Mild malformation of cortical development; clinical feature and surgical outcome related to histopathology

Hye Eun Kwon

Department of Medicine

The Graduate School, Yonsei University

Mild malformation of cortical development; clinical feature and surgical outcome related to histopathology

Directed by Professor Heung Dong Kim

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Hye Eun Kwon is approved.

Thesis Supervisor : Heung Dong Kim

Thesis Committee Member#1 : Se Hoon Kim

Thesis Committee Member#2 : Kyu Won Shim

The Graduate School
Yonsei University

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ABSTRACT

Mild malformation of cortical development; clinical feature and surgical outcome related to histopathology

Hye Eun Kwon

Department of Medicine

The Graduate School, Yonsei University

(Directed by Professor Heung Dong Kim)

Mild malformation of cortical development (mMCD), which classified by the Palmini et al. could not have mature clinical impact until now. This study aimed to show the clinical feature and surgical outcome associated with pathological finding, mMCD. Thirty-six of children and adolescents who underwent resective epilepsy surgery with confirmed mMCD by pathological finding were reviewed. All the patients were medically intractable to 2 or more antiepileptic drugs (AEDs) and/or ketogenic diet and were followed up for more than 2 years after surgery. Central nervous system comorbidities (such as prematurity, asphyxia, bleeding, hydrocephalus, early CNS infection and traumatic brain injury) were seen in 9 cases (25.0%). Twenty six cases (72.2%) presented as childhood onset epileptic encephalopathy, further divided by 20 Lennox-Gastaut syndrome and 6 West syndrome, while 10 cases (27.8%) presented as focal epilepsy (8 cases; extratemporal lesion, 2 cases; temporal lesion). For the age of seizure onset, 18 cases (50.0%) had started seizure before the age of 1 year, and 22 cases (61.1%) had seizures before the age of 2 year. Seventeen cases (47.2%) had non focal MRI abnormalities. The most frequent surgical procedure was 22 cases (61.1%) of multilobar

resections, followed by 102 cases (27.8%) of unilobar resection, and 4 cases (11.1%) of posterior quadrantectomy along with frontal lobectomy. The median postoperative followed-up duration was 4.8 years and final surgical outcome including reoperations, 22 cases (61.1%) had Engel I outcome. Six (27.3%) out of 22 Engel I cases were off all the AEDs. This study identified mMCD as an important pathologic finding related to comparable degree of epileptogenicity and supported the certainty of focal pathology of mMCD, could be successfully treated by resective surgery.

Key words: mild malformation of cortical development, pediatric epilepsy surgery

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I. INTRODUCTION

Recent classification of focal cortical dysplasia (FCD) by International League Against Epilepsy (ILAE) has introduced in 2011, [1] and there are changes from the classification by Palmini and colleagues. [2,3] One of the important changes is whether mild malformation of cortical development (mMCD), which is characterized by normal cortical architecture and abundant ectopically placed neurons in or adjacent layer 1 or in the white matters, is a subgroup as itself or not. They stated that mMCD should be included in the new ILAE FCD classification, although their clinical impact will need further clarification. There are few reports about the clinical feature and surgical outcome of mMCD and most reports are composed of smaller than 10 cases (Table 1). [4-6]

Collectively these reports provide information only for 51 epilepsy surgery cases with mMCD, too early for discussing clinical and surgical outcome related to this pathological finding. Kasper mentioned about that the clinical feature and surgical outcome of mMCD

would be different in terms of whether temporal location or not. [7] Krsek and colleagues showed mMCD had a comparable degree of epileptogenicity, and they showed surgery outcome on extra temporal cases, but it was the only study that analyzed mMCD outside the temporal lobe. [5] Not only, there was discrepancy between the interobserver and intraobserver for the pathological result of mMCD [8] but also neurons were physiologically present in cerebral white matter, which is particularly pronounced within temporal lobe. [9]

Over the last decade, this study observed seizure free outcome in mMCD pediatric surgical cases, and the goal of this study was to analyze our a lot of experience with mMCD cases in order to contribute to the clinical feature and surgical outcome of mMCD.

Table 1. Summary of previous publications on surgical treatment of patients with mMCD

Study	mMCD/all cases (%)	Years	Most frequent procedure	Engel class I + II (%)
Fauser et al.	8/67 (11.9)	1998-2003	Temporal resection	63+25=88
Krsek et al.	36 /200 (18.0)	1986-2006	Lobar resection	52+6=58
Mühlebner et al.	7 /50 (14.0)	2000-2013	Lesionectomy	71+15=86

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II. MATERIALS AND METHODS

1. Patients

We identified 36 patients pathologically confirmed as mMCD at Severance Children's Hospital from September 2003 and to April 2013. All the patients were medically intractable to 2 or more antiepileptic drugs (AEDs) and/or ketogenic diet and were followed up for more than 2 years after surgery.

2. Clinical characteristics and diagnostic work-up

Clinical features such as seizure onset age, age at surgery, epilepsy duration, AEDs prior to surgery, clinical spectrum of epilepsy and baseline developmental function were reviewed. Pre-operative cognitive function were tested using a neuropsychological scale by a psychologist or global development assessment by care takers. Developmental function was measured using age-appropriated standardized instruments, such as Korean-Wechsler intelligence scales for children (K-WISC) and Korean-Wechsler adults intelligence scales (K-WAIS) or the Bayley scales for infant development. Mental retardation (MR) was defined as a measured or estimated FSIQ <70.

Presurgical evaluations always included long-term video EEG monitoring, MRI and FDG-PET. Selected cases also underwent additional diagnostic tests including fMRI, diffusion tensor imaging and fiber tractography (DTI-FT) and interictal/ictal SPECT, according to feasibility; evaluation of these results was not included in this study.

3. Seizure outcomes

Seizure outcomes were annually assessed from outpatient visit and were classified

according to both Engel's classification scheme [10] and ILAE epilepsy surgery outcome evaluation. [11]

4. Neuropathological analysis

Brain tissue was analyzed at the department of pathology. Pathologist classified mMCD by Palmini et al with careful reevaluation. [2,3]

5. Statistical analysis

Kaplan-Meier survival analysis was used to calculate the probability of seizure freedom. Statistical analyses were done using SPSS version 18.0.

III. RESULTS

1. Demographic data and clinical profile

Demographic data and clinical profile are summarized in Table 2. All cases were children or adolescents. Twenty six cases (72.2%) presented as childhood onset epileptic encephalopathy (EE), further divided by 20 Lennox-Gastaut syndrome (LGS) and 6 West syndrome, while 10 cases (27.8%) presented as focal epilepsy (8 cases; extratemporal lesion, 2 cases; temporal lesion). Among the 20 LGS cases, 16 evolved from West syndrome and only 4 cases started with LGS. 77.8% of patients were suffered from daily seizure.

Central nervous system comorbidities (such as prematurity, asphyxia, bleeding, hydrocephalus, early CNS infection and traumatic brain injury) were seen in 9 cases (25.0%). MR before surgery was observed in 32 cases (88.9%). The median of seizure onset age was 1.0 year, 18 cases (50.0%) had started seizure before the age of 1 year, and 22 cases (61.1%) had seizures before the age of 2 year. The median of epilepsy duration was 5.0 years and patients had median number of 3 AEDs, 2 to 4 AEDs trials before surgery. Ketogenic diet was tried in 22 cases (61.1%).

Table 2. Demographic data and clinical profile

Characteristic		N (%)
Gender	Male/Female	19 (52.8)/17 (47.2)
Under 18 years		36 (100.0)
Clinical spectrum of epilepsy	Epileptic encephalopathy	26 (72.2)
	LGS/ West syndrome	20 (55.6)/6 (16.7)
	Focal epilepsy	10 (27.8)
	Extra-temporal/temporal lesion	8 (22.2)/2 (5.6)
Seizure frequency	Patients with daily seizures	28 (77.8)
CNS comorbidity		9 (25.0)
MR before surgery		32 (88.9)
History of ketogenic diet		22 (61.1)
	Median (interquartile range)	
Age at seizure onset, y	1.0 (0.4-5.8)	
Age at surgery, y	7.4 (3.6-12.5)	
Epilepsy duration, y	5.0 (1.4-7.1)	
Follow up duration, y	4.8 (3.4-7.5)	
No. of AEDs	3.0 (2.0-4.0)	

Abbreviations: LGS=Lennox-Gastaut syndrome; CNS=central nervous system; MR= mental retardation; AEDs=antiepileptic drugs

2. MRI findings

MRI features of the mMCD are summarized in Table 3. Sixteen cases (44.4%) had normal MRI scans. MRI abnormalities for cortical malformations were identified in 19 cases (52.8%) and diffuse brain atrophy was observed in 1 case (2.8%). Blurring of the gray/white matter junction was the most frequent feature, occurring in 12 cases (33.3%). White matter signal abnormality in FLAIR or T2 weighted was encountered in 11 cases (30.6 %) [increased signal change in 9 subjects (25.0%), decreased signal change in 2 (5.6%))], whereas gray matter signal change in FLAIR or T2 weighted was observed in 6 cases (16.7%). Lobar hypoplasia/atrophy was observed in 1 patient (2.8%).

Table 3. MRI findings

Characteristic	N (%)
Normal MRI	16 (44.4)
Other MRI abnormality (Diffuse brain atrophy)	1 (2.8)
MRI feature for cortical malformations	19 (52.8)
Individual MRI feature of mMCD	
Blurring of the gray/white matter junction	12 (33.3)
White matter signal abnormality in FLAIR or T2 weighted	11 (30.6)
Increased /decreased signal change	9 (25.0) /2 (5.6)
Gray matter increased signal abnormality in FLAIR or T2 weighted	6 (16.7)
Lobar hypoplasia/atrophy	1 (2.8)

Abbreviations: mMCD=mild malformation of cortical development

3. EEG findings

Long-term video EEG monitoring findings were presented in Table 4. There was no case who had a normal interictal EEG result. Slow background activity was seen in 29 cases (80.6%), and focal/lateralized asymmetric slowing was observed in 27 cases (75.0%). EEG findings, characterized by secondary generalized epileptic encephalopathy, such as hypsarrhythmia, generalized slow spike-wave complexes, and generalized paroxysmal fast activities, and electrodecrements were seen in 26 cases (72.2 %). Secondary bilateral synchrony was seen in 4 cases (11.1%). Focal or unilateral excitable EEG findings, such as spindle shaped fast activities, localized paroxysmal fast activities, brief ictal rhythmic discharges, focal subclinical seizure activities and repetitive rhythmic spike and wave discharges were seen in 23 cases (63.9%). We classified as EEG asymmetry in long term video EEG result, when it was included focal slowing, focal or unilateral excitable EEG findings, lateralized spike or sharp waves, or localized spike or sharp waves. Thirty one cases (86.1%) showed EEG asymmetry. And EEG asymmetric lesions were always concordant to surgical resection site.

Table 4. EEG findings

EEG characteristics	N (%)
Normal interictal EEG	0
Slow background	29 (80.6)
Focal or lateralized slowing	27 (75.0)
Secondary bilateral synchrony	4 (11.1)
GSSW, GPFA, electrodecrements /Hypsarrhythmia	20 (55.6) /6 (16.2)
Focal or unilateral excitable EEG findings [a]	23 (63.9)
EEG asymmetry	31 (86.1)

[a] Such as spindle shaped fast activities, localized paroxysmal fast activities, brief ictal rhythmic discharges, focal subclinical seizure activities and repetitive rhythmic spike and wave discharges were seen

Abbreviations: GSSW =generalized slow spike and wave discharges; GPFA=generalized paroxysmal fast activities

4. PET findings

All patients underwent FDG-PET scan. In 10 cases, we identified no signs of focal hypo- or hypermetabolism, whereas 2 cases showed diffuse hypometabolic area. FDG-PET and MRI abnormalities overlapped in the remaining cases; The relationship between FDG-PET and MRI abnormalities is specified in Table 5. There were 11 cases (30.6%) in whom the lesion was not detected in the MRI but in the PET, further divided by 6 cases were localized in same resection area and 5 cases were lateralized in same hemisphere.

Table 5. PET findings

PET findings	N (%)
No abnormality	10 (27.8)
Localized	17 (47.2)
Lateralized	7 (19.4)
Multifocal	2 (5.6)
MRI positive, PET negative	4 (11.1)
PET positive, MRI negative	11 (30.6)
MRI and PET negative	6 (16.7)

5. Surgical procedures

Surgical procedures are presented in Table 6. In terms of surgical procedures, 22 cases (61.1%) underwent multilobar resections (exceeding 1 lobar boundary), followed by 10 cases (27.8%) of unilobar resection, and 4 cases (11.1%) of posterior quadrantectomy along with frontal lobectomy.

As complications, 12 cases (33.3%) had morbidity and there was no mortality. Complications were included subdural hematoma (4 cases), weakness (3 cases), and wound infection (2 cases) and an impairment of visual field, venous infarction, and hydrocephalus in each 1 case.

Table 6. Surgical procedures in mMCD patients

Characteristic		N (%)
Median age at (first) surgery, y		7.4
Callostomy before resective surgery		6 (16.7)
Surgical procedure	Unilobar resection	10 (27.8)
	Multilobar resection	22 (61.1)
	Frontal resection+ PQ	4 (11.1)
Number of reoperation patients		5 (13.9)
mMCD location	Left /right	16/20 (44.1/55.6)
	Frontal (F)	8 (22.2)
	Temporal (T)	2 (5.6)
	Parietal (P)	0
	Occipital (O)	0
	Multilobar	26 (72.2)
	FT/FP/ FTP/FTO	15/1/1/1
	TO/TPO	1/2
	FTPO (subtotal hemispherectomy)	5

Abbreviations: mMCD=mild malformation of cortical development; PQ=posterior quadrantectomy

6. Seizure outcome

The median postoperative followed-up duration was 4.8 years interquarter-ranged from 3.4 years to 7.5 years. As final surgical outcome including reoperations, 22 cases (61.1%) were Engel I, 1 case (2.8%) were categorized as Engel II, 2 cases (5.6%) as Engel III and 11 cases (30.6%) as Engel IV. At last follow up, 27.3% (6/22) of Engel I were off all AEDs. Seizure outcome by ILAE was also determined. [8] Overall, 63.9 % (n=23) of cases are classified in either Engel I or II (free from or rare disabling seizures) and comparably, we classified 61.1% (n=22) as ILAE 1-3 (only auras or 1-3 seizure days per year). Thus, these showed similar pattern of surgical outcomes.

A Kaplan-Meier survival plot showed that seizure free rates after surgery dropped within 2 years, which reflected early recurrence of seizures, as shown in Figure 1. 10 patients were initially seizure free after the operation, but had recurred seizures during the follow up. In depth analysis of 11 surgery procedures (1 patient had re-operations), 4 procedures (36.4%) had seizure recurrence within a year, followed by 3 procedures (27.3%) between 1 to 2 years, and 4 (36.4%) remote recurrence 2 years after the surgery.

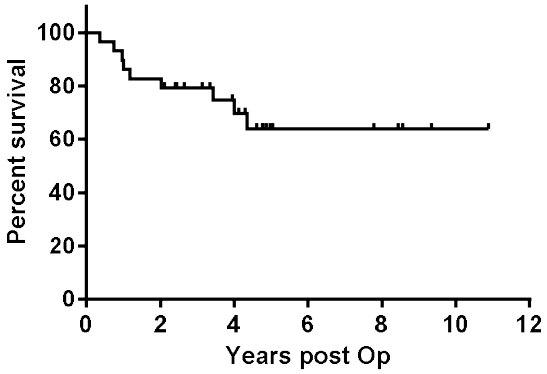

Figure 1. Kaplan-Meier curve showing long term postoperative outcome

7. Analysis of the "Surgical failure"

10 cases who did not become seizure free received additional examinations which always included prolonged EEG recording for minimum of 4 hours and MRI; 70.0% (7/10) had postoperative seizure onset arose from the operated hemisphere. The other 30.0% (3/10) cases showed uncertain seizure onset area because of lack of ictal seizure capture. Therefore, incomplete resection was the most likely explanation for continuing seizures in mMCD cases.

8. Reoperation

Reoperation was performed in 5 cases, which always included more extended resection adjacent to the previous operative lesion. The clinical characteristics and surgery outcome were shown in Table 7. They showed no focal abnormality in preoperative MRI finding, except 1 case. The surgery outcome of first operation was as follows; 3 cases were Engel IV, and other 2 cases were Engel I at first but recurred seizure later on. After the reoperation, 2 cases (40.0%) obtained seizure free outcome and among the other 3 cases, 2 cases were remained seizure free for 1 year, but recurred seizure during the AEDs reduction.

Table 7. Characteristics and surgery outcome of re-operated cases

Cases	Age at $1^{st}/2^{nd}$ surgery	Epilepsy syndrome	Pre-op MRI	Location of $1^{st}/2^{nd}$ surgery	Engel class
1	3.5/4.4	LGS	Diffuse brain atrophy	F/F-P	IV
2	4.5/5.4	FE	Abnormality	F/Insula	I-> IV
3	5.4/6.6	FE	No abnormality	F/F-PQ	I ->IV
4	13.3/16.2	LGS	No abnormality	T/T-P	I
5	15.4/22.1	FE	No abnormality	F/F-T	I

Abbreviations: op=operation; LGS=Lennox-Gastaut syndrome; FE=Focal epilepsy; F=frontal; P=parietal; PQ=posterior quadrantectomy; T=temporal

9. Patients who had performed corpus callostomy prior to resective surgery

Six cases (16.7%) had palliative surgical procedure, corpus callosotomy (CC) before resective surgery due to lack of focality in presurgical evaluations. Following CC, phase 1 presurgical evaluation was performed repeatedly in all 6 cases. All these patients were suffered from EE. Changes of post callosotomy presurgical evaluation results were observed. Lateralized EEG findings were observed in 4 cases, PET along with EEG findings or cerebral blood flows along with EEG findings in each 1 case were obtained. These findings were helpful in delineating the primary seizure focus in 4 LGS and 2 West syndrome cases. The clinical characteristics and surgical outcome in these patients were shown in Table 8.

Table 8. Characteristics and surgery outcome of corpus callosotomy cases

Cases	Age at cc/rec. surgery	Epilepsy syndrome	Pre-op MRI	Changes after CC finding	Engel class
1	2.3/2.9	WS	Suspicious	EEG	I
2	3.4/3.6	WS->LGS	Suspicious	EEG	I
3	4.5/4.9	LGS	Suspicious	EEG, PET	I
4	4.7/5.0	LGS	Negative	EEG	IV
5	7.5/8.9	LGS	Negative	EEG, Interictal SPECT	I
6	9.1/12.1	LGS	Suspicious	EEG	I

Abbreviations: cc=corpus callosotomy; rec.=resective; op=operation; WS=West syndrome ; LGS=Lennox-Gastaut syndrome

IV. DISCUSSION

This study is the first of composed of the largest number of patients focusing on the clinical features and surgical outcome of mMCD. Especially for pediatric intractable epilepsy, pediatric epilepsy surgery has had an attention and performed more frequently in the last decade. However, there was still limited number of surgical cases with childhood onset EE with negative MRI lesion. Because in infants and young children, localized brain lesion could produce generalized EEG abnormalities and generalized seizures which are specific childhood onset EE, such as West syndrome and LGS. [12,13] Although, this study could conduct the clinical feature of high proportion of childhood onset EE without definite MRI lesion associated with mMCD. As a result, mMCD was accounting for 33% of pathologically diagnosed as FCD at our center.

For the clinical implication, early report questioned about the certainty of mMCD with negative MRI finding. [7] Fauser and colleagues reported that the clinical severity was milder than other form of pathology such as FCD type II, and they showed success rate of 63% of seizure freedom. [6] As their cases were located in temporal lobe, the clinical severity and surgical outcome might be biased by the high rate of temporal resection. However, we believe our pediatric mMCD cases are clinically different from the reported cases of temporal locations of Fauser et al.

This study showed mMCD presented as early onset of seizure, 72.2% of childhood onset EE, wider distribution of pathology presented as surgical extent and high rate of MR before surgery. That is, even mildly dysplastic features in pathology, mMCD is highly epileptogenic. And, these features are very distinct from adult focal epilepsy as noted by circumscribed and well located FCD pathology. Krsek and colleagues who only identified

mMCD as an important pathological finding related to comparable degree of epileptogenicity and showed 52% of seizure free outcome in pediatrics resective epilepsy surgery. [5] Similarly, our result showed slightly better outcome as 61.1% of seizure freedom. Thus, these result supported the certainty of pathology of mMCD, also surgery outcome supported that mMCD as a focal pathology.

For the treatment strategy, the median epilepsy duration was 5.0 years and 61.1% of patients tried ketogenic diet before surgery. It can be infer that surgical plan might be not an early option but a last resort in this patient group. As less opportunity of surgery, mMCD was uncovered as both at pathological level and clinical profiles. This study also revealed that even patients who had EE with negative MRI finding successfully gained 66.7% (8/12) of Engel I outcome. In these cases, the plan for surgery is based on cortical abnormality detected by focal EEG findings revealed by long term video EEG result and FDG-PET, neurological exam and other presurgical evaluations. With regarding secondary generalized EE, where most epileptiform discharges are generalized, long term video EEG result showed prominent localization or lateralized abnormalities, side appropriated for surgery in this surgery. Among the 26 EE cases, there were 12 cases had negative MRI findings in this study. And these cases were helped surgery plan by EEG asymmetry (10 cases), or FDG-PET (8 cases). In addition, this study described 6 cases who had a prior callosotomy, then had become candidate for respective surgery. High rate of Engel I outcome (83.3%) was observed in these patients .This finding showed that callosotomy was helpful to identify for epileptic foci.[14,15] Thus, challenging but highly problematic patients, who had lack of evidence of focal lesion at a glance, but after careful presurgical evaluation or callosotomy, they could become candidate for resective surgery.

For the MRI finding, there was only one report of MRI features of mMCD. [5] In agreement with previous report, blurring of the gray-white matter junction was the most common abnormality and as high as 47.2% of negative MRI finding. [5] And other typical cortical abnormalities of FCD was also observed in mMCD, but known features of FCD type II such as increased cortical thickness, abnormal gyral/sulcal patterns, and transmantle sign are features were never observed. [5] Thus, demarcation of mMCD was far more difficult comparing than previously reported MRI feature of FCD type II.

This study observed that the CNS comorbidities could be associated with mMCD. Krsek and colleagues mentioned the pathogenic relationship between mild form of cortical malformation with acquired brain lesion. [5,16,17] They explained that mMCD with known prenatal and perinatal brain injury exhibited a higher frequency of abnormal neurologic findings, low IQ scores, higher incidence of slow EEG background activity, which could be explained by the presence of wide spread cortical and subcortical brain injury. [17] In addition, Marin-Padilla stated that early onset insult caused a phenomenon recently described as “progressive cortical dysplasia”. [18] Although, we excluded mMCD with definite destructive brain lesion in MRI scan, this study showed similar proportions of CNS comorbidity. Thus, it will be able to show stronger evidence for the association with the CNS comorbidity and mMCD, when including definite destructive brain in MRI findings.

Long term postoperative outcome analyzed that 63.6 % of seizure relapse occurred during the first and second year. This result shows that it is also important to follow–up patients, since seizure may recur up to 4.3 years after the surgery. In a depth analysis of postoperative investigations by long term EEG result, all cases who became not seizure

free had seizures still arose from the same hemisphere. Regarding the reoperation outcome, 4 of 5 cases regained Engel I outcome for a year, but 2 of them showed recurrence of seizure during the AEDs reduction. Thus, surgical failures in our series were caused, therefore, rather by incomplete resection of dysplastic cortex than by epileptogenic area located in the opposite hemisphere, the other studies supported as well.[19,20]

V. CONCLUSION

This study identified mMCD as an important pathologic finding related to comparable degree of epileptogenicity and supported the certainty of focal pathology of mMCD, could be successfully treated by resective surgery.

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Abstract (In Korean)

Mild malformation of cortical development 의 임상 양상 및 수술 성적 고찰

<지도교수 김흥동>

연세대학교 대학원 의학과

권혜은

Mild malformation of cortical development (mMCD) 의 임상 양상에 대한 조사는 희박하여 본 연구는 mMCD 의 임상 양상 및 뇌전증 수술 성적을 조사하였다. 세브란스 어린이 병원에서 수술 후 병리소견에서 mMCD 로 진단된 37명의 환자를 대상으로 하였다. 환자들은 수술 전 2가지 이상의 항경련제 또는 케톤생성 식이요법에도 불구하고 발작이 충분이 조절되지 않았고 수술 후 최소 2년 이상의 평가 기간을 가졌다. 과거력에서 미숙아, 뇌출혈, 수두증, 중추 신경계 감염 및 외상성 뇌손상의 빈도는 9명에서 확인되었다. 73.0%의 환자는 레녹스 가스토 증후군(21명) 및 웨스트 증후군 (6명)의 간질성 뇌병증 양상으로 분류되었고 나머지 27.0%는 부분 뇌전증으로 8명의 외측두엽 뇌전증과 2명의 측두엽 뇌전증으로 구분되었다. 전체 환자의 48.6%에서 발작이 1세 이전, 59.5%에서 2세 이전에 발작이 시작하였고 45.9%는 뇌 자기공명영상에서 이상 소견이 확인되지 않았다. 수술 방법은 다엽 절제술이 22명 (45.9%) 으로 가장 많았다. 수술 후 평균 4.9년 추적 관찰을 통해 23명(62.2%)의 환자는 발작이 조절되었으며 이들 중 7명의

환자는 항 경련제를 중단할 수 있었다. 이러한 결과로 미루어 mMCD 는 뇌전증을 유발할 수 있는 질병으로서 수술적 방법을 통해 성공적으로 치료 될 수 있다.

핵심이 되는 말: mild malformation of cortical development, 소아 뇌전증 수술