Focal cortical dysplasias: surgical outcome in 67 patients in relation to histological subtypes and dual pathology

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Summary
The purpose of this study was to assess whether the histological subtype of focal cortical dysplasia and dual pathology affect surgical outcome in patients with medically intractable epilepsy due to focal cortical dysplasia (FCD). We retrospectively analysed the outcome of 67 patients from 2 to 66 years of age at follow-up periods of 6 to 48 months after epilepsy surgery. Histological subtypes were classified according to Palmini and included a few cases with mild histological abnormalities corresponding to the definition of mild malformations of cortical development. The seizure outcome was classified according to Engel and evaluated at the last follow-up visit as well as at follow-up periods of 12 and 24 months after surgery. The outcome in patients with FCD and additional hippocampal pathology (dual pathology) was analysed separately. Distribution of histological subtypes differed in temporal and extratemporal localization, with a significantly higher extratemporal prevalence of FCD type 2. There was a tendency towards better postsurgical outcome related to the last follow-up visit in patients with more subtle abnormalities classified as mild malformations of cortical development (mMCD) (63% Engel Ia), FCD type 1a (67% Engel Ia) and FCD type 1b (55% Engel Ia) compared with patients with FCD type 2a (43% Engel Ia) and FCD type 2b (Taylor type) (50% Engel Ia). Considering the outcome at follow-up periods over 12 and 24 months, complete seizure-freedom was achieved significantly more often in patients with FCD type 1 and mMCD than with FCD type 2, and seizure reduction by less than 75% (Engel IV) occurred in more patients with FCD type 2a compared with the other subgroups. This tendency was seen in the whole patient group and in the extratemporal subgroup. Patients with dual pathology almost always had temporal lobe epilepsy; the outcome in this patient group was generally favourable (66% complete seizure-freedom at the last follow-up visit). The outcome remained almost constant with longer periods of follow-up. We conclude that patients with FCD type 1 and mMCD had a better outcome compared with those with more severe forms of cortical dysplasia. A higher incidence of FCD type 1 in temporal localization did not allow the effects of histological subtype and localization to be separated. A subanalysis of extratemporal FCDs, however, revealed a similar tendency for a better outcome with FCD type 1, suggesting that the histological subtype itself seems to be at least a relevant cofactor influencing postsurgical outcome.

Keywords: focal cortical dysplasia; histology; epilepsy; surgery; outcome

Abbreviations: FCD = focal cortical dysplasia; FDG-PET = [18F] fluorodeoxyglucose PET; MCD = malformation of cortical development; mMCD = mild malformation of cortical development

Introduction

The final organization of the cortical mantle is the result of a series of overlapping developmental processes: (i) proliferation of undifferentiated cells in the neuroepithelium; (ii) migration of neuroblasts; and (iii) cell differentiation and cortical organization. Impairment of any of these processes, due to a genetic effect or noxious environmental influences, usually results in malformations of cortical development (MCDs). MCDs are a heterogeneous group of focal and diffuse anatomical derangements. Focal cortical dysplasia (FCD) as a special subgroup of these malformations results from impairment in different stages of prenatal developmental processes. Some subtypes are thought to originate in the first trimester of gestation due to abnormal cell proliferation, others emerge later in the third trimester due to abnormal cortical organization (Barkovich et al., 2001). Such malformations are frequently associated with focal epilepsy (Li et al., 1995; Semah et al., 1998; Barkovich et al., 2001). The different times at which developmental disorders occur may affect the epileptogenicity of FCD, and also the outcome after epilepsy surgery.

Due to improved MRI techniques, including postprocessing of 3D data sets (Palmini et al., 1991b; Kuzniecky et al., 1995; Chan et al., 1998; Bastos et al., 1999; Kasubek et al., 2002; Wilke et al., 2003) FCDs are increasingly identified in epilepsy patients. Nowadays, focal cortical dysplasias are identified as the underlying pathology in up to 25% of patients with focal epilepsies (Kuzniecky et al., 1993).

About 76% of patients with FCD suffer from pharmacoresistant epilepsy (Semah et al., 1998). Thus, epilepsy surgery represents an important treatment option for these patients. Former reports had shown an inferior outcome of epilepsy surgery in patients with focal cortical dysplasias (Palmini et al., 1991a; Hirabayashi et al., 1993; Kuzniecky et al., 1993; Raymond et al., 1995; Wyllie et al., 1998; Hong et al., 2000; Sisodiya, 2000) compared with patients with benign tumors or hippocampal sclerosis. Several reasons for this have been discussed: an often extratemporal localization, poor morphological demarcation, and high epileptogenic potency of minimal residual tissue. Recent retrospective studies report a more favourable outcome following epilepsy surgery (Chassoux et al., 2000; Tassi et al., 2002; Bautista et al., 2003; Kral et al., 2003), especially in patients with unilobar lesions, early presurgical evaluation and early surgery.

Only a few studies (Keene et al., 1998; Chassoux et al., 2000; Kloss et al., 2002; Tassi et al., 2002; Kral et al., 2003; Rosenow et al., 1998) have so far addressed the impact of the different histological subtypes of FCD on the surgical outcome. Some studies concluded that FCD with balloon cells (Taylor type, Palmini type 2b) has the most favourable outcome (Chassoux et al., 2000; Tassi et al., 2002), while others found no differences between histological subtypes (Keene et al., 1998; Kloss et al., 2002) or even a better outcome when the degree of histopathological abnormalities was mild to moderate (Palmini et al., 1994). The role of dual pathology (FCD in the temporal lobe and additional hippocampal sclerosis) has also been the subject of controversial discussions (Mitchell et al., 1999; Thom et al., 2001; Tassi et al., 2002; Srikijvilaikul et al., 2003).

The aim of the present study was to analyse whether less severe forms of cortical dysplasia [mild malformation of cortical development (mMCD), FCD type 1] differ with regard to surgical outcome from more severe forms (FCD type 2). In addition, we studied the impact of different localizations and of the presence of dual pathology on the postsurgical outcome in 67 patients with focal cortical dysplasias. The wide spectrum of these lesions has resulted in various classifications and discrepancies in terminology (Mischel et al., 1995; Brännstrom et al., 1996; Leventer et al., 1999; Barkovich et al., 2001; Crino et al., 2002; Palmini and Lüders, 2002). In this study we refer to a classification based on histological features suggested by Palmini (Palmini and Lüders, 2002), which has been widely accepted as useful for neuropathological examination.

Patients and methods

From May 1998 to June 2003, a total of 67 patients were operated on for pharmacoresistant epilepsy due to FCD or mMCD at the University of Freiburg and followed up for 6–48 months postoperatively. The data were analysed retrospectively. All patients gave informed consent for use of collected data for scientific purpose.

Demographic data

Among the 67 patients there were 33 females and 34 males. The age at surgery ranged from 2 to 66 years (mean 21.3 years, median 17 years), the age at epilepsy onset ranged from <1 to 60 years (mean 6.3 years, median 4 years).

Presurgical evaluation

Presurgical evaluation was performed in the Epilepsy Centers of Freiburg, Heidelberg, and Kork, Germany.

All patients underwent presurgical MRI. MRI scans were acquired with a 1.5 tesla scanner (Siemens Magnetom Vision or Siemens Magnetom Symphony Erlangen, Germany) or with a 0.5 tesla scanner (Philips Gyroscan Best, The Netherlands). The following sequences were performed: T1-weighted images with and without gadolinium-DTPA, T2-weighted images, fluid-attenuated inversion recovery (FLAIR) images and MPRAGE (magnetization-prepared rapid gradient echo) sequences. If mesiotemporal epilepsy was suspected, axial images were acquired with a modified angulation parallel to the long axis of the temporal lobe to evaluate the mesiotemporal structures. MRI criteria suggestive of focal cortical dysplasia were gyration anomalies, focal thickenings of the cortex, blurring of the grey–white matter junction, and abnormal cortical and subcortical signal intensity.
Functional imaging with [18F]fluorodeoxyglucose positron emission tomography (FDG-PET) and ethyl cysteinate dimer single-photon emission computed tomography (ECD-SPECT) were used as ancillary examinations when needed. All patients underwent a comprehensive battery of neuropsychological tests (comprising the assessment of attention, memory, higher verbal and visual functions). Surface video EEG-monitoring using the 10–20 system was performed in all patients. Invasive EEG-monitoring was performed in 23 patients if the results from non-invasive examinations were inconclusive, the patient was seemingly non-lesional, or if the lesion was located close to eloquent areas.

**Surgical procedures**

The surgical procedures are summarized in Table 1. Thirty-three of 67 patients (49%) underwent isolated temporal lobe surgery (Table 1A). Six additional patients had multilobar resections including the temporal lobe or at least parts of the temporal lobe (Table 1B and C); these six patients are subsumed in the group of extratemporal surgery and are not considered in the calculation of outcome in the temporal lobe group.

Twenty-nine patients were diagnosed as having dual pathology with FCD in the temporal lobe and hippocampal sclerosis. In 23 of them anterior temporal lobe resection including the mesial structures was performed, in three of them both lesionectomy and amygdalohippocampectomy were performed, in two of them lesionectomy with extension to the occipital lobe and amygdalohippocampectomy were performed, and in one anterior lobe resection including the mesial structures and an additional frontal lesionectomy were performed.

Seven of the 33 patients with temporal surgery presented with FCD only. In three of them an anterior temporal lobe resection including the mesial structures was performed, in one of them lesionectomy and amygdalohippocampectomy were performed as the dysplastic lesion extended into the mesial structures, and in three a lesionectomy was performed without touching the mesial structures.

Thirty-four of 67 patients (51%) underwent extratemporal resection (Table 1C). Eighteen patients (28%) underwent frontal surgery (five frontal lobe resections, 13 lesionectomies), two patients (3%) occipital surgery (one occipital lobe resection, one lesionectomy), two patients (3%) parietal surgery (two lesionectomies), and 12 patients multilobar resection (four parieto-occipital lesionectomies, one frontoparietal lesionectomy, one occipital lobe resection with extension to the parietal lobe, one occipital lobe resection with extension to the temporal lobe, one parieto-temporo-insular lesionectomy, one temporo-insular lesionectomy and two temporo-occipital lesionectomies, one frontal lesionectomy and anterior temporal lobe resection).

**Neuropathological examination**

After excision, the 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 Klüver–Barrera myelin stain. For selected cases, additional special stains (Elastica–van Gieson, Reticulin, Bodian) were used. Additional immunohistochemical stainings were performed: in all 67 patients neurofilament immunohistochemistry was performed to visualize the orientation of neurons and to depict dysmorphic neurons or ectopic white matter neurons. Synaptophysin immunohistochemistry, another neuronal marker, was applied in 46 patients. In 60 patients, glial fibrillary acid protein (GFAP) immunohistochemistry was performed in order to demonstrate astrogliosis and/or balloon cells. In difficult cases additional

<table>
<thead>
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<th>Table 1 Surgical procedures</th>
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<tr>
<td><strong>(A) Surgery in temporal focal cortical dysplasia</strong></td>
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<tr>
<td>Surgery</td>
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<td>2/3 temporal lobe resection</td>
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<td>Lesionectomy + AHE</td>
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<td>Lesionectomy</td>
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<tr>
<td><strong>(B) Multilobar resections including the temporal lobe</strong></td>
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<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Multilobar lesionectomy + AHE</td>
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<td>Multilobar lesionectomy without AHE</td>
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<tr>
<td><strong>(C) Surgery in extratemporal focal cortical dysplasia</strong></td>
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<tr>
<td>Extratemporal surgery</td>
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<tr>
<td>Lobar resection</td>
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<tr>
<td>Lesionectomy</td>
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AHE = amygdalohippocampectomy; HS = hippocampal sclerosis; FCD = focal cortical dysplasia; MST = multiple subpial transsections.
immunohistochemical stainings were necessary. For example, vimentin immunohistochemistry was used in five patients to depict the rare presence of balloon cells. The proliferation marker Ki-67 was used in 12 patients with increased cellular density to exclude a ganglioglioma. Additionally, the pan-leucocyte marker leucocyte common antigen (LCA) and/or the microglial/macrophage marker CD68 were applied in 47 patients.

All operative specimens with previous histopathological diagnosis of any form of malformation of cortical development were reviewed by an experienced neuropathologist. Those specimens which fulfilled one or more of the following characteristics were classified as FCD, 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). These histological characteristics are demonstrated in Fig. 1.

**Fig. 1** Cytoarchitectural abnormalities in different histological types of FCD. (A) FCD 1a. Columnar arrangement of neurons (Klüver–Barrera). (B) FCD 1a. Clusters of oligodendrocytes (haematoxylin and eosin). (C) FCD 1b. Severe dyslamination immature neurons in the deeper layers of the cortex and heterotopic neurons in the white matter (neurofilament). (D) FCD 2a. Dysmorphic neurons (neurofilament). (E) FCD 2a. Dysmorphic neurons with aggregates of Nissl substance and lipofuscin (periodic acid Schiff). (F) FCD 2b. Balloon cells and dysmorphic neurons (Klüver–Barrera).
Specimens from eight patients who fulfilled MRI criteria of cortical dysplasia showed no cortical dyslamination but neuronal heterotopia (small aggregates of heterotopic white matter neurons) or at least 10 ectopically placed white matter neurons per high-power field (Kasper et al., 2003). In some of these patients additional ectopically placed neurons were found in the molecular layer. According to Palmini (Palmini and Lüders, 2002) these malformations were classified as mMCD.

Focal cortical dysplasia in temporal location associated with hippocampal sclerosis was described as dual pathology. The histological grading of hippocampal pathology was classified according to Wyler and colleagues (Wyler et al., 1995).

Postoperative follow-up
Follow-up data were collected at 3-monthly intervals in the first year and annually in the ensuing years in all patients. Mean follow-up time was 21.9 months, median 24 months, ranging from 6 months to 48 months. Surgical outcome was classified according to Engel (Engel and Rasmussen, 1993): (Ia) completely seizure-free; (I) seizure-free or auras only or convulsions with drug withdrawal only; (II) rare seizures; (III) and (IV) seizure-freedom after follow-up periods of 12 and 24 months respectively in mild (mMCD, FCD type 1) versus severe FCD (FCD type 2) in temporal versus extratemporal localization; and (ii) whether patients with dual pathology are less often seizure-free compared with patients without dual pathology. Choosing to compare FCD type 2 versus FCD type 1 and mMCD was based on different biological characteristics (i.e. more severe dyslamination and presence of dysmorphic neurons in FCD type II). We chose to compare non-seizure-free patients with seizure-free patients because borders between different non-seizure-free outcome classes are to some degree arbitrary and have a minor impact on postoperative quality of life.

In order to include a more detailed view on histological subgroups and currently recommended outcome, and in order to facilitate comparisons with other publications, additional data on outcome subclasses and on their distribution depending on the duration of postoperative follow-up are given.

For age at epilepsy onset and epilepsy surgery, and duration of follow-up periods, the mean and median are given.

Results

Statistical analyses
All statistical analyses were performed with the $\chi^2$ test. In total, eight $\chi^2$ tests were performed to answer the following questions. Two statistical analyses were performed with regard to the prevalence of different FCD types: (i) the prevalence of mild (mMCD, FCD type 1) versus severe FCD (FCD type 2) in temporal versus extratemporal localization; (ii) the prevalence of mild versus severe FCD in the presence versus absence of dual pathology. Six statistical analyses were performed with regard to outcome. Statistical analyses were done at follow-up periods of 12 and 24 months, as sufficient patient numbers were available at those follow-up times and in order to confirm results obtained at the first time: (i) and (ii) seizure-freedom after follow-up periods of 12 and 24 months respectively in mild (mMCD, FCD type 1) versus severe FCD (FCD type 2); (iii) and (iv) seizure-freedom after follow-up periods of 12 and 24 months respectively with regard to the presence or absence of dual pathology; (v) and (vi) seizure-freedom after follow-up periods of 12 and 24 months respectively in temporal versus extratemporal localization.

A probability ($P$) value of $<0.05$ was regarded as significant. For the restricted number of comparisons, no Bonferroni correction for multiple tests was performed.

The analyses were limited to the $a$ priori-defined questions (i) whether patients with more severe types of FCD are less often seizure-free compared with patients with milder forms; (ii) whether, in patients with FCD with a temporal localization, complete seizure-freedom can be achieved more frequently than in patients with FCD with an extratemporal localization; and (iii) whether patients with dual pathology are less often seizure-free compared with patients without dual pathology.

Choosing to compare FCD type 2 versus FCD type 1 and mMCD was based on different biological characteristics (i.e. more severe dyslamination and presence of dysmorphic neurons in FCD type II). We chose to compare non-seizure-free patients with seizure-free patients because borders between different non-seizure-free outcome classes are to some degree arbitrary and have a minor impact on postoperative quality of life.

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For age at epilepsy onset and epilepsy surgery, and duration of follow-up periods, the mean and median are given.

Results

Histology
Sixty-seven patients with focal cortical dysplasia were investigated. Histologically, eight patients showed characteristics of mMCD, 18 patients of FCD 1a, 20 patients characteristics of FCD 1b, seven patients characteristics of FCD 2a, and 14 patients characteristics of FCD 2b. Twenty-nine patients had additional histologically proven hippocampal sclerosis and were classified as dual pathology.

MRI
In all patients with extratemporal FCD/mMCD the lesion was discernible in MRI, except for one patient with a frontal cortical dysplasia (histologically FCD 2a), which was only identified by additional voxel-based 3D MRI analyses (Kassubek et al., 2002; Wilke et al., 2003). Similarly, in all seven patients with temporal FCD without dual pathology the lesion was discernible in MRI. In dual pathology of the temporal lobe MRI revealed FCD/mMCD in 28 of 29 patients, whereas hippocampal sclerosis was detectable in 21 of 29 patients. In these MRI-negative patients, hippocampal sclerosis was mild (grade I according to Wyler and colleagues) (Wyler et al., 1995).

Outcome
Standardized follow-up-evaluations were performed 6, 12, 24 and 48 months after surgery. Seizure outcome was analysed at each follow-up visit to evaluate outcome over time (Figs 2, 4, 6 and 7). Seizure outcome at the last follow-up visit is given for a general outcome overview of patients belonging to different subgroups (Table 2); details referring to defined follow-up periods are given separately.
Surgical outcome in the total group of FCD/mMCD-patients

Of the total group of FCD/mMCD patients, 57% were Engel class Ia, 66% were Engel class I, 25% had relevant decrease in seizure frequency (Engel class II and III), and 9% did not benefit from surgery (Engel class IV) (mean follow-up period 21.9 months, median 24 months, range 6–48 months) (Table 2).

Fig. 2  Outcome in relation to histological subtypes. M = months after surgery; Ia, I total, II, III, IV = Engel classification. Numbers above the bars are numbers of patients investigated in each group.
The surgical outcome of patients at the last follow-up visit in relation to different histological subtypes (classified according to Palmini) is summarized in Table 2 and Fig. 2.

In mMCD, 63% of the patients were Engel class Ia and I, 25% had a relevant decrease in seizure frequency (Engel class II and III) and 12% of the patients did not benefit from surgery (Engel class IV) (mean follow-up time 20.4 months, median 24 months).

In FCD type 1a, 67% of the patients were Engel class Ia and I, 27.5% had a relevant decrease in seizure frequency (Engel class II and III) and 5.5% did not benefit from surgery (Engel class IV) (mean follow-up time 26.0 months, median 24 months).

In FCD type 1b, 55% of the patients were Engel class Ia, 65% were Engel class I, 25% had a relevant decrease in seizure frequency (Engel class II and III) and 10% did not benefit from surgery (Engel class IV) (mean follow-up time 24.0 months, median 24 months).

In FCD type 2a, 43% of the patients were Engel class Ia, 57% were Engel class I, 14% had a relevant decrease in seizure frequency (Engel class II and III) and 29% did not benefit from surgery (Engel class IV) (mean follow-up time 18.8 months, median 12 months).

In FCD type 2b, 50% of the patients were Engel class Ia, 71.4% were Engel class I, 28.6% had a relevant decrease in seizure frequency (Engel class II and III) and none of the patients failed to benefit from surgery (Engel class IV) (mean follow-up time 15.7 months, median 12 months).

Figure 2 shows the postsurgical outcome at different points of time in the follow-up. The outcome remained almost constant with longer periods of follow-up; the Engel class changed over time in only eight patients. For these patients individual data are shown in Table 3.

Statistical analyses showed that the Engel class Ia outcome was significantly less frequently observed in patients with FCD type 2a/b compared with patients from the group with mild disturbances (mMCD, FCD type 1a, and FCD type 1b), both at follow-up periods of 12 (P = 0.03) and 24 months (P = 0.05).

In FCD type 2b, 40% of patients were seizure-free after 12 months and 25% after 24 months, and in FDC type 2a 20% of patients were seizure-free after 12 months and 33% after 24 months. Engel class IV outcome, however, was more frequently observed in patients with FCD type 2a than in patients with FCD type 2b at follow-up periods of 12 months (FCD

### Table 2

<table>
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<tr>
<th>Engel classification</th>
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<th>II</th>
<th>III</th>
<th>IV</th>
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</tr>
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<td>50%</td>
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<td>50%</td>
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N total = total number of patients; n = number of patients in the Engel subgroup; mMCD = mild malformation of cortical development; FCD = focal cortical dysplasia.

### Table 3

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<th>Patient number</th>
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### Surgical outcome in relation to different histological subtypes of focal cortical dysplasias

The surgical outcome of patients at the last follow-up visit in relation to different histological subtypes (classified according to Palmini) is summarized in Table 2 and Fig. 2.

In mMCD, 63% of the patients were Engel class Ia and I, 25% had a relevant decrease in seizure frequency (Engel class II and III) and 12% of the patients did not benefit from surgery (Engel class IV) (mean follow-up time 20.4 months, median 24 months).

In FCD type 1a, 67% of the patients were Engel class Ia and I, 27.5% had a relevant decrease in seizure frequency (Engel class II and III) and 5.5% did not benefit from surgery (Engel class IV) (mean follow-up time 26.0 months, median 24 months).

In FCD type 1b, 55% of the patients were Engel class Ia, 65% were Engel class I, 25% had a relevant decrease in seizure frequency (Engel class II and III) and 10% did not benefit from surgery (Engel class IV) (mean follow-up time 24.0 months, median 24 months).

In FCD type 2a, 43% of the patients were Engel class Ia, 57% were Engel class I, 14% had a relevant decrease in seizure frequency (Engel class II and III) and 29% did not benefit from surgery (Engel class IV) (mean follow-up time 18.8 months, median 12 months).

In FCD type 2b, 50% of the patients were Engel class Ia, 71.4% were Engel class I, 28.6% had a relevant decrease in seizure frequency (Engel class II and III) and none of the patients failed to benefit from surgery (Engel class IV) (mean follow-up time 15.7 months, median 12 months).

Figure 2 shows the postsurgical outcome at different points of time in the follow-up. The outcome remained almost constant with longer periods of follow-up; the Engel class changed over time in only eight patients. For these patients individual data are shown in Table 3.

Statistical analyses showed that the Engel class Ia outcome was significantly less frequently observed in patients with FCD type 2a/b compared with patients from the group with mild disturbances (mMCD, FCD type 1a, and FCD type 1b), both at follow-up periods of 12 (P = 0.03) and 24 months (P = 0.05).

In FCD type 2b, 40% of patients were seizure-free after 12 months and 25% after 24 months, and in FDC type 2a 20% of patients were seizure-free after 12 months and 33% after 24 months. Engel class IV outcome, however, was more frequently observed in patients with FCD type 2a than in patients with FCD type 2b at follow-up periods of 12 months (FCD...
type 2a 40%, FCD type 2b 0%) and 24 months (FCD type 2a 33%, FCD type 2b 0%) (Fig. 2). Due to low patient numbers in the class IV outcome, we did not perform statistical analysis.

An additional analysis of postsurgical outcome in relation to the histological subtype in the subgroup of extratemporally located FCDs showed a similar tendency. Best outcome was seen in mMCD and FCD type 1a, followed by FCD type 1b. Poorest outcome was seen in FCD type 2a.

The role of dual pathology

Dual pathology of the temporal lobe (hippocampal sclerosis and FCD in the neocortical temporal lobe) was observed in a large group of 29 patients (43%). In two the dysplastic area extended to the occipital lobe and one patient had an additional frontal dysplastic lesion. In our series there were no patients in whom extratemporal dysplasia was associated with an isolated hippocampal sclerosis without dysplasia in the temporal lobe.

Histologically, patients with dual pathology displayed severe abnormalities (FCD type 2a and type 2b) significantly (P = 0.0002) less frequently than patients without dual pathology (Fig. 3A and B): Most patients (93%) had mild MCD, FCD type 1a or type 1b. None of the patients with dual pathology had balloon cells (type 2b).

Postsurgical outcome at the last follow-up visit is given in Table 2: 66% of the patients were completely seizure-free (Engel class Ia), 69% were Engel class I, 21% had a relevant decrease in seizure frequency (Engel class II and III), and 10% did not benefit (Engel class IV) (mean follow-up time 22.8 months, median 24 months). Figure 4A shows the postsurgical outcome at different points of time in the follow-up. The outcome remained almost constant with longer periods of follow-up.

In the group of patients without dual pathology (Table 2) 50% were completely seizure-free (Engel class Ia), 63% were Engel class I, 29% had a relevant decrease in seizure frequency (Engel class II and III) and 8% did not benefit from surgery (Engel class IV) at the last follow-up visit (mean follow-up time 20.7 months, median 24 months). Figure 4B demonstrates the postsurgical outcome at different times during the follow-up. Differences between patients with dual pathology and with FCD only were not statistically significant at follow-up periods of 12 months (P = 0.58) and 24 months (P = 0.59).

Outcome in relation to the localization of the lesion

With temporal localization, 91% of the patients displayed histological abnormalities of mild to moderate degree (mMCD, FCD type 1a, and FCD type 1b). Only 9% of the patients had severe cortical dysplasia (FCD type 2a and type 2b) (Fig. 5).

With extratemporal localization, however, 48% of the patients displayed histological abnormalities of a mild to moderate degree (mMCD, FCD type 1a, and FCD type 1b) and 52% had severe cortical dysplasia (FCD types 2a and 2b). FCD type 2 was significantly more common in patients with extratemporal FCD (P = 0.0001).

As FCD subtypes were distributed inhomogeneously between temporal and extratemporal localizations, we also analysed seizure outcome in relation to the site of the lesion. In our series, FCD with temporal localization tended to have a better postoperative outcome than FCD with extratemporal localization (Table 2).

In temporal FCD, 67% of the patients were Engel class Ia, 70% were Engel class I, 21% had relevant decrease of seizure frequency (Engel class II and III) and 9% did not benefit from surgery (Engel class IV) at the last follow-up visit (mean follow-up time 23.6 months, median 24 months, range 6–48 months). In extratemporal FCD, 47% of the patients were Engel class Ia, 61.8% were Engel class I, 29.4% had a relevant decrease in seizure frequency (Engel class II and III) and 8.8% did not benefit from surgery (Engel class IV) at the last follow-up visit (mean follow-up time 20.2 months, median 34 months, range 6–48 months). Figure 6A and B displays the outcome at different points of time in the follow-up.

The differences between patients with temporal and extratemporal FCD, however, were not statistically significant at follow-up periods of 12 months (P = 0.18) and 24 months (P = 0.25).

Figure 6C shows the subgroup of patients with unilobar extratemporal FCD. In this subgroup, outcome was better compared with patients with extratemporal FCD including multilobar lesions.
Outcome in multilobar FCD, insular FCD and in patients with incomplete resection

In our series, 12 patients had multilobar involvement. In this small subgroup, complete seizure freedom was achieved in only 25% of the patients at the last follow-up visit (Fig. 7A).

We also analysed patients with insular involvement, as insular involvement has been described as a risk factor for poor outcome. In our series we had six patients with insular involvement; five of them underwent partial insular resection. Insular involvement in this small group appeared not to imply a poor outcome (Fig. 7B).

In seven patients (three with temporal FCD and four with extratemporal FCD) lesionectomy was incomplete by MRI criteria as the dysplasia involved eloquent regions (in three of these four patients additional multiple subpial transections were performed) or the dysplasia was very widespread (three patients) (Fig. 7C). Patients in this group could have any class of outcome.

Discussion

In the present study the outcome of epilepsy surgery in patients with different histological subtypes of focal cortical dysplasia was investigated.
In our series, we found that in patients with FCD type 2 complete seizure-freedom (Engel class Ia) was significantly less frequently achieved compared with patients with milder histological abnormalities (mMCD and FCD type 1) at postoperative follow-up periods of 12 and 24 months. Within the FCD type 2 group, FCD type 2a appeared to contribute more to the worse outcome.

The postsurgical outcome related to the histological subtype has only been investigated in few studies before (Keene et al., 1998; Chassoux et al., 2000; Kloss et al., 2002; Tassi et al., 2002b; Kral et al., 2003; Rosenow et al., 1998). Most of these studies agreed that FCD type 2b (with balloon cells) had a favourable outcome, although this subtype is supposed to be associated with clinically and electrocorticographically increased epileptogenicity compared with other subtypes (Rosenow et al., 1998). It is possible that in patients with balloon cells the frequent electrographical spike activity as well as a better demarcation of the lesion in MRI...
contribute to a good delineation of the affected tissue. A direct electrocorticographic–histopathological correlation, however, could demonstrate that areas containing balloon cells are less epileptogenic than closely located dysplastic regions without balloon cells. Areas with histological characteristics of FCD type 2a were considered to be more epileptogenic than areas with histological characteristics of FCD type 1 (Boonyapisit et al., 2003).

This seems to correlate with our finding that Engel class IV outcome was most frequently observed in FCD type 2a. As statistical analysis of this point would have implied multiple other comparisons (multiple regression analysis) on subtypes not justified by the number of patients included in this study, these data are given on a descriptive basis.

Additionally, we focused on the role of dual pathology in the temporal lobe. The coexistence of hippocampal sclerosis and temporal lobe developmental pathology is a well-known phenomenon. However, the importance of these abnormalities of the temporal lobe is controversial. It has been suggested that increased neuronal density in the white matter may be

Fig. 7 Outcome of patients with (A) multilobar FCD, (B) insular involvement and (C) incomplete resection. M = months after surgery; Ia, I total, II, III, IV = Engel classification. Numbers above the bars are numbers of patients investigated in each group.
merely an epiphenomenon as a consequence of white matter atrophy secondary to epilepsy-induced damage (Emery et al., 1997). Other authors have suggested that hippocampal sclerosis is a consequence of increased susceptibility to hyperthermia-induced seizures as a result of the presence of neuronal migration disorders in the temporal lobe (Germano et al., 1996). Finally, it has been proposed that hippocampal sclerosis and FCD of the temporal lobe have a common pathogenetic mechanism during embryogenesis (Raymond et al., 1994).

In our patients, the group with dual pathology of the temporal lobe had predominantly mild cortical abnormalities (93% mMCD, FCD types 1a and 1b). This patient group had a particularly favourable outcome. Our results are in line with other studies showing that patients with dual pathology of the temporal lobe often have only architectural cortical abnormalities (Srikijvilaikul et al., 2003) and that even in the presence of severe neuronal ectopia in the temporal lobe, with or without associated hippocampal sclerosis, these patients may have a favourable clinical outcome following surgery (Hardiman et al., 1988; Thom et al., 2001; Srikijvilaikul et al., 2003). In a recent study, postsurgical outcome in dual pathology was found inferior to the outcome in other subgroups of focal cortical dysplasia (Kral et al., 2003). This result may be due to a very small patient sample. The observed differences in outcome could be due to the following reasons. (i) Mild forms of FCD may have a better outcome only because they are preferentially located in the temporal lobe. A better outcome thus may be secondary to a better chance of achieving complete surgical removal of the affected tissue. (ii) The histological subtype itself has an impact on the outcome in patients with cortical dysplasias.

In favour of hypothesis (i), patients with temporal lobe cortical dysplasias (with and without dual pathology) tended to have a better postsurgical outcome than patients with extratemporal cortical dysplasia. Poorest results were seen in patients with multilobar FCD and in patients with incomplete resection of the lesion, which was more common in extratemporal FCD.

If localization were the only factor, a similar difference between outcome in different FCD types should not be found when analysing patients with extratemporal FCDs only. However, this tendency towards a better outcome in milder forms of FCD was similarly observed in the subgroup of patients with extratemporal FCD, indicating that the outcome is affected not only by the high coincidence of mild histological abnormalities with temporal localization but probably also by the histological subtype itself [hypothesis (ii)]. Possibly, FCD type 2a is histologically more widespread and the demarcation of FCD type 2a in MRI is less clear than in other subtypes. Or, even in the case of a similar demarcation, incompleteness of the resection results in higher recurrence rates in FCD type 2a because of a higher epileptogenicity of small amounts of remaining tissue. This hypothesis is also supported by the results of the above-mentioned study on direct electrocorticographic and histopathological correlations (Boonyapisit et al., 2003) showing that areas with characteristics of FCD type 2a are more epileptogenic than areas with characteristics of FCD type 1 and type 2b.

In summary, the postsurgical outcome tended to be better in milder histological abnormalities, the Engel Ia outcome being significantly more frequently achieved in patients with mMCD and FCD type 1 compared with patients with FCD type 2, and the Engel IV outcome occurring more frequently in patients with FCD type 2a compared with the other groups. Dual pathology did not imply a worse outcome with regard to postsurgical seizure-freedom. We confirmed that histological subgroups of focal cortical dysplasias are differentially distributed in temporal and extratemporal regions. As this influences outcome, it is difficult to decide whether these differences are to be attributed primarily to the histological subtype or to the localization. A subanalysis in extratemporal lesions, however, showed a similar tendency for better outcome in mild FCD, indicating that the histological subtype is at least a cofactor in the postsurgical outcome. Overall, at a mean follow-up period of 21.9 months (median 24 months) the postsurgical outcome in our patient group was better than in other studies, and patients had a good chance of seizure-freedom within the first 2 years after surgery.

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References


