1042–3680/02 $15.00 + .00

CLASSIFICATION ISSUES IN MALFORMATIONS CAUSED BY ABNORMALITIES OF CORTICAL DEVELOPMENT

André Palmini, MD, PhD, and Hans O. Lüders, MD, PhD

Malformations caused by abnormality(ies) of cortical development (MCD)* have been increasingly attracting the interest and attention of clinicians and neuroscientists involved with epilepsy. Advances in basic and clinical neuroscience have opened exciting roads for research on the mechanisms through which MCD can modify cortical excitability, leading to epilepsy and altered cortical function.

Knowledge about MCD as an etiology for partial and generalized epilepsy has seen a lot of progress in the last decade.[7,45,57,58] The greatest advances, however, are related to the uncovering of pathogenetic mechanisms,[26,27,31,73,77] the engineering of animal models,[18,19,36] the clarification of clinical-electrographic correlations,[25,29,60] and the delineation of surgical strategies[35,37,59,62] for the various types of MCD. On the other hand, these advances were not paralleled by the development of consensual, practical, and clinically sound nomenclature and classification schemes that could allow for further progress through improved communication at clinical, histopathologic, and basic science levels.

The pathogenesis of the different histopathologic patterns comprising the group of entities encompassed under the "umbrella terminology" of MCD is clearly multifactorial: genetic mutations,[27,31,32,40] in utero injuries at different stages of brain development,[20,56,69] and even perinatal or postnatal insults.[50,71] The type, timing, and severity of environmental insults or the type of genetic mutation and the impact of the abnormal gene product at different stages of brain development are likely to shape the various histopathologic and anatomic types of MCD.[27,31]

Some of the currently proposed classifications for MCD are heavily based on neuroimaging descriptions,[61] although others are based solely on histopathologic[45,62] or embryologic timing of the insult that may have led to the development of the cortical malformation.[52] The most comprehensive work toward a classification so far is that proposed by Barkovitch and colleagues,[8] who have included

*References 1, 8, 45, 55, 64, 69, 72, 75, and 76.

From the Porto Alegre Epilepsy Surgery Program, Neurology Service, Faculty of Medicine, and Hospital São Lucas, Pontificia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil (AP); and Department of Neurology, The Cleveland Clinic Foundation, Cleveland, Ohio (HOL)

embryologic, histopathologic, imaging, and genetic aspects within the same scheme. The major merit of this classification is to organize the different types of MCD within an embryologic-physiopathologic framework, recognizing that MCD can be caused by selective abnormalities in specific stages of cortical development: neuroglial proliferation and differentiation, neuronal migration, and postmigratory cortical organization. The result is a comprehensive classification, which may not be practical for everyday use, however. There are many sections and subsections, which clearly show how rich is the field of MCD but often leave the clinician and the scientist without a clinically sound pragmatic scheme in his or her mind. There are many more categories of rare entities or entities that only rarely present with intractable epilepsy (without other more obvious and incapacitating neurologic abnormalities) than those that comprise the types of MCD dealt with in everyday practice. Moreover, this classification[8] did not analyze in detail a key issue in current epileptology—the focal cortical dysplasia(s) (FCD), which are localized malformations increasingly associated with refractory seizures[49,53,60,65] and currently being dealt with surgically at most epilepsy surgery centers. The different aspects of the histopathologic findings of this latter group of architectural and cellular abnormalities have not been fully contemplated in any of the previous classification schemes, and this has left practicing epileptologists and neurosurgeons without a clear picture of how to anticipate the prognosis of the medical and surgical treatment of patients with these specific and frequent abnormalities. Along these lines, data generated recently have suggested that different types of MCD are associated with epilepsy syndromes and metabolic abnormalities[49,65] of varying and specific severity and prognosis,[16,33,55,63,70] stressing the need for a more clinically sound classification.

A classification scheme that could be of practical and broad application is proposed here. Its usefulness can only be known prospectively as indicated by its acceptance or rejection by those dealing with patients with MCD in everyday practice and as their major focus of research.

The authors' proposal is divided into three parts: (1) definition of selected key and at times controversial terminology for the histopathologic description of the MCD; (2) description of selected aspects of the FCD, which have contributed to confusion in the literature and should be clarified so as to permit the organization of a clear and simple classification; and (3) a classification proper, in which each entity is described and correlated with its most common histopathologic scenario and with the status of identification by MR imaging at this point. When appropriate, insights into pathogenesis, clinical features, and prognostic aspects also are included. (The sections on definition of terms and selected histopathologic aspects of MCD were the focus of the discussions among the panel of specialists with an expertise in MCD, and what follows is a synthesis of the contributions of that group.*)

DEFINITION OF TERMS: TOWARD A UNIFORM NOMENCLATURE

The first issue that raises some debate is the preferred terminology for this whole group of entities. There is a developmental common denominator whatever the mechanism of injury (genetic, intrauterine, or even perinatal).[50,71] By "developmental," it is meant that the injury has an impact at some point in the development of the cortical mantle and thus establishes the lesion. Because one or more of the mechanisms pertaining to corticogenesis can be affected, and because even the malpositioning of nodular or laminar aggregates of neuroblasts and glial cells in heterotopic positions

*Several of the concepts described here were generated through a panel discussion during a workshop in Cleveland, Ohio, in June 2000 on the terminology and classification of cortical dysplasias. Participants were (by alphabetic order): Andre Palmini, Giuliano Avanzini, Graheme Jackson, Hans Lüders, Harry Vinters, Imad Najm, Nancy Foldvary, Renzo Guerrini, Richard Prayson, Roberto Spreafico, and Thomas Babb.

actually represents interference with cortical formation (indeed, these cells were originally bound to the cerebral cortex), the term *malformations caused by abnormal cortical development* may be the most appropriate. Accordingly, the term *cortical dysplasias* should be applied only to the subtype of MCD in which the developmental abnormality is strictly or mostly intracortical. *Focal cortical dysplasia* would be a good term within this framework only. Further subtyping of FCD on the basis of histologic peculiarities is presented elsewhere in this article. Likewise, the term *neuronal migration disorders*, historically applied to all forms of MCD in the early 1990s,[64,72] would suggest that all MCD were caused by predominant interferences with migratory mechanisms. It is clear that other pathogenetic mechanisms also apply; thus, neuronal migration disorders are, again, only a subtype of MCD.

The terms used in the following sections should perhaps be better defined or replaced.

Microdysgenesis

This term has been the focus of significant confusion. Originally coined by Meencke and Janz[51] to describe minimal subtle abnormalities of intracortical architecture in patients with generalized epilepsies undergoing autopsy studies, *microdysgenesis* has been applied in the realm of the MCD in different ways. Some authors have used the term in connection with subtle derangements of cortical architecture discovered only retrospectively on histopathologic examination. Included were mild abnormalities such as those mentioned by Mischel and colleagues[52] as (1) cortical laminar disorganization, (2) single (or small aggregates of) heterotopic white matter neurons or neurons in the molecular layer, (3) a persistent subpial granular layer, and (4) marginal glioneuronal heterotopia. In contrast, others have used the term *microdysgenesis* to describe any type of MCD that was not seen on MR imaging, irrespective of the histopathologic characteristics.[41] Because many instances of MR imaging–negative MCD can be associated with severe histopathologic abnormalities, including dysplastic neurons and balloon cells,[10,17,24,60,62] there is a clear histologic incongruence between the two uses of the term *microdysgenesis*.

Perhaps this term should be abandoned, and a more specific nomenclature should be used. Because most of the mild abnormalities reviewed by Mischel and colleagues[52] involve cortical layer I, a proposal was made to subdivide the mildest forms of MCD into those characterized by ectopically placed neurons in or adjacent to layer I (neurons in the molecular layer, persistent subpial granular layer, and marginal glioneuronal heterotopia [Fig. 1]) and those in which the abnormalities are outside layer I (single [or small aggregates of] heterotopic white matter neurons, which are at times found at autopsy or on histopathologic examination of tissue excised at surgery).[34,39,41] Intracortical laminar disorganization (dyslamination) may be best conceptualized as the mildest form of FCD (see below), allowing for the abandonment of the term *microdysgenesis*.

Dysmorphic (Dysplastic) Neurons

These clearly are abnormal cells (Fig. 2). Their shape, orientation, and cytoskeleton are all abnormal. Nissl substance can be seen in clumps, and specific immunostaining for neurofilaments and some silver staining techniques show that there is an abnormal abundance of cytoplasmic neurofilaments.[73,74] Importantly, hematoxylin-eosin staining alone cannot disclose all the histologic characteristics of these abnormal cells. Dysmorphic neurons can be increased in size or not, and they correspond to the dysplastic neurons described by Taylor et al.[75] Dysmorphic neurons are characteristic of some types of FCD and not of others.

Balloon Cells

These are grossly abnormal cellular elements with a thin membrane, pale and eosinophilic cytoplasm, and eccentric nucleus (or

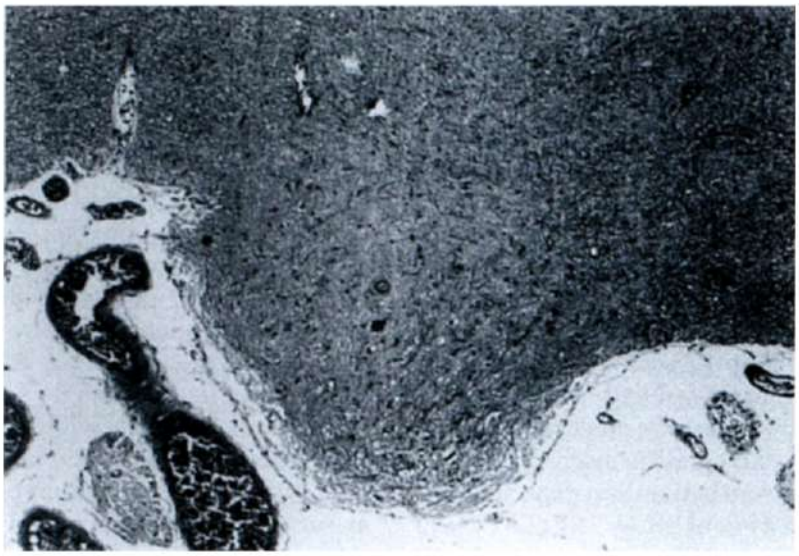

Figure 1. Histopathologic section of a marginal glioneural heterotopia (mild malformations caused by abnormalities of cortical development [MCD] involving layer I). Note the stretching of the pial lining with a heterotopic protusion (hematoxylin-eosine, original magnification × 10).

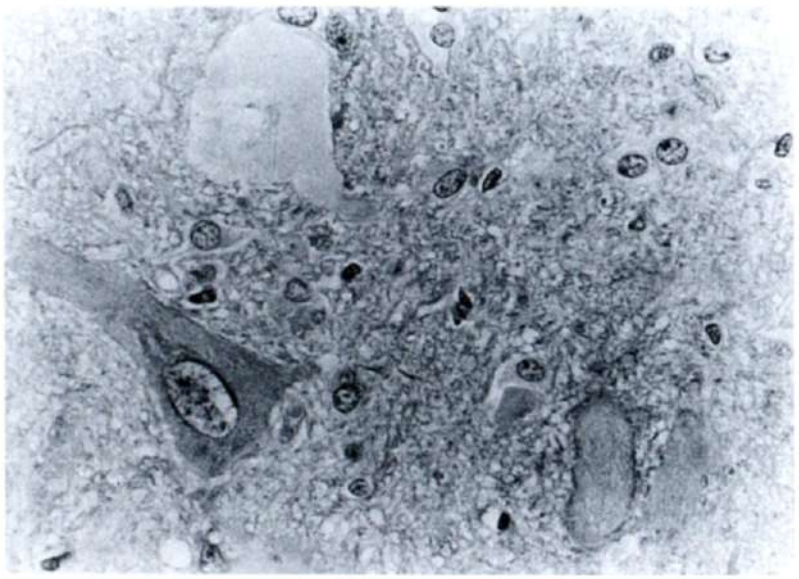

Figure 2. Enolase staining section showing a large, abnormally oriented dysmorphic (dysplastic) neuron on the left lower half of the image (original magnification × 40).

nuclei, as some are multinucleated) (Fig. 3). Usually, but not always, balloon cells are of increased size (occasionally, they are huge). Recommendations for staining include hematoxylin-eosin, glial fibrillary acidic protein (GFAP), neuron-specific enolase, and vimentin immunostaining, with the latter being fairly specific for these cells in the face of their uncommitted status between glial and neuronal lineages.[5,67,74] Interestingly, besides the common denominator of being vimentin-positive, some balloon cells are GFAP-positive and others are enolase-positive,[5,74] suggesting some degree of heterogeneity with partial commitment toward glial or neuronal lineage.

Giant Neurons

These are neurons increased in size in comparison with normal layer V pyramidal cells. In addition, they can be found scattered in any layer from layer II through layer VI. In contrast to truly dysmorphic neurons, however, giant neurons display a preserved pyramidal morphologic profile, and immunostaining does not show a pathologic excess of neurofilaments in the cytoplasm.

Immature Neurons

These are round (or oval) homogeneous cells with a large (immature) nucleus and a thin rim of cytoplasm. They are not dysmorphic or giant but are sometimes seen in association with these more abnormal cells. Occasionally, they can be found in macroscopic heterotopic nodules, but they also are found in FCD.[73,74]

(Microscopic) Neuronal Heterotopias

As discussed previously, the microscopic heterotopias could all be included under the terminology of MCD within or outside layer I. A proposal could be made that a cluster of at least 12 misplaced neurons might be enough to characterize a microscopic heterotopia. The macroscopic heterotopias (periventricular, subcortical nodular, band heterotopia),

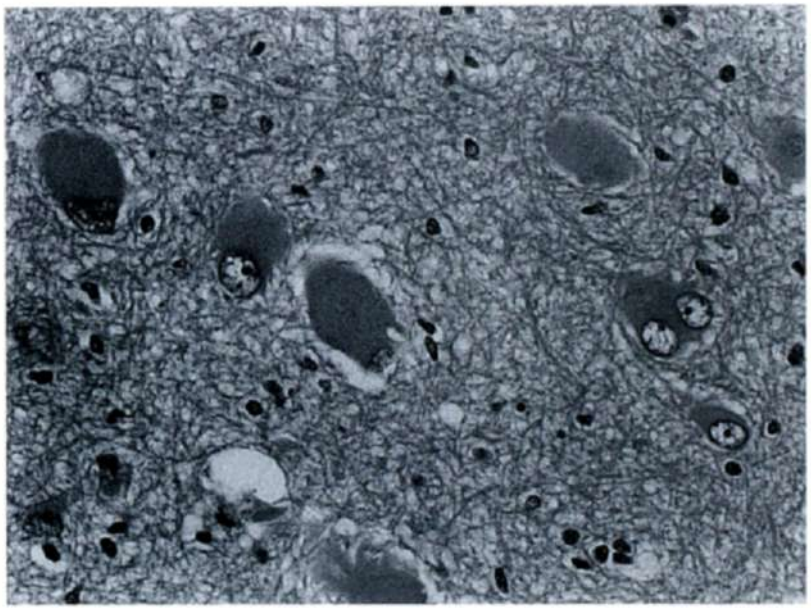

Figure 3. Histopathologic section of a collection of balloon cells in the cortical-subcortical transition. Note the opalescent, highly eosinophilic cytoplasm and the lack of laminar or columnar orientation. Some cells are binucleated (hematoxylin-eosin, original magnification × 40).

on the other hand, are already well-defined abnormalities of neuroblast migration.

SELECTED HISTOPATHOLOGIC ASPECTS OF MALFORMATIONS CAUSED BY ABNORMALITIES OF CORTICAL DEVELOPMENT: THE VARIOUS SCENARIOS OF FOCAL CORTICAL DYSPLASIAS

As discussed previously, there are several cellular elements that may occur in various combinations, leading to specific histopathologic pictures in cortical malformations. There is growing evidence that the exact combination of histopathologic abnormalities may relate to imaging identification and to clinical evolution of patients with epilepsy.[14, 16, 17, 33, 47, 55, 63, 70]

There has been some degree of heterogeneity in the clinical, surgical, and histopathologic literature, and terms like *focal cortical dysplasia, mild cortical dysplasia, Taylor type focal cortical dysplasia, balloon-cell dysplasia, non–balloon-cell dysplasia,* and *microdysgenesis*[17, 26, 41, 45, 58, 70, 73] all have been applied to describe architectural and cellular abnormalities of the cortical mantle. For instance, some authors use the term *Taylor type focal cortical dysplasia* only when balloon cells are present,[26, 30] although others, including Taylor and colleagues in their original report,[75] included some patients whose lesions had dysmorphic (dysplastic) neurons but lacked balloon cells. Although a definitive understanding of the relevance of each cell type or architectural abnormality among the various possible combinations relies on further developments in the mechanisms of corticogenesis and their relation to clinical and imaging findings, a tentative practical approach is attempted here.

Architectural Abnormalities (Dyslamination) Only

These are intracortical lesions that, when occurring unaccompanied by abnormal cellular elements, could be conceived as either representing the mildest end of the spectrum of FCD or included with the other types of mild MCD ("former microdysgenesis").

Architectural Abnormalities (Dyslamination) Plus Immature or Giant (but Not Dysmorphic or Dysplastic) Neurons

At times, dyslamination is associated with immature or giant neurons, thus comprising a more complex histopathologic picture. Whether the presence of these cells has any clinical meaning and deserves specific differentiation from those cases harboring only dyslamination is unclear. Because cells with increased size could theoretically facilitate in vivo recognition by imaging, it is tempting to retain such subclassification at this point.

Architectural Abnormalities (Dyslamination) Plus Dysmorphic Neurons but Without Balloon Cells

Irrespective of the occasional co-occurrence of giant or immature neurons, dysmorphic neurons are the hallmark of these lesions, that is, neurons with variable size but uniformly characterized by poor intracortical orientation and an intracytoplasmic accumulation of neurofilaments as seen through specific immunostaining techniques (Fig. 4).[73, 74] This accumulation of neurofilaments leads to a distorted morphologic profile of the perikarya, proximal axon, and dendrites. It is theoretically conceived that these are more severe abnormalities from a histopathologic standpoint.[52] In the original publication of Taylor et al,[75] 4 of 10 patients had this histopathologic picture.

Architectural Abnormalities (Dyslamination) Plus Dysmorphic Neurons Plus Balloon Cells

These lesions are considered to represent the most severe end of the spectrum of histopathologic abnormalities of FCD

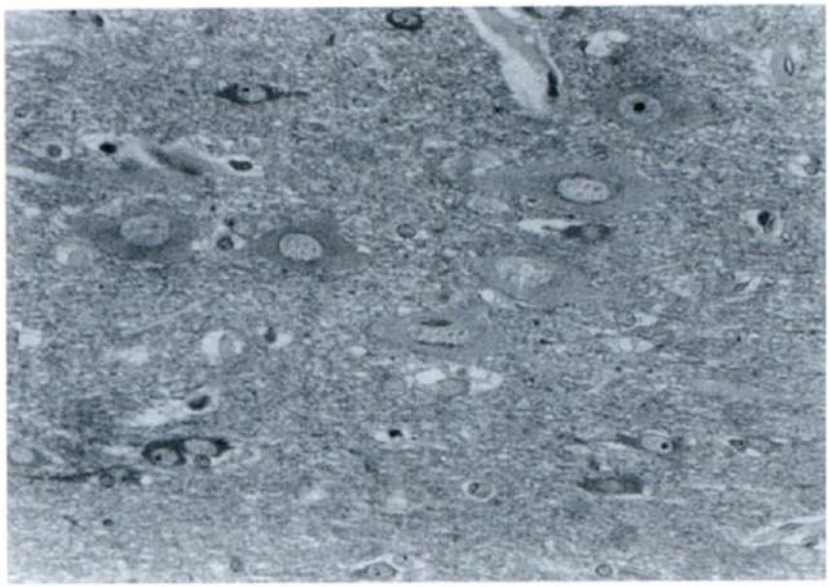

Figure 4. A group of dysmorphic neurons, which is the major histopathologic feature of this patient. Balloon cells were not present (Taylor-type [TT], focal cortical dysplasias [FCD] type IIa).

(Fig. 5).[52] Once again, irrespective of the presence of fewer abnormal cells, these lesions have in common the co-occurrence of dysmorphic neurons and balloon cells. Six of the ten original patients reported by Taylor et al[75] had this histopathologic picture.

There are preliminary data supporting the idea that those types of FCD displaying

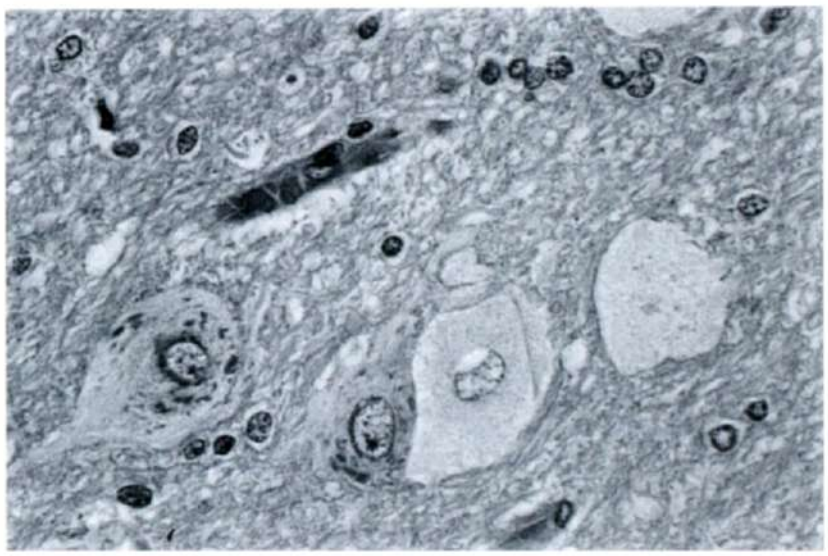

Figure 5. Co-occurrence of dysplastic (dysmorphic) neurons and balloon cells within the same lesion (TTFCD, type IIb). In this section note the peri-nuclear distribution of Nissl substance in the dysmorphic neurons on the left side of the image and the absence of this neuronal marker on the immediately adjacent balloon cells to the right (hematoxylin-eosin, original magnification × 40).

dysmorphic neurons, irrespective of the presence of balloon cells, are the ones associated with the higher degrees of epileptogenicity.[54,55] In addition, most reports correlating imaging and histopathologic abnormalities in FCD, broadly speaking, suggest that the types of FCD identified by imaging usually are those harboring dysmorphic neurons irrespective of the presence of balloon cells.[1,10,17,43,47] From a practical standpoint, it is relevant to clearly delineate the histopathologic scenarios defined previously, because this may allow a much clearer correlation between imaging, histopathologic findings, and clinical issues, particularly prognosis. The incorporation of these scenarios and clarification of the various histopathologic pictures usually subsumed under the term *microdysgenesis* is probably the most important proposal for the overall classification of MCD.

CLASSIFICATION ISSUES: HISTOPATHOLOGIC FINDINGS, IMAGING, AND POTENTIAL CLINICAL RELEVANCE

Taking into consideration the definition of terms and the re-evaluation of the histopathologic scenarios mentioned previously, a classification of MCD could be proposed at this point. Note that although some imaging and histopathologic correlations are suggested, there is no attempt to include an embryologic perspective in the classification. Advances in knowledge of the molecular neurobiology of these disorders may significantly change our view in terms of pathogenesis, and the exact stages in embryologic development during which specific MCD are produced are still a matter of research. For the time being, however, the subdivision suggested by Barkovitch and colleagues[8] into abnormalities of cell proliferation, migration, and cortical organization should be retained as a framework within which the entities described here could be embryologically conceptualized.

Mild Malformations Caused by Abnormalities of Cortical Development

Types

Type I: with ectopically placed neurons in or adjacent to layer I
- —Neurons in the molecular layer
- —Persistent subpial granular layer
- —Marginal glioneuronal heterotopia

Type II: with abnormalities outside layer I
- —Small aggregates of heterotopic white matter neurons
- —Dysgenesis of the hippocampal formation

Structural Imaging

Both types usually are invisible by current MR imaging methodology, except for some instances of macroscopic malformations of the hippocampus or the dentate gyrus.[11,48]

Histopathologic Findings

Histopathologic findings and subtyping are as described previously.

Potential Clinical Relevance

It has been shown that these mild MCD may be related to epilepsy and other behavior and cognitive abnormalities.[3,28,41,42,66] Because diagnosis usually is retrospective, clear clinical and epileptic profiles of patients harboring these mild malformations are not available. As a result, there is some debate on the role of these mild changes in the causation of epilepsy in general, but specially when the histologic abnormalities are found in mesial temporal structures, leading to microscopic heterotopia in the dentate gyrus, hippocampus, or parahippocampal gyri.[38,44] There is less disagreement on the relevance of macroscopic malformations in these mesial temporal structures for the genesis of temporal lobe epilepsy as recently shown by the group at Salpètrière. Furthermore, the association of mesial limbic malformations with schizophrenia and autism

has attracted the attention of nonepileptologists to the putative clinical consequences of mild MCD.[2, 15, 21]

Focal Cortical Dysplasias

Type I

Type I: without dysmorphic neurons or balloon cells
- —Ia: architectural abnormalities only (dyslamination accompanied or not by the other abnormalities of mild MCD)
- —Ib: architectural abnormalities plus giant or immature but not dysmorphic neurons

Structural Imaging

It is unclear at the present time whether or not type I FCD as defined here can be identified in vivo by current MR imaging techniques. Should a common nomenclature be used by different centers, imaging and histopathologic correlations are likely to clarify this issue.

Histopathologic Findings

Histopathologic findings are as described previously.

Potential Clinical Relevance

It is likely that some of these patients have epilepsy and that others do not, being either asymptomatic or presenting instead with learning disorders or other types of cognitive impairment. There are no specific data delineating a clinical or neurophysiologic profile of epileptic patients with type Ia or type 1b FCD. Because most of these mild abnormalities have hitherto defied in vivo imaging recognition, the only evidence there is concerns patients undergoing epilepsy surgery in whom such mild abnormalities were the only histopathologic finding.[12, 41, 45] This suggests that at least some patients with type Ia or Ib FCD can have medically refractory epilepsy. Whether this is a common occurrence or represents only the most severe end of the spectrum is unclear, however. Interestingly, surgical patients in whom these mild MCD were retrospectively found tended to have much better results in comparison with the surgical results obtained in other types of FCD.[12]

Type II

Type II: with dysmorphic neurons accompanied or not by balloon cells (Taylor type FCD)
- —IIa: architectural abnormalities plus dysmorphic neurons but without balloon cells (see Fig. 4)
- —IIb: architectural abnormalities plus dysmorphic neurons plus balloon cells (see Fig. 5)

Structural Imaging

These are the focal "dysplastic" lesions most readily identified by MR imaging. Nevertheless, one should be aware that several different imaging possibilities may accompany patients with Taylor type FCD. MR imaging can either be normal[17, 24, 47, 60] (despite high-quality protocols) or demonstrate one or more of the following: (1) focal areas of increased cortical thickness[7, 10, 17, 47]; (2) blurring of the cortical-subcortical transition,[7, 10, 17, 61]; (3) increased signal on T2-weighted, proton density, or fluid-attenuated inversion recovery (FLAIR) sequences (Fig. 6)[14, 17]; (4) extension of cortical tissue with increased signal from the surface to the ventricle (transmantle dysplasia)[9]; and (5) a cerebrospinal fluid cleft with a cortical dimple.[13]

Histopathologic Findings

Histopathologic findings are as detailed previously.

Potential Clinical Relevance

Type IIa and IIb FCD are characterized by truly abnormal and grossly dysmorphic cellular elements, which are accompanied by

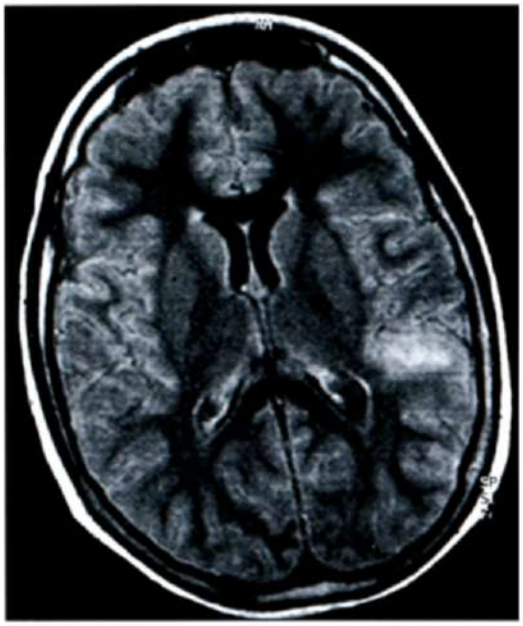

Figure 6. Fluid-attenuated inversion recovery (FLAIR) axial MR imaging of a patient with TTFCD histologically verified as type IIb. Note focal lesion with increased signal intensity on the left superior temporal region.

unquestionable abnormalities in inhibitory and excitatory neurotransmission. Data collected through immunocytochemical studies support an increase in excitatory amino acid neurotransmission and an overall decrease in intra- and peri-lesional inhibition.[26, 30, 54, 73] The net result is a high degree of intrinsic epileptogenicity, which has been demonstrated by experimental and clinical studies.[4, 25, 29, 53, 60, 62] Most patients diagnosed by imaging studies as harboring type IIa or IIb FCD lesions have medically intractable partial epilepsy, frequently with disabling motor and secondary generalized seizures. There is a high frequency of a history of status epilepticus, including epilepsia partialis continua, and scalp electroencephalography and acute electrocorticography often show continuous spiking or other highly epileptogenic patterns, suggesting some type of re-entrant excitatory circuitry unopposed by "weakened" inhibition (Fig. 7).[29, 53, 60, 62] These patients are often correctly diagnosed before operation, but surgical results are still not fully satisfactory in many of them. Issues related to a preferential localization around the perirolandic cortex and to a microscopic extension of abnormal tissue beyond the MR-imaged lesional margins are often mentioned to explain unsatisfactory results.

Dysplastic Tumors

There are at least two types of tumors that may be seen as representing the most severe end of the spectrum of FCD. Dysembryoplastic neuroepithelial tumor(s) (DNT) and gangliogliomas may be associated with surrounding

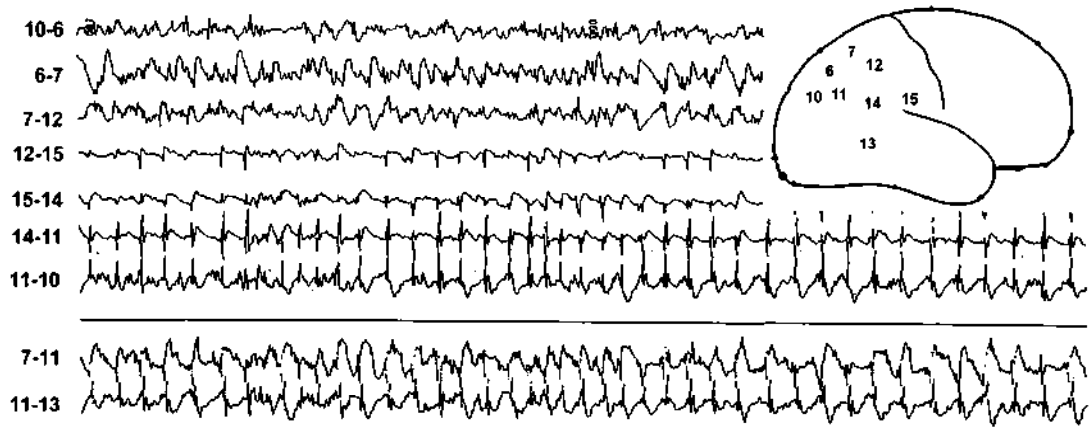

Figure 7. Markedly continuous focal spiking on the acute electrocorticogram (ECoG) of a 13-year-old girl with a dysplastic lesion (TTFCD, type IIa) on the right parietal cortex. Note maximal epileptic activity on electrode position #11.

cortical regions displaying abnormal cytoarchitecture (dyslamination) and large (at times dysmorphic) neurons and glial cells. In addition, subcortical heterotopic neurons can be seen.[22,65]

Structural Imaging and Histopathologic Findings

These lesions usually are restricted to the cortex and may present a combination of cystic and calcified areas. Perhaps the most striking imaging aspect is that the MR imaging signal is often irregular and poorly delimited, attesting to the presence of different histopathologic elements and the association of perilesional dysplastic and immediately subcortical heterotopic cells. There is no perilesional edema or mass effect.[22,65]

Clinical Relevance

Dysembryoplastic neuroepithelial tumors and gangliogliomas are benign lesions from an oncologic point of view. Nevertheless, they are often associated with medically refractory partial seizures, which usually manifest clinically before 20 years of age. Patients with DNT and epilepsy may be cured with surgery provided that complete resection is feasible. Remaining tumoral or dysplastic tissue may be associated with persistent seizures despite major lesion resection.[22,65]

Hemimegalencephaly

Structural Imaging

Hemimegalencephaly shows unequivocal asymmetry in the volume of the cerebral hemispheres. The dysplastic and abnormally large hemisphere displays grossly macrogyric cortex and diffusely increased signal in the subcortical white matter on T2-weighted, proton density, FLAIR acquisitions, and ipsilateral enlargement of the lateral ventricle (Fig. 8).[1,7,46] There is loss of demarcation between gray and white matter. Occasionally, the grossly abnormal hemisphere can also have lissencephalic, pachygyric, or polymicrogyric regions.

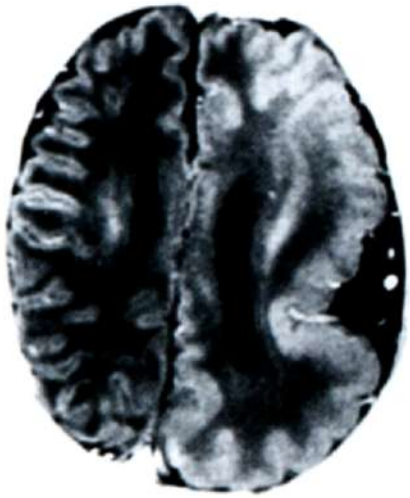

Figure 8. Axial MR image (inversion recovery) of an asymmetric brain. The left hemisphere is grossly malformed, much increased in volume, and accompanied by ipsilateral ventricular dilatation.

Histopathologic Findings

There usually is an association with dyslamination, widely scattered dysmorphic neurons, and balloon cells as well as with clusters of heterotopic neurons in the white matter. Invasion of the molecular layer by multinucleated glial cells can also be seen.[1,23,68] When polymicrogyria or pachygyria is part of the malformation, the characteristic histopathologic pictures are seen.

Polymicrogyria

Structural Imaging

Usually, a clustering of small gyri associated with some degree of cortical atrophy can be seen on MR imaging (Fig. 9*A*). At times, however, the fused microgyri can give the appearance of a thickened cortex with no or minimal sulci, thus suggesting pachygyria instead (see Fig. 9*B*). The common occurrence of some degree of atrophy adjacent to the lesion is a useful differentiating aspect. Occasionally, small polymicrogyric lesions may not be visualized by MR imaging.[7,46]

Histopathologic Findings

There is a clear derangement of the lamination pattern in comparison with the normal

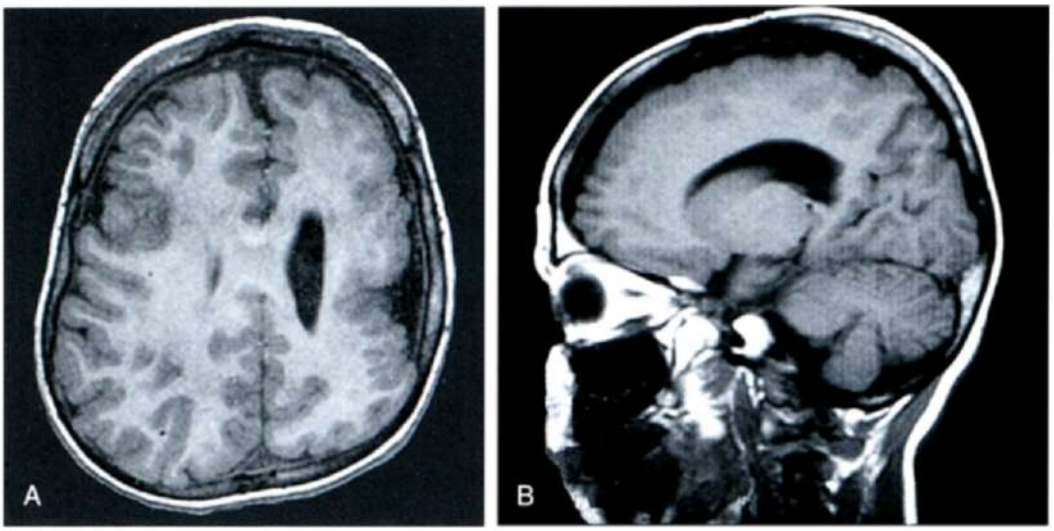

Figure 9. *A*, Axial T1-weighted MR image showing a polymicrogyric cortex on most of the left hemisphere with an accentuation in the centro-parietal region. Note the clustering of small gyri around an atrophic region. *B*, Sagittal T1-weighted MR image of the same patient. Note the extensive malformation which, in the more posterior frontal regions, has the appearance of an almost smooth (pachygyric) cortex. A few individualized small gyri can be seen in the frontal pole.

six-layered cortex. Most commonly, a four-layered pattern is seen, characterized by a molecular layer, a reasonably organized outer cellular layer, a cell-sparse layer, and a usually poorly organized inner cellular layer. Occasionally, however, a fully unlayered cortex is present (unlayered polymicrogyria).[46]

Schizencephaly

Structural Imaging

By definition, there is a cleft lined by polymicrogyric cortex communicating between the pial and the ependymal surfaces. The lips of the cleft may be juxtaposed (closed-lip schizencephaly) or separated for variable distances (open-lip schizencephaly). MR imaging usually depicts the anatomic abnormality.[6]

Histopathologic Findings

Interestingly, in addition to the several microscopic abnormalities seen in the polymicrogyria that surrounds the clefts, some schizencephalic lesions have more distinct histopathologic pictures. The latter encompass some large, immature, but well-oriented pyramidal neurons and, occasionally, even some balloon cells (H. I. Kim and A. Palmini, unpublished observations).

(Macroscopic) Neuronal Heterotopias

The imaging and histopathologic findings of the various types of neuronal heterotopia have been well described over the years, and the major characteristics of these types of MCD enjoy consensual views among experts. These include periventricular nodular heterotopia, subcortical nodular heterotopia (Fig. 10), band heterotopia or "double cortex" (Fig. 11), pachygyria, and lissencephaly.[46] The exact type of heterotopia is probably a function of the timing, type, and site of interference with the neuronal and glial elements participating in the migrational process of corticogenesis.[64] Recent discoveries regarding these heterotopias are all within the genetic and molecular biology fields. Familial studies have led to the discovery of several genes responsible for key aspects of neuronal migration and the associated mutations leading to the malformations.[27,31,40] From a conceptual

standpoint, these genetic studies have confirmed earlier impressions that entities like band heterotopia, diffuse pachygyria, and lissencephaly are all part of a continuum of severity of migratory derangements,[64] often (but perhaps not always) caused by gene mutations.

One important aspect regarding the histopathologic findings of these heterotopic nodules and bands of variable thickness is the fact that although immature, large neurons are an integral part of the picture; dysmorphic (dysplastic) neurons and balloon cells are not seen in these types of MCD.[65,74]

Miscellaneous Malformations Caused by Abnormalities of Cortical Development

Under this heading, the co-occurrence of MCD that differ from histopathologic, imaging, and perhaps pathogenetic standpoints could be conceived. These miscellaneous entities, exemplified by the co-occurrence of band heterotopia and Taylor type FCD (Kim HI, et al, unpublished observations) among several others, are likely to be helpful in improving understanding of the complex genetic and environmental interactions leading to MCD. Their mere existence should be a warning against attempts to oversimplify the pathogenetic understanding of these malformations.

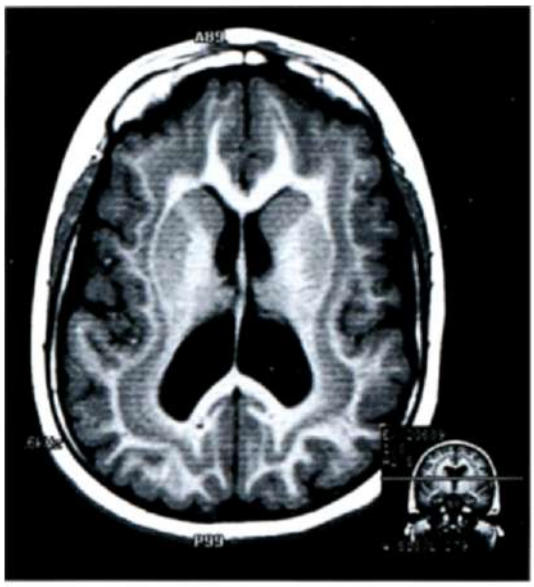

Figure 11. Axial T1-weighted MR image of a diffuse band heterotopia. Note the sharply demarcated band of neurons in between the cortex and the ventricles giving the appearance of a "double cortex."

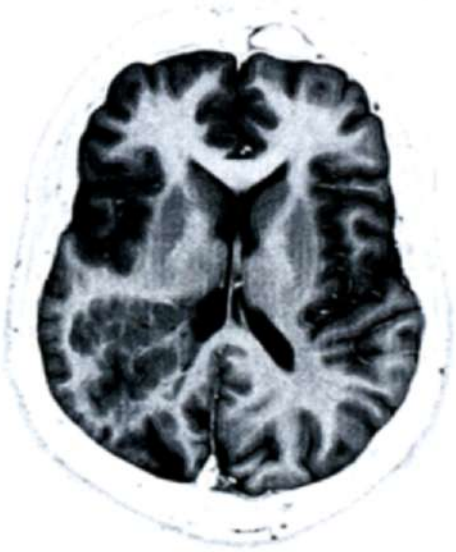

Figure 10. Axial MR image on inversion recovery displaying a collection of neuronal heterotopic nodules extending from the lateral ventricle to the subcortical white matter of the right parietal region. Note the abnormal gyration of the cortex overlying the malformation.

ACKNOWLEDGMENT

The authors acknowledge the help of Ligia Coutinho, MD, PhD in the selection and preparation of the neuropathologic pictures included here.

References

1. Adamsbaum C, Robain O, Cohen PA, et al: Focal cortical dysplasia and hemimegalencephaly: Histological and neuroimaging correlations. Pediatr Radiol 28:583–590, 1998
2. Akbarian S, Vinuela A, Kim JJ, et al: Distorted distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase neurons in temporal lobes of schizophrenics implies anomalous cortical development. Arch Gen Psychiatry 50:178–187, 1993
3. Akil M, Lewis DA: Cytoarchitecture of the entorhinal cortex in schizophrenia. Am J Psychiatry 154: 1010–1012, 1997

4. Avoli M, Bernasconi A, Mattia D, et al: Epileptiform discharges in the human dysplastic neocortex: In vitro physiology and pharmacology. Ann Neurol 46:816–826, 1999
5. Barbosa-Coutinho LM, Hilbig A, Calcagnotto ME, et al: Neuropathology of hard to control epilepsy. Study of 300 consecutive cases. Arq Neuropsiquiatr 57:405–414, 1999
6. Barkovitch AJ, Kjos B: Schizencephaly: Correlation of clinical findings with MR characteristics. AJNR Am J Neuroradiol 13:85–94, 1992
7. Barkovitch AJ, Chuang SH, Norman D: MR of neuronal migration anomalies. AJNR Am J Neuroradiol 8:1009–1017, 1987
8. Barkovitch AJ, Kuzniecky R, Dobyns W, et al: A classification scheme for malformations of cortical development. Neuropediatrics 27:59–63, 1996
9. Barkovitch AJ, Kuzniecky R, Bollen A, et al: Focal transmantle dysplasia: A specific malformation of cortical development. Neurology 49:1148–1152, 1997
10. Bastos AC, Comeau RM, Andermann F, et al: Diagnosis of subtle focal dysplastic lesions: Curvilinear reformatting from three-dimensional magnetic resonance imaging. Ann Neurol 46:88–94, 1999
11. Baulac M, de Grissac N, Hasboun D, et al: Hippocampal developmental changes in patients with partial epilepsy: Magnetic resonance imaging and clinical aspects. Ann Neurol 44:223–233, 1998
12. Brannstrom T, Nordborg C, Olivecrona M, et al: Disorders of neuronal migration in surgically resected epilepsy patients. Epilepsia 34:71, 1993
13. Bronen R, Spencer D, Fullbright R: Cerebrospinal fluid cleft with cortical dimple. MR imaging marker for focal cortical dysgenesis. Radiology 214:657–663, 2000
14. Bronen RA, Vives KP, Kim JH, et al: Focal cortical dysplasia of Taylor, balloon cell subtype: MR differentiation from low-grade tumors. AJNR Am J Neuroradiol 18:1141–1151, 1997
15. Burney BG, Potkin SG, Burney WE Jr: New morphological and neuropathological findings in schizophrenia: A neurodevelopmental perspective. Clin Neurosci 3:81–88, 1995
16. Caraballo R, Cersosimo R, Fejerman N: A particular type of epilepsy in children with congenital hemiparesis associated with unilateral polymicrogyria. Epilepsia 40:865–871, 1999
17. Chan S, Chin SS, Nordli DR, et al: Prospective magnetic resonance imaging identification of focal cortical dysplasia, including the non-balloon cell subtype. Ann Neurol 44:749–757, 1998
18. Chevassus-au-Louis N, Baraban SC, Gaiarsa JL, et al: Cortical malformations and epilepsy: New insights from animal models. Epilepsia 40:811–821, 1999
19. Chevassus-au-Louis N, Congar P, Represa A, et al: Neuronal migration disorders: Heterotopic neocortical neurons in CA1 provide a bridge between the hippocampus and the neocortex. Proc Natl Acad Sci USA 95:10263–10268, 1998
20. Colacitti C, Sancini G, Franceschetti S, et al: Altered connections between neocortical and heterotopic areas in methylazoxymethanol-treated rat. Epilepsy Res 32:49–62, 1998
21. Courchesne E: Brainstem, cerebellar, and limbic neuroanatomical abnormalities in autism. Curr Opin Neurobiol 7:267–278, 1997
22. Daumas-Duport C, Scheithauer BW, Chodkiewicz JP, et al: Dysembryoplastic neuroepithelial tumor: A surgically curable tumor of young patients with intractable partial seizures. Neurosurgery 23:545–556, 1988
23. De Rosa MJ, Secor DL, Barsom M, et al: Neuropathologic findings in surgically treated hemimegalencephaly: Immunohistochemical, morphometric, and ultrastructural study. Acta Neuropathol (Berl) 84:250–260, 1992
24. Desbiens R, Berkovic S, Dubeau F, et al: Life-threatening focal status epilepticus due to occult cortical dysplasia. Arch Neurol 50:695–700, 1993
25. Dubeau F, Palmini A, Fish D, et al: The significance of electrocorticographic findings in focal cortical dysplasia: A review of their clinical, electrophysiological and neurochemical characteristics. Electroencephalogr Clin Neurophysiol Suppl 48:77–96, 1998
26. Ferrer I, Pineda M, Tallada M: Abnormal local-circuit neurons in epilepsia partialis continua associated with focal cortical dysplasia. Acta Neuropathol (Berl) 83:647–652, 1992
27. Fox JW, Lamperti ED, Ekiolu YZ, et al: Mutations in filamin 1 prevent migration of cerebral cortical neurons in human periventricular heterotopia. Neuron 21:1315–1325, 1998
28. Galaburda AM, Sherman GF, Rosen GD, et al: Developmental dyslexia: Four consecutive patients with cortical anomalies. Ann Neurol 18:222–233, 1985
29. Gambardella A, Palmini A, Andermann F, et al: Usefulness of focal rhythmic discharges on scalp EEG of patients with focal cortical dysplasia and intractable epilepsy. Electroencephalogr Clin Neurophysiol 98:243–249, 1996
30. Garbelli R, Munari C, De Biasi S, et al: Taylor's cortical dysplasia: A confocal and ultrastructural immunohistochemical study. Brain Pathol 9:445–461, 1999
31. Gleeson JG, Minnerath SR, Fox JW: Characterization of mutations in the gene doublecortin in patients with the double cortex syndrome. Ann Neurol 45:146–153, 1999
32. Granata T, Farina L, Faiella A, et al: Familial schizencephaly associated with EMX2 mutation. Neurology 48:1403–1406, 1997
33. Guerrini R, Genton P, Bureau M, et al: Multilobar polymicrogyria, intractable drop attack seizures, and sleep-related electrical status epilepticus. Neurology 51:504–512, 1998
34. Hardiman O, Burke T, Phillips J: Microdysgenesis in resected temporal lobe neocortex: Incidence and clinical significance in focal epilepsy. Neurology 38:1041–1047, 1988
35. Hirabayashi S, Binnie CD, Janota I, et al: Surgical treatment of epilepsy due to cortical dysplasia: Clinical and EEG findings. J Neurol Neurosurg Psychiatry 56:765–770, 1993
36. Holmes GL, Sarkisian M, Ben-Ari Y, et al: Consequences of cortical dysplasia during development in rats. Epilepsia 40:537–544, 1999
37. Holthausen H, Teixeira VA, Tuxhorn I, et al: Epilepsy surgery in children and adolescents with focal cortical dysplasia. *In* Tuxhorn I, Holthausen H, Boenigk H (eds): Paediatric Epilepsy Syndromes and Their Surgical Treatment. London, John Libbey, 1990, pp 199–215

38. Houser CR, Swartz BE, Walsh GO, et al: Granule cell disorganization in the dentate gyrus: Possible alterations of neuronal migration in human temporal lobe epilepsy. Epilepsy Res 9:41–48, 1992
39. Kasper BS, Stefan H, Buchfelder M, et al: Temporal lobe microdysgenesis in epilepsy versus control brains. J Neuropathol Exp Neurol 58:22–28, 1999
40. Kato M, Kimura T, Lin C, et al: A novel mutation of the doublecortin gene in Japanese patients with X-linked lissencephaly and subcortical band heterotopia. Hum Genet 104:341–344, 1999
41. Keene DL, Jimenez CC, Ventureyra E: Cortical microdysplasia and surgical outcome in refractory epilepsy of childhood. Pediatr Neurosurg 29:69–72, 1998
42. Klaus P, Senitz D, Beckmann H: Cortical layer I changes in schizophrenia: A marker for impaired development? J Neural Transm 104:549–559, 1997
43. Kowacz J, Kratani J, Curren JG, et al: Focal cortical dysplasia—correlation between MRI findings and cytoarchitectural features of tissue resected from children. Neurology 54:A258, 2000
44. Kuhn HG, Dickinson-Anson H, Gage FH: Neurogenèsis in the dentate gyrus of the adult rat: Age-related decrease of neuronal progenitor proliferation. J Neurosci 16:2027–2033, 1996
45. Kuzniecky R, Garcia J, Faught E, et al: Cortical dysplasia in temporal lobe epilepsy: Magnetic resonance imaging correlations. Ann Neurol 29:293–298, 1991
46. Kuzniecky RI, Jackson GD: Developmental disorders. *In* Engel J Jr, Pedley TA (eds): Epilepsy: A Comprehensive Textbook. Philadelphia, Lippincott-Raven, 1997, pp 2517–2532
47. Lee BC, Schmidt RE, Hatfield GA, et al: MRI of focal cortical dysplasia. Neuroradiology 40:675–683, 1998
48. Lehéricy S, Dormont D, Semah F, et al: Developmental abnormalities of the medial temporal lobe in patients with temporal lobe epilepsy. AJNR Am J Neuroradiol 16:617–626, 1995
49. Li LM, Cendes F, Bastos AC, et al: Neuronal metabolic dysfunction in patients with cortical developmental malformations: A proton magnetic resonance spectroscopic imaging study. Neurology 50:755–759, 1998
50. Lombroso CT: Can early postnatal closed head injury induce cortical dysplasia ? Epilepsia 41:245–253, 2000
51. Meencke HJ, Janz D: The significance of microdysgenesis in primary generalized epilepsy: An answer to the considerations of Lyon and Gastaut. Epilepsia 26:368–371, 1985
52. Mischel OS, Nguyen LP, Vinters HV: Cerebral cortical dysplasia associated with pediatric epilepsy. Review on neuropathologic features and proposal for a grading system. J Neuropathol Exp Neurol 54: 137–153, 1995
53. Morioka T, Nishio S, Ishibashi H, et al: Intrinsic epileptogenicity of focal cortical dysplasia as revealed by magnetoencephalography and electrocorticography. Epilepsy Res 33:177–187, 1999
54. Najm I, Ying Z, Babb T, et al: Epileptogenicity correlated with increased N-methyl-D-aspartate receptor subunit NR2A/B in human focal cortical dysplasia. Epilepsia 41:971–976, 2000
55. Palmini A: Disorders of cortical development. Curr Opin Neurol 13:183–192, 2000
56. Palmini A, Andermann E, Andermann F: Prenatal events and genetic factors in epileptic patients with neuronal migration disorders. Epilepsia 35:965–973, 1994
57. Palmini A, Andermann F, Aicardi J, et al: Diffuse cortical dysplasia or the double-cortex syndrome: The clinical and epileptic spectrum in 10 patients. Neurology 41:1656–1662, 1991
58. Palmini A, Andermann F, Olivier A, et al: Focal neuronal migration disorders and intractable partial epilepsy: A study of 30 patients. Ann Neurol 30: 741–749, 1991
59. Palmini A, Andermann F, Olivier A, et al: Focal neuronal migration disorders and intractable partial epilepsy: Results of surgical treatment. Ann Neurol 30:750–775, 1991
60. Palmini A, Gambardella A, Andermann F, et al: Intrinsic epileptogenicity of human dysplastic cortex as suggested by corticography and surgical results. Ann Neurol 37:476–487, 1995
61. Palmini A, Andermann F, Olivier A, et al: Neuronal migration disorders: A contribution of modern neuroimaging to the etiologic diagnosis of epilepsy. Can J Neurol Sci 18(suppl):580–587, 1991
62. Palmini A, Gambardella A, Andermann F, et al: Operative strategies for patients with cortical dysplastic lesions and intractable epilepsy. Epilepsia 35(suppl):S57–S71, 1994
63. Palmini A, da Costa JC, Calcagnotto ME, et al: Patients with specific histopathological types of cortical dysplasia have specific degrees of severity of the epileptic condition. A study of 78 patients. Epilepsia 38(suppl 3):5, 1997
64. Palmini A, Andermann F, de Grissac H, et al: Stages and patterns of centrifugal arrest of diffuse neuronal migration disorders. Dev Med Child Neurol 35: 331–339, 1993
65. Raymond AA, Fish DR, Sisodiya SM, et al: Abnormalities of gyration, heterotopias, tuberous sclerosis, focal cortical dysplasia, microdysgenesis, dysembryoplastic neuroepithelial tumour and dysgenesis of the archicortex in epilepsy: Clinical, EEG and neuroimaging features in 100 adult patients. Brain 118:629–660, 1995
66. Raymond GV, Bauman ML, Kemper TL: Hippocampus in autism: A Golgi analysis. Acta Neuropathol (Berl) 91:117–119, 1996
67. Robain O: Introduction to the pathology of cerebral cortical dysplasia. *In* Guerrini R, Andermann F, Canapicchi R, et al (eds): Dysplasias of Cerebral Cortex and Epilepsy. Philadelphia, Lippincott-Raven, 1996, pp 1–9
68. Robain O, Floquet CH, Heldt N, et al: Hemimegalencephaly: A clinicopathological study of four cases. Neuropathol Appl Neurobiol 14:125–135, 1988
69. Roper SN: In utero irradiation of rats as a model of human cerebrocortical dysgenesis: A review. Epilepsy Res 32:63–74, 1998
70. Rosenow F, Lüders HO, Dinner DS, et al: Histopathological correlates of epileptogenicity as expressed by electrocorticographic spiking and seizure frequency. Epilepsia 39:850–856, 1998
71. Sarnat HB: Disturbances of late neuronal migrations in the perinatal period. Am J Dis Child 141:969–979, 1987

72. Simone IL, Federico F, Tortorella C, et al: Metabolic changes in neuronal migration disorders: Evaluation by combined MRI and proton MR spectroscopy. Epilepsia 40:872–879, 1999
73. Spreafico R, Battaglia G, Arcelli P, et al: Cortical dysplasia: An immunocytochemical study of three patients. Neurology 50:27–36, 1998
74. Spreafico R, Pasquier B, Minotti L, et al: Immunocytochemical investigation on dysplastic human tissue from epileptic patients. Epilepsy Res 32:34–48, 1998
75. Taylor DC, Falconer MA, Bruton CJ, et al: Focal dysplasia of the cerebral cortex in epilepsy. J Neurol Neurosurg Psychiatry 34:369–387, 1971
76. Van Bogaert P, David P, Gillain CA, et al: Perisylvian dysgenesis. Clinical, EEG, MRI and glucose metabolism features in 10 patients. Brain 121:2229–2238, 1998
77. Yamanouchi H, Jay V, Otsubo H, et al: Early forms of microtubule-associated protein are strongly expressed in cortical dysplasia. Acta Neuropathol (Berl) 95:466–470, 1998

Address reprint requests to

André Palmini, MD, PhD
Serviço de Neurologia
Hospital São Lucas da PUCRS
Avenida Ipiranga, 6690
Porto Alegre, RS
Brazil CEP 90610–000

e-mail: apalmini@conex.com.br