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CHAPTER

13. Focal (isolated) cortical dysplasia Type I

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Keypoints

- FCD Type I is more difficult to diagnose and more heterogenous than FCD Type II.
- FCD Type I should be classified according to the proposed WHO-classification of the FCDs but the exact classification of the histological changes remains challenging.
- Seizure outcome post-surgery in FCD Type I is less favourable in comparison to FCD Type II.
- Severe early onset drug-resistant epilepsies caused by multilobar, sub-hemispheric or hemispheric FCD Type Ia is most likely an underdiagnosed entity.

Patients with drug-resistant epilepsy and FCD ILAE Type II (Blümcke *et al.*, 2011) are regarded nowadays as excellent candidates for resective epilepsy surgery, especially if a lesion is located outside eloquent cortical areas. In contrast, the global picture in FCD ILAE Type I is less clear if not highly controversial. Because today's diagnostic ILAE classification tool is available since 2011 only, publications from different centers reporting surgical outcome in patients with FCD Type I are often not comparable to each other. Despite ongoing progress in diagnostic workup and surgical treatment of children with suspected FCD Type I, we have not achieved any general recommendation and this chapter will, therefore, discuss the many controversial aspects published over past decades.

Histological classification of FCD Type I – work in progress

A neuropathological agreement study testing the diagnostic (microscopic) classification of FCDs in surgical specimen according to Palmini and Lüders (2004) achieved good concordance for FCD Type IIa and IIb (Chamberlain *et al.*, 2009), but poor agreement was obtained for the histopathological classification of FCD Type I's. An *ad hoc* Neuropathology Task Force of ILAE's Diagnostic Methods commission has addressed this hitherto well-known challenge and published a revised classification system in 2011, which is now referred to as "ILAE classification of FCDs", (Blümcke *et al.*, 2011; see *Table III* in chapter 14). The ILAE classification separated Palmini's FCD Type I into isolated (pure) FCD Type Ia-Ic and those associated with other principle pathologies, *i.e.* hippocampal sclerosis, brain tumors, vascular malformations or any other brain lesion acquired during early life (FCD Types III a-d). Hence, criteria for the classification of FCD Type II's were left unchanged (see *Figure 3* in chapter 18). As mentioned above, three subtypes of FCD I can be histopathologically distinguished and the Task Force proposed to separate them as distinct clinico-pathological entities. Cortical specimens with an abnormal vertical organization and too many "microcolumns" should be classified as FCD Type 1a (*Figure 1*), changes referring to an abnormal 6-layered organization with horizontal dyslamination as FCD Type Ib (*Figure 2*) and a mixture of both vertical and horizontal abnormalities as FCD Type Ic.

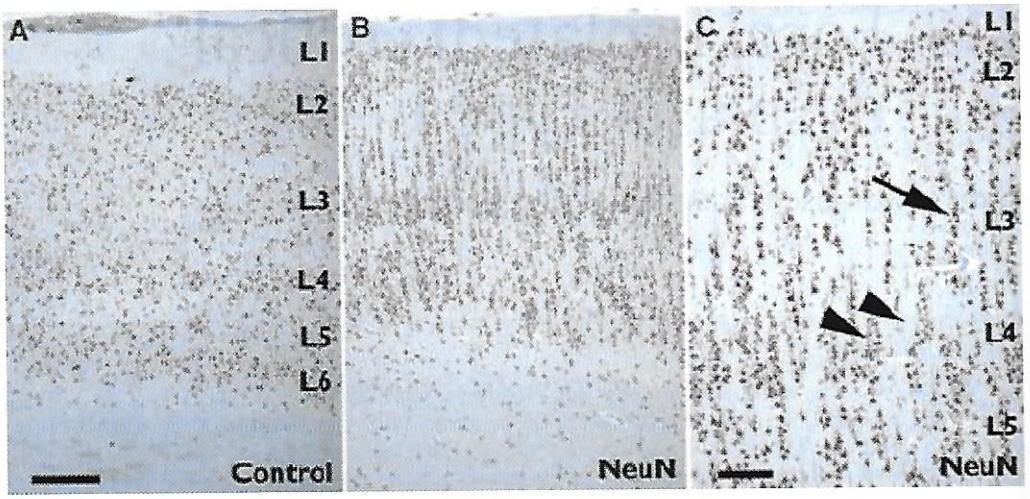


Figure 1

Histopathological findings in FCD type Ia (abnormal radial lamination and abundant microcolumns). 11-year-old girl with a 10-year history of drug-resistant seizures. A. Normal appearing neocortex adjacent to the lesion shown in B and C. Selective labeling of neuronal cell bodies using antibodies directed against NeuN reveals a characteristic layering of the human isocortex (L1-L6). Scale bar : 500 µm, also applies to B. B. Distinct microcolumnar arrangements of small diameter neurons can be detected in FCD type Ia, when surgical specimen is cut perfectly perpendicular to the pial surface and 4-µm paraffinembedded sections were used. MRI showed smaller cortical (parieto-occipito-temporal) lobes in affected versus non-affected hemispheres (Blümcke *et al.*, 2010). Hich magnification in C reveals abundant microcolumns, which are composed of more than eight neurons (arrow). In addition, layer 4 is less clearly visible (arrowheads). Scale bar : 100 µm.
(With permission from Blümcke *et al.*, 2011)

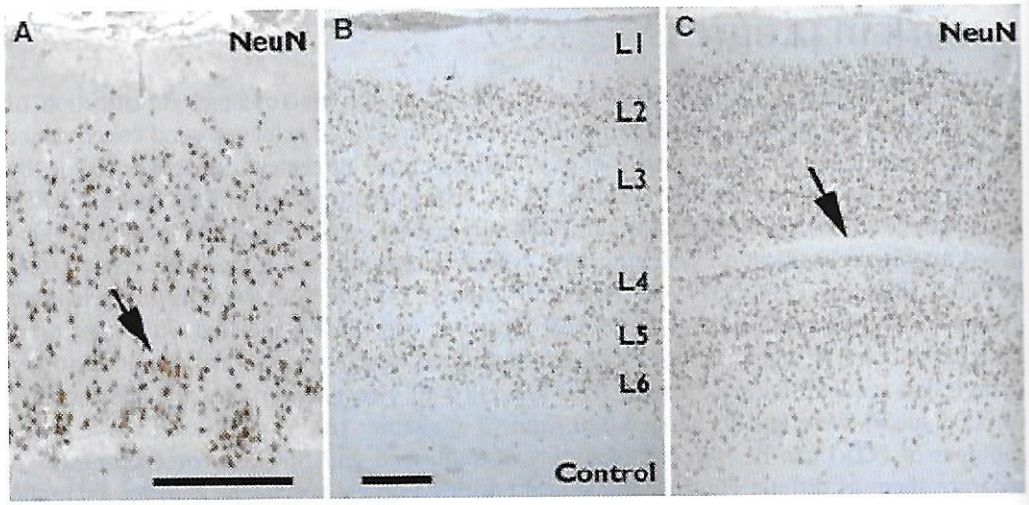


Figure 2

Histopathological findings in FCD type Ib (abnormal tangential layer composition). A. 3-yrea-old girl with drug-resistant epilepsy originating from the left parieto-occipital lobe. The cortex is thin (hypoplastic) and no layer can be detected. NeuN immunoreactivity. MRI showed a smaller cortical region. Scale bar : 500 µm. B. NeuN immunoreactivity in a surgical case showing normal layer formation (L1-L6) with a sharp boundary between cortex and white matter (same image as Fig. Ia). 4 µm of paraffin-embedded section with hematoxylin counterstaining. Scale bar : 500 µm, also applies to C. C. 23-year-old male patient with drug-resistant focal epilepsy since birth and a hyperintense MRI signal at the parieto-occipital region. Note the complete loss of layer 4 (arrow). In addition, there is no disctinction between supragranular layers L2 and L3. The border toward the white matter is blurred. (From Blümcke *et al.*, 2011.)

However, histological changes in FCD Type I are not restricted to cortical dyslamination. Blurred grey/white matter junctions with too many heterotopic neurons also in deep white matter regions (defined as > 500 µm from the grey/white matter boundary) are other consistent findings in this pathology (see examples of blurred grey/white matter junctions in *Figures 1B, 2C, 3B, 3D*). These changes were seen under the microscope in all patients with FCD Type 1a from the Vogtareuth series (Holthausen *et al.*, 2014b), but visible in only a few cases when reviewing high-resolution MRI. Another characteristic feature of FCD Type I, present in all cases with FCD Type 1a within the Vogtareuth series, is the reduction of the volume of the white matter, whereas the gross anatomical "Anlage" of the neocortex is preserved in patients with FCD Type Ia. The combination of an excess of microcolumns containing small/immature neurons, plus volume reduction of white matter, led to the intriguing hypothesis that these histological changes are the result of an arrested development or a delayed maturation at the second half of gestation or even perinatally (Hildebrandt *et al.*, 2005; Blümcke *et al.*, 2010; Sarnat & Flores-Sarnat, 2014; Sarnat *et al.*, 2015). This hypothesis was further supported by findings of Kršek *et al.* (2008; 2009; 2010) that children with FCD Type I have more often a history of pre- and perinatal adverse events than children with FCD Type II.

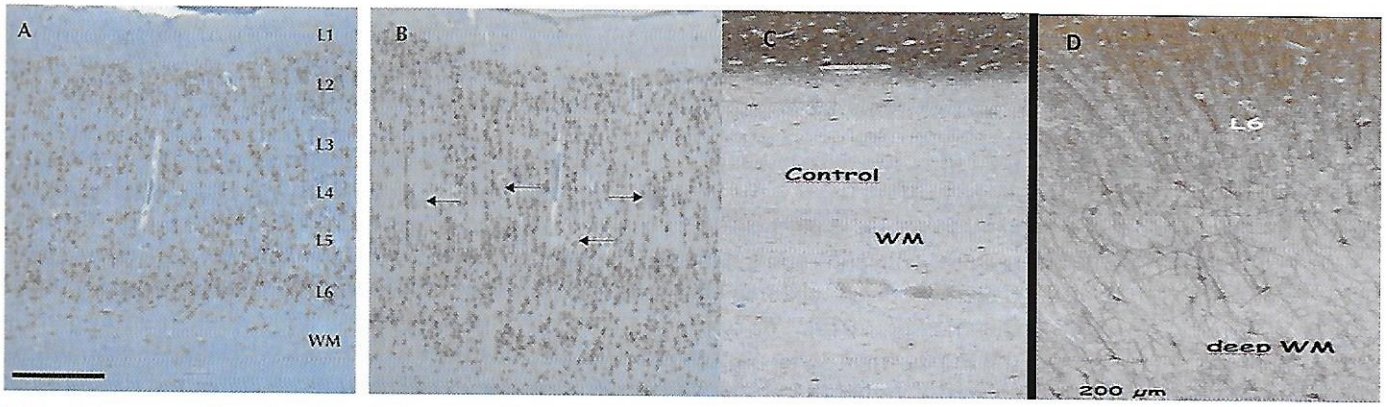


Figure 3

Examples of blurred grey-/white matter junctions. A = control, showing a well demarketed border between a cortex with a normal layering; B = showing how neurons in a specimen with FCD Type 1a (see excessive microcolumnar (vertical) dyslamination) are fading out towards the underlying white matter (visualized by NeuroN immunoreactivity). C and D with a different type of staining demonstration of a normal grey-/white matter junction (C) and a marked blurrring of the junction and heterotopic neurons within the deep white matter (D).

"Hypertrophic neurons" mentioned by the Palmini classification as hallmark in FCD Type I are not included into the ILAE-classification any longer as the *ad hoc* Task Force felt their significance was ambiguous and non-decisive. Histological hallmarks and their occurrence in different FCD subtypes are listed in *Table I.*

	Type Ia	Type Ib	Type Ic	Type IIa	Type IIb	Type IIIa	Type IIIb	Type IIIc	Type IIId
Cortical abnormalities	MC	LL	MC/LL	Dis	Dis	TLS/LL	MC/LL	MC/LL	MC/LL
Dysmorphic neurons	0	0	0	+	+	0	0	0	0
Balloon cells	0	0	0	0	+	0	0	0	0
Immature neurons	+	±	±	±	±	±	±	±	±
Hypertrophic neurons	±	±	±	±	±	±	±	±	±
WM changes	Het	Het	Het	Het/no ML	Het/ML	Het/LH	Het	Het	Het

MC: microcolumns; LL: loss of individual layers; Dis: entire cortical lamination (with exception of layer 1); TLS: temporal-lobe sclerosis; 0: not present; +: present; ±: variable; Het: increased heterotopic neurons in grey/white matter junction and deep white matter location; ML: myelin loss; LH: lentiform heterotopia; WM: white matter.

Table I

Histological hallmarks of different FCD-subtypes (with permission from Mühlebner & Blümcke, 2011)

A second study reported good interobserver agreement regarding the ILAE classification of FCDs Type I when neuropathologists have large expertise with epilepsy surgery, but the agreement remained still moderate among less experienced colleagues (Coras *et al.*, 2012). Particular improvement was reached by recognition of excessive microcolumns (*i.e.* vertical cortical dyslamination in FCD Ia) but less evident for classification of FCD Type Ib or Ic. The authors suggested to further elaborate education and training in order to increase diagnostic accuracy, *i.e.* ILAE's and ISN's annual summer school for Neuropathology and Epilepsy Surgery.

Table II

Good interobserver agreement in FCD IIb, fair in FCD IIa, moderate in FCD Ia, poor in FCD Ib and Ic (with permission from Coras *et al.*, 2012)

Round	FCD Ia	FCD Ib	FCD Ic	FCD IIa	FCD IIb	FCD IIIa	FCD IIIb	FCD IIIc	FCD IIId	No FCD	Mean
1	0.4821	0.3877	0.1319	1.0000	1.0000	0.8316	0.4869	0.7685	0.60602	0.3746	0.6360
2	0.7084	0.4287	-0.004*	1.0000	0.9565	0.7862	0.5113	0.6435	0.5465	0.4164	0.6532
3T	0.3252	0.1917	0.1509	0.4239	0.8045	0.5822	0.4407	0.6109	0.1800	0.2409	0.4060
3A	0.4220	0.4323	0.3438	0.5252	0.7828	0.7195	0.6101	0.7023	0.2951	0.2606	0.5056
3B	0.3185	0.1071	0.1608	0.4311	0.8555	0.5063	0.4451	0.5981	0.0571	0.2586	0.3884
3C	0.3763	0.0778	0.2137	0.3307	0.7136	0.4911	0.2171	0.4718	0.1955	0.1270	0.3265

3t: summary of third evaluation round including all 21 neuropathologists; 3A: neuropathologists with level A access to > 40 epilepsy surgery cases/year; 3B: neuropathologists reviewing 10-40 cases/year; 3C: neuropathologists seeing < 10 cases/year.
Kappa values were scored as follows: < 0.2: poor agreement; 0.2-< 0.4: fair agreement (yellow boxes); 0.4-< 0.6: moderate agreement (orange boxes); 0.6-< 0.8: good agreement (green boxes), 0.8-1.0: very good agreement (pink boxes).
* Kappa values can be negative in rare situations indicating that the observers agreed less than expected.

Even after the publication of the ILAE classification in 2011 (Blümcke *et al.*, 2011), the incidence of FCDs Type I in surgical series and the distribution of FCD Type I subclasses remained heterogeneous. Almost all FCD I are nowadays classified as Type Ic at UCLA (GD Mathern, personal communication), whereas the Vogtareuth series preferentially reveals FCD Ia. Other centers reported mixtures of classes FCD Ia-Ic (Kim *et al.*, 2012; Simpson & Prayson, 2014; Fauser *et al.*, 2015). We conclude that these differences most likely result from diagnostic thresholds when using various staining methods with or without systematic immunohistochemistry, rather than from patient selection. Bae *et al.* (2012) re-evaluated the classification of 117 specimen with MCD and FCD: 5/6 FCDs Type 1a according to Palmini's classification were shifted to FCD Type Ib according to the ILAE-classification. These "geographical" differences are also reflected in the very different incidences in numerous surgical outcome series.

In our experience *isolated* FCD Type I, classified according to the ILAE classification is a rare pathology. Of 154 children and adolescents operated between January 2002 and December 2013, 45 patients were diagnosed with FCD Type I. Twenty-eight of these had isolated FCD Type 1a; only 2 had FCD Type Ib, and none had FCD Type Ic (Holthausen *et al.*, 2014b). In the recently published surgical series of 60 operated children with FCD from Vienna, only 1 child had FCD Type 1a. There were no cases with FCD Type Ib or Ic (Mühlebner *et al.*, 2014). At a center in Tokyo, of 56 operated very young children with cortical dysplasia 6 had FCD Type I. Subtypes of FCD Type I were not mentioned (Otsuki *et al.*, 2013). Patients with FCD Type I were also rare in 2 publications from the Rothschild Foundation in Paris: in the report about invasive recordings in children younger than age 3 years, 18 had FCD Type IIb, 2 had non-specified "dysplasia", and only 1 had FCD Type I (Taussig *et al.* 2012). In their report of 19 children younger than age 5 years evaluated with stereo-EEG, there was 1 child with FCD Type Ib and 1 with FCD Type Ic, none with FCD Type Ia. There is no report from this group about patients with FCD Type I operated after non-invasive recordings. In contrast colleagues from the center in Seoul reported that 30 surgical specimens in a surgical series of 69 patients with FCD contained FCD Type I; 15 of them FCD Type Ia and 15 FCD Type Ib (Kim *et al.* 2012). A remarkably high number of 49 FCD Type Ib was diagnosed in a cohort of 211 patients with FCD operated at the center in Freiburg (Fauser *et al.*, 2015); another 10 had FCD Type Ia; FCD Ic was diagnosed in 8.

Other puzzling center-to-center differences have been published with respect to the predilection sites for the anatomical distribution of FCD Type I: at Miami Children's Hospital FCD Type I was found predominantly "fronto-temporal" (Kršek *et al.*, 2008), at the center in Vogtareuth predominantly posterior-temporal, temporo-occipital, temporo-parieto-occiptal or

sub-hemisheric (Kršek *et al.*, 2009, Holthausen *et al.*, 2014b); both are centers specialized in epilepsy surgery for young children. In the large series from the Claudio-Munari-Epilepsy Center in Milano, mainly treating adults, *isolated* FCD Type I was reported to be located within the temporal lobes in the overwhelming majority of cases (Tassi *et al.*, 2010). Several other previous series, also dealing mainly with adults, in which a preferential temporal localization of FCD Type I is mentioned, are series with a high percentage of associated HS which are not relevant anymore for discussion on isolated FCD Type I according to the ILAE classification.

The reason for this is that the problem of classifying white matter changes within the temporal pole in association with Ammon's horn sclerosis (which appear on MRI as volume reduction with increased signal in T2 and FLAIR) has been solved. These changes should be regarded as an acquired lesion within the white matter and not as dysplastic cortex (Thom *et al.* 2009; Garbelli *et al.* 2012). It has to be emphasized that neuropathologists must always have access to an anatomically well-preserved surgical brain specimen with appropriate landmarks to be able to achieve a reliable diagnosis (*e.g.* microcolumns are a normal feature of some cortical areas of the brain, especially within the superior temporal gyrus (Hildebrandt *et al.*, 2005). This is not always available nowadays, for example in disconnecting procedures such as posterior quadrant disconnections or hemispherotomies. When anatomically well represented, neocortex with appropriate planes of section to allow judgment of cortical layering is missing and heterotopic neurons in white matter remain the only abnormal finding, the diagnosis of mMCD Type II will always prevail over that of FCD Type I. A proposal for a "protocol in the neuropathological assessment of FCD in epilepsy resection specimen" and suggestions that histochemical and immunohistochemical stains should be used in FCDs Type I-Type III are available from a "practical guideline article invited by the Euro-CNS-Research Committee" (Blümcke & Mühlebner, 2011).

Imaging in isolated FCD Type I

• MRI in isolated FCD Type I

MRI detection rates also vary considerably between FCD subtypes. The detection rate was shown to be highest in FCD Type IIb and lowest in FCD Type I (Colombo *et al.*, 2003; Kršek *et al.*, 2008; 2009; Kim *et al.*, 2011; Leach *et al.*, 2014). FCD is the most frequent pathology in surgical specimens from patients with a negative MRI, but subclasses of FCD are usually not mentioned in these reports (review in Bast *et al.*, 2013 and in chapter 27 of this volume). However, MRI detection of FCD in young children is more difficult in general. FCDs (Type I and Type II) were the causative lesions in 51 of 405 children with spasms diagnosed over a period of 6 years at a center in Korea (Kang *et al.*, 2013): in a retrospective analysis of their MRIs FCD was suspected in only 41% patients younger than 1 year, but became confirmed in 88% (45/51) over time in the same series after the 1st year. MRIs of patients with isolated FCD Type I are read as normal in a high percentage of patients also due to the lack of experience with this type of lesion. Another reason for the low detection rate are insufficient MRI-protocols. We do not share (anymore) the widespread opinion that the MRI is negative in the majority of cases with FCD Type I. Due to an increased experience and employing a dedicated very high-resolution MRI-protocol (see Addendum in Holthausen *et al.*, 2014a) all the cases with isolated FCD Type Ia operated at the center in Vogtareuth over the last few years were correctly diagnosed on MRI. This is a marked improvement in comparison with the initial experience in children with FCD Type I, when the detection rate was just 35% (Kršek *et al.* 2009). Characteristic features for FCD Type I are reduction of the volume of the white matter of affected areas and subtle increased signals on T2-weighted images and FLAIR, but no abnormality of the gross architecture of the cortex (Colombo *et al.*, 2003; Widdes-Walsh *et al.*, 2005; Kršek *et al.*, 2008; 2009; Blümcke *et al.*, 2010; Holthausen *et al.*, 2014a, 2014b). When in publications or at conferences MRIs with thickened and plump gyri are demonstrated but the histology is judged as FCD Type I, there should be suspicion that the neuropathologist did not get the complete lesion. According to our experience the changes in FCD Type Ia are located temporal (always), temporo-occipital, within the entire posterior quadrant, sub-hemispheric or hemispheric (see *Figures 4 and 5*).

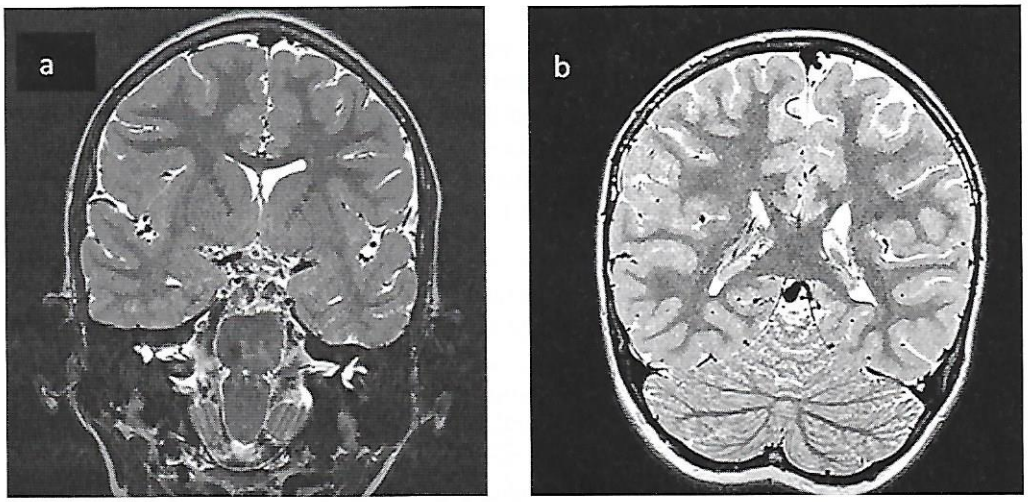


Figure 4

T2-weighted MRIs of a 5 year old girl with histological confirmed FCD Type Ia who became seizure free after a left sided temporo-(partial-)occipital resection. Reduction of the volume of the white matter left temporo-ocipital and subtle increased signal; no gross architecture abnormality. These changes are more prominent anterior- to midtemporal **(a)** and are fading out towards posterior temporal – occipital **(b)**.

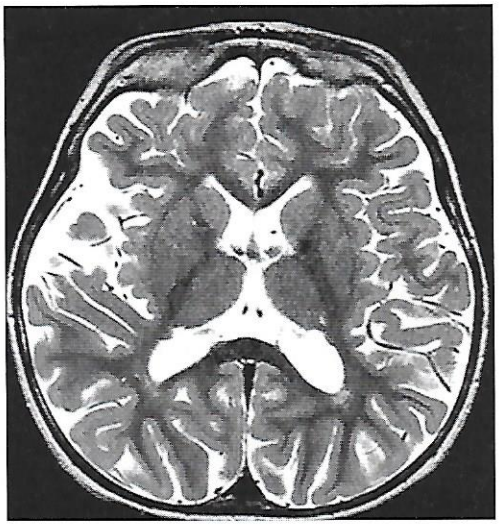


Figure 5

T2-weighted MRI of a 2 $^{1}/_{2}$ year old girl with a right sided "subhemispheric" FCD Type Ia. Note the subtle increased signal and the reduction of the white matter volume parieto-occipital and frontal. (With permission from Holthausen *et al.* 2014a.)

So far there is not a single case in the Vogtareuth FCD Type 1a series with involvement of frontal- or fronto-central areas without involvement of the temporal- or temporo-parieto-occipital area (Holthausen *et al.*, 2014b). In the very young age group, due to the lack of contrast in immature myelination, volume reduction of the white matter could be the only visible MRI pathology (*Figure 6*).

Whereas the detection rates should increase when colleagues get more familiar with this entity, the problem will remain that in FCD Type Ia it is almost impossible to delineate the extend of the lesion on the MRI. The histological changes can go far beyond the MRI-visible lesion. A very early onset of the epilepsy, *e.g.* within the first half year of life in a young child with changes on MRI as they are described in this section, which at first glance seems to be restricted to the temporal-/temporo-(parieto)-occipital area, could be taken as a hint that the lesion is much larger. Many children with FCD Type Ia and onset of epilepsy within the first or second year of life may also suffer from epileptic encephalopathies (Kršek *et al.*, 2009). Unfortunately, such subtle changes on MRI (when detected) as shown in *Figures 4, 5* and *6* are nonspecific. The same subtle increased signals on T2 and FLAIR can be seen in pure white matter changes, but pure white matter changes are not epileptogenic and do not cause severe epilepsies and marked epileptiform EEG-changes. Similar MRI changes can be seen in epileptic encephalopathies caused by molecular genetic mutations or chromosomal abnormalities. Thanks to a significant progress in genetic testing exclusion of many of such possible differential

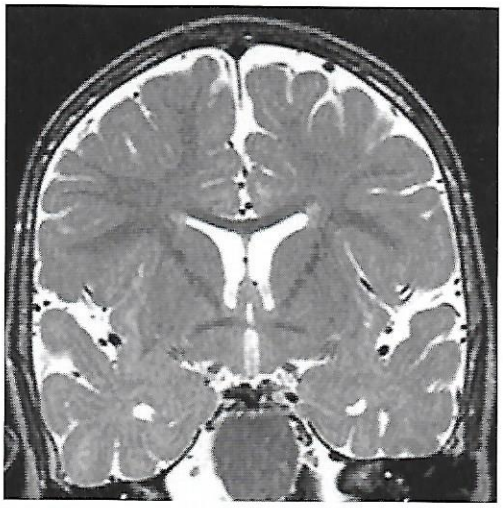


Figure 6

T2-weighted MRI of a 14 months old boy who became seizure-free post hemispherotomy, after a temporo-occipital resection had failed to render him seizure free. The left temporal lobe is smaller but there is no signal differences between both temporal lobes because of immature myelination at this age. Note the subtle increased signal and the reduction of the volume of the white matter left fronto-central.
With permission from Holthausen *et al.* 2014a.

diagnoses has become much easier, much faster and also much cheaper now, due to modern genetic diagnostics like "Targeted Next Generation Sequencing" (NGS) (Lemke *et al.*, 2012), or "whole exome sequencing" (Veraamah *et al.*, 2013; Escayg & Wong, 2014) and CGH-arrays (Zuberi, 2013).

• PET and SPECT in isolated FCD Type I

There are only limited data on the value of other neuroimaging tests in FCD Type I. In a study of Kršek *et al.* (2009), 14/19 patients presented with variable hypometabolic regions at ^{18}FDG-PET scans. When compared with high-resolution MRI finding, all possible correlations of pathologies detected by both tests were noted (*i.e.*, MRI-positive and PET-negative, PET-positive and MRI-negative, both positive and both negative findings). In only two subjects MRI and PET abnormalities precisely co-localized. We thus concluded interictal ^{18}FDG-PET did not significantly help in the presurgical evaluation of multilobar early-onset encephalopathies caused by FCD Type I in the Vogtareuth series. In a smaller series of patients with FCD and normal MRI findings, Kudr *et al.* (2013a) reported abnormal ^{18}FDG-PET scans in 3/5 children with FCD Type I. In only one case from these series, ^{18}FDG-PET hypomethabolism precisely co-localized with the intracranial EEG abnormality and the resection site in a patient that was post-surgically seizure-free; thus the practical value of ^{18}FDG-PET in the diagnostic work-up of FCD Type I patients was similar to the Vogtareuth series. Dorfmüller *et al.* (2014) reported 16 patients with different FCD subtypes evaluated with ^{18}FDG-PET before stereo-EEG and resective epilepsy surgery. Unfortunately subjects are not stratified according to histopathological FCD types in the section dealing with ^{18}FDG-PET results. Overall, PET correctly indicated the cerebral lobe(s) from which the seizures originated in 56% of cases. It is however noted that ^{18}FDG-PET underestimated the extent of the epileptogenic zones in patients with extensive multilobar FCD who underwent hemispherotomy.

Similar paucity of reliable data is seen with regards to ictal SPECT and SISCOM findings in FCD Type I since almost all available studies mixed various FCD types. In series from Miami, children with FCD Type I had more extensive hyperperfusion zones when compared with FCD Type II subjects and children scored as mild MCD according to previous FCD classification (Kudr *et al.*, 2013b). However, complete removal of the SPECT hyperperfusion zone reliably predicted postsurgical seizure freedom regardless of the FCD subtypes in these series (86% seizure-free patients when the zone of ictal hyperperfusion was completely resected; Kršek *et al.*, 2013). In the Prague series of children with FCD Type I and normal MRI findings (Kudr *et al.*, 2013a), 4/5 cases had localizing SISCOM findings; however, in none of them complete surgical removal of the SISCOM focus was reached (despite that, 2 patients have been rendered postoperatively seizure-free).

Seizures in FCD Type I

As mentioned in the paragraph on the histological classification, different centers have reported various predilection sites for FCD Type I, and consequently the whole spectrum of focal seizures. A particular diagnostic challenge are children with FCD Type I in whom the MRI is read as normal and who present with infantile spasms, "generalized" tonic-, "generalized" clonic- or multiple seizure types. In very young children with structural focal epilepsies, spasms, like spasms in idiopathic West-Syndrome, tend to occur in clusters on awakening or on falling asleep, and can give the impression of a generalized seizure disorder. Especially spasms due to lesions in the posterior part of the brain, which is the predilection site for FCD Type Ia, are frequently symmetric and bilateral synchronous (Gailly *et al.*, 1995). Asymmetries and asynchronies during brief spells, when recognized, may not be appreciated as hints of focality. "Generalized" seizures, a "generalized" EEG, a high seizure frequency and drug resistance right from the beginning, accompanied by an arrest of mental development or a loss of already acquired skills, may contribute to the impression that one is dealing with a syndrome other than an epileptic encephalopathy caused by a focal structural lesion, possibly amenable to epilepsy surgery. In MRI-negative cases such seemingly "global" features are the main reason for delays of referrals for presurgical evaluations. In the first Vogtareuth series 25% of the children with FCD Type I and 12.5% with FCD Type II had epileptic spasms (Kršek *et al.*, 2009); these rates were reverse in the Miami Children's Hospital cohort of patients with FCD (Kršek *et al.*, 2008).

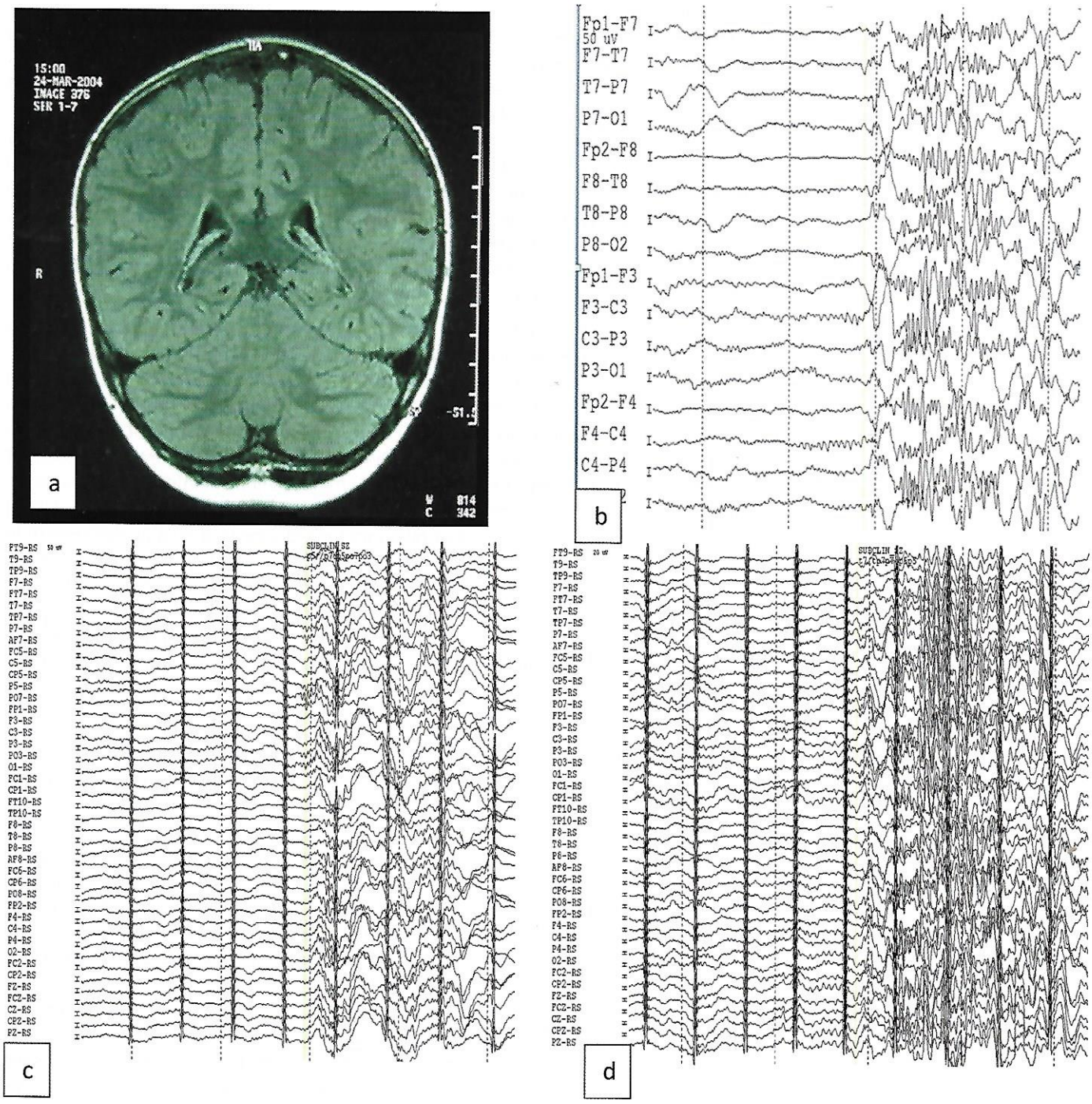
EEG in FCD Type I

In contrast to FCD Type II (*see chapter 14*) there is no characteristic EEG-pattern in FCD Type I. Kršek *et al.* (2009) found a significantly more frequent presence of continuous irregular slow in (all types of) FCD Type I as well as tendencies for background asymmetries and secondary bilateral synchrony. Children with FCD Type Ia have abundant epileptiform discharges (EDs) in their interictal EEG. The EDs may look generalized; their focal nature becomes more evident when the EEG is recorded with a 10/10 electrode-application and in referential montages with a non-cephalic electrode (*Figures 7b-7d*).

Unilateral multifocal EDs (*e.g.*, posterior and frontal) may indicate a widespread pathology but frontal sharp waves may be irritative EDs from frequent seizure spread from the posterior pathology to a normal frontal lobe. Irritative spikes over the contralateral posterior quadrant were a common finding in the Vogtareuth FCD Ia series. But with this peculiar pathology there are also cases in which the EEG gives a false impression of a more *circumscribed* focality, as it was the case in the child whose MRI is shown in *Figure 6*: prior to the first operation the EEG onset in countless asymmetric tonic seizures was posterior-temporo-occipital; after a temporo-occipital resection the EEG-seizure onset shifted to the fronto-central region. This is one of many examples which support the conclusion that in the FCD Type Ia cohort, the remaining dysplastic frontal- or fronto-central areas start to generate seizures after an initial posterior resection. Other reports after the introduction of the revised classification of the FCDs specifically dealing with the localizing and lateralizing value of the EEG in FCD Type I are pending.

Presurgical work-up and epilepsy surgery in FCD Type I

A meta-analysis, which came out prior to the ILAE classification of FCDs in 2011 revealed that in general postoperative seizure outcome in FCD Type I is worse in comparison to FCD Type II (Rowland *et al.* 2012). Whereas patients with FCD Type IIb outside eloquent cortical areas might have 80% chance and sometimes even higher to become seizure free (*see chapter 14*) the percentage of patients with *isolated* FCD Type I who become seizure free is 50% and less (Kršek *et al.*, 2008a, 2009b; Tassi *et al.*, 2012; Holthausen *et al.*, 2014b). Publications in which



Figures 7

MRI (FLAIR) and EEG of a 20 months old boy with a FCD histologically confirmed type 1a within the left posterior quadrant **(a)**. The patient did not become seizure free after a temporo-occipital resection but after a second operation when the entire parietal association area and the posterior portion of the SSMA were removed. An outside previous MRI has been read as normal. The "interictal" EEG from the same patient in b gives the impression of a generalized epileptiform activity. **c and d:** recordings of such bursts with 10/10-system-electrodes against a reference electrode at the right shoulder showing EEG-seizure onsets with variable locations over the left posterior quadrant.
(With permission from Holthausen *et al.* 2014a.)

better outcomes in FCD Type I were reported are from former times (Fauser *et al.*, 2006; Tassi *et al.*, 2002) when patients with the syndrome of mesial temporal sclerosis with MRI temporal pole changes such as blurring were labeled as FCD Type I on neuropathology; these MRI features are now correctly assigned as acquired degenerative changes (see Thom *et al.*, 2009 and Garbelli *et al.*, 2012; discussion in Blümcke & Coras, 2013 and Holthausen *et al.*, 2014a). Two studies reported no statistical outcome differences between FCD Type I and Type II, both dealt with a majority of adult patients: 1) Kim *et al.* (2012) mentioned that 30/69 patients with FCD had FCD Type I; 15 Type Ia, 15 Type Ib, and there was no statistical difference with respect to seizure outcome between FCD Type I (60% in FCD Type Ia; 73.3% in FCD Type Ib) and FCD Type II; 2) Fauser *et al.* (2015) reported equally good outcomes in FCD Type I and Type II in their most recent analysis of the Freiburg series; this report stands out because of the high number of patients with FCD Type Ib (see above, discussion in Blümcke & Coras, 2013).

Similarly to other focal structural lesions, a complete resection of the lesion (*i.e.*, dysplastic cortex) is the most important variable in order to achieve a long-term seizure-free outcome (Kršek *et al.*, 2010; Chern *et al.*, 2010; Rowland *et al.*, 2012; Hauptmann *et al.*, 2012). But FCD I lesions are often not seen (or recognized as such) on MRI and when they are, it is most often impossible to identify clear margins. Therefore, the recommendation of the "ILAE-Task Force for Pediatric Epilepsy Surgery" for which a test should be used in the presurgical work-up of patients with suspected FCD Type I resembles very much the recommendation for MRI-negative cases (Jayakar *et al.*, 2014; see chapter 27). In children with early-onset severe epilepsies caused by extended multilobar, sub-hemispheric or hemispheric FCD Type Ia, a reliable determination of the epileptogenic zone by long-term EEG-/video-monitoring, though undoubtedly mandatory to carry out, is often not possible. The EEG in these cases is often misleading, *e.g.* because of circumscribed ictal-onset zones over much bigger dysplastic areas not easy to recognize on MRI (see example in *Figure 6*), or because of multifocal or generalized seizure pattern and/or, due to variable seizure spread, abundant interictal irritative spikes over various regions, (unilateral and bilateral) in more circumscribed lesions.

Ancillary tests like PET, SPECT, MEG and 3D-source-imaging might be helpful when a temporary suppression of such "encephalopathic EEG" during the conduction of these tests can be achieved, *e.g.* by rapid oral loading with powerful drugs like phenytoin or vigabatrin or by I.V. infusion with *e.g.* benzodiazepines (HH, personal observation). But the usual concepts are often not applicable in children with extended FCD Type Ia, in particular not when they are severely mentally retarded. We agree with colleagues from the Mayo Clinic that in "epilepsy secondary to cortical dysplasia, especially if the dysplasia is not clearly seen on MRI as large a resection as can be safely accomplished should be done, particularly when the goal is palliative" (Bower *et al.*, 2015). Colleagues from the UCLA pediatric epilepsy surgery group, because of a high rate of re-operations in previous years after tailored resections, have expressed doubts whether children with onset of severe epilepsy within the first year of life caused by extended FCD (with "mild FCDs, *i.e.* FCD Type I" and "severe FCDs, *i.e.* FCD Type II") have a fair chance of a long-term seizure free outcome by surgical procedures other than hemispherectomy or hemispherotomy. It is explicitly stated in the publication by Hemb *et al.* (2010) that they have given up to perform large temporo-parieto-occipital resections, whether children have a preexisting hemiparesis or not – with the aim of achieving a higher rate of seizure free and better long-term cognitive outcome. Following this change of the approach, 70% of patients became seizure-free at six months of follow-up and 60% remained in remission after five years (Lerner *et al.*, 2009). This conceptual change might explain their experience with better seizure outcome in "FCDs" in comparison to "severe FCDs". Furthermore FCD Type I according to this report was found more often in adult patients with temporal lobe epilepsies and the FCDs were classified according to the older classification. In contrast a hemispherotomy was performed only once in the first published series of 24 consecutive patients from Vogtareuth with extended FCD Type I (the majority of them had isolated FCD Type Ia as revealed at a more recent analysis [Holthausen *et al.*, 2014b]); none of these children had a preexisting hemiparesis. But at that time only 21% became seizure-free, 22% were in Engel Class II (Kršek *et al.*, 2009b). Several patients became seizure free after 1 or 2 re-operations, of which some were hemispherotomies. This could mean that valuable time has been lost with respect to the possibility to reach

postoperative cognitive gains (Holthausen *et al.*, 2013). Nevertheless, multilobar or sub-hemispheric resections have not been abandoned at the center in Vogtareuth in these challenging patients (Pascher *et al.*, 2011). With the experience gained over the years results are much better now: at last follow up 14 of 28 patients with isolated FCD Type Ia operated from 2002 to 2013 are in Engel Class I (50%), 5 (18%) in class II and another 5 (18%) in class III (Holthausen *et al.*, 2014b).

Of note, not all patients with FCD Type Ia have extended lesions and present with early onset (1st and 2nd year of life) severe epilepsies. There are patients with lesions "restricted" in their extension from the temporal pole to the (mesial-)temporo-occipital junction and with later seizure onsets. In these cases, in particular when the dominant side is involved, the same diagnostic armamentarium (non-invasive and invasive) like in other focal epilepsies is used. At Miami Children's Hospital 49% children with FCD Type Ia and 43 % with FCD Type Ib according to Palmini and Lüders classification have become seizure free (Kršek *et al.*, 2008a); somewhat more than 50 patients were evaluated with subdural grids. But these cohorts differ from the Vogtareuth series by that almost half of the cases had associated other pathologies like HS or encephalomalacias, by the predominance of frontal- and temporal localizations, by an older age at surgery and by a better mental status. Out of 60 children from the center in Vienna only 1 patient (who did not become seizure-free) had FCD Type I (Type Ia) (Mühlebner *et al.*, 2014). Six out of 56 infants and young children with FCDs from the Center in Tokyo had FCD Type I; a further subclassification is not mentioned; half of them became seizure free; 2 underwent focal, 4 lobar resections (Otsuki *et al.* 2013). Thierty-one young patients of a cohort of 62 children with "posterior cortex epilepsies" operated at the Claudio-Munari-Epilepsy-Center in Milano had FCD, of which 9 were FCDs Type I; subclasses of Type I were not mentioned. Overall seizure outcome was excellent: 85.5% became seizure free, but whether the outcome was different or not between FCD Type II and Type I is not reported; 24/62 patients were investigated by stereo-EEG (Liava *et al.*, 2014). The only child with FCD Type I from a series of 21 children with FCD younger than 3 years, who underwent an evaluation with subdural grids at the Rothschild Foundation in Paris, did not become seizure free (Taussig *et al.*, 2012). The seizure outcome is not reported for the 2 children with FCD Type I out of 19 children with FCD younger than 5 years who were investigated with stereo-EEG by the same group (Dorfmüller *et al.*, 2014).

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