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Nervous System Malformations

John Gaitanis, MD and Tomo Tarui, MD

Abstract

PURPOSE OF REVIEW: This article provides an overview of the most common nervous system malformations and serves as a reference for the latest advances in diagnosis and treatment.

RECENT FINDINGS: Major advances have occurred in recognizing the genetic basis of nervous system malformations. Environmental causes of nervous system malformations, such as perinatal infections including Zika virus, are also reviewed. Treatment for nervous system malformations begins prior to birth with prevention. Folic acid supplementation reduces the risk of neural tube defects and is an important part of health maintenance for pregnant women. Fetal surgery is now available for prenatal repair of myelomeningocele and has been demonstrated to improve outcomes.

SUMMARY: Each type of nervous system malformation is relatively uncommon, but, collectively, they constitute a large population of neurologic patients. The diagnosis of nervous system malformations begins with radiographic characterization. Genetic studies, including chromosomal microarray, targeted gene sequencing, and next-generation sequencing, are increasingly important aspects of the assessment. A genetic diagnosis may identify an associated medical condition and is necessary for family planning. Treatment consists primarily of supportive therapies for developmental delays and epilepsy, but prenatal surgery for myelomeningocele offers a glimpse of future possibilities. Prognosis depends on multiple clinical factors, including the examination findings, imaging characteristics, and genetic results. Treatment is best conducted in a multidisciplinary setting with neurology, neurosurgery, developmental pediatrics, and genetics working together as a comprehensive team.

INTRODUCTION

The nervous system undergoes rapid developmental changes throughout gestation and continues to evolve after birth and into early adulthood. Disruption of the developing nervous system can occur at any stage. The timing and nature of disruptions account for the specific malformations that result, which include a myriad of conditions such as spina bifida, hydrocephalus, holoprosencephaly, lissencephaly, and focal cortical dysplasia. Resulting signs may include cognitive impairment, epilepsy, autism spectrum disorders, and motor and sensory impairment. Since brain malformations are defined by structural changes, neuroimaging is the fundamental diagnostic test. With improvements in ultrasound and

Address correspondence to Dr John Gaitanis, Tufts Medical Center, Floating Hospital for Children, 800 Washington St, Boston, MA 02111, JGaitanis@tuftsmedicalcenter.org.

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prenatal MRI, accurate diagnosis can now occur prenatally. Prompt diagnosis allows for interventions sooner, in some cases prior to delivery.

This article reviews common alterations of nervous system development and discusses them according to the embryologic stage in which the abnormality has its origin.¹ Emphasis is given to the clinical presentation and imaging characteristics of the known conditions.

BRIEF OVERVIEW OF EMBRYOLOGY

Brain and spinal cord development begins with neurulation, which is the process of neural tube formation that occurs in the third and fourth weeks of gestation. In the fifth and sixth weeks, prosencephalic development occurs, giving shape to the developing brain. Cortical development is divided into stages of cell proliferation, neuronal migration, and postmigrational cortical organization.^{1–3} Myelination and cortical organization are the final steps of brain development and continue well beyond birth.⁴

DISORDERS OF NEURULATION

Fusion of the neural tube begins at the level of the hindbrain (medulla and pons) and at least one other site and proceeds rostrally and caudally.⁵ Failure of rostral fusion disrupts brain development, resulting in anencephaly or encephalocele. Incomplete caudal fusion causes the spinal disorder myelomeningocele. Anencephaly occurs no later than day 24 of gestation. Encephalocele and myelomeningocele occur around day 26 of gestation.

Myelomeningocele

Myelomeningocele is the most common disorder of neurulation with which fetuses and infants can remain viable. Its incidence in the United States is approximately 0.2 to 0.4 per 1000 live births.⁶ The neurologic features of myelomeningocele relate to the level of involvement, presence of hydrocephalus, and other associated brain malformations.

Impairment of motor, sensory, and sphincter function relates to the level of involvement. Ambulation is one of the most important clinical concerns. Antigravity function of the iliopsoas and quadriceps muscles is required for walking. Ambulation can be impaired in children with spina bifida, even those with low neurosegmental lesions. Some children who learn to walk can lose ambulation in later childhood; this is particularly true in those with high-level lesions.⁷

Hydrocephalus is seen in approximately 90% of patients with lumbar lesions. Hydrocephalus develops later in gestation or postnatally. Newborns with myelomeningocele can be asymptomatic without recognizable clinical signs of increased intracranial pressure (lethargy, irritability, limited upward gaze, and rapidly expanding head circumference). Infants can become symptomatic up to 6 weeks after birth. Clinical signs are frequently absent; thus, neuroimaging is necessary for the prompt diagnosis of hydrocephalus. Infants demonstrating hydrocephalus require shunt placement immediately following myelomeningocele closure, as the closure stops CSF leakage and thus possibly worsens hydrocephalus unless CSF flow is diverted. Shunt placement at the time of

myelomeningocele closure can reduce surgical morbidities such as wound dehiscence and CSF leaks in the area of the myelomeningocele repair without increasing shunt complications.⁸

Myelomeningocele combined with inferior displacement of the cerebellar tonsils through the foramen magnum is termed the Arnold-Chiari malformation (Chiari type II). Of note, Chiari type I refers to displacement of the cerebellar tonsils through the foramen magnum without dysraphism. Other features of Chiari type II malformation include elongation and thinning of the upper medulla and pons and bony defects of the foramen magnum, occiput, and upper cervical vertebrae.

Myelomeningocele may be associated with brainstem malformations, with resulting brainstem dysfunction such as apnea, stridor, cyanotic spells, and dysphagia, which can become significant causes of morbidity and mortality. Periventricular nodular heterotopia is associated with Arnold-Chiari malformations in roughly one-third of patients.⁹ It is seen more commonly in patients with a low pontomesencephalic junction.

Diagnosis of myelomeningocele and Arnold-Chiari malformation begins prior to birth, and, increasingly, treatment also can begin prenatally. Associated brain and non-central nervous system (CNS) malformations can be detected by fetal sonography or MRI, which influences postnatal outcome. The rationale for fetal surgery was proposed by animal models and is intended to prevent progressive intrauterine damage of neural tissue exposed to the myelomeningocele lesion.¹⁰ A randomized trial of prenatal versus postnatal repair of myelomeningocele was stopped early because of the efficacy of prenatal surgery.¹¹ In that trial, prenatal surgery was associated with lower rates of shunt placement (40% versus 82%) and improvements in mental development and motor function. Complications of prenatal surgery included an increased risk of preterm delivery and uterine dehiscence at delivery.

In postnatal surgery, the myelomeningocele is closed as early as possible to prevent infection (usually within the first 48 hours of life). Brainstem dysfunction (which presents with intermittent apnea, bradycardia, swallowing dysfunction, nystagmus, or vocal cord paralysis) may require decompressive upper cervical laminectomy to reduce brainstem and cerebellar tonsillar compression due to Chiari II malformation. Such surgery is best performed within the first weeks after birth. Urinary dysfunction may necessitate daily catheterization to prevent urinary tract infections. Orthopedic follow-up is also needed for prevention and management of scoliosis and contractures. Given the wide range of systems affected in myelomeningocele, multidisciplinary clinics are helpful for coordinating care.

Ideally, treatment begins with prevention of the condition. The British Medical Research Council Vitamin Study Group conducted a randomized prevention trial that found daily oral supplementation with folic acid before conception and during early pregnancy substantially reduced the recurrence of neural tube defects in children of women who previously had a child with such a condition.¹² Currently, the US Public Health Service and Centers for Disease Control and Prevention (CDC) recommend that all women of childbearing age consume 0.4 mg of folic acid daily to prevent neural tube defects. Women who previously had a child with neural tube defects are recommended to consume 4 mg of folic acid daily to

prevent recurrence of a neural tube defect.¹³ Yet, even with folate fortification, myelomeningocele still occurs. In addition to folate deficiency, genetic and nongenetic etiologies are implicated, including gestational diabetes mellitus and medications (eg, valproic acid).¹⁴

DISORDERS OF PROSENCEPHALIC DEVELOPMENT

The forebrain takes shape during prosencephalic development beginning in the fifth week and continuing through the second and third months of gestation. Forebrain development can be divided into three stages: formation, cleavage, and midline development.¹⁵ Anomaly of prosencephalic formation (aprosencephaly, atelencephaly) is not viable and extremely rare, thus this article focuses on the latter two stages.

Disorders of Prosencephalic Cleavage

The rostral end of the neural tube expands to create the forebrain and prosencephalon. After development of the prosencephalon, the midline of the structure indents and cleaves into the telencephalon primordia of the bilateral cerebral hemispheres.

HOLOPROSENCEPHALY.—Included among disorders of prosencephalic cleavage is holoprosencephaly, in which the absence of hemispheric separation results in a single, large forebrain ventricle that can be first recognized on the prenatal ultrasound and fetal MRI (FIGURE 4–1). Alobar holoprosencephaly is the most severe form, in which the brain is a single spherical structure with a common ventricle and a malformed cortical mantle. Malformation may involve the dysplastic optic nerves and the olfactory bulbs and tracts. The thalamus and hypothalamus do not separate normally and may accompany hypopituitarism. Facial anomalies, when present, can range from as severe as cyclopia to as subtle as a single central incisor. Semilobar and lobar holoprosencephaly are less severe forms of the same anomaly (FIGURE 4–1).

Associated cortical malformations frequently cause epilepsy. Careful attention to the neuroimaging features is therefore necessary in providing an accurate prognosis.¹⁶

The etiology of holoprosencephaly is heterogeneous with both genetic and environmental causes. Gestational diabetes mellitus is the most common environmental cause and carries a 1% risk of holoprosencephaly (200 times greater than in the healthy population). Chromosomal abnormalities account for approximately 25% to 50% of holoprosencephaly cases, with trisomy 13 syndrome and trisomy 18 syndrome being the most common. Thus, karyotype and chromosomal microarray analysis can be the first genetic tests ordered.¹⁷ Single-gene mutations are found in roughly 25% of patients. Several genes are known to be causative (*SHH*, *SIX3*, *ZIC2*). The first gene discovered, the sonic hedgehog (*SHH*) gene at 7q36, is also the most common.¹⁷ *SHH* plays an important role in dorsal-ventral patterning.¹⁸ Assuming a clear environmental cause is not found, the evaluation typically begins with a chromosomal microarray followed by targeted gene sequencing if the chromosomal microarray is unremarkable.¹⁷ Genetic counseling is important given the heterogeneity of these disorders.

Abnormalities of Midline Prosencephalic Development

Abnormalities of midline prosencephalic development are typically less severe than holoprosencephaly and include agenesis of the corpus callosum¹⁹ and septooptic dysplasia.

AGENESIS OF THE CORPUS CALLOSUM.—Agenesis of the corpus callosum can be either partial or complete (FIGURE 4–2). With partial agenesis, the posterior portion is more affected. Agenesis of the corpus callosum can be isolated or complex based on absence/presence of associated CNS malformations. Both partial and complete isolated agenesis of the corpus callosum can have broad neurodevelopmental presentations from mild to severe impairments (CASE 4–1). According to a meta-analysis of 16 case series of prenatally diagnosed “isolated” agenesis of the corpus callosum, approximately 70% of patients have normal outcomes, 15% have mild to moderate neurodevelopmental disabilities, and 15% have severe disabilities such as speech delays, impaired comprehension, attention disorders, hypotonia, dyscoordination, or dysphagia.²⁰ Associated brain anomalies that are relevant to prognosis may be found in 15% of cases of isolated agenesis of the corpus callosum.²¹ Even in patients with normal intelligence, deficits of social cognition²² and executive functioning are observed.²³ Prognosis is therefore extremely difficult to predict in early infancy.²⁴

SEPTOOPTIC DYSPLASIA.—Septooptic dysplasia is characterized by optic nerve hypoplasia in combination with pituitary dysfunction and absence of the septum pellucidum. The clinical presentation is visual impairment in infancy (congenital nystagmus or poor visual engagement), hypopituitarism, or both. Occasionally, the infant may be prenatally diagnosed with absence of the septum pellucidum and later diagnosed with septooptic dysplasia during postnatal follow-up including ophthalmologic and endocrinologic follow-up. The causes are highly heterogeneous, including both environmental and genetic etiologies. Identified genes associated with septooptic dysplasia are *HESX1*, *OTX2*, *PROKR2*, *SOX2*, and *SOX3*. *HESX1*, *OTX2*, *SOX2*, and *SOX3* are homeobox genes essential for pituitary and forebrain development.^{25–27}

DISORDERS OF NEURONAL PROLIFERATION

In the human fetus, neuronal proliferation (neurogenesis) takes place between the second and fourth months of gestation.^{28,29} Neurons and glia are generated in the margin of cerebral ventricles (ventricular and subventricular zones). In the earliest phases, neuronal proliferation mostly generates neuroprogenitor cells themselves^{30,31}; then, in later phases, more cells exit from their proliferative cycle to become postmitotic neurons while the others remain stem cells. Eventually, the ratio of cells leaving the proliferative cycle increases until all the neurons within the proliferative unit become postmitotic.³² Abnormal neuronal proliferation results in conditions characterized by quantitative and qualitative anomalies of neurons and glia such as decreased proliferation, disordered proliferation, or abnormal differentiation/maturation.

Decreased Proliferation

Decreased neuronal proliferation results in microcephaly with or without abnormal cerebral morphology.

MICROCEPHALY/MICROLISSENCEPHALY.—Primary microcephaly is a condition of small head size and is defined when the birth head circumference is three or more standard deviations below normal. Primary microcephaly is a heterogeneous condition and can be caused by destructive processes (eg, hypoxia-ischemia, intrauterine infections) or from a genetically determined reduction in neuronal proliferation. Most genetic forms are recessively inherited. Mutations associated with primary microcephaly alter neuroprogenitor cell proliferation through cell cycle regulation (*MCPH1*, *CENPJ*, *CDK5RAP2*), centrosome function (*NDE1*), cell proliferation (*ASPM*, *STIL*), mitotic spindle formation (*WDR62*), or DNA repair (*PNKP*, *PCNT*). One of the most common genetic causes is microcephaly 5, caused by mutations in the abnormal spindlelike microcephaly-associated gene (*ASPM*).^{33,34} *ASPM* is essential for normal mitotic spindle activity in neuroprogenitor cells, and its disruption therefore affects neuronal proliferation.³⁵ Intellectual disability and a generalized simplification of the gyral pattern are common, but more severe gyral abnormalities have not been described.

A simplified gyral pattern is sometimes recognized in cases of microcephaly with a spectrum of severity, which, on the severe end, is termed *microlissencephaly*.^{36,37} Microlissencephaly may be associated with cerebellar and callosal anomalies³⁸ and clinically manifests with global developmental delay, intellectual disabilities, and seizures.³⁹ Thus, microlissencephaly is considered to be a distinct clinical entity from the more common microcephaly with a simplified gyral pattern.⁴⁰

Intrauterine infections, such as cytomegalovirus or Zika virus, have been associated with microcephaly as well as more extensive injuries or malformations. Five clinical features are particularly associated with Zika virus: (1) severe microcephaly with a partially collapsed skull (resembling anencephaly but with preserved skin overlying the skull), (2) thin cerebral cortices with subcortical calcifications, (3) macular scarring and pigmentary retinal mottling, (4) congenital contractures, and (5) early hypertonia or extrapyramidal symptoms (CASE 4–2).⁴¹

Disordered Proliferation

Malformations in this group are characterized by significantly abnormal neuroprogenitor cell proliferation as well as other malformations and occasionally abnormal growth outside the CNS.

HEMIMEGALENCEPHALY.—Hemimegalencephaly is the unilateral enlargement of just one cerebral hemisphere and is associated with unilateral overgrowth of the body, which is likely caused by disturbances in cellular differentiation, proliferation, and organization.⁴² Neuropathology extends beyond the size of the hemisphere and includes abnormal gyration, ventriculomegaly, and abnormally increased T2 signal of the white matter.^{42,43} Histology shows disorganized cortical lamination, subcortical heterotopia, and large dysmorphic neurons termed *balloon neurons*.^{44–46} The opposite hemisphere may be normal or have mild dysplasia and heterotopia.⁴⁷ Although most cases of hemimegalencephaly are nonsyndromic, it can be rarely associated with tuberous sclerosis complex,⁴⁸ hypomelanosis of Ito,⁴⁵ and linear nevus sebaceous syndrome.⁴⁹ All patients have epilepsy;

hemispherectomy is often required to treat intractable epilepsy, although some patients' epilepsy may be controlled medically.^{42,50}

Abnormal Neuronal Differentiation or Maturation

In abnormalities of maturation or differentiation, neurons exhibit immature or glial features. In cortical dysplasia or cortical hamartoma of tuberous sclerosis complex, dysplastic or characteristic balloon neurons can be seen,^{51,52} along with evidence of disrupted neuronal migration such as disorganized or absent lamination and malpositioned or heterotopic neurons in both gray and white matter.⁴⁷ Therefore, its pathology is combined with abnormalities in migration and differentiation or maturation. Dysplastic and balloon neurons may lack the cellular machinery to migrate properly through the cortical plate.⁴⁷

TUBEROUS SCLEROSIS COMPLEX.—Tuberous sclerosis complex⁵³ is a multisystem dominantly inherited condition. It has a high rate of spontaneous mutations, and approximately one-half of all patients do not have an affected parent. Two genes are causative for tuberous sclerosis complex, both of which result in similar clinical features. The *TSC1* gene, located on chromosome 9q34, encodes for the protein hamartin, which indirectly links the cell membrane to the cytoskeleton.⁵⁴ The *TSC2* gene, located at chromosome 16p13.3, encodes for the protein tuberlin, which functions in cellular signaling pathways.⁵⁴ Hamartin and tuberlin interact as part of a larger protein complex controlling cell growth and size.⁵⁴ Diagnosis of tuberous sclerosis complex is mostly clinical owing to the large size of *TSC1* and *TSC2* genes. Clinically, tuberous sclerosis complex is classified into three subcategories: definite, probable, and suspect, based on the type and number of abnormalities characteristic of the disease.⁵⁵ The disease is primarily recognized by lesions in the skin, kidneys, heart, and CNS.

In the brain, the characteristic features include cortical and subcortical hamartomas (FIGURE 4–4A, 4–4B, and 4–4C), subependymal nodules (FIGURE 4–4D), and subependymal giant cell astrocytomas. On MRI, cortical tubers appear as enlarged, atypically shaped gyri with abnormal signal intensity in the subcortical white matter (FIGURE 4–4A).⁵⁶ Microscopically, they resemble focal cortical dysplasia⁵⁷ with disorganized lamination and balloon neurons.⁴⁷ Cortical tubers may contribute to the pathogenesis of epilepsy. Infants with tuberous sclerosis complex predominantly develop infantile spasms. For further discussion on infantile spasms and their management, refer to the article “Epileptic Encephalopathies” by Shaun A. Hussain, MD, MS,⁵⁸ in this issue of *Continuum*.

Patients with tuberous sclerosis complex may develop progressive cognitive impairment. Seizures in children younger than 2 years of age, infantile spasms, and a high burden of cortical tubers are associated with a high risk for cognitive impairment. Autism is commonly seen in patients with tuberous sclerosis complex, especially in patients with temporal tubers, seizure onset before 3 years of age, or infantile spasms.⁵⁹ For more information on tuberous sclerosis complex, refer to the article “Neurocutaneous Disorders” by Tena Rosser, MD,⁶⁰ in this issue of *Continuum*.

FOCAL CORTICAL DYSPLASIA.—Focal cortical dysplasia strongly resembles the cortical tubers of tuberous sclerosis complex. Macroscopically, the lesions display wider-than-normal gyri and blurring of the gray-white junction.⁶¹ Focal cortical dysplasia is highly associated with medically refractory epilepsy and often requires epilepsy surgery to control the seizures.⁶²

Microscopically, features of focal cortical dysplasia are characterized as abnormal cortical lamination, dysmorphic cells (cytomegalic dysmorphic neurons and balloon cells), and abnormal cellular polarity.⁶³ The recent consensus classification proposed by the International League Against Epilepsy subclassifies focal cortical dysplasia into types I, II, and III.⁶⁴ Focal cortical dysplasia type I is characterized by abnormal radial or tangential migration. Cells observed in type I appear to be less dysmorphic or small dysmorphic cells (hypertrophic pyramidal neurons) in contrast to type II. Focal cortical dysplasia type II has disrupted cortical lamination and characteristic dysmorphic cells such as cytomegalic dysmorphic neurons and balloon cells. Type IIa only has cytomegalic dysmorphic neurons, and type IIb has balloon cells (CASE 4–3). Type II is relatively well visualized by MRI. Focal cortical dysplasia type III is associated with an additional brain lesion and subclassified as follows: IIIa (hippocampal sclerosis), IIIb (tumor), IIIc (vascular malformations), or IIId (acquired lesions in early life such as gliosis). On MRI, focal cortical dysplasia may be found to be funnel-shaped and slightly hyperintense lesions on T₂-weighted images (FIGURE 4–5). Typical funnel lesions have their bases oriented toward the pial surface and the tip into the white matter.⁶² Focal cortical dysplasia is increasingly detected along with advances in MRI techniques, especially in 3T images. Yet, focal cortical dysplasia type I may be radiographically occult as its anatomic alterations are so subtle and can only be detected on a microscopic level. Focal cortical dysplasia type I may be found in nonlesional specimens resected in epilepsy surgery.

DISORDERS OF NEURONAL MIGRATION

During the third through fifth months of gestation, neurons and glia produced from ventricular and subventricular zones migrate radially or tangentially to their final sites within the cerebral cortex.²⁸ Anomalies during this process result in a variety of cortical malformations with characteristic anatomic and pathologic features.

Heterotopia

Heterotopia refers to collections of ectopic neurons located outside the cortex.⁶⁵ Unlike cortical dysplasia, the neurons within heterotopias have a normal morphology. Thus, on MRI, a heterotopia appears isointense to normal gray matter, in contrast to dysplasia, which usually has abnormal signal intensity. The cortex overlying a heterotopia may appear normal or thinner with shallow sulci.⁵⁶

Periventricular nodular heterotopia is characterized by clusters of ectopic neurons forming periventricular nodules within the periventricular region. Cerebral cortex overlying these nodules is otherwise normal-appearing (FIGURE 4–6).⁶⁶ The nodules are rounded, irregular in shape, and dispersed within myelinated fibers. In periventricular heterotopia, some neurons migrate toward the cortex to formulate a normal-appearing six-layer cortex, while

ectopic neurons fail migration and remain within the subependymal region to form heterotopias. Most patients with periventricular nodular heterotopia have normal intelligence. Some patients may develop epilepsy, commonly in the middle teenage years.⁶⁷ Periventricular nodular heterotopia most often results from a mutation of the filamin A (*FLNA*) gene on chromosome Xq28.^{Ref64}^{67,68} Mutations of *ARFGEF2*, *ERMARD*, *FAT4*, *DCHS1*, and *LRP2* are also associated with periventricular heterotopias, although they usually have other features such as microcephaly (*ARFGEF2*),⁶⁹ agenesis of the corpus callosum, polymicrogyria (*ERMARD*),⁷⁰ or other syndromic features (*FAT4*, *DCHS1*,⁷¹ and *LRP2*⁷²).

Lissencephaly

Lissencephaly refers to a paucity of normal gyri and sulci resulting in a “smooth brain.” It is a heterogeneous condition and was previously divided into two pathologic subtypes: classic (type I) and cobblestone (type II). More recently, however, cobblestone malformations have been recognized as a distinct category of diseases associated with dystroglycanopathies.

CLASSIC LISSENCEPHALY.—Patients with classic lissencephaly have severe reduction in gyral formation manifesting either as agyria (a total absence of gyri) or pachygyria (a reduced number of abnormally large gyri). Radiographically, agyria appears as a smooth brain surface with diminished white matter and shallow, underopercularized sylvian fissures.⁵⁶ The gyri in pachygyria are reduced in number and have an abnormally broad and flat morphology.⁵⁶ Genetic investigations have been most fruitful in this malformation, and many responsible genes and molecular mechanisms have been discovered. Pachygyria has a posterior greater than anterior gradient in *LIS1*, *TUBA1A*, and *TUBB2B* mutations (FIGURE 4–7) and an anterior greater than posterior gradient in *DCX*, *ACTB*, and *ACTG1* mutations. Most children with lissencephaly have relatively severe cognitive and motor disabilities and seizures. Clinical severity is related to the degree of structural abnormality, with greater gyral simplification resulting in greater clinical impairment. Epilepsy is universal, and infantile spasms are a particularly common seizure type. EEG reveals characteristic, high-voltage beta activity.⁷³ Neurodevelopmental disabilities are severe, with intellectual disability, spastic quadriplegia, and microcephaly all occurring commonly.

Classic lissencephaly has a markedly thickened smooth cortex with a relatively unaffected cerebellum and brainstem. Mutations of the platelet-activating factor acetylhydrolase gene (*PAFAH1B1* [*LIS1*]) located on chromosome 17p13.3 is commonly seen, especially in cases with a posterior greater than anterior gradient.⁷⁴ The *LIS1* gene product interacts with microtubules functioning in intracellular molecular transport. Almost all patients have de novo heterozygous mutations of *LIS1*. Therefore, the recurrence risk of having a second affected child is very low. A microdeletion syndrome affecting this region manifests as Miller-Dieker syndrome, with other congenital anomalies (craniofacial, renal, cardiac, or gastrointestinal malformations).⁷⁵ Mutations of *TUBA1A*⁷⁶ and *TUBB2B*⁷⁷ are also categorized as tubulinopathies, which affect isoforms of tubulin, one of the components of microtubules. Tubulinopathies may be associated with lissencephaly, polymicrogyria, microcephaly, or any combination of these conditions.

Abnormalities of the doublecortin (*DCX* or *XLIS*) gene, located on the X chromosome, are also known to cause classic lissencephaly with an anterior greater than posterior gradient.⁷⁸ In affected hemizygous males, the phenotype is nearly indistinguishable from *LIS1*. However, carrier heterozygous females present with a disorder termed *double cortex*, also known as subcortical band heterotopia (FIGURE 4–8). In double cortex, heterotopic accumulations of neurons occur in the subcortical white matter, forming band heterotopia. The overlying cortex displays a relatively normal six-layered architecture. Random inactivation of the X chromosome accounts for this pattern. Neurons expressing a normal copy of *DCX* undergo normal migration, whereas those expressing a mutant copy remain arrested in the subcortical white matter. Since males have only one X chromosome, they develop classic lissencephaly.

COBBLESTONE MALFORMATIONS.—In contrast, cobblestone malformations develop from an overmigration of neurons beyond the disrupted basal membrane and the pial surface and onto the overlying subarachnoid tissue. Cobblestone malformations are sometimes associated with congenital muscular dystrophy and eye abnormalities (eg, Fukuyama type congenital muscular dystrophy, Walker-Warburg syndrome, and muscle-eye-brain disease). These disorders result from an impairment of glycosylation of α -dystroglycan,⁷⁹ affecting the brain, nerve, and skeletal muscle (TABLE 4–1^{80–86}).⁸⁷

DISORDERS OF POSTMIGRATIONAL DEVELOPMENT

Disorders of postmigrational development are caused by impairments of cortical organization after migration has taken place.

Polymicrogyria

Polymicrogyria is thought to develop at the latest stages of neuronal migration or the earliest phases of cortical organization.³ It often results from external (nongenetic) causes such as intrauterine cytomegalovirus infection⁸⁸ or placental perfusion failure.⁸⁹ Patients with genetic etiologies may present with focal but symmetric lesions such as bilateral perisylvian polymicrogyria. Polymicrogyria can occur in any conceivable region, and frontoparietal, perisylvian, and parietooccipital regions have all been observed. Common clinical presentations include epilepsy and cognitive impairment. More specific symptoms are associated with a specific region or regions involved, as is the case in bilateral perisylvian polymicrogyria.

Bilateral frontoparietal polymicrogyria is characterized by bilateral, symmetric polymicrogyria in the frontoparietal regions, with an anterior greater than posterior gradient.⁹⁰ MRI shows thin white matter with areas of T₂ prolongation, ventriculomegaly, and hypoplastic pons and cerebellar vermis.⁹⁰ Reflecting broadly localizing pathology, the clinical manifestations are relatively severe and include motor disability, seizures, and global developmental delays.^{65,90} Cerebellar abnormalities and dysconjugate gaze are also common.⁹⁰ The causative gene is *ADGRG1* (also known as *GPR56*),⁹¹ which forms part of the adhesion G protein–coupled receptor family.

Bilateral perisylvian polymicrogyria results in a clinical syndrome manifested by mild cognitive impairment, epilepsy, and pseudobulbar palsy.⁹² In childhood, the pseudobulbar palsy results in expressive speech delay and feeding difficulty. Bilateral perisylvian polymicrogyria is often a sporadic condition but has also been described in association with neurofibromatosis type 1⁹³ and Kabuki make-up syndrome.⁹⁴ Phosphoinositide-3-kinase regulatory subunit 2 (*PIK3R2*) is a kinase that is involved in cell growth, survival, proliferation, motility, and morphology and is associated with bilateral perisylvian polymicrogyria.⁵³

These polymicrogyria syndromes are the most commonly described. Polymicrogyria can be also seen in association with other brain malformations, genetic syndromes, or fetal brain injuries such as perinatal infection. Genes associated with polymicrogyria are increasingly being identified.

PRENATAL DIAGNOSIS AND COUNSELING OF BRAIN MALFORMATIONS

With advances in obstetric ultrasound, brain malformations have been increasingly recognized in the fetal period, especially in the second trimester, when a routine fetal anatomic evaluation has been offered to pregnant women in the United States. Open neural tube defects may be diagnosed even earlier, with maternal serum screening of α -fetoprotein in the first trimester. Concerning findings are further investigated with fetal MRI and genetic tests. Child neurologists play a central role in providing prenatal diagnosis and counseling to pregnant women and families in collaboration with a multidisciplinary team consisting of maternal fetal medicine, radiologists, neurosurgeons, geneticists, and neonatologists.⁹⁵ Child neurologists are essential in formulating a diagnostic plan, assessing prognosis, and providing postnatal care to affected children.⁹⁵

Lately, significant advances have been made in prenatal genetic diagnosis and fetal surgery, which is changing practice. Genotyping of fetal cells via chorionic villi sampling and amniocentesis (amniocytes) remains the gold standard of fetal genetic diagnosis. Chromosomal microarray and targeted sequencing have regularly been used for prenatal diagnosis of structural fetal anomalies including brain malformations. The detection rate of pathognomonic copy number variants of CNS anomalies remains low (approximately 15%), which makes prenatal diagnosis and counseling challenging.⁹⁶ Noninvasive prenatal testing has been introduced to detect fetuses with aneuploidies such as trisomies 21, 18, and 13 as well as sex chromosome aneuploidies by quantifying changes in the amount of cell-free DNA circulating in plasma of high-risk pregnant women. When applied to high-risk pregnant women, noninvasive prenatal testing has a high average sensitivity (trisomy 21 [99.4%], trisomy 18 [96.6%], trisomy 13 [86.4%], and sex chromosome aneuploidies [89.5%]) and a low average false-positive rate (trisomy 21 [0.16%], trisomy 18 [0.05%], trisomy 13 [0.09%] and sex chromosome aneuploidies [0.20%]).⁹⁷ However, the test is still considered a screening tool, and further confirmation is recommended with gold standard testing such as amniocentesis or chorionic villi sampling. Although noninvasive prenatal testing can be used to identify certain syndromic brain malformations such as Dandy-Walker malformation with the abovementioned trisomies, the implication to prenatal diagnosis of brain malformations is relatively limited. Detection of other microdeletion syndromes has

been reported in research, but clinical application is still under investigation in terms of cost, amount of labor, and clinical validity.⁹⁸ Using next-generation sequencing technology, whole-exome sequencing has been introduced, although technical, informational, and ethical controversies exist in the use of these advanced genome sequencing methods in prenatal diagnosis.⁹⁸

Fetal surgery of myelomeningocele is the first successful fetal therapy for prenatal neurologic disorders.¹¹ Fetuses with myelomeningocele that fulfill surgical criteria may benefit from fetal surgery (intrauterine closures of open neural tube defects by open fetal surgery in pregnant women). Fetal surgery may result in improved motor and cognitive outcomes. The procedures still have concerning risks for premature birth. Long-term outcome studies are ongoing.

CONCLUSION

Disorders of nervous system development can be a devastating diagnosis, particularly given their association with intellectual impairment, motor dysfunction, and epilepsy. Although patients benefit from therapeutic interventions, such as physical, occupational, and speech therapy, the magnitude of improvement is limited. Likewise, epilepsy treatments are limited in their response, and many patients remain refractory to multiple medication trials. Clearly, improved therapeutic options are needed for this group of conditions. It is hoped that advances in genetics will provide insight into novel treatment avenues. With detailed prenatal imaging and prenatal diagnosis, the potential also exists for initiating therapy prior to delivery.

Counseling and guidance remain important duties of the treating physician. In newly diagnosed children, a thoughtful and compassionate approach to the radiographic and genetic assessment offers parents insight into their child's condition. The genetics evaluation is particularly important for purposes of family planning.

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KEY POINTS

- Ambulation is one of the most important clinical concerns in patients with myelomeningocele. Antigravity function of the iliopsoas and quadriceps muscles is required for walking, but ambulation can be impaired in all children with spina bifida, even those with low neurosegmental lesions.
- Hydrocephalus is seen in approximately 90% of patients with myelomeningocele affecting the lumbar region. Newborns can be asymptomatic without recognizable clinical signs of increased intracranial pressure.
- Prenatal surgery for myelomeningocele is associated with lower rates of shunt placement and improvements in mental development and motor function.
- Oral supplementation with folic acid before conception and during early pregnancy substantially reduces the recurrence of neural tube defects in women who previously had a child with such a condition. All women of childbearing age are recommended to consume 0.4 mg of folic acid daily to prevent neural tube defects. Women who have had a child with a neural tube defect are recommended to consume 4 mg of folic acid daily.
- The etiology of holoprosencephaly is heterogeneous with both genetic and environmental causes. Gestational diabetes mellitus is the most common environmental cause and carries a 1% risk of holoprosencephaly. Chromosomal abnormalities account for approximately 25% to 50% of holoprosencephaly cases.
- Both partial and complete isolated agenesis of the corpus callosum can have broad neurodevelopmental presentations from mild to severe impairments.
- Septooptic dysplasia presents with visual impairment in infancy (congenital nystagmus or poor visual engagement), hypopituitarism, or both.
- Primary microcephaly is a heterogeneous condition and can be caused by destructive processes (hypoxia-ischemia, intrauterine infections) or from a genetically determined reduction in neuronal proliferation. Mutations associated with primary microcephaly alter neuroprogenitor cell proliferation through cell cycle regulation, centrosome function, cell proliferation, mitotic spindle formation, or DNA repair.
- All patients with hemimegalencephaly have epilepsy. Hemispherectomy is often required to treat intractable epilepsy, although some patients' seizures may be controlled medically.
- In the brain, characteristic features of tuberous sclerosis include cortical and subcortical hamartomas, subependymal nodules, and subependymal giant cell astrocytomas
- Patients with tuberous sclerosis complex may develop progressive cognitive impairment. Seizures in children younger than 2 years of age, infantile

spasms, and a high burden of cortical tubers are associated with a high risk for cognitive impairment. Autism is commonly seen in patients with tuberous sclerosis complex, especially in patients with temporal tubers, seizure onset before 3 years of age, or infantile spasms.

- Focal cortical dysplasia is highly associated with medically refractory epilepsy and often requires epilepsy surgery to control the seizures.
- Focal cortical dysplasia type I may be radiographically occult as its anatomic alterations are so subtle and can only be detected at the microscopic level. Focal cortical dysplasia type I may be found in nonlesional specimens resected in epilepsy surgery.
- Most patients with periventricular nodular heterotopia have normal intelligence, and some patients may develop epilepsy, commonly in the middle teenage years.
- Patients with classic lissencephaly have severe reduction in gyral formation manifesting either as agyria (a total absence of gyri) or pachygyria (a reduced number of abnormally large gyri).
- Most children with lissencephaly have relatively severe cognitive and motor disabilities and seizures. Clinical severity is related to the degree of structural abnormality, with greater gyral simplification resulting in greater clinical impairment. Epilepsy is universal, and infantile spasms are a particularly common seizure type.
- *LIS1* mutations are commonly seen in cases with a posterior greater than anterior gradient of agyria. Almost all patients have de novo heterozygous mutations of *LIS1*. The recurrence risk of having a second affected child is very low. A microdeletion syndrome affecting this region manifests as Miller-Dieker syndrome, with other congenital anomalies (craniofacial, renal, cardiac, or gastrointestinal malformations).
- Cobblestone malformations are sometimes associated with congenital muscular dystrophy and eye abnormalities. These disorders result from an impairment of glycosylation of α -dystroglycan, affecting the brain, nerve, and skeletal muscle.
- Bilateral perisylvian polymicrogyria results in a clinical syndrome manifested by mild cognitive impairment, epilepsy, and pseudobulbar palsy. In childhood, the pseudobulbar palsy results in expressive speech delay and feeding difficulty.
- Child neurologists play a central role in providing prenatal diagnosis and counseling to pregnant women and families in collaboration with a multidisciplinary team consisting of maternal fetal medicine, radiologists, neurosurgeons, geneticists, and neonatologists. Child neurologists are

essential in formulating a diagnostic plan, assessing prognosis, and providing postnatal care to affected children.

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CASE 4–1

A 36-year-old woman presented for a fetal neurology consultation at 31 weeks of gestation regarding a possible brain malformation in her female fetus. She had three healthy boys from previous pregnancies. At 30 weeks gestation, a routine obstetric ultrasound found her fetus had enlarged lateral ventricles (ventriculomegaly). Subsequent level II ultrasound by maternal fetal medicine additionally found an absent septum pellucidum and raised concern of agenesis of the corpus callosum. Fetal MRI found complete agenesis of the corpus callosum. Maternal serum testing for cytomegalovirus and toxoplasma titers were negative. Fetal echocardiogram was unremarkable. Amniocentesis to test chromosomal microarray was declined. Based on a presumed diagnosis of isolated agenesis of the corpus callosum, a broad spectrum of possible neurodevelopmental impairments was discussed with the woman. The remainder of the pregnancy was uneventful, and the infant girl was born via uncomplicated delivery at 39 weeks gestational age.

Her physical and neurologic examination were unremarkable. Postnatal MRI confirmed the diagnosis of complete agenesis of the corpus callosum. Chromosomal microarray testing of the child was negative. A diagnosis of isolated agenesis of the corpus callosum was confirmed. Her early development was normal, and at 18 months of age, the Bayley Scales of Infant and Toddler Development, Third Edition, found mild expressive language delay but otherwise age-appropriate cognitive, motor, socioemotional, and general adaptive development.

COMMENT

This case exemplifies the difficulty in prognosticating neurodevelopmental outcomes of agenesis of the corpus callosum prenatally and even postnatally. The case represents a milder end of the spectrum, with agenesis of the corpus callosum being the only recognizable malformation in this patient as well as having a normal chromosomal microarray study. However, more severe neurodevelopmental impairments can also occur in the same context.

CASE 4–2

A 29-year-old woman presented at her 35th week of pregnancy to establish obstetric care. She had moved from the Dominican Republic to the United States when her fetus was 11 weeks gestational age, and she had not received further prenatal care until the current presentation, at which time a fetal ultrasound detected significant fetal anomalies of severe microcephaly, small forebrain, scalloped parietal bones, and bilateral ventriculomegaly, as well as a dilated third ventricle. Fetal echocardiogram found levorotation and tricuspid valve thickening. She denied any symptoms of illness during the pregnancy.

An infant boy was born at 37 weeks gestation with severe microcephaly (head circumference of 29 cm), generalized hypotonia, poor suck, single palmar crease, rocker bottom feet, and respiratory distress in addition to the findings that had been seen on ultrasound. Chest x-ray showed right-sided diaphragmatic paralysis that required supplemental oxygen via continuous positive airway pressure and later nasal cannula.

Neonatal echocardiogram found a patent ductus arteriosus, patent foramen ovale, and right atrial and ventricular dilatation. Neonatal brain MRI identified agenesis of the corpus callosum (FIGURE 4–3A), pachygyria (FIGURE 4–3B), and parenchymal subcortical calcification (FIGURE 4–3C). The newborn was diagnosed with congenital Zika virus infection by serum IgM and real-time reverse transcription polymerase chain reaction. At 2 months of age, the child had marked microcephaly (head circumference of 32 cm), scalloped parietal bone, slanted occiput (FIGURE 4–3D and 4–3E), diffuse spasticity (FIGURE 4–3F), bilateral hearing loss, and cortical visual impairment.

COMMENT

This case exemplifies severe microcephaly and abnormalities in migration, neurodegeneration, and calcification characteristic of congenital Zika virus infection occurring in the early stage (before 11 weeks) of pregnancy.

CASE 4–3

A 6-year-old girl presented with seizures that had suddenly developed 1 day prior to initial neurologic evaluation. She had no significant past medical history, and her development had been normal. Her seizures involved head and eye deviation to the right with full extension of the right arm and flexion of the left arm at the elbow, which was followed by right-sided clonic activity. During some seizures, she appeared partially responsive. During the year following presentation, her seizures remained refractory, and with a high frequency of more than 20 per day, despite multiple trials of antiepileptic medications including oxcarbazepine, levetiracetam, gabapentin, and phenytoin. A phase I epilepsy surgery evaluation was performed and revealed that her seizures localized to central leads without a clear distinction between sides. Brain MRI demonstrated a linear band of T2/fluid-attenuated inversion recovery (FLAIR) hyperintense signal emanating from the base of the left supplementary motor cortex and extending toward the ventricle (FIGURE 4–5). Based on these findings, the patient underwent a phase II epilepsy surgery evaluation with electrocorticography. The interictal recording demonstrated slow rhythmic spike waves over the left frontal-central region. The ictal recording demonstrated paroxysmal fast activity with repetitive spike waves over the left frontal-central region in the area of the supplementary motor cortex. A focal cortical resection was performed over the region of the ictal onset. Pathology revealed focal cortical dysplasia type IIb. The patient developed transient right arm weakness for 1 month following surgery. The weakness subsequently fully resolved, and the patient no longer had seizures and was able to successfully taper off of her antiepileptic medications following the procedure.

COMMENT

This case demonstrates how focal cortical dysplasia can be the responsible epileptogenic lesion in refractory epilepsy. The seizures are often refractory to multiple pharmacologic treatments, and many patients are therefore appropriate epilepsy surgery candidates. If the lesion is fully resected, complete seizure cessation is possible.

FIGURE 4-1.

Semilobar holoprosencephaly. Coronal (*A*) and axial (*B*) fetal MRI at 20 weeks gestational age show a single ventricle, absence of the septum pellucidum, and incompletely formed interhemispheric fissure (absence of cleavage of frontal lobes [*B*, *arrow*]) consistent with holoprosencephaly. Coronal (*C*) and axial (*D*) MRI of a male newborn shows rudimentary temporal and occipital lobes consistent with semilobar holoprosencephaly. Partial fusion of thalamus (*D*, *arrowhead*) and incomplete hippocampal formation are additionally recognized.

FIGURE 4-2.

Agenesis of the corpus callosum. Fetal brain MRI (*A*, coronal; *B*, axial; *C*, sagittal) at 31 weeks gestational age showing complete agenesis of the corpus callosum. Characteristic findings are shown, including vertical (coronal) and parallel (axial) orientation of anterior horns of lateral ventricles and ventriculomegaly, especially of the posterior horns (colpocephaly). Full-term neonatal brain MRI (*D*, coronal; *E*, axial; *F*, sagittal) of the same patient with findings remnant to fetal MRI, such as parallel alignment of the bodies of lateral ventricles. Sagittal image shows abnormal radiant orientation of sulci (*F*). Late gestational development after 31 weeks, including gyrification, appears to have normally occurred without associated central nervous system anomalies, consistent with isolated agenesis of the corpus callosum.

FIGURE 4-3.

Imaging and photographs of the patient in CASE 4-2. Neonatal brain MRI identifying agenesis of the corpus callosum (*A*, sagittal T1-weighted image), pachygyria (*B*, axial T2-weighted image), and parenchymal subcortical calcification (*C*, axial T1-weighted image). Photographs showing marked microcephaly (head circumference of 32 cm), scalloped parietal bone, slanted occiput (*D*, *E*), and diffuse spasticity (overlapping fingers) (*F*).

FIGURE 4-4.

Tuberous sclerosis complex. MRI of a 4-month-old female infant with tuberous sclerosis complex. *Arrowheads* in T2 axial (*A, B*) and T1 coronal (*C*) images point to T2 high signal (and T1 low, not shown) cortical/subcortical (*A*) and cortical (*B, C*) tubers, and expanding gyri (*A*). T2 axial image (*D*) shows a subependymal nodule (*arrow*), as seen in approximately 98% of cases.

FIGURE 4-5.

Imaging of the patient in CASE 4-3 with focal cortical dysplasia. Axial fluid-attenuated inversion recovery (FLAIR) MRI shows hyperintense signal in the left frontal cortical/subcortical region (*arrow*). Affected gyri appear to be wider, and their gray-white matter boundary is blurred with a thin band of T2/FLAIR hyperintensity extending from the cortex to the ventricular margin.

FIGURE 4-6.

Periventricular nodular heterotopia. A 27-week fetus was initially referred for ventriculomegaly and found to have nodular heterotopia (*A, B, arrows*). Newborn MRI of this patient confirmed bilateral ventriculomegaly and periventricular nodular tissues with signal isointense to cortex suggestive for ectopic gray matter, notable in coronal (*C*) and axial (*D*) images.

FIGURE 4-7.

Lissencephaly and *TUBA1A* mutation. A fetal MRI at 21 weeks gestational age was ordered because of microcephaly. Axial (*A*) and coronal (*B*) images show shallow operculum, abnormally box-shaped temporal lobes suggesting diffuse cerebral malformation. Follow-up fetal MRI at 29 weeks gestational age (*C*, axial; *D*, coronal) show persistent shallow operculum (under-undulation) and absence of normal sulcations in frontal lobes consistent with anterior dominant lissencephaly. Abnormal hypoplastic temporal lobes were also persistent. Postnatal MRI (*E* and *F*, axial; *G*, coronal; *H*, sagittal) continued to show the same features consistent with anterior dominant lissencephaly. Genetic investigation determined a *TUBA1A* mutation.

FIGURE 4-8.

DCX mutation causing double cortex. Fetal MRI at 28 weeks gestational age showed smooth gyri and subcortical band heterotopia (*A*, axial; *B*, coronal; *arrowheads*), suggestive of lissencephaly. The image contrast was adjusted to accentuate T2 low-signal band in the subcortical region (*arrowheads*). Postnatal MRI (*C*, axial; *D*, coronal) of this patient confirmed subcortical band heterotopia (low-intensity signal in T2-weighted image band in subcortical white matter). The child developed global developmental delay and infantile spasms.

TABLE 4-1

Etiologic Summary of Brain and Spine Malformations and Their Investigation

Disorder	Incidence	Relatively Common Genetic Causes	Genetic Workup ^a	Notes
Neurulation				
Myelomeningocele	4.6/10,000 ⁸⁰	Copy number variants	Chromosomal microarray	Increased risk with gestational diabetes mellitus, folate deficiency, maternal medications (valproic acid)
Prosencephalic Development				
Holoprosencephaly	1/10,000 ⁸¹	25% to 50% chromosomal abnormalities; syndromic holoprosencephaly (eg, autosomal dominant, autosomal recessive); nonsyndromic holoprosencephaly (eg, <i>SHH</i> , <i>ZIC2</i> , <i>SIX3</i> , <i>TGIF1</i>)	First: chromosomal microarray Second: <i>SHH</i> , <i>SIX3</i> , and <i>ZIC2</i>	Increased risk with gestational diabetes mellitus ⁸²
Septooptic dysplasia	1/10,000 ⁸³	<i>HESX1</i>	<i>HESX1</i>	Look for visual impairments and hypopituitarism Younger maternal age
Neuronal Proliferation				
Microcephaly	1.5/10,000 ⁸⁴	Primary: <i>MCPH1</i> , <i>CENPI</i> , <i>CDK5RAP2</i> , <i>NDE1</i> , <i>PNKP</i> , <i>PCNT</i> Microcephaly plus polymicrogyria: <i>NDE1</i> , <i>WDR62</i>	May choose individual gene sequencing or available panel sequencing test	Look for nongenetic causes such as cytomegalovirus, Zika infections, intrauterine injuries
Megalencephaly	Not known	Though not common, postzygotic (mosaic) mutations of <i>FLNA</i> , <i>LIS1</i> , <i>DCX</i> , and genes in the PI3K-AKT pathway (<i>AKT3</i> , <i>PIK3CA</i> , <i>PIK3R2</i> in megalencephaly-capillary malformation-polymicrogyria syndrome) are reported	No practical approach Panel sequencing test for PI3K-AKT pathway may be considered, although yield is unknown	Look for associated extra-CNS anomalies
Focal cortical dysplasia	Not known	Focal cortical dysplasia type I: <i>NPRL2</i> Focal cortical dysplasia type II: <i>DEPDC5</i> , <i>MTOR</i> , <i>NPRL3</i> , <i>PIK3CA</i> Focal cortical dysplasia type II: <i>DEPDC5</i> , <i>MTOR</i> , <i>NPRL3</i> , <i>PIK3CA</i>	No practical approach May consider individual genes at left based on subtypes	Focal cortical dysplasia type I: prenatal, perinatal insults; focal cortical dysplasia Focal cortical dysplasia type II: mTOR pathway; focal cortical dysplasia Focal cortical dysplasia type III: acquired pathology
Axonal Development				
Agenesis of the corpus callosum	1.8/10,000 ⁸⁵	Copy number variants	Chromosomal microarray (17.3%) ⁸⁵	See if it is isolated or syndromic Look for associated brain malformations
Neuronal Migration				

Disorder	Incidence	Relatively Common Genetic Causes	Genetic Workup ^a	Notes
Heterotopia	Not known	Periventricular nodular heterotopia: <i>FLNA</i> , copy number variants	<i>FLNA</i> , chromosomal microarray	
Lissencephaly	Not known	Lissencephaly plus agenesis of the corpus callosum: <i>ARX</i> reelin type plus anterior greater than posterior gradient: <i>RELN</i> , <i>VLDLR</i> ; anterior greater than posterior gradient: <i>ACTB</i> , <i>ACTG1</i> , <i>DCX</i> , ⁸⁶ <i>DCX</i> (female subcortical band heterotopia), posterior greater than anterior gradient: eg. <i>LIS1</i> , <i>PAFAH1B1</i> , <i>TUBA1A</i> , <i>TUBB2B</i>	First: <i>LIS1</i> (posterior greater than anterior), <i>DCX</i> (anterior greater than posterior) Second: <i>TUBA1A</i> , <i>TUBB2B</i> (posterior greater than anterior); <i>ACTB</i> , <i>ACTG1</i> (anterior greater than posterior)	
Cobblestone malformations	Not known	<i>FCMD</i> , <i>FKBP</i> , <i>POMT1</i> , <i>POMT2</i> , <i>LARGE1</i> , <i>POMGNT1</i>	Based on clinical features, may consider individual genes listed at left	O-glycosylation of α -dystroglycan mutations Look for associated anomalies (eye anomalies, myopathies)
Disorders of Postmigrational Development				
Polymicrogyria	Not known	Bilateral frontoparietal, perisylvian polymicrogyria: <i>ADGRG1</i> (also known as <i>GPR56</i>) Asymmetric polymicrogyria: <i>TUBA8</i> , <i>TUBB2B</i> , <i>TUBB3</i> May seen in syndromes such as Zellweger syndrome	Bilateral: <i>ADGRG1</i> Asymmetric: based on clinical features, may consider panel sequencing test Also look for nongenetic causes, schizencephaly	Look for Cytomegalovirus vascular injuries
Schizencephaly	Not known	<i>EMX2</i>	Nongenetic causes, look for polymicrogyria	Look for cytomegalovirus, vascular injuries
Postmigrational microcephaly	Not known	<i>CASK</i> , <i>MECP2</i> (Rett syndrome), <i>UBE3A</i> (Angelman syndrome), <i>TSEN54</i>	Depending on clinical features, may consider individual genes listed at left	

CNS = central nervous system; mTOR = mammalian target of rapamycin.

^aSelections of genetic tests are based on the authors' personal preference. References are included if relevant articles support selection of genetic tests.