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Cognitive functioning after epilepsy surgery in children with mild malformation of cortical development and focal cortical dysplasia

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ABSTRACT

Mild malformation of cortical development (mMCD) and focal cortical dysplasia (FCD) subtypes combined are by far the most common histological diagnoses in children who undergo surgery as treatment for refractory epilepsy. In patients with refractory epilepsy, a substantial burden of disease is due to cognitive impairment. We studied intelligence quotient (IQ) or developmental quotient (DQ) values and their change after epilepsy surgery in a consecutive series of 42 children (median age at surgery: 4.5, range: 0–17.0 years) with refractory epilepsy due to mMCD/FCD. Cognitive impairment, defined as IQ/DQ below 70, was present in 51% prior to surgery. Cognitive impairment was associated with earlier onset of epilepsy, longer epilepsy duration, and FCD type I histology. Clinically relevant improvement of ≥10 IQ/DQ points was found in 24% of children and was related to the presence of presurgical epileptic encephalopathy (EE). At time of postsurgical cognitive testing, 59% of children were completely seizure-free (Engel 1A). We found no association between cognitive outcome and seizure or medication status at two years of follow-up. Epilepsy surgery in children with mMCD or FCD not only is likely to result in complete and continuous seizure freedom, but also improves cognitive function in many.

1. Introduction

Focal cortical dysplasia (FCD) subtypes, including mild malformation of cortical development (mMCD), are by far the most common histological diagnoses in children who undergo epilepsy surgery [1]. In FCD, focal cortical abnormalities are characterized by aberrant organization of cortical layers (type I), in which also abnormal neurons can occur (type II) [2]. The most subtle focal architectural abnormalities in the malformation of cortical development spectrum are classified as mMCD, with intact cortical architecture and absence of aberrant cells, but with excessive number of neurons in the molecular layer (type 1) or white matter (type 2) [3].

An important comorbidity in children and adults with refractory epilepsy is developmental delay. The underlying pathology, epileptic activity, and use of antiepileptic medication all contribute to cognitive disturbances [4]. In children with refractory epilepsy due to FCD, 53–68% have cognitive impairment (intelligence quotient (IQ) < 70) [5,6]. In children with so-called epileptic encephalopathy (EE), in which the epileptic activity further decreases the child's cognitive developmental abilities, early treatment is warranted to improve cognitive outcome [7].

Most studies reported overall cognitive improvement following epilepsy surgery [8–11]. In children with severe epilepsy who undergo surgery at young age and who often had preoperative developmental arrest or regression, clinically relevant increases in IQ scores of e.g., 7–10 or more points are often not achieved, although the child's cognitive age clearly starts to increase after surgery [7,12].

In general, postoperative cognitive outcome has been shown to correlate with seizure freedom [6,11,13–15], parental education [16], antiepileptic drug (AED) policies [15,17], preoperative seizure frequency [5], and with etiology [17,18]. Importantly, earlier onset [5,9,19–26] and longer duration [5,27] of epilepsy predict more severe cognitive impairment. Significant differences in cognitive outcome between patients with different FCD subtypes have not yet been reported [5,28].

The aim of this study was to assess pre- and postoperative cognitive functioning in children with mMCD/FCD and to identify its predictors. In

Abbreviations: AEDs, antiepileptic drugs; DQ, developmental quotient; EE, epileptic encephalopathy; FCD, focal cortical dysplasia; IQ, intelligence quotient; mMCD, mild malformation of cortical development.

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particular, we wanted to quantify the level of cognitive functioning – expressed as full-scale IQ scores – in these children, both before and after epilepsy surgery. Furthermore, we aimed to assess whether or not the following clinical factors determined a change in IQ scores after surgery: histopathological diagnosis, age at onset and at surgery, duration of epilepsy, preoperative high seizure frequency and EE, surgery type, and postoperative seizure and AED status.

2. Methods

All children were included who underwent epilepsy surgery between 2000 and 2012 at the University Medical Center Utrecht, had a histopathological diagnosis of an isolated FCD or mMCD, and underwent neuropsychological testing.

We reviewed the surgical database for all patients with a reported histological diagnosis that could be compatible with FCD (e.g., malformation of cortical development, microdysgenesis, dysplasia) and revised the histology according to the most recent International League Against Epilepsy (ILAE) classification [2]. Patients with dysplastic lesions in the context of other epileptogenic pathologies (FCD III types e.g., with mesiotemporal sclerosis or tumors) and those with complex or multifocal malformations of cortical development (e.g., polymicrogyria, hemimegalencephaly, tuberous sclerosis complex) were excluded.

Children were neuropsychologically assessed shortly before, one or two years after surgery. A range of tests was used, according to the age and cognitive level of the children, to determine their (full-scale) IQ. Most frequently used was the Wechsler Intelligence Scale for Children-III (WISC-III) (pre/post n = 17), other tests were Wechsler Intelligence Scale for Children Revised (WISC-R) (pre/post n = 5), Wechsler Adult Intelligence Scale (WAIS) (pre/post n = 3/4), Snijders-Oomen nonverbal intelligence tests (SON) (pre/post n = 3), Bayley Scales of Infant and Toddler Development – II (BSID-II) (pre/post n = 6/8), Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) (pre/post n = 3/2), and Kaufman Adolescent and Adult Intelligence Test (KAIT) (pre/post n = 1).

For children who scored below the lower end of the norms' range, or for whom the age-appropriate tests were too difficult to perform, a developmental quotient (DQ) was calculated, using the ratio mental age / calendar age × 100.

Change in IQ/DQ was defined as postsurgical (one or two years after surgery) minus presurgical IQ/DQ. An IQ or DQ change of 10 points was considered clinically meaningful. Ten IQ points is two-thirds of a standard deviation and three times the standard error of the most used test in this cohort, the WISC-III, and an IQ change of 10 is considered unlikely to be the result of retesting or related to errors inherent to the performed test. Ratio DQ is known to be less stable than normed IQ. For the main analysis, children with IQ and DQ scores were pooled. Separate analyses were performed for patients in whom normed IQ scores were obtained, to address possible influence of incorporating DQ in the analyses. Determinants for IQ/DQ change were additionally studied excluding patients with hemispheric surgery, to rule out this subgroup determines possible associations in the total cohort.

We categorized results of neuropsychological testing as normal (IQ > 85), mild delay (IQ 70–85), moderate delay (IQ 55–70), and severe delay (IQ < 55). In the latter group with severe delay, there were many children in whom norm IQ scores could not be determined. Children with IQ/DQ < 70 are considered to have cognitive impairment.

The following clinical information was collected from the electronic patient file: presence of an magnetic resonance imaging (MRI) lesion compatible with FCD or mMCD, presence of bilateral EE in the period prior to surgery, occurrence of generalized tonic–clonic seizures, seizure frequency, age at onset of epilepsy, location of seizure focus, location of surgery (multilobar, frontal, temporal, parietal, occipital), age at surgery, type of surgery (hemispheric versus focal), postsurgical seizure freedom (defined as Engel Ia; completely seizure-free since surgery), and the use of AEDs at latest follow-up and at time of latest neuropsychological assessment. We additionally used the dichotomized seizure outcome "Worthwhile seizure reduction" or not, corresponding with Engel classes 1–3, and defined as more than 50% reduction in seizure frequency.

Information on postsurgical seizure and medication status was completed by means of telephone interview, the time of which was noted as latest follow-up.

Acute postoperative seizures during the first month were not taken into consideration when classifying seizure outcome.

2.1. Statistical analysis

Statistical analysis was performed in SPSS Statistics version 25. For testing for normality, we used Shapiro–Wilk test, and histogram and Q-Q plot. Total intelligence quotient (TIQ) was normally distributed, and T-test (including Levene's test for testing equal variances) was used to compare groups, or analysis of variance (ANOVA) for the three pathology groups, with Bonferroni correction for post-hoc tests. Change in IQ/DQ, age at surgery, epilepsy onset, and duration had nonnormal distribution for which we used appropriate nonparametric tests, either Kruskal–Wallis or Mann–Whitney U. Fisher's exact test was used to analyze association between baseline characteristics, cognitive functioning categories and meaningful IQ/DQ change (≥7 points), and histology. Kendall Tau-C was used for the association between cognitive functioning categories and meaningful IQ/DQ change and presence of daily seizures, EE, type of surgery (focal versus hemispheric), seizure or AED freedom in order to account for ordinal ties. Pearson's R or Spearman's rank was used for the analysis of correlation. For comparing IQ/DQ before and after surgery-related samples, paired T-test was used, and for categories of cognitive functioning, Wilcoxon signed rank test.

3. Results

Between 2000 and 2012, 88 patients underwent epilepsy surgery and had a diagnosis of isolated FCD or mMCD according to the ILAE guidelines. Fifty-two were under the age of 18 years at time of surgery. The 42 who underwent cognitive testing at any time, either before surgery, after surgery, or both, were included. Of these, the revised pathological diagnosis was mMCD in 10, FCD I in 6, and FCD II in 26 children. For 30 patients, normed IQ scores could be calculated with age-appropriate tests both before and after surgery. In five children, only DQ scores could be determined pre- and postsurgery. One child had a normed IQ score pre- and DQ postsurgery. Three patients had no neuropsychological examination prior to surgery and one not after surgery. Two patients had presurgical IQ/DQ scores <55 that could not be further quantified, of which one with a postsurgical IQ and one with a DQ score.

Therefore, in 36 patients, IQ/DQ scores could be compared between pre- and postsurgery tests. In a total of 38 children, categories of functioning could be determined both before and after surgery.

The latest cognitive test was performed two years after surgery in 35 patients and at one year in 6 patients.

In three patients, re-resection was performed within one year and thus before having done their first postoperative neuropsychological evaluation. For these patients, postoperative seizure outcome and cognitive function was reported after the second surgery. Baseline functioning was tested prior to first surgery in all cases.

3.1. Clinical characteristics

Clinical characteristics of patients are presented in Table 1. Median age at onset and surgery were 2.3 and 10.0 years respectively, with no statistical difference between histological diagnoses. Children with FCD I and mMCD were more likely to undergo hemispheric surgery ($p = 0.004$) and presented more often with EE ($p = 0.005$).

Prior to surgery, 20/39 (51%) of all tested children had IQ/DQ values <70, with a mean score of 66 (distribution of IQ/DQ scores displayed in Table 2).

Table 1
Baseline characteristics.

	Total n = 42	mMCD 10 (24%)	FCD total 32 (76%)	FCD I 6 (14%)	FCD II 26 (62%)	p mMCD vs FCD I vs FCD II
Sex, male	24 (57%)	4 (40%)	20 (63%)	3 (50%)	17 (65%)	0.370
Age at epilepsy onset, median and range (years)	2.3 (0–12.0)	5.9 (0.0–10.0)	2 (0.0–12.0)	1.5 (0.0–8.0)	2.0 (0.0–12.0)	0.424
Age at surgery, median and range (years)	10.0 (0.2–18.5)	11.9 (1.0–16.3)	9.6 (0.2–18.5)	4.3 (0.6–15.8)	10.0 (0.2–18.5)	0.445
Duration of epilepsy, median and range (years)	4.5 (0–17.0)	4 (1–15)	5.5 (0–17)	2.5 (1–10)	6 (0–17)	0.239
Generalized seizures (ever)	30 (71%)	4 (60%)	24 (75%)	5 (83%)	19 (73%)	0.620
Generalized seizures (last year)	29 (69%)	5 (50%)	24 (75%)	5 (83%)	19 (73%)	0.387
Daily seizures	31 (74%)	7 (70%)	24 (75%)	5 (83%)	19 (73%)	1.000
Presence of epileptic encephalopathy presurgery	10 (24%)	4 (50%)	5 (24%)	3 (50%)	2 (8%)	**0.005**
Type of surgery						
Hemispheric	8 (19%)	2 (20%)	6 (19%)	4 (67%)	2 (8%)	**0.004**
Focal	32 (76%)	8 (80%)	28 (88%)	2 (33%)	26 (100%)	
Frontal	21 (62%)	3 (38%)	18 (56%)	1 (50%)	17 (71%)	0.074
Temporal	7 (21%)	3 (38%)	4 (13%)	1 (50%)	3 (13%)	
Parietal	4 (12%)	0	4 (13%)	0	4 (17%)	
Occipital	2 (6%)	2 (25%)	2 (6%)	0	2 (6%)	
Lateralization, left-sided	20 (48%)	6 (60%)	14 (44%)	2 (33%)	12 (46%)	0.681
MRI-negative lesion	6 (14%)	2 (20%)	4 (13%)	2 (33%)	2 (8%)	0.101
Reoperations (intracranial surgery)	7 (17%)	2 (20%)	5 (16%)	2 (33%)	3 (12%)	0.290
Engel 1A, year of latest cog test	24/41 (59%)	4 (40%)	20 (65%)	5 (83%)	15 (60%)	0.263
Engel 1A drug-free, year of latest cog test	16/41 (39%)	1 (10%)	15 (48%)	4 (67%)	11 (44%)	0.055
Engel 1–3 (worthwhile seizure reduction)	35/41 (85%)	9 (90%)	26 (84%)	6 (100%)	20 (80%)	0.566

p-Values in bold are significant at <0.05 level.

At time of the latest postoperative cognitive assessment, 24 (59%) were seizure-free, and 16 (39%) were also already free of medication. Thirty-five (85%) children achieved at least worthwhile seizure reduction (Engel 1–3). There was a trend towards less patients with mMCD diagnoses to be seizure- and medication-free at time of latest postsurgical cognitive testing ($p = 0.055$).

3.2. Determinants of presurgical cognitive functioning

All studied determinants of presurgical cognitive functioning are shown in Table 3a.

There were significant differences in presurgical IQ between the three pathology groups ($p = 0.004$). Patients with FCD I had significantly lower DQ/IQ (post-hoc testing FCD I versus mMCD: $p = 0.030$, versus FCD II: $p = 0.003$). The difference between FCD II and mMCD was not significant, and there was no statistical difference when only analyzing the children with normed IQ scores. There was no significant correlation between pathology groups and categories of cognitive functioning ($p = 0.097$), although it is striking that all children with FCD I had cognitive impairment. Higher presurgical cognitive functioning was strongly related to older age at epilepsy onset ($p = 0.001$). Patients with severe cognitive delay were operated earlier in life, but age at surgery was similar for the other categories of cognitive ability. Therefore, in the total group, age at surgery and IQ/DQ score were positively correlated ($p = 0.021$) while there was no association when excluding those with DQ scores, since 6 of 7 (86%) of them had severe delay. In patients with normed IQ scores, lower presurgical IQ was related to a longer duration of epilepsy ($p = 0.022$). Almost all patients with DQ scores had severe delay, and these children had shorter epilepsy duration, although differences in epilepsy duration between the four categories of presurgical cognitive functioning did not reach significance ($p = 0.112$).

Patients with daily seizures tended to be more often in the lowest categories of cognitive functioning ($p = 0.057$), and there was a trend for lower IQ/DQ in these children ($p = 0.052$).

In patients with a clinical presentation compatible with EE, there was an overrepresentation of patients with severe cognitive delay ($p = 0.017$), and IQ/DQ was lower but not significantly so ($p = 0.079$). Intelligence quotient/DQ was significantly lower in patients who were to undergo hemispheric surgery ($p = 0.031$).

Table 2
Cognitive functioning pre- and postsurgery.

	Before surgery	After surgery	p
Categories cognitive functioning			
Severe delay	8 (22%)	8 (22%)	0.248
Moderate delay	10 (22%)	11 (31%)	
Mild delay	14 (39%)	8 (22%)	
Normal	4 (11%)	9 (25%)	
Mean IQ/DQ (std, range)	66 (±18; 17–96)	70 (±20; 31–103)	**0.010**
Mean IQ, only formal IQ scores (std, range)	71 (±13; 46–96)	75 (±17; 49–103)	**0.029**

Numbers in this table are based on the 36 patients in whom both pre- and postsurgical cognition had been assessed. For 30 of these patients, normed IQ scores were available both pre- and postoperatively. Std: standard deviation. p-Values in bold are significant at <0.05 level.

3.3. Change in cognitive functioning after surgery

After surgery, the proportion of children in each of the four cognitive functioning categories did not significantly change, although relatively more had normal IQ after surgery (Table 2). When pooling IQ and DQ scores for all patients with both discrete pre- and postoperative values available ($n = 36$), mean quotients significantly increased from 66 to 70 ($p = 0.010$). Considering only the children in whom normed IQ scores could be determined ($n = 30$), mean IQ increased from 71 to 75 ($p = 0.029$).

Whether or not there was a clinically relevant IQ change could be determined in 37 children. Nine of these (24%) showed an improvement of ≥10 points, 2 (5%) deteriorated ≥10 points, and 26 (70%) had postsurgical scores within 10 IQ points of their presurgical scores.

3.4. Determinants of postsurgical cognitive functioning

All studied possible determinants of postsurgical cognitive functioning are shown in Table 3b.

Postsurgical IQ/DQ was strongly correlated with presurgical IQ/DQ. No significant correlation was seen between histological subtype and postoperative cognition. The relation between postsurgical cognitive functioning and duration of epilepsy and age at onset and surgery was similar to that found before surgery; younger ages at onset and at surgery were correlated with lower IQ ($p < 0.0005$ and 0.003 respectively). Patients with severe cognitive delay were operated far earlier ($p = 0.009$). Again, after exclusion of the children with only DQ available, there was no association between age at surgery and IQ. Lower postsurgical cognitive scores tended to correlate with longer epilepsy duration ($p = 0.068$).

Table 3a
Determinants of presurgical cognitive functioning.

	Category of cognitive functioning (n = 39)				p	IQ/DQ, all (n = 37)	p	IQ, only formal scores (n = 32)	p
	Severe delay 10 (26%)	Moderate delay 10 (26%)	Mild delay 14 (36%)	Normal 5 (13%)		Mean IQ (std)/correlation coefficient		Mean IQ (std)/correlation coefficient	
Pathology									
mMCD	3 (30%)	3 (30%)	2 (20%)	2 (20%)	0.097	69 (15)	**0.004**	71 (15)	0.823
FCD I	3 (50%)	3 (50%)	0	0		45 (24)		66 (2)	
FCD II	4 (4%)	4 (30%)	12 (52%)	3 (13%)		72 (15)		72 (15)	
Age at onset, median (range)	0.0 (0–7)	2 (0–8)	3 (0–12)	10 (6–12)	**0.001**	**Rs = 0.636**	**<0.0005**	**Rs = 0.562**	**0.001**
Age at surgery, median (range)	4.9 (0.6–14.5)	12.0 (4.3–18.5)	11.3 (1.8–17.7)	12.6 (10.1–14.6)	0.094	**Rs = 0.378**	**0.021**	Rs = 0.159	0.402
Duration of epilepsy median (range)	3.5 (1–14)	7 (2–17)	5.5 (2–14)	3 (1–5)	0.112	Rs = −0.051	0.763	**Rs = −0.403**	**0.022**
Daily seizures									
Yes	10 (36%)	7 (25%)	7 (25%)	4 (14%)	0.057	64 (20)	0.052	69 (15)	0.362
No	0	3 (27%)	7 (64%)	1 (9.1%)		74 (11)		74 (11)	
Epileptic encephalopathy									
Yes	6 (67%)	1 (11%)	1 (11%)	1 (11%)	**0.017**	49 (27)	0.079	73 (17)	0.799
No	4 (13%)	9 (30%)	13 (43%)	4 (13%)		71 (14)		71 (14)	
Type of surgery									
Focal	5 (16%)	8 (26%)	13 (42%)	5 (16%)	**0.008**	71 (15)	**0.031**	71 (15)	0.710
Hemispheric	5 (62%)	2 (25%)	1 (13%)	0		47 (23)		68 (4)	

Determinants of presurgical cognitive functioning. Thirty-two patients with normed IQ scores, 5 with DQ. In two patients, no further determination of IQ/DQ was possible other than <55. No presurgical testing in three children. Rs = Spearman correlation coefficient. Std: standard deviation. p-Values in bold are significant at <0.05 level.

Patients who suffered from EE, and those who underwent hemispheric surgery, were more often in the lowest categories of postsurgical cognitive functioning (p = 0.037 and p = 0.002). Intelligence quotient/DQ was also significantly lower in these patients (p = 0.015 and < 0.0005), but not when excluding patients with only DQ.

Table 3b
Determinants of postsurgical cognitive functioning.

	Category of cognitive functioning (n = 41)				p	IQ, all (n = 41)	p	IQ, only formal scores (n = 32)	p
	Severe delay 11 (27%)	Moderate delay 12 (29%)	Mild delay 8 (20%)	Normal 10 (24%)		Mean IQ (std)/correlation coefficient		mean IQ (std)/correlation coefficient	
Presurgical cog functioning						**r = 0.869**	**<0.0005**	r = 0.801	<0.0005
Severe delay	8 (80%)	2 (20%)	0	0	**<0.0005**				
Moderate delay	1 (10%)	8 (80%)	0	1 (10%)					
Mild delay	0	2 (14%)	8 (57%)	4 (29%)					
Normal	0	0	0	4 (100%)					
Pathology									
mMCD	3 (30%)	4 (40%)	0	3 (30%)	0.199	65 (27)	0.209	74 (19)	0.969
FCD I	3 (50%)	2 (33%)	0	1 (17%)		56 (28)		76 (24)	
FCD II	5 (20%)	6 (24%)	8 (32%)	6 (24%)		72 (17)		75 (15)	
Age at onset, median (range)	0 (0–6)	2 (0–9)	2.5 (0–5)	7 (2–12)	**<0.0005**	**Rs = 0.616**	**<0.0005**	**Rs = 0.457**	**0.009**
Age at surgery, median (range)	1.6 (0.2–14.5)	11.5 (4.3–18.5)	9.6 (1.8–15.7)	12.8 (5.4–17.7)	**0.009**	**Rs = 0.457**	**0.003**	Rs = 0.051	0.783
Duration of epilepsy median (range)	2 (0–14)	5.5 (2–17)	6.5 (2–14)	4.5 (1–10)	0.123	Rs = 0.165	0.304	Rs = −0.327	0.068
Daily seizures									
Yes	11 (36%)	9 (29%)	4 (13%)	7 (23%)	0.052	65 (22)	0.087	74 (17)	0.695
No	0	3 (30%)	4 (40%)	3 (30%)		78 (14)		78 (14)	
Epileptic encephalopathy									
Yes	6 (60%)	2 (20%)	0	2 (20%)	**0.037**	54 (28)	**0.015**	81 (19)	0.449
No	5 (16%)	10 (32%)	8 (26%)	8 (26%)		73 (17)		74 (16)	
Type of surgery									
Focal	4 (13%)	10 (32%)	8 (26%)	9 (29%)	**0.002**	75 (17)	**<0.0005**	76 (17)	0.656
Hemispheric	7 (70%)	2 (20%)	0	1 (10%)		47 (21)		71 (17)	
Seizure freedom									
Yes	7 (29%)	5 (21%)	5 (21%)	7 (29%)	0.646	71 (22)	0.377	78 (16)	0.261
No	4 (24%)	7 (41%)	3 (18%)	3 (18%)		65 (21)		71 (15)	
Freedom of AEDs									
Yes	5 (31%)	5 (31%)	4 (25%)	2 (13%)	0.342	63 (18)	0.265	71 (13)	0.262
No	6 (24%)	7 (28%)	4 (16%)	8 (32%)		71 (23)		77 (18)	
Worthwhile seizure reduction									
Yes	10 (29%)	10 (29%)	6 (17%)	9 (26%)	0.776	69 (21)	0.563	75 (17)	0.783
No	1 (17%)	2 (33%)	2 (33%)	1 (17%)		63 (27)		73 (14)	

Determinants of postsurgical cognitive functioning. Thirty-two children with normed IQ scores and 9 with DQ. One child did not undergo postsurgical cognitive testing. Rs = Spearman correlation coefficient. p-Values in bold are significant at <0.05 level.

There was no relation between cognitive functioning and freedom of seizures or of AEDs.

3.5. Determinants of change in cognitive functioning

Studied determinants of change in cognitive functioning are shown in Table 3c.

There was no relation between change in cognitive scores and presurgical cognition, epilepsy duration, nor with age at onset or surgery.

Five of eight (63%) patients with EE in whom IQ change could be assessed showed an improvement of ≥10 points, compared with only 4 of 29 (14%) patients without EE ($p = 0.017$). Change in IQ was significantly higher in patients with EE ($p = 0.049$). Children with FCD II diagnoses were more likely to have stable IQ/DQ after surgery and less likely to have an increase of 10 points or more, in comparison with children with mMCD and FCD I diagnoses ($p = 0.024$).

Change in IQ, and the proportion of patients with a clinically relevant change in IQ, were not different between patients who achieved seizure freedom and those with recurrent seizures, neither did AED discontinuation influence change in IQ.

Analyses were repeated with exclusion of patients who underwent hemispheric surgery; in this subgroup, 6 (20%) had clinically relevant TIQ improvement, 24 (80%) had stable scores, and no patients deteriorated. In this subgroup of patients, however, there was no significant correlation any more between presurgical EE and IQ/DQ change ($p = 0.177$) or between an increase of 10 or more IQ points and presurgical EE ($p = 0.094$). In this subgroup of patients who did not undergo hemispheric surgery, those with IQ improvement of ≥10 points had experienced later age at onset compared with patients with stable IQ ($p = 0.005$). The results of this subanalysis are shown in Supplement Table 1.

4. Discussion

In our study of cognitive functioning in 42 children who underwent surgery for refractory epilepsy due to mMCD or FCD, 51% had cognitive impairment prior to surgery. Cognitive functioning was poorer in patients with onset at younger age. Patients with severe cognitive impairment were often operated at very young age and consequently had the shortest epilepsy duration. In patients with IQ/DQ above 55, shorter epilepsy duration was related to better presurgical cognitive functioning. Focal cortical dysplasia I was infrequently diagnosed, but these patients all had cognitive impairment, and mean IQ/DQ was significantly lower than that in mMCD and FCD II.

We found an overall modest but statistically significant improvement of 4 mean IQ/DQ points, within 1 to 2 years after surgery. Relevant improvement of ≥10 IQ/DQ points was seen in 24% following surgery while cognitive functioning was stable in 70% and deteriorated in 5%. Only a diagnosis of EE predicted cognitive improvement after surgery. Postsurgical cognitive functioning was strongly related to presurgical functioning and had similar associations with clinical characteristics as presurgical functioning. There was no association between postoperative cognitive scores and seizure or medication status.

Other mMCD/FCD studies have found a similar prevalence of cognitive impairment [5,6]. Seizure activity and consequent network disturbances, the underlying pathology, and use of AEDs are all likely to contribute to cognitive impairment.

In a rat model for FCD, in which developmental abnormalities were caused by injection of methyloaxymethanol acetate and consequently frequent seizures were induced in one group, researchers found no relation between cognition in adolescence and history of early-life seizures and concluded that the cortical malformations were the substrate for cognitive impairment. However, these mice with cortical malformations had significantly lower brain weights compared with a

Table 3c
Determinants of change in cognitive functioning.

	Relevant IQ change (≥10 IQ points) (n = 37)			p	ΔIQ (n = 35)	p
	Deterioration n = 2 (5%)	Stable n = 26 (70%)	Improvement n = 9 (24%)		Median (range)/correlation coefficient	
Pathology						
mMCD	1 (11%)	5 (56%)	3 (33%)	**0.024**	1 (−12 – +18)	0.326
FCD I	1 (17%)	2 (33%)	3 (50%)		11 (−11 – +39)	
FCD II	0 (0%)	19 (86%)	3 (14%)		3 (−9 – +16)	
Presurgical cog functioning						
Severe delay	1 (11%)	5 (56%)	3 (33%)	0.451	6.5 (−12 – +14)	0.715
Moderate delay	1 (10%)	8 (80%)	1 (10%)		1 (−11 – +39)	
Mild delay	0	11 (79%)	3 (21%)		2.5 (−9 – +18)	
Normal	0	2 (50%)	2 (50%)		9 (−2 – +14)	
Presurgical IQ/DQ, mean (range)	61 (54–68)	66 (23–96)	65 (17–90)	0.908	Rs = −0.046	0.789
Age at onset, median (range)	4 (0–8)	2 (0–12)	6 (0–12)	0.116	Rs = 0.018	0.919
Age at surgery, median (range)	7.7 (1.0–14.3)	10.0 (1.8–18.5)	12.6 (0.6–17.7)	0.794	Rs = −0.006	0.973
Duration of epilepsy median (range)	3.5 (1–6)	6 (2–17)	4 (1–10)	0.165	Rs = −0.121	0.480
Daily seizures						
Yes	2 (7%)	18 (67%)	7 (26%)	1.000	4 (−12 – +16)	0.876
No	0	8 (80%)	2 (20%)		2.5 (−9 – +39)	
Epileptic encephalopathy						
Yes	1 (13%)	2 (25%)	5 (63%)	**0.017**	13 (−12 – +18)	**0.049**
No	1 (3%)	24 (83%)	4 (14%)		2 (−11 – +39)	
Type of surgery						
Focal	0	24 (80%)	6 (20%)	1.000	3 (−9 – +39)	0.611
Hemispheric	2 (29%)	2 (29%)	3 (43%)		8 (−12 – +18)	
Seizure freedom						
Yes	2 (9%)	14 (61%)	7 (30%)	0.573	7 (−12 – +39)	0.626
No	0	12 (86%)	2 (14%)		2 (−9 – +14)	
Freedom of AEDs						
Yes	2 (13%)	11 (73%)	2 (13%)	0.103	−2 (−12 – +16)	0.125
No	0	15 (68%)	7 (32%)		5 (−9 – +39)	
Worthwhile seizure reduction						
Yes	2 (6%)	21 (66%)	9 (28%)	0.528	4 (−12 – +39)	0.723
No	0	5 (100%)	0		1 (−2 – +8)	

Rs = Spearman correlation coefficient. p-Values in bold are significant at <0.05 level.

control group that received saline injections in utero, suggesting that methyloaxymethanol acetate injection causes more widespread abnormalities than those seen in human patients with FCD [29].

Despite the circumscript nature of dysplastic lesions in most patients with FCD or mMCD, widespread network disruption can be observed, even when their seizures remain focal. There is evidence of loss of optimal, small-world, network configuration and abnormal diffusivity and decreased anisotropy in white matter distant from, and even contralateral to, the lesion [30–33]. This results in cognitive deficits not directly associated with the location of a lesion. Following remission of epilepsy, both normalization of functional network organization and recovery of white matter bundle fractional anisotropy may be seen [30]. Also, AED drug load is associated with disturbed network parameters [32]. Drugs may have a generalized suppressive effect with alteration of neuronal excitability [32,34]. Consequently, many common AEDs are associated with cognitive problems. After diagnosis of epilepsy, there is more often a cognitive decline in patients with higher AED levels [35]. In addition, in a randomized blinded placebo-controlled trial in patients who are seizure-free, cognitive function improved if AED treatment was discontinued [36]. Likewise, a retrospective study in children who underwent epilepsy surgery showed improved postsurgical IQ and higher IQ change with reduction of AEDs [17].

In agreement with previous studies, we found a relation between poorer cognition and younger age at onset [5,9,19–26]. Presurgical impaired cognition was associated with longer duration of epilepsy, but only when excluding children with only DQ, of whom 6/7 (86%) had expedited surgical intervention due to catastrophic epilepsy syndromes. Kimura et al. found a similar relation between cognition and epilepsy duration when children were stratified by age at onset, but not when analyzing the complete cohort [5]. This is in agreement with another study that included only children that were operated before the age of three years [27].

With impairment of brain function due to seizure activity, longer exposure to epileptic activity would reasonably increase the gap in cognitive function with healthy developing peers.

A critical period in cognitive development during the first years of life has been suggested, which lays the foundation for subsequent development of higher-order skills [24]. Disruption during sensitive periods could result in more pronounced cognitive deficits later in life [37].

On the other hand, both lower IQ and an earlier epilepsy onset could be the consequence of a more severe underlying epileptogenic pathology, rather than being causally related [25].

Patients with severe cognitive delay were operated at younger age, but when excluding patients with only DQ – of whom 6/7 (86%) had severe delay – we did not observe a relation between age at surgery and pre- or postsurgical cognitive ability. In a cohort consisting only of patients undergoing hemispherectomies, worse cognition was related to surgery at younger age and shorter epilepsy duration [38].

Presurgical cognition was lower in patients with FCD I compared with those with mMCD or FCD II. A possible explanation is that FCD I lesions are typically more widespread – with more frequent hemispheric surgery in our cohort – and these patients presented more often with EE. The latter could also explain why differences in cognition between histological subtypes were not significant after surgery; we observed greater improvement in cognition in patients with previous encephalopathy and more children with clinically relevant IQ improvement among those with mMCD and FCD I histological subtypes compared with those with FCD II. Previous studies did not find a relation between cognition and histological subtype [5,28], however, these groups used the 2002 Palmini histological classification scheme, what can lead to discrepancies in classification, especially in more subtle abnormalities.

A large share of patients in our cohort showed improvement in cognitive level after surgery. Studies showed full-scale IQ to have high stability and reliability with test–retest coefficients exceeding 0.9. Large studies, including around 600 children evaluated WISC-III (the most used test in our cohort) for special education eligibility, found full-scale IQ to decrease −0.4 in a mean interval just under three years [39,40]. The average 4-point improvement in full-scale IQ on a group level we found is not likely due to retest effects, or retesting at older age since tests have been proven highly stable and are normed according to age. Although presurgical cognition has consistently been shown to be the strongest predictor of postsurgical functioning, as confirmed in our study, it does not necessarily relate to the change in IQ after surgery. For this outcome measure, the presence of presurgical EE was the only predictive factor in our study. This finding is in agreement with the concept of EE, in which epileptic activity by itself affects cognition more than what can be explained by the underlying pathology alone [41].

We did not observe an association between postoperative cognitive outcome and seizure status, although several studies have reported cognitive improvement to be dependent of seizure freedom [13–15], with more pronounced improvement after discontinuation of medication as well [15]. These studies had a follow-up of a minimum of 4 years up to 21 years after surgery. Although we observed overall improvement in cognition, it is likely that a longer follow-up period of more than two years is required to acknowledge the true effect of seizure freedom and medication policies on cognitive development following epilepsy surgery.

Our study has a number of limitations, besides those inherent to retrospective collection of clinical data and limited follow-up duration for cognition. Our moderate sample size precludes multivariate analyses and correction for possible interactions.

Environmental factors were not accounted for in this study. In a cohort of operated children with epilepsy of diverse etiology, there was more improvement in cognition in children of parents with higher education, but only in those who became seizure-free. Although this association was significant, the effect was small. In the same study, there was no relation between parental education and presurgical IQ [16]. A large twin study in a healthy British population showed the effect of genetics on intelligence to be similar among low and high socioeconomic status families [42].

Despite its limitations, the current study has enabled the assessment of clinically relevant determinants of cognitive outcome in a relatively homogeneous cohort of children with mMCD/FCD histopathological diagnoses revised following the most recent ILAE guidelines [2].

5. Conclusion

In children with mMCD and FCD, preoperative cognitive functioning is poorer when epilepsy onset is at younger age and duration of epilepsy is longer. Children with severe cognitive delay typically present with catastrophic epilepsy that warrants an aggressive therapeutic strategy and surgical intervention at very young age.

Surgical therapy in children with refractory epilepsy due to mMCD or FCD not only is likely to result in complete and continuous seizure freedom, but also improves cognitive function in a substantial proportion of children, independent of histological subtype.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.03.009.

Ethical statement

The study was approved by the institutional ethical committee and Biobank. 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. None of the authors has any conflict of interest to disclose.

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