Multi-focal occurrence of cortical dysplasia in epilepsy patients

Susanne Fauser,1 Sanjay M. Sisodiya,2 Lillian Martinian,2 Maria Thom,2 Christoph Gumbinger,1 Hans-Jürgen Huppertz,3 Claudia Hader,4 Karl Strobl,5 Bernhard J. Steinhoff,5 Marco Prinz,6 Josef Zentner7 and Andreas Schulze-Bonhage1

1 Epilepsy Center, Department of Neurosurgery, University of Freiburg, Germany
2 Department of Clinical and Experimental Epilepsy, Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK
3 Swiss Epilepsy Center Zürich, Switzerland
4 Department of Neuroradiology, University of Freiburg, Germany
5 Epilepsy Center Kork, Kehl-Kork, Germany
6 Department of Neuropathology, University of Freiburg, Germany
7 Department of Neurosurgery, University of Freiburg, Germany

Correspondence to: Dr Susanne Fauser, Epilepsy Center, University of Freiburg, Breisacher Straße 64, 79106 Freiburg, Germany
E-mail: Susanne.fauser@uniklinik-freiburg.de

This study describes the existence and the clinical and electrophysiological features of multi-focal cortical dysplasia in epilepsy patients. Five patients with intractable focal epilepsy are reported. All patients underwent invasive presurgical video-electroencephalography monitoring. Localization of dysplastic areas was based on high-resolution magnetic resonance scanning, surface and intracranial electroencephalography. Four patients underwent epilepsy surgery. Histological findings in focal cortical dysplasia (FCD) were classified according to Palmini. In addition, genetic examinations were performed in order to assess possible mutations in the genes for tuberous sclerosis complex. In four patients, FCDs were located in the same hemisphere. One case presented with bilateral FCDs. In three patients seizures arose from two separate dysplastic areas and in one patient, one lesion showed only interictal activity. In one further patient, seizures started exclusively from the hippocampus. In two of three patients with removal of the FCDs, the histological subtype was identical (Palmini type 2) and in one patient, histology differed between the lesions. All operated patients became seizure-free. In patients with FCD type 2, germ-line mutations in the tuberous sclerosis complex genes were not detectable. Dysplastic brain regions may not be restricted to a single brain region. Areas of FCD can have different degrees of epileptogenicity, ranging from electrographic silence to interictal epileptic discharges and initial involvement in seizure generation. Based on genetic analysis and clinical features, multi-FCD in this patient series was not likely to be related to tuberous sclerosis.

Keywords: focal cortical dysplasia; multi-focality; epilepsy; postoperative outcome

Abbreviations: CD 68 = cluster determinant 68; DNA = deoxyribonucleic acid; EEG = electroencephalography; FCD = focal cortical dysplasia; FLAIR = fluid-attenuated inversion recovery; Gadolinium-DTPA = gadolinium diethylenetriamine penta-acetic acid; GFAP = glial fibrillary acid protein; LCA = leucocyte common antigen; MPRAGE = magnetization-prepared rapid gradient echo;
Introduction

Focal cortical dysplasia (FCD) is generally considered as a circumscribed brain area which is characterized by abnormal cortical thickening and blurring of the grey–white matter boundary on high-resolution MR imaging (Chan et al., 1998; Bastos et al., 1999; Urbach et al., 2002) and histologically characterized by dyslamination with or without abnormal cytarchitectonic elements (Palmini and Lüders, 2002; Palmini et al., 2004). The growing detection of FCD underlying formerly ‘cryptogenic’ pharmacoresistant focal epilepsy suggests a high intrinsic epileptogenicity (Palmini and Lüders, 2002; Palmini et al., 2004). Histological dysplastic features were classified as suggested by Palmini (Palmini and Lüders, 2002): isolated architectural abnormalities (dyslamination) (FCD 1a), additional ‘immature neurons’ or giant neurons (FCD 1b), additional dysmorphic neurons (FCD 2a) and additional balloon cells (FCD 2b).

In this study, we report ictal and interictal EEG findings, genetic examinations and surgical outcome in five cases with multi-FCD, shown overtly by MRI.

Patients and Methods

Patients

All patients presented here were referred to the Epilepsy Center of the University Hospital of Freiburg, Germany, between 2002 and 2007 for presurgical evaluation and epilepsy surgery due to pharmacoresistant epilepsy. Three of the investigated patients were female. The age at epilepsy onset ranged from 0 to 18 years (mean 5.6 years, median 0 years), and the age when invasive recordings/surgery was performed ranged from 7 to 41 years (mean 25.4 years, median 33 years).

MRI examinations

MRI scans were acquired either with 1.5 Tesla scanner (Siemens Magnetom Vision or Siemens Magnetom Symphony) or with a 3 Tesla scanner (Siemens Magnetom TRIO). The following sequences were performed: T2-weighted images (axial and coronal, varying slice thickness from 1 to 3 mm), fluid-attenuated inversion recovery (FLAIR) images (2–6 mm slice thickness) and T2-weighted MPRAGE (magnetization-prepared rapid gradient echo) 3D data sets (1 mm voxel size) with and without gadolinium-DTPA. Additionally, coronal and axial images were acquired with a modified angulation perpendicular or parallel to the long axis of the temporal lobe to evaluate the mesiortemporal structures.

MRI criteria suggestive for FCD were gyration anomalies, focal thickening of the cortex, blurring of the grey–white matter junction and abnormal cortical and subcortical signal intensity. In addition, MRI post-processing procedures (i.e. morphometric MRI analyses) were performed as described elsewhere (Huppertz et al., 2005, 2008).

Histological examinations

In patients undergoing epilepsy surgery, excised tissue was fixed for 12–24 h in 10% buffered formalin, embedded in paraffin and sectioned. Staining was carried out using haematoxylin–eosin, periodic acid–Schiff (PAS) and Kluever-Barrera myelin stain. For selected cases, additional special stains (Elastica-van-Gieson, Reticulin, Bodian) were used. Additional immunohistochecmical stainings were performed with antibodies against neurofilament and microtubule associated protein to visualize the orientation of neurons and to depict dysmorphic neurons or ectopic white matter neurons and against synaptophysin, another neuronal marker. Glial fibrillary acid protein (GFAP) and vimentin immunohistochemistry was performed in order to better visualize astroglisis and/or balloon cells. Moreover, the proliferation marker Ki-67, the pan-leucocyte marker leucocyte common antigen (LCA) and the microglial marker CD 68 were applied.

Histological dysplastic features were classified as suggested by Palmini (Palmini and Lüders, 2002): isolated architectural abnormalities (dyslamination) (FCD 1a), additional ‘immature neurons’ or giant neurons (FCD 1b), additional dysmorphic neurons (FCD 2a) and additional balloon cells (FCD 2b).

In two patients undergoing hippocampal resection, histological grading of hippocampal pathology was classified according to Wyler et al. (1995) and Blümcke et al. (2007).

EEG recordings

All patients first underwent surface video-EEG monitoring. Since the results were inconclusive concerning localization and/or extension of the seizure onset zone, additional invasive video-EEG monitoring with subdural and/or depth electrodes was performed. The localization of invasive electrodes is depicted in Figs 1–5 for cases 1–5.

Genetic analyses

Surgical specimens were fixed overnight in formaldehyde and embedded in paraffin. DNA isolation from paraffin embedded tissue and blood was carried out with QIAamp DNA MiniKit
described elsewhere (Bender et al., 2002). Single strand conformation polymorphism (SSCP) analyses were performed to detect aberrant allelic distribution, and DNA was visualized by silver staining, according to standard protocols described elsewhere (Bender et al., 1996). Sequencing was performed if aberrant allelic distribution was visible in SSCP. The sequencing was performed in a MegaBace 500 Sequencer at the ‘Core Facility’ of the University of Freiburg. The visualization was carried out by the program ‘Chromas Version 1.45’. The base sequences were compared with data obtained from the National Centre of Biotechnology Information (NCBI) (TSC1 gene AL445645.10, TSC2 gene AC005600.1). In one patient (Case 5) genetic analyses as to TSC were performed to detect aberrant allelic distribution, and DNA was visualized by silver staining, according to standard protocols described elsewhere (Bender et al., 1996). Sequencing was performed if aberrant allelic distribution was visible in SSCP. The sequencing was performed in a MegaBace 500 Sequencer at the ‘Core Facility’ of the University of Freiburg. The visualization was carried out by the program ‘Chromas Version 1.45’. The base sequences were compared with data obtained from the National Centre of Biotechnology Information (NCBI) (TSC1 gene AL445645.10, TSC2 gene AC005600.1). In one patient (Case 5) genetic analyses as to TSC was performed by the Institute for Human Genetics of the University of Münster, Germany.

Postoperative follow-up

Follow-up data were collected at 3-month intervals in the first year and annually in the ensuing years, in all patients. Surgical outcome was classified according to Engel and Rasmussen (1993): (i) completely seizure free; (ii) seizure free or auras only or convulsions with drug withdrawal only; (iii) rare seizures (<2 seizures/year or ≥90% seizure reduction); (iii) reduction of seizure frequency ≥75%; and (iv) reduction of seizure frequency <75%.

Case reports

Clinical characteristics of patients with multi-FCDs are summarized in Table 1.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age at presurgical monitoring/surgery</th>
<th>Localization (MR imaging)</th>
<th>EEG evidence for location of seizure onset</th>
<th>Histology</th>
<th>Genetic polymorphisms</th>
<th>Outcome (Engel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7 years</td>
<td>1. Left temporal</td>
<td>Invasive (simultaneous seizure onset in the majority of seizures; few seizures with onset in lesion 1 only)</td>
<td>1. FCD 1b and 2b</td>
<td>no polymorphism</td>
<td>Ia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Left parietal</td>
<td></td>
<td>2. No histology, but presumably FCD 2 (MRI criteria of a transmantle dysplasia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11 years</td>
<td>1. Right temporal</td>
<td>Invasive (simultaneous seizure onset in the majority of seizures, one seizure with onset in lesion 1)</td>
<td>1. FCD 2a</td>
<td>TSC 2, Exon 10 (non-synonymous single nucleotide polymorphism&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>Ia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Right frontal</td>
<td></td>
<td>2. FCD 2a</td>
<td>TSC 2, Exon 10 (silent), TSC 2, Exon 30 (silent)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Mild right hippocampal sclerosis</td>
<td></td>
<td></td>
<td>TSC 2, Exon 10 (silent), TSC 2, Exon 30 (silent)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>33 years</td>
<td>1. Left temporal</td>
<td>Invasive (seizure onset only in lesion 1, interictal activity also in lesion 2)</td>
<td>1. FCD 2b</td>
<td>TSC 2, Exon 10 (missense&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>Only hippocampectomy, Ia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Left frontal</td>
<td></td>
<td>2. FCD 2b</td>
<td>TSC 2, Exon 10 (missense&lt;sup&gt;a&lt;/sup&gt;)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>35 years</td>
<td>1. Right frontal</td>
<td>Invasive (seizure onset only from lesion 3, FCDs only involved in seizure propagation)</td>
<td>Not available</td>
<td>Only hippocampectomy, Ia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Right temporo-occipital</td>
<td></td>
<td>Not available</td>
<td>No polymorphism</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Right hippocampal sclerosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>41 years</td>
<td>1. Right frontal</td>
<td>Invasive (seizure onset independently and simultaneously from lesion 3 and 2, not from 1)</td>
<td>Not available</td>
<td>No polymorphism</td>
<td>Ia No surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Right temporo-parietal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Left insular</td>
<td></td>
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</tbody>
</table>

<sup>a</sup> Polymorphism also present in non-TS control population without statistically significant differences in frequency.
Figure 1 The dysplastic areas of Case 1. (A) The left temporal dysplasia: transversal proton density-weighted image (TR 2185/TE 15, 3 mm slice thickness) and (B) the left parietal dysplasia (transmantle dysplasia): transversal T2-w image (TR 4500/TE 120, 3 mm). To demonstrate more clearly the area of seizure onset, the invasive electrodes are shown, contacts with seizure onset are marked by red dots. (C) An example of an invasive EEG recording (bipolar derivation, 30 μV/mm, 0.03 s, 120 Hz) of a series of simple partial myoclonic seizures with twitching of the right hemi-face. EEG and behavioural seizure onset (myoclonic jerks) are marked by the red arrow. Bursts of spikes and low amplitude fast activity are seen almost simultaneously over both lesions. (D and E) The histological findings in the temporal specimen of the patient: (D) dyslamination (Klüver-Barrera staining); (E) area with features of a FCD 2b with balloon cells (haematoxylin–eosin staining) in the temporo-posterior area.
that this lesion was also an FCD type 2 (Urbach et al., 2002; Krsek et al., 2008). The patient had no extracerebral clinical manifestations of tuberous sclerosis at the time of epilepsy surgery. A genetic examination gave no evidence for mutations in the TSC1 and TSC2 genes.

Case 2
This female patient has a positive family history of epilepsy (her mother, the brother of her mother and a cousin on the mother’s side suffered from epilepsy). Pregnancy and delivery were normal. First seizures occurred at the age of 8 months. The epilepsy remained pharmacoresistant throughout the course of disease. MRI showed two dysplastic areas: (i) in the right anterior temporal neocortex extending to the right amygdala (Fig. 2A and B); and (ii) in the right fronto-mesial cingulate gyrus (Fig. 2C and D). In addition, a mild hippocampal sclerosis was suspected, based on slightly reduced hippocampal volume and discrete hyperintensity. Surface EEG was not sufficient to determine the seizure onset zone, as no ictal activity was observable at the time of clinical seizure onset. During the later part of seizures, ~60s after seizure onset, bifronto-temporal rhythmic theta activity was discernible. Interictally, sharp waves were observed bitemporally and bifrontally with a right sided maximum.

At the age of 11 years, the patient underwent invasive video-EEG monitoring. Seizure semiology consisted of nocturnal proximal limb movements accompanied by vocalization, sometimes preceded by a feeling of panic. The patient was implanted with subdural strip electrodes covering both lesions (Fig. 2). During monitoring, eight seizures were captured. In seven seizures, onset of ictal activity was recorded over the right frontal lesion or simultaneously over both lesions (Fig. 2E). In one seizure, ictal activity started over the temporal lesion only (not shown). Both seizures were surgically removed (tailored lesionectomy right frontally and right 2/3 temporal lobe resection with amygdalo-hippocampectomy). The patient has remained seizure-free for 3 years. She had no postoperative neurological deficits. Histology showed FCD 2a in both dysplastic areas (Fig. 2F and G). The patient had no extracerebral clinical manifestations of tuberous sclerosis at the time of epilepsy surgery. A genetic examination for mutations in the TSC1 and TSC2 gene was negative.

Case 3
This male patient has a positive family history of epilepsy (one brother of his father suffered from epilepsy). Pregnancy and delivery were normal. First seizures occurred at the age of 5 months. The epilepsy remained pharmacoresistant throughout the course of the disease. MRI gave evidence of two lesions: (i) visual inspection showed a large area with cortical thickening and cortical-subcortical blurring in the left temporal lobe; and (ii) MRI post-processing with voxel-based morphometry additionally revealed an area of blurred grey-white matter transition suggestive for FCD in the left basal frontal lobe (Fig. 3A–D). Whereas surface EEG showed left temporal (and less frequently also right temporal) interictal spiking and a left temporal seizure onset, semiology (see below) suggested frontal lobe seizures.

At the age of 33 years, the patient underwent invasive video-EEG monitoring. Seizure semiology consisted of nocturnal hypomotor complex partial seizures. The patient was implanted with a depth electrode in the left hippocampus, and left temporal and frontal subdural strip electrodes (Fig. 3). During monitoring, more than 100 seizures were recorded. Seizure onset was always observed over the left temporal dysplasia (Fig. 3E). Interictally, there was an almost continuous and independent focus characterized by a repetitive bursting pattern or a rhythmic spiking pattern in the fronto-basal region (not shown) (Boonyapisit et al., 2003; Fauser and Schulze-Bonhage, 2006). The patient underwent extended temporal lobe resection and additional lesionectomy in the basal frontal lobe. Postoperatively, the patient has remained seizure-free for 3 years. He had no postoperative neurological deficits. Histology obtained from specimens of both areas showed FCD 2b (Fig. 3F and G). The patient had no extracerebral clinical manifestations of tuberous sclerosis at the time of epilepsy surgery. A genetic examination for mutations in the TSC1 and TSC2 gene was negative.

Case 4
This male patient has no family history of epilepsy. First seizures occurred at the age of 11 years. The epilepsy remained intractable. MRI showed right hippocampal sclerosis with volume loss and signal hyperintensity, and additional areas suggestive for FCD in the right superior frontal gyrus as well as in the right temporo-occipital region (Fig. 4A and B). Interictal surface EEG showed continuous right temporal slowing and intermittent bitemporal epileptiform discharges.
Ictal surface EEG showed widespread right temporal and occipital rhythmic theta activity.

At the age of 35 years, the patient underwent invasive video-EEG monitoring. Seizure semiology consisted of epigastric auras sometimes evolving into complex partial automotor seizures. The patient was implanted with a right hippocampal depth electrode and subdural strip electrodes over the dysplastic lesions (Fig. 4). During the monitoring, 24 seizures were recorded. In all of these seizures, first ictal activity was seen in the hippocampus (Fig. 4C). Spread of ictal activity to the dysplastic lesions was always observed, but relatively late in the course of the seizure (30–130 s after EEG seizure onset). Based on these intracranial EEG findings, the patient underwent a selective amygdalohippocampectomy. He has remained seizure-free for 3 years. No neurological sequelae were observed. Histology showed hippocampal sclerosis Grade 3 according to Wyler/MTS type 1a according to Blümcke. The patient had no extracerebral clinical manifestations of tuberous sclerosis at the time of epilepsy surgery. A genetic examination for mutations in the TSC1 and TSC2 genes was negative.

Case 5

This female patient has a positive family history of epilepsy (her brother suffers from epilepsy). Pregnancy and delivery were reported as normal. First seizures occurred presumably at the age of 18 years. The epilepsy remained pharmacoresistant against several antiepileptic drugs. MRI showed three areas strongly suggesting cortical dysplasia: (i) in the right frontal lobe (Fig. 5A); (ii) in the left insular region (Fig. 5C and D); and (iii) in the right temporo-parietal area (Fig. 5F and G). In the surface EEG, no ictal activity was discernible at seizure onset, only in one subclinical seizure a left temporal rhythmic activity was registered. Interictal spikes or sharp waves very rarely occurred over the left temporal and right frontal lobe.

At the age of 41 years, the patient underwent invasive video-EEG monitoring. Seizure semiology was characterized by an initial fear,
tachycardia and a flush, followed by manual automatisms and tonic posturing alternatively of the right and left arm. She was stereotactically implanted with depth electrodes in all of the three dysplastic areas (Figs 5B, E and H). During the monitoring, in 5 of 14 seizures ictal onset was seen in the left insular dysplasia (Fig. 5I), eight seizures arose simultaneously from the left insular and right temporo-parietal dysplasia, and in one seizure, ictal onset was observed in the right temporo-parietal lesion only (not shown). No seizure onset was observed in the right frontal lobe. Surgery was not performed in this patient. The patient had no extracerebral clinical manifestations of tuberous sclerosis at the time of presurgical evaluation. A genetic examination for mutations in the \textit{TSC1} and \textit{TSC2} genes was negative.

\section*{Discussion}

In this study, we report a series of five patients with MRI evidence for multi-FCD, supported by histology in three cases that were operated on. These patients represent a particularly interesting group, regarding both pathogenetic mechanisms and epileptogenic potential of cortical dysplasia.

The pathogenetic mechanisms underlying FCD are unclear. Genetic or environmental factors could be responsible for the development of FCD. In particular, a possible relationship with the tuberous sclerosis complex (TSC) is of interest, as TSC is characterized by multiple dysplastic brain areas (tubers) showing
Figure 3 The dysplastic areas of Case 3. (A and B) depict the left frontal (yellow crosswires) and the left temporal (red cross wires) dysplasia. (A) Transversal T$_1$-w MPRAGE (TR 9.7/TE 4, 1 mm); (B) corresponding ‘juncion’ image. (C and D) depict the left temporal dysplasia. (C) Transversal T$_2$-w (TR 6120/TE 104, 4 mm); (D) coronal T$_2$-w (TR 8160/TE 104, 3 mm). To indicate more clearly the area of seizure onset, the invasive electrodes are shown, contacts with seizure onset are marked by red dots. (E) Example of an invasive EEG recording (bipolar derivation, 30 μV/mm, 0.1 s, 120 Hz) at the beginning of a hypermotor complex partial seizure with an onset from the temporal lesion. The red arrow indicates EEG seizure onset in terms of a high frequent activity at the left temporo-posterior area (electrode contacts TBC4-6 and G A4-8). (F and G) depict histological features of a FCD 2b seen in both lesions: (F) large and irregular dysmorphic neurons (neurofilament immunostaining) and (G) balloon cells in the subcortical white matter (haematoxylin–eosin staining).
whether this predominance is intrinsically linked to the aetiology of this disease. Moreover, it remains open if the different lesions are connected by microscopic pathways that MRI cannot identify.

Epileptogenicity of these lesions was highly variable. In three of five invasively recorded patients, seizure onset from two different dysplastic areas could be proven (Cases 1, 2 and 5). In one patient (Case 3), however, the second dysplastic lesion showed only interictal activity during the period of invasive video-EEG recording. This lesion, interestingly, was not visible on MRI. In one patient (Case 4), seizures only arose from the sclerotic hippocampus, but not from the dysplastic areas evident on magnetic resonance imaging. The high variability in epileptogenicity of these lesions may explain why some patients with FCD become seizure-free despite an incomplete resection of the lesion (Sisodiya, 2002) and why others do not become seizure-free although all dysplastic tissue visible on MRI imaging was removed (Spreafico et al., 1998). Case 3 demonstrates that dysplastic areas could be occult on conventional MRI and only detectable by post-processing procedures of MRI data (Huppertz et al., 2008). The apparently simultaneous seizure onset in two lesions, as seen in Cases 1, 2 and 5, could either be explained by a tight network with very fast propagation of ictal activity as may be suggested in cases 1 and 2 who remained seizure-free postoperatively, or by a further MRI-occult epileptic region as supposed in Case 5, based on simultaneous seizure onset in both hemispheres.

Cases 1–3 show that surgical removal of two separate dysplastic lesions can result in long-lasting seizure-freedom. Thus, epilepsy surgery should be considered as an option in pharmacoresistant epilepsy even if multi-focality is suspected, based on EEG and/or MRI. Case 4, in whom only the hippocampus generated seizures, supports the view that multi-focal lesions do not preclude successful epilepsy surgery, if the epileptogenicity of lesions is properly assessed and resection is planned accordingly. Moreover, this case shows that several lesions need not necessarily function in a hierarchical fashion (Awad et al., 1991), supposing that the removal of a dominant ‘pacemaker’ leads to seizure onset from formerly entrained epileptogenic foci. Seizure-freedom in all patients with multi-FCD undergoing epilepsy surgery suggests a better outcome than the postoperative results in patients with multi-lobar contiguous FCD. Multi-lobar extent of FCD has been reported as a negative predictor for postoperative seizure freedom, only 30%–40% of patients reaching Engel class I outcome.

similar histology to FCD type 2b. In our study, no germ-line mutations in the TSC1 or TSC2 gene could be detected. According to Roach et al. (1998), clinical criteria for a definitive diagnosis of TSC require two or more distinct types of lesions, rather than multiple lesions of the same type in the same organ system. However, none of the patients in our study had subependymal nodules which are seen in 95% of patients with TSC (O’Callaghan, 2008) or extracerebral manifestations of tuberous sclerosis on clinical examination verified by dermatological examination including the use of Wood’s light, fundoscopy, echocardiography and renal ultrasound. Reports on TSC without extra-cerebral manifestations are rare. A computed tomography-based study in patients with tuberous sclerosis was published in 1986, describing positive radiological and negative extracerebral clinical features in 16% of 110 patients (Kingsley et al., 1986). Whereas in other malformations of the cortical development a multi-focal appearance has frequently been described (e.g. polymicrogyria, pachygyria) (Raymond et al., 1995), only one patient with three cortical dysplasias shown by MRI has been reported in the literature so far. However, in this patient no genetic analysis has been described (Yagishita and Arai, 1999). Our study cannot completely exclude clone- or cell-type restricted (somatic) gene changes. However, three of five patients with multi-FCD have a positive family history of epilepsy which could be an argument against a clone- or cell-type restricted somatic gene change and in favour of a familial predisposition. Information on the aetiology of epilepsy in the relatives was not available.

Three of five patients underwent surgical removal of the dysplastic tissue, and histology confirmed FCD type 2 according to Palmini and Lüders (2002) and Palmini et al. (2004) in all but one available specimen. In Case 1, histology was not available from the parietal lesion. The MRI finding of a transmantle dysplasia (Fig. 1E and F), however, is suggestive of a FCD type 2, as observed in the temporal specimen of the same patient. The identity of histological subtypes in both lesions of these patients hints to a similar point in time for the development of both lesions within one and the same patient. It could be speculated whether the predominance of FCD type 2 in this series of patients with multi-FCD is related to presurgical patient selection due to a better visualization of FCD type 2 on MRI compared to FCD type 1 or whether this predominance is intrinsically linked to the aetiology of this disease.

Figure 3 Continued.
postoperatively (Kloss et al., 2002; Fauser et al., 2004, 2008). It is obvious that patients with multi-focal dysplasia need extensive presurgical evaluation. This has recently been reviewed in patients with epilepsy due to tuberous sclerosis (Madhavan et al., 2007; Jansen et al., 2007). In none of our patients, with multi-FCD, was surface EEG sufficient to differentiate between the multiple dysplastic areas concerning seizure onset. In summary, despite the possible multi-focality of epileptogenesis, patients undergoing
Figure 5  The dysplastic areas of Case 5. (A) The right frontal dysplasia and (B) the implanted depth electrode. (A) coronal T$_2$-w FLAIR (TR 9000/TE 110, 2 mm); (B) coronal T$_1$-w MPRAGE (TR 9.7/TE 4, 1 mm). (C and D) depict the left insular dysplasia and (E) the implanted depth electrode (red dots mark contacts involved in seizure onset); (C) transversal T$_1$-w MPRAGE section; (D) corresponding so-called ‘extension’ image highlighting areas of abnormal gyration (i.e. grey matter extending abnormally deep into white matter; Huppertz et al., 2005); (E) sagittal T$_1$-w MPRAGE section. (F) and (G) depict the right temporo-parietal lesion and (H) the implanted depth electrode (red dots mark contacts involved in seizure onset); (F) and (H) coronal T$_1$-w MPRAGE section; (G) corresponding ‘extension’ image. (I) Example of an invasive EEG recording (bipolar derivation, 10 $\mu$V/mm, 0.03 s, 120 Hz) at the beginning of a complex partial seizure from the left insular lesion. In this example, the seizure possibly starts (first red arrow) with rhythmic spiking in the left insula. Few seconds later (second red arrow) a clear seizure pattern in terms of a low amplitude fast activity is seen in all contacts of the left insular depth electrode.
References


detailed presurgical evaluation have good chances for long-term seizure control after epilepsy surgery.