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FULL-LENGTH ORIGINAL RESEARCH

Etiology-specific response to antiseizure medication in focal epilepsy

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Abstract

Objective: In focal epilepsy, data on the etiology-specific response to antiseizure medication (ASM) are surprisingly sparse. In this study, we sought to reappraise whether seizure outcome of pharmacological treatment is linked to the underlying etiology. Furthermore, we assessed ASM load with respect to the cause of epilepsy.

Methods: Data were retrospectively obtained from the electronic database of the three sites of an academic adult epilepsy outpatient clinic. For each patient, presumed cause of epilepsy was categorized into one of nine etiological groups. Individual drug loads were calculated according to the 2020 World Health Organization Center for Drug Statistics Methodology ATC/DDD Index. Univariate and multivariate analyses were conducted to explore the association between different etiologies and outcome regarding 12-month seizure freedom as well as ASM load.

Results: A total of 591 patients with focal epilepsy were included in the final analysis. Ischemic stroke was the etiology with the highest rate of 12-month terminal seizure freedom (71.2%, 95% confidence interval [CI] = 57.9–82.2) and, considering all etiological groups, was an independent predictor of seizure freedom (odds ratio = 2.093, 95% CI = 1.039–4.216). The lowest rates of seizure freedom were observed in patients with hippocampal sclerosis (28.2%, 95% CI = 15.0–44.9) and malformation of cortical development (16.7%, 95% CI = 2.1–48.4). In patients with ischemic stroke, median ASM load (1.0, interquartile range [IQR] = .5–1.8) was significantly lower compared to that in patients with hippocampal sclerosis (median = 1.8, IQR = 1.2–3.0, $p = .008$) and brain tumors (median = 1.7, IQR = .7–3.2, $p = .049$).

Significance: Response to treatment with ASM is highly etiology-specific and best in patients with epilepsy due to ischemic stroke. Interestingly, this most favorable treatment outcome can be achieved by the lowest ASM load considering all etiological groups. In focal epilepsy, etiology should be taken into account when counseling patients about their expected seizure outcome with pharmacological treatment and when tailoring initial ASM doses.

KEYWORDS

drug load, hippocampal sclerosis, prognosis, seizure freedom, stroke

1 | INTRODUCTION

Estimating seizure outcome in epilepsy is of high importance with regard to counseling patients on overall prognosis and tailoring treatment decisions. Approximately 60%–70% of people with epilepsy (PwE) achieve seizure freedom with antiseizure medication (ASM); in mono- or polytherapy, treatment success in focal epilepsy (57%–62% seizure-free)[1,2] is generally lower as compared to genetic generalized epilepsy (68%–85%).[1,3,4] Beyond seizure control, equipollent therapeutic goals for PwE comprise minimal adverse effects of ASM and overall low interference of ASM with the patient's lifestyle,[5] both of which may be achieved by a preferably low drug load.

It is well-established scientific consensus that etiology of intractable focal epilepsy is the major predictor for seizure outcome after resective epilepsy surgery.[6–8] Curiously, there is only very limited evidence on the significance of etiology for pharmacological treatment success in focal epilepsy.

Twenty years ago, two studies assessed the etiology-specific response to ASM in patients with focal epilepsy, showing unfavorable findings in epilepsy caused by hippocampal sclerosis, whereas epilepsy due to stroke had the highest seizure freedom rates.[2,9] Stroke was not separated into ischemic and hemorrhagic forms. Furthermore, it remained unresolved whether the superior ASM treatment response in epilepsy of certain etiologies comes at the cost of intensified medical therapy, possibly associated with a higher burden of adverse effects. In the past 2 decades, a multitude of new ASMs have been approved,[10] and magnetic resonance imaging (MRI) techniques have improved significantly, allowing for better detection of smaller pathologies underlying focal epilepsy.[11] Both issues may impact the overall and the etiology-specific pharmacological treatment response in focal epilepsy.

In this study, we aimed to reappraise the response to ASM in patients with focal epilepsy caused by different etiologies. To this end, we assessed 12-month terminal seizure freedom and load of ASM in nine etiological groups.

Key Points

- In patients with focal epilepsy, response to treatment with antiseizure medication is highly etiology-specific
- Focal epilepsy due to ischemic stroke has the best outcome, resulting in 12-month terminal seizure freedom in >70% of patients
- Superior prognosis of postischemic stroke epilepsy is achieved by the lowest antiseizure medication load considering all other etiologies
- Etiology of focal epilepsy should be taken into account when counseling patients about the expected response to antiseizure medication

2 | MATERIALS AND METHODS

2.1 | Data source and patients

Data were obtained from the electronic database of the three sites of the adult epilepsy outpatient clinic of the Department of Neurology at Charité–Universitätsmedizin Berlin. The study was approved by the local ethics committee (EA4/022/20). Due to the retrospective design of this study, informed consent from individual patients was waived.

We included patients with a diagnosis of focal epilepsy according to the 2017 International League Against Epilepsy classification.[12] We only considered patients with ≥2 visits in the outpatient clinic, which had to be ≥12 months apart. The vast majority of patients had undergone head MRI following a standardized epilepsy protocol; in some cases, the etiology relied on head computed tomography findings only, for example, in patients with middle cerebral artery infarction and suitable seizure semiology. All patients who were allocated to "unknown etiology" had undergone head MRI. Exclusion criteria were insufficient documentation of clinical data in the database, previous resective epilepsy surgery, and concurrent neurostimulation (Figure 1). Our analysis comprised all visits to the outpatient clinic from January 2010 to March 2020. In Germany, academic epilepsy outpatient clinics, at least the one at the Charité, serve for the broad population of patients with epilepsy and do not focus on difficult-to-treat cases.

Parameters retrieved from the database were sex, age at last visit, duration of epilepsy, presumed etiology of epilepsy, 12-month terminal seizure freedom, number of all ASMs taken so far (including current medication), and number of ASMs including dosage at the last visit to the outpatient clinic.

Etiology of epilepsy was allocated to one of the following common groups: cerebrovascular malformation, hippocampal sclerosis, malformation of cortical development, brain tumor, hemorrhagic stroke, ischemic stroke, traumatic brain injury, other etiologies, and unknown etiology. Due to the undetermined role of microvascular leukoencephalopathy in the etiology of epilepsy, this MRI finding was subsumed into "unknown etiology."

2.2 | Primary and secondary outcomes

The primary outcome parameter was seizure freedom for ≥12 months as assessed at the last documented visit

in our outpatient clinics. Secondary outcome parameter was individual ASM load at the last documented visit. For each patient, the drug load was calculated according to the 2020 World Health Organization Center for Drug Statistics Methodology ATC/DDD Index using the formula "individual ASM dosage per day divided by defined daily dose (DDD)." In patients taking more than one ASM, the sum of all ratios was calculated and used for analysis. For example, a patient on 1500 mg levetiracetam per day (DDD of levetiracetam = 1500 mg) would have an ASM load of 1. A patient on 1500 mg levetiracetam and 150 mg lacosamide per day (DDD of lacosamide = 300 mg) would have an ASM load of 1.5.

2.3 | Statistical analysis

Data were checked for normal distribution using the Kolmogorov–Smirnov test. Categorial variables were analyzed with chi-squared tests. Accordingly, continuous data were analyzed with Mann–Whitney *U*-tests. The significance level was set at $p < .05$. Confidence intervals (CIs) for frequencies were calculated using the Clopper–Pearson method.

We conducted unadjusted and adjusted multiple logistic regression analyses to assess the association between etiology of epilepsy and seizure freedom. Etiology of epilepsy was entered as a categorical variable with unknown etiology used as reference. The model was adjusted for age, sex, duration of epilepsy, and number of ASMs taken so far, including current medication (inclusion method: enter, $p < .05$ [p in], $p < .1$ [p out], iteration 20, cutoff set at .26 and constant included).

To compare the ASM load of different etiologies of epilepsy at the last visit and the number of substances used in the patient's history, we performed Kruskal–Wallis tests and post hoc analyses with pairwise comparisons using Dunn procedure with a Bonferroni correction for multiple comparisons.

Statistical analyses were performed with SPSS Version 25 (IBM).

3 | RESULTS

3.1 | Study population

In our database, we identified 1318 patients with focal epilepsy. Of these, 727 patients were not eligible for inclusion. The patient selection is shown in Figure 1.

Our final analysis included 591 patients; 49.2% were female, median age at last visit was 52 years (interquartile range [IQR] = 37–67), and median duration of epilepsy was 14 years (IQR = 6–27). Median time between first and last documented visit was 5.2 years (IQR = 2.7–9.9). At the last visit, 47.7% (95% CI = 43.6%–51.8%) of patients were seizure-free for at least the previous 12 months; 323 of all patients were treated in monotherapy (54.7%), 240 in polytherapy (40.6%), and 28 patients (4.7%) were off ASM. The most commonly prescribed ASMs were lamotrigine (41.7% of patients with ASM), levetiracetam (41.2%), lacosamide (9.9%), and carbamazepine and oxcarbazepine (each 8.2%).

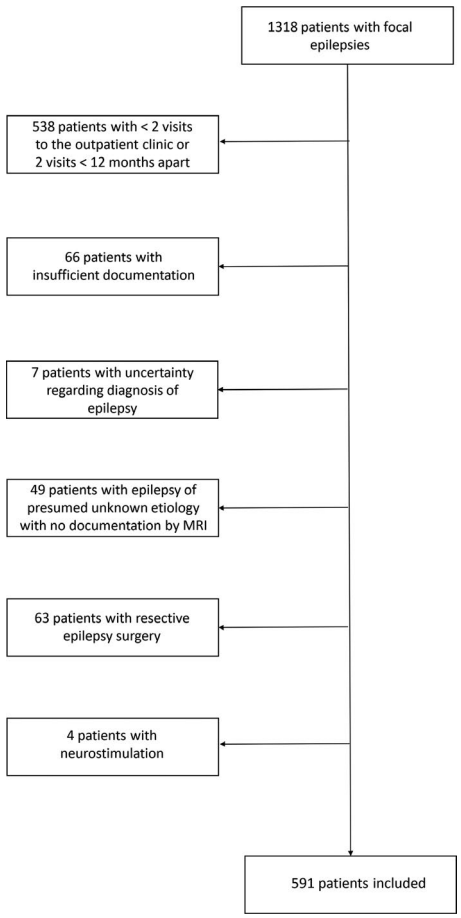

FIGURE 1 This flowchart illustrates patient selection and reasons patients were not eligible for inclusion

3.2 | Characteristics of patients with seizure freedom

In univariate analyses, seizure-free patients significantly more often had epilepsy caused by ischemic stroke than patients who were not seizure-free (14.9% vs. 5.5%, $p < .001$); they were less likely to have hippocampal sclerosis (3.9% vs. 9.1%, $p = .012$) and malformation of cortical development (.7% vs. 3.2%, $p = .030$). Seizure-free patients were older and had a shorter duration of epilepsy than patients who had seizures in the 12-month period prior to the last outpatient visit. Seizure freedom was also associated with a significantly lower ASM load and a lower number

of ASMs prescribed in the patient's history (Table 1). There was no statistically significant difference in duration of follow-up between patients who were seizure-free and those who were not (median 5.7 vs. 4.7 years, $p = .275$).

3.3 | Etiology-specific seizure freedom rates

Seizure freedom rates for different etiologies are shown in Table 2 and Figure 2. Ischemic stroke was the underlying etiology with the highest rate of seizure freedom (71.2%, 95% CI = 57.9–82.2). Hippocampal sclerosis and malformation of cortical development were the etiologies with the lowest seizure freedom rates (28.2% [95% CI = 15.0–44.9] and 16.7% [95% CI = 2.1–48.4], respectively).

When entered as a categorical variable into logistic regression analysis considering causes of epilepsy, with unknown etiology as a reference and adjustment for age, sex, duration of epilepsy, and total number of ASMs taken since diagnosis of epilepsy, ischemic stroke was independently associated with a higher odds of seizure freedom (odds ratio = 2.093, 95% CI = 1.039–4.216; Table 2).

Patients with ischemic stroke, compared to those with all other etiologies (including unknown), were significantly older, had a shorter duration of epilepsy, were more often seizure-free, and had a lower ASM load at the last visit (Table 3). Patients with hippocampal sclerosis had a longer duration of epilepsy, a higher ASM load, and a higher number of ASMs prescribed since diagnosis of epilepsy as compared to patients with other causes of focal epilepsy (Table 4).

3.4 | Etiology-specific drug loads

Loads of ASM for different etiologies of epilepsy are given in Table 5. Kruskal–Wallis test showed a significant difference between epilepsy etiologies ($\chi^2[8] = 31.032$, $p < .001$). Post hoc analysis with pairwise comparisons using Dunn procedure with a Bonferroni correction for multiple comparisons demonstrated a significantly lower drug load in patients with ischemic stroke as compared to those with hippocampal sclerosis (adjusted $p = .008$) and brain tumor (adjusted $p = .049$) as well as a significantly higher load in patients with hippocampal sclerosis compared to those with unknown etiology (adjusted $p = .029$). Figure 2 summarizes and contrasts the seizure freedom rates and ASM loads for the specific etiological groups.

The total number of ASMs prescribed since diagnosis of epilepsy also significantly differed with respect to the underlying etiology ($\chi^2[8] = 26.268$, $p = .001$). In post hoc analyses, pairwise comparisons showed that in patients with ischemic stroke as compared to those with hippocampal sclerosis, the number of previous and current ASMs was significantly lower ($p = .030$).

TABLE 1 Clinical variables associated with seizure freedom

Variable	Seizure-free, $n = 282$	Not seizure-free, $n = 309$	Statistical analysis
Female sex, *n* (%)	135 (47.9)	156 (50.5)	$p = .526$[a]
Age, years, median (IQR)	55 (39–70)	48 (35–62)	$p = .001$[b,c]
Duration of epilepsy, years, median (IQR)	11 (5–24)	17 (7–31.5)	$p = .001$[b,c]
All ASMs since diagnosis of epilepsy, *n*, median (IQR)	2 (1–3)	3 (2–5)	$p < .001$[b,c]
ASM load at last visit, median (IQR)	.8 (.4–1.3)	1.8 (1.0–3.0)	$p < .001$[b,c]
Seizure etiology, *n* (%)			
Cerebrovascular malformation	17 (6.0)	16 (5.5)	$p = .784$[a]
Hippocampal sclerosis	11 (3.9)	28 (9.1)	$p = .012$[a,c]
Malformation of cortical development	2 (.7)	10 (3.2)	$p = .030$[a,c]
Brain tumor	26 (9.2)	41 (13.3)	$p = .121$[a]
Hemorrhagic stroke	14 (5.0)	15 (4.5)	$p = .804$[a]
Ischemic stroke	42 (14.9)	17 (5.5)	$p < .001$[a,c]
Traumatic brain injury	27 (9.6)	28 (9.1)	$p = .830$[a]
Other etiologies	4 (1.4)	7 (2.3)	$p = .447$[a]
Unknown etiology	139 (49.3)	147 (47.6)	$p = .676$[a]

Abbreviations: ASM, antiseizure medication; IQR, interquartile range.

[a]Pearson chi-squared test.

[b]Mann–Whitney *U*-test,

[c]Statistically significant.

TABLE 2 Etiology-specific seizure freedom rates

Etiology	Seizure freedom rate, *n*/*N* (%)	Logistic regression, adjusted OR (95% CI)[a]
Unknown etiology	139/286 (48.6%, 95% CI = 42.7–54.6)	1 (reference)
Cerebrovascular malformation	17/33 (51.5%, 95% CI = 33.5–69.2)	.944 (.466–2.120)
Hippocampal sclerosis	11/39 (28.2%, 95% CI = 15.0–44.9)	.561 (.248–1.269)
Malformation of cortical development	2/12 (16.7%, 95% CI = 2.1–48.4)	.400 (.075–2.141)
Brain tumor	26/67 (38.8%, 95% CI = 27.1–51.5)	.827 (.446–1.535)
Hemorrhagic stroke	14/29 (48.3%, 95% CI = 29.4–67.5)	1.069 (.451–2.535)
Ischemic stroke	42/59 (71.2%, 95% CI = 57.9–82.2)	2.093 (1.039–4.216)
Traumatic brain injury	27/55 (49.1%, 95% CI = 35.4–62.9)	.866 (.464–1.617)
Other	4/11 (36.4%, 95% CI = 10.9–69.2)	.976 (.223–4.266)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Adjusted for age, sex, duration of epilepsy, and number of all ASMs taken since diagnosis of epilepsy.

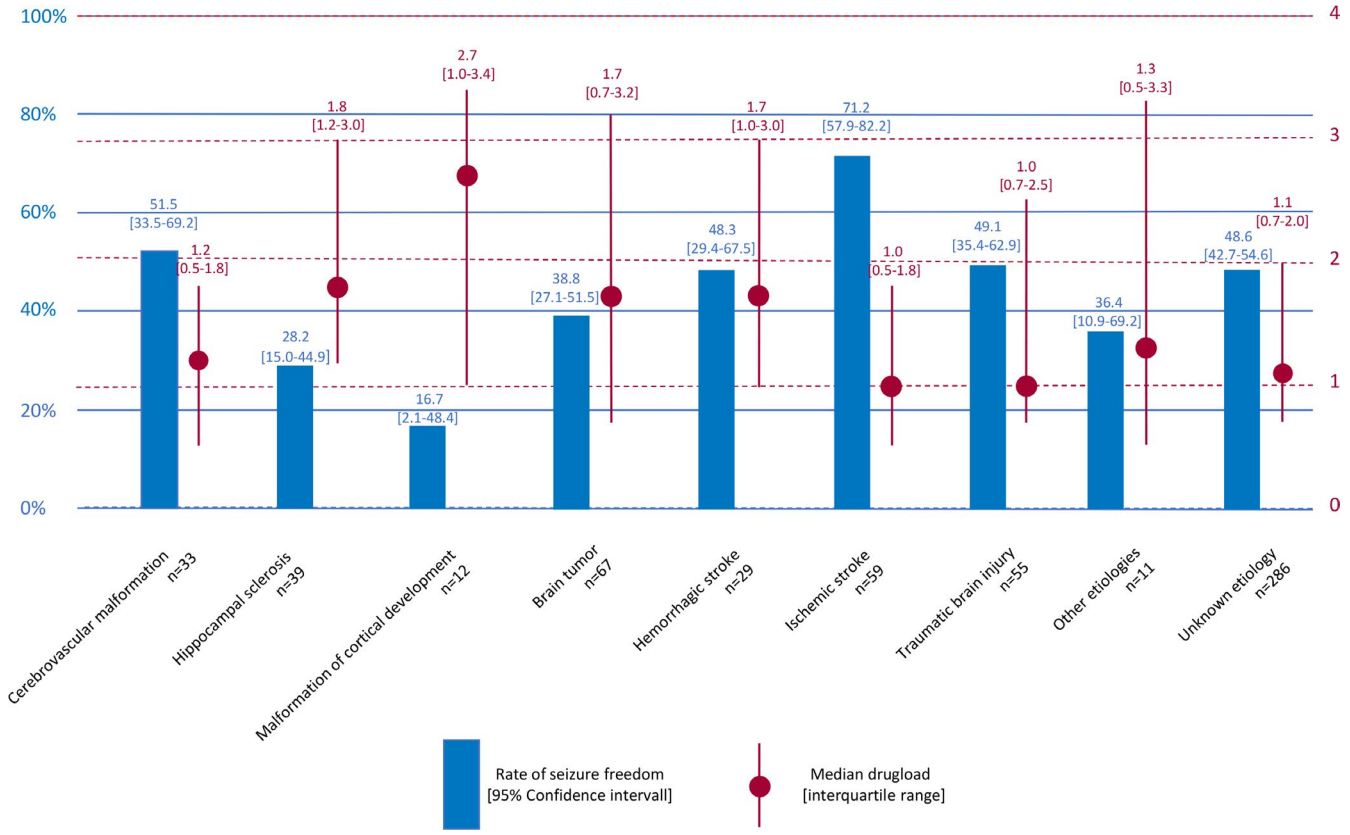

FIGURE 2 Comparison of seizure-freedom rates and drug loads for different epilepsy etiologies. Rate of seizure freedom for each etiology of epilepsy is represented by the blue bars (left y-axis). Median load of antiseizure medication for each etiology is represented by the purple dots (right y-axis), with the vertical lines indicating interquartile ranges. Load of antiseizure medication was calculated according to the 2020 World Health Organization Center for Drug Statistics Methodology ATC/DDD Index using the formula "individual antiseizure medication dosage per day divided by defined daily dose"

4 | DISCUSSION

In this study, we demonstrated that the response to ASM in focal epilepsy is highly etiology-specific. Almost three in four patients with epilepsy caused by ischemic stroke were seizure-free for at least the previous 12 months, which is superior to all other etiologies assessed. In contrast, hippocampal sclerosis (28%) and malformation of cortical development (17%) had a significantly lower rate of seizure

TABLE 3 Clinical variables associated with epilepsy caused by ischemic stroke

Variable	Patients with epilepsy caused by ischemic stroke, $n = 59$	Patients with epilepsy of other etiology, $n = 532$	Statistical analysis
Female sex, *n* (%)	24 (40.7)	264 (50.2)	$p = .166$[a]
Age, years, median (IQR)	73 (60–77)	50 (37–64)	$p < .001$[b,c]
Duration of epilepsy, years, median (IQR)	9 (5–17)	15 (6–29)	$p = .009$[b,c]
All ASMs since diagnosis of epilepsy, *n*, median (IQR)	2 (1–3)	2 (1–4)	$p = .069$[b]
Seizure-free at last visit, *n* (%)	40 (71.2)	240 (45.1)	$p < .001$[a,c]
ASM load at last visit, median (IQR)	1 (.5–1.8)	1.3 (.7–2.4)	$p = .019$[b,c]

Abbreviations: ASM, antiseizure medication; IQR, interquartile range.

[a]Pearson chi-squared test.

[b]Mann–Whitney *U*-test.

[c]Statistically significant.

TABLE 4 Clinical variables associated with epilepsy caused by hippocampal sclerosis

Variable	Patients with epilepsy caused by hippocampal sclerosis, $n = 39$	Patients with epilepsy of other etiology, $n = 552$	Statistical analysis
Female sex, *n* (%)	23 (59.7)	268 (48.6)	$p = .208$[a]
Age, years, median (IQR)	53 (41–69)	52 (37–67)	$p < .579$[b]
Duration of epilepsy, years, median (IQR)	35 (12–48)	13 (6–26)	$p < .001$[b,c]
All ASMs since diagnosis of epilepsy, *n*, median (IQR)	3 (2–6)	2 (1–4)	$p = .003$[b,c]
Seizure-free at last visit, *n* (%)	11 (28.2)	271 (49.1)	$p = .012$[a,c]
ASM load at last visit, median (IQR)	1.8 (1.2–3.0)	1.2 (.7–2.2)	$p = .002$[b,c]

Abbreviations: ASM, antiseizure medication; IQR, interquartile range.

[a]Pearson chi-squared test.

[b]Mann–Whitney *U*-test.

[c]Statistically significant.

freedom. Ischemic stroke also was independently associated with increased odds of 12-month seizure freedom as compared to the other etiological groups when adjusted for age, sex, duration of epilepsy, and number of ASMs taken so far. As secondary outcome, we also report ASM load to be etiology-specific in focal epilepsy. Interestingly, patients with epilepsy caused by ischemic stroke had the lowest drug load, which obviously was sufficient to result in the highest seizure freedom rate. Furthermore, in patients with post-ischemic stroke epilepsy, the number of previously and currently administered ASMs was significantly lower compared to that in patients with hippocampal sclerosis.

Counseling on the expected probability of seizure freedom with ASM treatment is paramount to meet the information needs of patients with epilepsy and to tailor drug doses. Nonetheless, the scarcity of data on the impact of underlying etiology is striking. More than 20 years ago, two studies assessed the etiology-specific response to ASM in focal epilepsy.[2,9] Since then, multiple new ASMs have been approved,[10] which may impact the response to treatment. In our study, 56.4% of patients on ASM received such novel compounds, confirming the necessity to reappraise the precedent data. In one study from 1998 on seizure outcome in focal epilepsy, the highest rate of seizure freedom (54%) was observed in patients with stroke; the lowest rate (11%) was seen in patients with hippocampal sclerosis.[9] In another study from 2001, 67% of patients with stroke were seizure-free, and seizure freedom was reported in 42% of patients with hippocampal sclerosis.[2] The surprisingly high seizure freedom rate in hippocampal sclerosis in the latter study may be explained by >70% of patients having newly diagnosed epilepsy and thus likely a small number of previously failed ASMs. In the current study, 28% of 39 patients with hippocampal sclerosis were seizure-free, which is still a considerably high rate. The group of 11 seizure-free patients so far have taken significantly fewer ASMs (median = 2 vs. 4, $p = .001$), which also hints at less severe forms of epilepsy; the 28 patients with drug resistance and hippocampal sclerosis either were ineligible candidates for resective surgery or had rejected the operation.

A more recent analysis of the etiology-specific treatment response was done in a post hoc analysis of the

TABLE 5 Comparison of ASM load according to etiology of epilepsy

Etiology	ASM load at last visit, median (IQR)	Statistical analysis	All ASMs since diagnosis of epilepsy, *n*, median (IQR)	Statistical analysis
Cerebrovascular malformation, $n = 33$	1.2 (.5–1.8)	$\chi^2[8] = 31.032$, $p < .001$[a,b]	2 (1–3)	$\chi^2[8] = 28.989$, $p < .001$[a,c]
Hippocampal sclerosis, $n = 39$	1.83 (1.2–3.0)		3 (2–6)	
Malformation of cortical development, $n = 12$	2.7 (1–3.4)		4 (2.5–6.5)	
Brain tumor, $n = 67$	1.67 (.67–3.2)		3 (2–5)	
Hemorrhagic stroke, $n = 29$	1.7 (1.0–3.0)		2 (2–4)	
Ischemic stroke, $n = 59$	1 (.5–1.8)		2 (1–3)	
Traumatic brain injury scar, $n = 55$	1 (.7–2.5)		2 (1–3)	
Other, $n = 15$	1.3 (.5–3.3)		4 (2–6)	
Unknown etiology, $n = 286$	1.1 (.67–2.0)		2 (1–4)	

Abbreviations: ASM, antiseizure medication; IQR, interquartile range.

[a]Kruskal–Wallis test.

[b]Significant differences in ASM load between ischemic stroke and brain tumor (Bonferroni adjusted $p = .049$), ischemic stroke and hippocampal sclerosis (adjusted $p = .008$), and hippocampal sclerosis and unknown etiology (adjusted $p = .029$).

[c]Significant differences in number of all ASMs since diagnosis of epilepsy between ischemic stroke and hippocampal sclerosis (adjusted $p = .030$).

Euro-Esli study on patients all of whom were treated with eslicarbazepine acetate in mono- or polytherapy. In that study, patients with epilepsy due to stroke compared to all other causes of focal epilepsy had a significantly higher 50% responder rate; that is, >50% fewer seizures with eslicarbazepine acetate than before.[13] However, there is no reason to assume that specific ASMs are more or less efficacious in focal epilepsy of different etiologies.

The three aforementioned studies did not differentiate strokes of ischemic versus hemorrhagic origin.[2,9,13] In our study, the response to treatment trended to be better in epilepsy caused by ischemic (71%) compared to hemorrhagic stroke (48%), and only ischemic stroke differed significantly from other etiologies. It is believed that the epileptogenic pathomechanisms between epilepsy caused by ischemic stroke and intracerebral hemorrhage differ. Pathogenesis of post-ischemic stroke epilepsy includes changes in regional cerebral blood flow, alteration of the blood–brain barrier, and remodeling of neuronal networks,[14] whereas epileptogenesis after intracerebral hemorrhage is mediated additionally by effects of hemosiderin disposition and mechanical effects due to hematoma expansion.[15] What is more, hemorrhagic stroke is a stronger risk factor for the development of epilepsy than ischemic stroke. In a large study on more than 750 000 stroke patients, 14.7% of patients with hemorrhagic stroke and 8.3% of patients with ischemic stroke developed epilepsy within 8 years after the index event.[16] Our results encourage differentiating between ischemic and hemorrhagic stroke when estimating the prognosis of epilepsies and the response to ASM.

To our knowledge, this study is the first to compare ASM loads between different etiologies of focal epilepsy. Patients with post-ischemic stroke epilepsy had the lowest ASM load, in particular if compared to those with brain tumor and hippocampal sclerosis. This finding is of high clinical relevance, as it unequivocally shows that the favorable response to ASM treatment in epilepsy due to ischemic stroke does not come at the cost of the need for higher ASM dosages. Even more, the dosages administered in ischemic stroke were even lower than in other etiologies, which generally decreases the probability of adverse effects, improves adherence to ASM intake, and likely increases quality of life.[17] The favorable response of poststroke epilepsy to ASM has been demonstrated in a small series with 35 patients, two thirds of whom had had ischemic strokes, as 16 patients (46%) became seizure-free with the first ASM.[18] In the present study, epilepsy due to ischemic stroke so far has been treated with a median of only two ASMs, which is significantly less than in epilepsy caused by hippocampal sclerosis. Thus, etiology-specific seizure freedom rates inversely correspond to the number of ASMs administered so far. The association between the number of previously failed ASMs and

the probability of seizure freedom has been demonstrated previously; the fewer ASMs have failed so far, the higher the chance of seizure freedom with the next compound, and vice versa.[19] This general observation has now been confirmed with respect to specific etiologies.

There are limitations to this study. First, although we report results from three sites of the epilepsy outpatient clinic of the Charité–Universitätsmedizin Berlin covering vast parts of the city with heterogenic patient populations, our methodological approach still has to be considered monocentric. Second, data were assessed in a specialized epilepsy outpatient clinic, which bears the risk of bias due to treatment of rather challenging cases and thus lower rates of seizure freedom. However, this bias would be true for all etiologies and would not impact the relative differences in response to ASM between the underlying causes of epilepsy. Furthermore, almost every second patient was seizure-free, which is what can be expected in the overall group of patients with focal epilepsy. Third, due to the retrospective nature of the study, differences in follow-up time between different seizure etiologies could not be ruled out. Pairwise comparisons revealed that there was a significant difference in duration of follow-up between patients with specific etiologies. For example, follow-up time was shorter in patients with brain tumor as compared to unknown etiology and hippocampal sclerosis. The analysis of follow-up time between different etiologies is summarized in the supplementary material (Table S1, online only). The cause of the difference in follow-up time is unclear, as we have no reliable information on the reason patients discontinue treatment at our outpatient clinic. One major cause could be mortality. As our study design required at least two visits to the outpatient clinic that had to be at least 12 months apart, it is plausible that the impact of mortality on the outcome of our study due to a reduced observation period is limited. Reassuringly, there was no statistically significant difference in duration of follow-up between patients who were seizure-free and those who were not. The validity of our data is also limited by differences in group sizes. Although the overall number of patients in our study was large, we had only few patients with, for example, malformation of cortical development. Finally, a potential source of bias could lie in incomplete data collection; for example, we could not differentiate affected vascular territories in ischemic stroke or primary versus secondary brain tumors.

5 | Conclusions

Our study demonstrates that in focal epilepsy, both the response to pharmacological treatment regarding rate of seizure freedom and ASM load are highly etiology-specific. Ischemic stroke was the etiology with the most favorable prognosis, whereas hippocampal sclerosis and malformation of cortical development were those with the worst. Patients with ischemic stroke underlying epilepsy obviously need a rather low ASM load to achieve a high probability of seizure freedom. Etiology should be considered when informing patients about their prognosis and when tailoring the doses of ASM. Further data on the etiology-specific response to pharmacological treatment of epilepsy are warranted to substantiate our findings. They may be extracted from existing large trials such as SANAD, which provide detailed information on previous or current neurological disorders likely corresponding to the underlying etiology.[20,21]

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CONFLICT OF INTEREST

J.I.D. and A.B.K. declared no conflicts of interest with respect to the research, authorship, and/or publication of this article. MH reports personal fees as speaker and consultant from Arvelle, Bial, Desitin, Eisai, GW Pharma, UCB, and Zogenix outside the submitted work. 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.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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