Malformations of cortical development and epilepsy

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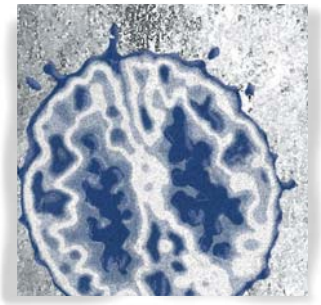

Malformations of cortical development (MCDs) are brain malformations that result from abnormalities affecting the normal processes of cortical development and involving cells that under normal circumstances would participate in formation of the cerebral cortex. Epileptic seizures result from paroxysmal, 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

Malformations of cortical development (MCDs) are macroscopic or microscopic abnormalities of the cerebral cortex that arise as a consequence of an interruption to the normal steps of formation of the cortical plate. The human cortex develops its basic structure during the first two trimesters of pregnancy as a series of overlapping steps, beginning with proliferation and differentiation of neurons, which then migrate before finally organizing themselves in the developing cortex. Abnormalities at any of these stages, be they environmental or genetic in origin, may cause disruption of neuronal circuitry and predispose to a variety of clinical consequences, the most common of which is epileptic seizures. A large number of MCDs have now been described, each with characteristic pathological, clinical, and imaging features. The causes of many of these MCDs have been determined through the study of affected individuals, with many MCDs now established as being secondary to mutations in cortical development genes. This review will highlight the best-known of the human cortical malformations associated with epilepsy. The pathological, clinical, imaging, and etiologic features of each MCD will be summarized, with representative magnetic resonance imaging (MRI) images shown for each MCD. The malformations tuberous sclerosis, focal cortical dysplasia, hemimegalencephaly, classical lissencephaly, subcortical band heterotopia, periventricular nodular heterotopia, polymicrogyria, and schizencephaly will be presented.

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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*

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.

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-

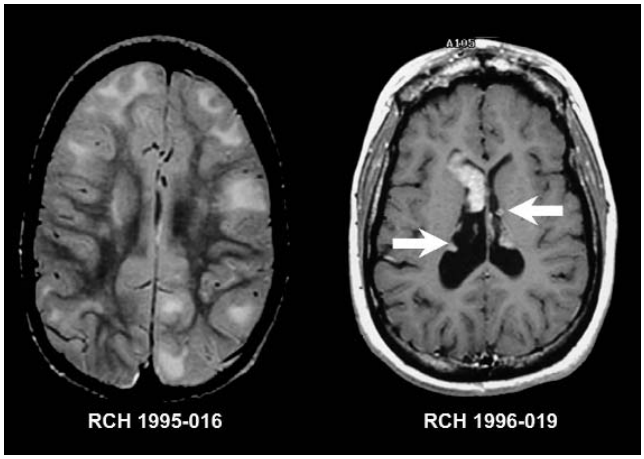

Figure 1. Imaging features of tuberous sclerosis. Axial T2-weighted MRI (left) and contrast-enhanced axial T1-weighted MRI (right). The image on the left shows multiple focal areas of broadened gyri, blurring of the gray-white junction and increased signal in the subcortical white matter typical of cortical 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,[7] 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.[8,9] Overall, approximately 80% of patients with TSC have epilepsy, whilst approximately 65% have intellectual disability of some degree.[5]

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,[10] hemimegalencephaly (HMEG),[11,12] focal megalencephaly, and cortical infoldings.[13]

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,[14] and *TSC2* on 16p13 which codes for tuberin.[15] Ninety percent of patients with TSC will have mutations in one of these genes.[16,17] 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.[18] 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 subadjacent 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.[19-21] 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.[22] Microdysgenesis has been found at autopsy more commonly in those with epilepsy compared with controls without epilepsy or other neurological disorders,[23] as well as in surgical specimens from patients with medically intractable epilepsy.[22,24] Despite this, it is still unclear what degree of "microdysgenesis" may fall within the normal spectrum.[25]

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.[26] 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.[27-29] Seizures from FCD may arise at any age from

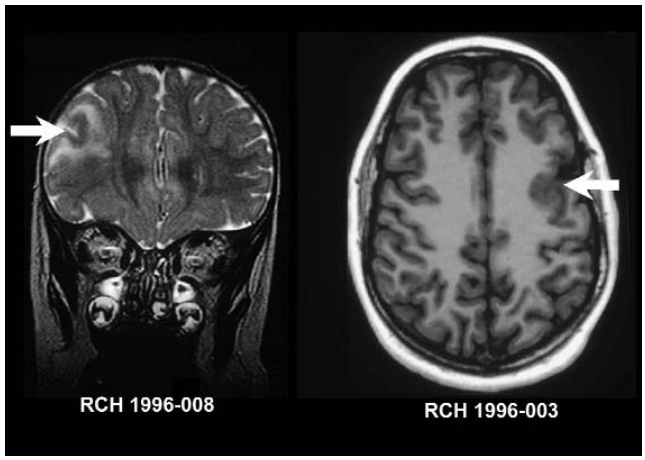

Figure 2. Imaging features of focal cortical dysplasia. Coronal T2-weighted MRI (left) and axial T1-weighted MRI (right) of two patients with focal cortical dysplasia. The image on the left shows area of gyral irregularity and increased subcortical signal (arrow) consistent with cortical dysplasia with signal change. The image on the right shows an area of unusual gyral formation and underlying thickening and blurring of the gray-white junction (arrow) consistent with cortical dysplasia without signal change. (No signal increase was seen on T2 weighted images.) MRI, magnetic resonance imaging

in utero seizures[30] until adulthood; however, patients usually present in childhood.[27] Extratemporal FCD is usually associated with an earlier age of seizure onset than temporal FCD.[27,31,32] 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,[33] 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[34] and in vitro using cortex resected from patients with intractable epilepsy.[35,36]

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.[37] 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.[20,38,39] White matter signal may be abnormal in the region of a FCD producing intractable seizures.[26,40] 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.[41] 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.[42]

Another form of FCD affecting one or other posterior quadrant of the brain has also been described as "posterior quadrantic dysplasia."[43] 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 *CNTNAP2* were recently identified in Amish children with cortical dysplasia, macrocephaly, and intractable seizures with subsequent language regression.[44]

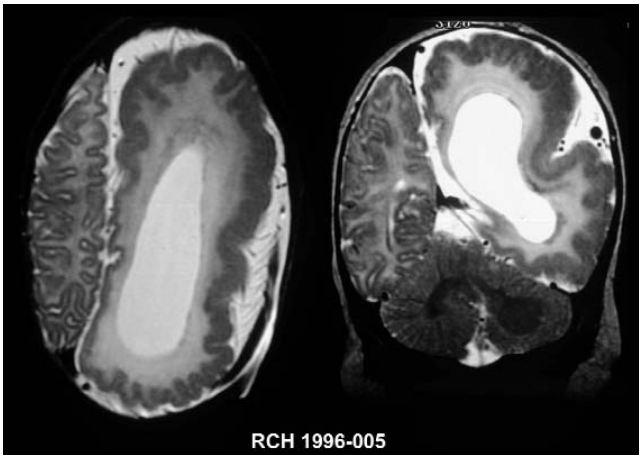

Figure 3. Imaging features of hemimegalencephaly. Axial T2-wieghted MRI (left) and coronal T2-weighted MRI (right) of an infant with hemimegalencephaly showing an enlarged and dysmorphic left hemisphere containing an enlarged lateral ventricle, periventricular heterotopic gray, excessive white matter, abnormal white matter signal, and gyral irregularity suggestive of polymicrogyria, all characteristic of hemimegalencephaly. MRI, magnetic resonance imaging

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.[45] Macroscopically, one hemisphere is enlarged and there is usually cortical dysgenesis, white-matter hypertrophy, and a dilated and dysmorphic lateral ventricle. The majority of the cerebral hemisphere is affected, with no clear predilection for right or left hemisphere.[46] 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.[47-49]

The clinical triad of HMEG is typically: (i) intractable partial seizures from the neonatal period or early infancy, (ii) hemiparesis, and (iii) developmental delay.[50] Although

the seizures are partial in origin, children may present with tonic seizures, or infantile spasms and the electroclinical features of Ohtahara syndrome[51] 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.[52,53] Seizures are usually resistant to medical therapy and control may only be achieved by surgery such as anatomical or functional hemispherectomy.[53-55]

HMEG has been seen in association with both neurocutaneous and overgrowth syndromes. Neurocutaneous associations include the linear nevus sebaceous syndrome,[56] hypomelanosis of Ito,[57] tuberous sclerosis,[11] and neurofibromatosis.[58] Approximately 50% of cases of linear nevus sebaceous syndrome have associated HMEG.[59] 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.[37,46] The ipsilateral ventricle is usually enlarged and dysmorphic, often with extension of the posterior horn of the lateral ventricle across the midline.[46,60,61] There may be enlargement of the ipsilateral cerebellar hemisphere and brain stem, an appearance which has been named "total hemimegalencephaly." [62] The typical imaging features of HMEG are shown in *Figure 3*.

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.[63] L1CAM is known to be involved in regulation of neuroblast migration and axonal development.

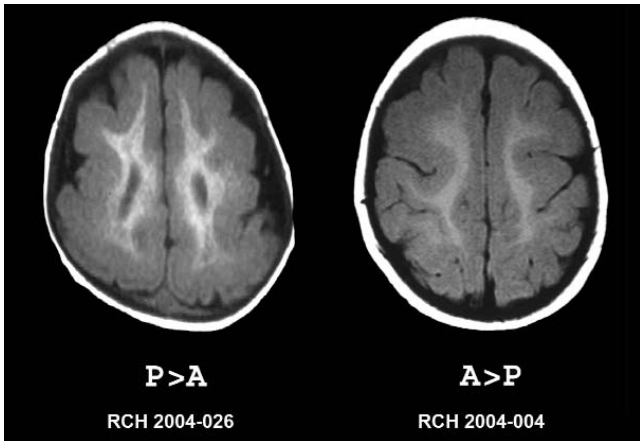

Figure 4. Imaging features of classical lissencephaly contrasting the P>A gradient with the A>P gradient. Axial T1-weighted MRI scans. The image on the left shows near-complete agyria posteriorly transitioning to pachygyria anteriorly. This is the P>A gradient consistent with a mutation of the *LIS1* gene. The image on the right shows severe pachygyria anteriorly transitioning to mild pachygyria posteriorly. This is the A>P gradient consistent with a mutation of the DCX gene. MRI, magnetic resonance imaging

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.[64] Classical LIS is a different malformation to cob-

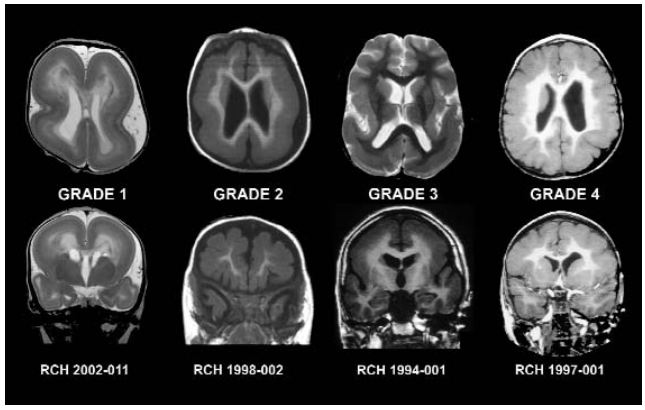

Figure 5. Imaging features of classical lissencephaly showing the four severity grades. All images are T1- or T2-weighted MRI scans. The top row shows axial scans and the bottom row coronal scans. Grade 1 is near complete agyria, grade 2 is posterior agyria and rudimentary shallow gyri anteriorly, grade 3 is posterior agyria and anterior pachygyria, and grade 4 is generalized pachygyria. MRI, magnetic resonance imaging

blestone LIS (or cobblestone dysplasia), previously referred to as "type II LIS." [64] 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 and Rolandic fissures and failure of opercularization of the insular areas.[65] 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.[65-67] 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.[68] 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,[69] and LIS associated with agenesis of the corpus callosum and *ARX* mutations.[70] The pathological findings in these rarer forms of LIS may be somewhat different to those described above.[68]

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.[71-75] 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.[76] 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.[77] 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.[75] Several different patterns of LIS are recognized using MRI, which led to development of a detailed grading system[78,79] 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*.[80] 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.[78,81] The six known genes associated with causation of LIS are *LIS1*,[82] *DCX*,[83] *ARX*,[70] *RELN*,[69] *YWHAE*,[76] and *TUBA1A*.[84] 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.[85] Mutations in the *LIS1* gene are the most common cause of LIS.[81] 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[87] or subcortical laminar heterotopia.[88] 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.[65] 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.[89] 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.[89,90] There are usually no associated brain anomalies or other congenital malformations, although occasionally the SBH can merge anteriorly with pachygyric cortex which has been described as a "pachy-band."[79] Microscopic examination of SBH shows the band to consist of a superficial zone of disorganized neurons, an intermediate zone of small neurons with some columnar organization and a deeper zone where the heterotopia may break into nodules. The overlying cortex has a normal histological appearance.[65] All forms of SBH are thought to be a defect of neuroblast migration with neurons that fail to migrate completely forming the heterotopic band.[91]

Patients with SBH will usually have mild-to-moderate intellectual disability and a mixed seizure disorder with onset at any age, but occasionally delayed until the second or third decade.[87,92,93] The spectrum of epilepsy and intellectual disability is wide with severity roughly correlating with the thickness of the heterotopic band.[92] Typical SBH shows a striking skewing of sex ratio to females,[87,91] although the malformation has rarely been reported in males as well.[94-97] Occasional patients with mild partial forms of SBH may appear asymptomatic.[90] Patients with SBH usually have no dysmorphic features or other congenital anomalies.

SBH is rarely recognized using CT scanning and when seen may be mistaken for lissencephaly, and partial forms may be difficult to appreciate, even using MRI. MRI will show a four-layered cerebral parenchyma composed of (from ventricle to cortex); (i) normal periventricular white matter; (ii) layer of heterotopic gray matter; (iii) thin layer of subcortical white matter; and (iv) normal cortical gray matter,[92] as shown in *Figure 6*.

Mutations in two genes have been identified as causing SBH; the *DCX* gene and the *LIS1* gene. The vast majority of both sporadic and familial cases of the most common form of SBH (bilateral, symmetric, and with a frontal predominance) are due to mutations of *DCX*.[89,98] As *DCX* is carried on the X chromosome males with mutations in *DCX* will usually have classical lissencephaly whereas females will have SBH. It is assumed that females with SBH secondary to *DCX* mutations have two populations of neurons; those with the mutant gene inactive that migrate normally and form the cortex, and those with the normal gene inactivated that migrate abnormally and form the heterotopic band. Carriers of mild *DCX* mutations may show no evidence of SBH on MRI, but may have intellectual disability or epilepsy.[99] A few cases of posterior SBH have been found to be due to somatic mutations of the *LIS1* gene.[100] SBH has also been reported in association with trisomy 9p[101] and in a family without mutations of either the *DCX* or *LIS1* genes,[102] suggesting that mutations in other genes may also result in SBH phenotypes.

Periventricular nodular heterotopia

Heterotopia are defined as groups of cells found in an inappropriate location in the correct tissue of origin. Nodular gray matter heterotopia are relatively common in the brain, most often found in the periventricular or subcortical white matter, suggesting a failure of migration of neurons normally destined for the cerebral cortex. They are thus correctly defined as MCDs. Heterotopia may occur in isolation, in association with other developmental anomalies of the brain or as part of a multiple congen-

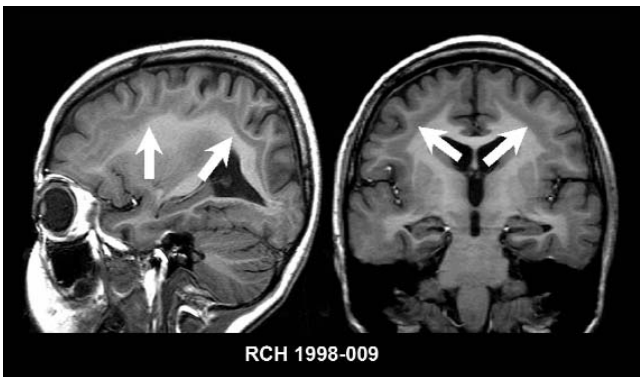

Figure 6. Imaging features of subcortical band heterotopia. Sagittal (left) and coronal (right) T1-weighted MRIs showing typical features of subcortical band heterotopia with bilateral, symmetric band of tissue with identical signal to cortical gray matter interspersed in the subcortical white matter between the normal cortex and the lateral ventricle. MRI, magnetic resonance imaging

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.[103]

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.[104] Studies using depth electrodes in patients with PNH and epilepsy have shown the nodules to be intrinsically epileptogenic[105] and temporal lobe surgery for patients with PNH and associated hippocampal sclerosis has generally been unsuccessful.[106] 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.[107] 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.[24] Unilateral or focal PNH may occur in combination with subcortical nodular heterotopia (SNH) or in association with other MCDs such as PMG.[3,108,109] 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.

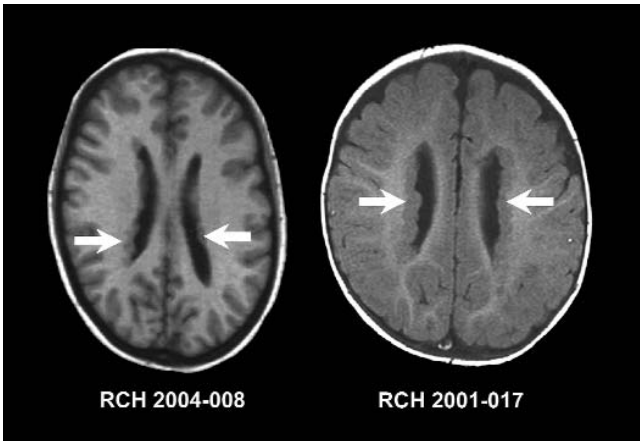

Figure 7. Imaging features of periventricular nodular heterotopia. Axial T1-weighted MRI showing two patients with bilateral periventricular nodular heterotopia. manifest by nodules of tissue with identical signal to cortical gray matter located in the periventricular region (arrows). The image on the 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

Mutations in the *FLNA* gene were identified in families with multiple affected members with bilateral periventricular nodular heterotopia.[110] *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,[111] 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.[110] Although approximately 80% of familial cases of PNH have *FLNA* mutations, mutations have been detected in only approximately 20% of sporadic PNH patients.[112] Those with mutations usually have a typical bilateral PNH pattern,[113] with most patients with atypical PNH not having *FLNA* mutations.[112,114] 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.[115]

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 porencephalic 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.[65] 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]

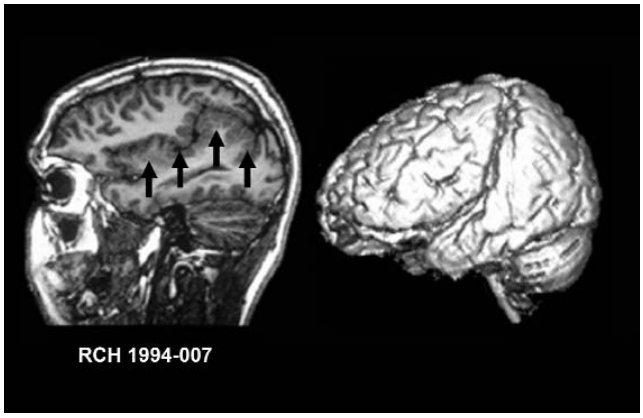

Figure 8. MRI features of polymicrogyria. T1-weighted parasagittal image (left) of a patient with perisylvian polymicrogyria (PMG) showing an abnormally extended Sylvian fissure surrounded by overfolded gray matter with an irregular surface and stippling of the gray-white junction (arrows). The image on the right is a 3D surface reconstruction of another patient with perisylvian PMG highlighting the abnormal extension and orientation of the Sylvian fissure. MRI, magnetic resonance imaging

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.[121] 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.[131] 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%,[121,122,132] although seizure onset may not occur until the second decade, however usually between the ages of 4 and 12.[133] Seizure types include atypical absence (62%), atonic and tonic drop attacks (73%), generalized tonic-clonic (35%) and partial (26%).[133] 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[122,133,134] 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.[133] Seizures may be daily and intractable in at least 50% of patients.[133]

Using CT and low field strength MRI, PMG is difficult to discern and may only appear as thickened cortex.[135-138] 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.[139] 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.[140] Diffusely abnormal white matter signal should raise the question of an in utero infection (such as cytomegalovirus [CMV]) or a peroxisomal disorder.[141-143] 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.[140] 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.[141,144-146] 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.[143,147,148] Zellweger syndrome has been found to be due to mutations in the *PEX* family of genes.[149,150] 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.[151] All modes of inheritance have been suggested although an X-linked inheritance pattern appears most frequent.[152] The gene for bilateral frontoparietal PMG has been identified as *GPR56*, yet the function of this gene in cortical development is unclear.[153] 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.[154,155] Mutations in the gene *SRPX2* have been found in one family with BPP,[156] 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.[157]

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."[158,159] 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[158]"). Clefts are frontal or parietal in approximately 65%, and temporal or occipital in approximately 35%.[160] 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.[161] 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 closed-lipped SCZ typically present with hemiparesis or motor delay whereas patients with open-lipped SCZ typically present with hydrocephalus or seizures.[162] 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.[162,163] Outcome is worst for those with bilateral open-lipped SCZ and best for those with unilateral closed-lip SCZ.[162,164] 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.[162,165] An interesting finding is that some patients with SCZ have relatively minor clinical problems relative to the appearance of their malformation.[166-169]

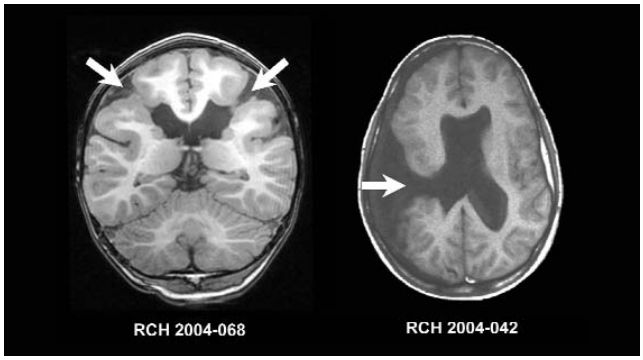

Figure 9. Imaging features of schizencephaly. Coronal T1- (left) and axial T1 (right)-weighted MRI scans. Both images show full-thickness clefts lined by irregular gray matter (arrows). The image on the left shows bilateral closed-lip schizencephaly (SCZ) and the image on the right shows right open-lipped SCZ and agenesis of the septum pellucidum. MRI, magnetic resonance imaging

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.[136,170]

The etiology of SCZ remains highly controversial, and there are likely both genetic and non-genetic causes. In SCZ, there is definite evidence for nongenetic causes such as congenital CMV infection[144,171] and in utero ischemic insults.[172] There is also now ample evidence supportive of a genetic etiology for some cases of SCZ, including reports of a number of familial cases.[173-175] A few patients with both familial and nonfamilial SCZ were found to have mutations in the homeobox gene *EMX2*.[176,177] Unfortunately, other researchers have failed to reproduce these results, raising the question as to the true role of *EMX2* in SCZ.[174]

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 anticonvulsant 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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Malformaciones del desarrollo cortical y epilepsia

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 representativas de resonancia nuclear magnética para cada una de ellas. Se presentan las malformaciones de la esclerosis tuberosa, displasia cortical focal, hemimegalencefalia, lisencefalia clásica, heterotopia subcortical en banda, heterotopia nodular periventricular, polimicrogiria y esquizencefalia.

Malformations du développement cortical et épilepsie

Les malformations du développement cortical (MDC) sont des anomalies macroscopiques ou microscopiques du cortex cérébral qui surviennent comme conséquence d'une interruption des étapes normales de formation de la lame corticale. Le cortex humain développe ses structures de base pendant les deux premiers trimestres de la grossesse, par le biais d'une série d'étapes chevauchantes, commençant par la prolifération et la différenciation des neurones qui migrent ensuite avant de s'organiser finalement dans le cortex en développement. Les anomalies survenant à chacune de ces étapes, qu'elles soient d'origine environnementale ou génétique, peuvent interrompre le circuit neuronal et prédisposer à des conséquences cliniques variées, la plus fréquente étant les crises épileptiques. Un grand nombre de MDC ont été décrites à ce jour, chacune avec ses caractéristiques pathologiques, cliniques et d'imagerie propres. Les causes de la plupart de ces MDC ont été déterminées en étudiant les sujets atteints, et de nombreuses MDC seraient secondaires des mutations affectant des gènes du développement cortical. Cet article mettra en évidence les malformations corticales humaines les plus connues associées à l'épilepsie. Les caractéristiques pathologiques, cliniques, d'imagerie et étiologiques de chaque MDC seront résumées, des images d'IRM (imagerie par résonance magnétique) illustrant chacune d'entre elles. Les malformations telles la sclérose tubéreuse de Bourneville, la dysplasie corticale focale, l'hémiencéphalomégalie, la lissencéphalie classique, l'hétérotopie en bandes sous-corticale, l'hétérotopie nodulaire périventriculaire, la polymicrogyrie et la schizencéphalie seront présentées.

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