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Antiseizure Medication Trials Before Referral in Pediatric Patients Undergoing Epilepsy Surgery

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BACKGROUND AND OBJECTIVES: Drug-resistant epilepsy is defined as failure of 2 appropriately chosen and tolerated antiseizure medications (ASMs), after which referral for surgical evaluation is recommended. However, many children undergo additional ASM trials before referral. We aimed to identify preoperative factors associated with a higher number of ASM trials before referral in a nationwide, population-based pediatric epilepsy surgery cohort.

METHODS: We conducted a retrospective study of all children (younger than19 years) undergoing resective epilepsy surgery at the national pediatric epilepsy surgery center in Finland between 2002 and 2022. Patients were identified from a prospective surgical registry. Preoperative clinical characteristics, including etiology, seizure frequency, and resection location, were analyzed. Patients were categorized according to ≤3 vs >3 ASM trials before referral. Univariable and multivariable logistic regression analyses were performed to identify independent predictors of referral after >3 ASM trials. Seizure outcomes 2 years after the final surgery were classified using the Engel classification.

RESULTS: Among 239 children, the median number of ASM trials before referral was 4.0 (IQR, 3.0); 68% were referred after >3 ASMs. Younger age at epilepsy onset, daily seizures, and extratemporal, multilobar, or hemispheric resections were independently associated with referral after >3 ASM trials. Compared with patients referred after ≤3 ASMs, those referred after >3 ASMs had longer onset-to-referral intervals and were less likely to achieve Engel class 1 (odds ratio 2.0, 95% CI 1.0-3.9, $P = .047$) and more likely to require reoperation (20.9% vs 5.3%, $P = .002$). The number of prereferral ASM trials decreased over time.

CONCLUSION: In this population-based cohort, most children underwent more ASM trials than recommended before referral for epilepsy surgery. Greater ASM exposure was associated with more severe epilepsy phenotypes. These findings reinforce the importance of timely recognition of drug-resistant epilepsy and consideration of surgical evaluation alongside escalation of ASM trials.

KEY WORDS: Neurosurgery, Epilepsy surgery, Drug-resistant epilepsy, Pediatric neurosurgery

Epilepsy is the most common neurological disorder in childhood, affecting 0.3% to 1% of children; up to one-third develop drug-resistant epilepsy (DRE).[1,2] The International League Against Epilepsy (ILAE) defines DRE as failure to achieve sustained seizure freedom after adequate trials of 2 appropriately chosen and tolerated antiseizure medications (ASMs), whether used as monotherapy or in combination.[3] DRE is associated with poorer quality of life for both patients and caregivers, neurocognitive sequelae, and increased mortality compared with the general population. Epilepsy surgery is an effective treatment of DRE and has been shown to be cost-effective compared with medical therapy alone. Benefits include improved quality of life, better cognitive outcomes, and reduced all-cause mortality.[4-15]

ABBREVIATIONS: ASM, antiseizure medication; **DRE,** drug-resistant epilepsy; **HUH,** Helsinki University Hospital; **ILAE,** International League Against Epilepsy; **LEATs,** low-grade epilepsy-associated tumors; **MCD,** malformations of cortical development.

In 2022, ILAE recommended that all patients aged 70 years and younger be offered timely referral to an epilepsy center with surgical expertise. Despite strong evidence and international guidelines supporting epilepsy surgery, it is still frequently regarded as a last resort treatment. In real-world pediatric cohorts, referral for surgical evaluation often occurs after 4 to 6 ASM trials.[16-19]

Observational studies have suggested that longer epilepsy duration is associated with poorer postoperative seizure outcomes.[20-23] Early referral after DRE onset is therefore crucial, as time to referral represents a potentially modifiable factor influencing seizure outcomes. However, the reasons for delayed epilepsy surgery referral are not yet fully understood. Contributing factors may include delays in recognizing or diagnosing DRE, geographic distance to a specialized epilepsy center, and sociodemographic barriers (such as insurance status). Delays may also vary between countries due to differences in healthcare system structures.[19,24-30]

Helsinki University Hospital (HUH) is the national referral center for pediatric epilepsy surgery in Finland. Continued ASM trials after DRE onset may prolong time to surgical evaluation. Therefore, the aim of this study was to identify preoperative factors associated with a higher number of ASM trials before referral in a strictly defined, population-based pediatric epilepsy surgery cohort. We included only patients undergoing resective surgery, as palliative procedures (eg, neurostimulation or corpus callosotomy) have fundamentally different therapeutic objectives.

METHODS

A retrospective analysis of all children undergoing resective epilepsy surgery in HUH between 2002 and 2022 was conducted. The cohort was ascertained through our epilepsy surgery register, which prospectively collects data on characteristics and postoperative outcomes of all epilepsy surgery patients treated at our center. Patients were included if they were younger than 19 years of age at the time of their first surgery. Seizure data were obtained at the 2 years follow-up after the last surgery and classified using the Engel classification.[31]

Data Collection

We collected data on preoperative clinical characteristics such as etiology and location of the lesion. Seizure frequency was categorized as follows: daily, weekly (1-6 per week), monthly or less (<4 per month). Epilepsies were further classified based on the guidelines outlined in the 2022 position paper by ILAE.[32] For statistical analysis, we categorized the epilepsies into 2 groups: the first group included syndromes with combined generalized and focal seizures (Combined type), such as Infantile Epileptic Spasms Syndrome, Epileptic Encephalopathy with Spike and Wave Activation in Sleep (Developmental Epileptic Encephalopathy with Spike and Wave Activation in Sleep, previously called Continuous Spikes and Waves during Slow-Wave Sleep/Electrical Status Epilepticus in Sleep), and Lennox-Gastaut Syndrome. The second group consisted of focal syndromes or focal nonsyndromic epilepsies (Focal type), including Rasmussen Syndrome and Sturge-Weber Syndrome.

Data Analysis

The normality of continuous variables was assessed using the Shapiro-Wilk test, supported by visual inspection of histograms and Q-Q plots. Because all tested continuous variables were non-normally distributed ($P < .001$), nonparametric tests were used.

Categorical variables were compared using χ^2 test, and continuous variables using the Wilcoxon rank-sum test or Kruskal-Wallis's test, as appropriate. Results for continuous variables are reported as medians with IQR.

We compared variables between patients with ≤3 and >3 ASMs trialed before referral. The initiation of a third appropriately chosen and tolerated ASM was used as a clinically meaningful proxy for DRE onset, because it indicates that 2 previous ASM trials have failed.

To identify independent predictors of referral after trial of >3 ASMs, we performed univariable logistic regression for each preoperative variable. Variables with $P \leq .10$ in univariable analyses were then entered into a multivariable logistic regression model to estimate adjusted odds ratios (ORs). A linear regression model was used to assess temporal trends in the number of ASM trials before referral, and a separate linear regression model was used to evaluate the association between the number of ASM trials and the time from epilepsy onset to referral.

In addition, to explore the association between the ASM groups and Engel 1 outcome, we used a multivariable logistic regression adjusted for relevant predictors of Engel 1 outcome based on previous literature (Time from onset to surgery, location of resection, etiology, reoperation).

Figures 1-3 were generated using ChatGPT version 5.2.

Statistical significance was set to $P < .05$ (two-tailed). We performed all statistical analysis with SPSS, version 29.

Ethics Approval and Data Availability

The study protocol was approved by the ethics committee of HUH. Under the Finnish Law, informed consent is not required for a retrospective study based on hospital records.

RESULTS

Baseline Characteristics

The median number of ASM trials before referral was 4.0 (3.0). The median age at epilepsy onset was 2.6 years (5.9). The median time from epilepsy onset to referral was 3.4 years (IQR 5.7), and from referral to surgery 0.7 years (1.0). The number of ASMs trialed before referral is presented in Figure 1. Extratemporal resections were most common, followed by temporal, hemispheric, and multilobar procedures. Malformations of cortical development (MCDs) were the most frequent etiology, followed by hemispheric etiologies, low-grade epilepsy-associated tumors (LEATs), hippocampal sclerosis, and other structural causes. The number of ASMs trialed before referral decreased over time (Figure 2).

Median ASM Trials

Median ASM trials differed by several preoperative factors. Patients with age at onset ≤1 year had a higher median number of ASM trials than those with onset >1 year (5.0 vs 4.0, $P < .001$). Patients without remission had a higher median ASM count than

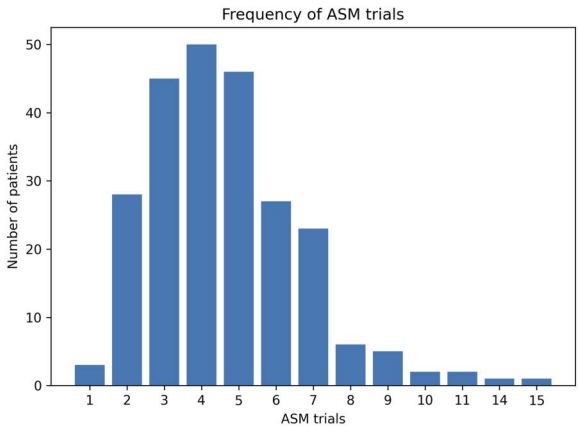

FIGURE 1. *Histogram showing the frequency distribution of the number of ASMs trialed before referral. The median number of ASMs before referral was 4.0 (3.0). Nearly 70% of patients had received more than 3 ASM trials before referral. Generated using ChatGPT version 5.2. ASM, antiseizure medication.*

those with remission (5.0 vs 4.0, $P = .048$). Median ASM trials also varied by seizure frequency (daily 5.0, weekly 4.0, monthly or less 3.0, $P < .001$), resection location (temporal 4.0 vs extratemporal/hemispheric/multilobar 5.0, $P < .001$), and etiology ($P < .001$), with higher medians in MCDs and hemispheric etiologies (both 5.0) and lower medians in LEATs (3.0).

Comparison Between ≤3 ASM and >3 ASM Before Referral

Compared with patients referred after ≤3 ASMs, those referred after >3 ASMs had a younger age at epilepsy onset (median 2.0 vs 3.6 years; $P < .001$) and a longer time from onset to referral (3.9 vs 2.6 years; $P = .046$). Detailed comparisons of baseline characteristics are presented in Table 1.

Referral after >3 ASMs was more common among patients with age at onset ≤1 year than among those with onset >1 year (81.3% vs 62.2%, $P = .004$). Likewise, higher seizure frequency was associated with referral after >3 ASMs ($P < .001$): 78.2% of patients with daily seizures were referred after >3 ASMs, compared with 62.5% with weekly seizures and 48.0% with monthly or less frequent seizures. Patients with combined epilepsy syndromes were more often referred after >3 ASMs than those with focal, nonsyndromic epilepsies (82.9% vs 65.7%, $P = .044$). Resection location also differed ($P = .001$), with referral after >3 ASMs most common among hemispheric procedures (90.3%), followed by multilobar (77.4%) and extratemporal resections (69.6%), and least common among temporal resections (53.3%). Etiology was similarly associated with referral after >3 ASMs ($P = .008$): referral after >3 ASMs was most frequent in hemispheric etiologies (86.5%) and other structural focal etiologies (72.2%), followed by MCDs (69.6%) and hippocampal sclerosis (59.3%), and least frequent in LEATs (46.9%).

Seizure Outcomes

In seizure outcomes (Table 2) after the final surgery, patients referred after ≤3 ASMs (n = 76) more often achieved Engel class 1

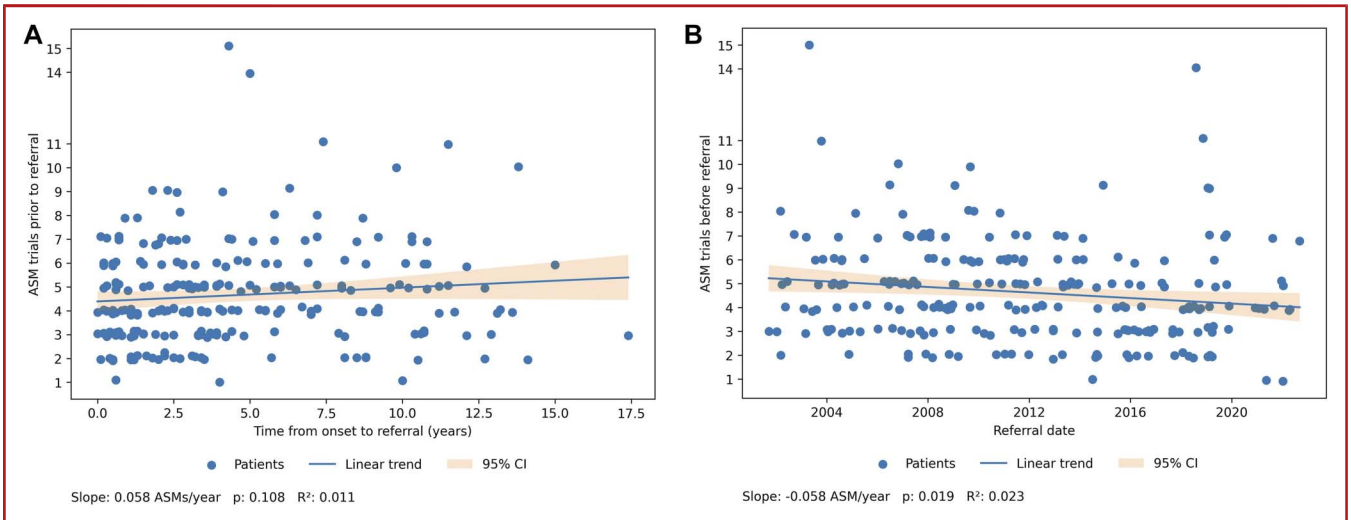

FIGURE 2. **A**, *Scatter plot illustrating the relationship between time from epilepsy onset to referral (years) and the number of ASM trials before referral. The linear regression line (blue) with 95% CI (shaded area) demonstrates a nonsignificant trend toward a higher number of ASM trials with longer onset-to-referral interval (slope 0.058 ASMs/year; P = .108; R^2 = 0.011).* **B**, *Scatter plot showing the temporal trend in the number of ASM trials before referral by calendar year of referral. The linear regression line (blue) with 95% CI (shaded area) indicates a significant decrease in the number of ASM trials over time (slope −0.058 ASMs/year; P = .019; R^2 = 0.023). Generated using ChatGPT version 5.2. ASM, antiseizure medication.*

TABLE 1. Baseline Characteristics

	≤3 ASM n = 76	>3 ASM n = 163	*P*	Median ASM	*P*
Age at onset	3.6 (7.3)	2.0 (5.0)	<.001		
Time to referral	2.6 (4.4)	3.9 (5.3)	.046		
Time from referral to surgery	0.7 (0.9)	0.7 (1.0)	.74		
Time to surgery	3.7 (5.3)	4.9 (6.1)	.052		
Side of surgery (%)			.74		.71
Left	36 (30.8)	81 (69.2)		4 (2.0)	
Right	40 (32.8)	82 (67.2)		4.5 (3.0)	
Referral hospital (%)			.38		.46
Secondary	32 (35.2)	59 (64.8)		4.0 (3.0)	
Tertiary	44 (29.7)	104 (70.3)		5.0 (3.0)	
Age at onset	3.6 (7.3)	2.0 (5.0)	<.001		
Age at onset ≤1 y (%)			.004		<.001
Yes	14 (18.7)	61 (81.3)		5.0 (3.0)	
Over	62 (37.8)	102 (62.2)		4.0 (2.0)	
Remission[a] (%)			.19		.048
No	45 (28.8)	111 (71.2)		5.0 (3.0)	
Yes	31 (37.3)	52 (62.7)		4.0 (2.0)	
MRI negative at referral (%)			.46		.48
No	51 (30.4)	117 (69.6)		4.5 (3.0)	
Yes	25 (35.2)	46 (64.8)		4.0 (3.0)	
MRI negative final (%)			.62		.99
No	68 (31.2)	150 (68.8)		4.0 (4.0)	
Yes	8 (38.1)	13 (61.9)		4.0 (4.0)	
Seizure frequency (%)			<.001		<.001
Daily	29 (21.8)	104 (78.2)		5.0 (2.0)	
Weekly	21 (37.5)	35 (62.5)		4.0 (2.0)	
Monthly or less	26 (52.0)	24 (48.0)		3.0 (2.0)	
Epilepsy syndromes (%)			.044		.29
Focal, nonsyndromic	70 (34.3)	134 (65.7)		4.0 (3.0)	
Combined	6 (17.1)	29 (82.9)		5.0 (2.0)	
History of IESS (%)			.19		.058
No	66 (34.4)	126 (65.6)		4.0 (3.0)	
Active	4 (17.4)	19 (82.6)		5.0 (2.0)	
Successfully treated (%)	6 (25.0)	18 (75.0)		5.0 (5.0)	

TABLE 1. Continued.

	≤3 ASM n = 76	>3 ASM n = 163	*P*	Median ASM	*P*
Location of resection (%)			.001		<.001
Temporal	35 (46.7)	40 (53.3)		4.0 (2.0)	
Extratemporal	31 (30.4)	71 (69.6)		5.0 (3.0)	
Hemispherotomy	3 (9.7)	28 (90.3)		5.0 (3.0)	
Multilobar	7 (22.6)	24 (77.4)		5.0 (3.0)	
Etiologies (%)			.008		<.001
MCD	38 (30.4)	87 (69.6)		5.0 (3.0)	
LEAT	17 (53.1)	15 (46.9)		3.0 (3.0)	
Hippocampal sclerosis	11 (40.7)	16 (59.3)		4.0 (2.0)	
Hemispheric etiologies	5 (13.5)	32 (86.5)		5.0 (3.0)	
Other, structural focal	5 (27.8)	13 (72.2)		4.0 (3.0)	

ASM, antiseizure medication; IESS, infantile epileptic spasms syndrome; LEAT, low-grade epilepsy-associated tumor; MCD, malformation of cortical development.
[a]Seizure freedom for a period exceeding 1 year at any point during the epilepsy course prior to surgery.

than those referred after >3 ASMs (77.6% vs 58.3%), whereas Engel class 3 to 4 outcomes were more common in the >3 ASM group (33.1% vs 9.2%; overall Engel distribution $P < .001$). Reoperations were also more frequent among patients referred after >3 ASMs (20.9% vs 5.3%; $P = .002$).

In the multivariable logistic regression model, referral after ≤3 ASMs was independently associated with higher odds of achieving Engel class 1 outcome (OR 2.0, 95% CI 1.0-3.9, $P = .047$), as was LEAT etiology compared with MCDs (OR 5.2, 95% CI 1.3-20.3, $P = .017$). Reoperation was independently associated with lower odds of Engel 1 outcome (OR 0.4, 95% CI 0.2-0.8, $P = .01$). Full results are presented in Table 3.

Predictors of >3 ASM Trials Before Referral

After univariable logistic regression, variables meeting the prespecified selection criteria for multivariable analysis were age at epilepsy onset, seizure frequency, epilepsy type, resection location, and etiology (Table 4). In the multivariable model, younger age at onset was associated with referral after >3 ASM trials (OR 0.9,

TABLE 2. Seizure Outcomes After the Final Surgery

	≤3 ASM n = 76	>3 ASM n = 163	*P*
Engel (%)			<.001
1	59 (77.6)	95 (58.3)	
2	10 (13.2)	14 (8.6)	
3	2 (2.6)	17 (10.4)	
4	5 (6.6)	37 (22.7)	
Reoperations (%)	4 (5.3)	34 (20.9)	.002

ASM, antiseizure medication.

TABLE 3. Multivariable Logistic Regression for Predictors of Engel Class 1 Seizure Outcome

	OR (CI 95%)	*P*
Time from onset to surgery	1.0 (0.9-1.0)	.35
≤3 ASM	2.0 (1.0-3.9)	.047
Reoperations	0.4 (0.2-0.8)	.010
Location of resection		
Temporal	Ref	
Extratemporal	0.7 (0.3-1.8)	.47
Hemispherotomy	3.0 (0.3-27.7)	.33
Multilobar	0.4 (0.1-1.1)	.069
Etiologies		
MCD	Ref	
LEAT	5.2 (1.3-20.3)	.17
Hippocampal sclerosis	0.5 (0.2-1.8)	.32
Hemispheric etiologies	0.5 (0.1-3.6)	.48
Other, structural focal	0.9 (0.3-2.7)	.85

ASM, antiseizure medication; LEAT, low-grade epilepsy-associated tumor; MCD, malformation of cortical development; OR, odds ratio; Ref, reference category.

TABLE 4. Univariable Logistic Regression for Predictors of >3 Antiseizure Medication Trials Before Referral

	OR (CI 95%)	*P*
Side		.74
Left	1.1 (0.6-1.9)	
Right	Ref	
Referral hospital		.38
Secondary	0.8 (0.4-1.4)	
Tertiary	Ref	
Age at onset	0.89	.001
Remission	0.7 (0.4-1.2)	.18
MRI negative at referral	0.8 (0.4-1.4)	.46
MRI negative final	0.8 (0.3-1.9)	.52
Seizure frequency		<.001
Daily	3.9 (1.9-7.8)	<.001
Weekly	1.8 (0.8-3.9)	.14
Monthly or less	Ref	
Epilepsy syndromes		
Focal, nonsyndromic	Ref	
Combined	2.5 (1.0-6.4)	.005
Active infantile spasms	2.4 (0.8-7.2)	.13
Location of resection		.003
Temporal	Ref	
Extratemporal	2.0 (1.1-3.7)	.028
Hemispherotomy	8.2 (2.3-29.2)	.001
Multilobar	3.0 (1.2-7.8)	.024
Etiologies		.014
MCD	Ref	
LEAT	0.4 (0.2-0.9)	.018
Hippocampal sclerosis	0.6 (0.3-1.5)	.30
Hemispheric etiologies	2.8 (1.0-7.7)	.048
Other, structural focal	1.1 (0.4-3.4)	.82

LEAT, low-grade epilepsy-associated tumor; MCD, malformation of cortical development; OR, odds ratio; Ref, reference category.

95% CI 0.8-1.0), resection location was also independently associated with referral after >3 ASM trials: extratemporal (OR 2.3, 95% CI 1.0-5.4), hemispheric procedures (OR 12.6, 95% CI 1.2-133.2), and multilobar resections (OR 3.3, 95% CI 1.0-10.4), each compared with temporal resections. Daily seizure frequency was also independently associated with referral after >3 ASM trials (OR 4.0, 95% CI 1.9-8.6), compared with monthly or less frequent seizures. These results are illustrated in Table 5 and Figure 3. In a sensitivity analysis using age at onset ≤1 year as the age variable, estimates for the other covariates were unchanged, and age at onset ≤1 year was not statistically significant (Table 6).

DISCUSSION

In this nationwide population-based cohort of children undergoing resective epilepsy surgery, we identified independent predictors of >3 ASM trials before referral. Younger age at epilepsy onset, daily seizures, and extratemporal, multilobar, or hemispheric resections were significantly associated with a higher ASM burden. The number of ASM trials before referral decreased over time, which may reflect increased awareness of timely surgical evaluation and adaptation of national care pathways.[33]

TABLE 5. Multivariable Logistic Regression for Predictors of >3 Antiseizure Medication Trials Before Referral

	OR (CI 95%)	*P*
Age at onset	0.9 (0.8-1.0)	.038
Seizure frequency		
Daily	4.0 (1.9-8.6)	<.001
Weekly	2.2 (1.0-5.1)	.058
Monthly or less	Ref	
Epilepsy syndromes		
Focal, nonsyndromic	Ref	
Combined	1.0 (0.3-3.0)	.97
Location of resection		
Temporal	Ref	
Extratemporal	2.3 (1.0-5.4)	.046
Hemispherotomy	12.6 (1.2-133.2)	.035
Multilobar	3.3 (1.0-10.4)	.042
Etiologies		
MCD	Ref	
LEAT	0.8 (0.3-2.0)	.61
Hippocampal sclerosis	2.5 (0.8-8.1)	.13
Hemispheric etiologies	0.6 (0.08-3.9)	.56
Other, structural focal	2.7 (0.8-9.6)	.13

LEAT, low-grade epilepsy-associated tumor; MCD, malformation of cortical development; OR, odds ratio; Ref, reference category.

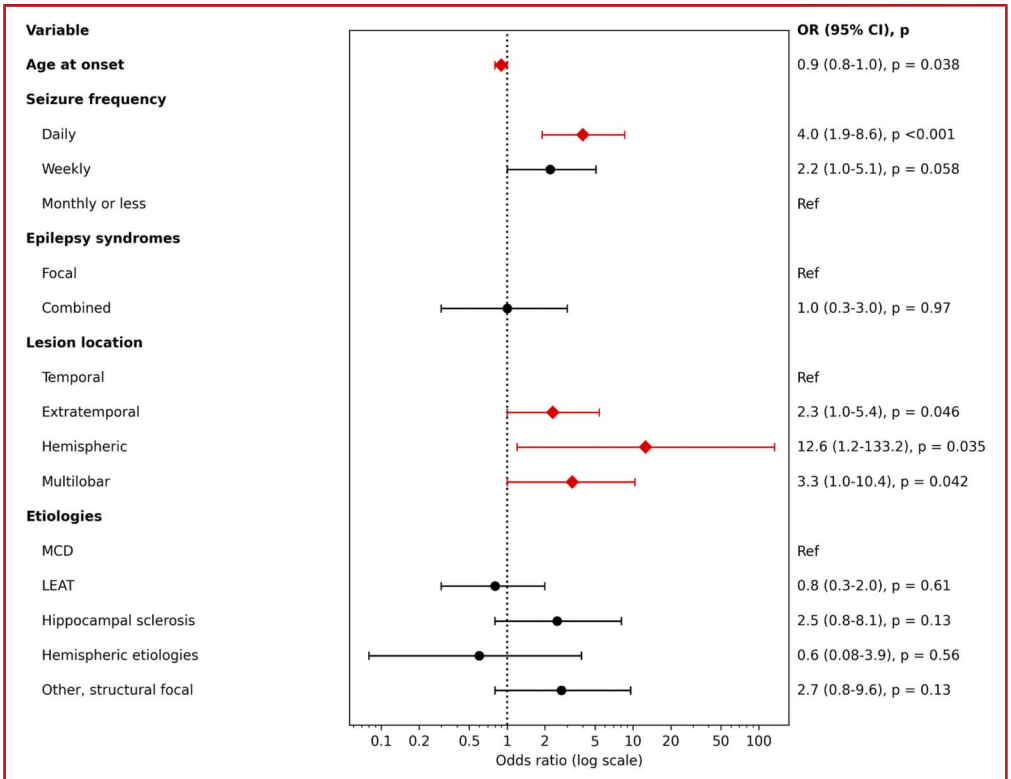

FIGURE 3. *Forest plot showing adjusted ORs with 95% CIs for referral after >3 ASM trials. The vertical dashed line indicates OR = 1 (no association). Younger age at epilepsy onset (OR 0.9, 95% CI 0.8-1.0), daily seizure frequency (OR 4.0, 95% CI 1.9-8.6), and extratemporal (OR 2.3, 95% CI 1.0-5.4), hemispheric (OR 12.6, 95% CI 1.2-133.2), and multilobar resections (OR 3.3, 95% CI 1.0-10.4), were independently associated with referral after >3 ASM trials. Generated using ChatGPT version 5.2. ASM, antiseizure medication; LEAT, low-grade epilepsy-associated tumor; MCD, malformation of cortical development; OR, odds ratios.*

ASM Trials

In our cohort, patients received a median of 4 ASM trials before referral, and nearly 70% had more than 3 trials before referral. This is broadly consistent with previous studies reporting a mean of 4 to 6 ASMs before referral.[16-18] However, disparities exist, as a recent North American study of more than 1700 children referred for presurgical evaluation reported that approximately 50% were referred after failure of 2 ASMs.[34]

As Finland has a publicly funded healthcare system, major differences in access related to insurance status are unlikely to explain delayed referral. Moreover, our previous work showed that referral delays and the number of ASM trials before referral were broadly similar across the country, arguing against substantial geographic barriers to accessing the national epilepsy surgery center.[35] In line with this, we observed no significant differences in ASM trials before referral between patients referred from secondary vs tertiary (university) hospitals. Furthermore, in our linear regression model, a higher number of ASM trials was not associated with a longer onset-to-referral interval, indicating that excess ASM use does not necessarily reflect delayed referral.

Nevertheless, the median number of ASM trials before referral exceeded the ILAE-recommended threshold for surgical evaluation indicating that referral often occurred only after additional medication escalation despite national recommendations to refer once DRE is diagnosed. Once a patient has failed trials of 2 appropriately chosen and tolerated ASMs, the likelihood of achieving seizure freedom with further ASM trials is significantly reduced.[3] For example, in focal cortical dysplasia, a potentially surgically remediable etiology, failure of even a first ASM has been associated with a substantially high risk of subsequent drug resistance.[36] Together, these observations support early consideration of referral to a comprehensive epilepsy surgery center once DRE is suspected or established.

Predictors of More ASM Trials Before Referral

In our study, patients undergoing extratemporal, multilobar, or hemispheric resections were more often referred after >3 ASM trials. The lesion locations likely reflect more severe epilepsy phenotypes. Temporal lobe surgery, the most established

TABLE 6. Sensitivity Analysis for Predictors of >3 Antiseizure Medication Trials Before Referral Using Age at Onset ≤1 year as the Age Variable

	OR (CI 95%)	*P*
Age at onset ≤1 y	1.9 (0.9-4.0)	.091
Seizure frequency		
Daily	3.8 (1.7-8.1)	<.001
Weekly	1.9 (0.9-4.4)	.12
Monthly or less	Ref	
Epilepsy syndromes		
Focal, nonsyndromic	Ref	
Combined	1.1 (0.3-3.2)	.93
Location of resection		
Temporal	Ref	
Extratemporal	2.5 (1.1-5.7)	.036
Hemispherotomy	12.9 (1.2-143.1)	.037
Multilobar	3.4 (1.1-10.8)	.036
Etiologies		.20
MCD	Ref	
LEAT	0.8 (0.3-2.0)	.62
Hippocampal sclerosis	2.6 (0.8-8.5)	.12
Hemispheric etiologies	0.6 (0.1-4.2)	.59
Other, structural focal	2.6 (0.7-9.1)	.14

LEAT, low-grade epilepsy-associated tumor; MCD, malformation of cortical development; OR, odds ratio; Ref, reference category.

approach, was predominantly associated with identifiable and often more localized etiologies such as LEATs and hippocampal sclerosis (63% of the temporal cohort). By contrast, extratemporal and multilobar resections were more frequently linked to MCDs, and hemispheric procedures were typically performed for catastrophic epilepsy. Consistent with greater disease severity outside the temporal lobe, daily seizures were less common in the temporal group (41.3%) than in the extratemporal (56.9%), hemispheric (80.6%), and multilobar (61.3%) groups. However, because we lacked precise initiation dates for individual preoperative ASMs, we could not determine whether the higher ASM burden reflected longer or more intensive treatment escalation before referral.

Younger age at epilepsy onset was also associated with a higher number of ASM trials before referral. Early-onset epilepsies are often accompanied by a substantial burden of cognitive and behavioral comorbidities and higher rates of drug resistance, reflecting complex and extensive underlying etiologies.[37-39] Underlying etiologies are often developmental or hemispheric in nature, including extensive cortical malformations or perinatal vascular insults. Accordingly, hemispheric procedures and multilobar resections are overrepresented in the youngest surgical populations, accounting for approximately 45.6% to 68.9% of surgeries in children younger than 3 years, compared with roughly one-third in broader pediatric epilepsy surgery cohorts.[16,40-43]

Overall, the association between extratemporal location, early onset, and a higher number of ASM trials likely reflects more severe epilepsy phenotypes that prompt repeated medication escalation before referral. In our previous study, onset-to-referral intervals were similar across age-at-onset groups and resection locations, indicating that these factors do not necessarily prolong time to referral.[35] Rather, the higher ASM burden may reflect more rapid or intensive medication escalation before referral, even within comparable time intervals. Accordingly, future efforts should emphasize timely recognition of DRE and prompt referral after the failure of 2 ASMs for surgical evaluation among children with early-onset epilepsy and those with suspected extratemporal, multilobar, or hemispheric epilepsy.

Seizure Outcomes

We found that patients referred after ≤3 ASM trials had a significantly higher rate of seizure freedom than those referred after >3 trials. A previous study, similarly reported that referral after failure of >2 ASMs was independently associated with worse seizure outcomes; however, that analysis did not adjust for clinically important prognostic factors such as resection location and etiology.[34] In the multivariable analysis, referral after ≤3 ASMs trials was independently associated with higher odds of Engel class 1 outcome. However, this finding should be interpreted cautiously, as the better outcomes in the ≤3 ASM group may partly reflect underlying clinical characteristics, including a higher proportion of more clearly localized and surgically favorable epilepsies, such as temporal lobe epilepsy and LEATs. Furthermore, the observational design precludes causal inference and residual confounding from unmeasured factors cannot be excluded.

An additional argument for earlier surgical evaluation, rather than continued escalation of ASM trials, is the potential to reduce cumulative ASM exposure and its adverse effects, particularly on cognition and neurodevelopment. This may be especially relevant in patients with structural etiologies such as focal cortical dysplasia, which are strongly associated with drug resistance and for which additional ASM trials rarely result in sustained seizure control.[36] Accordingly, the literature supports considering surgical evaluation even in selected patients with a structural lesion in a noneloquent area who are seizure-free on 1 or 2 ASMs, given favorable reported seizure outcomes and acceptable complication risk in this cohort.[44,45]

Strengths and Limitations

The main strength of our study is that HUH serves as the national pediatric epilepsy surgery center in Finland, enabling a nationwide, population-based cohort of children undergoing

epilepsy surgery. In addition, pediatric neurology services are widely available in Finland, and most children with epilepsy receive specialist follow-up regardless of regions.[46] This likely results in relatively uniform treatment pathways and consistent access to pediatric neurology expertise, thereby reducing confounding related to variability in treating physician background and practice patterns. However, the publicly funded, single-center nature of the Finnish system may limit generalizability to settings with fragmented care, private insurance, or different referral cultures, where additional barriers to surgical evaluation may exist.

The presented data include only patients who underwent surgery, as our surgical registry does not systematically capture information on presurgical DRE evaluations in patients who did not proceed to epilepsy surgery. Consequently, we were unable to assess whether the factors associated with referral after >3 ASM trials similarly apply to patients who were evaluated but ultimately not considered eligible for resective surgery.

Furthermore, precise initiation dates for each ASM were not available, and therefore we could not determine the duration of individual trials, whether doses were maximized, or whether ASMs were trialed sequentially or concurrently. A higher ASM count may therefore not necessarily reflect a longer treatment course, as some patients may have undergone rapid sequential trials over a shorter period.

In addition, the cohort includes only patients who ultimately underwent resective surgery, and children undergoing palliative procedures were excluded, which may limit generalizability to the broader population of children with DRE.

As this was a retrospective study, it is subject to inherent limitations, including potential selection bias, missing data, and variability in the completeness and consistency of clinical documentation.

CONCLUSIONS

Our study demonstrates that in a population-based cohort of children undergoing resective epilepsy surgery, the median number of ASM trials before referral for presurgical evaluation was 4, which exceeds the ILAE recommendation to refer after failure of 2 ASMs. Extratemporal and multilobar resections, hemispheric procedures, daily seizure frequency, and younger age at onset were associated with a higher number of ASM trials before referral, likely reflecting more severe epilepsy phenotypes. The number of prereferral ASM trials decreased over time probably reflecting increased awareness of surgical options. These findings reinforce the importance of timely recognition of DRE and consideration of surgical evaluation alongside escalation of ASM trials, although our conclusions are based on patients undergoing resective surgery and may not be directly applicable to candidates for palliative procedures. Given the observational nature of this study, the relationship between the number of ASM trials and seizure outcomes should be interpreted with caution.

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COMMENTS

This nationwide study underscores how often children with drug-resistant epilepsy still undergo multiple additional antiseizure medication (ASM) trials before evaluation for surgery, despite clear ILAE guidance to refer after failure of 2 appropriately chosen drugs. The median of 4 pre-referral ASM trials in this cohort, and the fact that nearly 70% of children exceeded the recommended threshold, highlight a recalcitrant gap between evidence-based recommendations and real-world practice in a publicly funded, ostensibly equitable health system.

Crucially, greater ASM exposure clustered in those with earlier onset, daily seizures, and extratemporal, multilobar, or hemispheric resections—phenotypes that are both more severe and often less likely to respond to continued medical therapy. While worse seizure outcomes in children with more ASM trials likely reflect underlying disease complexity rather than a simple causal effect of delay, the association between referral after 3 ASMs and higher odds of Engel I outcome supports the principle that surgical centers should be engaged as soon as drug resistance is suspected. Beyond seizure control, earlier evaluation offers an opportunity to reduce cumulative medication burden and its cognitive and developmental consequences, particularly in children with structural etiologies for whom further pharmacologic escalation rarely restores durable seizure freedom.

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The authors provide a retrospective, population based cohort from Finland, evaluating children undergoing respective epilepsy surgery between 2002 and 2022. The study includes 239 children, with mean age of onset of epilepsy 2.6 years.

The authors show through multivariable logistic regression that referral after ≤3 ASM (anti-seizure medication) was independently associated with higher odds of Engel Class 1 outcome. Referral after >3 ASM increased time to referral and increased the likelihood of not having Engel Class 1 outcome.

These are compelling data that provide an argument for earlier referral for surgical evaluation in patients with complex epilepsy (epilepsy that is not easily controlled with 1 or 2 ASM). While prospective data are needed, and this study is limited to the Finnish population, this study provides additional evidence that early surgical intervention provides improved seizure freedom rates compared to delayed surgery in patients with drug-resistant epilepsy.

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