Assessment and surgical outcomes for mild type I and severe type II cortical dysplasia: A critical review and the UCLA experience

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SUMMARY
Recent findings on the clinical, electroencephalography (EEG), neuroimaging, and surgical outcomes are reviewed comparing patients with Palmini type I (mild) and type II (severe) cortical dysplasia. Resources include peer-reviewed studies on surgically treated patients and a subanalysis of the 2004 International League Against Epilepsy (ILAE) Survey of Pediatric Epilepsy Surgery. These sources were supplemented with data from University of California, Los Angeles (UCLA). Cortical dysplasia is the most frequent histopathologic substrate in children, and the second most common etiology in adult epilepsy surgery patients. Cortical dysplasia patients present with seizures at an earlier age than other surgically treated etiologies, and 33–50% have nonlocalized scalp EEG and normal magnetic resonance imaging (MRI) scans. 2-(18F)Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) is positive in 75–90% of cases. After complete resection, 80% of patients are seizure free compared with 20% with incomplete resections. Compared with type I, patients with type II cortical dysplasia present at younger ages, have higher seizure frequencies, and are extratemporal. Type I dysplasia is found more often in adult patients in the temporal lobe and is often MRI negative. These findings identify characteristics of patients with mild and severe cortical dysplasia that define surgically treated epilepsy syndromes. The authors discuss future challenges to identifying and treating medically refractory epilepsy patients with cortical dysplasia.

KEY WORDS: Review, Malformations of cortical development, Seizure, EEG, MRI, FDG-PET, SPECT, MEG-MSI, Intracranial electrodes, Hippocampal sclerosis, Glutamate, GABA, NMDA.

In 1971, David Taylor and colleagues published a seminal paper describing a brain anomaly associated with epilepsy “distinctive enough to stand on its own” (Taylor et al., 1971). The authors described the relevant histopathology as:

. . . localized disruption of the normal cortical lamination by an excess of large aberrant neurons scattered randomly through all but the first layer. The aberrant nerve cells stood out partly because of their numbers and their inappropriate size, and partly because of their bizarre structure. Mainly pyramidal in shape, they pointed in all
directions and were at times crowded together. . . . The Nissl substance, particularly that adjacent to the nucleus, tended to be unusually dense and to have a wild, tigroid appearance. . . . In seven of the 10 cases the anarchy was aggravated by the addition of malformed cells of uncertain origin with large, sometimes multiple, nuclei surrounded by an excess of opalescent, pseudopodic cytoplasm. . . . For the present, therefore, it would seem best to look on these abnormalities as a particular form of localized cortical dysplasia [emphasis added] in which anomalous populations of neurones, and often of glia, underlie the electrical and clinical manifestations of certain focal forms of epilepsy.

The authors acknowledged, in the Discussion, the histopathologic similarities between their lesions and cortical tubers in patients with tuberous sclerosis complex (TSC). However, they also recognized that their patients with cortical dysplasia did not show the typical radiographic, cutaneous, and somatic stigmata associated with TSC. They concluded the report by stating that the link between cortical dysplasia and TSC was “remote, if it exists at all.”

Most of the cases described by Taylor and colleagues would today be classified as severe cortical dysplasia. This “new” lesion was identified in 3% of their operative epilepsy cases (Taylor et al., 1971). Cortical dysplasia, therefore, was initially considered a rare malformation of cortical development associated with epilepsy. That notion has substantially changed in the last 15 years. This is illustrated in a PubMed search of peer-reviewed publications using the terms “cortical dysplasia” and “epilepsy” (Fig. 1). From 1971, after the initial study by Taylor and colleagues, to 1990 only a few papers were published. By comparison, from 1991–2007, the number of published papers on this topic has increased dramatically. This is due in part to the increased detection of cortical dysplasia lesions with modern neuroimaging. With increased detection, it became apparent that cortical dysplasia involved a spectrum of histopathologic abnormalities ranging from mild to severe. In other words, the prevalence of cortical dysplasia in epilepsy surgery patients was higher than originally appreciated. In addition, the histopathology was frequently “open to interpretation,” and only recently has cortical dysplasia been consistently graded into mild and severe types.

This review describes the clinical characteristics and outcomes for epilepsy surgery patients, with a focus on newly identified features that distinguish patients with mild Palmini type I from those with severe type II cortical dysplasia (Palmini et al., 2004). With this goal in mind, this article excludes findings on other malformations of cerebral development, such as lissencephaly, schizencephaly, TSC, hemimegalencephaly, and hypothalamic hamartoma. We emphasize findings from patients undergoing surgical procedures, and do not address palliative procedures such as corpus callosotomy and neurostimulation devices. The article begins by describing the histopathologic criteria for defining mild type I and severe type II cortical dysplasia using the Palmini classification system. Next, we discuss the clinical features of patients with cortical dysplasia that distinguish them from other epilepsy surgery patients, and the different clinical characteristics of patients with mild type I and severe type II dysplasia. The next section outlines the presurgical assessment of patients with cortical dysplasia to determine the electroencephalography (EEG) and neuroimaging features and how they differ between patients with mild and severe cortical dysplasia. Mechanisms of pathogenesis and epileptogenesis obtained from studies of human cortical dysplasia tissue are briefly discussed, followed by a review of the surgical procedures and outcomes in patients with cortical dysplasia and epilepsy. Finally, we summarize the review by outlining clinical and research challenges that can guide future investigations in the diagnosis and treatment of patients with cortical dysplasia and epilepsy.

**Materials and Methods**

Three resources were used to accomplish the goals of this review. The first source was peer-reviewed publications obtained from a PubMed search using the terms in Fig. 1 and the added phrase “surgery.” Reports of studies were included if they contained more than 20 patients, were published in English from 2002–2008 (to emphasize recent findings), contained presurgical information and

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**Figure 1.**

Frequency histogram showing the number of articles by year of publication. PubMed was surveyed using the search terms “epilepsy” and “cortical dysplasia” and publication year, and the number of citations counted. *Epilepsia* © ILAE
the number of patients seizure-free after surgery, and, if possible, separated patients into those with mild and severe cortical dysplasia (Table 1) (Palmini & Luders, 2002; Palmini et al., 2004). In addition, the studies should allow exclusion of patients with TSC, hemimegalencephaly, and coexistent tumors. They could include patients with hippocampal sclerosis and cortical dysplasia (dual pathology). If studies included patients with dual pathology we attempted to abstract data for only those patients with cortical dysplasia alone. If multiple reports from the same institution were identified, data were abstracted as if it were one cohort (Krsek et al., 2008a, 2008b). Similarly, if centers published their series over time with expanding cohorts, then the most recent studies were reviewed (Kim et al., 1999, 2008).

Twelve cohorts were identified providing data from epilepsy surgery centers in North America, Europe, Asia, and South America (Table 2; first column). Additional studies were included to supplement data for 2-(18F) fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) and ictal single proton emission computed tomography (SPECT) in the presurgical evaluation of patients with cortical dysplasia (Table 2), magnetic resonance imaging (MRI) features (Table 6), and predictors of surgical outcome (Table 7). Collectively these studies provide information on more than 850 epilepsy surgery patients with cortical dysplasia. By comparison, a previous review identified 64 articles published from 1971–1999 with 373 epilepsy surgery patients with cortical dysplasia and other malformations of cortical development (Sisodiya, 2000). Most of the earlier reports contained fewer than 20 patients. In the current review, the average was 72 patients per cohort with a range of 21–164 cases per center (Table 2; second column). The mean accrual per study was 9 years with a range of 3–20 years, and studies collected patients from 1986–2006 (Table 2; third column). Four studies reported mostly pediatric patients (Table 2; first four studies), two studies included a mix of pediatric and adult patients (Table 2; studies 5 and 6), and six studies were from mostly adult surgical centers (Table 2; last six studies). Two studies emphasized positive MRI scans and reported data on patients with only severe cortical dysplasia (Cohen-Gadol et al., 2004; Kral et al., 2007). Overall, for all 12 cohorts the average age at surgery was 17 years, with a range from a few months of age to 66 years (Table 2; fourth column).

The second resource was data from the University of California, Los Angeles (UCLA) Pediatric and Adult surgical programs. This cohort consisted of all patients with cortical dysplasia who had surgery from 2000–2007 (n = 97). This interval was chosen because the presurgical and neuroimaging protocols were standardized, and the histopathology was graded using the Palmini classification scheme. Excluded from the UCLA cohort were patients with cortical dysplasia operated on from 1986–1999 (n = 65) before we routinely classified patients into Palmini grades (although most were severe type II dysplasia) (Mischel et al., 1995). Also excluded were patients with mild malformations of cortical development (mMCD; Table 1), tuberous sclerosis complex (TSC), cortical dysplasia associated with tumors [e.g., dysembryoplastic neuroepithelial tumor (DNET), ganglioglioma], hemimegalencephaly, hippocampal sclerosis, and patients who had undergone previous resective surgery. Informed consent was obtained to use data for research purposes, and the presurgical clinical protocols and operative approach have been previously published (Mathern et al., 1999; Cook et al., 2004; Cepeda et al., 2005; Salamon et al., 2006, 2008).

The final source was a further analysis of data from 305 patients as part of the 2004 International League Against Epilepsy (ILAE) survey of 20 pediatric epilepsy surgery centers (Harvey et al., 2008). The centers were from Europe, United States, and Australia (see Appendix for investigators and locations). This analysis compared children with cortical dysplasia (n = 158) with other common etiologies in pediatric epilepsy surgery patients (n = 147; Table 3). Of note, the ILAE survey did not catalog children into those with mild and severe cortical dysplasia.

### Table 1. Palmini histopathologic grading system for cortical dysplasia tissue

<table>
<thead>
<tr>
<th>Grade</th>
<th>Severity</th>
<th>Histopathologic description</th>
</tr>
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<tbody>
<tr>
<td>mMCD</td>
<td>Very mild vs. questionable dysplasia</td>
<td>Normal cortex with excess ectopic neurons in the molecular layer (layer I) or subcortical white matter</td>
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<tr>
<td>Type I</td>
<td>Mild</td>
<td>Cortical disorganization and dyslamination without abnormal dysmorphic–cytomegalic neurons or balloon cells. Type IA is cortical disorganization with no other abnormalities. Type IB is cortical disorganization with immature or hypertrophic but not dysmorphic neurons</td>
</tr>
<tr>
<td>Type II</td>
<td>Severe</td>
<td>Cortical disorganization and dyslamination with abnormal dysmorphic–cytomegalic neurons and balloon cells. Sometimes referred to as Taylor’s type cortical dysplasia. Type IIA contains dysmorphic–cytomegalic neurons without balloon cells. Type IIB contains balloon cells</td>
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</table>

mMCD, mild malformation of cortical development. Sometimes termed microdysgenesis.
### Table 2. Recent publications on surgical treatment of patients with cortical dysplasia. Cases listed by mean age of cohort (youngest to oldest)

<table>
<thead>
<tr>
<th>Study/Location</th>
<th>N Years</th>
<th>Mean age (Range)</th>
<th>CD % all cases</th>
<th>Loc interictal EEG, %</th>
<th>Loc ictal EEG, %</th>
<th>Normal-nonspecific MRI, %</th>
<th>FDG-PET, %</th>
<th>SPECT-SISCOM, %</th>
<th>Intracranial electrodes, %</th>
<th>Comp., %</th>
<th>% Type I</th>
<th>Focal-lobar operation, %</th>
<th>% Sz free</th>
<th>% HS</th>
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<tr>
<td><strong>Clinical studies</strong></td>
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<td></td>
</tr>
<tr>
<td>Krssek et al. (2006c); Vogtareuth, Germany</td>
<td>40 2002–2005</td>
<td>7 (1–18)</td>
<td>32</td>
<td>42</td>
<td>10</td>
<td>75</td>
<td>N/A</td>
<td>N/A</td>
<td>30</td>
<td>N/A</td>
<td>60</td>
<td>25</td>
<td>42</td>
<td>5</td>
</tr>
<tr>
<td>Hader et al. (2004); Sick Children Toronto</td>
<td>39 1989–2001</td>
<td>10 (0.2–18)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>18</td>
<td>N/A</td>
<td>N/A</td>
<td>38</td>
<td>N/A</td>
<td>N/A</td>
<td>87</td>
<td>(20/23)</td>
<td>N/A</td>
</tr>
<tr>
<td>Krssek et al. (2008a); Miami Childrens</td>
<td>164 1986–2006</td>
<td>10 (0.2–25)</td>
<td>58</td>
<td>77</td>
<td>34</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>48</td>
<td>18</td>
<td>57</td>
<td>44</td>
<td>55</td>
<td>19</td>
</tr>
<tr>
<td>Park et al. (2006); Seoul Nat Childrens</td>
<td>30 1995–1999</td>
<td>10 (1.5–18)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>26</td>
<td>N/A</td>
<td>N/A</td>
<td>64</td>
<td>60</td>
<td>26</td>
<td>47</td>
<td>80</td>
<td>67</td>
</tr>
<tr>
<td>Hader et al. (2004); Sick Children Toronto</td>
<td>145 1990–2005</td>
<td>11 (0.2–50)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>3 (2/67)</td>
<td>N/A</td>
<td>N/A</td>
<td>48</td>
<td>34</td>
<td>24</td>
<td>39</td>
<td>85</td>
<td>63</td>
</tr>
<tr>
<td>Alexandre et al. (2006); Ribeirao Preto Brazil</td>
<td>41 1996–2002</td>
<td>19 (1–44)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>63</td>
<td>27</td>
<td>N/A</td>
<td>N/A</td>
<td>40</td>
<td>N/A</td>
<td>67</td>
<td>80</td>
<td>62</td>
</tr>
<tr>
<td>Fauser et al. (2006, 2008); Freiburg, Germany</td>
<td>120 1998–2005</td>
<td>21 (1–66)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>3 (2/67)</td>
<td>N/A</td>
<td>N/A</td>
<td>50</td>
<td>N/A</td>
<td>56</td>
<td>77</td>
<td>66</td>
<td>23</td>
</tr>
<tr>
<td>Tassi et al. (2002); Milan</td>
<td>52 1996–2000</td>
<td>24 (2–42)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>34</td>
<td>N/A</td>
<td>N/A</td>
<td>67</td>
<td>N/A</td>
<td>71</td>
<td>81</td>
<td>54</td>
<td>33</td>
</tr>
<tr>
<td>Kim et al. (2008); Seoul National</td>
<td>145 1995–2005</td>
<td>25 (3–51)</td>
<td>40</td>
<td>76</td>
<td>54</td>
<td>69</td>
<td>(92/133)</td>
<td>(60/106)</td>
<td>57</td>
<td>(107/124)</td>
<td>86</td>
<td>9</td>
<td>81</td>
<td>80</td>
</tr>
<tr>
<td>Kral et al. (2007); Bonn, Germany</td>
<td>49 1989–2001</td>
<td>25 (5–47)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>41</td>
<td>10</td>
<td>0</td>
<td>94</td>
<td>76</td>
<td>N/A</td>
</tr>
<tr>
<td>Cohen-Gadol et al. (2004); Yale</td>
<td>22 1987–2001</td>
<td>26 (2–58)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>59</td>
<td>14</td>
<td>78</td>
<td>(9/7)</td>
<td>(5/12)</td>
<td>42</td>
<td>68</td>
<td>9</td>
<td>0</td>
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<tr>
<td>Siegel et al. (2006); Mayo Clinic</td>
<td>21 1993–1997</td>
<td>33 (18–58)</td>
<td>42</td>
<td>62</td>
<td>28</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>89</td>
<td>52</td>
<td>29</td>
<td>58</td>
<td>86</td>
<td>52</td>
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<td><strong>Imaging studies</strong></td>
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<tr>
<td>Gupta et al. (2004); Cleveland Clinic</td>
<td>18 1996–2000</td>
<td>60</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>53</td>
<td>(9/15)</td>
<td>(8/15)</td>
<td>42</td>
<td>68</td>
<td>9</td>
<td>0</td>
<td>100</td>
<td>59</td>
</tr>
<tr>
<td>Kim et al. (2000); Sungkyunkwan Univ; Seoul</td>
<td>19 1995–1998</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>59</td>
<td>14</td>
<td>78</td>
<td>(9/7)</td>
<td>(5/12)</td>
<td>42</td>
<td>68</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td>(Totals)</td>
<td>72 (868)</td>
<td>17</td>
<td>49</td>
<td>28</td>
<td>36</td>
<td>75</td>
<td>(200/411)</td>
<td>(414/608)</td>
<td>(288/805)</td>
<td>(181/242)</td>
<td>(114/201)</td>
<td>(448/847)</td>
<td>(64/478)</td>
</tr>
</tbody>
</table>

N/A, not available. Percentage based on total N unless indicated in parentheses. Comp, complications; HS, hippocampal sclerosis; Sz, seizure.
The cytoplasm of these cells often contains neurofibrillary tangle-like cytoplasmic inclusions, irregular clumping of the Nissl substance around the nucleus, and cytoplasmic vacuolization (Vinters, 2002; Hildebrandt et al., 2005). Dysmorphic–cytomegalic neurons can be pyramidal or nonpyramidal, and a proportion of cytomegalic neurons are γ-aminobutyric acid (GABA)ergic (Andre et al., 2007). These neurons are thought to have been improperly formed in the periventricular proliferative zone during initial neurogenesis or are remnants of cells that reside in the normal human subplate that failed to undergo cell death during later phases of cortical development (Barkovich et al., 2005; Cepeda et al., 2005b).

3) Balloon cells. (40% of cases) These consist of large abnormal cells with abundant opalescent eosinophilic cytoplasm and eccentric nuclei (Fig. 2E; arrow). Balloon cells may be immunoreactive for proteins associated with glia and neurons, but they have more morphologic characteristics of glial cells (Kerfoot et al., 1999; Cepeda et al., 2003). Like dysplastic neurons, these cells are thought to be abnormally formed, early generated cells or residual radial glial typically found during normal cortical development (Ying et al., 2005; Cepeda et al., 2006; Lamparello et al., 2007).

4) Excessive heterotopic neurons in the cortical molecular layer. (40% of cases) This histologic feature of the normal developing cerebral cortex is considered a sign of abnormal cortical development if identified in the postnatal brain (Dehay & Kennedy, 2007). This feature consists of excessive numbers of neurons in layer I of the cerebral cortex, some of which are probably Cajal-Retzius cells (Thom et al., 2003).

5) Marginal and nodular glioneuronal heterotopia. (30% of cases) Marginal heterotopia consists of (usually disorganized) neuroglial tissue extruding through the pial surface into the subarachnoid space. Nodular heterotopia can be large collections of neuroglial tissue dispersed in the cortex and white matter. Both are signs of severe cortical dysplasia and probably represent abnormal migrations of neurons and glia during cerebral development.

6) Polymicrogyria. (27% of cases) This consists of multiple folds of cortical neurons, often with a fused unlayered pial surface. It is usually associated with severe cortical dysplasia, probably from overproduction of late generated neurons residing in upper cortical layers (Andres et al., 2005). Polymicrogyria generally appears as thickened cortex on MRI (Salamon et al., 2006).

7) Immature neurons. (15% of cases) These are round or oval cells with a large immature nucleus and thin rim of cytoplasm. These cells are often found in clusters, and mostly in younger patients with cortical dysplasia (Cepeda et al., 2007). The presence of immature neurons is considered a sign of incomplete cortical development in the postnatal human cortex.

8) Persistence of the subpial or superficial granular cell layer (SGL). (8% of cases) The SGL is normal during cerebral development (Ying et al., 2005; Cepeda et al., 2006; Lamparello et al., 2007).

### Table 3. Comparison of pediatric epilepsy surgery patients (<18 years) with cortical dysplasia versus tumors, atrophy and hippocampal sclerosis from 2004 ILAE survey of 20 centers

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Cortical dysplasia (n = 158)</th>
<th>Tumor-atrophy-hippocampal sclerosis (n = 147)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at seizure onset (years)</td>
<td>2.6 ± 3.4</td>
<td>5.1 ± 4.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age at surgery (years)</td>
<td>7.9 ± 5.3</td>
<td>10.7 ± 4.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Seizure duration (years)</td>
<td>5.3 ± 4.5</td>
<td>5.5 ± 4.5</td>
<td>0.705</td>
</tr>
<tr>
<td>Daily seizures, %</td>
<td>70</td>
<td>48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MRI positive, %</td>
<td>81</td>
<td>100</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intracranial electrodes, %</td>
<td>36</td>
<td>20</td>
<td>0.0025</td>
</tr>
<tr>
<td>Types of operations, %</td>
<td>15</td>
<td>17</td>
<td>0.012</td>
</tr>
<tr>
<td>Hemispherectomy</td>
<td>62</td>
<td>73</td>
<td></td>
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<tr>
<td>Lobar/Focal resection</td>
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Data presented as mean ± SD or percentages. Modified from Harvey et al. (2008). Significant p-values (p < 0.05) are indicated in bold type.

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**Histopathology of Cortical Dysplasia: Mild Type I And Severe Type II**

The key histopathologic criterion that defines cortical dysplasia is cortical disorganization and dyslamination (Taylor et al., 1971; Mischel et al., 1995). This consists of an irregular arrangement of cortical neurons, loss of normal cortical laminar organization, irregular clustering, and neurons showing abnormal polarity and misdirected apical dendrites (Fig. 2B, C; arrows). These histopathologic features are consistent with improper formation of the cerebral cortex and define mild cortical dysplasia. Often associated with cortical disorganization are other histopathologic findings that denote more severe abnormal cortical development. Using the UCLA cohort from 2000–2007, the other histopathologic features of cortical dysplasia, in descending order of frequency, include:

1) Excessive heterotopic white matter neurons. (99% of cases) These are randomly dispersed single or groups of neurons in the subcortical white matter most often seen in regions with overlying cortical disorganization (Fig. 2B; asterisk). This finding has been attributed to abnormal neuronal migration or secondary to overproduction of cortical neurons in the periventricular proliferative zone during cerebral development (Andres et al., 2005; Mathern et al., 2007).

2) Dysmorphic–cytomegalic neurons. (52% of cases) This manifests as irregularly shaped neurons that are often several times the size of normal neurons (Fig. 2D; arrow). The cytoplasm of these cells often contains neurofibrillary tangle-like cytoplasmic inclusions, irregular clumping of the Nissl substance around the nucleus, and cytoplasmic vacuolization (Vinters, 2002; Hildebrandt et al., 2005). Dysmorphic–cytomegalic neurons can be pyramidal or nonpyramidal, and a proportion of cytomegalic neurons are γ-aminobutyric acid (GABA)ergic (Andre et al., 2007). These neurons are thought to have been improperly formed in the periventricular proliferative zone during initial neurogenesis or are remnants of cells that reside in the normal human subplate that failed to undergo cell death during later phases of cortical development (Barkovich et al., 2005; Cepeda et al., 2005b).

3) Balloon cells. (40% of cases) These consist of large abnormal cells with abundant opalescent eosinophilic cytoplasm and eccentric nuclei (Fig. 2E; arrow). Balloon cells may be immunoreactive for proteins associated with glia and neurons, but they have more morphologic characteristics of glial cells (Kerfoot et al., 1999; Cepeda et al., 2003). Like dysplastic neurons, these cells are thought to be abnormally formed, early generated cells or residual radial glial typically found during normal cortical development (Ying et al., 2005; Cepeda et al., 2006; Lamparello et al., 2007).

4) Excessive heterotopic neurons in the cortical molecular layer. (40% of cases) This histologic feature of the normal developing cerebral cortex is considered a sign of abnormal cortical development if identified in the postnatal brain (Dehay & Kennedy, 2007). This feature consists of excessive numbers of neurons in layer I of the cerebral cortex, some of which are probably Cajal-Retzius cells (Thom et al., 2003).

5) Marginal and nodular glioneuronal heterotopia. (30% of cases) Marginal heterotopia consists of (usually disorganized) neuroglial tissue extruding through the pial surface into the subarachnoid space. Nodular heterotopia can be large collections of neuroglial tissue dispersed in the cortex and white matter. Both are signs of severe cortical dysplasia and probably represent abnormal migrations of neurons and glia during cerebral development.

6) Polymicrogyria. (27% of cases) This consists of multiple folds of cortical neurons, often with a fused unlayered pial surface. It is usually associated with severe cortical dysplasia, probably from overproduction of late generated neurons residing in upper cortical layers (Andres et al., 2005). Polymicrogyria generally appears as thickened cortex on MRI (Salamon et al., 2006).

7) Immature neurons. (15% of cases) These are round or oval cells with a large immature nucleus and thin rim of cytoplasm. These cells are often found in clusters, and mostly in younger patients with cortical dysplasia (Cepeda et al., 2007). The presence of immature neurons is considered a sign of incomplete cortical development in the postnatal human cortex.

8) Persistence of the subpial or superficial granular cell layer (SGL). (8% of cases) The SGL is normal during cerebral development (Ying et al., 2005; Cepeda et al., 2006; Lamparello et al., 2007).
cortical development, found in midgestation, and disappears before birth. In the postnatal brain, this is a sign of abnormal cortical development. The SGL is thought to produce GABAergic neurons during human cortical development (Bystron et al., 2008). In patients with cortical dysplasia, the SGL is often seen in a patchy distribution.

(9) Other histopathologic features that are not specific for abnormal cortical development but are often identified in association with cortical dysplasia include: Chaslin’s gliosis (92%), cortical and white matter calcifications (37%), encephalomalacia, and white matter gliosis (27%).

Classification schemes have been proposed to catalog patients with cortical dysplasia into subgroups based on histopathologic and neuroradiologic criteria (Mischel et al., 1995; Raymond et al., 1995; Tassi et al., 2002; Palmini et al., 2004; Barkovich et al., 2005). The classification proposed by Palmini and Luders is the one currently used by many surgical centers and the one under evaluation in this review (Table 1). It divides patients into those
with mild type I and severe type II cortical dysplasia, with
two subgroups within each major class (Palmini & Luders,
2002; Palmini et al., 2004). The main distinction between
mild type I and severe type II cortical dysplasia is the pres-
ence of dysmorphic–cytomegalic neurons and balloon
cells. Other characteristics of the malformed cerebral cor-
text are not components of the Palmini classification sys-
tem (see Critical Review). Another category, termed
mMCD or microdysgenesis, consists of normal cortical
organization with an excess of neurons in the subcortical
white matter or molecular layer. Without cortical disorgan-
ization and dyslamination, it is controversial whether
mMCD represents a “true” form of cortical dysplasia
(Kasper, 2005). With the exception of our discussion on
dual pathology and hippocampal sclerosis, for the most
part we exclude discussions of mMCD in this review.

**Clinical Characteristics of Epilepsy Surgery Patients with Cortical Dysplasia**

As a group, patients with cortical dysplasia are younger
at seizure onset and surgery and have greater seizure fre-
cuency compared with most other etiologies in epilepsy
surgery patients. In the 2004 ILAE survey of 20 pediatric
epilepsy surgery centers, cortical dysplasia was the most
frequent etiology in patients younger than age 18 years
(Fig. 3A; blue bar). In pediatric epilepsy surgery patients,
the next most common substrates were tumors, infections
and ischemic stroke (atrophy/stroke), and hippocampal
sclerosis (Fig. 3A; green, orange, and red bars). By com-
parison, cortical dysplasia was the third most common etiology
behind hippocampal sclerosis and tumors in a
report of mostly adult epilepsy surgery patients (Fig. 3B)
(Becker et al., 2006). In other reports, cortical dysplasia
was the second most common etiology in mostly adult epi-
lepsy surgery patients (Raymond et al., 1995; Semah
et al., 1998). In the 2004 ILAE survey of pediatric centers,
children with cortical dysplasia were younger at seizure
onset and surgery compared with those with tumors, atro-
phy/stroke, and hippocampal sclerosis (Table 3). In addi-
tion, 70% of pediatric patients with cortical dysplasia had
daily seizures compared with 48% of children with other
substrates (Table 3).

In published studies, patients with cortical dysplasia
made up 14% of all patients undergoing epilepsy neuro-
surgery (Table 2; fifth column). Cortical dysplasia was a
more common etiology in studies with younger cohorts
(Table 2; 32–58%) compared with older cohorts (4–23%).
In the UCLA cohort from 2000–2007, cortical dysplasia
was found in 21% of combined adult and pediatric epi-
lepsy surgery patients, and was the second most common
etiology behind hippocampal sclerosis. In the UCLA
cohort, those with cortical dysplasia had a younger age at
seizure onset and surgery compared with patients with
hippocampal sclerosis and mesial temporal lobe epilepsy
(Fig. 4A–D). In fact, in the UCLA series, the age at seizure
onset was 1 year or less in 48% of patients with cortical
dysplasia (median 1.3 years). This compares with a med-
ian age of seizure onset of 11 years for patients with hip-
pocampal sclerosis (Fig. 4C). Furthermore, in the UCLA
cohort, the incidence of cortical dysplasia by age at sur-
gery was highest in younger patients (Fig. 4E). Cortical
dysplasia was the histopathologic substrate in 75% of
infants and children operated upon in the first 2 years of
life, compared with less than 10% in those having surgery
at an age older than 21 years (Siegel et al., 2005). Similar
findings were reported in the 2004 ILAE of pediatric
epilepsy surgery centers, where cortical dysplasia was
found in 67% of children operated on in the first year of
life compared with 25% in those aged 15–18 years
(Harvey et al., 2008).

**Characteristics of Patients with Mild Type I and Severe Type II Cortical Dysplasia**

Most studies report that patients with severe type II cor-
tical dysplasia are younger at presentation compared with
those with mild type I cortical dysplasia (Palmini et al.,
From the UCLA pediatric and adult surgical cohorts, frequency histograms showing (A) age at seizure onset and (B) age at surgery for patients with cortical dysplasia compared with those with (C) hippocampal sclerosis and (D) temporal lobe epilepsy (TLE). Mean [years ± standard deviation (SD)] and median data are also shown. The age at seizure onset and surgery is younger for patients with cortical dysplasia compared with those with hippocampal sclerosis (t-tests; p < 0.0001). (E) Histogram indicating the percentage of patients with cortical dysplasia by age at surgery. At younger than age 3 years, more than 66% of cases had cortical dysplasia compared with less than 10% for patients older than age 21 years.

Epilepsia © ILAE
Figure 5.
From the pediatric and adult UCLA surgical cohorts with cortical dysplasia, bar graphs showing mean [years ± standard deviation (SD)] age at seizure onset (top row; Age Sz Onset), age at surgery (2nd row; Age Surg), seizure duration (3rd row; Sz Duration), and seizure frequency (bottom row; Total Szs). The left column compares patients with mild Palmini type I (red bars) and severe Palmini type II (blue bars) cortical dysplasia, and the right column patients with hemispheric and multilobar operations (orange bars) and those with lobar and focal resections (yellow bars). T-test results are indicated above each bar graph. The results of the two-factor analysis of variance (ANOVA) are shown between the graphs. Patients with hemispheric/multilobar and type II cortical dysplasia were younger at age at seizure onset and surgery (top two rows; p < 0.002), had shorter seizure duration (third row; p < 0.0001), and higher frequency of seizures per day (bottom row; p < 0.02) compared with lobar/focal cases with type I cortical dysplasia.

Presurgical Evaluation

The presurgical evaluation for patients with cortical dysplasia is often challenging. Cortical dysplasia patients often present with variable epilepsy-related symptoms depending on the age at presentation, and the location and size of the lesion. In addition, EEG and MRI may not localize to the lesion. Therefore, multiple diagnostic modalities are usually necessary to detect areas of cortical dysplasia in the presurgical evaluation of patients with intractable epilepsy.

Semiology

There is no particular seizure semiology that characterizes patients with mild and severe cortical dysplasia compared with other epilepsy surgery patients. Patients with cortical dysplasia can present with focal ictal behavioral signs and symptoms referable to any lobe of the brain. The seizures may suggest involvement of multiple lobes or a cerebral hemisphere, or present with bihemispheric features. Generalized clinical and EEG features are often characteristic of younger patients with cortical dysplasia and other etiologies (Chugani et al., 1990; Cross et al., 2006; Wyllie et al., 2007). Hence, clinicians cannot diagnose that a patient has cortical dysplasia or whether they have mild or severe dysplasia based exclusively on ictal semiology.

Scalp EEG

There are no distinctive interictal or ictal scalp EEG “signatures” that are exclusively associated with cortical...
dysplasia in patients with refractory epilepsy. The EEG can show interictal background slowing, interictal spikes and polyspikes, and ictal events with electrographic characteristics similar to other patients with intractable epilepsy who are undergoing presurgical evaluation (Noachtar et al., 2008). In fact, if there is a characteristic it is that interictal and ictal EEG findings often do not localize to the MRI-identified lesion in patients with cortical dysplasia. In the published literature, interictal findings were reported to localize to one region on scalp EEG in 49% of patients with cortical dysplasia (Table 2; sixth column; 32–62%). Likewise, ictal findings localized to one region on scalp EEG in 68% of epilepsy surgery patients with cortical dysplasia (Table 2; seventh column; 42–77%). Similar findings were found in the UCLA cohort (Table 4). Focal or regional interictal scalp EEG findings were noted in 47%, focal background slowing in 81%, ictal spike trains or continuous epileptiform discharges (CEDs) in 64%, and focal ictal onsets in 44% of epilepsy surgery patients with cortical dysplasia.

The published literature and data from the UCLA series also indicate that there are no consistent EEG findings that differentiate patients with mild type I from severe type II cortical dysplasia (Krsek et al., 2008a, 2008c). For example, in the UCLA cohort, patients with severe type II cortical dysplasia compared to those with mild type I dysplasia were more likely to have interictal EEG focal background slowing and spike trains, but there were no differences in the incidence of localized interictal epileptiform discharges and ictal onsets (Table 4). Of note, another study recently reported that EEG slowing was more common in patients with mild type I compared with severe type II cortical dysplasia (Krsek et al., 2008c). In addition, UCLA patients with focal and lobar areas of cortical dysplasia by MRI were just as likely to present with localized interictal and ictal EEG findings as patients with more

**Table 4. From pediatric and adult patients at UCLA, clinical, EEG, neuroimaging, and outcome characteristics in patients with type I and type II cortical dysplasia (2000–2007)**

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>All CD cases (n = 97), %</th>
<th>Type I (n = 33), %</th>
<th>Type II (n = 64), %</th>
<th>p-Value (Type I vs. II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Side-right</td>
<td>48</td>
<td>61</td>
<td>42</td>
<td>0.08</td>
</tr>
<tr>
<td>Gender—Female</td>
<td>49</td>
<td>67</td>
<td>41</td>
<td>0.05</td>
</tr>
<tr>
<td>Type of epilepsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal lobe epilepsy</td>
<td>22</td>
<td>58</td>
<td>5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Extratemporal/nonhemi</td>
<td>45</td>
<td>32</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Hemispheric epilepsy</td>
<td>33</td>
<td>10</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemispherectomy</td>
<td>14</td>
<td>6</td>
<td>19</td>
<td>0.0024</td>
</tr>
<tr>
<td>Multilobar resection</td>
<td>23</td>
<td>6</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Lobar resection</td>
<td>31</td>
<td>48</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Focal resection</td>
<td>32</td>
<td>39</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Lobe involved</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>50</td>
<td>31</td>
<td>58</td>
<td>0.0195</td>
</tr>
<tr>
<td>Temporal</td>
<td>54</td>
<td>65</td>
<td>50</td>
<td>0.19</td>
</tr>
<tr>
<td>Parietal</td>
<td>46</td>
<td>31</td>
<td>53</td>
<td>0.05</td>
</tr>
<tr>
<td>Occipital</td>
<td>24</td>
<td>11</td>
<td>29</td>
<td>0.08</td>
</tr>
<tr>
<td>History of infantile spasms</td>
<td>27</td>
<td>15</td>
<td>41</td>
<td>0.0191</td>
</tr>
<tr>
<td>Status epilepticus @ surgery</td>
<td>16</td>
<td>9</td>
<td>20</td>
<td>0.16</td>
</tr>
<tr>
<td>Interictal scalp EEG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal/regional discharges</td>
<td>47</td>
<td>42</td>
<td>50</td>
<td>0.61</td>
</tr>
<tr>
<td>Focal background slowing</td>
<td>81</td>
<td>62</td>
<td>93</td>
<td>0.011</td>
</tr>
<tr>
<td>Spike trains/CEDs</td>
<td>64</td>
<td>37</td>
<td>78</td>
<td>0.007</td>
</tr>
<tr>
<td>Ictal scalp EEG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal/regional onsets</td>
<td>44</td>
<td>46</td>
<td>44</td>
<td>0.89</td>
</tr>
<tr>
<td>MRI-positive</td>
<td>78</td>
<td>63</td>
<td>98</td>
<td>0.0041</td>
</tr>
<tr>
<td>MRI feature (see Fig. 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thick gray matter</td>
<td>24</td>
<td>7</td>
<td>67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blurred gray—white junction</td>
<td>59</td>
<td>14</td>
<td>73</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Decreased T2 white matter</td>
<td>27</td>
<td>11</td>
<td>41</td>
<td>0.0003</td>
</tr>
<tr>
<td>Increased T2 gray matter</td>
<td>58</td>
<td>7</td>
<td>35</td>
<td>0.44</td>
</tr>
<tr>
<td>Increased T2 white matter</td>
<td>36</td>
<td>56</td>
<td>59</td>
<td>0.89</td>
</tr>
<tr>
<td>Cortical atrophy</td>
<td>19</td>
<td>21</td>
<td>18</td>
<td>0.79</td>
</tr>
<tr>
<td>FDG-PET positive</td>
<td>98</td>
<td>97</td>
<td>98</td>
<td>0.14</td>
</tr>
<tr>
<td>Intracranial electrodes</td>
<td>6</td>
<td>10</td>
<td>1</td>
<td>0.0085</td>
</tr>
<tr>
<td>Postsurgery seizure free</td>
<td>80</td>
<td>74</td>
<td>82</td>
<td>0.36</td>
</tr>
</tbody>
</table>

**CEDs**, continuous epileptiform discharges. Significant p-values (p < 0.05) are indicated in bold type.
diffuse multilobar and hemispheric cortical dysplasia (Table 5). Hence, scalp EEG studies may localize interictal and ictal abnormalities to the eventual area of resection in only 50–68% of patients with cortical dysplasia undergoing presurgical evaluation, and do not distinguish patients with mild and severe cortical dysplasia (Raymond et al., 1995).

### Structural MRI

There are several features on structural MRI that identify areas of cortical dysplasia in intractable epilepsy patients (Sankar et al., 1995; Yagishita et al., 1997; Lee et al., 1998; Tassi et al., 2002; Colombo et al., 2003; Raybaud et al., 2006; Widdess-Walsh et al., 2006). The MRI findings include: (1) increased thickness of the cortical gray matter, often with abnormal gyral patterns (Fig. 6A; arrow); (2) blurring of the gray–white matter junction (Fig. 6D; arrow); and (3) increased T2 and fluid attenuated inversion recovery (FLAIR) signal intensity in the subcortical white (Fig. 6B, 6E and 6F; arrows) and gray matter (Fig. 6C; arrow). MRI white matter abnormalities can extend to the ventricle, termed “transmantle dysplasia” (Barkovich et al., 1997) (Fig. 6E; arrow). Cortical and white matter atrophy, calcifications, and contrast enhancement within the lesion have been reported but are not specific MRI features for cortical dysplasia (Bronen et al., 1997; Urbach et al., 2002).

### Table 5. Localized interictal and ictal scalp EEG findings based on MRI size of cortical dysplasia from pediatric and adult UCLA surgical cohort

<table>
<thead>
<tr>
<th>EEG feature</th>
<th>Multilobar/ Hemispherectomy, %</th>
<th>Lobar/ Focal, %</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interictal EEG</td>
<td>50</td>
<td>50</td>
<td>0.99</td>
</tr>
<tr>
<td>Ictal EEG</td>
<td>75</td>
<td>50</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Figure 6.
Magnetic resonance imaging (MRI) features of cortical dysplasia. Qualitative MRI findings can include (A) thickened gray matter (arrow), (B) T2 hyperintensity in the subcortical white matter (arrow), (C, F) T2 hyperintensity of the gray matter (arrow), (D) blurring of the gray–white matter junction (arrow), and (E) transmantle sign (arrow).
When present, the constellation of MRI findings is diagnostic for cortical dysplasia in patients with intractable epilepsy. However, MRI findings can often be subtle and difficult to detect, especially for patients with mild type I and those with very small foci of severe type II cortical dysplasia (Figs. 7 and 8). In published studies, structural MRI was reported as normal or not specific for the diagnosis of cortical dysplasia in a substantial proportion of patients (Table 2; eighth column). This ranged from 100% abnormal MRI scans from Bonn, Germany, where all cases had type II cortical dysplasia (Kral et al., 2007) to 54% normal MRI scans in the adult series from Seoul, Korea, where many patients had type I cortical dysplasia (Kim et al., 2008). In the 2004 ILAE survey, 19% of children with cortical dysplasia had normal or subtle MRI scans compared with 0% for those with tumors, stroke, and hippocampal sclerosis (Table 3). In the UCLA series, 22% of patients with cortical dysplasia had normal MRI scans (Table 4). Of note, the original report by Taylor and colleagues described lesions that were not visible on gross macroscopic evaluation of the cortical specimen in six (60%) of their surgical specimens (Taylor et al., 1971).

Normal MRI scans are reported more frequently in patients with mild type I (36% and 37%) compared with severe type II cortical dysplasia (2% and 15%; Tables 4 and 6). Put another way, in recent studies 51% (85 of 166; range 7–94%) of patients with normal MRI scans at the time of surgery were found to have cortical dysplasia on histopathology (Chapman et al., 2005; Lee et al., 2005; McGonigal et al., 2007). In published studies and the UCLA series, MRI features of cortical dysplasia such as increased gray matter thickness, blurring of the gray–white junction, and increased T2 signal in the white matter were more often associated with severe type II compared with mild type I cortical dysplasia (Tables 4 and 6). By comparison, encephalomalacia and periventricular leukomalacia were more frequently reported in patients with mild type I cortical dysplasia (Tables 4 and 6) (Krsik et al., 2008c). However, no MRI features, except transmantle sign, were specific for severe cortical dysplasia. The transmantle sign has been reported in only 34% of patients with type II cortical dysplasia (Table 6). Hence, although MRI can identify cortical dysplasia in patients with refractory epilepsy with high specificity, this imaging modality does not detect a substantial proportion of individuals with mild type I and a few with severe type II cortical dysplasia in small foci.

FDG-PET, ictal SPECT, and MEG-MSI

With patients presenting with nonlocalized scalp EEG and normal MRI, many centers incorporate additional functional and neuroimaging studies into the multimodality presurgical evaluation to increase the detection of patients with cortical dysplasia. Of these tools, FDG-PET has been shown to be one of the more sensitive techniques.

**Figure 7.**
Difficult to identify extratemporal severe type II cortical dysplasia by magnetic resonance imaging (MRI) in two patients. (A, B) This 4-year-old presented with seizures beginning at age 17 months. The seizures were characterized by tonic events involving the left body lasting usually less than a minute. The seizures could cluster resulting in status epilepticus. With the severe cluster of seizures there would be a left-sided Todd’s paralysis that could last for weeks. Interictal and ictal electroencephalography (EEG) showed abnormalities over the right hemisphere that were nonlocalizing. The MRI shows an area of thickened cortex involving most of the right insula (arrows). Histopathology showed a type II dysplasia without balloon cells. This child has been seizure free after a right cerebral hemispherectomy. (C, D) This 19-year-old presented with seizures at age 9 years that involved left upper extremity tonic events. Interictal and ictal EEG findings localized to the Cz and C4 electrodes. Numerous MRI scans had been interpreted as normal, although a subtle change was noted over one gyrus (C; arrow). Magnetoencephalography (MEG)–magnetic source imaging (MEG-MSI) localized a cluster of interictal spikes over the right frontal parietal region (D; cluster of yellow marks). Histopathology disclosed type II cortical dysplasia with balloon cells. This person has been seizure free postsurgery after a focal cortical resection.
in identifying areas of cortical dysplasia (Chugani et al., 1990; Cohen-Gadol et al., 2004). Contemporary studies indicate that FDG-PET detects interictal hypometabolism localized to areas of cortical dysplasia in approximately 75% of patients (Table 2; ninth column; 60–92%). Many patients with cortical dysplasia and normal MRIs are reported to have positive FDG-PET scans (Kim et al., 2000). In the UCLA series of 22 patients with normal or subtle MRI findings, 14 (64%) showed areas of hypometabolism on FDG-PET scans.

To increase the sensitivity of FDG-PET, the UCLA group recently modified the technique whereby pseudocolored FDG-PET images representing escalating levels of hypometabolism were overlaid onto the structural MRI (Fig. 9) (Burri et al., 2008). This method identified cortical dysplasia in 98% of patients in the UCLA cohort, including a substantial proportion of patients with mild type I dysplasia with previously interpreted normal MRI scans (Table 4) (Salamon et al., 2008). Hence, FDG-PET can be a very useful tool in detecting cortical dysplasia in patients undergoing presurgical evaluation for their intractable epilepsy, especially if the MRI is normal or nonspecific for cortical dysplasia.

Ictal SPECT is another neuroimaging tool that has been applied to patients with probable cortical dysplasia (Gupta et al., 2004). Studies indicate that 57% of cortical dysplasia patients have localized ictal SPECT scans (Table 2; 10th column; 42–64%). Like FDG-PET, some patients with a normal MRI show positive ictal SPECT scans. Areas of cortical dysplasia often produce abundant interictal discharges when sampled with intracranial EEG (Palmini et al., 1991; Ishibashi et al., 2002). Hence, magnetoencephalography (MEG)–magnetic source imaging (MEG-MSI) should be a valuable tool for identifying epileptogenic areas of cortical dysplasia by mapping areas that produce frequent interictal discharges (Fig. 7D). Although MEG-MSI has been available for several years, there are limited publications reporting the use of this technique in patients with cortical dysplasia. These studies report localized MEG-MSI scans in 97% (30 of 31) of patients with cortical dysplasia, and suggest that there may be differences in the distribution of spikes in patients with type I and type II disease (Otsubo et al., 1993; Morioka et al., 1999; Bast et al., 2004; Hader et al., 2004). This is similar to the initial UCLA experience, in which all 18 patients with cortical dysplasia sampled with MEG-MSI had positive localized studies prior to surgical resection (Fig. 7D). Therefore, MEG-MSI is likely a promising and underutilized technique that could improve the detection and localization of areas of cortical dysplasia in patients with refractory epilepsy. However, further studies are necessary to validate this technique in patients with cortical dysplasia (Knowlton et al., 2006; Wu et al., 2006).

**Intracranial EEG**

Because of the above-noted limitations of scalp EEG and MRI, patients with suspected cortical dysplasia are often implanted with intracranial electrodes to localize areas of ictal onset. The percentage of patients with...
cortical dysplasia undergoing intracranial electrode procedures varies considerably from center to center. In published studies, 53% of patients with cortical dysplasia were reported to have intracranial electrode studies (Table 2; 11th column; 30–86%). In the ILAE survey, 36% of pediatric patients with cortical dysplasia had intracranial electrodes compared with 20% for children with other etiologies (Table 3). By comparison, in the UCLA cohort, intracranial electrodes were implanted in 6% of patients with cortical dysplasia (Table 4). Published studies do not report a difference in the use of intracranial electrodes in patients with mild type I (45%) compared with severe type II (47%) cortical dysplasia (Tassi et al., 2002; Widdess-Walsh et al., 2005; Krsek et al., 2008a,c). By comparison, in the UCLA cohort, more patients with type I (Table 4; 10%) had intracranial electrodes compared with those with type II cortical dysplasia (1%).

Once implanted, detection of ictal onset zones using intracranial electrodes is often not straightforward in patients with cortical dysplasia. Initial studies using electrocorticography described interictal “continuous epileptiform discharges” (CEDs) and fast frequency patterns as a hallmark for detecting areas of cortical dysplasia (Palmini et al., 1995; Gambardella et al., 1996; Whiting & Duchowny, 1999). Subsequent studies, however, found that these intracranial EEG findings were associated with nondysplastic etiologies (Guerreiro et al., 2003; Turkdogan et al., 2005). Likewise, in a recent study, 35% of ictal onsets were reported as diffuse, involving more than a dozen intracranial electrodes; in 42% of patients the ictal onsets were at more than one site with repeated seizures, and in 49% of cases the onsets were reported as being at the edge of the grid outside the region of electrode coverage (Widdess-Walsh et al., 2007). These findings indicate that the epileptogenic region is often deep or distant from the site of intracranial electrode placement. Likewise, another intracranial electrode study reported that areas of dysplasia that contained balloon cells (type IIB) were less likely to demonstrate ictal-onset EEG patterns compared with regions that contained dysmorphic–cytomegalic neurons without balloon cells (type IIA) (Boonyapisit et al., 2003). However, other reports indicate that complete removal of the cortical dysplasia lesion including areas containing balloon cells provides the best chance of seizure freedom after surgery (Kim et al., 2008; Krsek et al., 2008b; Mathern, 2008). Furthermore, the finding of postexcision spikes on intracranial EEG recordings does not predict whether patients will become seizure free after surgery (Krsek et al., 2008c). Hence, using intracranial electrodes, there are no specific interictal or ictal EEG signs that identify areas of cortical dysplasia, and ictal onsets are often ill-defined and diffuse or do not overlap with areas of severe dysplasia.

### Coexistent Neuropathology

Cortical dysplasia has been associated with other brain pathologic changes that could be independent epileptogenic lesions. This is often referred to as “dual pathology,” and includes the following main groups of substrates.

#### Tumors and infarcts with cortical dysplasia

Low-grade tumors are associated with seizures and may have regions adjacent to the lesion that on histopathology are very similar to areas of cortical dysplasia. The tissue contains disorganized cortex with large abnormal neurons
It is reported that cortical dysplasia is found in 4–20% of patients with DNET and gangliogliomas (Honavar et al., 1999; Widdess-Walsh et al., 2005; Park et al., 2006). It is unknown whether patients with low-grade tumors and cortical dysplasia have clinical characteristics that are different from those of patients with only low-grade tumors. Likewise, it is unclear whether dysplastic cortex contributes to seizure generation in patients with tumors. Similarly, 10% of patients with perinatal infarcts are reported to show cortical dysplasia on histopathology (Marin-Padilla et al., 2002; Prayson & Frater, 2003). More studies are needed to better define the clinical features of patients with cortical dysplasia and low grade tumors and infarcts.

**Hippocampal sclerosis with cortical dysplasia**

There is considerable controversy about whether hippocampal sclerosis is the “cause” or “result” of coexistent...
mMCD and mild type I cortical dysplasia in a subgroup of patients with temporal lobe epilepsy. It has been proposed that hippocampal sclerosis can be the result of a “second-hit,” whereby a preexisting structural abnormality (like abnormal temporal lobe cortical development) predisposes individuals to developing hippocampal sclerosis as a result of initial precipitating injuries (IPIs) (Raymond et al., 1995; Blumcke et al., 2002). Other studies have hypothesized that cortical disorganization and cerebral atrophy is an epiphenomenon from an early life IPI and not a developmental disorder or an independent epileptogenic lesion (Kasper et al., 1999; Mathern et al., 2002a, 2002b; Kalnins et al., 2004).

There is support for both of these concepts in the literature. For example, hippocampal sclerosis was reported in 20% of patients with cortical dysplasia in recent studies (Table 2; last column; 5–33%). Nearly all of these cases had mild type I cortical dysplasia or mMCD. A higher incidence of hippocampal sclerosis and mild cortical dysplasia is usually reported in adult compared with pediatric cohorts (Table 2) (Srikijvilaikul et al., 2003; Fauser et al., 2004; Krsek et al., 2008b). Furthermore, the incidence of IPIs is reported to be higher in patients with mild type I compared with severe type II cortical dysplasia (Fauser & Schulze-Bonhage, 2006; Krsek et al., 2008a,c).

Other clinicopathologic and neuroimaging studies report few if any meaningful clinical differences in patients with or without subtle cortical dysplasia and temporal lobe epilepsy from hippocampal sclerosis (Kasper et al., 2003; Mitchell et al., 2003; Diehl et al., 2004; Kalnins et al., 2004; Seidenberg et al., 2005; Adachi et al., 2006). Many patients with mMCD and mild type I cortical dysplasia and hippocampal sclerosis are reported to have smaller atrophic temporal lobes (Colombo et al., 2003; Bast et al., 2004; Andres et al., 2005; Chandra et al., 2007). Furthermore, in patients with dual pathology, ictal onsets using intracranial electrodes were reported to arise from the area of hippocampal sclerosis and not from the region of dysplasia (Fauser & Schulze-Bonhage, 2006). Likewise, most studies have reported minimal differences in becoming seizure free in patients who have or do not have mMCD and mild cortical dysplasia along with hippocampal sclerosis (Srikijvilaikul et al., 2003; Krsek et al., 2008a). Such findings raise doubts about whether subtle cortical lesions, like mMCD and type I cortical dysplasia, constitute independent epileptogenic foci in patients with hippocampal sclerosis and temporal lobe epilepsy, or if these lesions predispose a person to febrile seizures and IPIs.

Obviously, more carefully designed studies are necessary to discern what constitutes cortical dysplasia in patients with hippocampal sclerosis. In the future, it would be appropriate to separate patients with well-characterized mild and severe cortical dysplasia from those with mMCD and microdysgenesis in order to determine the incidence of hippocampal sclerosis with dysplasia. Likewise, future studies should determine if the presence or absence of temporal lobe encephalomalacia and cortical injury correlates with histopathologic criteria for cortical dysplasia with and without hippocampal sclerosis.

**Surgical Procedures, Locations, and Outcomes**

**Types of surgery and their brain locations**

As might be expected from the description of the characteristics of patients with mild and severe cortical dysplasia, there are differences in the type of surgical resections and in age at seizure onset and surgery (Leiphart et al., 2001). In published studies, 72% of patients with cortical dysplasia had focal or lobar resections, and the remaining had multilobar or hemisphere operations (Table 2; 14th column). Most of the focal lobar resections were in adult compared with pediatric cohorts (Table 2). In the ILAE survey of pediatric epilepsy surgery patients, 38% of patients with cortical dysplasia had hemispheric or multilobar resections, compared with 27% for other etiologies (Table 3). In the UCLA series, 37% of patients with cortical dysplasia had hemispheric or multilobar operations, and most of those patients had type II dysplasia (Table 4).

In the published literature, 56% patients had type I cortical dysplasia (Table 2; 13th column). In adult cohorts, up to 80% of patients were reported to have type I cortical dysplasia (Kim et al., 2008). In the UCLA series, 66% of patients had type II cortical dysplasia, which is similar to studies of other younger cohorts (Table 4) (Salamon et al., 2008). Similarly, all lobes of the brain may be involved in patients with cortical dysplasia. However, more adult patients present with type I cortical dysplasia involving the temporal lobe compared with younger patients who present with type II dysplasia in extratemporal regions, including the frontal lobe (Table 4). This finding holds true even if patients with hippocampal sclerosis are excluded from the analysis. As demonstrated in several studies, including the UCLA series, there are no clinical differences based on gender or side of resection in patients with type I or type II cortical dysplasia (Table 4) (Tassi et al., 2002; Widdess-Walsh et al., 2005).

**Postoperative seizure freedom**

The percentage of patients who were seizure free after resective surgery for cortical dysplasia is generally favorable and nearly similar to patients undergoing epilepsy surgery for other etiologies (Spencer & Huh, 2008). In recent studies, 60% of patients are reported to be seizure free after surgery at last follow-up (Table 2; 15th column; 42–87%). In the UCLA series, 82% of patients were seizure free after surgery with 1–2 years of follow-up (Salamon et al., 2008). This is an improvement from studies published from 1971–1999, which reported that
38–40% of patients with cortical dysplasia were seizure free after surgery (Sisodiya, 2000). Of Taylor’s initial report of patients with cortical dysplasia, 60% were seizure free after surgery (Taylor et al., 1971).

For cortical dysplasia patients, the most consistently reported predictor of seizure freedom is complete resection of the lesion. Complete resection is generally defined as removal of the lesion on neuroimaging or the interictal and ictal onset zones in patients undergoing intracranial electrode recordings. Based on these criteria, 30–35% of patients with cortical dysplasia have incomplete resection (Jayakar et al., 2008; Kim et al., 2008; Krsek et al., 2008a, 2008b). Patients with complete resection have a 77% chance of becoming seizure free, compared with 20% for those with incomplete resections (Table 7). The most frequently cited reason for incomplete resections is that areas of cortical dysplasia, often not visible on MRI, were located in cortical regions, the resection of which would lead to unacceptable motor, sensory, visual, or language deficits (Marusic et al., 2002). In cortical dysplasia patients with incomplete resections, seizure recurrence usually happens within 6 months of surgery (Mathern et al., 1999; Widdess-Walsh et al., 2007).

Other clinical variables reported to predict seizure freedom probably interplay with incomplete resection of the cortical dysplasia lesion. Some studies have reported that fewer patients with type I cortical dysplasia are seizure free when compared with those with type II dysplasia (Tassi et al., 2002; Chung et al., 2005; Fauser et al., 2008; Kim et al., 2008). Other studies have reported more favorable outcomes for patients with mild type I cortical dysplasia, although a significant proportion of these patients also had hippocampal sclerosis (Fauser et al., 2004). Hence, it would be helpful if future studies reported outcomes in patients with mild and severe cortical dysplasia without dual pathology. Likewise, an extratemporal location, ill-defined ictal EEG onsets, secondary generalized tonic–clonic seizures, use of intracrani electrode electrodes, and large resections were reported to correlate with poor seizure control after surgery (Hudgins et al., 2005; Widdess-Walsh et al., 2005; Alexandre et al., 2006; Park et al., 2006; Kral et al., 2007; Kim et al., 2008). These correlations probably relate to the difficulty in imaging mild type I cortical dysplasia, especially in extratemporal locations. Of note, a few mostly adult studies have reported that shorter seizure durations correlated with a higher chance of becoming seizure free after surgery (Fountas et al., 2004; Siegel et al., 2006; Fauser et al., 2008). This finding has not been replicated in pediatric patients with cortical dysplasia (Krsek et al., 2008a).

Studies of long-term seizure control after surgery in patients with cortical dysplasia report variable results. Some studies with mostly mild type I cortical dysplasia, including a proportion of patients with hippocampal sclerosis, report stable or increased rates of becoming seizure free, four or more years after surgery (Kloss et al., 2002; Hamiwka et al., 2005; Krsek et al., 2008a). Other studies with mostly severe type II cortical dysplasia and type I without hippocampal sclerosis have shown that 15–17% of patients who were seizure free 2 years after surgery have reoccurrence of seizures three or more years after the operation (Mathern et al., 1999; Kral et al., 2007; Widdess-Walsh et al., 2007). More studies on larger uniformly defined cohorts are necessary to judge if patients remain seizure free many years after surgery, and whether there are differences in patients with mild and severe cortical dysplasia.

**Antiepilepsy medications**

The number of patients with cortical dysplasia off medications after surgery varies from study to study. In the published literature, from 14–41% of patients with cortical dysplasia were reported as not taking antiepilepsy drugs 1–2 years after surgery (Kral et al., 2007; Krsek et al., 2008b). In the UCLA series, 22% of patients with cortical dysplasia were not taking medications 2 years after surgery. In the UCLA cohort, there were no differences in the percentage of patients off medications for those with mild or severe cortical dysplasia.

**Complications and reoperations**

Morbidity and mortality are generally low in patients undergoing surgery for cortical dysplasia. In published studies since 2002, one death (0.2%) was reported (Alexandre et al., 2006). Transient and permanent complications were reported in 13% of patients, of which 11% resolved within 3 months of surgery leaving a permanent complication rate of 2% (Table 2; 12th column). Most transient complications include increased mild neurologic deficits and infections. Permanent complications include new neurologic deficits and acquired hydrocephalus. In the contemporary UCLA series, no deaths were reported, 22% had transient complications that resolved within 3 months of surgery, and permanent complication rate was 2%, consisting of patients that required cerebrospinal

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**Table 7. Percentage of patients with cortical dysplasia seizure free based on complete or incomplete resection of MRI and EEG focus**

<table>
<thead>
<tr>
<th>Study</th>
<th>Complete resection</th>
<th>Incomplete resection</th>
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<tr>
<td>Kloss et al. (2002)</td>
<td>80% (21/26)</td>
<td>17% (5/30)</td>
</tr>
<tr>
<td>Kim et al. (2008)</td>
<td>82% (77/94)</td>
<td>30% (17/56)</td>
</tr>
<tr>
<td>Krsek et al. (2008b)</td>
<td>70% (72/103)</td>
<td>22% (10/96)</td>
</tr>
<tr>
<td>Alexandre et al. (2006)</td>
<td>86% (12/14)</td>
<td>50% (9/18)</td>
</tr>
<tr>
<td>Weighted average</td>
<td>77% (182/237)</td>
<td>20% (41/200)</td>
</tr>
</tbody>
</table>

Chi-square: p < 0.0001.
fluid (CSF) shunts (Jahan et al., 1997). There are no reported differences in surgical complications in patients with type I and type II cortical dysplasia.

With a 30% chance of an incomplete resection, it is not surprising that many patients with cortical dysplasia undergo repeat surgery. In published studies, 14% of patients with cortical dysplasia undergo a reoperation for failure of seizure control after a first surgery (range 13–15%) (Kloss et al., 2002; Krsek et al., 2008a, 2008c). In the UCLA series, 5% of patients with cortical dysplasia had reoperations. The success rate with repeat surgery has not been consistently reported (Siegel et al., 2005). In one series, 4 of 6 patients (66%) became seizure free after reoperation (Krsek et al., 2008c). In the UCLA series, 2 of 4 patients (50%) with cortical dysplasia were seizure free after a second operation. To date, studies have not reported if the rate of reoperation is different in patients with mild or severe cortical dysplasia.

Neuropsychologic outcomes

Developmental assessments before surgery indicate that 33–68% of patients with cortical dysplasia have reduced intelligence scores. However, the results have been inconsistent as to whether patients with type I or type II cortical dysplasia have worse presurgical neuropsychological assessments. Studies have reported that patients with type I dysplasia have worse intelligence scores than those with type II dysplasia (Tassi et al., 2002; Krsek et al., 2008c). Other studies report that patients with type II dysplasia are worse than those with type I, or that there are no differences in intelligence scores based on histopathologic grade (Klein et al., 2000; Widdess-Walsh et al., 2005; Park et al., 2006; Krsek et al., 2008a). It is important to note that the size of the lesion is probably another factor to consider in assessing intelligence scores in patients with cortical dysplasia. In one study, more children with extensive cortical dysplasia on neuroimaging were reported to show severe mental retardation compared with those with focal cortical dysplasia (Klein et al., 2000). Another study reported a higher frequency of maladaptive behavioral disorders in patients with mild compared with severe cortical dysplasia, but no differences were found in the incidence of attention deficit hyperactivity disorder and disorders of speech and language (Krsek et al., 2008c). Hence, more comprehensive studies are needed to explain the variability in neuropsychological profiles in patients with mild and severe cortical dysplasia that may depend on duration of epilepsy, age at seizure onset, and extent of disease on neuroimaging. Of note, there are preliminary data supporting the notion that with early surgery and seizure freedom, children with cortical dysplasia may have improved developmental scales, and this depends on stopping the seizures within 2 years of onset (Jonas et al., 2004, 2005). It is unclear if early surgery is beneficial in adult patients with cortical dysplasia presenting with new-onset epilepsy.

**Pathogenesis and Epileptogenesis of Cortical Dysplasia**

Potential mechanisms of pathogenesis that explain epileptogenesis are beginning to emerge from studies of tissue removed at surgery from patients with cortical dysplasia. The findings from these studies have not always been consistent, and this may depend in part on the age of the patients and whether they have mild type I or severe type II cortical dysplasia. Initially, it was thought that mechanisms of epileptogenesis might involve an increase in AMPA and NMDA–receptor mediated cellular excitation or a loss of GABA-containing neurons leading to reduced cellular inhibition (Spreafico et al., 1998; Kerfoot et al., 1999; Najm et al., 2000; Alonso-Nanclares et al., 2005). However, these ideas were probably overly simplistic as they did not take into account developmental changes in cellular receptors and circuits in dysplastic tissue (Andre et al., 2004; Avoli et al., 2005).

Recently, most investigators have focused on how abnormal cortical development can induce or contribute to epileptogenesis in cortical dysplasia tissue (Najm et al., 2007). Recent morphologic and in vitro electrophysiologic studies support the notion that areas of severe type II cortical dysplasia involve a more significant and earlier failure of cortical development than mild type I dysplasia (Andre et al., 2004; Cepeda et al., 2006; Andre et al., 2007, 2008). If correct, then seizure generation has been hypothesized to be the consequence of incomplete cellular maturation, and pathogenetic mechanisms will likely vary in mild and severe cortical dysplasia tissue. These research endeavors are still in their infancy; more studies are needed to understand possible mechanisms of epileptogenesis in cortical dysplasia tissue, and if the mechanisms are different in cases of mild compared with severe disease.

**Critical Review and Future Challenges**

From this literature review, the 2004 ILAE survey, and the UCLA cohort, a picture emerges of the clinical characteristics of patients with cortical dysplasia and the features that distinguish those with mild Palmini type I from severe Palmini type II cortical dysplasia. The most consistent findings are summarized in Table 8, and begin to describe what may become unique epilepsy surgery syndromes involving patients with cortical dysplasia. Although we have learned a great deal over the last decade from retrospective surveys of surgical cohorts, our knowledge
of the clinical, electrographic, neuroimaging, and histopathologic elements of patients with cortical dysplasia should be considered rudimentary and incomplete. Future studies would benefit from prospective multicenter collaborations that test current assumptions and ideas about the pathogenesis of cortical dysplasia and how this tissue generates seizures. A list of pertinent questions that could form the focus of the next generation of research investigations is indicated in the following.

Are we using the best histopathologic classification system to define cortical dysplasia? Do patients form distinct subgroups, or is there a continuous spectrum of histopathologic abnormalities of altered cortical development that defines patients with cortical dysplasia and correlates with clinical features of their epilepsy?

For clinical and basic researchers, the introduction of the Palmini classification system was an important step to uniformly define the nomenclature and grading of patients with cortical dysplasia. Furthermore, as illustrated in this review, there are some clinical and neuroimaging differences found when comparing patients with mild type I with severe type II cortical dysplasia. However, most of the reported differences in patients with type I and type II cortical dysplasia involve age at presentation, seizure frequency, and imaging with minimal or no differences in seizure semiology, interictal and ictal EEG, and other findings. In addition, the Palmini grading system has shown few substantial and consistently reported differences comparing patients with type IA with type IB and patients with type IIA with type IIB cortical dysplasia (Table 1) (Boonyapisit et al., 2003; Lawson et al., 2005; Widdess-Walsh et al., 2005; Krsek et al., 2008a). Hence, it appears that there are inherent limitations to the Palmini system. In other words, results using the Palmini classification system are similar to earlier schemes that separated patients into those with mild and severe cortical dysplasia based on histopathologic criteria (Mischel et al., 1995; Tassi et al., 2002).

The Palmini scale relies as major criteria on the presence or absence of dysmorphic–cytomegalic neurons and balloon cells and does not take into consideration other histopathologic features of abnormal cortical development. Likewise, the Palmini scale does not consider the potential value of quantitative morphometric techniques and immunohistochemical staining in classifying patients with cortical dysplasia (Kerfoot et al., 1999; Andres et al., 2005). Hence, future investigations may wish to determine if patients with cortical dysplasia fit into clearly definable histopathologic subgroups, or does the histopathology follow a continuous spectrum of cytologic and histologic abnormalities. Preliminary analysis of the UCLA series suggests that a continuous histopathologic classification system might be better suited for epilepsy surgery patients with cortical dysplasia (Fig. 10A). In this figure, the frequency of patients with increasing histopathologic elements of abnormal cortical development is plotted. Most patients have two to five features consistent with cortical dysplasia. Furthermore, the distribution overlaps between patients with mild type I and severe type II cortical dysplasia using the Palmini system (Fig. 10B). By using more histopathologic characteristics of abnormal cortical development in a classification system it may be possible to develop a grading system that better captures the broad clinical characteristics of patients with cortical dysplasia. Such a system might also address if mMCD and microdysgenesis can be uniformly and clearly defined and readily distinguished from milder forms of cortical dysplasia.

Table 8. Summary of clinical characteristics of patients with cortical dysplasia

<table>
<thead>
<tr>
<th>All patients with cortical dysplasia</th>
</tr>
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<tbody>
<tr>
<td>Constitutes the most frequent histopathology in children and the second or third most common etiology in adults</td>
</tr>
<tr>
<td>Typically present with seizures and have surgery at an earlier age than other etiologies in epilepsy surgery patients</td>
</tr>
<tr>
<td>Most epilepsies surgical cases less than 3 years of age involve cortical dysplasia</td>
</tr>
<tr>
<td>About 15% of cases with cortical dysplasia will present with status epilepticus, and 30% with a history of infantile spasms</td>
</tr>
<tr>
<td>About 50% of patients with cortical dysplasia will present with localizing interictal and 68% with localized ictal scalp EEG findings</td>
</tr>
<tr>
<td>MRI is abnormal with signs specific for cortical dysplasia in about 65% of cases</td>
</tr>
<tr>
<td>FDG-PET is positive in approximately 75–90% of patients with cortical dysplasia. Ictal SPECT is positive in slightly over 50% of cases</td>
</tr>
<tr>
<td>Overall, 60% are seizure free after surgery. About 80% of patients with complete resection are seizure free compared with 20% with incomplete resections</td>
</tr>
<tr>
<td>Mild type I vs. severe type II cortical dysplasia</td>
</tr>
<tr>
<td>In children, about half of patients will have mild cortical dysplasia. In adults, the majority have mild cortical dysplasia</td>
</tr>
<tr>
<td>Patients with severe cortical dysplasia are generally younger at age at surgery, age at seizure onset, have shorter seizure duration, and higher seizure frequencies than mild type I cases</td>
</tr>
<tr>
<td>Severe type II cortical dysplasia is most often extratemporal or hemispheric while mild type I dysplasia is most often temporal and lobar/focal</td>
</tr>
<tr>
<td>Approximately 90–100% of patients with type II dysplasia will show MRI abnormalities compared with 15–60% of patients with type I cortical dysplasia</td>
</tr>
<tr>
<td>There is a suggestion that about 15% of patients with type II cortical dysplasia may relapse with seizure many years after surgery</td>
</tr>
<tr>
<td>Size of cortical dysplasia based on neuroimaging</td>
</tr>
<tr>
<td>Hemispherectomy/multilobar cases are generally younger at age at surgery, age at seizure onset, and have shorter seizure duration than lobar/focal cases for patients with both mild and severe cortical dysplasia</td>
</tr>
</tbody>
</table>

Table 8. Summary of clinical characteristics of patients with cortical dysplasia

Surgical Treatment of Cortical Dysplasia

Epilepsia, 50(6):1310–1335, 2009
Should a classification system of patients with cortical dysplasia take into account the size of the lesion on neuroimaging?

In this review, we showed that there were clinical differences comparing patients with mild and severe cortical dysplasia. We also showed that age at seizure onset, age at surgery, and seizure frequency correlated independently with the size of the lesion on MRI (Fig. 5). This raises the question of whether a comprehensive classification system for patients with cortical dysplasia should incorporate neuroimaging characteristics into the scheme. Neuroimaging features can be assessed noninvasively and quantitatively (Andres et al., 2005; Barkovich et al., 2005). This might include size (Fig. 5) along with specific MRI features such as thickened gray matter and the transmantle sign (Table 6, Fig. 6). Whatever the features, any neuroimaging classification system should identify areas of cortical dysplasia in patients undergoing presurgical evaluations, and predict the histopathologic grade of the lesion.

Are there different etiologies in patients with milder forms of cortical dysplasia?

There is considerable confusion about the presence or absence of abnormalities of cortical development if the MRI is normal or shows encephalomalacia in patients with mild cortical dysplasia. Therefore, it would be important for future studies to address whether the histopathologic features in patients with mMCD and mild cortical dysplasia are different depending on MRI features. It would also be important to discern whether the histopathologic characteristics of mMCD and mild cortical dysplasia are different in patients with temporal lobe epilepsy with and without hippocampal sclerosis and in patients with other dual pathologies such as perinatal strokes (Marin-Padilla, 1999; Marin-Padilla et al., 2002).

What is the incidence of cortical dysplasia in patients with refractory epilepsy?

A substantial proportion of patients with cortical dysplasia have nonlocalizing foci using scalp EEG and “normal” MRI scans. Many of these are adult patients with mild cortical dysplasia. This raises the important question: How many patients with cortical dysplasia are we missing by using current noninvasive presurgical protocols that rely heavily on positive structural MRI scans? The answer could be a substantial number. Hence, an important challenge will be to validate “newer” presurgical protocols and technologies that can noninvasively screen patients with refractory epilepsy for the presence of subtle cortical dysplasia and improve our accuracy in identifying patients with this disorder. This will be
especially important for patients with mild cortical dysplasia without coexistent hippocampal sclerosis that are currently MRI negative.

Several older and newer structural and functional neuroimaging techniques are candidate tools that might increase detection of cortical dysplasia in refractory epilepsy patients (Hwang et al., 2001; Akhtari et al., 2006). For MRI, these techniques might include magnetic resonance spectroscopy (MRS) using high (>3T) field strength magnets, diffusion tensor imaging (DTI), dynamic perfusion imaging, functional MRI, and structural image analysis to quantify areas of gray and white matter abnormalities (Eriksson et al., 2001; Raybaud et al., 2006; Widjaja et al., 2007). Newer PET ligands, such as flumazenil and alpha-(11C)methyl-L-tryptophan, need to be tested in patients with mild and severe cortical dysplasia, and new PET ligands developed perhaps based on findings from studies of excised cortical dysplasia tissue (Juhasz et al., 2000a, 2000b).

Newer methods of EEG source imaging with high density scalp electrodes need to be studied in patients with mild and severe cortical dysplasia (Sperli et al., 2006).

Are there different long-term surgical outcomes for patients with mild and severe cortical dysplasia?

At present, there appear to be minimal differences in the percentage of patient’s seizure free 1–2 years after surgery, if the area of cortical dysplasia is completely removed. However, it is unclear if patients remain seizure free four or more years after surgery, and if outcomes vary depending on whether they had mild or severe cortical dysplasia. Hence, long-term studies of outcomes are needed to determine if there are differences in the percentage of patients who are seizure free along with developmental and psychosocial results for patients with mild and severe cortical dysplasia. These studies should exclude patients with dual pathology, such as hippocampal sclerosis, who are known to be capable of independent epileptogenesis, so that uniform populations of patients with cortical dysplasia are studied.

Is there a developmental explanation for the greater number of patients with mild cortical dysplasia who have lesions in the temporal lobe relative to those with severe dysplasia with lesions in extratemporal locations?

If cortical dysplasia represents a malformation of cortical development, then understanding why different lobes of the brain are involved with mild and severe dysplasia may offer clues to the pathogenesis of this disorder. Understanding pathogenesis might predict mechanisms of epileptogenesis that would be useful to develop into treatments.

What are the mechanisms of epileptogenesis in cortical dysplasia tissue? Do mechanisms differ in patients with mild and severe cortical dysplasia? Can mechanisms gleaned from basic science research be developed into novel treatments for patients with cortical dysplasia?

A current frustration for clinical teams that treat patients with cortical dysplasia is the realization that a substantial number of patients cannot undergo complete resection of the MRI lesion or EEG focus because it involves areas of important functional cortex. Another future challenge will be to develop novel therapies that might control seizures so that more patients with cortical dysplasia can be successfully treated without increasing the risk of new neurologic deficits. This may involve nonsurgical remedies developed on the basis of mechanisms learned from the basic science laboratory, involving abnormal cells and circuits in cortical dysplasia tissue. These therapies will also need to include emerging knowledge of the genetic abnormalities that may be different in patients with mild and severe cortical dysplasia (Ljungberg et al., 2006). Hence, there is a need for more resources devoted to understanding the mechanisms of epileptogenesis and pathogenesis along with genetics in patients with cortical dysplasia, and whether these mechanisms are different in those with mild and severe disease. The use of human tissue also offers the unique opportunity to try new pharmacologic treatments as an adjunct in therapy discovery for patients with cortical dysplasia. Therefore, it is anticipated that in the future we will understand more about the clinical characteristics and mechanisms of epileptogenesis in patients with mild and severe cortical dysplasia, which can be translated into novel therapies that may be targeted to the distinct histopathologic elements found in this malformation of cortical development.

Acknowledgments

This study was supported by NIH grants R01 NS38992 and P05 NS02808. Harry V. Vinters was supported in part by the Daljit S. and Elaine Sarkaria Chair in Diagnostic Medicine, Susan Koh and Rintat Jonas assisted in collecting EEG data on the UCLA cohort. The following individuals are acknowledged for providing data as part of the ILAE survey of pediatric epilepsy surgery centers (Harvey et al., 2008): P. Van Boraert, X. De Tiege, Belgium; Brussels; E. Gaily Finland, Helsinki, Hospital for Children and Adolescents; O. Delandale, C. Bulteau, M. Fohlen, France, Paris, Foundation Rothschild; R. Sassen, Germany, Bonn; H. Holthausen, T. Pieper, Germany, Vogtareuth; O. van Nieuwenhuizen, Netherlands, Utrecht, Wilhelmina Children’s Hospital; B. Rydenhag, Sweden, Göteborg, Sahlgrenska University Hospital; P. Amark, Sweden, Stockholm, Karolinska, Astrid Lindgren Children’s Hospital; J. H. Cross, W. Harkness, C. Dunkley, United Kingdom, London, Great Ormond Street Hospital for Children; NHS Trust; A. S. Harvey, W. Maixner, Melbourne, Royal Children’s Hospital; D. Gill, J. Lawton, Sydney, Children’s Hospital Westmead & Sydney Children’s Hospital; J. Rivielo, Boston, Children’s Hospital Boston; D. Lachhwani, E. Wyllie, Cleveland, Cleveland Clinic Foundation; D. Nordli, L. Laux, Chicago, Children’s Memorial Hospital; S. Koh, Los Angeles, University of California, Los Angeles; M. Duchowny, P. Jayakar, Miami, Miami Children’s Hospital; J. Gates, F. Ritter, Minnesota, Minnesota Epilepsy.
We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest: The authors disclose no financial conflict of interest.

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