Approximately one third of all children with seizure disorders are not controlled with standard antiepileptic therapy. A high proportion of these intractable cases are associated with lesions acquired prenatally. Indeed, developmental lesions account for about 85% of the preadolescent surgical caseload for epilepsy. This article will review the most common types of developmental lesions associated with epilepsy and discuss how clinical and epileptogenic features of these lesions may relate to treatment outcomes.

**Definitions of Cortical Dysplasia**

During the midgestation neurologic development of primates, populations of neuroblasts from the subventricular zone migrate outward guided by the process of radial glial cells to take up positions in what is destined to become the cerebral cortex. This migration and the subsequent accretion of the cortex’s neuronal layers is a highly time-sensitive—and vulnerable—process.

Any missteps in this carefully orchestrated developmental sequence can produce a host of cortical malformations. Some of the most obvious morphologic or histocytochemical abnormalities include dyslamination, cytoskeletomegaly, disordered apical dendrites, excessive dendritic branching, abnormal neurofilamentous material, hypertrophic rough endoplasmic reticulum, excessive mitochondria, and intranuclear inclusions of cytoplasm. Cells endowed with such aberrant features, especially neurons with a high degree of synaptic conductivity and excessive mitochondrial power generation, tend to be extremely epileptogenic.

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Developmental abnormalities are now often referred to as malformations of cortical development (MCD) or, more simply, cortical malformations. Cortical dysplasia is another term commonly found in the literature along with neuronal migration disorders (a term highlighting the developmental pathophysiology described above) and microdysgenesis (a term most often applied to lesions without obvious gross structural correlates, such as microscopic cortical dysplasias, which account for many cases of cryptogenic partial epilepsies). These terms are often used interchangeably in clinical practice.
**Clinical Manifestations**

Epilepsy is not the only clinical manifestation of the MCDs. Cognitive impairments ranging from mild dysfunction to more severe cognitive delay and mental retardation are seen in a high proportion of these cases. Somatic dysmorphisms are another potential manifestation. Even a partial listing of the pediatric syndrome types associated with developmental lesions (Table 1) indicates the variety of settings in which such cases will present.

Before the first microscopic confirmation of cortical dysplasia associated with temporal lobe epilepsy, focal seizures were generally attributed to gliosis, tumors, vascular malformations, and other abnormalities visible to the naked eye. Today, 30 years after that first report, the role of cortical dysplasia in causing partial epilepsy is well established, and the clinical features of patients with cortical dysplasia are well known. In children, cortical dysplasias most often involve the extratemporal cortex and are often associated with very frequent seizures, developmental delay, and abnormalities on magnetic resonance imaging (MRI).

Medical treatment of cortical dysplasia is often ineffective. In one study of 4 different types of epilepsy associated with cortical dysplasia, more than half of all patients showed no change after antiepileptic drug (AED) treatment.4 The proportion of patients becoming permanently seizure-free was uniformly low (eg, 1 of 34, or 3%, for patients with diffuse bilateral disease and 2 of 10, or 20%, for bilateral cases).

Until the introduction of subdural recording, outcomes with surgery in cortical dysplasia have also been disappointing. Studies from the early 1990s, before the use of intracranial monitoring, reported seizure freedom in fewer than 20% of surgeries for cortical dysplasia.5 This is well below the expected success rate for surgeries for epilepsy associated with pathologies such as brain tumors or hippocampal sclerosis.

**The Root(s) of the Problem**

Difficulties in treating epilepsy associated with cortical dystrophy can be traced to a complex set of overlapping structural and functional features related to these developmental abnormalities.

**Widespread Structural Disturbances**

In recent years, cortical dysplasias have been shown to involve more widespread and patchy portions of the cortex than indicated by routine electroencephalogram (EEG) or imaging studies. In many patients with focal cortical dysplasia or hippocampal sclerosis, for example, MRIs reveal widespread and extensive anatomic abnormalities beyond the visually identified focal epileptogenic region.6 Similarly diffuse structural disorganization is found in cases involving the syndromes of gelastic epilepsy and hypothalamic hamartomas,6 early infantile epileptic encephalopathy,7 and periventricular leukomalacia.8 These abnormalities are rarely detected with routine EEGs or imaging studies, and they have been uniformly resistant to surgical cure.

**Extreme Epileptogenesis**

A second property of cortical dysplastic lesions is their extreme epileptogenesis. Cultured neurons from patients with cortical dysplasia typically show high rates of repetitive firing and extreme bursts of high-frequency epileptogenic activity compared to cells from other

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**Table 1. Syndromes Associated with Cortical Dysplasias**

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<tr>
<th>Syndrome</th>
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<tr>
<td>Lissencephalic</td>
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<tr>
<td>Miller-Dieker Syndrome</td>
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<tr>
<td>Walker-Warburg Syndrome</td>
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<tr>
<td>Fukuyama syndrome</td>
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<tr>
<td>Myotonic dystrophy</td>
</tr>
<tr>
<td>Metabolic</td>
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<tr>
<td>Zellweger syndrome</td>
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<td>Menkes’ syndrome</td>
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<tr>
<td>Neonatal adrenoleukodys trophy</td>
</tr>
<tr>
<td>Neurocutaneous</td>
</tr>
<tr>
<td>Tuberous sclerosis complex</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
</tr>
<tr>
<td>Hypermelanosis of ftc</td>
</tr>
<tr>
<td>Incontinentia pigmenti</td>
</tr>
<tr>
<td>Epidermal nevus syndrome</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Aicardi’s syndrome</td>
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<tr>
<td>Angelman’s syndrome</td>
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<tr>
<td>Smith-Lemli-Opitz syndrome</td>
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<tr>
<td>Noonan’s syndrome</td>
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<tr>
<td>Waardenburg’s syndrome</td>
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<td>Ehlers-Danlos syndrome</td>
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patients with temporal lobe epilepsy that is not associated with cortical dysplasia (Figure 1). The extreme excitability of these cells may be caused by decreased numbers of inhibitory neurons or excesses of excitatory neurons, both of which have been confirmed in immunocytochemical studies. Clinically, EEG recordings and placement of depth electrodes confirm the characteristic repetitive epileptiform discharges in dysplastic lesions.

**ABERRANT PROPAGATION**

Complex patterns of epilepsy propagation are another extraordinary feature of developmental lesions. These lesions have the propensity to create epileptic discharges in unpredictable and non-contiguous sites within the brain, which further explains the difficulty in developing a curative surgical plan for these patients. The skipping propagation patterns may involve aberrant circuitry through tangential migration, but the underlying mechanism is not well understood. These lesions are also capable of activation patterns, which is seen when one area of the EEG continues to discharge after the primary focus has stopped (Figure 2).

**ABNORMAL CORTICAL ORGANIZATION**

In some patients with cortical dystrophy, subtle abnormalities in functioning may also be present. These organizational problems are often difficult to confirm, especially if they involve the language cortex, but cases of atypical motor homunculi and aberrant sensorimotor organization have been reported.

**SUBCORTICAL EPILEPTOGENICITY**

To further complicate matters, evidence of epileptic discharges originating from subcortical sites has now been discovered in patients with cortical dysplasias. Nodular heterotopia was the first to be confirmed, but studies involving depth electrode and imaging techniques such as single photon emission computed tomography (SPECT) have now documented other epileptogenic zones beneath the cortex, including hypoxic/hamartastic hamartoma, double cortex, and cerebellar ganglioglioma. Congenital tumors of the cerebellum, in fact, probably account for virtually all cases of hemifacial spasms in infants.
IMPROVING THERAPY

The increasing quality and frequency of communication between neurologists and radiologists is rapidly improving the diagnostic evaluation of these subtle developmental lesions. Refinements in multimodal imaging now often allow documentation of lesions with a level of detail and targeting that richly complements information from the neurologic examination. As the case is worked up, one examination provides information for another; for example, from EEG and video, to MRI, to petricial SPECT, to surgery, and then to postsurgical MRI. Such interchanges between neurologists and imaging specialists probably accounts for much of the previous decade’s progress in managing these notoriously difficult-to-treat malformations.

Combined with these new diagnostic capabilities, the emerging understanding of cortical malformations as widespread, and possibly even remote or subcortical, lesions has led to improved surgical outcomes. Use of subdural electrodes has provided another major boost to the success of surgery for children with cortical dysplasia. Although still far from optimal, surgical outcomes from pediatric centers with access to subdural electrodes has significantly improved over those without invasive monitoring (Table 2).20-22 Overall, about half of the children with cortical dysplasia who undergo the surgery become seizure-free after surgery. The key predictor of outcome in these surgeries is the completeness of the resection. One recent retrospective study evaluating pre- and perioperative variables in 75 children with medically intractable partial epilepsy found that completeness of resection was the only significant predictor of outcome, with 92% of patients with complete resection achieving good outcomes (class 1 or 2) versus 50% of patients with incomplete resections ($P < 0.001$).22 Overall, 59% of the children were seizure-free after surgery. In this analysis, completeness was defined by parameters such as whether the resection included the entire gross anatomic abnormality or the entire epileptogenic zone, including the region of epileptogenic onset and areas with significant interictal abnormalities (e.g., active spiking, frequent intermittent fast activity, and electrodecremental response).

Complete resection of structural abnormalities and epileptogenic zones are often limited by the proximity of the dysplastic tissue to eloquent cortex. Because developmental lesions by their very nature tend to be dispersed through the brain and only randomly apparent on EEG, even aggressive surgical strategies will often be suboptimal compared to surgery for the more discrete abnormalities of nondevelopmental etiology.

More complete excision of these dispersed cortical dysplasias will depend on fundamental advances in characterization of their functional and anatomic extent. Clinical studies correlating these attributes to surgical outcomes will help guide selection of both surgical candidate and surgical technique. Eventually, the new experimental models of developmental lesions may also serve as a testing ground for development of more targeted and rational pharmacological therapies.

The cortical dysplasias are notoriously and intrinsically heterogeneous in origin, pathophysiology, and presentation. Treatment, to be successful, will require a similarly varied and individualized approach.

QUESTIONS & ANSWERS

What is a proper sequence of imaging studies in the child with a developmental lesion?

Dr. Duchowny: In general, the whole brain can be surveyed in T1 axial and T1 sagittal images, with T2 also used for axial and coronal images. The T2-weighted and inversion recovery MRIs are often useful, and the fluid-attenuated inversion recovery is particularly helpful in outlining subtle areas of dysplasia. For temporal lobe defects, the neocortex can be surveyed carefully with thin 1- to 3-mm cuts with no gaps. The head is centered in the gantry at about 30 degrees to obtain these cuts. Also, to explore areas of potential

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Seizure-Free Patients After Surgery (%)</th>
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<tbody>
<tr>
<td>Holthausen 1997</td>
<td>31</td>
<td>29 (52%)</td>
</tr>
<tr>
<td>Wykle 1998</td>
<td>31</td>
<td>16 (52%)</td>
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<tr>
<td>Paolicchi 2000</td>
<td>42</td>
<td>22 (52%)</td>
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Table 2. Increasing Success of Surgery for Cortical Dysplasia: Results from 3 Centers with Access to Subdural Electrodes
abnormality, MRI surface coils can be focused on specific areas.

When a child with intractable seizures is referred from a primary care physician along with records including an MRI scan that was read as normal, is repeat neuroimaging worthwhile to detect occult abnormalities?

Dr Duchowny: With surgery as a possibility, repeating the MRI is always a good idea. In our center, we find a significant number of abnormal MRIs in patients with normal MRIs in the record. Community hospitals are looking for a wide variety of disorders when they take an MRI, so a lot can be gained from ordering the epilepsy-specific MRI sequences.

Have you ever had an epilepsy patient with an initially normal MRI who subsequently developed an abnormal MRI?

Dr Duchowny: Yes, we had one patient recently who presented with epilepsy and had a normal MRI. Two months later, the MRI showed a highly malignant glioma and the patient died. This was unusual, though. If an MRI is normal, it generally stays normal. On the other hand, we usually don't find epilepsy-related tumors in patients who do not have epilepsy.

What are we learning from our surgical failures in cortical dysplasia?

Dr Duchowny: One important lesson learned is to operate on intraictally active areas. Not targeting these areas that “pick up the torch” from the primary seizure focus has led to many patients having postsurgical seizure recurrence. Many of our current failures, however, are hard to explain. I suspect many are due to missed areas of epileptogenicity in the area near the resection rather than in remote areas. We simply do not see it in our initial evaluation because it is not there. In adult temporal lobectomy failures, some failures may be explained by dual pathology and extratemporal symptomatology; certain patients, for example, begin with an orbitofrontal presentation with autonomic findings and complex motor stereotypes then switch to a hippocampal symptomatology involving epigastric discomfort or oroalimentary automatisms. If the orbital frontal cortex is the only site resected, the surgery typically fails, which is why we have moved to 2-lobe resections.

Are generalized epilepsies really caused by small widely dispersed cortical dysplasias?

Dr Duchowny: This has been debated and, in fact, many cases of symptomatic generalized epilepsies are more likely based on microscopic or histologic abnormalities and rapid secondary generalization than on a primary generalized process. Cases of subcortical cortical dysplasia rarely generalize and usually involve focal or regionally lateralized propagation pathways. The idiopathic generalized epilepsies, most agree, are truly generalized.

REFERENCES