

Imaging of malformations of cortical development

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Received March 9, 2009; Accepted June 23, 2009

ABSTRACT – Malformations of cortical development (MCD) include a broad range of disorders that result from disruption of the major steps of cortical development: cell proliferation in germinal zones, neuronal migration and cortical organization. With the improvement and increased utilization of modern imaging techniques, MCD have been increasingly recognized as a major cause of seizure disorders. The advent of Magnetic Resonance Imaging (MRI), in particular, has revolutionized the investigation and the treatment of patients with epilepsy. High-resolution MRI may elucidate the type, the extension and the localization of MCD; therefore, in a group of patients suffering from drug-resistant partial epilepsy (DRPE), MRI greatly contributes to the identification of subjects who are suitable for surgical treatment. In the recent past, many efforts were addressed to establish the MRI diagnostic criteria for a peculiar group of MCD, namely focal cortical dysplasias (FCD), histopathologically distinguished as types I and II. Some subtle FCD, which were previously cryptic to imaging investigation, can now be recognized by MRI, however their detection and specification remains challenging. This review will re-visit the neuroimaging findings, including structural MRI, PET, co-registered PET/MRI, MEG and diffusion tensor imaging (DTI) of FCD types I and II. Three major issues will be discussed: 1) the morphological MRI features of the FCDs, 2) the utility of PET and MEG and the use of co-registration methods and 3) diffusion tensor imaging (DTI) as a future modality of investigation, which may add additional informations regarding the microstructure of the grey matter (GM) and white matter (WM) in cortical dysplasia.

Key words: focal cortical dysplasia, MRI, PET, magnetoencephalography, diffusion tensor

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Presented at the "Malformations of Cortical Development and Epilepsy" Symposium, organized in Istanbul, Turkey (October 30-31, 2008) by the ILAE Commissions of Neurobiology and Therapeutic strategies together with the Cerrahpaşa Medical Faculty of Istanbul University.

Different classification systems for MCD with emphasis on focal cortical dysplasias

Malformations of cortical development are a fascinating group of disorders that result from disruption of the major steps of cerebral cortical development: cell proliferation/apoptosis in germinal zones, neuronal migration (both radial and tangential) and cortical organization (formation of lamina, extension of neurites and formation and refinement of synaptic connections). From an embryological and genetic perspective, it makes sense to classify these malformations according to the developmental stage when disruption is purported to cause the anomaly. This is the basis for the currently most utilized classification scheme (Barkovich *et al.*, 2005) (*table 1*) which is particularly suited for malformations with known causes, such as lissencephalies, dystroglycanopathies (cobblestone malformations) and some forms of heterotopia. When malformations are more heterogeneous, with multiple causes (both genetic and environmental) or with no familial cases (presumably acquired disorders), the classification is more difficult.

Group I comprises disorders with decreased proliferation or proliferation of abnormal cells and includes microcephalies, focal cortical dysplasias (FCD) with balloon cells (BC), hemimegalencephalies, tuberous sclerosis, dysembryoplastic neuroepithelial tumours and gangliogliomas/gangliocytomas. Group II includes lissencephalies, dystroglycanopathies and heterotopia. Group III includes polymicrogyrias, schizencephalies, cortical dysplasia without BC and "microdysgenesis" (note: the term microdysgenesis has been replaced by the term "mild MCD" [mMCD] in the Palmini classification of FCDs; Palmini *et al.*, 2004).

The genetics and embryology of many of these disorders are at least partly understood and their classification is made much easier as a result. Indeed, many are classified primarily by the affected genes rather than phenotype. However, many of the disorders are poorly understood and a lack of understanding of embryology or genetics makes the disorders more difficult to classify. Examples of poorly understood disorders are FCDs, hemimegalencephalies and polymicrogyrias. Close examination of these disorders suggests that etiology is likely to be heterogeneous. Because of the lack of understanding of the underlying causes of these disorders, their pathological and imaging characteristics are useful for temporary classification. Indeed, grouping disorders together based on pathological or imaging characteristics can be useful in helping to better study genetic causes and, subsequently, embryogenesis.

The term FCD includes a broad spectrum of architectural and cytoarchitectural disorders of different severity that seem to comprise a spectrum. Taylor and his colleagues (Taylor *et al.*, 1971) first described a distinctive distur-

Table 1. Classification scheme.

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| <p>I. Malformations due to abnormal neuronal and glial proliferation or apoptosis</p> <p>A. Decreased proliferation/increased apoptosis or increased proliferation/decreased apoptosis-abnormalities of brain size</p> <ol style="list-style-type: none"> 1. Microcephaly with normal to thin cortex 2. Microlissencephaly (extreme microcephaly with thick cortex) 3. Microcephaly with extensive polymicrogyria 4. Macrocephalies <p>B. Abnormal proliferation (abnormal cell types)</p> <ol style="list-style-type: none"> 1. Non-Neoplastic <ol style="list-style-type: none"> a. Cortical hamartomas of tuberous sclerosis b. Cortical dysplasia with balloon cells c. Hemimegalencephaly (HMEG) 2. Neoplastic (associated with disordered cortex) <ol style="list-style-type: none"> a. DNET (dysembryoplastic neuroepithelial tumor) b. Ganglioglioma c. Gangliocytoma <p>II. Malformations due to abnormal neuronal migration</p> <p>A. Lissencephaly/subcortical band heterotopia spectrum</p> <p>B. Cobblestone complex/congenital muscular dystrophy syndromes</p> <p>C. Heterotopia</p> <ol style="list-style-type: none"> 1. Subependymal (periventricular) 2. Subcortical (other than band heterotopia) 3. Marginal glioneuronal <p>III. Malformations due to abnormal cortical organization (including late neuronal migration)</p> <p>A. Polymicrogyria and schizencephaly</p> <ol style="list-style-type: none"> 1. Bilateral polymicrogyria syndromes 2. Schizencephaly (polymicrogyria with clefts) 3. Polymicrogyria or schizencephaly as part of multiple congenital anomaly/mental retardation syndromes <p>B. Cortical dysplasia without balloon cells</p> <p>C. Microdysgenesis</p> <p>IV. Malformations of cortical development, not otherwise classified</p> <p>A. Malformations secondary to inborn errors of metabolism</p> <ol style="list-style-type: none"> 1. Mitochondrial and pyruvate metabolic disorders 2. Peroxisomal disorders <p>B. Other unclassified malformations</p> <ol style="list-style-type: none"> 1. Sublobar dysplasia 2. Others |
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Note: the term "Microdysgenesis" was discarded and substituted with mMCD in the Palmini classification (Palmini *et al.* 2004).

bance of cortical structure that we now identify as FCD type II. This entity was subsequently divided into two subtypes based on the presence or absence of BC (type IIA and type IIB). Since then, a number of different classification systems have been proposed based on histopathological features (Tassi *et al.*, 2002 ; Palmini *et al.*, 2004) and different subtypes have been recognized reflecting the

degree of abnormality: mMCD type I and II, FCD type IA and IB, FCD type IIA and IIB (Blümcke *et al.*, 2009). Histological features and some clinical histories have led to suggestions that mMCD and both types of FCD may result from both malformative and disruptive processes.

FCDs may be isolated but some (particularly type I) are associated with other pathologies: hippocampal sclerosis (HS) in the temporal lobe (Raymond *et al.*, 1994; Ho *et al.*, 1998; Diehl *et al.*, 2004), developmental tumours such as dysembryoplastic neuroepithelial tumours and gangliogliomas and traumatic/ischemic brain injury. Large series will be necessary to verify if isolated or associated forms of FCDs have different electroclinical presentation and surgical outcome; if so, it may be reasonable to classify these separately from FCDs.

FCDs presenting with partial epilepsies and amenable to surgery

Pre-surgical evaluation

In the pre-surgical evaluation of patients with drug-resistant epilepsy, high-quality MRI is required, aimed to evaluate the entire brain, but specifically the area of the brain suspected to be the epileptogenic zone (EZ), based on the electroclinical hypothesis, where the structural lesion is presumably located.

Therefore, knowledge of the electroclinical presentation is mandatory for performing a proper MRI examination. Indeed, the precise definition of the EZ, the cortical area of seizure generation and propagation, is a major task in candidates for surgery, since it can influence the surgical planning and the extent of surgical resection. Different pre-surgical strategies can be followed for this purpose, including clinical observation, electrophysiological invasive and non-invasive procedures and both morphological and functional imaging.

MRI is the imaging modality most frequently used to assess brain pathology in patients with DRPE. FCDs are the most common group of MCDs in patients presenting with intractable epilepsy and they are the most common cause of epilepsy in children (Urbach *et al.*, 2002; Tassi *et al.*, 2002; Fauser *et al.*, 2004; Hildebrandt *et al.*, 2005; Krsek *et al.*, 2009).

In many cases, surgical resection of the epileptogenic lesion can control the seizures when the role of the lesion is precisely evaluated pre-operatively. Anatomical MRI plays a major role in defining the morphological alterations in cortical dysplasia: the location and full extent of the lesion and the relationship of the lesion to the eloquent areas of the brain.

Functional MRI (fMRI) using the Blood Oxygen Level Dependent (BOLD) technique is now commonly utilized for the direct visualization of eloquent areas of the brain

activated by different tasks (sensory-motor, linguistic, etc.), facilitating their topographic correlations with structural lesions.

In spite of technical advances of MR imaging, subtle types of cortical dysplasia can be easily missed by conventional MRI; in this situation, other imaging modalities, such as ictal/interictal SPECT, FDG-PET or MEG, should be used, if available, to locate the abnormality. Once another modality suggests the possible region of epileptogenicity, the “negative” MRI examination should be re-evaluated.

DTI is a promising MR technique in patients with epilepsy, which may add information regarding the microstructural integrity of the grey and white matter in cortical dysplasia. The tri-dimensional reconstruction of the white matter tracts (a technique known as tractography) allows one to draw a better topographic correlation between axonal tracts and lesions, to evaluate whether the white matter tracts are modified by the cortical dysplasia, and to prepare the surgical approach by identifying eloquent bundles.

Imaging studies

MRI findings in mMCD-FCDs

Many published studies report the MRI characteristics of FCD, however only a minority have attempted to identify differential imaging characteristics for the various subtypes of FCD, including FCD type I (Tassi *et al.*, 2002; Colombo *et al.*, 2003a; Colombo *et al.*, 2003b; Ruggieri *et al.*, 2004; Lawson *et al.*, 2005; Widdess-Walsh *et al.*, 2006; Fauser *et al.*, 2004; Krsek *et al.*, 2008b). Up to now only one report has dealt with the imaging findings in mMCD (Krsek *et al.*, 2008b).

The MRI diagnosis of FCD relies on the detailed analysis of several features including: cortical thickness, blurring of the grey/white matter junction with disappearance of subcortical white matter digitations, white matter signal abnormalities with or without extension all throughout the cortical mantle (the transmante sign), grey matter signal changes, abnormal gyral/sulcal patterns and focal and/or lobar hypoplasia/atrophy.

Current opinions suggest the following distinctive imaging characteristics for the various subtypes of FCDs.

FCD type I

Prominent lobar/sublobar hypoplasia/atrophy are common findings in this subtype of dysplasia. They are frequently associated with volume loss of the subcortical WM, which exhibits moderately increased signal on T2WI and heavily T2W FLAIR images and decreased signal on T1W images, either 3D volumetric Gradient Echo T1W or heavily T1W Inversion Recovery (IR) images. Mild blurring at the GM/WM junction with normal cortical thickness is usually observed. Abnormal gyral/sulcal patterns can be present.

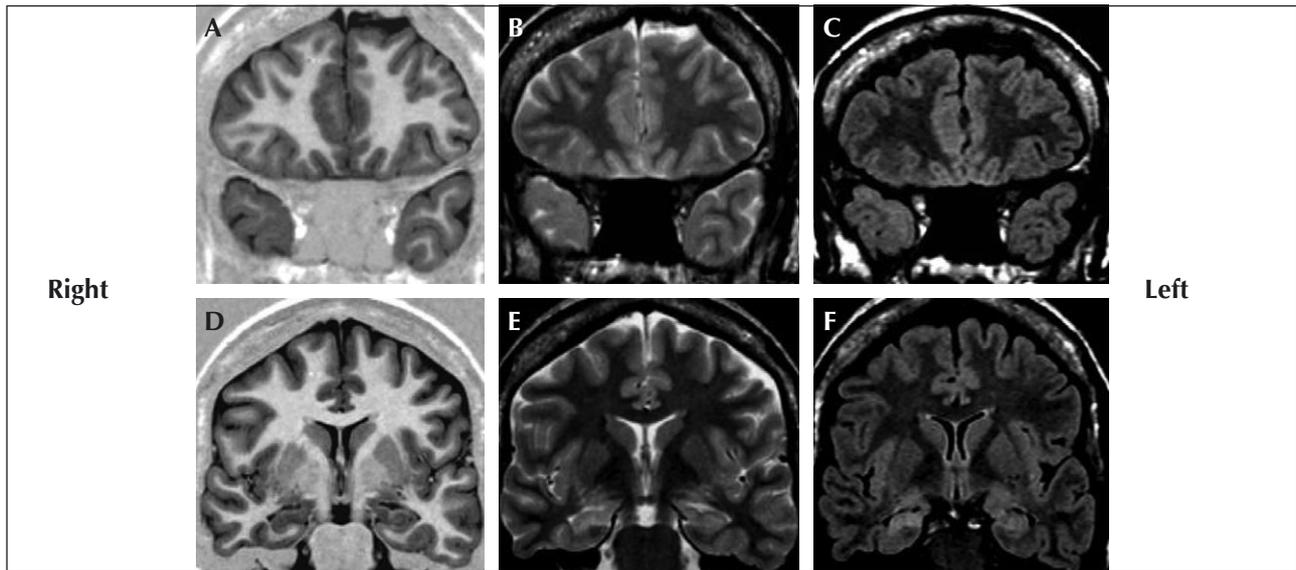


Figure 1. Focal cortical dysplasia type I A with ipsilateral hippocampal sclerosis (“dual pathology”) in a 31-year-old female. Coronal MR images: turbo spin-echo inversion-recovery T1-weighted (A, D), turbo spin-echo T2-weighted (B, E), turbo spin-echo FLAIR T2-weighted (C, F) obtained respectively at the level of the temporal pole and of the head of the hippocampus. Hypoplasia of the right temporal pole is recognizable, with volume loss of the white matter which exhibits mild hyperintensity on T2-weighted images. Mild blurring of the cortical-white matter junction is visible on both T1- and T2-weighted images (A-C). The right hippocampus is atrophic, with decreased signal on IR-T1W images and increased signal on T2W images, consistent with hippocampal sclerosis.

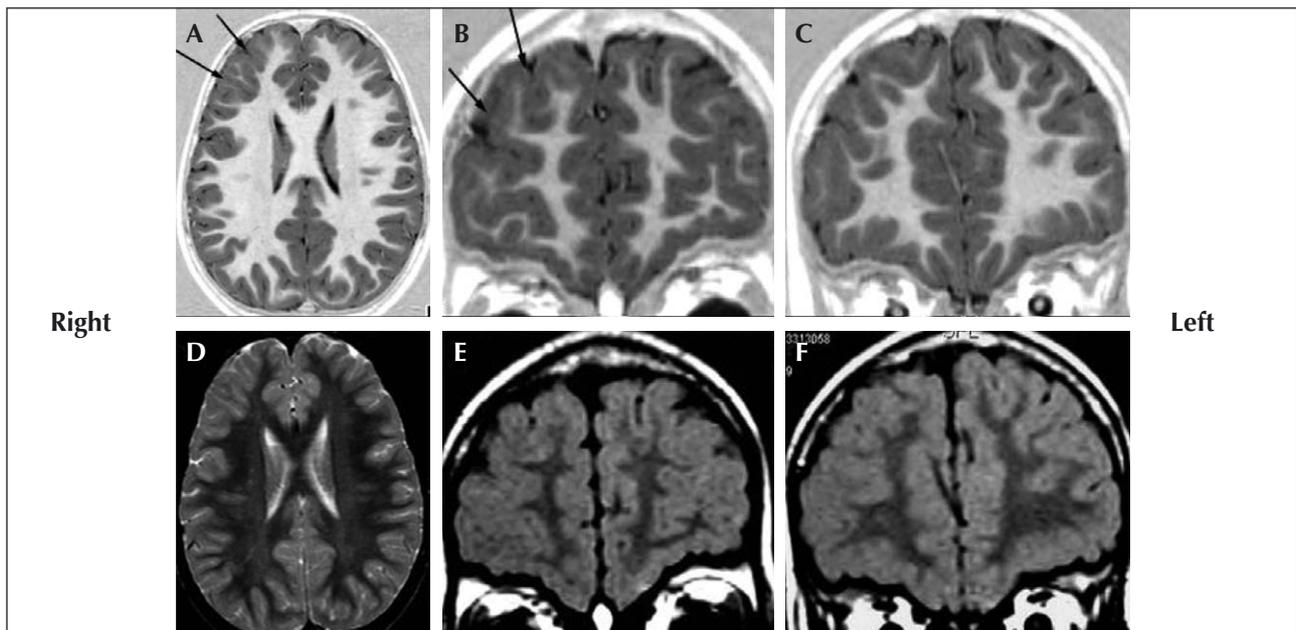


Figure 2. Focal cortical dysplasia type I A of the right frontal cortex in a 9-year-old boy. Transverse turbo spin-echo inversion-recovery T1-weighted image (A) and transverse spin-echo T2-weighted image (D). Coronal turbo spin-echo inversion-recovery T1-weighted images (B, C) and coronal turbo spin-echo FLAIR T2-weighted (E, F). Abnormal gyration along the right frontal convexity is seen (arrows) with mild blurring of the GM/WM junction and mild hypoplasia of the anterior frontal lobe. No signal alterations of the subcortical WM are seen.

FCD type I is most commonly found in the temporal lobe where it is associated with ipsilateral hippocampal sclerosis (HS) in more than 70% of cases, representing the so called “dual pathology” (Raymond *et al.*, 1994; Ho *et al.*, 1998; Diehl *et al.*, 2004) (figures 1, 2). No specific MR findings distinguish FCD type IA from type IB. In contrast to type IA, FCD type IB is frequently temporal-located and can be located everywhere in the brain, it occasionally may mimic FCD type II.

FCD type II

FCD type II is usually characterized by increased cortical thickness, pronounced blurring of the GM/WM junction both on T1WI and T2WI in a certain number of cases, increased subcortical WM signal on T2WI and heavily T2W FLAIR images and decreased signal on T1W images, either 3D volumetric Gradient Echo T1W or heavily T1W Inversion Recovery (IR) images. The WM signal alterations frequently taper towards the ventricle, reflecting the involvement of radial glial-neuronal bands. This transmantle sign is almost exclusively found in FCD type II. Blurring between cortex and WM on T1WI and T2WI is usually more pronounced than in FCD type I (figure 3). Abnormal cortical gyration and sulcation, better evaluated on 3D surface rendering, are frequent findings in FCD type II and sometimes focal enlargement of the sub-

arachnoid spaces seem to point at the dysplastic lesion, assisting in the diagnosis.

Increased T2-signal within affected cortex is far more common in FCD type II than in FCD type I; however usually the grey matter remains hypointense compared with underlying white matter on T2WI. FCD type IIA and type IIB are indistinguishable by MRI, however there is a tendency for FCD type IIB to be better delineated in comparison to other histopathological types. FCDs type II most often occur in extratemporal locations with predilection for the frontal region.

mMCD (mild MCD)

A recent report (Krsek *et al.*, 2008b) has analyzed the imaging findings in a group of patients classified by histology as having mMCD type II, all located within the temporal lobe. The major MRI feature was lobar hypoplasia and atrophy, found in 29% of the cases. However this feature is typical of FCD type I and is thus of limited value in distinguishing between the two entities. Mild GM/WM blurring and mild WM signal abnormalities are less frequent in mMCD than in other subtypes of FCD. Changes in cortical thickness, abnormal gyral/sulcal pattern, the transmantle sign of WM signal alteration and GM signal abnormalities are usually not encountered in mMCD.

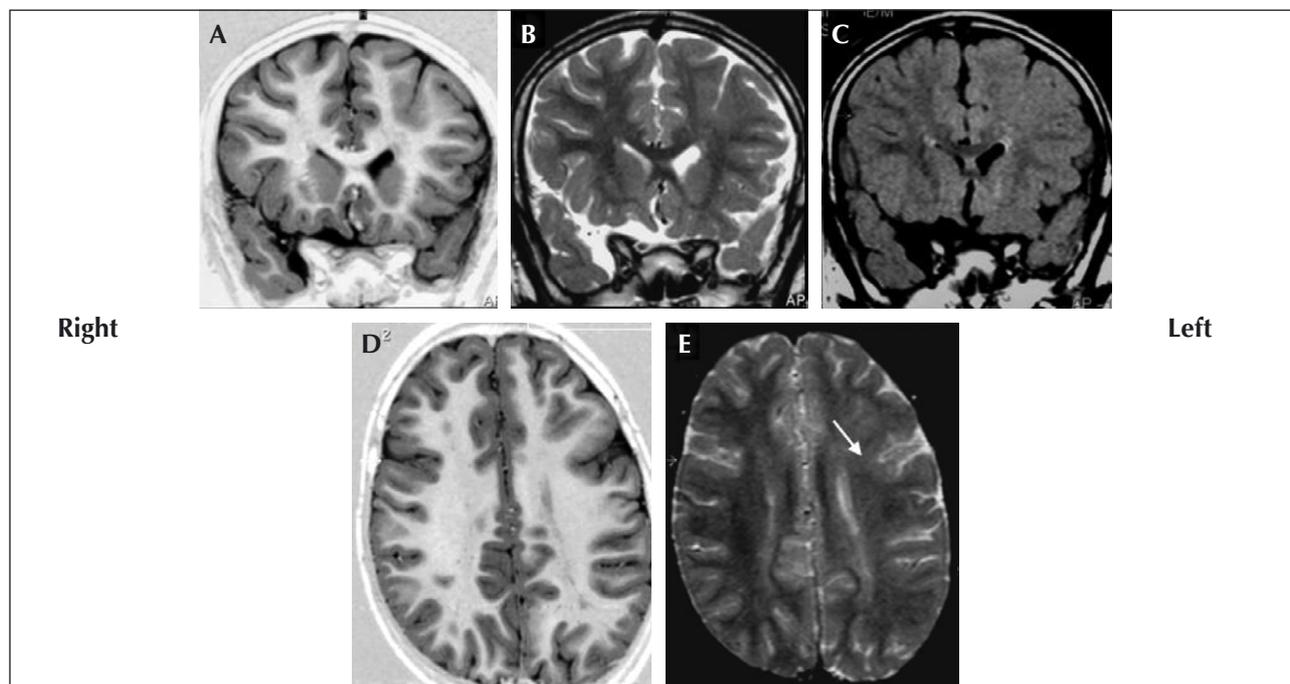


Figure 3. Focal cortical dysplasia type II B of the left frontal cortex in a 6-year-old boy. Coronal turbo spin-echo inversion-recovery T1-weighted image (A), coronal turbo spin-echo T2-weighted image (B) and coronal turbo spin-echo FLAIR T2-weighted image (C). Transverse turbo spin-echo inversion-recovery T1-weighted image (D) and transverse turbo spin-echo T2-weighted image (E). Along the sulcus which separates the first from the second frontal gyrus on the left, the cortex appears thickened and shows blurred demarcation with the white matter, both on T1W and T2W images. Mild increased signal on T2WI of the subcortical white matter is seen, connecting to the ventricle (transmantle sign) (arrow). Abnormal gyration of the dysplastic cortex is also present (D, E).

FCDs associated with tumours

FCDs (particularly type I) can be found in association with developmental tumours, such as dysembryoplastic neuroepithelial tumours (DNET) and gangliogliomas (GG). On MRI, the presence of the tumour is suggested by mass effect of the lesion (sometimes very subtle), and by the presence of cystic components mixed with solid portions and variable calcifications. When the MRI images suggest the presence of an associated tumour, contrast medium should be injected for evaluation of possible foci of enhancement within the tumour, facilitating the diagnosis. At neuropathology, the dysplastic lesion is usually found along the boundaries of the tumour but they may be intermingled (*figure 4*).

New MRI Concepts in FCD

In the recent meeting in Istanbul, the neuroradiologists emphasized the need for the careful redefinition of some terminology used in imaging descriptions and for the identification of the most specific MRI sequence for certain MR findings. For instance, the term “*blurring*”, which describes poor definition between grey and white matter, is reported in many papers as one of the most sensitive radiological markers of FCD. For histology it may reflect something different, namely the presence of densely heterotopic neurons in the subcortical white matter, dysmyelination and reduced number of myelinated fibers. The blurring is reportedly more pronounced in the dysplastic lesions with greater disturbance of cortical

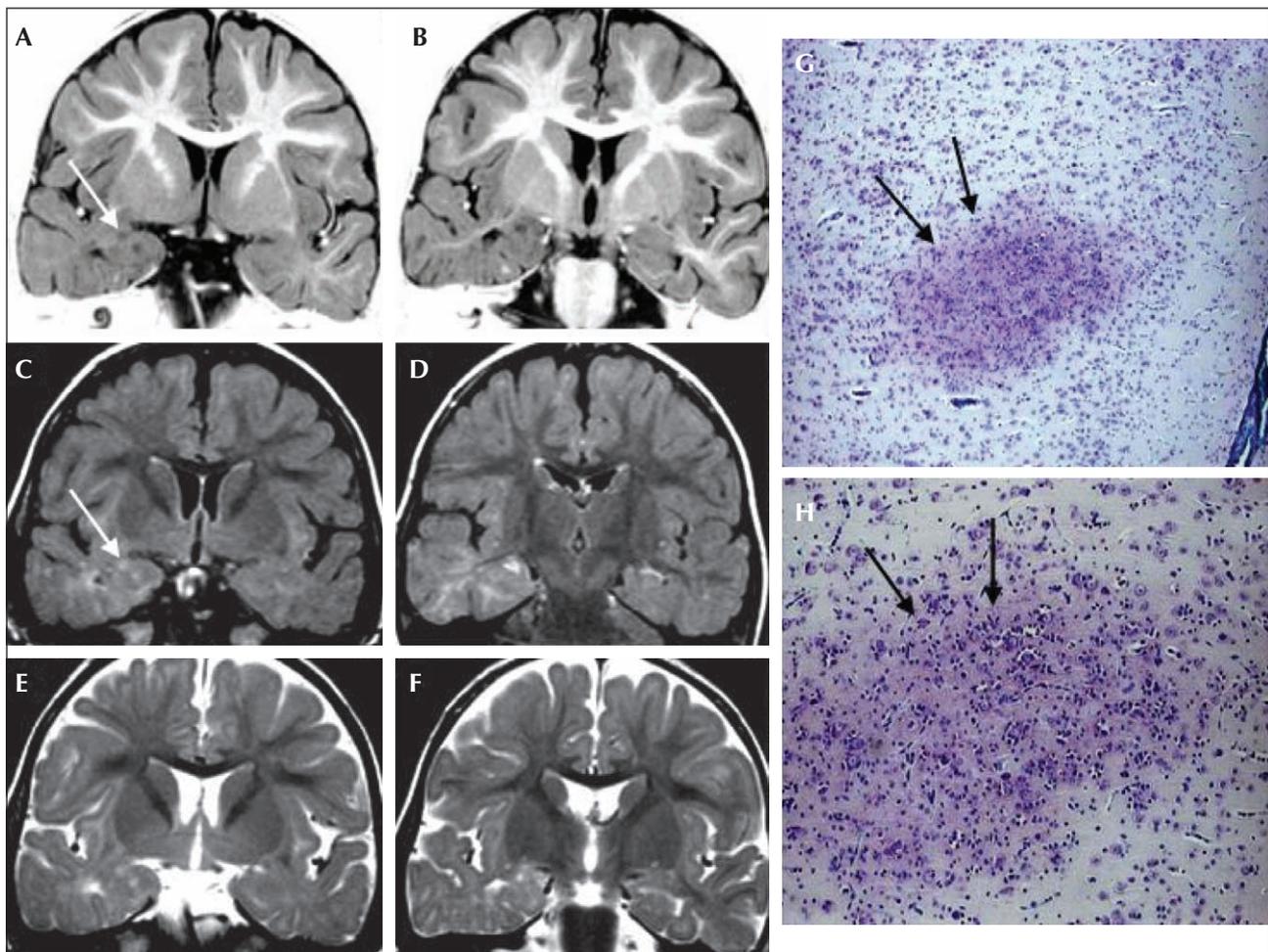


Figure 4. Focal cortical dysplasia type I B associated with dysembryoplastic neuroepithelial tumor (DNET) in a 3-year-old boy. MR coronal turbo spin-echo inversion-recovery T1-weighted images (**A, B**); coronal turbo spin-echo FLAIR T2-weighted images (**C, D**) and coronal turbo spin-echo T2-weighted images (**E, F**). Histology slides (**G, H**). Diffuse abnormal hyperintensity of white matter in the right temporal lobe, with blurring of the cortical-white matter junction on T1WI which shows sharper demarcation on T2WI. Within the uncus-amygdala some locations, hypointense on T1WI (white arrow, **A**) and hyperintense on T2WI (white arrow, **C**), are recognizable; these proved to be islands of cystic DNET (black arrows, **G, H**) surrounded by dysplastic cortex.

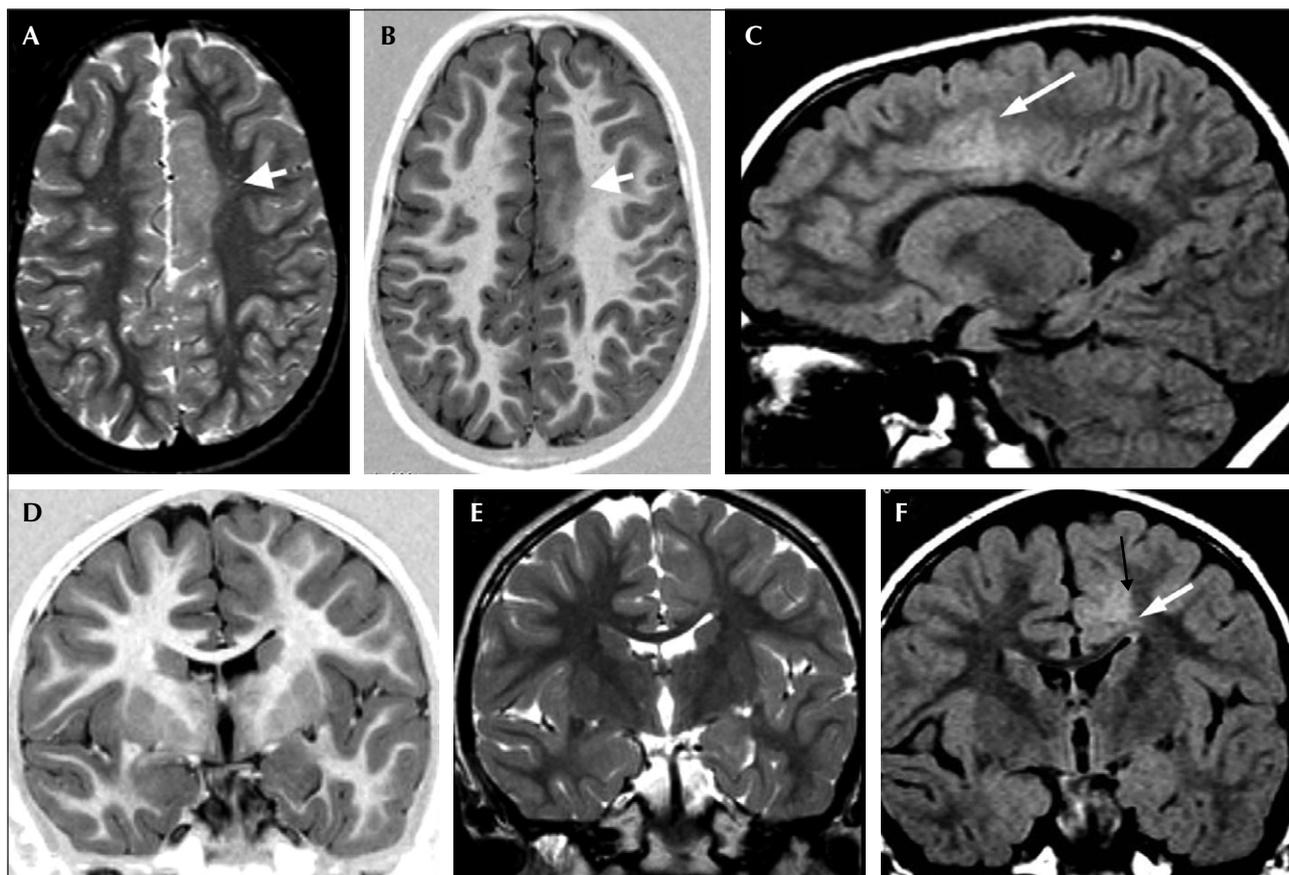


Figure 5. Focal cortical dysplasia type II B of the left frontal cortex in a 9-year-old female. Transverse turbo spin-echo T2-weighted image (A) and transverse turbo spin-echo inversion-recovery T1-weighted image (B). Sagittal turbo spin-echo FLAIR T2-weighted image (C). Coronal turbo spin-echo inversion-recovery T1-weighted image (D), coronal turbo spin-echo T2-weighted image (E) and coronal turbo spin-echo FLAIR T2-weighted image (F). Thickening of the left paramedian frontal cortex which shows a *blurred demarcation* with the white matter both on T1W and T2W either transverse and coronal images (white arrows, A-B, D-E). On FLAIR coronal sequence (F) the junction between GM/WM seems to be more defined (black arrow), contrary to what is most frequently observed. The hyperintensity of the WM, extending toward the ventricle (transmantle sign) is better appreciated on FLAIR sequences (white arrows, C, F).

structure, namely FCDs type II (Tassi *et al.*, 2002 ; Colombo *et al.*, 2003a ; Colombo *et al.*, 2003b ; Krsek *et al.*, 2008b). However, growing experience with this type of lesions suggests that in a number of cases a much sharper demarcation between the cortex and the adjacent WM may be found (*figures 5, 6*). This difference is likely due to variable myelination in subcortical white matter (due to state of maturation, reactive astrogliosis or the malformation itself) that is variably detected by T1WI and T2W images. In addition, due to intrinsically poor contrast between grey matter and white matter, FLAIR T2W sequences frequently fail in defining the junction, over-estimating the blurring.

Another term that should probably be revised is “*cortical thickening*”, frequently reported as a characteristic MRI feature, especially of FCD type II. This finding is not supported by any specific histopathological studies that have examined the true thickening of the cortical ribbon; indeed, it is usually not reported in histopathological

observations. The neuroradiologists noted that abnormal subcortical white matter in FCD type II, can be isointense to cortex and, thus, produces the “blurring” and give a *false appearance* of cortical thickening.

Therefore, it is a **consensus opinion** of the neuro-radiologists that *blurring* and *cortical thickness* should be evaluated specifically and individually on T2WI, 3D volumetric Gradient Echo T1WI and heavily T1W Inversion Recovery (IR) images, which provide the best GM/WM differentiation. On the contrary, FLAIR-T2W sequences, having less contrast resolution between cortex and WM, seem to be less appropriate in this regard; FLAIR sequences, however, are certainly superior for detecting even very subtle cortico-subcortical signal alterations.

The consensus opinion is that cortical thickening should only be reported if the cortex appears thick on both T1W and T2W sequences that are windowed for high levels of contrast, in at least two planes.

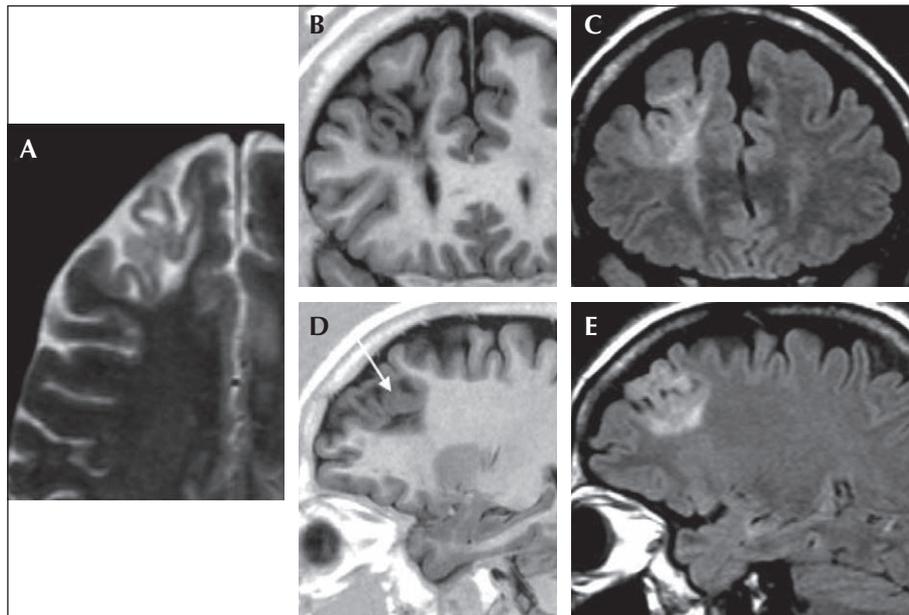


Figure 6. Focal cortical dysplasia type II B of the right frontal cortex in a 41-year-old female. Transverse turbo spin-echo T2-weighted image (magnification) (A); coronal turbo spin-echo inversion-recovery T1-weighted image (B) and coronal turbo spin-echo FLAIR T2-weighted image (C). Sagittal turbo spin-echo inversion-recovery T1-weighted image (D) and sagittal turbo spin-echo FLAIR T2-weighted image (E). Abnormal gyration of the left frontal cortex which presents very sharp demarcation with the white matter both on T1W and T2W images. Pronounced increased signal of the subcortical white matter on T2WI which tapers toward the ventricle (transmantle sign). The dysplastic cortex appears of normal thickness in (A) and (B). In (D) focal thickening of the cortex seems to be present (arrow), probably due to convolution of gyri.

The authors suggest that many of the cases with “blurred GM/WM junction” and “cortical thickening” on MRI are better described by the term “pseudo-thickening” of the cortex, contrary to the cases with sharp GM/WM junction in which the cortex appears to have relatively normal thickness (figure 6).

In addition, the authors noted that *the age of the patients* greatly influences the selection of the most appropriate MR sequences for the evaluation of blurring and cortical thickness. In adult patients, with complete myelination, both T2W and T1W images (3D Gradient Echo T1WI and heavily T1W Inversion Recovery [IR]) appear to be suitable for this purpose.

Infants have incomplete myelination and areas of subcortical white matter that are physiologically immature can appear isointense to cortex at various times on T1W and T2W images. An important point is that in areas of FCD the subcortical white matter may sometimes be isointense to cortex (and, therefore, appear as blurring or thick cortex) on T1WI but will almost always look hyperintense to cortex on T2WI, better delineating the junction with the cortex and showing true cortical thickness. When we recall that FLAIR T2WI shows poor contrast between cortex and underlying white matter, it becomes clear that T2W sequences are essential to the MR protocol and are the most suitable for evaluating GM/WM blurring and the true thickness of the cortex, at any age.

It is important to note, as well, that contrast between cortex and white matter in children is maximal before myelination begins; therefore, if seizures begin in neonates/young infants, a scan should be obtained immediately. Before 6 months of age, the hypointensity on T2W images of the cortical dysplasia is very clear in contrast to the hyperintensity of the unmyelinated white matter. During myelination, contrast between grey and white matter diminishes, making detection of FCDs much more difficult. If the first MR study is obtained, for any reason, between ages of 6 months and 18 months, a second scan will probably be required when myelination is largely completed (after the age of 30 months).

In summary, from an MR imaging perspective, mMCD and FCD type I may be completely cryptic or may be revealed by hypoplasia/atrophy of the area of the brain containing the dysplastic cortex and by mild blurring of the cortical-white matter junction on both T1W and T2W images. FCD type II is most commonly associated with T2 hyperintensity of the underlying white matter and with variably blurred or fairly sharp cortical-white matter junction, better evaluated on T2W images. Sometimes the white matter abnormality extends all the way from cortex to the lateral ventricle; this “transmantle sign” is a radiological hallmark of this subtype of FCD.

PET, MEG, DTI

Positron emission tomography (PET)

18-fluorodeoxyglucose (18F-FDG) PET represents a useful tool for pre-surgical evaluation of epilepsy. 18F-FDG PET has been reported to be 75-100% sensitive in localizing areas with FCD (Sood and Chugani, 2006 ; Kloss *et al.*, 2002). Although in most cases the FCD visualized by MRI lies within the region of brain responsible for generating seizures (the EZ) it may not constitute the entire EZ in all cases. This can explain the poor surgical outcome reported in some cases in which the surgical intervention has been based on MRI alone (Sisodiya *et al.*, 2000). 18F-FDG PET may help to disclose subtle cortical dysplasias and to better define the most peripheral portion of dysplastic lesions that can be occult on MRI. In FCD, the boundaries of the cortical abnormality are usually larger on 18F-FDG PET imaging than on MRI (Kim *et al.*, 2000). Given the important and parallel roles of MRI and 18F-FDG PET in pre-surgical evaluation, co-registration of MRI images and 18F-FDG PET images may enhance pre-surgical management of intractable epilepsy (*figure 7*). Usually, FDG PET shows hypometabolism in the cortical dysplasia. However, FCDs can sometimes appear normal or hypermetabolic on 18FDG PET (Ozkara *et al.*, 2007). The reason for the difference in glucose metabolism in these cases is uncertain.

However, the authors underline the importance to monitor the patients with continuous EEG during the PET study to evaluate the presence of ictal activity at the time of radioactive tracer injection.

The 18F-FDG PET scans are performed using a whole body positron tomography system, with 15 cm FOV and 3.0 mm slice thickness, using a standard protocol (Salamon *et al.*, 2008). The grey scale 18F-FDG PET

scans are internally scaled relative to the basal ganglia and initially interpreted qualitatively without knowledge of the structural MRI.

18F-FDG PET and MRI image co-registration is performed using commercial fusion software. Fused images are displayed as multi-coloured images with each colour change corresponding to approximately a 15% difference in 18F-FDG uptake. The borders of the areas of PET hypometabolism or hypermetabolism are determined based on the asymmetry of uptake as compared to contralateral structures.

The sequence in assessing the co-registration scans is as follows:

- the fusion scans are created with colour-coded grading (white as greatest metabolism followed by red, orange, yellow, green and blue, in descending order);
- by visual assessment, asymmetric areas of abnormal metabolism are identified. Most of the cases show significant differences in colour scale as compared to the contralateral structure. Thus, areas of abnormal metabolism are readily identifiable as different from normal metabolic cortex;

- in cases where the visual asymmetry is more subtle, the visual assessment is supplemented by using the Bq/ml ratio to define whether an area was abnormal. A difference of 10% is accepted to be significant (Salamon *et al.*, 2008).

MRI and 18F-FDG PET co-registration provides additional information and can be helpful both in terms of surgical planning and surgical outcome. Compared with the 2000-2003 cohort before the use of 18F-FDG PET/MRI co-registration, between 2004 and 2007 more patients with FCD had surgery with a higher percentage of FCD type I (15% in 2000-2003 vs 60% in 2004-2007). The approach incorporating 18F-FDG PET/MRI co-registration into the pre-surgical evaluation showed 77% post-operative

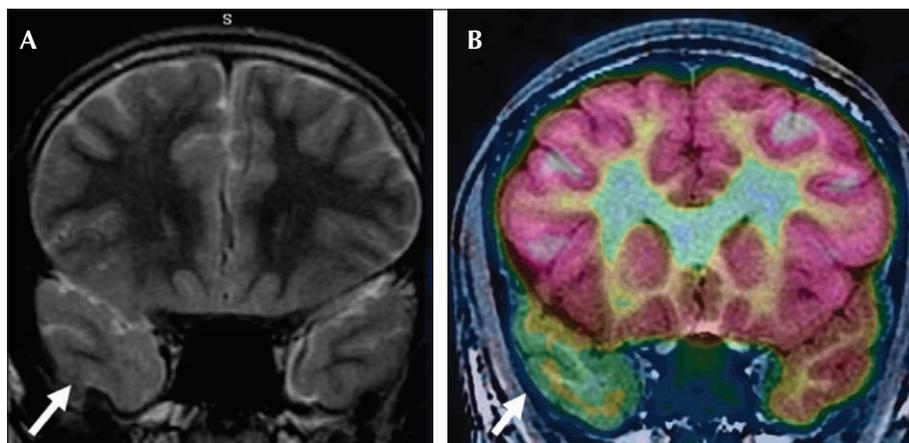


Figure 7. Thirteen-year-old boy with intractable epilepsy. T2 weighted coronal image (A) shows subtle indistinctness in the gray-white matter differentiation of the right temporal pole suggesting the presence of FCD (long white arrow). PET-MRI co-registration (B) shows obvious hypometabolism (short white arrow) in the right temporal pole.

seizure freedom in FCD type I and 88% in FCD type II, considering 2.0 ± 1.1 years of follow up (Salamon *et al.*, 2008 ; Lerner *et al.*, 2009).

In comparison, in studies of epileptic patients where the use of anatomical and functional multimodality imaging co-registration was either absent or very limited for pre-surgical planning, only 69-76% of patients were Engel Class I-II at a similar follow-up period, and only 30-50% when pre-surgical MRI was non-lesional (Cohen-Gadol *et al.*, 2006 ; Elsharkawy *et al.*, 2008).

Reasons for this lower rate of favourable outcome without co-registered image-guided surgery include difficulty in delineating the EZ and correlating it with relevant structural anatomy (Murphy *et al.*, 2004). Importantly, one study found that MRI detected 83% of severe FCD, whereas 18F-FDG PET detected 90% (Kim *et al.*, 2000). For subtle FCD, however, MRI identified only 13% as compared to 86% with 18F-FDG PET. This study suggests that 18F-FDG PET is more sensitive than MRI and that it is particularly useful when MRI is normal, especially for cases of FCD type I.

Magnetoencephalography (MEG)

MEG is a technique that maps inter- and intra-ictal dipole sources. The findings can be superimposed upon the anatomical MR imaging. MEG has been used to define localization of the EZ in non-lesional cases of FCD. The pattern of dipole sources can be different for the different subtypes of FCD. For example, when "clusters" are defined as comprising 20 or more spike sources within an area of 1 cm in diameter and scattered regions defined as less than 6 spike sources, it was shown that clustered MEG findings were more likely seen for FCD type II. Scattered and more bilateral distribution of the spike sources were more likely to be seen in the more subtle types of dysplasia (mMCD or FCD type I). MEG also has an important role in anatomically localizing specific functional zones: motor, sensory and language zones can be identified non-invasively using MEG (Baumgartner and Pataria, 2006).

In summary, PET- or MEG-guided re-evaluation of MRI can help identify previously unrecognized subtle abnormality and help to improve surgical results.

Diffusion tensor imaging (DTI)

Unlike conventional MR imaging that provides images resulting from the relaxation parameters T1 and T2 of the brain components, diffusion imaging provides contrast based upon the extent, directionality and organization of the motion of free (unbound) water. Diffusion tensor imaging (DTI) evaluates and quantifies diffusion tridimensionally in each of the image voxels. In a fascicular structure like the brain, diffusion is more restricted in the direction perpendicular to the fibers than parallel to them: the random water motion therefore occurs in an ellipsoid which can be defined by three measurable eigenvalues:

major λ_1 (long axis, parallel to the fibers), medium λ_2 and minor λ_3 (perpendicular to the fibers). The trace D is defined as the sum of the three eigenvalues λ , in mm^2/sec ; mean diffusivity is defined as $MD=D/3$, in mm^2/sec . Fractional anisotropy is an index of anisotropy that varies between 0 (*i.e.* maximum isotropy in a sphere, with no perpendicular restriction) and 1 (*i.e.* maximum anisotropy, total perpendicular restriction); it is unitless. Anisotropy results from the fascicular organization of the white matter: the more coherent the fibers in the voxel, the higher fractional anisotropy will be. On the contrary, fractional anisotropy may be decreased by fibers crossing, high cellularity, demyelination and gliosis. Perpendicular λ_2 and λ_3 reflect the size of the extracellular space between the fibers; they are increased in case of loss of myelin or rarefaction of fibers. The combination of these parameters offers the best MR evaluation available today for the microstructure of the brain.

In addition to quantitative DTI, anatomical DTI uses fractional anisotropy mapping and fiber tracking. Directional fractional anisotropy mapping describes the gross orientation of the tracts; by convention left-right orientation is shown in red, dorso-ventral orientation is shown in green and cranio-caudal orientation is shown in blue. Fiber tracking uses the directional information of contiguous voxels to re-create the course of the white matter fascicles, using various post-processing methods. Anatomical DTI data may be used to evaluate changes in the organization of the white matter bundles dependent on an area of cortical dysplasia (Widjaja *et al.*, 2007, 2008, 2009).

Because the cortex is abnormal in MCD, its connectivity is likely to be modified and the microstructure of the underlying white matter is expected to be abnormal. In FCD, in addition, heterotopic neurons, abnormal myelination (myelin pallor on histology) and even gliosis may be found. All this may affect both the quantitative data (eigenvalues and fractional anisotropy) and fiber mapping. Several reports have addressed this topic in the last decade (Eriksson *et al.*, 2001 ; Lee *et al.*, 2004 ; Gross *et al.*, 2005). In a recent report of 13 children with FCD (eight cases), as well as subcortical (two cases) and subependymal (one case) heterotopias, unilateral schizencephaly (one case) and unilateral polymicrogyria (one case), reduced fractional anisotropy and increased perpendicular λ_2 and λ_3 have been demonstrated in the white matter adjacent to the cortical malformation, suggesting abnormal myelin or more randomness of axonal pathways (Widjaja *et al.*, 2007). Also, alteration in the course and volume of the main white matter tracts connected to the malformed cortex was shown by fiber tracking.

These changes were not significantly different between MR-identified FCD and other MCD and were similar in patients with and without epilepsy. In other reports, areas of increased diffusivity and reduced fractional anisotropy have also been found beyond the margins of

the MR-visible abnormality (Eriksson *et al.*, 2001 ; Dumas de la Roque *et al.*, 2005). This suggests that microdysplasia may be detected in tissue that looks normal on conventional imaging, and therefore suggests a greater potential of DTI to detect mMCD. This parallels the fact that MEG spike sources may also extend beyond the limits of an MR-visible lesion (Widjaja *et al.*, 2008). Therefore there is a possibility that DTI might be helpful in detecting microstructural dysplastic changes that cause refractory epilepsy with normal-looking MR imaging (Chen *et al.*, 2008), which are still relatively common (Krsek *et al.*, 2008b).

This however raises several questions. The first is whether DTI may differentiate between different varieties of CD (mMCD, FCD I/II), which would be useful as the post-surgical prognosis may depend on the histological changes; at this point the answer is negative. The second question concerns the specificity of the findings. As noted before, diverse pathogenetic processes, whether developmental or epileptogenic, may increase diffusivity and decrease fractional anisotropy. Using DTI, it is therefore not possible to identify whether the microstructural changes are related to the histology of the mMCD/FCD itself, to remote disruptive changes that induced a cortical dysplasia or to the effects of the repeated seizures on the brain, locally or at a distance along the epileptogenic networks.

Fiber tracking can also be used in the pre-surgical assessment, to identify the anatomical relationship between the lesion to be resected and the adjacent eloquent fiber bundles. The reconstruction of the Meyer's loop in cases of temporal lobectomy (Widjaja and Raybaud, 2008) and of the pyramidal tract in cases of frontal surgery, and their co-registration with the morphological MR images could greatly help the neurosurgeon.

In summary, DTI certainly is a tool that may help to better evaluate the brain parenchymal changes in the context of refractory partial epilepsy, but more correlation with electroclinical and pathological data is needed to understand the data and fully appreciate its potential usefulness. □

Disclosures.

None.

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