

## RESEARCH ARTICLE

# Deep characterization of refractory epilepsy due to mild malformation of cortical development with oligodendroglial hyperplasia (MOGHE) and insights into the role of invasive monitoring

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## Abstract

**Objective:** Epilepsy surgery is an effective treatment option for patients with medically refractory epilepsy due to mild malformation of cortical development with oligodendroglial hyperplasia (MOGHE). The success of surgery depends on the accurate localization of the epileptogenic zone, which can be challenging due to the subtle imaging features. The aim of this project was to provide an in-depth electro-clinical characterization of MOGHE in patients with medically intractable epilepsy, and to assess the role of stereo-electroencephalography (SEEG) in tailoring the resection and optimizing surgical outcome.

**Methods:** This single-center retrospective study analyzes a cohort of patients with medically intractable focal epilepsy who underwent surgery and had confirmed MOGHE on pathology evaluation. Clinical data, including demographics, electroclinical features (scalp EEG and invasive monitoring when available), surgical interventions, and postoperative outcomes were extracted from electronic medical records.

**Results:** Of 23 patients identified, 10 (43%) underwent SEEG as part of their standard care. Seizure outcome data were available for 22 patients in this series. Median post-operative follow-up duration was 3.8 years. Fourteen patients (64%) were seizure-free (Engel 1). Seizure freedom in the SEEG group was 80% ( $n = 8/10$ ), in comparison to the non-SEEG group (50%,  $n = 6/12$ ). Success rate was related to complete resection of the regions sampled by SEEG electrodes involved in ictal onset, and a more extensive resection of the lesion (or near total lobectomy).

**Significance:** Our results underscore the pivotal role of SEEG in enhancing surgical outcomes in patients with drug-resistant epilepsy due to MOGHE. SEEG proved particularly beneficial in defining resection margins, especially in cases where non-invasive data were discordant, scalp EEG patterns were generalized

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or poorly localized, and imaging findings were nonspecific, diffuse, or normal, making lesion identification challenging.

**KEYWORDS**

epilepsy, focal cortical dysplasia, malformation of cortical development, stereo-EEG

## 1 | INTRODUCTION

Mild malformation of cortical development with oligodendroglial hyperplasia (MOGHE) is a rare but increasingly recognized cause of refractory focal epilepsy. It was first described in 2017,<sup>1</sup> and it was recently introduced in the updated International League Against Epilepsy (ILAE) classification of focal cortical dysplasia (FCD).<sup>2</sup> Contrary to the classically recognized FCDs, MOGHE is characterized by abnormalities that involve the juxtacortical white matter without significant histopathological cortical abnormalities. The typical findings on pathology include heterotopic neurons in the white matter, oligodendroglial cell hyperplasia with excessive proliferation, and areas of patchy hypomyelination.<sup>1,3-5</sup>

Recent studies have suggested that genetics, specifically somatic mutations in *SLC35A2* that encodes a uridine diphosphate galactose (UDP-galactose) transporter, may play a role in the pathogenesis of MOGHE.<sup>3,5,6</sup> Despite this knowledge, the exact mechanisms by which UDP-galactose transporter deficiency leads to in situ epileptogenicity of MOGHE lesions remain unknown.

Scalp electroencephalography (EEG) features in patients with MOGHE and epilepsy were described in several reports,<sup>3,7-10</sup> highlighting the widespread and multifocal nature of interictal discharges, without much elaboration on the patterns observed. Multiple studies have examined the magnetic resonance imaging (MRI) characteristics of these lesions, emphasizing that although abnormalities are often present, imaging features may be subtle, leading to missed detection in up to 40% of cases.<sup>6,8,10</sup>

Outcome data in available small series of patients with medically intractable epilepsy due to MOGHE<sup>4,7,10-13</sup> suggest that epilepsy surgery may present an effective treatment option in carefully selected patients, and the success rate of epilepsy surgery in MOGHE varies, with seizure freedom rates ranging from 25%<sup>11</sup> to 73% of patients.<sup>3</sup> This underscores the importance of early recognition of patients with suspected MOGHE, and appropriate presurgical evaluation and surgical planning in optimizing outcomes for this challenging patient population. This range of success rates also highlights the variability in surgical outcomes, suggesting that accurate localization and delineation of the epileptogenic zone may play a role in determining operative success.

### Key points

- Mild malformation of cortical development with oligodendroglial hyperplasia (MOGHE) causes drug-resistant focal epilepsy and presents major challenges for epileptogenic zone localization.
- This study provides detailed electro-clinical characterization of surgically treated MOGHE patients.
- There is a trend for higher seizure freedom compared with non-stereo-electroencephalography (SEEG) surgical approaches.
- Optimal outcomes were linked to more complete resections of the ictal zone.

The role of invasive extra-operative monitoring in these cases is not well defined. It is critical to better understand the unique clinical and diagnostic features of MOGHE in order to refine treatment strategies and improve patient outcomes. In this study, we sought to define the electro-clinico-imaging characteristics of patients with medically intractable epilepsy due to MOGHE and to evaluate the utility and indications for stereo-EEG (SEEG) in this challenging patient population.

## 2 | MATERIALS AND METHODS

Data for this retrospective single-center study were obtained from an institutional review board (IRB)-approved data registry containing demographic and clinical data obtained in the course of routine clinical care from patients with medically intractable focal epilepsy due to malformations of cortical development. All patients in this study underwent surgical treatment for epilepsy at Cleveland Clinic between 1997 and 2024, and had pathologically confirmed MOGHE by an expert neuropathologist (I.B.). The recommendations for an SEEG implantation or decision to proceed with surgery, including the type and extent of the resection, were made at a formal, multidisciplinary patient management

conference. Outcome data were available in the patient registry. Data of interest included demographic information, electro-clinical characteristics (including scalp and invasive EEG, when available), neuro-imaging results, type and extent of surgery, and post-surgical seizure outcomes.

## 2.1 | Electro-clinical data

Information regarding the patients' seizure history, including age at seizure onset, seizure semiology, pre-operative seizure frequency, and number of trials of medication, were extracted from the epileptologists' clinic notes.

We collected information regarding intellectual disability (ID) for all patients included in the study. When available, standardized intelligence quotient (IQ) scores were extracted from the medical record and used as the primary measure to stratify the severity of cognitive deficits. In cases where IQ testing was not documented, we reviewed available information regarding the patient's profession, educational attainment, or any clinical documentation describing cognitive difficulties, which served as supportive indicators of functional capacity. Because adaptive functioning scores were not consistently available across patients, severity of intellectual disability was classified exclusively on the basis of IQ scores. Patients were stratified into the following ID categories: mild (IQ 50–70), moderate (IQ 35–49), severe (IQ 20–34), and profound (IQ <20).

Seizure frequency was sorted into categorical variables as “daily,” “weekly,” “monthly,” and “yearly.” These were defined as follows

- Daily: Seizures occur at least once a day.
- Weekly: Seizures occur at least once a week, but less than every day.
- Monthly: Seizures occur at least once a month, but less than every week.
- Yearly: Seizures occur at least once a year, but less than every month.

All patients had a scalp video-EEG evaluation before surgery. Interictal and ictal EEG, as well as videos of seizures, were re-evaluated for the purpose of this study. The focus was on the morphology and distribution of interictal discharges, which were categorized as generalized (bilateral synchronous), regional (localized to a specific region with amplitude-based maxima), or lateralized (uniformly distributed within one hemisphere). Ictal EEG onset and evolution patterns were similarly reviewed and classified.

## 2.2 | Neuroimaging data

Neuroimaging data included a high-resolution epilepsy protocol brain MRI in all cases, and a [<sup>18</sup>F] fluorodeoxyglucose–positron emission tomography (FDG-PET) scan in 22 of 23 patients.

MRI analysis involved a comprehensive review process that combined the initial interpretation from the clinical radiology reports with additional assessments conducted by expert epilepsy neuroradiologists during the multidisciplinary patient management conference.

Analysis of FDG-PET scans focused on identifying focal regions of hypometabolism that corresponded to the anatomic location of the MRI-identified lesion, the resected area, or the epileptogenic zone as identified through SEEG. The degree of hypometabolism was assessed based on the original review documented in the radiology report.

## 2.3 | Stereo-EEG data

We reviewed the data of all patients who underwent SEEG evaluation. The data reviewed included the electrode implantation map and the interictal and ictal EEG data, including seizure videos. Electrode placement was confirmed in relation to the identified MRI abnormality (when present), and the anatomic regions of the epileptogenic zone were examined using previously co-registered imaging files in CURRY software (*Compumedics Neuroscan*). Stereo-EEG–onset pattern descriptions were defined using the classification of Lagarde et al.<sup>14</sup>

## 2.4 | Surgical information

All patients underwent surgical resection at Cleveland Clinic. The estimation of the size of resected tissue was performed based on the description of the resected area in the operative note, as well as from review of the post-operative imaging, when available (i.e., 17/23 patients). For patients who underwent SEEG evaluation (10/23 patients, 43%), post-operative MRI was uploaded to the co-registration CURRY software platform, and reconstructions were performed using other non-invasive data (preoperative MRI, PET, ictal single-photon emission computed tomography [SPECT], magnetoencephalography [MEG]) and electrode positions to assess the extent of the resection in comparison to the onset zone and MRI abnormality. For patients who underwent multiple surgeries (3/23 patients, 13%), the type and extent of surgery were summarized as the cumulative result of all surgeries

combined. Follow-up duration was considered from the date of the last surgery. The surgery type and extent were classified into three categories:

- Lesionectomy: Refers to resections that were limited to the MRI-detected abnormality, typically performed without invasive guidance, except in rare cases where SEEG confirmed that the seizure-onset zone was confined to the MRI lesion.
- Partial lobectomy: Resections that were larger than the MRI abnormality and, when invasive monitoring was performed, included ictal-onset zones extending beyond the imaging-defined lesion.
- Subtotal lobectomy: Whenever a near-complete (function sparing) lobectomy was completed, regardless of the completion of invasive monitoring.

Resections involving multiple lobes: These resections were categorized based on the extent of the surgery. For instance, if only part of each affected lobe was resected, the procedure was classified as a partial lobectomy. Conversely, if a more extensive resection was performed, such as a subtotal lobar resection of two or more lobes (e.g., a temporo-parieto-occipital [TPO] resection), it fell under the subtotal lobectomy category.

## 2.5 | Histopathology review

We performed a retrospective review of all patients with focal epilepsy who were submitted to the epilepsy surgery program of the Cleveland Clinic and with surgical resection of brain tissue between 1997 and 2024. The brain tissue biorepository database (Research Electronic Data Capture [REDCap], USA) was searched for cases primarily diagnosed as “Cortical Dysplasia” ( $n = 1129$ ). All hematoxylin and eosin (H&E)-stained microscopy glass slides from this series were retrieved from the histology archives of the Department of Anatomic Pathology ( $n = 10161$ ), digitized with an APERIO slide scanner (LEICA, Germany) and digitally reviewed with the APERIO scanscope platform. Classifying histopathology features for MOGHE were applied as recently published by the ILAE,<sup>2</sup> that is, recognition of clusters of increased oligodendroglial cell density together with excess of heterotopic neurons in the white matter.

## 2.6 | Data analysis

Descriptive statistics characterized the study population. Non-normally distributed variables were summarized with medians and interquartile ranges (IQRs). Categorical

variables were reported as frequencies and percentages and analyzed using chi-square tests of independence to assess associations with seizure freedom. A  $2 \times 2$  contingency table was constructed for each variable (seizure-free vs not seizure free; presence vs absence). Fisher's exact test was used if any expected cell count was  $< 5$ .

For epilepsy duration, distributions were tested for normality using Shapiro–Wilk. Homogeneity of variance was assessed with Levene's test; if unequal, an independent-sample  $t$  test with Welch's correction was applied.

Outcomes across resection types were compared using Fisher's exact test for a  $3 \times 2$  table. The Cochran–Armitage test for trend assessed whether smaller resections correlated with lower favorable outcome rates. Logistic regression with extent of resection as an ordinal predictor estimated odds ratios per step decrease in resection size.

All statistical tests were two-tailed, with  $p < .05$  considered statistically significant. Analyses were performed using Python's SciPy statistical library (version 3.10).

## 3 | RESULTS

From a dataset of 1129 surgeries for refractory epilepsy (1997–2024) that were independently reviewed by one of the co-authors (I.B.), a total of 23 cases of MOGHE were identified. Resective surgeries were performed in various brain regions, including the frontal lobe ( $n = 13$ , 57%); temporal lobe ( $n = 4$ , 17%); temporo-parietal region ( $n = 2$ , 9%); temporo-occipital region ( $n = 2$ , 9%); and temporo-parieto-occipital region ( $n = 2$ , 9%).

### 3.1 | Demographics and clinical characteristics

As detailed in Table 1, the median age at seizure onset in our cohort was 5 years (IQR: 2–13) and the median age at time of surgery was 24 years (IQR: 8–28). The majority of patients experienced seizures with high frequency, with 43% ( $n = 11$ ) reporting daily seizures and 26% ( $n = 6$ ) experiencing weekly seizures. About 83% of patients ( $n = 19$ ) exhibited a focal seizure semiology, with or without secondary bilateral tonic-clonic seizures. Infantile spasms were observed as the initial seizure presentation in 17% of cases ( $n = 4$ ). No patients with later onset ( $\geq 5$  years) had infantile spasms, whereas three of the seven patients (43%) with earlier onsets did ( $\chi^2 = 2.83$ ,  $df = 1$ ,  $p = .093$ ). Given the small sample size and the presence of a zero cell, Fisher's exact test was performed, which demonstrated a statistically significant association ( $p = .047$ ).

Overall, these findings indicate that eight patients in the cohort (38%) exhibited ID, with the majority (88%)

**TABLE 1** Detailed demographic, clinical and histopathological findings of patients.

Case number	Sex	Age at onset (years)	Duration (years)	Initial semiology	Semiology at time of surgery	Seizure frequency	Number of ASM trials	Intellectual disability	SEEG	Final Engel outcome	Engel outcome at 1 year
1	Male	.7	7.5	Infantile spasms	Face tonic → Asymmetric tonic	Weekly	5	Mild	Yes	I	I
2	Female	1	1	Infantile spasms	Spasms → axial tonic → bilateral tonic/clonic	Daily	12	Mild	No	I	I
3	Male	10	15	GTC	Aura → dialeptic	Daily	3	None	Yes	IV	I
4	Male	7	18	Abdominal → autonomic/automotor	Axial tonic	Monthly	10	Mild	Yes	I	I
5	Female	1.5	1	Dialepsis	Atonic	Daily	7	Mild	No	I	I
6	Male	8	16	GTC	Aura → automotor → GTC	Monthly	4	None	Yes	I	I
7	Female	13.5	4.5	GTC	Aura → automotor → GTC	Weekly	6	None	No	I	NA
8	Male	.8	2	Spasms/atonic/axial tonic	Spasms/asymmetric tonic	Daily	5	Mild	No	III	III
9	Female	17	13	GTC	Aura → loss of awareness	Yearly	6	None	Yes	III	I
10	Male	10	26	Aura (déjà vu)	Face tonic → GTC	Monthly	2	None	No	I	III
11	Male	3	5	Axial tonic	Axial tonic	Daily	2	Moderate	No	I	III
12	Male	16	9	Aura → GTC	Aura → GTC	Daily	3	None	No	II	I
13	Male	9	10	Gaze deviation → automotor	Gaze deviation → automotor		15	Mild	No	III	I
14	Female	17	7	Aura → aphasic → GTC	Aura → aphasic → GTC	Monthly	3	None	Yes	I	NA
15	Male	3	3	Myoclonic / dialeptic / GTC	Axial tonic / head clonic / myoclonic	Daily	3	None	No	I	I
16	Female	2.5	41.5	Hypermotor	Autonomic → Hypermotor	Daily	5	Mild	Yes	I	III
17	Male	9	15	Dialeptic	Gaze deviation → automotor → GTC	Daily	4	None	No	N/A	I
18	Female	5	15	Dialeptic	Aura → Automotor	Daily	3	None	No	II	I
19	Male	1	19	Infantile spasms	Complex motor	Weekly	8	None	No	III	I
20	Male	5	41	Aura → axial tonic → complex motor	Aura → Complex motor	Weekly	10	None	Yes	I	II
21	Female	2.5	26.5	Blinking → upward eye deviation	Aura → Hypermotor	Daily	5	None	Yes	I	NA
22	Female	20	8	Dialeptic → automotor	Automotor → GTC	Weekly	7	None	Yes	I	I
23	Female	16	9	Gaze deviation → GTC	Gaze deviation → GTC	Monthly	6	None	No	II	II

Abbreviations: ASM, antiseizure medication; FCD, focal cortical dysplasia; GTC, generalized tonic-clonic; MCD, malformation of cortical development; NA, not available.

classified as mild. Standardized IQ scores or equivalent assessments were documented in 15 patients. Based on these scores, a single patient met criteria for moderate ID (IQ 35–49), whereas seven patients fell within the range of mild ID (IQ 50–70). Among the remaining cases, the patients demonstrated no evidence of ID, as inferred from their occupational history and functional status.

The chi-square test demonstrated a significant association between earlier age at onset (<5 years) and the presence of ID ( $\chi^2=4.52$ ,  $df=1$ ,  $p=.034$ ); Fisher's exact test confirmed this finding, also showing a statistically significant association (odds ratio [OR]=12;  $p=.023$ ).

### 3.2 | Imaging characteristics

As shown in Table 3, MRI findings were abnormal in 83% ( $n=19$ ) of cases. Remarkably, 50% of these MRI studies were initially reported as normal, but subsequent reviews by a neuroradiologist specializing in epilepsy identified subtle abnormalities. The most common MRI findings included gray–white matter blurring (74%;  $n=14$ ), cortical thickening (42%;  $n=8$ ), or white matter changes (21%;  $n=4$ ), such as increased T2 signal and reduced myelin arborization.

In one case without evident MRI abnormalities, a morphometric analysis program (MAP)–defined “positive” region (using post-processing and voxel-based morphometry) identified a questionable lesion within the left posterior middle temporal gyrus. This was later found to be part of the epileptogenic zone, although the lesion remained difficult to detect even upon focused review of the conventional MR images. Among four MR-negative cases, the resections involved the temporo-occipital ( $n=1$ ), lateral temporal ( $n=1$ ), and frontal ( $n=2$ ) lobes. Stereo-EEG was utilized in three of these four MRI-negative cases to localize the epileptogenic zone.

In our cohort, PET demonstrated hypometabolism concordant with the epileptogenic region in 73% of cases (16/22), although most showed only mild abnormalities (69%, 11/16). Notably, in three MRI-negative patients, PET identified a focal hypometabolic area that corresponded to the seizure-onset zone as shown by SEEG.

### 3.3 | Scalp EEG data

Interictal and ictal EEG findings are detailed in Table 2. The interictal EEG was generalized in 65% ( $n=15$ ) of cases, regardless of the age at epilepsy onset or the age at time of recording. Patients with generalized interictal epileptiform discharges ( $n=15$ ) had a median epilepsy

duration of 8 years (IQR 3.7–15), whereas those without generalized discharges ( $n=8$ ) had a median duration of 21 years (IQR 12.1–30.1). Patients with generalized interictal discharges tended to have a shorter duration of epilepsy compared to those without generalized discharges (Welch's  $t$  test =  $-2.70$ ,  $p=.025$ ). The most common interictal pattern was generalized slow spike-and-wave complexes, which were regionalizing or lateralizing (maximal activity in one region/hemisphere) in 53% ( $n=8/15$ ) of cases. A stereotyped interictal EEG pattern was observed in patients with generalized interictal discharges (Figure 1), characterized by slow spike-and-wave complexes that became slower and broader and were accompanied by generalized polyspikes during sleep.

The ictal EEG showed a generalized onset in 61% ( $n=14/23$ ) of cases (Table 2), with 8 of these demonstrating lateralizing or regionalizing features pointing to the side or lobe of the resection (maximal activity in one hemisphere or region). Among 14 patients with generalized ictal EEG, 64% ( $n=9$ ) were found to have frontal lobe epilepsy. Generalized ictal EEG was more commonly associated with earlier epilepsy onset of less than 5 years (Chi-square analysis,  $p=.0206$ ). No significant association was found between interictal EEG, ictal EEG patterns, and the lobe of surgery ( $p=.35$ ; Table 3).

### 3.4 | Stereo-EEG data

Ten patients (43%) underwent SEEG evaluation. The primary reasons for invasive monitoring included the absence of a lesion on MRI ( $n=3$ ); discordant and/or non-localizing non-invasive data, that is, generalized or non-localizing ictal EEG patterns ( $n=4$ ); and to further delineate the extent of the epileptogenic zone in MRI-positive cases ( $n=3$ ). For the remaining three patients, SEEG was indicated because of discordant non-invasive data and the desire for further localization of the epileptogenic zone, while localizing and delineating the extent of eloquent regions. The median age at the time of SEEG was 26.5 years (IQR: 24–34.25), with median epilepsy duration of 15.5 years (IQR: 7.75–32; Table 4).

The median number of implanted electrodes per patient was 14.5 (IQR: 12–15.3). Bilateral SEEG implantation was performed in two patients (20%), with an asymmetric hemispheric preference. Among the seven patients with MRI-identified lesions, the median number of intralobular electrodes was 2 (IQR: 1–2). Of note, the median number of electrodes involved in seizure onset was 4.5 (IQR: 2–5.25).

Interictally, continuous spiking in a discrete area (1–2 electrodes) was noted in three patients. In one of these three cases, the EEG onset was restricted solely to the

**TABLE 2** Detailed non-invasive (MRI, PET, scalp EEG), invasive (stereo-EEG) and outcome data.

Case number	MRI lesion location	PET abnormalities (lesion location)	Degree of PET hypometabolism	Interictal EEG	Ictal EEG	SEEG	SEEG onset location	SEEG onset type	Surgery location	Type of surgery	Follow-up (years)	Engel outcome
1	Left F opercular	Left F and T	Mild	Gen SWC, PSPK, Left Frontal SW	Gen, max Right FC	Yes	Left MFG, IFG, OF	LVFA (with slow)	Left dorsolateral, IFG, MFG	Partial lobectomy	.11	I
2	Right basal TO	Right inferior O	Mild	Gen and bilateral multiregional SPK and PSPK (hypsarhythmia)	Gen	No	N/A	N/A	Right TO	Subtotal lobectomy	7.23	I
3	Right T	None	N/A	Gen SWC, PSPK, bilateral TP SW	Gen	Yes	Right post basal T	Rep SPK then LVFA	Right TP	Lesioneectomy	6.20	IV
4	Right T	Left > Right mesial T	Mild	Gen SWC, PSPK max Right	Gen	Yes	Right STG, T pole	LVFA	Right Temporal including mesial structures	Subtotal lobectomy	5.82	I
5	Left TO	Left TO	Mild	Gen and multiregional SW, max Left TO, hypersarhythmia >80%	Gen	No	N/A	N/A	Left TO; Left post P <sup>a</sup>	Subtotal lobectomy	2.37	I
6	No lesion identified	Right posterior basal and lateral T	Mild	Bilateral (Right TP, TO, Left FT) SPK	Right TP	Yes	Right fusiform, lingula, post ITG/MTG	PSPK + LVFA (with slow)	Right TO	Subtotal lobectomy	.20	I
7	Right F	Right OF	Mild	Gen SW, PSPK, max Right T	Gen and lat Right	No	N/A	N/A	Right IFG, OF	Partial lobectomy	1.68	I
8	Left TO	None	N/A	Gen and multiregional left and right	Gen	No	N/A	N/A	Left TPO	Subtotal lobectomy	1.30	III
9	No lesion identified	Left lateral TP	Mild	Left TP, PO	Left TPO	Yes	L fusiform, ITG, T operc, MTC, SMG, angular	LVFA (with slow)	Left lateral T (sparing anterior/mesial structures)	Partial lobectomy	5.01	III
10	Left lateral OF	N/D	N/A	Left F SW	Left F	No	N/A	N/A	Left IFG, OF	Partial lobectomy	9.73	I
11	Right F	Hypermetabolism Right F	N/A	Gen and Left F SWC	Gen max Right	No	N/A	N/A	Right precentral F; premotor F	Lesioneectomy; subtotal lobectomy	4.08	I
12	Left TP (Posterior perisylvian)	Left lateral posterior T	Mild	Left T SW	Lat Left	No	N/A	N/A	Left TP	Lesioneectomy	5.74	II
13	Right mesial T	Right T	Mild	Gen and lat Right SWC and PSPK	Gen	No	N/A	N/A	Right anterior T including mesial structures	Partial lobectomy	.47	III
14	Left mesial T and basal TO	Left TP	Moderate-severe	Multiregional and lateralized Left SW	Left TP	Yes	Left basal temporo-occipital and angular gyrus	LVFA (with slow)	Left anterior and basal T	Partial lobectomy	2.86	I
15	Right mesial F	Right dorso-mesial F	Moderate-severe	Gen SWC max Right F	Gen max Right	No	N/A	N/A	Right SFG	Lesioneectomy	1.11	I
16	Left OF	Left OF	Moderate-severe	Left FT SW	Non-localizable and Left FT	Yes	Left gyrus rectus	Rep SPK/PSPK	Left OF, gyrus rectus	Lesioneectomy	1.82	I
17	Right OF	Right OF	Moderate-severe	Gen SWC and PSPK, max Right F	Gen max Right F	No	N/A	N/A	Right F	Subtotal lobectomy	N/A	N/A
18	No lesion identified	None	N/A	Gen max Left FC	Non-localizable and lat Left	No	N/A	N/A	Left F	Partial lobectomy	10.08	II

(Continues)

TABLE 2 (Continued)

Case number	MRI lesion location	PET abnormalities (lesion location)	Degree of PET hypometabolism	Interictal EEG	Ictal EEG	SEEG	SEEG onset location	SEEG onset type	Surgery location	Type of surgery	Follow-up (years)	Engel outcome
19	Right OF	Right F	Mild	Gen max Right F, Right F, SW	Right FC	No	N/A	N/A	Right F	Lesionectomy	12.71	III
20	Left SFG	None	N/A	Left F, SW	Left FC	Yes	Left OF, F operc	LVFA (with slow)	Right F	Partial lobectomy	7.96	I
21	No lesion identified	Left anterior T	Mild	Left FT, SW	Non-localizable and lat Left	Yes	Left T pole, entorhinal gyrus, hippocampus	Rhythmic beta	Left IFG; OF; T; post OF	Partial lobectomy	3.50	I
22	Right OF	Right F	Mild	PSPK gen max Right F, SWC Right FT	Right F	Yes	Right OF and pars orbitals	PSPK + LVFA (with slow)	Left OF	Partial lobectomy	5.42	I
23	Right MFG	Right dorsal F	Mild	Gen SWC max Right F	Gen max R	No	N/A	N/A	Right MFG	Lesionectomy	1.86	II

Abbreviations: FC, fronto-central; FT, fronto-temporal; Gen, generalized; IFG, inferior frontal gyrus; ITG, inferior temporal gyrus; Lat, lateralized; LVFA, low-voltage fast activity; max, maximum; MFG, middle frontal gyrus; MTG, middle temporal gyrus; N/A, not applicable; N/D, not done; OF, orbitofrontal; Operc, operculum; post, posterior; PSPK, polyspike; rep, repetitive; SEEG, stereo-EEG; SFG, superior frontal gyrus; SPK, spike; SWC, spike and wave complex; TO, temporo-occipital; TP, temporo-parietal; TPO, temporo-parieto-occipital.

<sup>a</sup>For patients who underwent multiple surgeries, they are all listed and separated by a double column. Follow-up duration was considered from the date of the last surgery.

electrode contacts that were continuously active, interictally (Case 16). In another patient (Case 14), the most active electrode was outside the seizure-onset zone and lesion, and its exclusion from resection still resulted in a good postoperative outcome (Engel class I). In the third patient (Case 1), interictal spiking occurred in the MRI abnormality but not in the seizure-onset zone; resecting the corresponding tissue including the irritative and seizure-onset zones led to a favorable outcome (Engel I). Diffuse spike-and-wave discharges, occasionally accompanied by polyspikes and low-voltage fast activity, were observed in 50% ( $n=5$ ) of cases, involving multiple ipsilateral and contralateral electrodes in bilaterally implanted patients. All but one of these cases had generalized patterns on interictal scalp EEG.

Four ictal onset patterns were identified (Table 3):

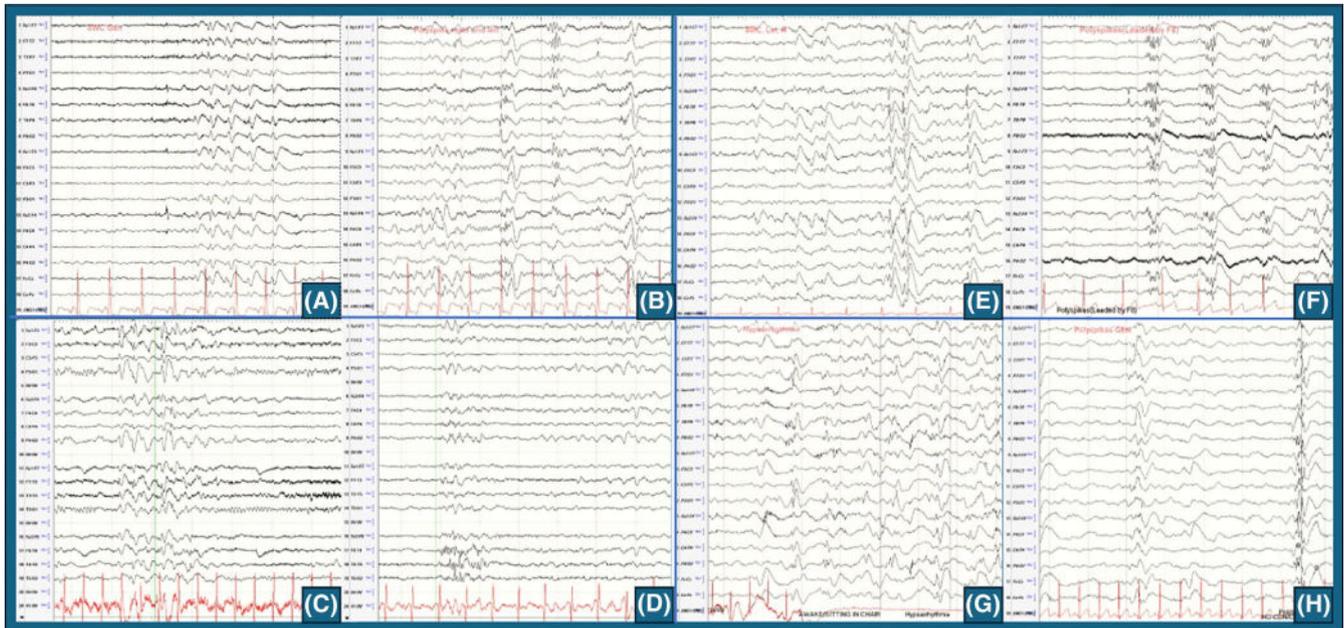
1. Low-voltage fast activity with slow wave: A slow wave with overriding low-amplitude gamma frequency activity (60%;  $n=6$ , Figure 2).
2. Polyspikes followed by low-voltage fast activity (20%;  $n=2$ , Figure S1).
3. Repetitive spiking ( $n=1$ , Figure S2).
4. Evolving rhythmic beta activity ( $n=1$ ).

The majority of patients exhibited either type 1 or 2 of the ictal-onset patterns (Table 4). Of interest, the ictal-onset patterns observed were not associated with seizure outcomes. An unusual case (Figure S3) exhibited a highly restricted onset limited to a single electrode within the lesion, characterized by repetitive spiking. Further details on SEEG-onset locations and patterns are provided in Table 2.

### 3.5 | Seizure outcome

Postoperative seizure outcome data were available for 22 patients. Median duration to last follow-up was 3.8 years (IQR=1.3–6.2). Engel I outcome at the time of the last follow-up was achieved in 64% ( $n=14/22$ ) of the patients. Patients with seizure onset before age 5 showed a trend toward better outcomes (78% vs 54%), but the difference was not statistically significant with this sample size (Fisher's exact  $p=.22$ ; Table 3). There was no correlation between the age at seizure onset ( $p=.45$ ), duration of epilepsy ( $p=.8$ ) and good outcome using a logistic regression model.

In our series, four patients had infantile spasms at seizure onset and 50% ( $n=2$ ) had a good outcome postoperatively. Only one of the four patients underwent SEEG, despite a visible lesion in the left frontal opercular region, 7.5 years after seizure onset, and the resection



**FIGURE 1** Interictal scalp EEG findings for several patients of various ages showing similar morphology and distribution of slow spike and wave complexes, as well as polyspikes during sleep. Case 3 (top left box) is a 25-year-old with epilepsy since the age of 10 years, with a lesion in the left posterior temporal region, whose interictal EEG showed generalized slow spike and wave complexes during wakefulness (A) and generalized polyspikes during sleep (B). Case 4 (bottom left box) is a 25-year-old with epilepsy diagnosed at the age of 7 years, in the setting of a lesion in the right temporal pole; interictal EEG showing generalized spike and wave complexes during wakefulness (C) and generalized polyspikes during sleep (D). Case 7 (top right box) is an 18-year-old with epilepsy onset at the age of 13.5 years, in the setting of a right inferior frontal lesion, whose interictal EEG showed generalized spike and wave discharges during wakefulness (E) and generalized polyspikes during sleep (F). Case 2 (bottom right box) is a 23-month-old patient with onset at the age of 12 months in context of a right temporo-occipital lesion, with an interictal EEG showing high-amplitude slow spike and wave complexes during wakefulness (G) and generalized polyspikes during sleep (H).

extended beyond the visible lesion as detailed in Table 2. The other case with good outcome (Case 2) had a large temporo-occipital resection without invasive guidance, a year after onset.

The role of SEEG guidance was particularly significant, as those patients who underwent SEEG-guided resections ( $n=10$ ) showed better outcomes (80% Engel Class I;  $n=8/10$ ) as compared to non-SEEG cases (50%;  $n=6/12$ ); however, this was not statistically significant (Table 4).

Surgical outcomes also varied considerably depending on the type of resection, SEEG guidance, and the lobe involved. Post-operative MR images following these various types of resections—lesionectomy, partial lobectomy, and subtotal lobectomy—are illustrated in Figure S3. The relationship between surgery type/extent (i.e., lesionectomy, partial lobectomy, and subtotal lobectomy) and seizure outcome is presented in Table S5.

Lesionectomy, targeting only the MRI-detected lesion, was performed in 27% ( $n=6$ ) of cases. Seizure freedom was achieved in 33% ( $n=2/6$ ). Among these, one patient undergoing SEEG-guided lesionectomy achieved seizure freedom. Partial lobectomy, which extends beyond the MRI-visible lesion but spares the majority of the lobe, was the most commonly performed procedure, undertaken in

46% ( $n=10$ ) of cases. This approach yielded a higher seizure freedom rate of 70% ( $n=7/10$ ), with four of these successful outcomes occurring in patients with frontal lobe epilepsy. In addition, SEEG-guided partial lobectomies achieved a 90% seizure freedom rate ( $n=4/5$ ). Subtotal lobectomy, the most extensive resection type encompassing a substantial portion of the lobe, was performed in 27% ( $n=6$ ) of cases. These patients achieved higher success rates, with 83% ( $n=5/6$ ) attaining Engel I outcome. Among these, the two patients who underwent SEEG-guided subtotal lobectomies both achieved postoperative seizure freedom.

We compared outcomes across resection types (subtotal lobectomy, partial lobectomy, lesionectomy) using Fisher–Freeman–Halton exact testing (approximated by chi-square test due to small sample size). Good outcome rates differed across groups (83%, 70%, and 33%, respectively), but this difference was not statistically significant ( $\chi^2=3.55$ ,  $p=.17$ ). When resection extent was modeled as an ordinal variable in logistic regression, each step increase in resection size was associated with 3.35-fold higher odds of good outcome (95% confidence interval [CI]: .83–13.5), suggesting a trend toward better outcomes with larger resections.

**TABLE 3** Summary of electro-clinical characteristics of the 23 cases.

	Total	Engel I outcome	
Total number of cases	23	<i>n</i> = 14/22 (64%)	
Median age at seizure onset, years	5 [IQR 2–13]		
Age at onset <5	<i>n</i> = 9/23 (39%)	<i>n</i> = 7/9 (78%)	<i>p</i> = .22
Age at onset ≥5	<i>n</i> = 14/23 (61%)	<i>n</i> = 7/13 (54%)	
Female	<i>n</i> = 10/23 (43%)		
Median duration of epilepsy, years	10 [IQR = 5–18]		<i>p</i> = .80
Seizure semiology			
Infantile spasms	<i>n</i> = 4/23 (17%)	<i>n</i> = 3/4 (75%)	<i>p</i> = .55
Other	<i>n</i> = 19/23 (83%)	<i>n</i> = 11/18 (61%)	<i>p</i> = .21
Seizure frequency			
Daily	<i>n</i> = 11/23 (48%)	<i>n</i> = 6/11 (55%)	<i>p</i> = .25
Weekly	<i>n</i> = 6/23 (26%)	<i>n</i> = 4/6 (67%)	<i>p</i> = .48
Monthly	22% ( <i>n</i> = 5)	<i>n</i> = 4/5 (80%)	<i>p</i> = .68
Yearly	4% ( <i>n</i> = 1)	0	<i>p</i> = .89
Developmental delay	<i>n</i> = 8/23 (34%)	<i>n</i> = 6/8 (75%)	<i>p</i> = .49
Mild	<i>n</i> = 7/8 (88%)		
Moderate	<i>n</i> = 1/8 (12%)		
Abnormal MRI			
Total	<i>n</i> = 19/23 (83%)	<i>n</i> = 12/18 (67%)	<i>p</i> = .53
GW blurring	<i>n</i> = 14/19 (74%)		
Thickened cortex	<i>n</i> = 8/19 (42%)		
White matter changes	<i>n</i> = 4/19 (21%)		
Lesion location on MRI			
Frontal	<i>n</i> = 11/19 (58%)	<i>n</i> = 8/10 (80%)	<i>p</i> = .31
Temporal	<i>n</i> = 3/19 (16%)	<i>n</i> = 1/3 (33%)	<i>p</i> = .52
Temporo-occipital	<i>n</i> = 4/19 (21%)	<i>n</i> = 3/4 (75%)	<i>p</i> = .35
Temporo-parietal	<i>n</i> = 1/19 (5%)	0	<i>p</i> = .75
PET			
Hypometabolism (lesion)	73% ( <i>n</i> = 16/22)	<i>n</i> = 10/14 (71%)	<i>p</i> = .36
Mild	<i>n</i> = 11/16 (69%)		
Moderate–severe	<i>n</i> = 5/16 (31%)		
MEG			
Total	<i>n</i> = 19/23 (83%)		
Abnormal MEG	<i>n</i> = 18/19 (95%)	<i>n</i> = 11/17 (65%)	<i>p</i> = .42
Localizing dipoles	<i>n</i> = 14/18 (78%)	<i>n</i> = 8/13 (62%)	<i>p</i> = .38
Interictal EEG			
Generalized without localizing features (with multiregional/ bilateral)	<i>n</i> = 7/23 (30%)	<i>n</i> = 4/7 (57%)	<i>p</i> = .55
Generalized with lateralizing/localizing features	<i>n</i> = 8/23 (35%)	<i>n</i> = 4/7 (57%)	<i>p</i> = .57
Unilateral/regional (without generalized)	<i>n</i> = 7/23 (30%)	<i>n</i> = 5/7 (71%)	<i>p</i> = .49
Multiregional and bilateral without generalized	<i>n</i> = 1/23 (4%)	<i>n</i> = 1/1 (100%)	<i>p</i> = .91

Note: Association with good outcome for categorical variables was established using chi-square test or Fisher's exact test when appropriate, and for continuous predictors such as epilepsy duration, a logistic regression was undertaken. The *p*-values are represented in the table.

**TABLE 4** Summary of SEEG findings and seizure outcomes.

		% Engel I outcome
Patients who underwent SEEG	<i>n</i> = 10/23 (43%)	<i>n</i> = 8 (80%)
Median age at SEEG, years	26.5 [IQR 24–34.25]	
Median duration of epilepsy, years	15.5 [IQR 7.75–32]	
Median number of implanted electrodes per patient	14.5 [IQR 12–15.25]	
Abnormal MRI, lesion	<i>n</i> = 7/10 (70%)	
Median number of electrodes in the lesion	2 [IQR 1–2]	
Median number of electrodes in the onset zone	4.5 [IQR 2–5.25]	
Location of the epileptogenic zone		
Frontal	<i>n</i> = 5/10 (50%)	
Partial lobectomy	<i>n</i> = 4/5 (90%)	100% ( <i>n</i> = 4)
Lesionectomy	<i>m</i> = 1/5 (10%)	100% ( <i>n</i> = 1)
Temporal	<i>n</i> = 3/10 (30%)	
Partial lobectomy	<i>n</i> = 2/3 (67%)	50% ( <i>n</i> = 1)
Subtotal lobectomy	<i>n</i> = 1 (33%)	100% ( <i>n</i> = 1)
Temporo-occipital	<i>n</i> = 2 (20%)	
Lesionectomy	<i>n</i> = 1/2 (50%)	0
Subtotal lobectomy	<i>n</i> = 1/2 (50%)	100% ( <i>n</i> = 1)
Onset pattern		
LVFA (with slow)	<i>n</i> = 6/10 (60%)	83% ( <i>n</i> = 5)
PSPKs and LVFA	<i>n</i> = 2/10 (20%)	50% ( <i>n</i> = 1)
Repetitive PSPKs/SPKs	<i>n</i> = 1/10 (10%)	100% ( <i>n</i> = 1)
Evolving rhythmic beta	<i>n</i> = 1/10 (10%)	0

Abbreviations: LVFA, low-voltage fast activity; MRI, magnetic resonance imaging; PSPK, polyspike; SPK, spike.

Patients who underwent frontal lobe surgery had a higher observed rate of good outcome than non-frontal lobe (75% vs 50%), corresponding to an OR of 3.0. However, this difference did not reach statistical significance in this sample (Fisher's exact  $p = .38$ ). All patients with frontal lobe lesions who underwent SEEG-guided resections achieved seizure freedom.

## 4 | DISCUSSION

### 4.1 | Clinical and electrophysiological insights

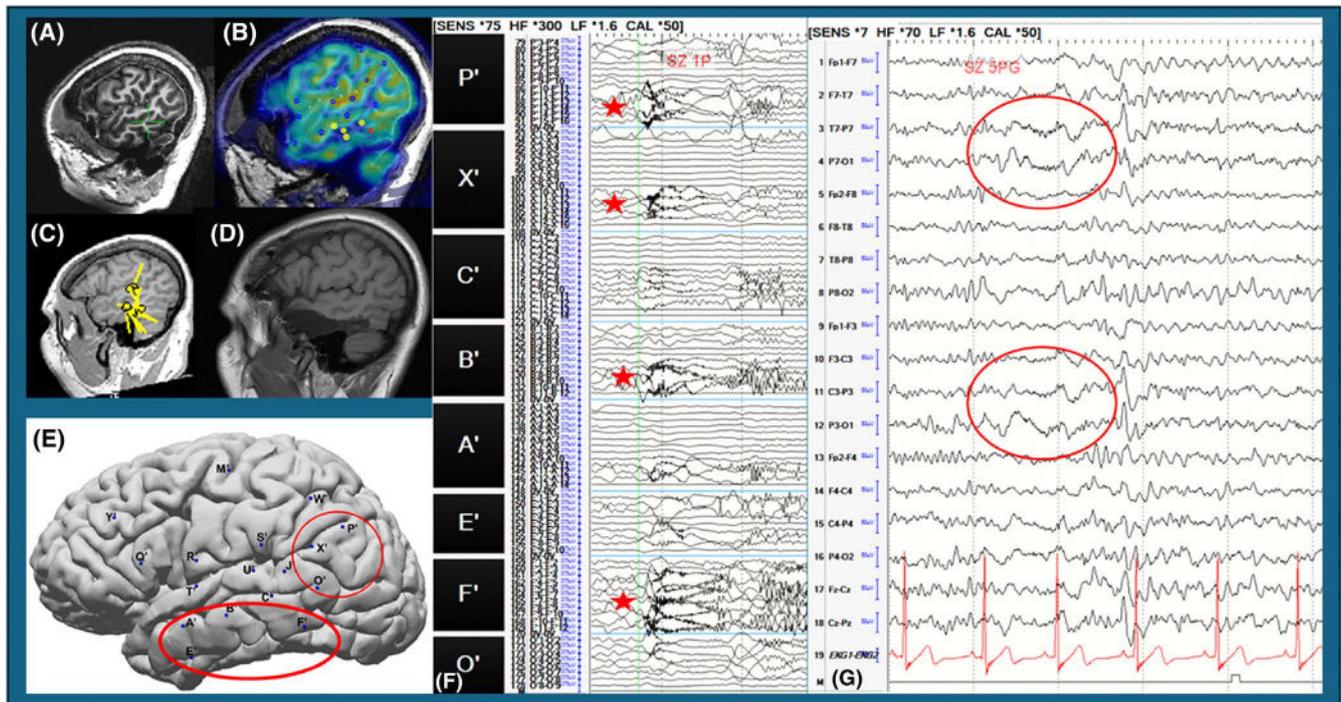
In our cohort, seizure onset occurred predominantly during early childhood, aligning with prior reports.<sup>1,3,7,9–11,15</sup> The median age at seizure onset was somewhat older than previously described (5 years in our series vs .5–3 years in other series),<sup>1,3,7,9,10</sup> and the duration between epilepsy diagnosis and surgical intervention had a median of 10 years, which

is comparable to findings in FCD studies.<sup>16–18</sup> Focal seizure semiology was the most common presentation, with infantile spasms observed exclusively in patients whose epilepsy onset occurred before 2 years of age.

Similarly to prior reports,<sup>8,10</sup> interictal scalp EEG patterns in most patients exhibited generalized slow spike-and-wave discharges with regional maxima. These patterns were more pronounced in younger patients with shorter epilepsy duration and often evolved into slower, broader discharges with polyspikes during sleep. Patients with localized or lateralized interictal discharges tended to have a longer duration of epilepsy, suggesting a shift in network dynamics over time.

### 4.2 | Imaging features and SEEG insights

MRI abnormalities were present in 83% of cases, consistent with the existing literature<sup>1,7,9–11</sup> and 50% of initial MRI interpretations were normal, highlighting the necessity for enhancing detection rates, as these abnormalities are



**FIGURE 2** This figure highlights a patient (Case 9 in Tables 1 and 2) with refractory focal epilepsy arising from the left basal temporal region. The patient had a non-lesional MRI (A), with voxel-based morphometric (VBM) post-processing identifying a focus of abnormal gray–white differentiation in the left lateral, middle temporal gyrus (green cross). PET (B) showed concordant hypometabolism in the same region, which also correlated with the location of MEG dipoles represented as yellow dots in images (B and C). Post-resection MRI is represented in (D), confirming resection of the implicated basal temporal region. The SEEG implantation map is represented in (E), with the presumed epileptogenic zone (i.e., networks underscoring seizure onset and early organization) circled in red. Electrode recordings capturing the SEEG onset pattern are shown in (F), with low-voltage fast activity seen synchronously across several electrodes (red stars) in the basal temporal and inferolateral parietal regions. Of note, there was correlation with ictal scalp findings (G) of subtle fast activity (red circles) in the posterior temporal and temporo-parietal distributions.

frequently subtle. Consistent with previous reports,<sup>1,7,10,11</sup> the most common imaging feature was gray–white matter blurring, underscoring the need for detailed review of dedicated high-resolution MRI studies.

PET revealed hypometabolism concordant with the presumed epileptogenic region in the majority of cases, even though often mild. In MRI-negative cases, it identified a focal metabolic abnormality that was concordant with invasive studies, suggesting its potential role in localizing the epileptogenic zone in these patients.

The ictal-onset zone delineated by SEEG was often found to extend beyond the anatomic boundaries as defined by imaging, suggesting that the epileptogenic zone might not be restricted to the MRI abnormality.<sup>19–21</sup> Our results also suggest that SEEG provides crucial insights into the localization and extent of the epileptogenic zone, demonstrating early synchronization across multiple electrodes in and around the lesion. Notably, ictal-onset patterns were dominated by low-voltage fast activity, often without pre-ictal spiking, synchronous across several electrodes within or near the MRI abnormality. These findings highlight the limitations of relying solely on

neuroimaging and non-invasive EEG modalities for pre-surgical planning, and they emphasize the value of SEEG in refining the definition of the epileptogenic network.

### 4.3 | Surgical outcomes and the role of SEEG

Our results show a favorable Engel I outcome in 64% of patients who underwent surgical resection with or without SEEG. Of interest, patients who underwent SEEG-guided resections achieved better seizure outcomes (80% of patients) compared to those who underwent surgery without SEEG (50%). These findings are rather unexpected and demonstrate the significant contribution of SEEG-based definition of the epileptogenic zone in the patients. The difference between the two groups in favor of SEEG is not typically seen in patients with lesional MRI and may be due to the challenges of non-invasive localization and definition of the extent of the epileptogenic zone in MOGHE, with implicated epileptogenic zone networks extending beyond the MRI-defined borders of any apparent lesion. This underscores

the utility of SEEG in optimizing surgical strategies and decision-making, particularly in cases with discordant non-invasive data and/or subtle imaging findings.

Resections extending beyond the MRI-defined lesion margins were associated with better outcomes, consistent with the broader epileptogenic network detected by SEEG. Conversely, limited lesionectomies, particularly those performed without SEEG guidance, had the poorest outcomes (33% had Engel I outcome), emphasizing the importance of a comprehensive evaluation to delineate the epileptogenic zone and concomitantly highlighting a dissociation between the identified pathology and its inherent epileptogenicity.

Of interest, in rare cases where the EZ was highly localized and restricted to a single electrode, targeted lesionectomy achieved good seizure outcomes. This variability in epileptogenic zone organization highlights the need for individualized (tailored) surgical strategies in MOGHE, as the success of surgical interventions in this cohort is more closely linked to the pre-surgical approach and extent of resection, rather than preoperative clinical variables and results of non-invasive tests.

Although prior studies suggest that children with epileptic spasms and MRI-visible lesions may achieve favorable outcomes without invasive monitoring, our cohort included only a small number of patients with infantile spasms, limiting our ability to draw firm conclusions regarding the role of SEEG in this subgroup; nevertheless, our experience indicates that pediatric patients with clearly demarcated lesions may be appropriate candidates for direct resection without invasive evaluation, as long as the resection extends beyond the visible lesion.

## 5 | CONCLUSIONS

This study highlights the clinical, imaging, and electrophysiological characteristics of MOGHE, emphasizing the importance of SEEG in guiding surgical resection. Our findings herein suggest that the epileptogenic zone in MOGHE often extends beyond MRI-visible lesions, necessitating tailored surgical strategies.

## 6 | LIMITATIONS

Somatic genetic analysis was available for only a subset of patients at the time of this study, which limits comprehensive evaluation of the contribution of *SLC35A2* mutations to the clinical and surgical phenotype of MOGHE.

## ACKNOWLEDGMENTS

The authors declare no competing interests. The authors received no specific funding for this work and thank

their institution for providing a supportive research environment.

## FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## CONFLICT OF INTEREST STATEMENT

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

## DATA AVAILABILITY STATEMENT

Raw data are not publicly available due to privacy restrictions. Data sharing is not applicable to this research project as it is independently conducted without financial support from any public entity, governmental agency, or funding body that mandates data sharing. In addition, the resources available for anonymizing, securing, and managing shared data are limited within the scope of this study. These constraints, coupled with the necessity to safeguard participant privacy, adhere to ethical guidelines and further justify the decision to restrict data sharing in this instance. Analysis scripts used in this work are provided on demand. These may be made available in alternative formats upon request and under appropriate transfer agreements.

## SOCIAL MEDIA AND ARTICLE PROMOTION

This study provides detailed electro-clinical characterization of surgically treated MOGHE patients and highlights the impact of SEEG on their outcome.

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## SUPPORTING INFORMATION

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

**How to cite this article:** Khoury J, Blümcke I, Busch RM, Krishnan B, Bulacio J, Bingaman W, et al. Deep characterization of refractory epilepsy due to mild malformation of cortical development with oligodendroglial hyperplasia (MOGHE) and insights into the role of invasive monitoring. *Epilepsia*. 2026;00:1–14. <https://doi.org/10.1002/epi.70118>