Focal cortical dysplasia: long term seizure outcome after surgical treatment

T Kral, M von Lehe, M Podlogar, H Clusmann, P Süßmann, M Kurthen, A Becker, H Urbach, J Schramm

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See end of article for authors' affiliations

Correspondence to:
Dr Thomas Kral, Department of Neurosurgery, University of Bonn, Medical Centre, Sigmund Freud Strasse 25, 53105 Bonn, Germany; Thomas.Kral@ukb.uni-bonn.de

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Background: Studies of long term outcome after epilepsy surgery for cortical malformations are rare. In this study, we report our experience with surgical treatment and year to year long term outcome for a subgroup of patients with focal cortical dysplasia (FCD).

Methods: We retrospectively analysed the records of 49 patients (females $n = 26$; males $n = 23$; mean age 25 (11) years) with a mean duration of epilepsy of 18 years (range 1–45). Preoperative MRI, histological results based on the Palmini classification and clinical year to year follow-up according to the International League Against Epilepsy (ILAE) classification were available in all patients.

Results: 98% of patients had a lesion on preoperative MRI. In addition to lobectomy ($n = 9$) or lesionectomy ($n = 40$), 14 patients had multiple subpial transections of the eloquent cortex. The resected tissue was classified as FCD type II b in 41 cases with an extratemporal (88%) and FCD type II a in 8 cases with a temporal localisation (100%). After a mean follow-up of 8.1 (4.5) years, 37 patients (76%) were seizure free, a subgroup of 23 patients (47%) had been completely seizure free since surgery (ILAE class 1a) and 4 patients (8%) had only auras (ILAE class 2). Over a 10 year follow-up, the proportion of satisfactory outcomes decreased, mainly within the first 3 years. During long term follow-up, 48% stopped antiepileptic drug treatment, 34% received a driver's license and 57% found a job or training.

Conclusion: Surgical treatment of epilepsy with FCD is not only successful in the short term but also has a satisfying long term outcome which remains constant after 3 years of follow-up but is not associated with better employment status or improvement in daily living.

With the development of high resolution MRI in the past decade, cortical malformations have been detected more often in patients with drug resistant epilepsy.^{1–2} Visualisation by MRI has aided diagnosis and surgical treatment of the largest group of cortical malformations (ie, the focal cortical dysplasias (FCDs)). Successful short term follow-up with seizure free rates of 40–86% were described in several studies^{3–9} but only a few focused on long term outcome.^{10–12} Most of these studies did not analyse subgroups of patients with the same histopathology, as other malformations or low grade gliomas were also included. The Engel classification,¹³ and not the newer International League Against Epilepsy (ILAE) classification,¹⁴ was used to describe the seizure outcome in all studies, and a year to year follow-up, important for the long term course of these patients, was not included.

The first aim of this study was a reclassification of all FCD cases according to the new Palmini classification¹⁵ to define a homogenous histopathological group. The second aim was to analyse the year to year long term outcome with respect to seizures according to the ILAE classification, antiepileptic drug (AED) use and socioeconomic outcome (eg, driving license and employment status).

MATERIALS AND METHODS

Over a 12 year period (1989–2001), 1202 patients were operated on in the epilepsy surgery programme. A subgroup of 40 patients who underwent resection of FCDs were analysed in a previous study⁸ in terms of surgical procedure and short term follow-up (last available seizure outcome according to Engel classes).

Selection criteria for patients in this study were: preoperative MRI, neuropathological reclassification of a FCD, follow-up longer than 36 months, year to year follow-up of seizures,

postoperative AED use and socioeconomic data. The study population comprised 49 patients.

Postoperative MRI was available in a subgroup of 20 patients. The analysis was performed using clinical charts, MRI evaluation, histological review and telephone interview for information on seizure follow-up, AED use, driving license and employment status.

The final study group included 26 females and 23 males with a mean age of 25 years (range 5–47). Mean seizure onset was 8 years (range 0–23) and mean seizure duration was 18 years (range 1–45). The details of the preoperative workup for epilepsy surgery candidates at our institution have been described in detail previously^{15a}; 13 patients had an ictal single photon emission computed tomography. Invasive EEG monitoring via chronically implanted electrodes was performed in the following cases:

- inconclusive or even discordant results from non-invasive procedures, especially from interictal and ictal EEG or
- non-lesional high resolution MRI or questionable lesions not clearly distinguishable from normal tissue or
- localisation of assumed epileptogenic lesions close to or overlapping with eloquent areas, thus requiring electrical stimulation for cortical mapping.

Invasive procedures with chronically implanted subdural or depth electrodes were carried out in 20 patients to obtain additional information about the ictal focus or as a mapping procedure in eloquent areas, whenever non-invasive recordings revealed inconclusive results.

Abbreviations: AED, antiepileptic drug; FCD, focal cortical dysplasia; ILAE, International League Against Epilepsy; MST, multiple subpial transection

The rationale for the surgical treatment of FCDs was removal of the MRI documented lesion in addition to removal of the epileptogenic zone, as suggested by preoperative clinical and electroencephalographic evaluations.

In cases of epileptogenic activity in eloquent areas, a multiple subpial transection (MST) was performed ($n = 14$). Electrocorticography was used in eight patients after resection to check the surrounding cortical area for residual spiking activity.

The neuropathological classification of lesions was carried out according to the classification of Palmini and colleagues.¹⁵ In the present collective, lesions were clearly characterised as FCD type II a or FCD II b (ie, FCD type II a consisting of large dysplastic neurons whereas in FCD type II b, so-called balloon cells with eccentric nuclei and opaque cytoplasm were found). In our group of specimens, FCD type I lesions characterised by cortical dyslamination, abundant microcolumnar architecture and solitary giant or immature but not dysplastic neurons, were not observed. Diagnostic procedures comprised various routine immunohistochemical reactions using antibodies against glial fibrillary acidic protein, synaptophysin, neurofilament protein, vimentin and Ki67, as described in detail elsewhere.¹⁶

Seizure outcome was classified according to the ILAE classification based on year to year and last postoperative seizure status¹⁴:

- Class 1a: completely seizure free since surgery; no auras.
- Class 1: completely seizure free, excluding early postoperative seizures.
- Class 2: only auras; no other seizures.
- Class 3: 1–3 seizure days per year; with or without auras.
- Class 4: 4 seizure days per year to 50% reduction in baseline seizure days; with or without auras.
- Class 5: <50% reduction in baseline seizure days to 100% increase in baseline seizure days; with or without auras.
- Class 6: >100% increase in baseline seizure days; with or without auras.

There were no patients with >100% increase in baseline seizure days (class 6) in this study.

Postoperative AED treatment and socioeconomic outcome (ie, regaining a driving license and employment status) were evaluated with seizure outcome. Employment status was subdivided into six classes—out of work, part time work, full time work, job training, receiving a pension and living in a social home care.

Statistical analysis

Clinical and surgical variables were analysed using commercially available statistical software. The χ^2 test, the Fisher exact test and the rank sum test were used for univariate analysis. A p value of ≤ 0.05 was accepted as indicating significance.

RESULTS

Surgery and histology

All 49 patients had resective surgery, either lobectomy (ie, standard anterior temporal lobectomy in most cases ($n = 9$)) or lesionectomy ($n = 40$), and additional MST of eloquent but non-lesional cortex with ictal activity in 14 patients. After the 31 extratemporal (frontal $n = 25$; parietal $n = 4$; occipital $n = 2$), 15 temporal and 3 multilobar resections, meningitis ($n = 2$) and a deep vein thrombosis ($n = 1$) were controlled successfully with medical treatment. A permanent mild hemiparesis occurred after infarction of the capsula interna ($n = 1$) and after evacuation of a postoperative intracerebral haemorrhage ($n = 1$). A temporary mild hemiparesis or hemihyesthesia after extratemporal surgery was seen in four patients after MST. There was no postoperative mortality.

Histological examination indicated FCD in all cases, according to the Palmini classification type II b in 41 specimens from which 36 (88%) were localised extratemporally. All eight cases with type II a FCD were temporal. In a subgroup of 20 patients in whom postoperative MRI was available, complete resection of FCD was found in 18 patients. Two patients with an unsatisfactory seizure outcome after the first resection had ictal activity within or near a residual FCD seen on MRI. An extended re-lesionectomy was required 1 and 8 years after the first surgery in these cases.

Seizure outcome

Mean follow-up was 8.1 (4.5) years, and 23 of 49 patients had a 10 year follow-up. The last available seizure outcomes were: seizure free in 37 (76%) patients, and a subgroup of 23 (47%) patients had been completely seizure free since surgery (ILAE class 1a).

The 12 patients who were not seizure free but had a reduction in seizure frequency were analysed in more detail. Three subgroups were identified. In the largest subgroup ($n = 7$), seizure outcome and ILAE class were unchanged between the first year of follow-up and the latest available outcome. In the second subgroup ($n = 4$), seizure outcome decreased to ILAE class 4 or 5 during the first 3 years of follow-up. In one patient, the ILAE class improved from class 5 to 4 after 10 years of follow-up when the antiepileptic medication was changed.

Table 1 Year to year and latest available seizure outcome (International League Against Epilepsy classification) of 49 patients who underwent epilepsy surgery for focal cortical dysplasia

	Year 1 ($n = 40$)	Year 2 ($n = 40$)	Year 3 ($n = 38$)	Year 4 ($n = 30$)	Year 5 ($n = 28$)	Year 6 ($n = 25$)	Year 7 ($n = 23$)	Year 8 ($n = 20$)	Year 9 ($n = 18$)	Year 10 ($n = 18$)	Last available outcome ($n = 49$)
Class 1	2 (5%)	2 (5%)	0	1 (3.3%)	2 (7.1%)	2 (8%)	2 (8.7%)	1 (5%)	1 (5.5%)	1 (6.3%)	5 (10%)
Class 1a	27 (68%)	26 (65%)	24 (63%)	19 (63%)	18 (64%)	14 (56%)	12 (52%)	11 (55%)	9 (50%)	8 (50%)	28 (57%)
Class 2	2 (2.5%)	4 (10%)	6 (16%)	3 (10%)	2 (7.1%)	2 (8%)	2 (8.7%)	2 (10%)	2 (11%)	2 (12.5%)	4 (8%)
Class 3	3 (7.5%)	1 (2.5%)	1 (2.6%)	1 (3.3%)	1 (3.6%)	1 (4%)	1 (4.3%)	1 (5%)	1 (5.5%)	1 (6.3%)	1 (2%)
Class 4	4 (10%)	4 (10%)	4 (10.5%)	3 (10%)	2 (7.1%)	3 (12%)	3 (13%)	2 (10%)	2 (11%)	2 (12.5%)	8 (16%)
Class 5	3 (7.5%)	3 (7.5%)	3 (7.9%)	3 (10%)	3 (10.7%)	3 (12%)	3 (13%)	3 (15%)	3 (16.7%)	2 (12.5%)	3 (6%)

International League Against Epilepsy classification¹⁴:

Class 1a: completely seizure free since surgery; no auras.

Class 1: completely seizure free, excluding early postoperative seizures.

Class 2: only auras; no other seizures.

Class 3: 1–3 seizure days per year; with or without auras.

Class 4: 4 seizure days per year to 50% reduction in baseline seizure days; with or without auras.

Class 5: <50% reduction in baseline seizure days to 100% increase in baseline seizure days; with or without auras.

Class 6: >100% increase in baseline seizure days; with or without auras (no patients in this study).

Table 2 Subgroup of nine patients with a decrease in International League Against Epilepsy classes during the 10 year follow-up

	Year 1 (n = 9)	Year 2 (n = 9)	Year 3 (n = 9)	Year 4 (n = 8)	Year 5 (n = 8)	Year 6 (n = 8)	Year 7 (n = 7)	Year 8 (n = 5)	Year 9 (n = 5)	Year 10 (n = 5)
Class 1	1 (11%)	1 (11%)	2 (22%)	1 (13%)	1 (13%)	1 (13%)	1 (14%)	1 (20%)	1 (20%)	1 (20%)
Class 1a	5 (56%)	4 (44%)		2 (25%)	2 (25%)	1 (13%)	1 (14%)	1 (20%)	1 (20%)	1 (20%)
Class 2	1 (11%)		2 (22%)							
Class 3	2 (22%)	2 (22%)	1 (11%)	1 (13%)	1 (13%)	1 (13%)	1 (14%)	1 (20%)	1 (20%)	
Class 4		1 (11%)	2 (22%)	2 (25%)	2 (25%)	3 (38%)	2 (29%)			1 (20%)
Class 5		1 (11%)	2 (22%)	2 (25%)	2 (25%)	2 (25%)	2 (29%)	2 (40%)	2 (40%)	2 (40%)

Significant deterioration was observed within the first 3 years of follow-up.

International League Against Epilepsy classification¹⁴:

Class 1a: completely seizure free since surgery; no auras.

Class 1: completely seizure free, excluding early postoperative seizures.

Class 2: only auras; no other seizures.

Class 3: 1–3 seizure days per year; with or without auras.

Class 4: 4 seizure days per year to 50% reduction in baseline seizure days; with or without auras.

Class 5: <50% reduction in baseline seizure days to 100% increase in baseline seizure days; with or without auras.

Class 6: >100% increase in baseline seizure days; with or without auras (no patients in this study).

Analysing the year to year follow-up, favourable seizure outcome (ILAE classes 1a, 1 and 2) decreased from 84% to 70% during the 10 year period. The decrease was seen mainly within the first 3 years of follow-up (table 1) which was pronounced when analysing the subgroup with deterioration in seizure outcome regardless of ILAE class (table 2).

Demographic data, localisation of resection, type of resection and histological results (FCD types II a or b) had no significant impact on the decrease in seizure outcome. Analysing the subgroup of 20 patients in whom postsurgical MRI was available, complete resection was seen in 18 patients. Thirteen patients (72%) in this subgroup were seizure free after long term follow-up (ILAE classes 1a or 1). Five patients were never seizure free (ie, n = 2 ILAE class 2, n = 1 ILAE class 3, n = 3 ILAE class 4 and n = 1 ILAE class 5).

Antiepileptic drugs and socioeconomic outcome

In most patients, AED treatment (n = 44), employment status (n = 47) and regaining a driver's license (n = 47) were evaluated against the last available seizure outcome. In 18 of 21 patients, seizure freeness was associated with stopping AED treatment for longer than 24 months. Sixteen of these patients successfully obtained their driver's license. A positive but non-significant trend in employment status (available in 47 of 49 patients) with a favourable seizure outcome was observed (table 3). Six of 11 patients (55%) with ILAE classes 3, 4 or 5 versus 21 of 36 patients (58%) with ILAE classes 1a, 1 and 2 had full time work, part time work or job training after surgery.

Table 3 Employment status after surgery according to the last available seizure outcome

Employment status	ILAE classes 1a, 1 and 2 (n (%))	ILAE classes 3, 4 and 5 (n (%))
Total	36* (100)	11* (100)
Job training	9 (25)	1 (9)
Full time work	2 (6)	2 (18)
Part time work	10 (28)	3 (27)
Out of work	6 (17)	1 (9)
Receiving a pension	4 (11)	2 (18)
Living in social home care	5 (14)	2 (18)

ILAE, International League Against Epilepsy.

*Employment status was available in 37 of 38 patients with ILAE classes 1a, 1 and 2 seizure outcome and in 10 of 11 patients with ILAE classes 3, 4 and 5 seizure outcome.

ILAE classes 1a, 1 and 2 were summarised as "favourable outcome" and ILAE classes 3, 4 and 5 as "poor outcome".

To summarise these long term follow-up data, 48% stopped AED treatment, 34% had received a driver's license and 57% had a job or training after surgery.

DISCUSSION

This is the first study to analyse the long term year to year seizure outcome, according to the ILAE classification, and socioeconomic follow-up after epilepsy surgery for FCD. As shown in other series, the resections and subpial transections were generally safe with no mortality and a low rate of permanent neurological morbidity.^{3 17}

Several studies of epilepsy surgery, which did not focus solely on malformative lesions, described a decrease in seizure free rates during long term follow-up. Extratemporal localisation and the histopathological finding of dysplastic lesions were associated with this long term worsening, which is in contrast with our study.^{18–22} Series which analysed mostly short term follow-up after resection of malformative lesions included cases with malformations other than FCD, dual pathology or low grade gliomas, and used the Engel classification, and not the new ILAE classification.^{3 5–7 17 23} There are only three studies describing long term follow-up, exclusively after FCD resection (ie, >36 months (in a subgroup),¹² 60 months¹¹ and 75 months¹⁰ compared with 97 months (= 8.1 years) in this study). In contrast with the findings of our study, Fountas *et al* described young age at surgery as an important predictor of successful long term seizure outcome in a small series of 13 patients.¹¹ A second prognostic factor was preoperative detection and complete resection of FCD, illustrated on pre- and postoperative MRI studies,^{4 5 10} which was confirmed in cases that underwent a second surgical procedure. The epileptogenic zone may extend beyond the pathological cortical area found on neuroimaging. Invasive EEG or electrocorticography can help to define the resection border in such cases. Guidance by intraoperative histopathology, as described by Cohen-Gadol,¹⁰ may be difficult in patients with dysplastic lesions.

In the subgroup with an outcome of ILAE classes 3, 4 and 5, the year to year analysis allowed us to distinguish patients with an unsatisfactory seizure outcome for the whole observational period from patients with a decrease during the first 3 years of follow-up. Comparable studies are available only after temporal lobe epilepsy surgery but with different histopathological findings. In these, worsening of seizure control within the first 6 years of follow-up was observed, and negative prognostic factors such as preoperative bilateral interictal discharges or ictal contralateral propagation were described. Preoperative detection of FCD on MRI as a predictive factor for poor long term seizure outcome has also been described.^{18 24} For such

reasons, it is difficult to compare the long term results after temporal lobe surgery with different histological findings and this study group after cortical dysplasia resection.

Whether or not incomplete lesionectomy is associated with worse seizure outcome immediately after surgery or during long term follow-up is not known. Two patients with incomplete FCD resection and five patients with complete FCD resection in this study had an outcome of ILAE class 3, 4 or 5. To date, the decrease in seizure outcome after FCD resection during long term follow-up remains unexplained. It is possible that future development of high field MRI (>3.0 Tesla) will help to better delineate malformative lesions, possibly defining subtle abnormalities close by.

As expected, good seizure outcome was associated with less AED treatment and a positive trend in employment status. Twenty-one patients (47%) had discontinued anticonvulsant medication in this study, which is comparable with the results of the Yale group in which 59% of patients after FCD resection were maintained on monotherapy or without anticonvulsant medication.¹⁰

Employment status has never been published following epilepsy surgery for FCD. Contrary to other epilepsy surgery series, being seizure free was not associated with a significant improvement in employment status or daily living activities, such as the ability to drive.²⁵⁻²⁶

In conclusion, surgical treatment of drug resistant epilepsy with focal cortical dysplasia is associated not only with successful short term seizure outcome but also with a satisfying long term outcome. Satisfactory seizure outcome is not invariably associated with a good socioeconomic outcome and an independent life. The decrease in seizure outcome observed within the first 3 years of follow-up is still unexplained and has to be analysed in larger prospective studies.

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Authors' affiliations

T Kral, M von Lehe, M Podlogar, H Clusmann, P Süßmann, J Schramm,
Department of Neurosurgery, Medical Centre, University of Bonn, Bonn, Germany

M Kurthen, Swiss Epilepsy Centre, Zürich, Switzerland

A Becker, Department of Neuropathology, Medical Centre, University of Bonn, Bonn, Germany

H Urbach, Department of Neuroradiology, Medical Centre, University of Bonn, Bonn, Germany

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