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Malformations of cortical development

Trudy Pang, MD,

Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Ramin Atefy, MD, and

Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Volney Sheen, MD PhD

Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Abstract

Background—Malformations of cortical development (MCD) are increasingly recognized as an important cause of epilepsy and developmental delay. MCD encompass a wide spectrum of disorders with various underlying genetic etiologies and clinical manifestations. High resolution imaging has dramatically improved our recognition of MCD.

Review Summary—This review will provide a brief overview of the stages of normal cortical development, including neuronal proliferation, neuroblast migration, and neuronal organization. Disruptions at various stages lead to characteristic MCD. Disorders of neurogenesis give rise to microcephaly (small brain) or macrocephaly (large brain). Disorders of early neuroblast migration give rise to periventricular heterotopia (neurons located along the ventricles), whereas abnormalities later in migration lead to lissencephaly (smooth brain) or subcortical band heterotopia (smooth brain with a band of heterotopic neurons under the cortex). Abnormal neuronal migration arrest give rise to over-migration of neurons in cobblestone lissencephaly. Lastly, disorders of neuronal organization cause polymicrogyria (abnormally small gyri and sulci). This review will also discuss the known genetic mutations and potential mechanisms that contribute to these syndromes.

Conclusion—Identification of various gene mutations has not only given us greater insight into some of the pathophysiologic basis of MCD, but also an understanding of the processes involved in normal cortical development.

Keywords

Cortical development; malformations; genes

Introduction

Malformations of cortical development (MCD) are an important cause of epilepsy and developmental delay. It is estimated that up to 40% of children with refractory epilepsy have a cortical malformation¹. MCD encompasses a large spectrum of disorders related to abnormal cortical development with varied genetic etiologies, anatomic abnormalities, and

clinical manifestations. Whereas many of these disorders were previously diagnosed at autopsy, the use of MRI has dramatically improved our ability to recognize these MCD.

Cerebral cortical development involves a set of highly complex and organized events, including neural stem cell proliferation, migration, and finally neuronal differentiation. Disruptions of these various stages may result in MCD. Disorders due to abnormalities of cell proliferation may cause microcephaly (meaning small brain), megalencephaly (meaning large brain), or cortical dysplasia (meaning focal areas of abnormal neuronal architecture). Disorders of initiation of neuronal migration result in periventricular heterotopia (meaning abnormal nodules of neurons located along the ventricular wall). Disorders of later migration and motility cause disruption of the normal six-layered cortex, such as classical lissencephaly (meaning smooth brain) and subcortical band heterotopia (meaning heterotopic neurons located midway between the surface of the brain and lateral ventricles). Finally, disorders of neuronal arrest can result in neurons that fail to stop upon reaching their intended destination in the cerebral cortex and over-migrate onto the cortical surface as seen in cobblestone lissencephaly. Although cortical development has been separated into these stages, there is significant overlap between the stages and many abnormalities may cause dysfunction at more than one level. Thus, malformation syndromes are typically classified based on the earliest disruption of development. These concepts serve as the basis for the latest classification scheme for these disorders².

The pathogenesis of these malformations is multifactorial: genetic mutations or environmental insults, whether acquired in utero at different stages of brain development, or during the perinatal or postnatal period after corticogenesis may all contribute to the development of these syndromes^{3,4}. The timing, severity, and type of environmental influences, as well as genetic factors, will ultimately determine the type and extent of malformation syndrome.

Work in elucidating the genetic basis of various MCD has given us greater insight and understanding into the underlying pathophysiologic basis of these disorders, and will form the focus of this review. Different mutations of the same gene can cause different phenotypes, based on the degree of protein dysfunction (so termed genotype-phenotype correlation). Loss or disruption of the functional domains within a gene ultimately determines the phenotype of the disorder. Alternatively, specific mutations in a given gene can also lead to a gain of function for the aberrant protein. Mosaicism can occur when the mutation is present in a subpopulation of cells, whereas germ line mutations typically lead to expression of the mutant gene in all cells. Functional mosaicism occurs due to X-inactivation in which the mutation is present on one X chromosome but not the other. The mutant gene is thus expressed only in cells in which the mutant gene is found on the active X chromosome. This process explains why affected females are often less severely affected than males who have the same mutation. An understanding of some of the underlying genetic basis for these disorders will play an important role in genetic counseling of affected individuals and their families.

Normal cortical development

Human cortical development encompasses a series of complex and overlapping processes, including neuronal precursor proliferation at the ventricular zone, neuroblast departure from the ventricular zone, neuroblast migration, migration arrest, and neuronal organization.

Neuronal progenitor cells originate from the periventricular and subventricular zones and undergo different patterns of development and migration paths, before they eventually populate the cerebral cortex. Neural precursor cells may undergo cell division in symmetric and asymmetric patterns. Symmetric cell division yields two identical daughter cells that

continue to divide in a similar fashion and serve to replenish the population of progenitor cells. Asymmetric cell division leads to two different types of cells: 1. progenitor cells that re-enter the cell cycle, 2. immature neuronal cells (neuroblasts) that will migrate into the overlying cortical plate⁵.

Migration of neuroblasts begins with appropriate orientation of the cells prior to departure from the ventricular zone and these neuroblasts must have the ability to adhere to the scaffolding created by the radial glia that guide them during migration. To ensure correct orientation, the neuroblasts actually move in a retrograde fashion and make contact with the ventricular surface before migrating out to the cortical plate⁶. Excitatory or glutamatergic cortical neurons have a leading process that adheres to the radial glial fibers as they migrate radially from the ventricular zone to the cerebral cortex. Inhibitory or GABAergic cortical interneurons originate from the germinal zone of the basal ganglia and the ventricular zone. Rather than migrating radially, immature neurons from the lateral, medial, and caudal ganglionic eminences migrate tangentially first, and then radially to the various layers of the cerebral cortex^{6,7,8,9}.

Migrating neurons must stop in their appropriate laminar position once they reach the cortical plate. The cerebral cortex develops in an “inside-out” fashion. In other words, the earlier generated neurons form the deeper layers (V/VI) while later-generated neurons migrate past the earlier formed neurons to form the superficial layers (II/III). Both structural barriers at the pial surface of the brain and molecular stop signals are involved in mediating neuronal migration arrest¹⁰. Finally, cortical connections formed during gestation and infancy are modified through pruning of synapses and cellular apoptosis.

Disorders due to abnormal neurogenesis

The balance between cell proliferation and cell death determines the ultimate number of neurons or glia in the developed brain. Diffuse perturbations in this delicate balance (or perturbations occurring very early in development such that subsequent cell progeny are affected) results in microcephaly or macrocephaly. Focal disruptions (typically due to mosaicism) can lead to focal cortical dysplasia.

Microcephaly

Microcephaly, or small brain, refers to a head circumference that is more than two standard deviations below the population mean after correction for age and sex. It may result from abnormal cell division or proliferation. A number of processes can cause microcephaly and are often accompanied by involvement of other organ systems. Primary microcephaly, known as microcephaly vera, refers to a small brain which results from processes affecting cortical development alone without involvement of other organs. On pathologic examination, occasionally, a simplified gyral pattern (oligogyria) and disruption of the gray matter along the ventricular zone may be seen, along with hypomyelination and cerebellar hypoplasia. Clinically, these patients have mental retardation and some may also have epilepsy. Radiographic findings are determined by the underlying cause of microcephaly. In primary microcephaly, a grossly normal brain (Figures 1A and 1B) is frequently seen on brain MRI¹¹.

Four autosomal recessive genes are associated with microcephaly (Table 1), namely, *Microcephalin*, *ASPM* (*abnormal spindle-like, microcephaly-associated*), *CDK5RAP2* (*CDK5 regulatory subunit associated protein 2*) and *CENPJ* (*centromere protein J*). These genes seem to play a role in cell division during neurogenesis at the ventricular neuroepithelium. The *Microcephalin* gene is thought to also play a role in DNA repair. Abnormal DNA repair due to loss of the *Microcephalin* gene causes increased neural

progenitor cell death along the ventricles. Additional studies suggest that the Microcephalin protein is a centrosomal protein¹² and plays a role in the control of cell-cycle timing¹³. *ASPM* is a gene that encodes for a very large centrosomal protein¹⁴ that is essential for normal neuroblast mitotic spindle function in *Drosophila*¹⁵. *CDK5RAP2* and *CENPJ* encode for centrosomal proteins that are found at the spindle poles of mitotic cells, along the ventricular neuroepithelium. Thus, all of the known genes for microcephaly vera play an important role in neurogenesis by regulation of microtubules and cell cycle progression during cell division^{16,17}.

Disruption of genes involved in microtubule and centrosome function in mice results in similar impairments in neural progenitor proliferation and cause microcephaly¹⁸. For example, Nde1 is a microtubule-associated protein required for centrosome duplication, and the formation and function of the mitotic spindle. Nde1 expression is also associated with the centrosome, kinetochore, and spindle. Phosphorylation of the protein during mitosis causes it to associate with mitotic spindles and participate in dynein-mediated transport of kinetochore proteins to spindle poles along microtubules during proliferation. Loss of mouse Nde1 function in cortical progenitors causes defects in mitotic progression, mitotic orientation, and mitotic chromosome localization in cortical progenitors. This disruption in centrosome duplication and mitotic spindle assembly produces a small brain in Nde1 deficient mice.

Hemimegalencephaly

Hemimegalencephaly is characterized by overgrowth of one hemisphere, a part of a hemisphere, or one hemisphere with partial involvement of the other hemisphere. The pathology typically reveals cortical dysplasia, white matter abnormalities, abnormal cell types, and polymicrogyria. Hemimegalencephaly may be an isolated finding or it may exist as a feature of a number of syndromes, including neurocutaneous syndromes such as Klippel-Trenauney syndrome and hypomelanosis of Ito¹⁹. Not surprisingly, given the significant brain malformation, patients typically have mental retardation and almost always have epilepsy which can become intractable. Seizures may begin within the first 6 months of life, often with partial onset arising from the enlarged area of the brain with or without secondary generalization. Infantile spasms and atonic seizures can also occur. Typical MRI findings include enlargement of at least one lobe or one hemisphere, with the occipital region being the most frequently involved¹¹. The underlying white matter may also demonstrate abnormal T1 and T2 signal intensities. The cortex is often thick with pachygyria and heterotopia are commonly seen scattered in various locations. The lateral ventricle is usually enlarged with a straight and pointed frontal horn. The underlying genetic abnormalities are still unclear and additional work is needed to elucidate the heterogeneous genetic bases of this disorder.

Focal cortical dysplasia

Focal cortical dysplasia (FCD) represents a heterogeneous entity resulting from a variety of causes²⁰. Pathological examination demonstrates a range of findings such as dysplastic neurons, balloon cells, and lamination disorganization^{21,22}. FCD can occur throughout the brain, but it has a predilection for the frontal and temporal lobes²². It is one of the most common forms of focal developmental disorder diagnosed in patients with partial epilepsy, constituting approximately 25% of patients^{23,24}. Of these patients, approximately 76% have medically refractory seizures²⁵. For the majority of patients, the onset of epilepsy occurs within the first 11 years of life, with generalized tonic-clonic, tonic, simple partial and complex partial seizures²². High-resolution MRI plays a key role in the diagnosis of the disorder and typically shows blurring of the junction between gray and white matter, gyral thickening, and abnormal signal such as T2 prolongation in the underlying white matter¹¹.

Given the heterogeneity of the disorder, no single genetic abnormality has been identified as a cause.

Disorders due to abnormal neuronal migration

Successful neuronal migration involves several stages: initial departure of neuroblasts from the ventricular zone, motility for migration to the cortical plate, and finally arrest of migration at the appropriate layer. Disruptions at any of these stages results in MCD.

Periventricular heterotopia

Periventricular heterotopia (PH) refers to nodules of neurons found along the ventricular wall of the lateral ventricles, with an apparently normal cerebral cortex. This condition most likely represents a disorder of the initiation of migration in a small subpopulation of neurons while the majority of neurons successfully migrate out to the cerebral cortex. Pathologically, the nodules consist of normal appearing neurons and glial cells, with myelinated fibers and gliosis²⁶.

Affected patients often develop various types of seizures as the presenting symptom. While some patients manifest with seizures during the first few years of life, the majority of patients present in adolescence. Approximately 90% of patients with PH have epilepsy²⁷, which may be easily controlled or refractory. There is no clear relationship between the epilepsy severity and extent of nodular heterotopia. In general, these patients have normal intelligence. However some patients may have learning problems such as impaired reading fluency that is out of proportion to their intelligence²⁸.

Brain imaging using MRI demonstrates the typical nodules along the ventricular walls (Figure 1C). The pattern of involvement can be used to help to distinguish those with X-linked dominant versus those with autosomal recessive mutations. Patients with X-linked dominant mutations typically have bilateral, nearly contiguous periventricular nodular heterotopia with thinning of the corpus callosum and posterior fossa abnormalities, such as cerebellar hypoplasia, and enlarged cisterna magna²⁹. On the other hand, patients with autosomal recessive mutations have microcephaly, slightly enlarged ventricles, and delayed myelination³⁰. Symmetrical nodular heterotopia lining the ventricles are again seen and the overlying cortex may be thinned with abnormal gyri¹¹.

PH can be caused by genetic mutations or it can be acquired due to extrinsic factors, such as infection, injury, or radiation^{31,32,33}. So far, X-linked dominant mutations in *FLNA* (*Filamin A*) and autosomal recessive mutations in *ARFGEF2* (*ADP-ribosylation factor guanine exchange factor 2*) are associated with PH (Table 1). *FLNA* is an actin-binding phosphoprotein that stabilizes the cytoskeleton and mediates focal adhesions along the ventricular epithelium³⁴. *ARFGEF2* encodes for the BIG2 protein which converts guanine diphosphate (GDP) to guanine triphosphate (GTP) and thereby activates the ADP-ribosylation factors (ARFs). ARFs regulate vesicle trafficking and the transport of molecules from the interior of the cell to its surface, where they may attach and interact with other substances, or be secreted by the cell. In this respect, *ARFGEF2* may assist in the transport of *FLNA* to the cell surface. *FLNA* may subsequently be required for the initial attachment of neurons onto the radial glial scaffolding prior to migration from the ventricular zone³⁵. Failure of migratory neurons to attach onto the radial glia could lead to heterotopia formation. Alternatively, both proteins are highly expressed along the neuroepithelial lining, and likely influence cell adhesion. Loss of neuroependymal integrity, similar to that seen with cobblestone lissencephaly, could lead to nodule formation along the lateral ventricles³⁵.

Additional insight into the pathogenic mechanisms underlying this cortical malformation has been gained from mice that develop periventricular heterotopia. Sarkisian and colleagues recently reported that loss of MEKK4, a MAP kinase that regulates the Stress-activated Protein Kinase Activator SEK-1, results in heterotopia formation in mice³⁶. Interestingly, phosphorylation of FLNA at Ser2152 depends on MEKK4/SEK1 signaling and phosphorylation at this site regulates FLNA localization at the cell membrane. Other studies have shown that the *hyh* (hydrocephalus with hop gait) mouse phenotype is due to a mutation in the *Napa* gene, which encodes for the vesicle trafficking protein α Snap³⁷. Loss of α Snap function leads to denudation of the neuroepithelium and heterotopia formation³⁸ (personal observations). The α Snap protein is involved in SNAP receptor (SNARE)-mediated vesicle fusion and thus, similar to *ARFGEF2* mutations in humans, suggesting that it plays a role in vesicle trafficking in PH formation. Finally, recent studies have suggested that the actin regulating RhoGTPase Cdc42 can disrupt the neuroependymal lining, vesicle trafficking of polarized protein, and lead to heterotopic neurons along the ventricle^{39,40}. As actin is required for some forms of vesicle trafficking, it is possible that disruption of genes which are directly or indirectly linked to vesicle transport may be responsible for PH formation.

Subcortical band heterotopia

Subcortical band heterotopia, also known as “double cortex” syndrome, refers to a band of subcortical heterotopia neurons, located midway between the ventricles and the cerebral cortex⁴¹. The disorder is seen primarily in females and typically causes varying degrees of mental retardation and almost all of them have epilepsy. Approximately two thirds of patients with epilepsy ultimately develop intractable seizures⁴².

MRI of the brain in subcortical band heterotopia demonstrates two parallel layers of gray matter: a thin outer ribbon and a thick inner band, separated by a very thin layer of white matter between them (Figure 1D). The severity of epilepsy and developmental delay is directly correlated with the degree of migration arrest, as indicated by the thickness of the subcortical band heterotopia⁴³.

Subcortical band heterotopia is caused by mutations in the microtubule-associated *DCX* gene. The DCX protein is thought to direct neuronal migration by regulating the organization and stability of microtubules, necessary for neuronal motility. The malformation is seen only in females, as the gene is found on the X-chromosome. Since there are two X chromosomes in females, after X-inactivation, only some neurons lose doublecortin function. These neurons with the mutant *DCX* gene fail to migrate into the cortex and thus form the underlying heterotopic band, while neurons which express the normal gene successfully migrate out to the cortical plate. Males with *DCX* mutations develop classical lissencephaly.

Classical (Type I) Lissencephaly

Lissencephaly refers to “smooth brain” in which there is loss of the normal gyri and sulci of the brain. The severity of the malformation may range from agyria and pachygyria, to subcortical band heterotopia with a relatively normal gyral pattern. The cortex lacks the normal lamination and consists of only 4 layers instead of the typical 6 layers. Patients usually have severe mental retardation, epilepsy, and often also have microcephaly.

Several genes have been identified giving rise to classical lissencephaly: *LIS1* (*Lissencephaly1*, autosomal dominant)⁴⁴, *DCX* (*Doublecortin*, X-linked dominant)⁴⁵, *TUBA1A* (*Tubulin alpha 1A*, autosomal dominant)^{46,47}, *ARX* (*Aristaless*, X-linked dominant)⁴⁸, and *RELN* (*Reelin*, autosomal recessive)⁴⁸ (Table 1). Some characteristic

differences in the clinical and radiographic presentation of these different lissencephaly disorders help to differentiate the causative genes.

Mutations in the *LIS1*, *DCX*, and *TUBA1A* generally cause similar clinical phenotypes, including microcephaly, mental retardation, with or without epilepsy, and motor deficits. The severity of isolated lissencephaly may be related to the type and location of the mutation⁴⁹. Complete deletions of the *LIS1* and contiguous genes on chromosome 17p13.3 cause Miller-Dieker Syndrome (MDS). MDS is characterized by lissencephaly with additional distinct facial features, including prominent forehead, bitemporal hollowing, short nose with upturned nares, protuberant upper lip, and small jaw^{50,51}. Mutations in *ARX* cause the X-linked lissencephaly syndrome with ambiguous genitalia (XLAG)⁵². These patients have neonatal-onset epilepsy, hypothalamic dysfunction causing temperature dysregulation, chronic diarrhea, and ambiguous genitalia (micropenis and cryptorchidism)⁵³. Mutations in *RELN* give rise to seizures, developmental delay and hypotonia. Moreover, the loss of cerebellar organization likely contributes to ataxia.

MRI of the brain in classical lissencephaly demonstrates an hour-glass configuration with areas of pachygyria and agyria and a shallow Sylvian fissure (Figure 1E). Differences in the location of involvement may be used to differentiate between *LIS1* and *DCX* mutations^{11,54}. The parietal and occipital regions are more severely affected in patients with *LIS1* mutations, whereas the frontal and temporal regions are more severely affected in patients with *DCX* mutations. MRI of the brain in patients with *TUBA1A* mutations demonstrate pachygyria or agyria, cerebellar hypoplasia with particular involvement of the inferior vermis, brainstem hypoplasia, partial or complete agenesis of the corpus callosum, and ventricular dilatation^{46,47}. Additionally, the posterior gyral malformations were more severe than the anterior regions, creating a posterior-anterior gradient. In individuals harboring *ARX* mutations, the lissencephaly is again worse posteriorly than anteriorly (posterior agyria and anterior pachygyria) and there is absence of the corpus callosum by MRI. The cortex is moderately thickened (5-10mm) with white matter signal abnormalities as well as a cystic or fragmented basal ganglia^{52,48}. Finally in *RELN* mutations, the lissencephaly is associated with cerebellar hypoplasia and hippocampal and brainstem abnormalities.

Both *LIS1* and *DCX* proteins appear to be regulators of microtubules, which are a part of the cytoskeleton of a cell, regulating cellular shape and motility. The *DCX* protein interacts with microtubules and contributes to their stability^{41,55,56}. The *LIS1* protein also likely interacts with microtubule-binding proteins and regulates neuronal migration by binding microtubules and assisting with the forward translocation of the cell soma toward the leading edge of the migrating cell^{57,58}. Neurons which are heterozygous for the *LIS1* mutation have reduced cell motility⁵⁷. Disruption of microtubule function through *LIS1* mutations also interferes with spindle orientation and mitosis^{18,59}. This interruption in cell proliferation may contribute to the microcephaly seen in this disorder, as well as the ectopic localization of a heterogeneous population of differentiated neurons within the deep layers of the lissencephalic cortex⁵⁹.

The *TUBA1A* gene encodes for brain-specific alpha tubulin. Alpha and beta tubulins are the main component of microtubules required for cell movement. Human mutations in *TUBA1A* are thought to affect the folding of tubulin heterodimers and also influence interactions with proteins that bind microtubules (doublecortin and kinesin KIF1A)⁶⁰. Given that microtubules play an important role in neuronal migration, it would be reasonable to postulate that disruption of microtubular function could lead to deficits in the motility of neuronal progenitor cells and lissencephaly^{46,47}.

ARX is a homeobox gene which is expressed in the ganglionic eminences and the neocortical ventricular zone⁶¹. In mice with *ARX* mutations, there is an accumulation of immature neurons in lateral and medial ganglionic eminences and both radial and tangential migration toward the cortex and striatum are significantly reduced⁶¹. Impaired differentiation of cortical GABAergic interneurons is also observed in those neurons harboring the mutation. In addition to lissencephaly, mutations in the *ARX* gene cause a variety of other neurologic conditions including X-linked West syndrome⁶², X-linked mental retardation⁶³, myoclonic epilepsy⁶², and Partington disease (dystonia, epilepsy and mental retardation)⁶⁴. As homeobox genes initiate a cascade of cellular events, it is difficult to ascertain which particular pathways cause the underlying lissencephaly. However, the *ARX* gene clearly plays an important role in proliferation of neural precursors and differentiation of the forebrain.

Appropriate cell migration relies on proper intracellular and extracellular molecular signals. *LIS1*, *DCX*, and *TUBA1A* mutations seem to affect the intrinsic motility of neural progenitor cells. Extrinsic signals and cellular interactions also play an important role in guiding appropriate cellular migration. Reelin is a signaling glycoprotein secreted by the early neurons on the surface of the cerebral cortex known as the Cajal Retzius cells. Activation of the Reelin signaling pathway is thought to be essential for proper positioning of migratory neurons into the appropriate lamina of the cortex⁶⁵. In mice, loss of reelin causes disorganized lamination of the cerebral cortex⁶⁶, whereby the layers are inverted, with earlier born cells forming the superficial layers of cortex and later born neurons forming the deeper layers.

While disruption in microtubule and microtubule associated proteins such as doublecortin, lissencephaly1 and alpha-tubulin would understandably alter neuronal motility and migration, the potential role of reelin in giving rise to lissencephaly is not entirely clear. However, phenotypic similarities between the *reeler* mouse mutant and genetically modified mice null for cyclin dependent kinase 5 (cdk5)⁶⁷ or cdk5 activator p35 (p35 inverted layering)⁶⁸ do suggest a shared pathway. Mice lacking p35, cdk5, or reelin all show disrupted lamination and inverted lamination. The Lis-1 interacting protein Ndel1 has been shown to be a cdk5 substrate, and to be involved in neuronal motility. Cdk5 is also a substrate for the microtubule associated protein tau⁶⁹. Thus, cdk5 might connect Reelin signaling with other lissencephaly protein complexes such as the Ndel1–Lis1 complex to control microtubule dynamics and neuronal migration.

Inhibitory interneurons, or GABAergic neurons, constitute approximately 20-30% of all cortical neurons. As mentioned earlier, they originate from the medial, lateral and caudal ganglionic eminences, migrate tangentially at first, and then radially before distribution within the different layers of the cerebral cortex. These interneurons are classified into subtypes and animal studies have shown that the *Lhx6* gene is preferentially expressed in some tangentially migrating GABAergic interneurons. The *Lhx6* gene encodes for one of the homeodomain transcription factors that regulate neuronal subtype specifications and cell fate decisions⁷⁰. More recently, Liodis and colleagues demonstrated that *Lhx6* plays an important role in the normal tangential and radial migration of these interneurons during embryogenesis⁷¹.

Disorders due to abnormal neuronal migration arrest

Cobblestone (Type II) lissencephaly

Cobblestone lissencephaly, also known as type II lissencephaly, refers to the nodular appearance of the cerebral cortex caused by disorganization of the cortical layers, and over-

migration of neurons through the pial surface of the brain into the leptomeninges. It is associated with various eye abnormalities and congenital muscular dystrophies.

Based on severity, cobblestone lissencephaly has been divided into three different classes. The mild form is seen in Fukuyama congenital muscular dystrophy (FCMD) that affects primarily the Japanese population⁷². Patients typically present with hypotonia and generalized weakness in infancy. The majority of patients are unable to walk unsupported⁷³. Mental retardation is a universal finding and some patients also have epilepsy. The moderate form is seen in muscle-eye-brain disease (MEB) that primarily affects the Finnish population⁷⁴. Early onset of severe myopia, glaucoma, optic disc pallor and retinal hypoplasia are the typical eye findings. Patients also have mental retardation, myoclonic jerks, and congenital muscular dystrophy. Finally, the more severe form of cobblestone lissencephaly is seen in Walker-Warburg Syndrome (WWS) which typically results in death within a few months after birth⁷⁵. Ophthalmologic abnormalities include retinal dysplasia, microphthalmia, cataracts, and glaucoma. Again, congenital muscular dystrophy is a key feature.

Brain imaging using MRI demonstrates the typical cobblestone lissencephaly (Figure 1F) as well as a spectrum of CNS abnormalities of varying degrees of severity¹¹. All of the abnormalities are most severe in Walker-Warburg syndrome. A “Z-shaped” hypoplastic brainstem is considered a key feature. Other typical MRI findings include abnormal signal in the white matter due to hypomyelination and polymicrogyria as seen in FCMD, which is particularly associated with frontal polymicrogyria with occipital cobblestone lissencephaly. Aqueductal stenosis with hydrocephalus, vermian hypogenesis, cerebellar agyria-micropolygyria, patchy abnormal white matter signal, and agenesis or hypogenesis of the corpus callosum can also be seen, as in MEB disease in the Finnish population⁷⁶. WWS is the most severe form and may demonstrate all of the previously mentioned findings, as well as occipital encephalocele¹¹.

Cobblestone lissencephaly follows an autosomal recessive inheritance pattern. Four associated genes have been identified: *POMT1* (*Protein-O-mannosyltransferase 1*) and *POMT2* (*Protein-O-mannosyltransferase 2*) for WWS, *POMGnT1* (*Protein O-mannose 1,2-N-acetylglucosaminyltransferase*) linked to chromosome 1p32-34 for the Finnish MEB disorder^{77,78}, and *Fukutin* on chromosome 9q31 for FCMD⁷⁹ (Table 1). All of these genes are involved in the glycosylation of alpha dystroglycan, which are highly glycosylated proteins and act as receptors for the multiple extracellular matrix molecules that maintain stability of the cell surface. Mutations in these genes affect the O-glycosylation of alpha dystroglycan, thereby compromising the integrity of the dystrophy-associated extracellular matrix adhesion complex and lead to weakening of the structural integrity of the superficial marginal zone or the cortex. Migratory neurons are then able to “over-migrate” beyond this structural barrier onto the pial surface, forming the typical cobblestone, or bumpy surface.

Disruption in the basal lamina along the surface of the brain in mice similarly leads to a cobblestone phenotype in mice. Presenilin1 (PS1) is a transmembrane protein, located in the Golgi apparatus, and best known for its processing of amyloid precursor protein. Presenilin1-deficient mice develop a cortical dysplasia resembling human cobblestone lissencephaly, with leptomeningeal fibrosis and migration of cortical-plate neurons beyond their normal position into the marginal zone and subarachnoid space. PS1 deficiency interferes with the ability of the leptomeningeal cells to support the Cajal-Retzius cells and maintain an intact pial basement membrane, resulting in both over migration of neurons and premature termination of neuronal migration of both radially migrating neurons and Cajal-Retzius neurons. Pathologic examinations reveal a loss of the Cajal-Retzius neurons within the marginal zone, depletion of the extracellular matrix protein reelin and chondroitin sulfate

proteoglycans⁸⁰. Another animal model to demonstrate the importance of the surface basement membrane utilizes isolated deletions of various basement membrane constituents or receptors, such as alpha 6 integrin, resulting in abnormal laminar organization of the brain and retina, with ectopic neuronal growth on the brain surface, similar to WWS⁸¹. Loss of integrin linked kinase in mice results in a similar lissencephalic phenotype⁸². Integrin linked kinase is a scaffold and kinase that links integrin receptors to the actin cytoskeleton and to signaling pathways involved in extracellular matrix deposition. Overall, disruption of mouse or human genes involved in basal lamina formation appear to be responsible for the development cobblestone lissencephaly.

Disorders due to abnormal neuronal organization

Cortical organization involves a process of synaptogenesis and neuronal maturation which are further refined via synapse pruning and apoptosis.

Polymicrogyria and Schizencephaly

Polymicrogyria refers to an excessive number of small gyri separated by shallow sulci, giving the surface of the cortex its characteristic lumpy appearance. Polymicrogyria can be focal or diffuse, unilateral or bilateral. Unilateral involvement may be associated with variable cognitive impairment, congenital hemiparesis, focal seizures⁸³, and visual field defects⁸⁴. Deletion of 22q11.2 has been found to be associated with polymicrogyria and seems to have a predisposition for the right hemisphere⁸⁵.

Bilateral involvement of the cortex is frequently seen, with a symmetric or asymmetric distribution, affecting the frontal, fronto-parietal, parieto-occipital, perisylvian, and mesial occipital regions. There is a wide spectrum of clinical manifestations owing to the various locations that are involved. For example, bilateral frontoparietal polymicrogyria is associated with developmental delay, hypertonicity, ataxia, and refractory seizures⁸⁶. Congenital bilateral perisylvian syndrome (CBPS) is one of the best described syndromes. Affected patients have pseudobulbar palsy, spastic quadriplegia, and epilepsy. Between 50-85% of patients develop seizures, ranging from atypical absence, tonic, atonic, and generalized tonic-clonic seizures⁸⁷. Imaging of the brain using MRI demonstrates small irregular gyri and an indistinct gray and white matter junction¹¹. The thickness of the cortex may be normal or abnormally thick or thin.

Familial patterns have been recognized in bilateral frontoparietal, bilateral perisylvian, and generalized polymicrogyria. Bilateral frontal and parietal polymicrogyria seem to be associated with mutations in the *G-protein-coupled receptor* gene (*GPR56*)^{88,89}. Expression of this gene appears to be highest in the neuronal progenitor cells along the ventricular and subventricular zones. The assumption is that this gene plays a role in regional organization of the brain.

Schizencephaly is classified within the same group as polymicrogyria. Schizencephaly refers to a cleft extending from the cerebral cortex to the ventricle and is typically lined by polymicrogyric cortex. It is in fact considered to be an extreme form of polymicrogyria⁹⁰. Schizencephaly can be unilateral or bilateral and tends involve the insular, precentral and postcentral regions¹¹. Type I schizencephaly refers to “closed-lip” clefts or small defects that are fused. In contrast, type II schizencephaly refers to “open-lip” clefts or large defects which are filled with fluid. The neurologic manifestations of the disorder depend on the anatomic location and type of the abnormality. Patients with type I lesions tend to be mildly affected and have partial seizures or spastic hemiparesis. On the other hand, patients with type II defects (open cleft) tend to have severe developmental delay, microcephaly, seizures, and spasticity. In particular, those with bilateral involvement have spastic quadriplegia and

severe cognitive impairment. Non CNS manifestations have also been reported, such as gastroschisis, and bowel atresias⁹¹. Radiographically, in addition to the schizencephaly seen on MRI, an absent or deficient septum pellucidum may be seen and is often associated with temporal or occipital clefts¹¹. The gray matter lining the cleft is nodular, with a polymicrogyric appearance.

Familial cases have been identified and have helped to shed light on the genetic basis of the disorder⁹². The inheritance pattern is still unclear although the mutations are thought to be autosomal dominant⁹³. Initial reports suggest that EMX2 gene mutations may be associated with type II schizencephaly⁹²; however, this finding needs to be confirmed in additional studies.

Management

As discussed above, the phenotype of MCD is extremely heterogeneous and the severity of the neurologic deficits can be quite varied, ranging from relatively mild to severe. Not surprisingly, given the abnormalities in the cerebral cortex, patients frequently suffer from epilepsy which may be refractory to pharmacologic treatment. Those patients who fail 3 antiepileptic medications are less likely to have their seizures controlled with additional trials of medications and epilepsy surgery should be considered. In addition to better seizure control, the goals of the surgery may include improvement of cognitive and psychosocial function, and ultimately better quality of life. The goals obviously need to be balanced against the risk of potential functional deficits that might result from the surgery. A detailed step-wise presurgical evaluation must be undertaken to evaluate whether the patient is an appropriate surgical candidate.

Vagus nerve stimulation (VNS) was approved in 1997 as adjunct treatment of refractory epilepsy for patients age 12 and older⁹⁴. The device is implanted surgically and delivers stimulation to the vagus nerve at various frequencies, but the exact mechanism is unknown. Up to 43% of patients may experience a greater than 50% reduction of seizure frequency at the end of 2 years⁹⁵. Thus, VNS is an option for patients who may not be good surgical candidates or who have failed surgery.

Aside from seizure control, management of these patients requires a multidisciplinary team approach to address both the medical and the psychosocial aspects of the disorder. As the genetic basis for many of these disorders have been identified, genetic testing may be possible for the patient as well as the family members. Appropriate genetic counseling may be an important aspect of management particularly for parents are planning to have more children.

Conclusion

With recent advances in neuroimaging, there is a significant increase in the recognition of MCD as a cause of epilepsy and neurologic dysfunction. Research in delineating the genetic and molecular basis of these disorders has given us greater insight into the pathogenesis of not only the malformations, but also the processes involved in normal cortical development. From a clinical perspective, improved diagnosis of MCD will allow for better treatment of symptomatic epilepsy (including offering surgical options when appropriate). The possibility of genetic testing and genetic counseling for families also play an important role in the overall management of patients with MCD. Hopefully, further research in elucidating the genetic and pathophysiologic mechanisms of MCD will lead the development of potential treatment strategies at various stages of development.

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Figure 1.

A. Normal brain. Axial T1-weighted MRI. Camera lucida rendering of the normal brain is to the right. **B. Microcephaly.** Axial T1-weighted MRI in a patient with a *ASPM* mutation. Camera lucida rendering to the right shows the region of disruption (grey) along the ventricular zone giving rise to microcephaly. **C. Periventricular heterotopia.** Axial T2-weighted brain MRI of a patient with a *FLNA* mutation. Note the nodules of heterotopic gray matter lining the lateral ventricles bilaterally. Camera lucida rendering to the right shows regions of disruption (grey) involving gray matter nodules along the lining of the ventricle. **D. Subcortical band heterotopia.** Axial T1-weighted brain MRI of a patient with a *DCX* mutation. Note the thick band of gray matter running deep and parallel to the thinned outer cortex. A thin band of white matter separates the outer cortex and the inner subcortical band of heterotopic neurons. Camera lucida rendering to the right shows the region of disruption (grey) involving a band of neurons midway between the cortical surface and ventricles. **E. Classical lissencephaly (Type I lissencephaly).** Axial T1-weighted brain MRI of type I or classic lissencephaly in a patient harboring a *LIS1* mutation. The brain has an “hour-glass” appearance with agyria and pachygyria. Note the greater severity of lissencephaly in the parietal and occipital lobes. Camera lucida rendering to the right shows a region of disruption (grey) demonstrating a disruption in the lamination of the cortex. **F. Cobblestone lissencephaly (Type II lissencephaly).** Axial T2-weighted brain MRI of type II or cobblestone lissencephaly. Note the cobblestone appearance of the thinned cortex, absent corpus callosum, and severely enlarged ventricles. Camera lucida rendering to the right shows regions of disruption (grey) demonstrating nodules of neurons on the surface of the cortex.

Table 1**Malformations of cortical development with associated genes and clinical features**

Developmental stage	Cortical malformation	Genetic cause	Clinical features
Abnormal neurogenesis	Microcephaly	<i>ASPM</i>	Mental retardation, not generally associated with epilepsy, autosomal recessive inheritance
		<i>Microcephalin</i>	
		<i>CDK5RAP2</i>	
		<i>CENPJ</i>	
	Hemimegalencephaly	Unknown	Mental retardation, early onset seizures (frequently intractable epilepsy), +/- neurocutaneous syndrome
	Focal cortical dysplasia	Unknown	Most common, focal and generalized Seizures
Abnormal neuronal migration	Periventricular heterotopia	<i>FLNA</i>	Normal intelligence, adolescent onset seizures, X-linked disorder with male lethality
		<i>ARFGEF2</i>	Mental retardation, microcephaly, autosomal recessive inheritance, rare
	Subcortical band heterotopia	<i>DCX</i>	Subcortical band heterotopia in females, mental retardation, epilepsy, X-linked disorder
	Lissencephaly	<i>LIS1</i>	Miller-Dieker syndrome (characteristic facial features), autosomal dominant inheritance
		<i>DCX</i>	Lissencephaly in males, X-linked
		<i>TUBA1A</i>	Lissencephaly, clinical features similar those caused by <i>LIS1</i> and <i>DCX</i> , de novo mutations
		<i>ARX</i>	Associated with ambiguous genitalia, hypothalamic dysfunction, neonatal epilepsy, X-linked disorder
		<i>RELN</i>	Associated with cerebellar hypoplasia, epilepsy, autosomal recessive inheritance
Abnormal arrest in neuronal migration	Cobblestone lissencephaly	<i>Fukutin</i>	Fukuyama congenital muscular dystrophy
		<i>POMGnT1</i>	Muscle-eye-brain disease
		<i>POMT1</i>	Walker-Warburg Syndrome
Abnormal neuronal organization	Polymicrogyria	<i>GPR56</i>	Bilateral frontoparietal polymicrogyria, Epilepsy
	Schizencephaly	<i>EMX2</i>	Type 2 (open cleft)