Disorders of Cortical Development and Epilepsy

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There has been an impressive increase in our ability to identify and categorize patients with cortical development lesions over the past decade. The clinical features associated with disorders of cortical development (DCD) have been described, and epilepsy has been shown to be a frequent symptom. In this review, we categorize DCD based on their structure and discuss their underlying causes and clinical features. Just as the cause of each type of disorder is thought to be unique, each disorder also has distinct types of seizures, treatment strategies, and electroencephalographic features. Studies in human tissue and animal models of DCD have begun to shed light on why DCD are associated with epilepsy. Aberrant synaptic connections within the dysplastic tissue and between the dysplastic tissue and more normal-appearing adjacent tissue form an abnormal, hyperexcitable network that increases seizure susceptibility. In the future, strategies for blocking formation of the aberrant networks may prevent the development of epilepsy.

The past decade has brought increased recognition that abnormal development of the central nervous system produces malformations that are frequently associated with refractory epilepsy. Through the use of high-resolution magnetic resonance imaging (MRI), disorders of neuronal migration, cell survival, and differentiation can be diagnosed in patients with epilepsy. According to MRI, 12% of adults with refractory epilepsy also have disorders of cortical development (DCD). The true incidence is probably higher because MRI fails to detect some DCD that are present on pathological inspection. Seizures are the most common clinical feature of DCD, and they occur in 75% of children with DCD as diagnosed using MRI. This review will highlight recent advances in understanding the causes of DCD, explain how DCD contribute to the formation of epilepsy, and present current treatment strategies and possible future options.

To better understand DCD it is necessary to briefly discuss normal brain development. The neocortex is derived from a plate of rapidly dividing cells that line the ventricle wall. The newly born cells migrate away from the ventricular region toward the pial surface. Each neuronal precursor, depending on its date of birth, migrates a set distance and develops a specific neuronal phenotype appropriate to its final location. One recent discovery of particular relevance to epilepsy is that many or potentially all inhibitory γ-aminobutyric acid–expressing interneurons are derived from the ganglionic eminence and migrate along a tangential path to populate the neocortex. This carefully orchestrated migration produces the highly structured, 6-layered neocortex. Once an immature neuron arrives at its final location, it establishes a specific set of connections by extending an axon and dendrites. Disruption of neuronal development at each stage will potentially produce unique clinical phenotypes. In this review, we describe 4 types of DCD that are often associated with epilepsy.

LISSENCEPHALY, AGYRIA, AND PACHYGYRIA

Lissencephaly is a severe type of DCD. On gross inspection, the brain appears smooth because of a paucity of gyri and sulci. Lissencephaly comprises a spectrum of cortical structural abnormalities with subdi-
visions based on histopathological criteria, extent of lesion, and syndromic features. In lissencephaly type 1, the neocortex deviates from the normal 6 layers, most often having only 4 poorly organized layers. In lissencephaly type 2, the cortex is unlayered, with a cobblestone surface and thickened meninges. The extent of cortical involvement varies from agyria, with a smooth cortex and no sulci, to pachgyria, with focal areas of abnormally thickened and widened gyri surrounded by regions of cortex with a more normal appearance. The terms lissencephaly, agyria, and pachgyria are sometimes used interchangeably because of a lack of agreed-on criteria for distinguishing among these abnormalities.

Clinically, the lissencephalies are a heterogeneous group of disorders; Miller-Dieker syndrome (MDS) is the best-recognized syndrome associated with lissencephaly type 1. There are variable clinical features in MDS, including dysmorphic facies and heart and kidney abnormalities, and lissencephaly as a constant feature. It is best understood as a contiguous gene deletion syndrome on the short arm of chromosome 17. The primary gene responsible for MDS, LIS1, was identified in 1993. Mutations and deletions of LIS1 have been identified in isolated lissencephaly and as a part of larger deletions associated with the more extensive features of MDS. In addition to MDS, X-linked and other familial forms of lissencephaly have been identified (Table). To date, in addition to the LIS1 gene, the molecular bases for one X-linked and one autosomal recessive form of lissencephaly (doublecortin [DCX] and reelin [RELN] genes, respectively) have been characterized. Walker-Warburg syndrome includes hydrocephalus, retinal dysplasia, muscle disease, and lissencephaly type 2. Walker-Warburg syndrome and its related disorders, muscle-eye-brain disease and Fukuyama type congenital muscular dystrophy, all appear to be related to mutations in the fukutin (FCMD) gene.

All forms of lissencephaly share several clinical features, including mental retardation, motor delays, axial hypotonia, and seizures. The seizures tend to start in the first months of life, with infantile spasms, large myoclonic jerks, and tonic seizures being the most common types. There are reports of pachgyria associated with adult-onset complex partial seizures that do not appear to be inherited. An electroencephalogram (EEG) with persistent, rhythmic fast-frequency discharges of very high amplitude (>100 µV) is characteristic of lissencephaly. In the first years of life, the frequencies increase from Δ and θ range to predominantly α and β. The electrophysiologic bases of the high-frequency discharges and seizures are poorly understood but should be aided by the recent development of animal models deficient in lissencephaly-related genes.

**HETEROTOPIAS**

Heterotopias are clusters of neurons and glia that form a nodule of gray matter in an inappropriate location. They may be single or multiple and may be found lining the ventricles, in the deep white matter, in the subcortical white matter, or in the leptomeninges. The overlying cerebral cortex can be normal or show a disruption of cortical layers or cellular organization. The genetic bases for several familial forms of heterotopias have been identified. Mutations in the DCX gene produce lissencephaly in men and subcortical band heterotopia (previously called double cortex) in women. DCX has a novel sequence and appears to stabilize microtubules. The genetic basis for X-linked periventricular nodular heterotopia seen in women is now known to result from mutations in filamin-1 (FLN1). The mechanism involved in the formation of the heterotopias remains uncertain, but it may be related to FLN1’s actin-binding domains. Thus, the pathogenesis for both familial forms of heterotopia appears to be related to abnormalities of the cytoskeleton. Single or unilateral heterotopias have been associated with several metabolic diseases (Table), although most cases of heterotopia appear to be sporadic.

Heterotopias are frequently associated with refractory epilepsy, normal findings on neurologic examination, and normal intelligence. The mean age of epilepsy onset is late childhood to early adolescence. Complex partial seizures are the most common type, with generalized tonic-clonic seizures, simple partial seizures, and infantile spasms being less common. On an EEG, the epileptiform discharges are unilateral or bilateral depending on the location of the heterotopias. The seizures are often refractory to medication and surgery unless most heterotopias can be resected. On surface and intracranial EEGs, the temporal lobe appears involved in the initiation or early propagation of seizures in some patients with nodular heterotopias. Isolated temporal lobectomies did not produce seizure freedom even when hippocampal sclerosis was also present. Using tract-tracing techniques, there appear to be neuronal connections among different heterotopias and among the heterotopias and more normal-appearing adjacent cortex. This network of connections may explain why it is difficult to localize seizure onset.

Two animal models of heterotopia, the methylazoxymethanol acetate teratogenic model and the tish rat, have been useful in studying how heterotopias produce epilepsy. Exposing pregnant rats to the alkylating agent methylazoxymethanol acetate produces heterotopias by inhibiting cell division and migration in the developing cortex. The animals have cognitive problems as well as a lowered seizure threshold. There appear to be orthodromic and antidromic neuronal connections between the heterotopia and the surrounding neocortex and hippocampus. The heterotopia and the surrounding cortex have altered excitatory and inhibitory neurotransmitter receptor subunits, an increase in intrinsically bursting neurons, and prolonged depolarization potentials. The tish rat is a spontaneous mutant with clinical seizures. Its morphologic characteristics are most similar to those of humans with subcortical band heterotopia. There is a subcortical ribbon of heterotopic gray matter separated by a myelinated axon tract from a more normal-appearing cortex, as well as functional synaptic connections between the heterotopia and the overlying cortex that traverse the white matter. Surprisingly, when these connections are severed, it is the overlying cortex that appears to have a lower seizure threshold. In both the methylazoxymethanol acetate and tish models, there are
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**Abnormalities**
- Smooth brain lacking gyri and sulci
- Misplaced collection of neurons and glia
- Multiple thin small gyri
- Normal, thickened cortex with loss of the gray-white matter junction (varies)

**Gross**
- Smooth brain lacking gyri and sulci
- Misplaced collection of neurons and glia
- Multiple thin small gyri
- Normal, thickened cortex with loss of the gray-white matter junction (varies)

**Microscopic**
- Poorly organized, 4-layered cortex
- Normal cells
- Loss of layer V pyramidal cells
- Loss of cortical layers

**Etiology**
- AD, AR, and XD, with 4 genes identified in which mutations interfere with cell migration
- XD, with 2 genes identified in which mutations interfere with cell migration
- CMV infection
- Metabolic disease
- Bilateral or unilateral familial

**Clinical symptoms**
- Motor delay with axial hypotonia
- Mental retardation
- Seizures
- Seizures
- Isolated

**Seizure types**
- IS
- MC
- Tonic
- CPS
- GTC
- SP
- IS
- Absence

**EEG results**
- High amplitude, generalized fast activity
- Unilateral or bilateral sharps or spikes
- Frequent temporal discharges

*AD indicates autosomal dominant; AR, autosomal recessive; XD, X-linked dominant; CMV, cytomegalovirus; IS, infantile spasms; MC, myoclonic seizures; CPS, complex partial seizures; GTC, generalized tonic-clonic seizures; SP, simple partial seizures; and EEG, electroencephalogram.

Electrical connections between the heterotopia and surrounding cortex. In addition, the surrounding cortex has independent physiological abnormalities, suggesting that it may be involved in the initiation of seizures.

**POLYMICROGYRIA**

Polymicrogyria, as the name suggests, is composed of many abnormally small gyri. Histologically, the gyri have a decreased number of neurons, with the neuronal loss most pronounced in the middle cortical layers, especially layer V, although marked variability among cases is typical. The presence of normal-appearing neuronal layers on either side of layer V suggests that migration is grossly intact. The cause of most cases of polymicrogyria is thought to be an intrauterine insult such as hypoxia-ischemia, fetal demise of a twin, or cytomegalovirus infection (Table).26

In a few cases of polymicrogyria, a maternal respiratory or cardiac arrest occurred during the early part of the second trimester just as neuronal migration was finishing.27 There are numerous reports of sporadic and familial cases of polymicrogyria that include unilateral, bilateral, perisylvian, parieto-occipital, and diffuse types. The existence of familial cases suggests a genetic cause, though to our knowledge, no genes have yet been identified.28 Clinically, seizures, mental retardation, and some evidence of upper motor neuron dysfunction such as weakness or spasticity corresponding to the polymicrogyric cortex may be present.29

Polymicrogyria may be involved in the initiation of seizures.29,30 The presence of normal-appearing neuronal layers on either side of layer V suggests that migration is grossly intact. The cause of most cases of polymicrogyria is thought to be an intrauterine insult such as hypoxia-ischemia, fetal demise of a twin, or cytomegalovirus infection.26 Several seizure types have been associated with polymicrogyria, including infantile spasms and complex partial, hemimyoclonic, and myoclonic seizures. The onset of epilepsy occurs during a wide range of ages from childhood to middle age. The EEG tends to demonstrate sharp waves and slowing across a relatively broad area that includes the polymicrogyria.

In the freeze lesion model of polymicrogyria, a rat pup has a small region of cortex supercooled. If this is performed around the time of birth, the supercooled area will become an abnormal 4-layered cortex. Although there are no spontaneous seizures, slices of the cortex are hyperexcitable.30 There appears to be an excessive ingrowth of axons with synapse formation in the area surrounding the lesion.31 The axons that would normally form synapses within the lesion instead innervate the surrounding cortex. A lowered seizure threshold, as measured by prolonged depolarizations, is not within the lesion but in the adjacent normal-appearing cortex.30 There is an increased ratio of excitatory to inhibitory postsynaptic potentials in the area surrounding the lesion. Similar to the tish and methylazoxymethanol acetate models, abnormal synaptic connections formed in the normal-appearing cortex adjacent to the freeze lesion may be involved in the initiation of seizures.

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CORTICAL DYSPLASIA

The original description of cortical dysplasia was based on 10 patients who had resective surgery for refractory epilepsy.32 On histologic evaluation there was loss of the gray-white matter junction due to increased neurons in the white matter, loss of lamination, and giant abnormal cells with poorly organized processes. The cause of cortical dysplasia is unknown and likely variable. The size of the dysplasia varies from small microscopic lesions to hemimegalencephaly, where an entire hemisphere is grossly dysplastic. The loss of lamination and increased neurons in the white matter suggest that a defect in migration may underlie some cases. The large abnormal-appearing cells may express immature neuronal markers or a mixture of neuronal and glial markers, suggesting that an abnormality in cellular differentiation may be involved.33 On MRI, common features include loss of the gray-white matter junction and nonenhancing signal changes.

Clinically, focal epilepsy, with an onset in childhood or adolescence, and some mental deficiencies are the most common symptoms of cortical dysplasia34 (Table). Cortical dysplasia has been extensively studied in humans because 50% of children and up to 18% of adults undergoing surgery for refractory epilepsy have cortical dysplasia present on histologic examinations.35,36 Surface and intracranial EEGs have identified focal rhythmic sharp-wave discharges, lasting from several seconds to almost continuously, as characteristics of cortical dysplasia.37 While there usually is overlap between an MRI-identified dysplasia and the EEG abnormality, there often are extensive electrographic abnormalities outside the area of a visible lesion.

The increasing use of surgical resection for the treatment of cortical dysplasia provides epileptic tissue for histologic, molecular biological, and electrophysiologic examination. Numerous abnormalities have been described in dysplastic tissue. There is an overall decrease in some types of γ-aminobutyric acid–inhibitory neurons and increases in certain subtypes of the glutamate N-methyl-D-aspartate (NMDA) receptors,2,38,39 which suggests a loss of inhibition and a shift in the pattern of excitation. Electrophysiologic examinations, performed on epileptic human brain slices, found a large network of neurons undergoing prolonged repetitive depolarization.40 Blocking the excitatory NMDA and non-NMDA glutamate receptors prevented depolarization. Similarly, blockade of the inhibitory γ-aminobutyric acid receptors augmented depolarization. Further refinement of this technique should facilitate the identification of receptor subtypes and the involved cell types.

TREATMENT STRATEGIES

The DCD are often refractory to medical treatment, including polypharmacy. Now that specific expression patterns of certain excitatory neurotransmitter receptor subunits have been found in some DCD, a more specific pharmaceutical approach to DCD-related epilepsy should be possible. Currently, the best treatment option for seizure freedom is a tailored surgical resection. A good surgical outcome, up to 60% seizure freedom, depends on careful mapping and removal of all areas with epileptiform discharges.41 There appears to be an extensive electrical network among the DCD, adjacent, and even distant cortical structures. Leaving portions of the network intact may explain why half of patients continue to have seizures after surgery.

Although the DCD are present at birth, most patients do not develop seizures until years later. This provides a window of time in which the formation of epilepsy might be blocked. Hopefully, we should soon have a better understanding of the molecular and cellular changes that DCD undergo leading to the formation of epilepsy. This knowledge may allow a scientifically based therapeutic trial for the prevention of epilepsy by focusing on blocking the formation of an epileptiform network. One possible strategy is to block aberrant connections between the DCD and the surrounding cortex. Already, a long list of cytokines and growth factors appear to be altered by seizures and/or block seizures in animal models of epilepsy and might be candidates for an epilepsy prevention trial.42 Alternatively, increasing the number of inhibitory synaptic connections within the DCD and between the DCD and the normal cortex might be possible as molecular cues for inhibitory synapse formation are identified.6 Treatment strategies for DCD-related epilepsies should blossom during the next decade as our understanding of their pathophysiologic characteristics increases.

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