

Malformations of cortical development and epilepsies: neuropathological findings with emphasis on focal cortical dysplasia

Ingmar Blümcke¹, Harry V. Vinters², Dawna Armstrong³, Eleonora Aronica⁴, Maria Thom⁵, Roberto Spreafico⁶

¹ Department of Neuropathology, University Hospital Erlangen, Erlangen, Germany

² Daljit S. and Elaine Sarkaria Chair in Diagnostic Medicine, Departments of Pathology, Laboratory Medicine (Neuropathology) and Neurology, UCLA Medical Center, and David Geffen School of Medicine at UCLA, Los Angeles, USA

³ Texas Children's Hospital and The Methodist Hospital, Houston, USA

⁴ Department of (Neuro)Pathology, Academic Medical Center, University of Amsterdam, and Stichting Epilepsie Instellingen Nederland, Heemstede, The Netherlands

⁵ Neuropathology, Institute of Neurology, University College London, UK

⁶ Department of Epilepsy Clinic and Experimental Neurophysiology - Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milano, Italy

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ABSTRACT – Structural brain abnormalities can be increasingly recognized in patients suffering from intractable focal epilepsies using high-resolution imaging techniques. Epilepsy surgery has become a successful treatment option for many of these patients. A broad spectrum of malformations of cortical development (MCD) can be histopathologically identified in resective surgical brain samples. Here, we discuss neuropathological findings and available classification systems in children and adult patients. Particular emphasis will be paid to the classification system for focal cortical dysplasias (FCD), which can be histopathologically distinguished as type I and II. Also mild forms of cortical malformations (mMCD) may be present, including heterotopic neurons in white matter location. However, different cohorts of epilepsy patients may present with similar histopathological findings and clinico-pathological correlations are not always comparable with respect to outcome prediction. We will, therefore, discuss also the difficulties to classify some FCD variants. Notwithstanding, the underlying pathomechanisms in all FCD entities need to be specified. A comprehensive approach taking all currently available data into consideration will be mandatory to further develop our current understanding of FCDs, and to continuously improve our concept for a reliable classification system.

Key words: epilepsy, development, cortical dysplasia, neuropathology

Correspondence:

I. Blümcke
Department of Neuropathology,
University Hospital Erlangen,
Schwabachanlage 6,
91054 Erlangen, Germany
<Ingmar.Bluemcke@uk-erlangen.de>

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Malformations of cortical development (MCD) are increasingly recognized in patients suffering from intractable focal epilepsies (Barkovich *et al.*, 2005). The histopathological spectrum of MCD is large ranging from prominent to only minute changes (*table 1*). Whereas schizencephalic brain lesions, hemimegalencephaly, polymicrogyria, nodular or band heterotopias can be reliably diagnosed *in vivo*, focal cortical dysplasias (FCD) often escape imaging techniques (MRI) and may considerably vary in their size and localization (Guerrini *et al.*, 2008). Hence, we will particularly focus on the peculiar histopathological aspects of FCD, either appearing as an isolated lesion within the cerebral hemisphere, or in conjunction with another principle lesion, *i.e.* mesial temporal lobe sclerosis (MTS), glio-neuronal tumour or glial scarring.

According to the current classification system (Palmini *et al.*, 2004), FCD can be histopathologically distinguished as type I and II. FCD type IA refers to architectural disturbances of cortical lamination and FCD type IB includes additional cytoarchitectural abnormalities, *i.e.* hypertrophic pyramidal neurons outside layer V (Tassi *et al.*, 2002). Also, mild forms of cortical malformations (mMCD) should be distinguished, including heterotopic neurons in layer I (mMCD type I) or within white matter location (mMCD type II). However, different cohorts of epilepsy patients can present with similar histopathological findings. FCD type IA may occur within the temporo-polar region of adult patients suffering from mesial temporal sclerosis and tailored resection strategies usually gain successful seizure control (Fauser *et al.*, 2004).

FCD type IA can also be identified outside the temporal lobe and in young children with “catastrophic” multilobar epilepsies and psycho-motor retardation (Hildebrandt *et al.*, 2005). Neurosurgical resection does not always sufficiently control seizure activity in these young patients

(Krsek *et al.*, 2009). We will, therefore, also discuss the difficulties to differentiate these lesions as separate variants of FCD type I using the current classification system. Notwithstanding, the underlying pathomechanisms in all FCD variants need to be specified. FCD type II presents with gross histopathological changes including dysmorphic neurons (FCD type IIA) and additional balloon cells (FCD type IIB). These lesions have first been described by Taylor *et al.* (1971), and can be readily observed by MRI often showing a “transmantle” sign. Histopathological examination of surgical specimens usually corroborates the diagnostic subtype (Urbach *et al.*, 2002; Pasquier *et al.*, 2002). Recent molecular-biological studies identified the insulin-growth factor receptor cascade to be involved in the pathogenesis of FCD type IIB and indicate that FCD type IIA and IIB are pathogenetically distinct (Majores *et al.*, 2005).

Systematic neuropathological examination of surgical specimens is mandatory to classify variants of cortical dysplasias which then will allow a subsequent molecular-genetic and/or -biological analysis. This neuropathological approach will help to establish a comprehensive classification system as a prerequisite for pre- and post-surgical management of patients with chronic intractable epilepsies, but also to support stratification of clinical outcome studies and targeted search for new anti-epileptic drugs.

Pathology of hemispheric and other congenital epileptogenic lesions

Cerebral malformations are extremely variable in severity though not always symptomatic (Ellison *et al.*, 2004; Vinters *et al.*, 1998). Some types of malformation (*e.g.* anencephaly) are incompatible with prolonged survival; clinical manifestations of most types of neocortical

Table 1. Clinico-pathological findings in epilepsy patients with cortical malformations. Summary of 561 patients with intractable epilepsies and histopathologically confirmed malformations of cortical development. The data were obtained from the German Reference Center for Epilepsy Surgery (www.epilepsie-register.de) and European Epilepsy Brain Bank (www.epicure-bank.org).

| MCD | Number | Age | Onset | Duration |
|---------------------|--------|------|-------|----------|
| Hemimegalencephaly | 13 | 2.2 | 0 | 2.2 |
| Polymicrogyria | 33 | 7.7 | 2.0 | 5.5 |
| FCD type I | 75 | 11.6 | 3.5 | 6.8 |
| FCD type IIa | 36 | 16.7 | 2.6 | 12.8 |
| FCD type IIb | 182 | 18.6 | 4.3 | 14.6 |
| FCD (NOS) | 133 | 20.8 | 7.9 | 13.3 |
| mMCD | 46 | 28.0 | 10.1 | 17.6 |
| Hamartia-toma | 34 | 25.3 | 8.9 | 16.0 |
| Nodular heterotopia | 9 | 29.6 | 13.0 | 18.5 |

FCD: focal cortical dysplasia; NOS: not otherwise specified; mMCD: mild malformation of cortical development; Age OP mean (in years); Onset mean (in years); Duration mean (in years).

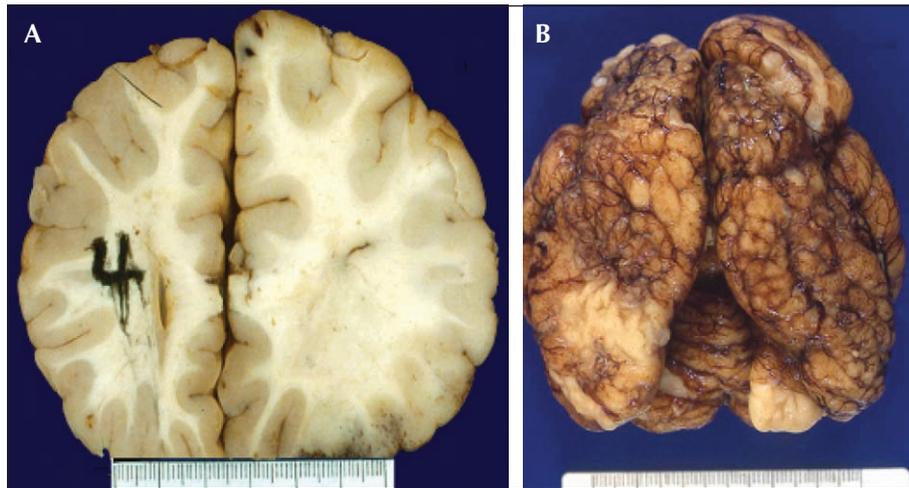


Figure 1. Malformations of cortical development; autopsy findings. **A)** Hemimegalencephaly of the right hemisphere. **B)** Bilateral polymicrogyria. Not all abnormalities of the cerebral cortex seen in epileptic infants and children are “malformative” and result from deranged mechanisms of neuronal migration and maturation. As a consequence, destructive lesions are also found in corticectomy specimens obtained from infants and children with intractable epilepsy. Intra-uterine or perinatal anoxic-ischemic insults may cause extensive necrotic cavitation in both the cerebral cortex and subcortical white matter, described as cystic-gliotic encephalopathy (*figure 2*).

malformation include varying combinations of mental retardation, cerebral palsy, focal neurological deficits and intractable seizures. Smaller, very focal or milder malformations may be asymptomatic and discovered only when neuroimaging is performed or at autopsy. Many cortical malformations can now be detected *in utero* by the use of ultrasound and MRI. MCDs are usually treatable by surgery only when they are focal or, at most, involve one cerebral hemisphere (hemimegalencephaly [HME]; *figure 1A*). It is important to note that many cerebral malformations are not surgically remediable, usually because they involve both cerebral hemispheres in equal or comparable measure. Whereas some cerebral (including hemispheric) malformations now have a well established genetic basis (Guerrini *et al.*, 2008), other serious malformations (ones which may or may not have a cortical component), e.g. Chiari malformation type II, are sporadic. Many malformations are difficult or impossible to “model” in animals because they lack the neocortical complexity of the human brain.

Some MCDs are frequently associated with intractable seizures and are considered to result from neuronal migration and/or organization abnormalities (Barkovich *et al.*, 2005; Farrell *et al.*, 1992). They may involve both cerebral hemispheres, resulting in either a hyperconvoluted cortical ribbon with miniature thin gyri (polymicrogyria [PMG]; *figure 1B*) or an entirely smooth-surfaced brain (lissencephaly, agyria, pachygyria). In contrast, abnormal neuronal and glial proliferation or apoptosis may result in HME, a condition in which one cerebral hemisphere is much larger than the other (De Rosa *et al.*, 1992; Salamon *et al.*, 2006). Histopathologically, features of multifocal

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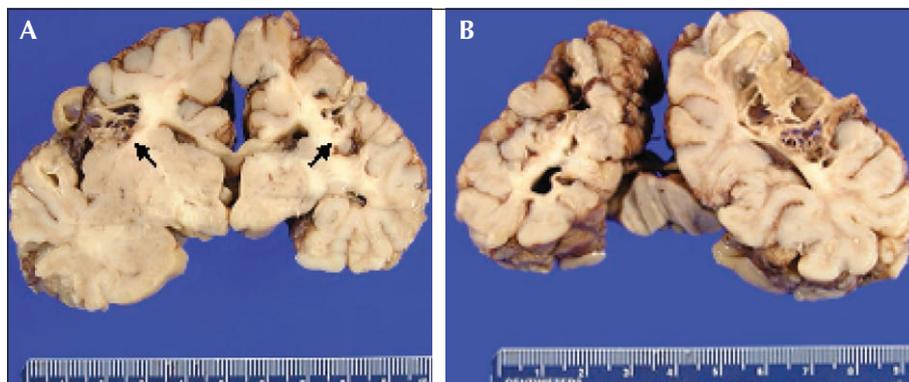


Figure 2. Acquired cystic-gliotic encephalopathy. Different coronal slices from the same infant, with extensive tissue destruction in the middle cerebral artery territories (arrows in **A**), somewhat more prominent on the right (**B**); the infant was one of twins who died at 6 months of age, was born at 34 weeks gestation and experienced a complicated intra-uterine and postnatal course.

cortical dysplasia, and sometimes hemi-lissencephaly, can be observed in HME.

However, the epileptogenic pathomechanism needs to be clarified. Besides brain trauma and vascular disorders, other pathogens may include encephalitis, physical insults or chemical toxins (Cendes *et al.*, 1995). Previous studies postulate that early brain injuries compromise pre- and post-natal maturation of the neocortex which may result in “progressive” development of focal cortical dysplasia, if the injury remains circumscribed (Marin-Padilla *et al.*, 2002). The diverse spectrum of focal cortical dysplasia, either isolated or associated with such a principle lesion, will be discussed in the following chapter.

Neuropathological findings in focal cortical dysplasias

Focal cortical dysplasias (FCD) represent architectural and cytoarchitectural abnormalities within the neocortex and adjacent white matter, which are usually confined to a single hemispheric lobe. According to the current classification system, two major variants of FCD should be distinguished (Palmini *et al.*, 2004).

The characteristic histological finding in FCD type IA presents as neocortical dyslamination. This “vague” description includes the following features: diminution of cortical thickness, blurring of layer boundaries and compromised vertical organization with increased/persisting microcolumnar arrangement and aggregates of smaller (immature) neurons (*figure 3A*). In other variants, absence of individual cortical layers can be observed, particularly affecting

cortical layer II (*figure 3C*) or IV (*figure 3D*). An abnormal supragranular layer is frequently encountered in MTLE specimens of the temporal lobe (*figure 3B, C*). Ectopic white matter neurons are virtually always present. The architectural abnormalities occur either isolated in one or more cortical lobes, or associated with a principle lesion, *i.e.* hippocampal (mesial temporal) sclerosis, glioneuronal tumours, vascular malformations or glial scarring. However, cytological (cytoarchitectural) abnormalities are not encountered for FCD type IA.

Cytoarchitectural dysplasia refers to the presence of abnormal hypertrophic pyramidal-like cells (*syn.* cytomegalic neurons, giant neurons) and were classified as FCD type IB (*figure 4*). At the microscopic level, hypertrophic pyramidal-like cells are larger than layer V pyramidal neurons and localize to other layers. They have a central nucleus and preserve a pyramidal morphology, with apical dendrites and increased cytoplasmic neurofilament content. Similar to FCD type IA, cortical layering is mostly retained although boundaries between individual layers may be blurred.

FCD type II is characterized by the occurrence of dysmorphic (*syn.* dysplastic), often bizarre structured neurons in grey and/or white matter (FCD type IIA) and the presence of balloon cells (*syn.* TS cells) similar to those observed in tuberous sclerosis (FCD type IIB). This severe FCD variant was originally described by Taylor *et al.* (1971). The cortical layering and architecture is almost destroyed within the central portion of the lesion. However, this can pose difficulties for the distinction between FCD IB and IIA, if surgical tissue is fragmented or not entirely available for neuropathological examination.

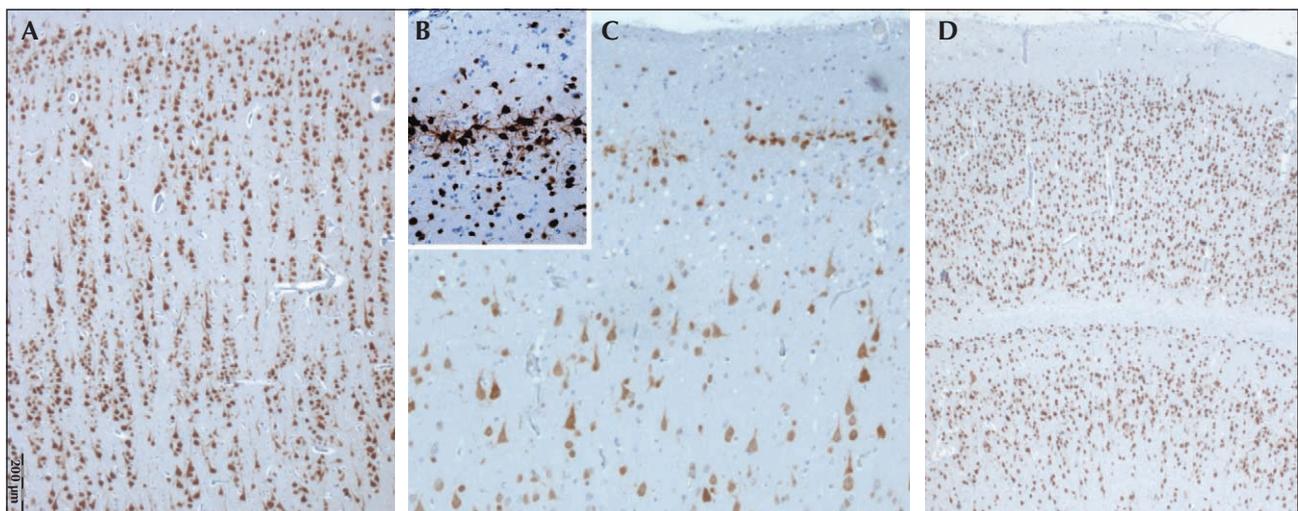


Figure 3. Histological hallmarks of FCD type IA. NeuN-immunohistochemistry specifically highlights the neuronal cell population. Compromised vertical organization is visible in (A) (obtained from the occipital lobe of an epileptic young child). (C) Abnormal supragranular layering with loss of small pyramidal cells and clustering (with higher magnification in B; MTLE specimen). (D) In this specimen, layer 4 is missing. Cortical architecture of other layers is normal. There was no evidence for a hypoxic or other pre-/perinatal lesion in this young child. Scale bar in A = 200 μ m.

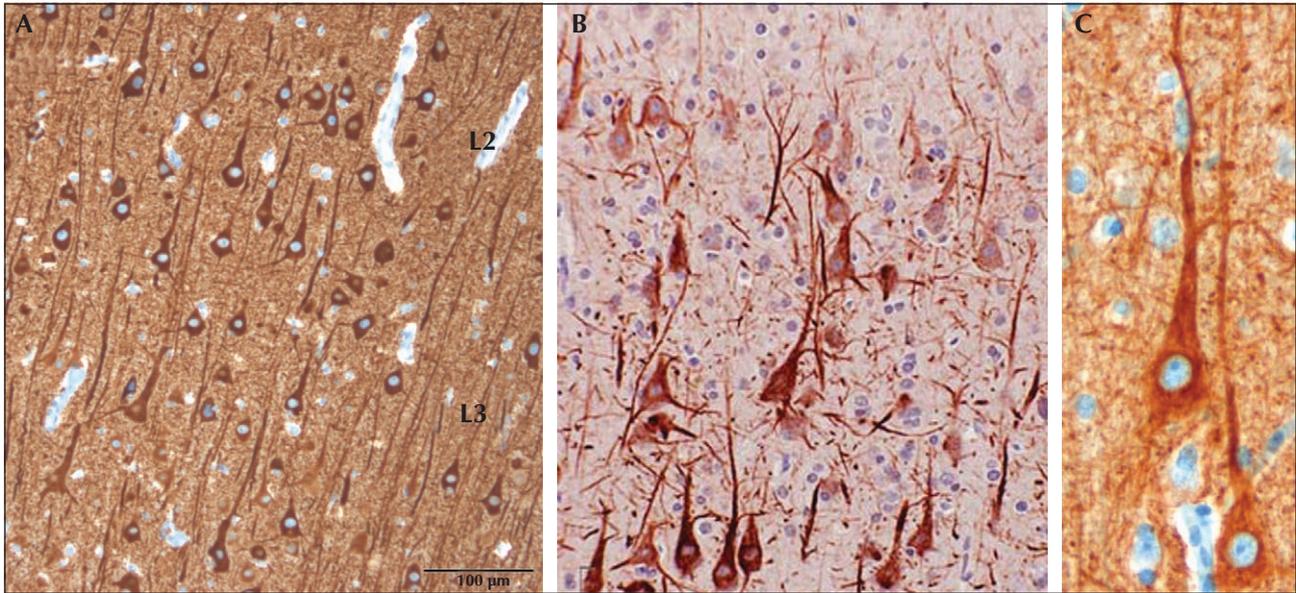


Figure 4. Histological hallmarks of FCD type IB. Hypertrophic neurons (in layers 2 and 3; L2, L3 in **A**) are the hallmarks of FCD Type IB. These abnormal neurons retain their pyramidal cell (**B**) and an apical dendrite (**C**), but accumulate neurofilament proteins within the cytoplasm. Cortical layering is mostly retained although boundaries between individual layers may be blurred. Map2 staining in **A**; neurofilament staining in **B** and **C**. Scale bar in **A** = 100 µm.

Abnormal neuronal morphology includes a rather “globose”, instead of pyramidal, shape with enlarged somal size, abnormal orientation and cell clusters, abnormal dendritic patterns, abnormal distribution of intracytoplasmic organelles (clustered Nissl substance) and high neurofilament content in the cell body (*figure 5A-D*). Balloon cells are also huge in size, with a thin membrane and pale eosinophilic cytoplasm. Balloon cells often present with more than one nucleus, which are eccentrically localized. This peculiar cell population usually lack specific glial or neuronal differentiation patterns when applying immunohistochemical reactions (GFAP, neurofilaments). Instead, most balloon cells retain immature cell markers such as vimentin, CD34 and nestin.

FCDs constitute the major class of cortical malformations when reviewing series of surgical brain specimens obtained from patients with intractable epilepsies (*table 1*); FCD type IIB being the most frequent.

Isolated persistence of neurons in the molecular layer and increased cellularity in the white matter or perivascular oligodendrocyte cluster are subsumed under the term of mild cortical dysplasia (mMCD; Palmiini *et al.*, 2004). Notwithstanding, mMCDs can be frequently observed in association with all other FCD type I or II variants. However, there is considerable discrepancy with respect to the neuropathological diagnosis of such neuronal heterotopias as well as their functional impact on epileptogenesis. The following chapter will, therefore, review and discuss this peculiar matter with particular emphasis on neurons in the white matter.

Heterotopic single neurons in the white matter and their impact on neuropathological diagnosis

The perception of an excess of single white matter neurons in post mortem analysis of patients with epilepsy, occurring in a variety of syndromes, has long been noted by neuropathologists (Meencke and Janz, 1984), forming part of the spectrum of features termed *Microdysgenesis*. This presumed developmental anomaly has been variably reported following qualitative inspection of tissues resected from patients with focal epilepsies (Eriksson *et al.*, 2005). Due to the lack of precise definitions *Microdysgenesis*, as a diagnostic term, was discarded and under current criteria for dysplasias, an excess of neurons in the white matter falls under *mild MCD type II* (Palmiini *et al.*, 2004), defined as “*microscopic neuronal heterotopias outside layer I*”. Precise diagnostic criteria, however, still remain undefined.

White matter neurons (or single interstitial neurons) are a normal finding in mature cortex. A proportion is likely to be remnants of subplate cells, important for the establishment of thalamo-cortical pathways during development. In mature cortex white matter neurons have varied morphologies and include excitatory as well as inhibitory interneurons and are likely to be functionally integrated into cortical circuits (Torres-Reveron and Friedlander, 2007). As many mature white matter neurons share morphological and phenotypic characteristics with cortical

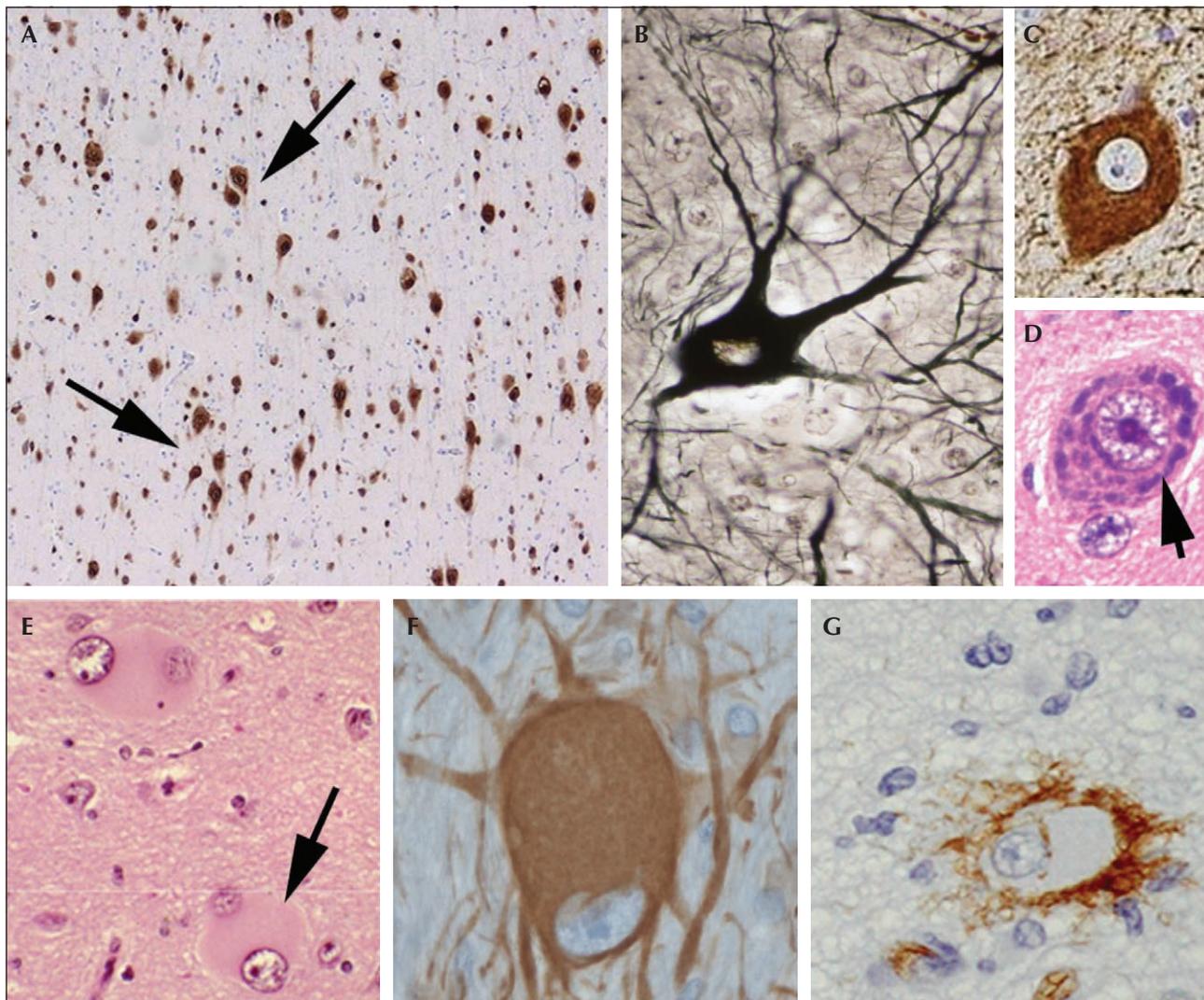


Figure 5. Histological hallmarks of FCD type IIA and IIB. **A**) Low power magnification of the cortex in FCD IIB using NeuN reveals complete loss of layering and many enlarged, clustered dysmorphic (syn. dysplastic) neurons (arrows). **B**) Silver impregnation. Dysmorphic neurons accumulate neurofilament protein (**C**) and have clustered Nissl substance (arrow in **D**). HE staining of balloon cells reveal opac undifferentiated cytoplasm (arrow in **E**). **F**) Vimentin immunoreactivity is consistently found in balloon cells. **G**) Aberrant labelling of the onco-fetal epitope CD34 in balloon cells.

neurons (figure 6C-E), the distinction of “heterotopic” from indigenous white matter neurons is not feasible in routine diagnostic practice. In contrast, for FCD Type II dysmorphic neuronal types are typically present in the white matter, which are more easily appreciated as abnormal.

Establishing numerical criteria for white matter neurons in epilepsy tissues has been addressed in several publications (table 2). These studies are mandatory as reliable standards for the histopathological diagnosis of mMCDs or other FCD/MCD variants. It is of note that only the knowledge of pathological vs normal levels will clarify

the impact of white matter neurons in epileptogenesis and/or pharmaco-resistance. So far, different principle pathologies have been studied, including MTS, mild MCDs, FCD I or FCD II. Data obtained are not easy to amalgamate or compare when considering that different anatomical regions of white matter, as well as quantitative techniques (e.g. stereology versus cell-profile counts, 4 μm versus 20 μm sectioning), were applied (Andres *et al.*, 2005; Hildebrandt *et al.*, 2005; Thom *et al.*, 2001). However, all studies confirm excessive numbers of white matter neurons in epilepsy patients, although to various degrees.

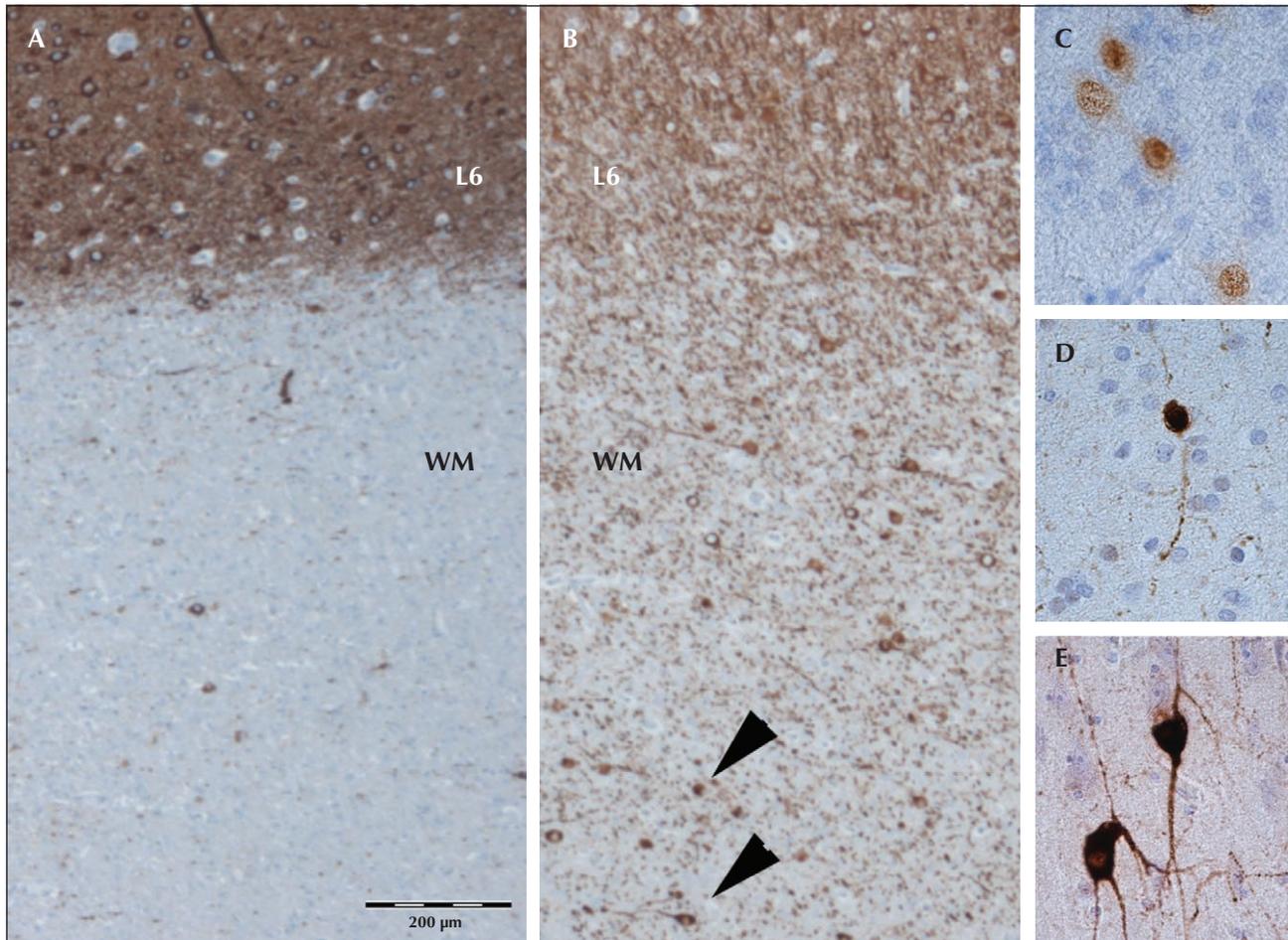


Figure 6. White matter neurons in epilepsy tissue. Map2 staining at the interface between the grey (layer 6, L6) and the white matter (WM) in a control case (A), demonstrating that this junction is often ill-defined in epilepsy tissue (B). In addition, abundant neurons can be observed in deeper parts of the white matter (arrowheads in B). C-E) White matter neurons share immunophenotypic characteristics with normal cortical neurons: Tbr1 (E), calretinin (D), neuropeptide Y (E). Scale bar = 200 μm.

There are three major issues to be further discussed with respect to the classification and functional significance.

- We suggest that mMCD type II should be diagnosed as a separate entity only in those specimens in which no principle lesion can be otherwise encountered, because excessive neurons are “common” features in all FCD variants, as well as MTS and neoplastic specimens.

- The functional significance of the heterotopic neuronal cell population needs further confirmation. It will be a major experimental and electrophysiological challenge to prove functional integration of these heterotopic cells into epileptogenic neuronal networks. Characterization of an aberrant molecular phenotype may be helpful.

- Correlations between neuronal numbers in white matter with neuroimaging changes of the temporal lobe white matter, including increased T2 signal and loss of definition between the grey-white matter (Choi *et al.*, 1999; Meiners *et al.*, 1999) present another clinical challenge. Yet, a

recent study aiming to precisely co-register MRI and pathology specimens has failed to show any correlation between stereologically acquired white matter NeuN-cell densities and abnormal T2 signalling (Eriksson *et al.*, 2007).

The possible explanation for any excess of white matter neurons in epilepsy is either a developmental abnormality (*i.e.* heterotopic neurons following failure of normal migration), a maturational abnormality (abnormal persistence of subplate neurons following corticogenesis) or alternatively neurogenesis, possibly influenced by seizures (Gonzalez-Martinez *et al.*, 2007).

Association between neoplastic glioneuronal lesions and FCD

Long-term epilepsy associated glioneuronal tumours (GNT) mainly comprise gangliogliomas (GGs) and dysembryoplastic neuroepithelial tumours (DNTs, *figure 7*). Both

Table 2. Quantitative studies of white matter neuronal densities. Selected studies are listed in chronological order and grouped according to similar methodologies which have shown some consistency in the findings. In practice, assessments made on thin MAP2 or NeuN stained sections in deep white matter which show an excess of 20/mm² in epilepsy patients may prove a practical way to measure this pathology.

| Study | Pathology | Preparation | Method | Result in epilepsy (control values if tested) |
|--|---|---------------------------------|---|--|
| Nissl stain, profile cell counting (2D) in TLE | | | | |
| (Hardiman <i>et al.</i> 1988a) | Temporal lobe epilepsy (n = 49) | Nissl | Profile counting (2d) "deep" white matter | 4/mm ² (No controls > 4/mm ²)* |
| (Emery <i>et al.</i> , 1997) | Temporal lobe epilepsy (n = 22) | Nissl | Profile counting (2d) All TL white matter | 4.11/mm ² * (2.35/mm ²) |
| Nissl stain stereology (3D) in TLE | | | | |
| (Thom <i>et al.</i> , 2001) | ATL adjacent to HS (n = 31) | Nissl (cresyl violet) | Stereology (3d) All white matter | 1 160/mm ³ * |
| (Bothwell <i>et al.</i> , 2001) | ATL adjacent to HS (50% Brodmann area 36) (n = 10) | Nissl | Stereology (3d) All white matter | 1 010/mm ³ |
| Immunostained sections cell profile counts (2D) | | | | |
| (Hildebrandt <i>et al.</i> , 2005) | FCD I and II (No difference between type I and II) (n = 25) | MAP2 on 4 micron thick sections | Cell profile (2d) 1mm ³ of deep white matter | 21.4 ± 6.8/mm ² (10.5 ± 2.9/mm ²)* Controls |
| (Eriksson <i>et al.</i> , 2006) | ATL adjacent to HS (n = 10) | NeuN on 7 micron thick sections | Cell profile (2d) ROI in deep white matter | 23.4/mm ² (No control group) |

ATL: anterior temporal lobe; ROI: Region of interest.

* Indicates series where epilepsy cases were significantly different from control values.

neoplasms are rare, with an incidence of approximately 1.3% of all brain tumours (Blumcke and Wiestler, 2002; Luyken *et al.*, 2004), but are frequent in children and young adults suffering from pharmacologically intractable focal epilepsy. However, the differentiation between a neoplastic and dysplastic lesion is often difficult to obtain, either using electrophysiology (EEG recording), imaging, histopathology or molecular-genetic analysis.

Dysplastic disorganization of the cortex near but separate from the tumour has often been observed and particularly studied in DNTs (Ferrier *et al.*, 2006; Prayson *et al.*, 1993). The large majority of glioneuronal tumours present either with mild malformations of cortical development (mMCD) or with FCD type IA; only a few cases have been reported to be associated with FCD type II (Ferrier *et al.*, 2006). Whether FCD occurring in association with a glioneuronal tumour represents a distinct entity (different from isolated FCDs) is a matter of ongoing debate.

The maldevelopmental and dysembryoplastic nature of glioneuronal tumours is likely to compromise always normal maturation of the adjacent neocortex. However, none of the current classification systems for tumours of the central nervous system, nor malformations of cortical development specifically address or clarify this issue. Beside the matter of classification, cortical disorganization (including intracortical spreading of glial and neuronal tumour cells) may significantly contribute to the pathomechanism of epileptogenesis and will need further consideration.

Surgical outcome

Long-term follow-up studies of a large series of patients revealed favourable outcomes for patients with supratentorial GNTs, with only rare cases of tumour recurrence or malignant progression to glioblastoma reported for GGs (Luyken *et al.*, 2003; Majores *et al.*, 2008). Limited information is available about recurrence or malignant transformation of DNT (Maher *et al.*, 2008). The large majority of patients with GNTs became seizure free after surgical resection. Short duration of epilepsy before surgery, absence of secondary generalized seizures or status epilepticus, absence of additional pathologies and complete resection predicted a better post-operative seizure outcome (Aronica *et al.* 2001b; Luyken *et al.*, 2003). Thus, an early identification of GNTs associated with chronic intractable epilepsy, followed by a prompt referral to epilepsy surgery centres provides the best chance for curing epilepsy and preventing its recurrence and possible malignant transformation. However, it has not been systematically studied whether failure of post-surgical seizure relief results from unrecognized cortical disorganization in the vicinity of the resection site.

Mechanisms of epileptogenesis in GNTs

The cellular mechanism(s) underlying epileptogenicity of glioneuronal tumours and/or the perilesional cortical tissue are still not clearly defined. Intrinsic epileptogenicity is supported by electrocorticography, surgical and immu-

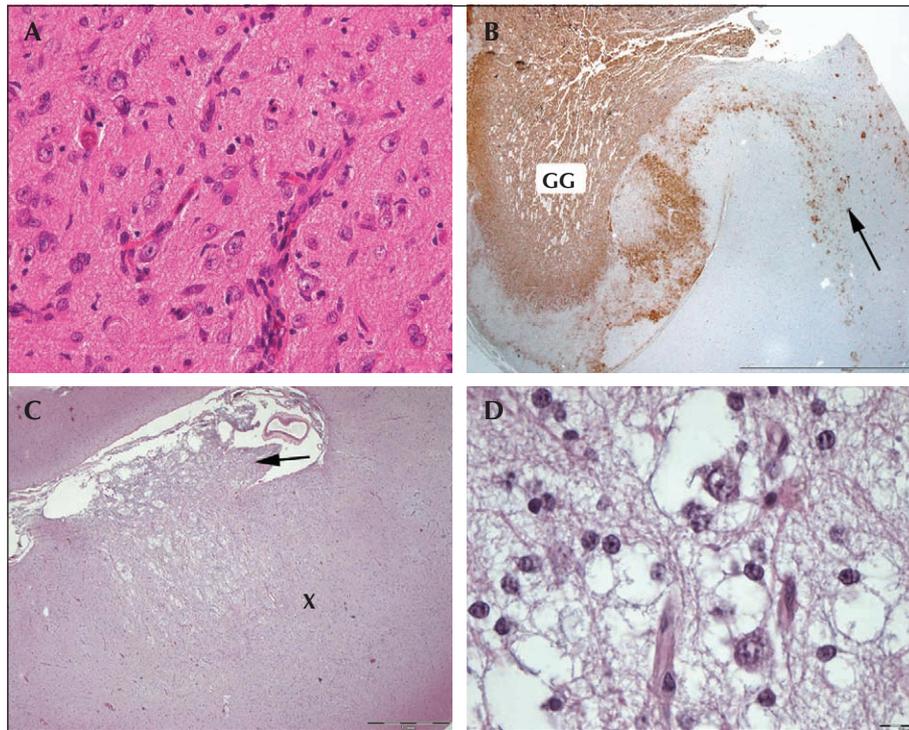


Figure 7. Histopathological features of glioneuronal tumours. **A-B** Ganglioglioma (GG) with admixture of dysplastic neurons and neoplastic glial cell elements (HE staining). Prominent CD34 immunoreactivity in the mass tumour, which also extends into adjacent neocortex (arrow in **B**). The distinction between small tumour islands and FCD can be difficult. **C-D** Dysembryoplastic neuroepithelial tumour with a specific glioneuronal element (**D**). Note the tumour extension into the subarachnoid space (arrow in **C**) and blurred delineation from adjacent neocortex (x).

nocytochemical studies, suggesting the presence of a hyperexcitable neuronal component (Aronica *et al.* 2001a; Ferrier *et al.*, 2006; Kirschstein *et al.*, 2003). Developmental alterations compromising the balance between excitation and inhibition are likely to play a role in the pathogenesis of epileptic focal discharges in patients with GNTs (Aronica *et al.*, 2007). Recent evidence points to the inflammatory response as a contributing factor in the epileptogenicity of these developmental lesions (Ravizza *et al.*, 2006). Similarly to other brain tumours (such as gliomas), the peritumoral region may also be relevant for the generation and propagation of seizure activity (van Breemen *et al.*, 2007). However, architectural abnormalities observed in the vicinity of a glioneuronal tumour, although histopathologically similar to isolated FCD, should be regarded as an acquired form, similar to the concept of “progressive” cortical dysplasia in early brain injury (Marin-Padilla *et al.*, 2002).

Molecular-genetic findings in GNTs

Molecular-genetic and histopathological findings support the concept of a developmental pathogenesis in glioneuronal tumours, *i.e.* aberrant expression of stem cell markers such as CD34 (Blumcke *et al.*, 1999). Indeed, GNTs have been incorporated into the classification of malformations

of cortical development, possibly resulting from an alteration of the early stage of corticogenesis and characterized by abnormal cell types, including FCD and tuberous sclerosis complex-associated cerebral lesions (Barkovich *et al.*, 2005). In particular, recent studies suggest a common role for the phosphatidylinositol 3-kinase (PI3K)-mTOR pathway in the molecular pathogenesis of glioneuronal tumours, FCD type IIB and cortical tubers (Becker *et al.*, 2001; Samadani *et al.*, 2007). Molecular-genetic studies may help to better define the pathogenic relationship between GNTs and other MCDs and help to achieve a classification system, which combines histological features with pathogenic mechanisms.

Clinico-pathological correlations

Published studies correlating the clinical presentation of epilepsy patients (including imaging and post-surgical seizure relief) with histopathological findings highlight various areas of interest and also continuous debate.

– FCD type IIB is the most frequently recognized MCD entity, and most patients benefit from surgical resection strategies.

Table 3. Different classification systems of focal cortical dysplasias.

| | | | | |
|--|---|---|--|--|
| Tassi <i>et al.</i> <i>Brain</i> 2002 (Milano) | Architectural dysplasia: abnormal cortical lamination and ectopic neurons in WM | | Cytoarchitectural dysplasia: ... plus NFP-positive giant neurons outside layer V | Taylor-Typ ... plus dysmorphic neurons and balloon cells |
| Palmini <i>et al.</i> <i>Neurology</i> 2004 (ILAE) | mMCD type I Ectopic neurons in layer I mMCD type II Neuronal heterotopia outside layer I | FCD type IA: Isolated architectural abnormalities | FCD type IB: ... plus giant, not dysmorphic neurons | FCD type IIa: dysmorphic neurons, no balloon cells FCD type IIb: dysmorphic neurons and balloon cells |
| Barkovich <i>et al.</i> <i>Neurology</i> 2005 | Not visible at MRI | Abnormal cortical organization | Abnormal cortical organization | Abnormal neuronal and glial proliferation |

– The distinction between FCD type IB and IIA is difficult to achieve and there is no good clinical correlation available.
– Post-surgical seizure relief is ambiguous in FCD type I and the current classification system may need modification to anticipate the different clinico-pathological entities.
– The latter differences between FCDs encountered in children compared with adults; mainly TLE patients need further consideration. However, this chapter will also stress the importance of a comprehensive classification system available to epilepsy surgery centres throughout the world to obtain a reliable stratification of FCD cohorts.

Different classification systems of focal cortical dysplasias

Classification issues have been a matter of scientific debate for many years (*table 3*). The lack of precise etiological knowledge will remain a major obstacle to clearly define distinct clinico-morphological variants. Thus, different classification systems have been proposed and introduced during the last decade, relying either on histopathological examination (Mischel *et al.*, 1995), imaging and genetic findings (Barkovich *et al.*, 2005) or combining clinical and histopathological aspects (Palmini *et al.*, 2004). Notwithstanding, a clinico-pathological approach taking into account many different parameters and disciplines (neurology including electrophysiology, neuropsychology, neuroradiology, neurosurgery and neuropathology) will be most reliable to achieve prediction of post-surgical outcome.

However, an important prerequisite to establish any classification is a clear definition of terms used for pathological descriptions. Most epilepsy centres use the Palmini classification system 2004, which resulted from an ILAE consensus conference in 2002. Long-term experience using this classification system further promotes the reliable distinction of FCD type IIB. Besides good inter-observer agreement of histopathology reports, imaging findings and electrophysiological characterization also coherently confirm this disease variant. As a matter of

fact, most patients benefit from surgical resection strategies (*table 4*).

In contrast, FCD Type IIA is less well characterized and only few studies address this peculiar disease variant (Krsek *et al.*, 2008). Since numbers of reported patients remain small, future work will be warranted to achieve a better knowledge about clinical management and therapy strategies in this patient cohort. A recent study claimed that retained motor function, as well as ictal onset, associates preferentially with FCD type IIA (Boonyapisit *et al.*, 2003), and this intriguing finding will need further confirmation. Molecular-genetic studies, however, revealed differences between FCD IIA and FCD IIB (Majores *et al.*, 2005). Difficulties regarding the differentiation between FCD type IIA and IB will need to be considered by better histological definition of hypertrophic vs dysmorphic neurons, as already discussed above.

The spectrum of FCD type I is not well defined in the Palmini classification and distinguishes only two variants. The fact that histological variants comprise a very large spectrum, that is less clearly described and often includes more than one feature, make such dichotomic classifica-

Table 4. Favourable post-surgical seizure relief in patients with FCD type IIB. Surgical outcome refers to complete seizure relief 12 months after operation (Engel I).

| References | # Patients | Classification | Surgical outcome |
|---------------------------------------|------------|----------------|-------------------|
| Taylor <i>et al.</i> 1971 | 10 | Histology | 60% ^a |
| Urbach <i>et al.</i> 2002 | 22 | Histology | 100% ^b |
| Tassi <i>et al.</i> 2002 | 15 | Histology | 75% |
| Fauser <i>et al.</i> 2004 | 14 | Histology | 70% |
| Kresk <i>et al.</i> 2008 ^c | 35 | Histology | 75% |
| Kresk <i>et al.</i> 2009 ^c | 16 | Histology | 75% |
| Total | 112 | | 76% |

^a Patients reported as “fit free”.

^b Seizure relief obtained in all patients with complete resection of MRI visible lesion.

^c This author reported two independent patient cohorts from Germany and Florida, respectively.

tion difficult to apply. More importantly, meta-analysis shows a broad variation in clinical histories (including all different age groups), as well as outcome prediction. The mean age at epilepsy onset is younger than for FCD type II, and EEG and clinical histories differ widely. Some patients present with multilobar lesions and a clinical-electrophysiological picture of epileptic encephalopathy. Neuroradiological features in FCD type I are diverse and blurred grey-white matter boundaries and thickened cortex are common, but in some cases no or only subtle MRI pathology is visible (Krsek *et al.* 2008, 2009) (table 5).

The comparison between FCDs histopathologically identified in children vs adults is another field of controversy. A large series of 298 epilepsy surgical reports (patients operated from 1986-2006 at The Methodist Hospital and Texas Children's Hospital) was reviewed. The pathological spectrum of 117 children (< 1-18 years) was compared with that of 181 adults (19-54 years). Although FCD were more frequent in children (45 cases vs 39 adult cases), histological diagnoses were found to be the same, suggesting that the etiology may be similar. In children and adults there was no convincing example of FCD type IB pathology. The similar histology did not indicate, however, on a structural basis, why children require early surgery and adults a more delayed surgery. Additional anatomic and pathologic characteristics of each group were then compared to identify factors that could influence the epilepsy and necessitate early surgical treatment. These comparisons revealed that in children there were more male patients, more FCD type II, more involvement

Table 5. "Controversial" post-surgical outcome prediction in patients with FCD type I. Surgical outcome refers to complete seizure relief 12 months after operation (Engel I).

| References | # Patients | Classification | Surgical outcome |
|---------------------------------------|------------|----------------|-------------------------------|
| Tassi <i>et al.</i> 2002 | 31 | Histology | 43% ^a |
| Fauser <i>et al.</i> 2004 | 38 | Histology | 55-67% ^b |
| Kresk <i>et al.</i> 2008 ^e | 79 | Histology | 45-49% ^d |
| Kresk <i>et al.</i> 2009 ^e | 24 | Histology | 21% ^c |
| Total | 172 | | 21-67% (47%) |

^a 43% of patients presented with hippocampal sclerosis; mean age at operation was 27 years.

^b 87% of patients presented with hippocampal sclerosis; mean age at operation was 21.3 years.

^c No patient presented with hippocampal sclerosis; mean age at operation was 6.8 years.

^d 87% of patients presented with hippocampal sclerosis; mean age at operation was 10.7 years.

^e This author reported two independent patient cohorts from Germany and Florida, USA.

of the frontal lobes and multiple lobes and more cases of FCD associated with tumours than in adults. These differences may account for the greater need for an earlier surgical intervention in children.

This review of surgical reports of FCD and mild MCD in adults and children included cases that preceded the Palmieri classification system; assignment of the FCD type was thus made based on the descriptions in the

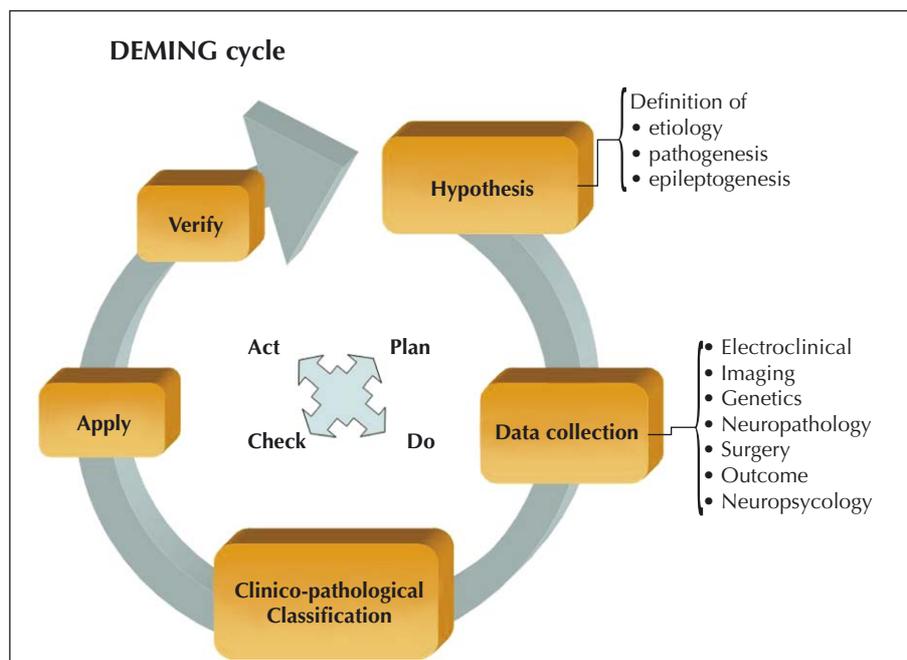


Figure 8. The deming cycle for continuous improvement of scientific concepts.

pathology reports. For this study, Taylor's definitions of focal cortical dysplasia (Taylor *et al.*, 1971) were used for reports by a single observer. This correlated generally with Palmini's type II criteria, although there were questions about specific definitions; e.g. dysmorphic neurons, giant neurons, dyslamination. The distinction of type I FCD from the mild MCD presented some problems and the surgical reports included descriptions of microdysgenetic features that had not been included or were ambiguously described in the proposed classification system, e.g. cortical clusters (Hardiman *et al.* 1988b), blurring of grey-white junction (Meencke and Janz, 1984). This review of epilepsy surgery reports in children and adults emphasizes the need for a careful redefinition of some histological criteria and for a validation of the conclusions by re-examination of the surgical material using refined definitions.

Conclusion

A comprehensive approach taking all currently available data into consideration is mandatory to further develop our current understanding of FCDs and to establish a reliable classification system. This should include various clinical disciplines as well as basic neurosciences. A deming cycle (*figure 8*) should consider most recent and modern technical advances as well as progress in neurodevelopmental knowledge to guarantee continuous refinement and improvement of our concepts. □

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Disclosures.

None.

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