Malformations of cortical development (MCDs) are brain malformations that result from abnormalities affecting the normal processes of cortical development and involving cells that under normal circumstances would participate in formation of the cerebral cortex. Epileptic seizures result from paroxysmal, uncontrolled discharges of electricity from the brain that arise predominantly from the cerebral cortex. It is not surprising therefore that MCDs are often associated with recurrent seizures, and that these seizures may be difficult to control. The seizures in MCDs arise as a consequence of either malpositioning of normal cortical neurons or...
the presence of abnormal cortical neurons which results in abnormal cortical circuitry and a subsequent imbalance between the excitatory (glutaminergic) and inhibitory (γ-aminobutyric acid [GABA]ergic) systems which would normally control electrical discharges and prevent spontaneous abnormal electrical discharges and seizures.

The precise incidence of MCDs is not known; however, they have been diagnosed with increased frequency since the use of magnetic resonance imaging (MRI) to investigate patients with epilepsy, mental retardation, and congenital neurological deficits. It is estimated that 25% to 40% of intractable or medication-resistant childhood epilepsy is attributable to MCDs,1,2 and that at least 75% of patients with MCDs will have epilepsy.3 A large number of MCDs have now been identified and classified using embryologic, genetic, and imaging criteria.4 Contrary to previous assumptions, the majority of these disorders are now thought to have a genetic basis, although environmental causes such as in utero infection or ischemia are still possible. At the time of preparation of this manuscript, mutations in over 30 genes have been identified as causes of MCDs. MCD syndromes with specific clinical, imaging, and genetic criteria are being defined and delineated.

The aim of this review is to discuss the main types of MCDs encountered in clinical practice, highlighting those MCDs in which epilepsy is a frequent accompaniment. The different MCDs shall be discussed in the order in which they are currently classified, based on the presumed timing of the “insult,” be it genetic or environmental, within the overlapping stages of cortical development. Each MCD shall be discussed in terms of its pathological, clinical, imaging, and etiological features.

### Selected abbreviations and acronyms

- **FCD**: focal cortical dysplasia
- **HMEG**: hemimegencephaly
- **LIS**: lissencephaly
- **MCD**: malformation of cortical development
- **MRI**: magnetic resonance imaging
- **PMG**: polymicrogyria
- **PNH**: periventricular nodular heterotopia
- **SBH**: subcortical band heterotopia
- **SCZ**: schizencephaly
- **TSC**: tuberous sclerosis

### MCDs as a consequence of abnormal neuronal and glial proliferation or differentiation

#### Tuberous sclerosis

Tuberous sclerosis complex (TSC) is a multisystem syndrome characterized by hamartomata in multiple organ systems, including abnormal proliferation of neurons and glia in the central nervous system. The brain is the most frequently affected organ, but other organs including skin, eyes, heart, and kidneys may be involved.5 Typical brain abnormalities include cortical tubers, subependymal nodules, and subependymal giant cell astrocytoma. The pathological features of cortical tubers may be indistinguishable from those of some forms of focal cortical dysplasia (FCD), showing large bizarre neurons, atypical astrocytes, and subpial fibrillary gliosis.

TSC is one of the most common causes of MCDs, with a birth incidence of 1/6000.6 The clinical features of TSC are highly variable, depending on what organ systems are involved and the location of and severity of involvement within the affected organs. Neurological symptoms include seizures, intellectual disability, and behavioral problems. Some patients may have minimal or no neurological features despite showing abnormalities in other organ sys-

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Figure 1. Imaging features of tuberous sclerosis. Axial T2-weighted MRI (left) and contrast-enhanced axial T1-weighted MRI (right). The image on the left shows multiple focal areas of broadened gyri, blurring of the gray-white junction and increased signal in the subcortical white matter typical of cortical tubers. The image on the right shows multiple subependymal nodules (arrows) consistent with subependymal hamartoma and a large enhancing lesion at the right foramen of Monro consistent with a giant cell astrocytoma. MRI, magnetic resonance imaging.
tems or carrying a mutation in one of the two known TSC genes, whilst others may be neurologically asymptomatic despite known cerebral lesions. Seizures may commence at any age and are usually partial seizures originating in cortical tubers. Infantile spasms are common, with seizures arising in infancy. The severity of neurological symptoms in TSC generally correlates with the patient’s tuber count, although this may not hold true for an individual patient. Evidence suggests that the presence and severity of epilepsy is the most important variable associated with intellectual disability. Overall, approximately 80% of patients with TSC have epilepsy, whilst approximately 65% have intellectual disability of some degree.

MRI may show cortical tubers, subependymal nodules, giant cell astrocytoma, and linear white matter abnormalities, as shown in Figure 1. Computerized tomography (CT) scanning may be required to adequately show calcifications, which are most commonly seen in subependymal nodules. In addition to these typical findings, MRI may also detect cerebellar tubers, subtle cortical dysplasia, transmantle dysplasia, hemimegalencephaly (HMEG), focal megalencephaly, and cortical infoldings. TSC is an autosomal dominant syndrome with high penetrance. Based on the study of affected families, two genes have been identified; TSC1 on 9q34 which codes for hamartin, and TSC2 on 16p13 which codes for tuberin. Ninety percent of patients with TSC will have mutations in one of these genes. Hamartin and tuberin cooperate in pathways that control cell growth and thus are associated with defective control of neuronal and glial proliferation or differentiation.

**Focal cortical dysplasia**

The term “focal cortical dysplasia” (FCD) was first used by Taylor et al in 1971 to describe a histological abnormality seen in surgical specimens from 10 patients with epilepsy. The abnormality was described as a “malformation,” visible by histology and characterized by the “congregations of large, bizarre neurons...(and) in most ...cases, grotesque cells ... present in the depths of affected cortex and in the subjacent white matter.” Most methods of classification divide FCD according to both the degree of dysplasia (architectural or cytoarchitectural dysplasia) and the presence or absence of abnormal cells, primarily balloon cells or large dysmorphic neurons. FCD shows a spectrum of severity in terms of its gross morphology, topography, and microscopic features.

At the mildest end of the spectrum is “microdysgenesis,” which is poorly defined and refers to subtle developmental cortical abnormalities including neuronal heterotopia, undulations of cortical layering, or neuronal clusters amongst cell-sparse areas. Microdysgenesis has been found at autopsy more commonly in those with epilepsy compared with controls without epilepsy or other neurological disorders, as well as in surgical specimens from patients with medically intractable epilepsy. Despite this, it is still unclear what degree of “microdysgenesis” may fall within the normal spectrum. It has been suggested that the term FCD only be applied to lesions with architectural abnormalities such as dyslamination or the presence of abnormal cells within the cortex. The extent of FCD may be highly variable, ranging from focal areas involving part of a gyrus, to involvement of one or more gyri to transmantle dysplasia, lobar dysplasia, hemispheric dysplasia, or multifocal bilateral dysplasia.

Apart from TSC, no particular dysmorphic, neurocutaneous, or multiple congenital anomaly syndromes have been described in which FCD is a feature. The most common clinical sequelae of FCD are seizures, developmental delay or intellectual disability, and focal neurological deficits. Seizures from FCD may arise at any age from...
in utero seizures until adulthood; however, patients usually present in childhood. Extratemporal FCD is usually associated with an earlier age of seizure onset than temporal FCD. Seizures may be simple partial, complex partial, or secondarily generalized, depending on the location of the FCD and the age of the patient. The seizure disorder may be intractable and life-threatening, and surgical resection of the area of FCD may be required to control seizures, as they are often resistant to anticonvulsant medications. FCD has been shown to be intrinsically epileptogenic, both in vivo using corticography during epilepsy surgery and in vitro using cortex resected from patients with intractable epilepsy. FCD is rarely visible on CT, and may not be visible even with high-quality MRI. Subtle abnormalities in gyration, cortical thickness, and the gray-white junction may be a clue to underlying FCD. Some forms of FCD may show increased signal on FLAIR and T2-weighted images which has been thought to represent the presence of balloon cells. White matter signal may be abnormal in the region of a FCD producing intractable seizures. It is not clear whether this represents dysplastic white matter, or an effect of continued seizure activity producing advanced myelination. Imaging examples of FCD with and without T2 signal increase are shown in Figure 2.

Barkovich and colleagues have described two forms of cortical dysplasia with characteristic imaging appearances. In focal transmantle dysplasia (FTD) there is a wedge of dysplastic tissue from the lateral ventricle to the cortical surface. Histology showed the features of FCD with balloon cells as well as white-matter astrogliosis, and MRI shows a wedge of disorganized tissue with increased T2 signal. FTD may also be seen in patients with TSC. Sublobar dysplasia is characterized by a deep infolding of the cortex with a thickened cortex and possible poor gray-white differentiation in the malformed region. There are associated brain abnormalities including ventricular dysmorphism and callosal and cerebellar dysgenesis. Tissue was not available for pathological examination. Another form of FCD affecting one or other posterior quadrant of the brain has also been described as “posterior quadrantic dysplasia.” This form of FCD is alternately known by the clumsy term “hemihemimegalencephaly.” Apart from FCD due to TSC, the etiology of FCD remains unknown. There is no good evidence for environmental causes. There are no published multiplex pedigrees for typical forms of FCD other than families with TSC. However homozygous mutations in the gene CNT-NAP2 were recently identified in Amish children with cortical dysplasia, macrocephaly, and intractable seizures with subsequent language regression.

Hemimegalencephaly

HMEG is a brain malformation characterized by the presence of an abnormally enlarged and dysplastic cerebral hemisphere. The contralateral cerebral hemisphere usually appears normal, except for being compressed or distorted, although a recent study demonstrated reduced size. Macroscopically, one hemisphere is enlarged and there is usually cortical dysgenesis, white-matter hyper trophy, and a dilated and dysmorphic lateral ventricle. The majority of the cerebral hemisphere is affected, with no clear predilection for right or left hemisphere. The microscopic features of HMEG can vary significantly. These may include polymicrogyria (PMG), heterotopic grey matter, cortical dyslamination, bizarre enlarged neurons, balloon cells, blurring of the gray-white junction, and an increase in the number of both neurons and astrocytes. The clinical triad of HMEG is typically: (i) intractable partial seizures from the neonatal period or early infancy, (ii) hemiparesis, and (iii) developmental delay. Although
the seizures are partial in origin, children may present with tonic seizures, or infantile spasms and the electroclinical features of Ohtahara syndrome or West syndrome. With the exception of the hemiparesis, the developmental abnormalities may in part be the consequence of intractable seizures, and the developmental outcome may be more favorable if seizures are well controlled from an early age. Seizures are usually resistant to medical therapy and control may only be achieved by surgery such as anatomical or functional hemispherectomy. HMEG has been seen in association with both neurocutaneous and overgrowth syndromes. Neurocutaneous associations include the linear nevus sebaceous syndrome, hypomelanosis of Ito, tuberous sclerosis, and neurofibromatosis. Approximately 50% of cases of linear nevus sebaceous syndrome have associated HMEG. On MRI the cortical gray matter is almost uniformly abnormal, showing areas of thickening and gyral simplification similar to pachygyria or overfolding that resembles polymicrogyria (PMG). In both cases the gray-white junction appears indistinct. White matter is generally markedly increased in volume, and often contains tissue isointense to cortical gray matter, consistent with gray-matter heterotopia. There may be white-matter signal change consistent with either dysmyelination or advanced myelination. The ipsilateral ventricle is usually enlarged and dysmorphic, often with extension of the posterior horn of the lateral ventricle across the midline. There may be enlargement of the ipsilateral cerebellar hemisphere and brain stem, an appearance which has been named “total hemimegalencephaly.”

The etiology of HMEG remains unknown. There are no clear environmental causes or associations with known chromosomal abnormalities. It is generally assumed that HMEG results from a defect leading to excessive proliferation of both neurons and astrocytes and the known association of HMEG with other disorders of cellular proliferation such as TSC and neurofibromatosis supports this hypothesis. One study has shown the abnormal expression of the L1 neural cell adhesion molecule (L1CAM) in 10 children with HMEG compared with 23 controls. L1CAM is known to be involved in regulation of neuroblast migration and axonal development.

MCDs as a consequence of abnormal neuronal migration

Classical lissencephaly

The term lissencephaly (LIS) has generally been used to describe disorders in which the mature brain is deficient in gyration. Classical LIS was previously known as “type I” LIS. Classical LIS is a different malformation to cob-
blestone LIS (or cobblestone dysplasia), previously referred to as “type II LIS.” The terms classical LIS, type I LIS, and agyria/pachygyria all still appear in the current literature and all refer to the same malformation. The macroscopic hallmarks of classical LIS are reduced or absent gyration combined with thickening of the cerebral cortex. Most cases are a combination of agyria (absent gyration) and pachygyria (broad, simplified gyration), with total agyria or total pachygyria being unusual. On macroscopic inspection the brain shows poorly developed Sylvian andRolandic fissures and failure of opercularization of the insular areas. The brain size and weight are usually at the lower range of normal. Associated abnormalities may include enlarged lateral ventricles, absence of the claustra and external capsules, abnormalities of the corpus callosum, persistent cavum septum pellucidum, hypoplasia of the pyramidal tracts, heterotopia of the inferior olives, and less often abnormalities of the cerebellum. Microscopic examination shows a thick and poorly organized cortex with four rather than the normal six layers. From the cortical surface inwards, these consist of: (i) a poorly defined marginal zone with increased cellularity; (ii) a superficial cortical gray zone with diffusely scattered neurons; (iii) a relatively neuron-sparse zone; and (iv) a deep cortical gray zone with neurons often oriented in columns. The deep cortical gray zone is much thicker than the superficial cellular layer, and consists of large numbers of neurons presumed to have arrested their migration prematurely. Other forms of LIS have recently been described, including LIS associated with cerebellar hypoplasia and RELN mutations, and LIS associated with agenesis of the corpus callosum and ARX mutations. The pathological findings in these rarer forms of LIS may be somewhat different to those described above.

The clinical manifestations of LIS are variable depending on: (i) the severity and topography of the malformation; (ii) associated congenital brain abnormalities; and (iii) congenital abnormalities in other organ systems. Intractable epilepsy may be an independent contributor to intellectual disability and developmental delay. The common clinical features of classical LIS include severe or profound intellectual disability, early hypotonia (which may persist or evolve to mixed axial hypotonia and limb spasticity), epileptic seizures (usually presenting as infantile spasms) and feeding problems. The Miller-Dieker syndrome (MDS) is a contiguous gene deletion syndrome with the deletion of multiple genes at the tip of the short arm of chromosome 17, including both the LIS1 and YWHAE (14-3-3ε) genes which are both required for normal brain development. Children with MDS have a severe form of LIS associated with facial dysmorphism and occasionally other congenital abnormalities, and have a severely shortened life expectancy. Moderate and severe forms of LIS can usually be diagnosed using CT scanning. The cerebral surface appears smooth with absent opercularization and a characteristic “figure eight” appearance. Milder forms of LIS and accompanying brain malformations such as cerebellar abnormalities may be missed using CT scanning. Using 1.5T MRI the gyral pattern (agyria or pachygyria), thickened cortex and other brain abnormalities can readily be appreciated. Several different patterns of LIS are recognized using MRI, which led to development of a detailed grading system which considers both the severity of the gyral pattern simplification and the gradient along the anterior to posterior axis. Most patients have a posterior to anterior (P>A) gradient in which the gyral malformation is more severe posteriorly than anteriorly. This pattern is seen most often as a consequence of a mutation in the LIS1 gene, but may also occur with mutations of TUBA1A. Others have the reverse anterior to posterior (A>P) gradient, which is seen most commonly as a consequence of mutations in the DCX gene. Figure 4 shows the imaging features of the two main gradients of LIS, and Figure 5 shows different grades of LIS severity.

Six genes associated with LIS syndromes have been identified, and in approximately 80% of cases, a genetic cause can be found, usually an abnormality of the LIS1 or DCX genes. The six known genes associated with causation of LIS are LIS1, DCX, ARX, RELN, YWHAE, and TUBA1A. These genes are all known to be required for optimal migration of neurons during brain development. All but the ARX gene are required for normal radial migration of neurons whereas the ARX gene is required for normal tangential migration. Mutations in the LIS1 gene are the most common cause of LIS. The LIS1 protein is not only required for neuronal migration, but it is also required for cellular proliferation and intracellular transport (reviewed in ref 86).

**Subcortical band heterotopia**

Subcortical band heterotopia (SBH) is alternately known as double cortex or subcortical laminar heterotopia. The term SBH is preferable to double cortex, as the het-
erotopic gray matter lacks cortical lamination and organization, and does not resemble a cerebral cortex other than being composed of gray matter. SBH is characterized macroscopically by bilateral bands of heterotopic gray matter located in the white matter between the lateral ventricular walls and the cortex.\(^6\) The overlying cortex appears normal with the exception of mildly shallow sulci. In the most typical forms, the bands are bilateral and symmetric and slightly more prominent anteriorly.\(^8\) Occasionally the bands are seen restricted to the frontal lobes (partial frontal) or rarely the occipito-parietal regions (partial posterior) and unilateral and asymmetric bands have also been reported.\(^8\)\(^,\)\(^9\)\(^,\)\(^0\)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(...
Ital anomaly syndrome. Macroscopically, periventricular or subependymal heterotopia are nodular masses of gray matter adjacent to or protruding into the walls of the lateral ventricles. They may be single, multiple, and separated or contiguous. Microscopically, the heterotopic gray matter forms clusters of rounded, irregular nodules separated from each other by layers of myelinated fibers. Both neurons and glia may be present with a pattern ranging from apparent disorganization to one with rudimentary lamination.

The most frequent manifestation of periventricular nodular heterotopia (PNH) is epilepsy, occurring in 80% to 90% of patients with most having various types of partial seizures, which are usually intractable. Studies using depth electrodes in patients with PNH and epilepsy have shown the nodules to be intrinsically epileptogenic and temporal lobe surgery for patients with PNH and associated hippocampal sclerosis has generally been unsuccessful. Most patients with PNH have normal intelligence, although the curve may be shifted slightly to the left with an average IQ of approximately 85. This data applies best to the more common forms of PNH, with manifestations of the variant syndromes generally being more severe. There is a skewed sex ratio towards females among patients with bilateral PNH.

In typical PNH, MRI will show nodular masses of gray matter, lying adjacent to the lateral ventricles and often protruding into the lumen, as seen in Figure 7. The signal intensity is identical to that of cortical gray matter. Functional studies using fluorodeoxyglucose positron emission tomography (FDG-PET) and hexamethylpropyleneamine oxime single positron emission computed tomography (HMPAO-SPECT) have shown changes in metabolic activity and perfusion to be almost identical in the heterotopic nodules and normal overlying cortex. Most are located along the lateral ventricular walls, although they may occasionally be seen posteriorly or medially. The nodules may be single or multiple, unilateral or bilateral, large or small, and symmetric or asymmetric. They may be contiguous or separated to resemble “pearls on a string.” PNH differ from the subependymal nodules of TSC, which are usually smaller, fewer, inhomogeneous, and calcified, and have signal intensity resembling white matter. PNH may be associated with additional brain anomalies such as cerebellar vermis hypoplasia, and is the most common MCD found in association with hippocampal sclerosis. Unilateral or focal PNH may occur in combination with subcortical nodular heterotopia (SNH) or in association with other MCDs such as PMG. Typical bilateral PNH may be associated with mild-to-moderate hypoplasia of the corpus callosum or cerebellum, the latter primarily involving the vermis. Usually, PNH is limited to the periventricular region but may occasionally form a larger mass that may deform or displace the lateral ventricle.

Mutations in the FLNA gene were identified in families with multiple affected members with bilateral periventricular nodular heterotopia. FLNA is located on the long arm of the X-chromosome, and mutations in males are thought to be lethal, thus explaining the female predominance of PNH. FLNA may be necessary for efficient cell motility, possibly by promoting actin networks at the leading edge of motile cells or by keeping cells attached to supporting cells until the necessary signal for cell locomotion. Defects in these functions may account for defective initiation of neuronal migration in bilateral PNH. Although approximately 80% of familial cases of PNH have FLNA mutations, mutations have been detected in only approximately 20% of sporadic PNH patients. Those with mutations usually have a typical bilateral PNH pattern, with most patients with atypical PNH not having FLNA mutations. An autosomal recessive form of PNH with microcephaly has been found to be due to mutations in the ARFGEF2 gene in a small number of children from consanguineous parents.

Figure 7. Imaging features of periventricular nodular heterotopia. Axial T1-weighted MRI showing two patients with bilateral periventricular nodular heterotopia. Manifest by nodules of tissue with identical signal to cortical gray matter located in the periventricular region (arrows). The image on the left shows scattered nodules separated by normal white matter, whereas the image on the right shows contiguous nodules completely lining the lateral ventricle. MRI, magnetic resonance imaging
Bilateral PNH is also described in association with structural abnormalities of chromosome 5p.116 It is likely that PNH is a genetically heterogeneous disorder secondary to abnormalities of genes involved in neuroblast proliferation or initiation of neuroblast migration.

**MCDs as a consequence of abnormal cortical organization**

**Polymicrogyria**

Polymicrogyria (PMG) refers to a cerebral cortex with excessive microscopic gyration, and is probably one of the most common of the MCDs. Macroscopically PMG appears as an irregular cortical surface. The distribution of PMG varies significantly from unilateral forms, to bilateral symmetric and asymmetric forms. The perisylvian cortex is the most frequently affected area and the affected Sylvian fissures may appear extended and superiorly orientated posteriorly as shown in Figure 8. PMG is reported to occur at the periphery of many poren cephalic or hydranencephalic defects.117,118 There may be a variety of associated brain malformations, including ventriculomegaly and abnormalities of the corpus callosum, brain stem, and cerebellum, although PMG is usually the isolated brain malformation. PMG may show a variety of histological patterns, but all show abnormal cortical lamination, excessive folding and fusion of adjacent gyri.66 Two main forms of PMG are described; unlayered and layered, the latter of which has been described as the “true” or “structured” PMG.119 Occasionally, both forms are found in the same patient, suggesting that they may be variations of the same malformation.120 The clinical sequelae of PMG are highly variable depending on the extent and location of the PMG, the presence of other brain malformations, and the influence of complications such as epilepsy. In addition, PMG is reported as an occasional component in multiple different syndromes or disorders including metabolic disorders, chromosome deletion syndromes, and multiple congenital anomaly syndromes. These patients may have a wide spectrum of clinical problems other than those attributable to the PMG. Some patients with PMG have fewer clinical problems than would be expected for the location and extent of cortex involved. The most common form of PMG involves the perisylvian regions in a bilateral and symmetric pattern. The combination of bilateral perisylvian PMG (BPP) associated with oromotor dysfunction and a seizure disorder has been called the “congenital bilateral perisylvian syndrome,” and is the best described syndrome with PMG. Detailed clinical data is published in over 50 patients with this distribution of PMG,121,122 with the first description appearing in the German pathological literature in 1905.123 Patients with BPP typically have oromotor dysfunction including difficulties with tongue (tongue protrusion and side to side movement), facial and pharyngeal motor function resulting in problems with speech production, sucking, and swallowing, excessive drooling, and facial diplegia. They may also have an expressive dysphasia in addition to dysarthria. More severely affected patients have minimal or no expressive speech, necessitating the use of alternate methods of communication such as signing. On examination there is facial diplegia, limited tongue movement, a brisk jaw jerk, and frequent absence of the gag reflex.122 In patients presenting in childhood there may be other abnormalities including arthrogryposis, hemiplegia, and hearing loss, although there is limited pediatric data available.124 There may be mild-to-moderate intellectual disability in up to 75% of cases.121 Motor dysfunction may include limb spasticity, although this is rarely severe if present. Other patterns of PMG have been described including unilateral perisylvian PMG,125 bilateral frontal PMG,126 bilateral frontoparietal PMG,127 bilateral parasagittal parieto-occipital PMG,128 bilateral parieto-occipital PMG,129 multilobar PMG,130 and bilateral
generalized PMG. The clinical features of these rarer forms of PMG vary from those seen in BPP, although epilepsy and some degree of developmental delay are common accompaniments. The frequency of epilepsy in PMG is 60% to 85%, although seizure onset may not occur until the second decade, however usually between the ages of 4 and 12. Seizure types include atypical absence (62%), atonic and tonic drop attacks (73%), generalized tonic-clonic (35%) and partial (26%). It is rare for the partial seizures to secondarily generalize. Occasionally patients develop bilateral facial motor seizures with retained awareness. A small number of patients may present with infantile spasms in contrast to patients with LIS, TSC, or FCD, in which the frequency of spasms is higher. Electroencephalography (EEG) typically shows generalized spike and wave or multifocal discharges with a centroparietal emphasis. Seizures may be daily and intractable in at least 50% of patients. Using CT and low field strength MRI, PMG is difficult to discern and may only appear as thickened cortex. The only role for CT in the evaluation of PMG is to assess for evidence of calcification which is seen in PMG resulting from congenital CMV infection. Using high-quality 1.5T MRI with appropriate age-specific protocols, it is now possible to reliably differentiate PMG from other MCDs. Polymicrogyric cortex often appears mildly thickened (6 to 10 mm) on imaging due to cortical overfolding rather than true cortical thickening. With better imaging (such as inversion recovery) using thin contiguous slices, microgyri and microsulci may be appreciated as shown in Figure 8. T2 signal within the cortex is usually normal, although there may be delayed myelination or high T2 signal in the underlying white matter. Diffusely abnormal white matter signal should raise the question of an in utero infection (such as cytomegalovirus [CMV]) or a peroxisomal disorder. There may be an expansion of the subarachnoid space over PMG, and this may contain excessive or anomalous venous drainage, especially in the Sylvian fissures. Other developmental anomalies may also be seen including ventricular enlargement or dysmorphism and abnormalities of the corpus callosum and cerebellum, although the patterns and prevalence of these associated brain malformations are poorly documented. Few topics in the field of MCDs have generated as much discussion as the etiology and pathogenesis of PMG. Initial theories of PMG suggested that it was the result of a vascular defect such as arterial ischemia. Numerous etiologies, both genetic and nongenetic, have since been reported in association with PMG. Nongenetic causes other than hypoxia or hypoperfusion mainly relate to congenital infections including CMV. There are a multitude of reports of PMG in association with genetic factors, either as part of a known genetic disease or a multiple congenital anomaly syndrome, in association with a structural chromosomal abnormality, or in families with multiple affected members and/or consanguinity. There is an association of PMG with some metabolic diseases including Zellweger syndrome, although the pathological changes differ from typical PMG. Zellweger syndrome has been found to be due to mutations in the PEX family of genes. Despite the long-held assumption that most forms of PMG are the result of a nongenetic insult, familial cases and examples of PMG occurring in other genetic syndromes and structural chromosomal abnormalities are now abundant in the literature, as reviewed in Jansen and Andermann. All modes of inheritance have been suggested although an X-linked inheritance pattern appears most frequent. The gene for bilateral frontoparietal PMG has been identified as GPR56, yet the function of this gene in cortical development is unclear. Our experience and recent data from the mouse suggest that the pathological changes have features in common with cobblestone cortical malformation rather than typical PMG. Mutations in the gene SRPX2 have been found in one family with BPP, but thus far mutations in this gene have not been reported in other patients with BPP PMG is also reported as a component of several chromosomal deletion syndromes, particularly the 22q11.2 deletion syndromes such as the DiGeorge and velocardiofacial syndromes.

Schizencephaly

“Schizencephaly” (SCZ) is a term first used by Yakovlev and Wadsworth in 1946 to describe “true clefts formed in the brain as the result of failure of development of the cerebral mantle in the zones of cleavage of the primary cerebral fissures.” SCZ is differentiated from clefts in the cerebral mantle that arise as a consequence of destructive lesions, which Yakovlev and Wadsworth call “encephaloclastic porencephalies,” now known simply as porencephaly. As part of the definition of SCZ, the clefts must be lined by abnormal gray matter described as “microgyria,” a term now synonymous with PMG. Macroscopically, the...
clefts of SCZ can be unilateral or bilateral and “open-lipped” or “closed-lipped,” as shown in Figure 9. In open-lipped clefts, the walls of the clefts do not appose each other. In closed-lipped clefts the walls of the cleft are apposed and often fused, although a line of continuity between the lateral ventricle and subarachnoid space is usually visible (the “pia ependymal seam”). Clefts are frontal or parietal in approximately 65%, and temporal or occipital in approximately 35%. Other brain malformations may accompany SCZ. Most are rare, with the exception of agenesis of the septum pellucidum which is present in approximately 70% of cases. Microscopically, the gray matter lining the clefts of SCZ is consistent with PMG, often indistinguishable from other forms of PMG.

The clinical features of SCZ are well described in the literature, and depend on two factors: (i) unilateral vs bilateral SCZ and (ii) open vs. closed-lipped SCZ. Patients with with closed-lipped SCZ typically present with hemiparesis or motor delay whereas patients with open-lipped SCZ typically present with hydrocephalus or seizures. In a large series of 47 children with different types of SCZ, Packard et al found a prevalence of epilepsy in 57% and moderate-to-severe developmental delay in 83%. The median age for seizure onset was 13 months, although those with open-lipped SCZ generally had seizure onset at an earlier age than those with closed-lipped SCZ. The most common seizure type was complex partial, although infantile spasms, tonic, atonic, and tonic-clonic seizures were also reported. The severity and type of seizures does not appear to correlate with the topography of the SCZ. Outcome is worst for those with bilateral open-lipped SCZ and best for those with unilateral closed-lip SCZ. A large number of patients have associated brain abnormalities which may account for the severity of some cases. These included agenesis of the septum pellucidum, focal cortical dysplasia, and dysgenesis of the corpus callosum. An interesting finding is that some patients with SCZ have relatively minor clinical problems relative to the appearance of their malformation.

Routine structural MRI scanning is usually sufficient to diagnose SCZ and determine whether the SCZ is open- or closed-lipped. Subtle SCZ may recognizable by a “puckering” or “dimple” outwards of the lateral ventricle at the point at which the cleft reached the ventricular margin (seen in the left image in Figure 9). The cleft is lined by gray matter. The presence of white matter or T2 signal increase suggestive of gliosis lining the cleft suggests that the lesion is porencephaly rather than SCZ. The gray matter lining the cleft has the imaging appearance of PMG with apparent cortical thickening, an irregular surface, and stippling of the gray-white interface. SCZ may be asymmetric, and the contralateral hemisphere should be closely evaluated for the presence of a milder SCZ or PMG of another form. Agenesis of the septum pellucidum is a common finding and hypoplasia of the optic nerves may be present in up to 30% of cases, placing some forms of SCZ in the septo-optic dysplasia spectrum.

The etiology of SCZ remains highly controversial, and there are likely both genetic and non-genetic causes. In SCZ, there is definite evidence for non-genetic causes such as congenital CMV infection and in utero ischemic insults. There is also now ample evidence supportive of a genetic etiology for some cases of SCZ, including reports of a number of familial cases. A few patients with both familial and nonfamilial SCZ were found to have mutations in the homeobox gene EMX2. Unfortunately, other researchers have failed to reproduce these results, raising the question as to the true role of EMX2 in SCZ.

Conclusion

MCDs are significant causes of neurological and developmental disability and epileptic seizures are an associated symptom in over three quarters of patients. The seizures may arise at any age, but epilepsy will usually commence in childhood and is often resistant to anti-convulsant medications. Surgery may have a role in the treatment of seizures caused by these malformations.
Discrete cortical malformation syndromes with specific pathological, clinical, imaging, and genetic syndromes are being defined, and this knowledge has improved the clinician’s ability to provide more accurate prognostic and genetic counseling to affected families, including prenatal testing for certain disorders. The study of these disorders has provided researchers with a unique opportunity to investigate the mechanisms of epileptogenesis. In addition, MCDs have provided molecular biologists and developmental neurobiologists with another method by which to identify new genes and mechanisms for the normal development of the human cerebral cortex.

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Las malformaciones del desarrollo cortical (MDC) son anormalidades macro o microscópicas de la corteza cerebral que surgen como consecuencia de una interrupción de las etapas normales en la formación de la placa cortical. La corteza cerebral desarrolla su estructura básica durante los dos primeros trimestres del embarazo como una serie de etapas sobrepuestas, que se inician con la proliferación y diferenciación de neuronas las cuales luego migran antes de organizarse finalmente en la corteza desarrollada. Las anormalidades en cualquiera de estas etapas, sean ellas de origen ambiental o genético, pueden causar interrupción de los circuitos neuronales y predisponer a una variedad de consecuencias clínicas, siendo las más comunes las convulsiones epilépticas. Actualmente se ha descrito un gran número de MDC, cada una con sus características patológicas, clínicas y de imágenes. Las causas de gran parte de estas MDC se han determinado mediante el estudio de sujetos afectados, y actualmente se ha establecido que muchas de ellas son secundarias a mutaciones en genes del desarrollo cortical. Esta revisión destaca lo mejor conocido de las malformaciones corticales humanas asociadas con la epilepsia. Se resumen las características patológicas, clínicas, de imágenes y etiológicas de cada MDC, con imágenes representa-tivas de resonancia nuclear magnética para cada una de ellas. Se presentan las malformaciones de la escle-rosis tuberosa, displasia cortical focal, hemimega-lencefalia, lissancefalia clásica, heterotopia subcorti-cal en banda, heterotopia nodular periventricular, polimicrogiria y esquizencefalia.

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