

Long-term seizure outcome after epilepsy surgery in patients with mild malformation of cortical development and focal cortical dysplasia

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Summary

Focal cortical dysplasia (FCD) and mild malformation of cortical development (mMCD) are frequent histopathologic diagnoses in patients who undergo surgery for refractory epilepsy. Literature concerning surgical outcome in patients with mMCD, as well as its contrast with FCD, has been scarce. We studied 88 patients with a histopathologic diagnosis of isolated FCD ($n = 57$) or mMCD ($n = 31$), revised according to the latest International League Against Epilepsy (ILAE) guidelines, who underwent resective or disconnective surgery. Our findings suggest differences between mMCD and FCD in clinical presentation and surgical outcome after surgery. Patients with mMCD developed seizures later in life, and their lesions had a predilection for location in the temporal lobe and remained undetected by magnetic resonance imaging (MRI) more frequently. A diagnosis of mMCD has a less favorable surgical outcome. Still, 32% of these patients reached continuous seizure freedom (Engel class 1A) at a latest median follow-up duration of 8 years, compared to 59% in FCD. A histopathologic diagnosis of mMCD, extratemporal surgery, and indication of an incomplete resection each were independent predictors of poor outcome.

KEYWORDS

FCD, mMCD, neuropathology, neurosurgery, refractory epilepsy, seizure freedom

1 | INTRODUCTION

Focal cortical dysplasia (FCD) and mild malformation of cortical development (mMCD) are frequent histopathologic diagnoses in patients who undergo epilepsy surgery.¹ The 2011 International League Against Epilepsy (ILAE) classification system differentiates FCD type I and II as lesions that are isolated from type III, which is associated with other adjacent pathology.² The most subtle architectural abnormalities

in the FCD spectrum are classified as mMCD, with intact cortical architecture and absence of aberrant cells, but with an excessive number of neurons in the molecular layer (type 1) or white matter (type 2).³

Several factors have been reported to predict postoperative seizure freedom in mMCD/FCD, of which complete resection is most consistently identified.^{4,5} In the few surgical outcome studies that also included mMCD, worse outcome was suggested for mMCD and FCD type I, compared to type II FCD.^{6,7}

TABLE 1 Clinical characteristics and seizure outcome in relationship to histologic subtype

	Total n = 88	mMCD n = 31 (35%)	FCD total 57 (65%)	FCD I 8 (9%)	FCD IIa 20 (23%)	FCD IIb 29 (33%)	Statistics mMCD vs FCD
Baseline characteristics							
Sex, female	43 (49%)	17 (55%)	26 (46%)	5 (63%)	6 (30%)	15 (52%)	<i>P</i> = 0.504
Age at epilepsy onset, median and range (y)	6 (0-38)	10 (0-38)	3 (0-26)	4.5 (0-17)	3.5 (0-22)	3 (0-26)	<i>P</i> = 0.001
Age at surgery, median and range (y)	15.8 (0.23-48.1)	21.8 (1.0- 48.1)	13.7 (0.2-45.0)	9.7 (0.55-40.3)	13.0 (0.23-44.9)	14.5 (0.74-45.0)	<i>P</i> = 0.022
Duration of epilepsy, median and range (y)	8 (0-37)	9 (1-33)	8 (0-37)	4.5 (1-23)	5 (0-37)	10 (1-36)	<i>P</i> = 0.500
Generalized tonic-clonic seizures	61/88 (69%)	19 (61%)	42 (74%)	6 (75%)	15 (75%)	21 (72%)	<i>P</i> = 0.238
Daily seizures	52/88 (59%)	13 (42%)	39 (68%)	6 (75%)	10 (50%)	23 (79%)	<i>P</i> = 0.023
Site of surgery							<i>P</i> < 0.001
Frontal surgery	41 (47%)	7 (23%)	34 (60%)	2 (25%)	12 (60%)	20 (69%)	<i>P</i> = 0.002
Temporal surgery	27 (31%)	17 (55%)	10 (18%)	3 (38%)	4 (20%)	3 (10%)	<i>P</i> = 0.001
Parietal surgery	6 (7%)	0	6 (11%)	0	2 (10%)	4 (14%)	<i>P</i> = 0.086
Occipital surgery	2 (2%)	1 (3%)	1 (2%)	0	0	1 (3%)	<i>P</i> = 1.000
Multilobar surgery	12 (14%)	6 (19%)	6 (11%)	3 (38%)	2 (10%)	1 (3.4%)	<i>P</i> = 0.331
Lateralization, left sided	39/88 (44%)	15 (48%)	24 (42%)	3 (38%)	9 (45%)	12 (41%)	<i>P</i> = 0.655
MRI-negative lesion	23/88 (26%)	14 (45%)	9 (16%)	4 (50%)	4 (20%)	1 (3.4%)	<i>P</i> = 0.005
Resective surgery (vs disconnective surgery)	76/88 (86%)	26 (84%)	50 (88%)	4 (50%)	18 (90%)	28 (97%)	<i>P</i> = 0.747
Long-term invasive monitoring	41/88 (47%)	14 (45%)	27 (47%)	1 (13%)	9 (45%)	17 (59%)	<i>P</i> = 1.000
Indication for incomplete resection (first surgery)	16/76 (18%)	4 (13%)	12 (21%)	2 (25%)	2 (10%)	8 (28%)	<i>P</i> = 0.400
Reoperations (intracranial surgery)	11/88 (12.5%)	3 (25%)	8 (14%)	2 (25%)	1 (5%)	5 (17%)	<i>P</i> = 0.740
Outcome							
Engel IA	43/87 (49%)	10 (32%)	33 (59%)	4 (50%)	10 (53%)	19 (66%)	<i>P</i> = 0.025
Engel IA AED-	31/87 (36%)	7 (23%)	24 (43%)	3 (38%)	7 (36.8%)	14 (48%)	<i>P</i> = 0.066
Follow-up duration, median and range (y)	7 (2-14)	6 (2-12)	7 (0-14)	7.5 (3-13)	7 (3-14)	5 (2-14)	<i>P</i> = 0.682

Clinical features and postoperative outcome in relation to FCD subtypes. Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous nonparametric variables.

Test values with significance at 95% confidence level are marked in bold. Engel class IA, completely seizure-free ever since surgery at last follow-up; Engel IA AED-, complete seizure and antiepileptic drug freedom at last follow-up.

Although mMCD is relatively underexposed in recent literature, it is a common diagnosis, with 2.9% of all epilepsy surgery cases, compared to 2.8% and 9% for FCD I and II, respectively.¹ We aimed to elucidate differences in clinical characteristics and seizure outcomes between mMCD and FCD subtypes, and to identify determinants of postoperative seizure freedom.

2 | METHODS

The pathologic diagnosis of all 634 patients who underwent epilepsy surgery between 2000 and 2012 in our center and had a histopathologic report compatible with FCD or mMCD (eg, MCD, microdysgenesis, dysplasia) were reviewed according to the 2011 ILAE classification.⁸ To avoid effects of associated pathology on outcome, patients with complex MCD, neurocutaneous syndromes, and FCD III subtypes were not included.

A lesionectomy—preferably en bloc—was performed for distinct lesions. Intraoperative electrocorticography (ECoG) was used on indication to tailor resection. Disconnective surgery (functional hemispherectomy or frontal or posterior disconnection) was indicated in more widespread or multilobar seizure-onset zones. Patients were included only when a tissue sample of the disconnected area was sent for pathologic investigation.

The revised diagnosis was based on the following immunohistochemical stainings: hematoxylin & eosin (H&E), neuronal nuclei, antibody neurofilament H non-phosphorylated, Vimentin, glial fibrillary acidic protein, and microtubule-associated protein 2. All samples were revised (AM and TV) and—if necessary—reclassified according to the 2011 ILAE classification system. In instances of nonconsensus, the senior pathologist (EA) was consulted.

Age at epilepsy onset and surgery, seizure duration, generalized tonic-clonic seizures (GTCS) ever to have occurred, seizure frequency (daily or less frequent), location of surgery (frontal, temporal, parietal, occipital, multilobar), magnetic resonance imaging (MRI) lesion identified (visual assessment only), and surgery type (lesionectomy, lobectomy, (sub)lobar disconnection, functional hemispherectomy) were collected from patients' files. Indication for incomplete resection was based on intraoperative assessment by the surgeon, ECoG, or on postoperative MRI (if performed). Information on postsurgical seizure and medication status was collected by telephone interview, 2-14 years following surgery.

Seizure outcome was classified as seizure freedom (completely seizure-free ever since surgery [Engel class 1a]) or not (all other Engel classes) at last follow-up. Acute postoperative seizures during the first month were not taken into consideration. In addition, seizure and medication freedom at last follow-up was noted ("Engel 1a AED-"). In case of a reoperation within 2 years, seizure outcomes were measured

after the second surgery. The tissue sample with most obvious pathologic features was considered for the definitive histopathologic diagnosis.

2.1 | Analysis

Ages at onset and surgery, and duration of epilepsy and follow-up failed tests for normality, therefore Mann-Whitney *U* was used to study differences between pathologies and test influence on outcome. Fisher exact tests were used to examine association between FCD subtype and MRI visibility, age at surgery (dichotomized at < or ≥18 years), presence of GTCS, site of lesion, indication for incomplete resection, and seizure freedom and cure. Logistic regression was used for multivariate analysis of seizure outcome. To reduce multicollinearity, several determinants were not analyzed in multivariate logistic regression and location was dichotomized into extratemporal (including multilobar) and temporal surgery. By including only the following variables, variance inflation factors are kept below 2.5 and condition index below 15: sex, MRI negative, only focal vs also GTCS, daily seizures, duration of epilepsy, lateralization, extratemporal surgery, indication for incomplete resection, and histopathologic diagnosis of mMCD vs FCD.

3 | RESULTS

Eighty-eight consecutive patients were included, of whom 11 (13%) underwent 2 intracranial surgical procedures, 7 (8%) within 2 years after first surgery. Revised histology was mMCD type 1 (n = 6), mMCD type 2 (n = 25), FCD type Ia (n = 3), FCD Ib (n = 4), FCD Ic (n = 1), FCD IIa (n = 20), and FCD IIb (n = 29).

Clinical characteristics of pathology categories are listed in Table 1. Seizure onset was significantly later in mMCD (median 10 years) compared to FCD (median 3 years). Age at surgery was older in mMCD (median 21.8 years) than in FCD (median 13.7 years).

FCD was more often localized in the frontal lobes (60%) compared to mMCD (23%), although FCD type I subtypes (25%) had a distribution similar to that of mMCD. mMCD was more frequently located in the temporal lobe (55%) compared to FCD (18%).

A significantly larger portion of mMCD (45%) lesions was not detected on MRI compared to FCD (16%; see Figure 1 for example of MRI lesion in mMCD).

3.1 | Seizure outcome

Outcome data were missing for one patient. For the remaining 87, follow-up ranged from 2-14 years (median 7 years). Follow-up duration was similar between histologic subtypes.

Forty-three patients (49%) reached continuous complete seizure freedom at last follow-up, and 31 (36%) were also free of antiepileptic medication (Table S1).

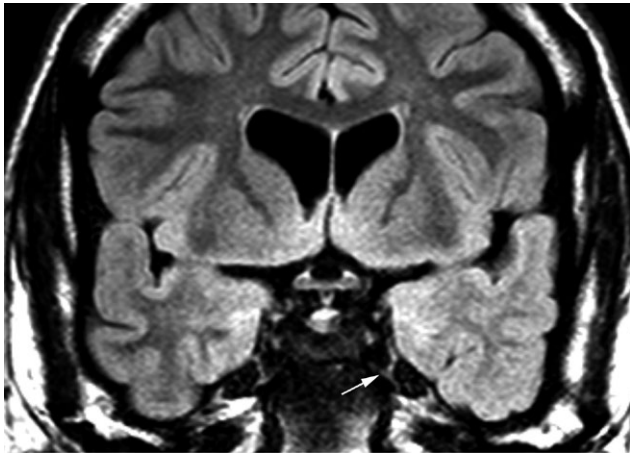


FIGURE 1 The patient was diagnosed with mMCD type 2, onset at age 16 years, with complex partial seizures and secondarily generalized tonic-clonic seizures. Coronal 3T MRI fluid-attenuated inversion recovery (FLAIR) images revealed blurring of the gray-white matter interface in the left temporal lobe. No indication for hippocampal sclerosis. Patient underwent anterior temporal lobe resection at age 19 years. Engel class 1C (some disabling seizures after surgery, but free of seizures for last two years) at 10 years of follow-up. Recurrence at 7 years, and again achieving seizure freedom with medication since. mMCD, mild malformation of cortical development

Seizure freedom was significantly more common after surgery for FCD (59%) than for mMCD (32%). Patients with mMCD tended to be less likely free of seizures and medication (23%) compared to FCD (43%). Results of logistic regression analysis are displayed in Table 2. Indication of incomplete surgery and mMCD diagnosis (vs FCD) both univariately negatively predicted continuous seizure freedom at last follow-up. In multivariate logistic regression analyses, both mMCD and incomplete resection remained significant predictors, as did extratemporal resection. In multivariate analysis only the presence of daily seizures predicted seizure and medication freedom at last follow-up. Older age at surgery and presence of daily seizures were negative predictors in univariate analysis.

4 | DISCUSSION

For 31 of 88 (35%) of all patients with isolated malformations of cortical development—those with complex and neurocutaneous disorders excluded—mMCD was a common diagnosis, whereas FCD type I was relatively rare with only 9%. FCD II was found in more than half of the patients (FCD type IIb 33%, type IIA 23%). In a recent multicenter study including 1612 patients with mMCD and FCD, FCD II was equally frequent (53%) but mMCD was not more common than FCD I (both 17%).¹ However, 13% of patients with MCD had lesions

TABLE 2 Determinants of favorable seizure outcome

	Engel 1A	95% CI	Engel IAAED-	95% CI
Univariate odds ratio of determinant for favorable outcome				
Age at surgery (y)	NS	NS	0.96*	0.92-1.00
Daily seizures	NS	NS	3.43*	1.27-9.24
Indication for incomplete resection (only resective surgery)	0.18*	0.04-0.92	NS	NS
mMCD (vs FCD)	0.33*	0.13-0.84	0.39 [†]	0.14-1.05
Multivariate odds ratio of determinant for favorable outcome				
Daily seizures	NS	NS	4.06*	1.13-14.60
Extratemporal surgery	0.20*	0.05-0.88	NS	NS
Indication for incomplete resection	0.20*	0.04-0.99	NS	NS
mMCD (vs FCD)	0.12**	0.03-0.44	0.35 [†]	0.11-1.14

* $P \leq 0.05$, ** $P \leq 0.05$, [†] trend, $P \leq 0.1$, NS: not significant, $P > 0.1$

Test values with significance at 95% confidence level are marked in bold. Engel class 1A, completely seizure-free ever since surgery at last follow-up; Engel 1A AED-, complete seizure and antiepileptic drug freedom at last follow-up.

Univariate logistic regression, odds ratios, and 95% confidence intervals. Determinants with $P > 0.1$ omitted from table: female sex, age at epilepsy onset (y), duration of epilepsy (y), generalized tonic-clonic seizures, right-sided, extratemporal, frontal, temporal, parietal, occipital, multilobar surgery, MRI-negative lesion, disconnective surgery, and follow-up duration. Multivariate logistic regression: entry of determinants for seizure outcome with constraints by multicollinearity. Determinants without significant relation with any outcome measure are omitted from table: sex, epilepsy duration, MRI-negative lesion, and bilateral seizures.

reported as “FCD not otherwise specified.” Moreover, difference in FCD subtyping was thought to have arisen due to the lack of an international classification system before the ILAE consensus of 2011. Recent consecutive cohort studies including adult patients, in which tissue was (re)classified according to ILAE histopathologic classification, did not include mMCD diagnoses, and the ratio between FCD I and FCD II varied from 26%/74% to 44%/56%.^{5,9,10} In our cohort the proportion of FCD I was relatively low. There are several explanations for these differences in presented histology. Observer variability possibly remains despite efforts to harmonize histopathologic classification, and with current definitions especially the milder pathologies can be debatable. Not having mMCD formally included in the ILAE classification system might compel classification of very subtle dysplastic lesions as FCD I, when mMCD would be more suitable. Discrepancy in utilization of immunohistochemical methods may also play a role in variability in subclassification. Although ILAE type II FCD is an established entity, there is still debate concerning the definitive identifying histologic and contrasting clinical features of mMCD vs FCD I.¹¹

Our findings suggest that clinical characteristics help differentiate patients with mMCD from those with other FCD subtypes. They had onset of epilepsy later in life and consequently underwent operation at an older age, the majority (61%) even at adult age, whereas only 32% of patients with FCD underwent operation during adulthood. Epilepsy duration did not differ significantly between histologic subtypes.

Younger age at onset and surgery in patients with FCD II compared to FCD I has been reported previously.⁹ Patients with mMCD were less likely to have highly frequent (daily) seizures.

As reported in previous studies,^{9,12,13} we observed a predilection of FCD II types for the frontal lobe, whereas mMCD and FCD I were most often localized in the temporal lobes. In cases of multilobar lesions, mMCD and FCD I were most often diagnosed.

In our series, epilepsy surgery resulted in a continuing seizure freedom rate of 49% at a median follow-up of 7 years; 36% had also discontinued antiepileptic medication. Patients with mMCD were less likely to reach seizure freedom. Patients with FCD IIb diagnoses had a distinctively higher chance of favorable outcome. A number of studies did not show significant differences in seizure outcome between different histologic subtypes.^{5,9,10,14} It must be noted that no, or very few, mMCD cases were included in these studies. In addition, pathology was not a predictor of outcome in a study that did include 29 mMCD cases.⁷ In a study by Kim et al, more patients with FCD (85/145, 59%) were seizure-free at last follow-up compared to mMCD (9/21, 43%).⁶ Others studies, not including mMCD, showed a less favorable

outcome in patients with FCD I histology.^{15,16} The inferior outcome after surgery in mMCD is likely due to difficulties in determining location and margins on imaging and during surgery, complicating accurate identification and complete removal of the epileptogenic zone. Although we did not see indication for incomplete resection more often in patients with mMCD, residual lesions are most likely the best explanation for the difference in seizure outcome, albeit these might not be suspected based on intraoperative observations by the surgeon, ECoG, or post-surgical imaging. Complete resection of the lesion is the most reported predictor of favorable outcome, along with factors that facilitate this: temporal focus, severe pathologic features, and a MRI-defined lesion.⁴ Accordingly, in our multivariate analyses, mMCD, extratemporal surgery, and indication for incomplete resection were predictors of unfavorable seizure outcome. We could not reproduce a relation between absence of an MRI lesion and surgical outcome, also not when analyzing individual histological subgroups. Patients with highly frequent, daily seizures were more likely to discontinue medication after complete seizure freedom. An explanation might be that in these patients the positive effect on daily life after successful surgery is more outspoken and is an encouragement for earlier discontinuation of medication.

5 | CONCLUSION

Our results suggest that mMCD has a differentiating clinical presentation, which may be relevant in predicting seizure outcome after epilepsy surgery. Patients with mMCD develop seizures later in life, compared to FCD ILAE type I and II. mMCD has a predilection for temporal lobes and remains undetected by MRI more frequently. A diagnosis of mMCD has a less favorable surgical outcome. Nonetheless, one-third of these patients are expected to reach complete and ongoing seizure freedom, thus making the consideration of surgical treatment worthwhile.

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DISCLOSURE

None of the authors have any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ETHICAL STATEMENT

The study was approved by the institutional ethical committee and Biobank.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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