoing background activity, that is (2) rhythmic rather than irregular, (3) focal rather than diffuse, (4) of higher frequency rather than lower at onset, (5) sustained for tens of seconds, (6) evolving in frequency, amplitude, and spatial distribution, and (7) associated with behavioral change. As always there are exceptions to the above, such as the loss or flattening of background activity often referred to as an "electrodecremental" event or seizure onset. The question here is whether the apparent absence of activity relates more to the recording characteristics of our electrodes and amplifiers rather than to an actual secession of activity. Equally important is recognizing EEG changes that are less likely to represent a seizure onset and thus should not be used to localize the focus. Irregular slowing is thought by many, including myself, to be a change seen in cortex surrounding the focus rather than a marker of ictal activity. Similarly, regional changes in background rhythms without associated high-frequency discharges are not localizing. These include periodic sharp waves that may be recorded after a neocortical seizure onset.

Jayakar (this issue) advises looking for abnormal background rhythms and not just ictal events. Sick cortex produces a different EEG background than does healthy cortex, and such areas are seizure prone. Unfortunately, the same sick cortex may generate poorly formed seizure activity, as well as background rhythms. The so-called "subtle transformation" from an abnormal background rhythm to seizure activity can be very difficult to appreciate, so it is prudent to pay particular attention to sick cortex when attempting to identify seizure onset.

Nearly everyone agrees that the earliest EEG change is the most important for localization. A frequent problem is how to interpret this change when it appears to be widespread. Is the seizure unlocalized or simply unlocalizable by the electrodes implanted. Spatial undersampling may be the culprit, and it is a major concern when interpreting intracranial EEG. As has been known for some time, the recording properties of intracranial electrodes tend to make them very ''nearsighted.'' Local near-field cortical activity is of significantly higher amplitude than that from cortex only a few millimeters and certainly centimeters away. Successfully identifying the epileptogenic focus is made more likely if its general location has been determined by noninvasive procedures and if sufficient numbers of electrodes are used to cover this area. ICEEG should not be considered an exploratory procedure. If you have no idea from where seizures may be coming, the limited spatial sampling of this technique is likely to lead to failure or worse, a wrong localization. This is particularly true of neocortical epilepsies which are more diverse in their location and extent than classic mesial temporal epilepsy. Given the expense, time, effort, and potential morbidity of ICEEG, it makes little sense to proceed without a reasonable expectation of obtaining adequate focus localization.

Even if the intracranial EEG changes appear to be focal from our electrode array, can we be certain it represents the seizure origin and not ictal activity that has propagated from some other region where we do not have electrodes? There is no consensus on how this can be achieved reliably. We look for behavioral alterations before EEG change to warn us of this possibility, but neocortical seizures can spread with lightning speed, making this observation less likely. Some believe that low-voltage gamma activity or focal DC shifts are only observed at the initial focus. Less optimistic colleagues recount the old adage among intracranial electroencephalographers that ''seizures only begin where there are electrodes.'' Certainly further investigations are needed to help identify distinguishing criteria or analysis techniques.

Advances in intracranial EEG recording, particularly the increase in electrode numbers, has brought with it problems as well. At many epilepsy centers, 100 or more electrode contacts may be used in a single patient. Appreciating the location of these electrodes relative to the underlying cortex and to each other is often very difficult. Accordingly, the spatial analysis of these intracranial EEG data is often quite confusing when looking simply at traces. The spatiotemporal character of intracranial voltage fields may provide new localizing information; however, to accomplish this, the locations of electrodes and cortex need to be defined and displayed in a two- or preferably three-dimensional representation. All of these data are currently available, but seldom are they combined and used to interpret ICEEG. In many respects ICEEG interpretation is at a stage similar to scalp EEG analysis 10 years ago, when quantitative and computer-assisted techniques were seldom used and localization was based principally on pattern recognition.

Since that time there have been significant strides in scalp EEG interpretation using a variety of digital techniques including voltage topography, source localization (such as dipole modeling), and spectral and coherence analyses. Many of these same techniques will probably find useful applications with intracranial EEG.

Under few circumstances except surgical evaluations do we get the opportunity to record directly from the human brain. These are our most valuable data, both by providing diagnostic and localizing information for the patient and by allowing us to advance our knowledge of the electrophysiology of the brain. With these data we can directly validate and thus more efficiently improve our noninvasive techniques. It is time to look critically once more at our methods. Just because we have been interpreting ICEEG for 25 years does not necessarily mean that there are not better ways to do it. Although pressures for clinical productivity encourage us simply to localize the seizure focus and move on to the next case, it is worthwhile for all concerned to take the extra time to learn how to get more information from intracranial EEG, lest we find ourselves in the near future constrained both by old ideas and new regulations that limit further opportunity to learn.

Intracranial EEG is obtained when surgery is actively considered, not as an ''exploratory procedure'' [27]. It is obtained by placing strip or grid electrodes in the subdural space. Subdural electrodes measuring 2–4 mm in diameter made of platinum alloy are embedded in polyurethane and placed either by way of a craniotomy (for grids) or under fluoroscopy through burr holes (for strips). EEG recording (electrocorticography, ECoG) and electrical stimulation (functional mapping) can be performed by way of the electrodes. The risk for infection and hemorrhage is less than 1% [116].

There are two approaches to obtaining intracranial EEG before resective surgery that are described here.

One-stage operative strategy

A one-stage operation uses ECoG in the operating room immediately before the resection. This strategy uses interictal activity to direct the resection. Generally, ECoG is used to ''fine tune'' a resection in which there is already relative clarity of the relationship of the lesion to the epileptogenic zone.

Interictal ECoG features used to define the epileptogenic zone include (1) consistent focality in interictal spiking, (2) rhythmic features, (3) trains of focal fast beta activity, and (4) focal attenuation of background [27,117–119]. ECoG that reveals almost continuous focal rhythmic discharges may not require ictal recordings. The one-stage strategy using ECoG is typically used to tailor resection of a tumor that manifests with seizures. It is also useful when there is congruence between the imaging lesion and the ictal onset zone. A major advantage of a one-stage procedure is the limitation of cost

and risk for infection. Awake intraoperative ECoG to allow mapping of eloquent cortex, however, is particularly difficult in children [120]. Furthermore, ECoG is performed in the operating room while the child is under the influence of general anesthesia that may suppress or occasionally paradoxically activate spikes.

Two-stage operative strategy

In a two-stage operation, subdural electrodes are placed during the initial operation and the patient is then moved to a monitoring unit [118,120–124]. Seizures are captured and the ictal onset zone defined [125]. Functional mapping is performed if necessary and the relationship of eloquent cortex to the epileptogenic zone is defined. These data then allow a tailored resection at a second operation several days later [126,127]. This strategy is used when the epileptogenic zone is discrete, imaging lesions are not present, or the planned resection is adjacent to eloquent cortex [27]. Disadvantages with a two-stage strategy include the increased cost and risk for infection. Intracerebral depth electrodes seem to be of limited importance in children and are not discussed here.

Resection of regions most active on ECoG seem to be important for successful outcomes, although removal of all discharging areas may not be necessary to achieve seizure control [128]. Surgical outcomes can be predicted by intracranial EEG [129–133]. Intraoperative cortical stimulation elicited a habitual aura in 37% of 29 patients. Patients in whom stimulation elicits a habitual aura have a good prognosis for becoming seizure-free following resection. Lateralizing clinical features were seen in almost two thirds of patients: contralateral head deviation occurred in half, 59% had visual field defects contralateral to the epileptogenic area, and 64% had abnormal imaging studies ipsilateral to the side of surgery [52].

Functional cortical mapping plays an important role in tailored neocortical resections [102,134]. Defining the relationship between eloquent cortex and the epileptogenic zone is important in planning the resection [117, 135,136]. Typically, a margin of at least 0.5–1 cm is required to spare function. Language cortex can be mapped in children older than 4 years [110], or more recently in children as young as age 2.5 years [135,136].

Summary

The presurgical evaluation should result in a clear understanding of whether surgery can be undertaken and its associated risks and potential for benefit. The results of surgery are best when there is congruence in the seizure semiology, the irritative zone on interictal EEG, and the ictal onset zone with the epileptogenic lesion as defined on MRI and PET, and when there is a clear understanding of the ictal onset zone's relationship to eloquent cortex as defined by neuropsychologic evaluation, the intracarotid amobarbital test, and cortical functional mapping.

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