BMC Medicine

RESEARCH

Open Access

The response to anti-seizure medications and the development of pharmacoresistant epilepsy in malformations of cortical development

Pu Miao[1,2], Meiping Ying[1,3], Ruotong Chen[1], Yuyu Yang[1], Yao Ding[1], Junming Zhu[1], Jianhua Feng[2], Jin Wang[4], Thandar Aung[5], Shuang Wang[1*] and Bo Jin[4*]

Abstract

Background Malformations of cortical development (MCD) are a group of congenital brain malformation disorders commonly associated with pharmacoresistant epilepsy (PRE). While studies often focus on surgery outcomes, the pharmacological treatment is still imperative and the odyssey to PRE remains underexplored. We aim to investigate the influence of anti-seizure medications (ASMs) on the development of PRE in this specific patient population.

Methods We retrospectively included a cohort of epilepsy patients with MRI-confirmed MCD due to abnormal cell proliferation and apoptosis (group I, mainly FCD II), and abnormal neuronal migration (group II, mainly heterotopia, lissencephaly, and polymicrogyria) from March 2013 to June 2023. The clinical features of group I and group II were compared. Factors associated with PRE were analyzed. The time to development of PRE with different ASMs was assessed using Kaplan–Meier survival analysis.

Results Of 259 enrolled patients with epilepsy and MRI-confirmed MCD (group I, $n=121$; group II, $n=138$), 73.4% met the criteria for PRE. The median duration of follow-up from seizure onset to the last visit or surgery was 103 months (IQR 45–174), with group I showing a significantly higher PRE rate than group II (90.1% vs. 58.7%, $p=0.000$). Binomial regression analysis identified the significant predictors of PRE in MCD patients: high pretreatment seizure frequency (OR = 2.506), group II patients (OR = 0.248), and failure of the first ASM (OR = 5.885). Sodium channel blockers (SCBs) were the most prescribed initial ASMs and demonstrated a higher response rate than other ASMs. Kaplan–Meier analysis revealed that using SCBs as the first ASM significantly prolongs the time to PRE, with a median of 72 months for SCB users versus 48 months for non-SCB users.

Conclusions Our findings indicate a high prevalence of PRE that varies among different subtypes of MCD. Early appropriate selection of ASMs, particularly SCBs, can significantly delay the time to PRE onset, offering a promising strategy for managing this complex patient population. Tailoring pharmacological approaches is crucial for optimizing outcomes, and further research is warranted to optimize treatment strategies.

*Correspondence:
Shuang Wang
wangs77@zju.edu.cn
Bo Jin
jinbo0111@zju.edu.cn
Full list of author information is available at the end of the article

Highlights

(1) High prevalence of PRE in MCD patients, varying by subtype.

(2) Early use of SCBs significantly delays PRE onset.

(3) Tailored ASMs are essential for improving outcomes in MCD.

Keywords Malformations of cortical development, Pharmacoresistant epilepsy, Sodium channel blockers

Backgrounds

Malformations of cortical development (MCD) encompass a group of congenital disorders that disrupt normal brain cortical development due to genetic, infectious, vascular, or metabolic factors [1–3]. Based on the disruption of key stages of cortical development, MCD are classified into three subtypes: abnormal cell proliferation and apoptosis, abnormal cell migration, and abnormal post-migrational development [1, 3]. The main clinical presentations of MCD include epilepsy and varying degrees of developmental delay or intellectual disability, typically presenting in childhood and early adulthood [3].

As epilepsy is particularly notable for its high rate of pharmacoresistance [4–6], recent literature has increasingly focused on surgical outcomes rather than pharmacological treatments for MCD patients with epilepsy. While surgical intervention is recognized as an effective option, particularly for those with FCD II [7, 8], other subtypes of MCD, such as FCD I and polymicrogyria, surgical treatment often yields poor results, representing the worst prognoses for epilepsy [9]. Thus, for patients who are not yet candidates for surgery, selecting the appropriate antiseizure medication (ASM) remains vital, especially at the initial presentation. However, existing research on the medical treatment outcomes for MCD primarily focuses on the risk factor for pharmacoresistant epilepsy (PRE) without specifying details about the types of drugs used, and the findings are inconsistent across studies. For epileptic patients with FCD, the failure of the first ASM and the presence of focal to bilateral tonic–clonic seizures are significant predictors of pharmacoresistance [10, 11]. MCD related to abnormal migration and post-migrational development shows that unilateral lesion distribution and low seizure frequency at onset are linked to epilepsy remission [5]. Notably, one recent study indicates that failure to respond to sodium valproate in genetic generalized epilepsy is a key predictor of refractory epilepsy [12]. The associations between the types of drugs that fail in initial ASM treatment and PRE related to MCD remain unclear.

Therefore, the current research aimed to evaluate the clinical features of MCD subtypes and the development of PRE within a large, single-center cohort. We hypothesized that failure of the first ASM is a significant risk factor across all patients with MCD and that the choice of initial ASM may influence pharmacoresistant patterns.

Methods

Patient selection and inclusion criteria

This study retrospectively enrolled patients diagnosed with epilepsy associated with MCD who had their initial consultation at the epilepsy center of the Second Affiliated Hospital of Zhejiang University between March 2013 and June 2023. This study was carried out in accordance with the World Medical Association Declaration of Helsinki and approved by the Medical Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine (2022–0336). Written informed consent was obtained from all participants. As a tertiary epilepsy center, our facility serves a diverse range of patients, including those with newly diagnosed epilepsy, intractable cases necessitating pre-surgical assessment, and complex cases referred from primary or secondary epilepsy centers.

We selected patients with MCD confirmed by 3 T-MRI, categorized into group I (abnormal cell proliferation and apoptosis), and group II (abnormal neuronal migration), based on the latest practical guidelines [1]. Group I included patients with macrocephaly and brain overgrowth spectrum, FCD type II, and tuberous sclerosis (TSC). Group II comprised patients with heterotopia (including periventricular nodular heterotopia or subcortical heterotopia), lissencephaly (including lissencephaly and subcortical band heterotopia), polymicrogyria (including schizencephaly), and combined MCD (the co-occurrence of at least two different types of MCD). Patients with incomplete or unreliable clinical data were excluded from the study. Additionally, patients classified as group III, who are associated with abnormal post-migrational development, were excluded, as nearly all such cases at our center were FCD I and FCD III, exhibiting normal or non-typical neuroimaging.

The clinical characteristics selected for inclusion include demographic data and features identified in existing literature as being associated with the risk of pharmacoresistance [13–15]. These features encompass gender, age at onset of epilepsy, pre-treatment seizure frequency,

presence of sleep-related seizures, history of status epilepticus, seizure semiology, EEG and imaging features, occurrence of febrile seizures, and comorbidities such as developmental delay, intellectual disability, or psychiatric behavioral abnormalities. The abnormal EEG background was defined as the abnormal background in the posterior head region. Additionally, we recorded the dates of prescription for the first, second, and third ASMs, along with the response to each ASM during the follow-up period.

Definitions and outcomes

PRE was defined as when a third ASM was administered due to the inefficacy of two appropriate ASM, following the ILAE criteria [14]. Additionally, patients who underwent surgical treatment were considered as PRE [10, 11]. Seizure freedom (SF) was defined as being seizure-free for at least 12 months or for three times the longest inter-seizure interval prior to treatment, whichever was longer. Patients were considered to have pharmacoresistance if they did not achieve SF. The time to PRE was defined as the date when the first ASM was prescribed subtracted from either the date when the third ASM was prescribed or the date of initial epilepsy surgery (including resection, vagus nerve stimulation, radiofrequency thermocoagulation, and laser interstitial thermotherapy). The seizure frequency before the initial treatment of more than once per day is defined as high seizure frequency. Sodium channel blockers (SCBs) included carbamazepine (CBZ), oxcarbazepine (OXC), lamotrigine (LGT), lacosamide (LCM), and phenytoin (PHT) [16]. "SF at the last follow-up" refers to the absence of seizures for a duration of at least 12 months or three times the longest inter seizure interval before treatment, whichever was longer, at the end of the follow-up period.

Statistical analysis

For continuous variables (age at seizure onset) were normally distributed in two-group comparisons (group I and group II; PRE and non-PRE), 2-sample *t*-test was used. If not, the Wilcoxon rank-sum test was applied. The chi-square test was utilized for categorical variables (surgery, sex, pretreatment seizure frequency, sleep-related seizures, focal to bilateral T-C, status epilepticus, EEG background, interictal epileptic discharge, MRI lesion location, history of febrile seizure, perinatal sentinel events, neuropsychiatric symptoms, failure of the first ASM, no.of ASMs used, PRE, surgery, surgical outcome). For MRI lesion location, Bonferroni correction was further applied to correct for multiple comparisons. Binomial regression was conducted to analyze the predictors of PRE. Kaplan–Meier survival analysis was performed to assess the differences in the time to PRE based on whether SCBs were used as the first ASM. The end-point event was defined as the point at which patients met the criteria for PRE, with survival time calculated as the date of the last follow-up minus the date of first ASM usage. Statistical analyses were carried out using SPSS and GraphPad prism 10, with significance set at $p < 0.05$.

Data availability statement

Anonymized data not published in this article will be made available upon request from any qualified investigator.

The datasets analyzed during the study are available from the corresponding author on reasonable request.

Results

Patient demographics

There were 296 MCD patients confirmed by MRI or pathology after surgery, and we enrolled 259 patients with MRI-confirmed MCD, comprising 131 females (50.6%), with 121 patients in group I and 138 in group II. For the excluded 37 patients, 18 had normal brain MRI, and 19 patients had abnormal MRI, such as hippocampal sclerosis and encephalomalacia. The pathological diagnosis of 37 patients was FCD I or FCD III (Fig. 1; Table 1). The most common subtype of MCD was FCD II ($n = 108$ patients, 41.7%), followed by heterotopia ($n = 64$ patients, 24.7%) and polymicrogyria (including schizencephaly, $n = 38$, 14.7%). The remaining subtypes included hemimegalencephaly ($n = 3$, 1.1%), TSC ($n = 10$, 3.9%), lissencephaly ($n = 17$, 6.6%), and combined MCD (co-occurrence of at least 2 different types, and all of them were classified as group II, $n = 19$, 7.3%). The mean age at seizure onset was 12.2 ± 9.9 years, and the median age was 11 years (an interquartile range [IQR] 4–18 years). The median duration of follow-up from seizure onset to the last visit or surgery was 103 months (IQR 45–174 months).

Out of the 259 patients, 190 (73.4%) met criteria for PRE. Of these, 101 patients (53.2%) underwent surgery (85 patients for resection, 7 patients for vagus nerve stimulation, 3 patients for radiofrequency thermocoagulation, and 6 patients for laser interstitial thermotherapy), with 77 (76.2%) being SF at the last follow-up (median 36 months, IQR 22–60 months). The remaining 89 patients with PRE were still exploring various ASMs; among them, 30 patients (33.7%, 30/89) achieved SF at the last visit (124 months, IQR 77–228 months). Additionally, 69 patients (26.6%) were non-PRE, and 56 of them were seizure free at the last follow-up (117 months, IQR 48–169 months). For 13 patients who neither met the diagnosis of PRE nor achieved SF, nine of them have used two ASMs, and the period of those SF did not meet the definition of SF, a third ASM has not been added yet.

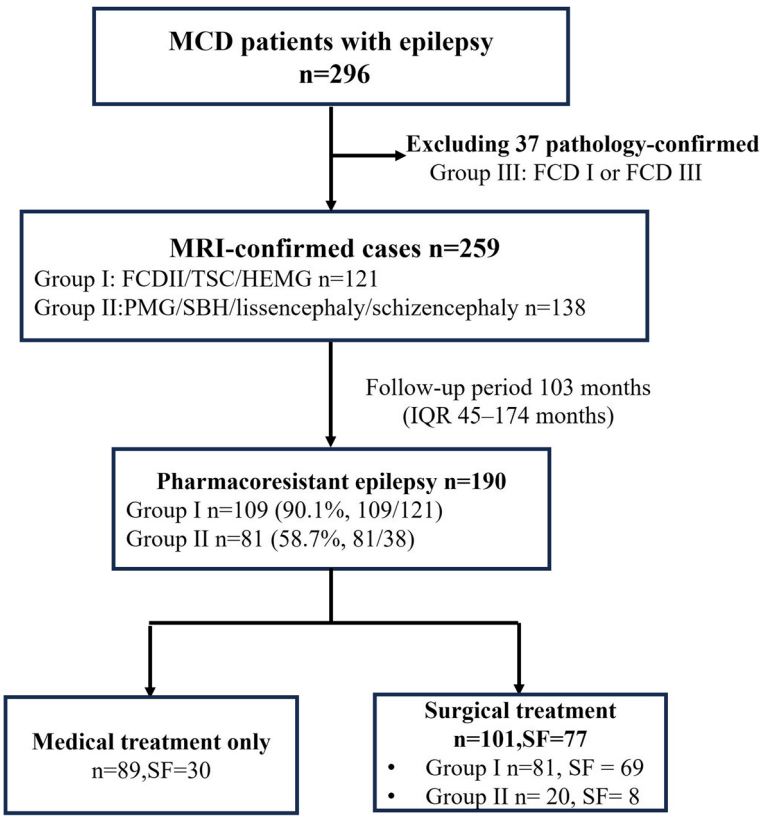

Fig. 1 Flow diagram of enrolled patients

Additionally, four patients who have only used one ASM and their seizures have not been completely controlled, a second ASM has not been added yet.

Clinical characteristics of MCD subtypes

Among the 259 patients, the two subtypes were nearly equally represented (group I: 121, group II: 138, ratio of 1:1.1). Clinical variables, such as gender and seizure features (including presence of sleep-related seizures, focal-to-bilateral tonic–clonic seizures, history of status epilepticus, and history of febrile seizures) showed no statistically significant differences between the two subtypes.

However, patients in group I exhibited an earlier age of seizure onset ($p=0.000$) and a higher pretreatment seizure frequency ($p=0.000$) compared to those in group II. Additionally, sleep-related seizures were more prevalent in group I (43.8%) compared to group II (31.9%, $p=0.048$). Although there were no statistically significant differences in the EEG background between the two groups, group II tended to exhibit more normal interictal EEG findings compared to group I, which showed a higher prevalence of interictal epileptiform discharges (IEDs) ($p=0.000$). At the last follow-up, patients in group I were prescribed more ASMs (3.57 ± 1.49) than those in group II (2.70 ± 1.35, $p=0.000$). The clinical characteristics of the entire MCD cohort, as well as the differences between group I and group II, are presented in Table 1.

Factors associated with PRE

The rate of PRE among all MCD patients was 73.4% (190/259), with a median time to PRE of 36 months (IQR 12–84 months). Group I had a higher PRE rate than group II (90.1% vs 58.7%, $p=0.000$). Factors, such as age at seizure onset, pretreatment seizure frequency, IEDs, location of MRI lesions, and failure of the first ASM, were noted to have statistically significant differences between PRE and non-PRE patients (Table 2). Binomial regression analysis identified high pretreatment seizure frequency ($p=0.011$, OR = 2.506, 95% CI 1.233 ~ 5.095), MCD subtypes ($p=0.001$, OR = 0.248, 95% CI 0.111 ~ 0.553) and failure of the first ASM ($p=0.000$, OR = 5.885, 95% CI 2.954 ~ 11.724) as significant predictors of PRE (Additional file 1: Fig.S1).

Initial ASM response rate of SCBs and non-SCBs

SCBs were the most prescribed initial ASM ($n=129$), followed by valproic acid ($n=65$) and levetiracetam ($n=42$).

Table 1 The comparison of the clinical features between the two groups

Clinical variables	Group I (FCDII/TSC/HMEG)	Group II (PMG/SBH/lissencephaly/schizencephaly)	Effect size	*p*
	n=121	*n*=138		
Age at seizure onset (years, IQR)	7(3.0,13.0)	15(7.3, 20.0)	0.367	0.000**
Sex，female	58(47.93%)	73(52.90%)	0.050	0.425
Pretreatment seizure frequency			0.418	0.000**
Low frequency	57(47.11%)	119(86.23%)		
High frequency	64(52.89%)	19(13.77%)		
Sleep-related seizures	53(43.80%)	44(31.88%)	0.123	0.048*
Focal to bilateral T-C	64(52.89%)	78(56.52%)	0.036	0.558
Status epilepticus	9(7.44%)	14(10.14%)	0.047	0.445
EEG background			0.050	0.421
Normal	113(93.39%)	132(95.65%)		
Abnormal	8(6.61%)	6(4.35%)		
Interictal epileptic discharge			0.259	0.000**
Normal	8(6.61%)	36(26.09%)		
Abnormal	113(93.39%)	102(73.91%)		
MRI lesion location			0.642	0.000**
Cingulate cortex	3(2.48%)[a]	0(0.00%)[a]		
Frontal	64(52.89%)[a]	13(9.42%)[b]		
Multi	20(16.53%)[a]	110(79.71%)[b]		
Occipital	8(6.61%)[a]	2(1.45%)[b]		
Parietal	11(9.09%)[a]	7(5.07%)[a]		
Temporal	15(12.40%)[a]	6(4.35%)[b]		
History of febrile seizure	13(10.74%)	12(8.70%)	0.035	0.578
Perinatal sentinel events	7(5.79%)	5(3.62%)	0.051	0.556
Neuropsychiatric symptoms	16(13.22%)	23(16.67%)	0.048	0.439
Failure of the first ASM	89(73.55%)	90(65.22%)	0.354	0.147
PRE	109(90.08%)	81(58.70%)	0.354	0.000**
Surgery	81(66.94%)	20(14.49%)	0.537	0.000**
SF after surgery at last follow-up	69(85.19%)	8(36.36%)	0.423	0.000**

For MRI lesion location，Bonferroni correction was further applied to correct for multiple comparisons: each superscript letter represents a subset of the categorical classes. At the 0.05 level, the column proportions of the same superscript letter are not statistically different from each other (e.g. Cingulate cortex in group I and group II with the same letter a); the column proportions of the same superscript letter are statistically different from each other (e.g. frontal in group I and group II with different letter a vs b)

FCD II Focal cortical dysplasia type II, *TSC* Tuberous sclerosis complex, *HMEG* Hemimegaloencephaly, *PMG* Polymicrogyria, *SBH* Subcortical band heterotopia, *IQR* Interquartile range, *focal to bilateral T-C* focal to bilateral tonic-clonic, *ASM* Anti-seizure medication, *PRE* Pharmacoresistant epilepsy, *SF* Seizure freedom

*$p < 0.05$

**$p < 0.001$

SCBs demonstrated a higher response rate compared to the other medications as initial ASMs ($p < 0.001$, Fig. 2a), a finding that was validated in both group I ($p = 0.002$) and group II ($p = 0.020$, Fig. 2b,c).

Kaplan–Meier curve analysis revealed that selecting SCBs as the first ASM significantly prolonged the time to developing PRE among MCD patients, with a median time of 72 months for SCB users compared to 48 months for those using non-SCBs (Log-rank $p = 0.0037$, Fig. 3a). Baseline clinical data were consistent across both groups (Additional file 2: Table S1). Further analysis indicated that patients who failed to respond to SCBs as the first ASM experienced the earliest onset of PRE (median time: 48 months), while patients who responded successfully to SCBs as the first ASM had the latest onset (median time 360 months, Fig. 3b, Log-rank $p < 0.001$).

Among the 129 patients who received SCBs as their first ASM, 54 responded effectively. By the end of the follow-up, 28 patients had developed into PRE. Among them, 14 patients started to reduce their medication

Table 2 Univariate analysis between PRE and non-PRE patients

Clinical variables	Non-PRE *n*=69	PRE *n*=190	Effect size	*p*
Age at seizure onset (years)	15 (5.0,21.5)	10 (4.0,17.0)	0.210	0.002*
Sex，female	35(50.72%)	93(48.95%)	0.016	0.800
Pretreatment seizure frequency			0.320	0.000**
Low frequency	64(92.75%)	112(58.95%)		
High frequency	5(7.25%)	78(41.05%)		
Sleep-related seizures	25(36.23%)	72(37.89%)	0.015	0.807
Focal to bilateral T-C	43(62.32%)	99(52.11%)	0.091	0.144
Status epilepticus	6(8.70%)	17(8.95%)	0.004	0.950
EEG background			0.028	0.650
Normal	66(95.65%)	179(94.21%)		
Abnormal	3(4.35%)	11(5.79%)		
Interictal epileptic discharges			0.216	0.001**
Normal	21(30.43%)	23(12.11%)		
Abnormal	48(69.57%)	167(87.89%)		
MRI lesion location			0.298	0.000**
Cingulate cortex	0(0.00%)[a]	3(1.58%)[a]		
Frontal	8(11.59%)[a]	69(36.32%)[b]		
Multi	49(71.01%)[a]	81(42.63%)[b]		
Occipital	1(1.45%)[a]	9(4.74%)[a]		
Parietal	7(10.14%)[a]	11(5.79%)[a]		
Temporal	4(5.80%)[a]	17(8.95%)[a]		
History of febrile seizure	8(11.59%)	17(8.95%)	0.040	0.524
Perinatal sentinel events	4(5.80%)	8(4.21%)	0.033	0.591
Neuropsychiatric symptoms	11(15.94%)	28(14.74%)	0.015	0.811
Failure of the first ASM	40(57.97%)	40(21.05%)	0.353	0.000**

For MRI lesion location，Bonferroni correction was further applied to correct for multiple comparisons: each superscript letter represents a subset of the categorical classes. At the 0.05 level, the column proportions of the same superscript letter are not statistically different from each other (e.g. Cingulate cortex in group I and group II with the same letter a); the column proportions of the same superscript letter are statistically different from each other (eg. frontal in group I and group II with different letter a vs b)

focal to bilateral T-C, focal to bilateral tonic-clonic, *ASM* Anti-seizure medication, *PRE* Pharmacoresistant epilepsy

*$p< 0.05$

**$p<0.001$

because they had been seizure free for more than 2 years. However, all these patients experienced a recurrence after the dosage reduction. For further Kaplan–Meier curve analysis, we excluded these 14 cases that responded to SCBs but experienced relapse due to the dosage reduction. Those who experienced treatment failure progressed to PRE earlier than those with successful outcomes (Fig. 4, Log-rank $p<0.001$). In group I, there was no significant difference in PRE onset between SCBs responders and non-responders (median time, 48 months vs 54 months, Log-rank $p=0.249$). However, in group II, patients responding to SCBs developed PRE much later than those who experienced treatment failure (median time, 60 months vs 360 months, Log-rank $p<0.001$, Fig. 4).

FCD II and initial ASM response rate

As FCD II ($n=108$) was the most common type of MCD in our cohort, we further analyzed the initial ASM response rate of SCBs in FCD II. SCBs were the most prescribed initial ASM ($n=58$), which demonstrated a higher response rate compared to the other medications as initial ASMs ($p<0.001$, Additional file 1: Fig. S2a). Kaplan–Meier curve analysis revealed that selecting SCBs as the first ASM significantly prolonged the time to developing PRE among FCD II patients, with a median time of 48 months for SCB users compared to 15 months for those using non-SCBs (Log-rank $p=0.001$, Additional file 1: Fig.S2b). Among the 58 patients who received SCBs as their first ASM, there was no significant difference in PRE onset between SCBs responders and non-responders (median time, 60 months vs 48 months, Log-rank $p=0.207$, Additional file 1: Fig.S2c).

Discussion

Our large, single-center cohort of epileptic patients with MRI-confirmed MCD reveals clinical characteristics across subtypes, based on the latest guidelines of classification [1], with all exhibiting high rates of PRE, although the rate was higher in group I than in group II. Notably, failure of the first ASM emerged as the most significant risk factor for developing PRE. Our findings demonstrate that utilizing SCBs as the first ASM is associated with a higher response rate than other ASMs and a significantly prolonged time to developing PRE. Furthermore, the choice between SCBs and non-SCBs as the initial ASM influences the time to PRE in the overall cohort of epileptic patients with MCD and across different subtypes, irrespective of whether these patients respond to SCBs or not.

Previous research has often focused on individual MCD subtypes, often lacking comparative analyses. Our study addresses this gap by examining the overall MCD cohort and its subtypes. In our earlier cohort study [17], prior to the latest classification guidelines, we demonstrated that FCD exhibited an earlier onset age, higher seizure frequency, and more frequent occurrence of epileptiform discharges on EEG compared to gray matter heterotopia, polymicrogyria, and schizencephaly. These findings are reaffirmed in our expanded cohort. Notably, group I, primarily consisting of FCD II patients, exhibited a greater propensity for sleep-related epilepsy compared to other subtypes, aligning with existing literature

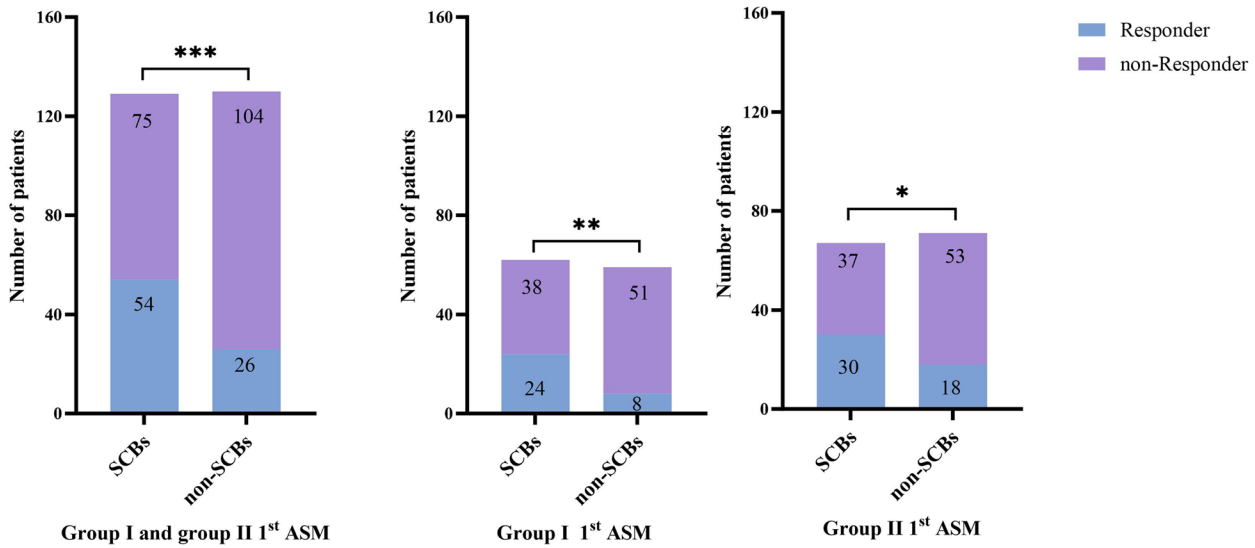

Fig. 2 Response rates to the first ASM are illustrated, detailing the distribution of initial ASM types used among all MCD patients (**a**), MCD group I patients (**b**), and MCD group II patients (**c**). **a** SCBs show a significantly higher response rate than other ASMs ($p < 0.001$). **b** A greater response rate for SCBs compared to other ASMs among group I patients ($p = 0.002$). **c** SCBs exhibited a higher response rate than other initial ASMs in group II patients ($p = 0.020$)

[18, 19]. FCD II is recognized as a leading cause of sleep-related seizures in focal epilepsy, with smaller lesions being more likely to trigger sleep seizures [18, 20]. This may explain why patients in group II, who have more extensive lesions, do not display this clinical feature, suggesting that the underlying pathophysiology may contribute to this difference.

All subtypes in our cohort share high rates of PRE, with an overall PRE rate of 73.36%, significantly higher than the general epilepsy cohort rate of 30% [21]. Sultana and colleagues investigated the factors associated with PRE and reported that the most common contributors included younger age of seizure onset, symptomatic epilepsy (often linked to structural brain abnormalities), abnormal EEG, and high baseline seizure frequency [22]. This suggests that the higher PRE rate in our cohort may be partly due to the inclusion of patients with structural brain abnormalities. Meanwhile, we found significant differences in PRE rates between group I and group II, with group I showing a higher rate of PRE (group I vs group II, 90.08% vs 58.70%). This disparity may be due to the predominance of FCD in group I, which has a PRE rate exceeding 90%. Our finding aligns with the recent literature indicating similarly high rates in children with

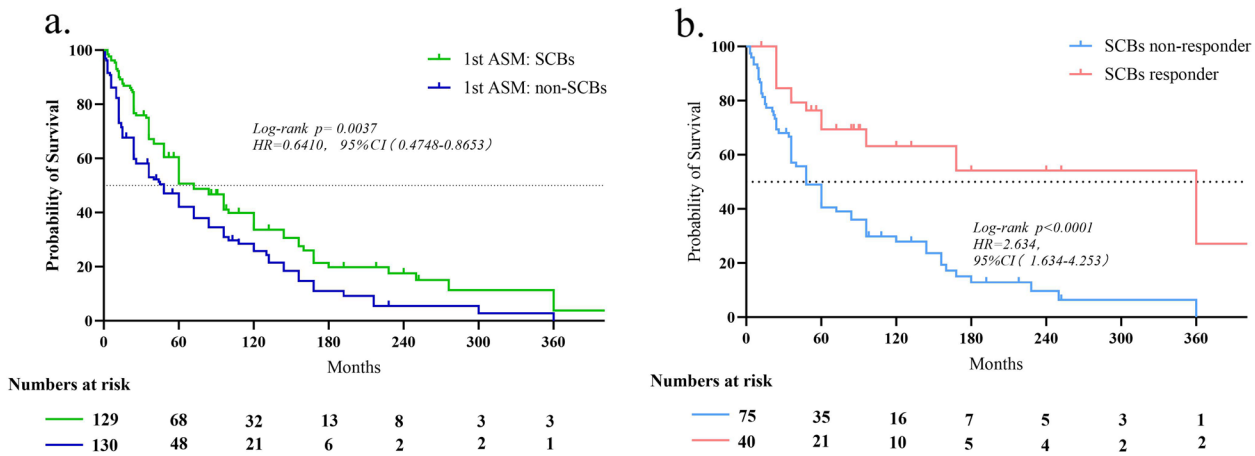

Fig. 3 Kaplan–Meier PRE estimates: **a** selecting SCBs as the first ASM (green curve) significantly prolongs the time to developing PRE compared to those who did not (purple curve); **b** patients who failed to respond to SCBs as the first ASM experienced the earliest onset of PRE (blue curve) compared to patients who responded successfully to SCBs as the first ASM (red curve)

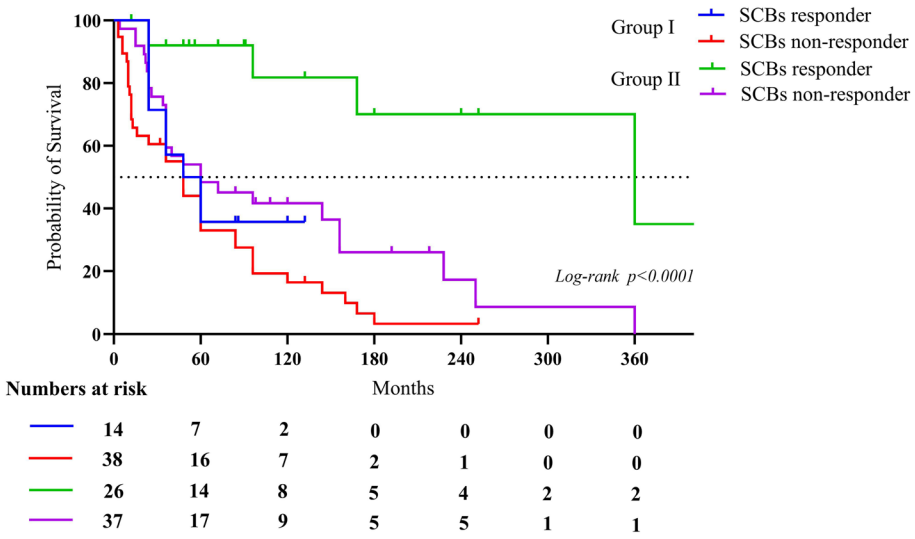

Fig. 4 Kaplan–Meier PRE estimates in subgroups: Among the patients who received SCBs as their first ASM, patients in group I who failed to respond to SCBs had the earliest time to PRE (red curve) and patients in group II who responded successfully to SCBs had the latest time to PRE (green curve)

neuroimaging diagnoses of FCD [4]. The pronounced PRE associated with FCD may be linked to unique pathological mechanisms and genetic factors distinct from those in group II.

As previously discussed, research on the treatment prognosis for epilepsy and MRI-identified MCD patients has primarily focused on specific subtypes and surgical outcome [4, 6, 8, 10]. Patients with MCD, particularly in pediatric cohorts, exhibit the highest rates of seizure recurrence post-surgery, highlighting the challenges associated with surgical interventions [23]. Consequently, pharmacological treatment remains crucial for managing symptoms of chronic conditions such as epilepsy. The physician's role is to identify the most effective ASM that can control or reduce seizures, especially when selecting the first medication. It has been suggested that the type of ASM that produced no response effects the probability of achieving seizure freedom with subsequent drugs [15]. Non-response to valproic acid in individuals with genetic generalized epilepsies is the most important predictor of PRE [12]. Nathan et al. reported that failure of the first ASM is associated with an increased risk and earlier onset of PRE in FCD-related epilepsy population [11]. Therefore, the selection of the first ASM is crucial, particularly for our cohort of patients with MCD, as most of them can be identified through MRI. Identifying the optimal first-line pharmacotherapy is of significant clinical importance, influencing both the subsequent decisions in drug treatment and the timing of surgical intervention considerations.

However, there is limited research specifically addressing drug selection for MCD patients, particularly regarding the first ASM. In our MCD cohort, SCBs emerged as the preferred first-choice medication, demonstrating superior therapeutic efficacy compared to other ASMs across all subgroups. A recent muti-omics study of genetic landscape of MCD highlighted the important role of mTOR-MAP kinase and glycosylation pathways [24], with alterations in the these pathways potentially enhancing sodium ion channel function [25, 26]. This may explain why SCBs are particularly effective in epileptic patients with MCD. Intriguingly, the choice of SCBs as the initial treatment appears to influence the progression toward PRE, regardless of therapeutic outcomes. In our cohort, patients in group I (primarily FCD type II) who were not prescribed SCBs as the first ASM experienced the earliest onset of PRE. Given the favorable surgical outcomes in FCD II patients [27], those who fail initial treatment with SCBs should be referred to a tertiary epilepsy center for surgical evaluation. Conversely, the complexity of surgical treatment in group II is higher, and the postoperative outcomes do not surpass those of group I (83.95% vs 52.94%). A recent study confirmed the heterogeneity and the complexity of the epileptogenic network in nodular heterotopia, with lower SF rates post-surgery for other MCD types (excluding FCD I, FCD II, FCD III, and MOGHE) compared to FCD II [28, 29]. In our study, it is worth noting that choosing SCBs early in group II could potentially extend the time before reaching PRE, providing valuable insights for treatment decisions.

Our study has several limitations. First, as a retrospective, single-center analysis conducted at a tertiary epilepsy center with a specialized surgery program, many patients were selected for surgical evaluation due to refractory epilepsy, which may introduce selection bias regarding PRE. However, this bias does not significantly impact the comparisons between groups or the analysis of PRE patterns. Additionally, our study represents one of the largest studies focusing a range of MCD subtypes in epileptic patients. Second, the retrospective study brings about the limitation in the definition of "time to PRE". It would be more accurate to define the time to PRE by the time till the occurrence of a seizure after the introduction of a second ASM in a sufficient dosage. Third, we only included patients with clearly MRI-identified MCD. Those with post-migrational MCD (group III), including FCD I and FCD III, were excluded, as these conditions often require postoperative pathological confirmation. Clinical practice often relies on a combination of clinical features, EEG results, and imaging characteristics for treatment decisions, with postoperative pathology typically being considered later. Therefore, the role of SCBs in this cohort should be interpreted within the context of MRI-confirmed MCD, and further studies are needed to assess the generalizability of these results across other MCD subtypes.

Conclusions

Our study highlights the high prevalence of PRE in a large and diverse cohort of patients with MCD, with particularly elevated rates observed in group I. The failure of the first ASM emerged as the most significant risk factor for the development of PRE. SCBs were the most utilized initial ASMs and were associated with a prolonged time to the development of PRE, especially in group II patients, who experienced a significant delay in the onset of PRE when SCBs were effective. This suggests the importance of early and appropriate ASM selection in managing MCD-related epilepsy, as it can substantially impact patient outcomes. Overall, our study reinforces the necessity of tailored pharmacological strategies and encourages further research to explore the mechanisms underlying PRE and the long-term effects of early ASM selection on patient quality of life in this specific cohort of patients.

Abbreviations

ASM Antiseizure medication
CBZ Carbamazepine
FCD Focal cortical dysplasia
IEDs Interictal epileptiform discharges
LCM Lacosamide
LGT Lamotrigine
MCD Malformations of cortical development
OXC Oxcarbazepine
PRE Pharmacoresistant epilepsy
PHT Phenytoin
SCBs Sodium channel blockers
TSC Tuberous sclerosis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04019-9.

Additional File 1. FigS1. Binomial logistic regression of predictors of PRE among patients with MCD and epilepsy. FigS2. FCD II and ASM response rate. (a) SCBs show a significantly higher response rate than other ASMs among FCD II patients. (b) Selecting SCBs as the first ASM (blue curve) significantly prolongs the time to developing PRE among FCD II patients compared to those who did not (red curve). (c) Patients who failed to respond to SCBs as the first ASM did not experience the earliest onset of PRE (blue curve) compared to patients who responded successfully to SCBs as the first ASM (purple curve).

Additional File 2. Table S1. The clinical features between patients use or not use SCBs as the first ASM.

Acknowledgements

The authors thank all the staff involved in this study, as well as the patients and their families for their participation and cooperation.

Authors' contributions

Pu Miao and Bo Jin designed the study and wrote the main manuscript text. Shuang Wang offered most of the MCD patients and helped revise the manuscript. Meiping Ying,Ruotong Chen and Yuyu Yang followed up the patients.Yao Ding, Junmin Zhu and Jin Wang offered their paitents to our study. Thandar Aung helped revise the manuscript. All authors reviewed the manuscript.

Funding

This study was supported by the Zhejiang Province Natural Science Foundation major project (grant number: LD24H090003) and the National Natural Science Foundation of China (grant number: 82101515, 82001366, 82171437).

Data availability

The datasets analyzed during the study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine (2022–0336).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Neurology, School of Medicine, Epilepsy Center, Second Affiliated Hospital, Zhejiang University, Hangzhou 310009, China. [2]Department of Pediatric, School of Medicine, Second Affiliated Hospital, Zhejiang University, Hangzhou 310009, China. [3]Department of Special Examination, Hospital of Traditional Chinese Medicine, Affiliated to Zhejiang University of Traditional Chinese Medicine, Hangzhou 310007, China. [4]Department of Neurology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou 310018, China. [5]Department of Neurology, Epilepsy Center, University of Pittsburgh Medical Center, Pittsburgh, PA, USA.

Received: 6 December 2024 Accepted: 18 March 2025
Published online: 07 April 2025

References

1. Severino M, Geraldo AF, Utz N, Tortora D, Pogledic I, Klonowski W, Triulzi F, Arrigoni F, Mankad K, Leventer RJ, et al. Definitions and classification of malformations of cortical development: practical guidelines. Brain. 2020;143(10):2874–94.
2. Raybaud C, Widjaja E. Development and dysgenesis of the cerebral cortex: malformations of cortical development. Neuroimaging Clin N Am. 2011;21(3):483–543, vii.
3. Barkovich AJ, Guerrini R, Kuzniecky RI, Jackson GD, Dobyns WB. A developmental and genetic classification for malformations of cortical development: update 2012. Brain. 2012;135(Pt 5):1348–69.
4. Zvi IB, Enright N, D'Arco F, Tahir MZ, Chari A, Cross JH, Eltze C, Tisdall MM. Children with seizures and radiological diagnosis of focal cortical dysplasia: can drug-resistant epilepsy be predicted earlier? Epileptic Disord. 2022;24(1):111–22.
5. Licchetta L, Vignatelli L, Toni F, Teglia A, Belotti LMB, Ferri L, Menghi V, Mostacci B, Di Vito L, Bisulli F, Tinuper P. Long-term Outcome of Epilepsy and Cortical Malformations Due to Abnormal Migration and Postmigrational Development. Neurology. 2022;99(1):e23–32.
6. Wu P, Liu Q, Liu X, Sun Y, Zhang J, Wang R, Ji T, Wang S, Liu X, Jiang Y, et al. Clinical features of unilateral multilobar and hemispheric polymicrogyria (PMG)-related epilepsy and seizure outcome with different treatment options. Epilepsia Open. 2024;9(4):1480–92.
7. Englot DJ. Lesional Epilepsy in Children: Removing Doubt to Cut It Out. Epilepsy Currents. 2023;23(3):150–2.
8. Takahashi YK, Baba S, Kawashima T, Tachimori H, Iijima K, Kimura Y, Saito T, Nakagawa E, Komaki H, Iwasaki M. Treatment odyssey to epilepsy surgery in children with focal cortical dysplasia: Risk factors for delayed surgical intervention. Seizure. 2024;120:5–11.
9. Lamberink HJ, Otte WM, Blümcke I, Braun KPJ. Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study. Lancet Neurol. 2020;19(9):748–57.
10. Chang P, Xie H, Illapani VSP, You X, Anwar T, Pasupuleti A, Vu TA, Vezina LG, Gholipour T, Oluigbo CO, et al. Focal to bilateral tonic–clonic seizures predict pharmacoresistance in focal cortical dysplasia–related epilepsy. Epilepsia. 2023;64(9):2434–42.
11. Cohen NT, Chang P, You X, Zhang A, Havens KA, Oluigbo CO, Whitehead MT, Gholipour T, Gaillard WD. Prevalence and Risk Factors for Pharmacoresistance in Children With Focal Cortical Dysplasia–Related Epilepsy. Neurology. 2022;99(18):e2006–13.
12. Gesche J, Khanevski M, Solberg C, Beier CP. Resistance to valproic acid as predictor of treatment resistance in genetic generalized epilepsies. Epilepsia. 2017;58(4):e64–9.
13. Löscher W, Potschka H, Sisodiya SM, Vezzani A, Barker EL. Drug Resistance in Epilepsy: Clinical Impact, Potential Mechanisms, and New Innovative Treatment Options. Pharmacol Rev. 2020;72(3):606–38.
14. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069–77.
15. Perucca E, Perucca P, White HS, Wirrell EC. Drug resistance in epilepsy. The Lancet Neurology. 2023;22(8):723–34.
16. Brodie MJ. Sodium Channel Blockers in the Treatment of Epilepsy. CNS Drugs. 2017;31(7):527–34.
17. Chen W, Jin B, Aung T, He C, Chen C, Wang S, Ding Y, Ding F, Wang C, Li H et al. Response to antiseizure medications in epileptic patients with malformation of cortical development. Ther Adv Neurol Disord. 2021;12:14:17562864211050027.
18. Wang Y, He C, Chen C, Wang Z, Ming W, Qiu J, Ying M, Chen W, Jin B, Li H et al. Focal cortical dysplasia links to sleep-related epilepsy in symptomatic focal epilepsy. Epilepsy Behav. 2022;127:108507.
19. Nobili L, Cardinale F, Magliola U, Cicolin A, Didato G, Bramerio M, Fuschillo D, Spreafico R, Mai R, Sartori I, et al. Taylor's focal cortical dysplasia increases the risk of sleep-related epilepsy. Epilepsia. 2009;50(12):2599–604.
20. Jin B, Zhang Z, Wang C, Li H, Zhao X, Wang S, Chen C, He C, Zheng Y, Geng Y, et al. Focal thalamocortical circuit abnormalities in sleep related epilepsy caused by focal cortical dysplasia type II. Seizure. 2022;99:153–8.
21. Kalilani L, Sun X, Pelgrims B, Noack-Rink M, Villanueva V. The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis. Epilepsia. 2018;59(12):2179–93.
22. Sultana B, Panzini MA, Veilleux Carpentier A, Comtois J, Rioux B, Gore G, Bauer PR, Kwon CS, Jetté N, Josephson CB, Keezer MR. Incidence and prevalence of drug-resistant epilepsy: a systematic review and meta-analysis. Neurology. 2021;96(17):805–17.
23. Yu H, Liu Q, Wang R, Liu C, Sun Y, Wang Y, Ji T, Wang S, Liu X, Jiang Y, Cai L. Long-term seizure and developmental outcomes of epilepsy surgery in children under 3 years old: A single-center study of 113 patients. CNS Neurosci Ther. 2024;30(1): e14481.
24. Chung C, Yang X, Bae T, Vong KI, Mittal S, Donkels C, Westley Phillips H, Li Z, Marsh APL, Breuss MW, et al. Comprehensive multi-omic profiling of somatic mutations in malformations of cortical development. Nat Genet. 2023;55(2):209–20.
25. Tyrrell L, Renganathan M, Dib-Hajj SD, Waxman SG. Glycosylation alters steady-state inactivation of sodium channel Nav1.9/NaN in dorsal root ganglion neurons and is developmentally regulated. J Neurosci. 2001;21(24):9629–37.
26. Hui JB, Silva JCH, Pelaez MC, Sévigny M, Venkatasubramani JP, Plumereau Q, Chahine M, Proulx CD, Sephton CF, Dutchak PA. NPRL2 Inhibition of mTORC1 Controls Sodium Channel Expression and Brain Amino Acid Homeostasis. eNeuro. 2022;9(2).
27. Willard A, Antonic-Baker A, Chen Z, O'Brien TJ, Kwan P, Perucca P. Seizure Outcome After Surgery for MRI-Diagnosed Focal Cortical Dysplasia: A Systematic Review and Meta-analysis. Neurology. 2022;98(3):e236–48.
28. Zanello M, Garnier E, Carron R, Jegou A, Lagarde S, Makhalova J, Medina S, Bénar CG, Bartolomei F, Pizzo F. Stereo-EEG-based ictal functional connectivity in patients with periventricular nodular heterotopia-related epilepsy. Epilepsia. 2024;65(4):e47–54.
29. Yu H, Sun Y, Liu C, Wang Y, Liu Q, Ji T, Wang S, Liu X, Jiang Y, Cai L. Clinical characteristics and post-operative outcomes in children with malformation of cortical development related drug-resistant epilepsy: 428 cases in one pediatric epilepsy center. CNS Neurosci Ther. 2024;30(9): e70031.

Publisher's Note