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ORIGINAL COMMUNICATION

# Seizures and epilepsy in multiple sclerosis: epidemiology and prognosis in a large tertiary referral center

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## Abstract

**Background** Seizures and epilepsy may substantially add to the burden of disease in multiple sclerosis (MS), whereas the exact prevalence and prognosis of seizures and epilepsy in patients with MS remains largely unknown.
**Objectives** We aimed to investigate the epidemiology and prognosis of seizures and epilepsy in MS.
**Methods** We retrospectively analyzed a cohort of 4078 MS patients from a single tertiary referral clinic.
**Results** After excluding 37 patients with unconfirmed MS and alternative seizure etiologies, we found seizures attributable to MS in 1.5% and epilepsy in 0.9% of patients. 40.4% of patients with a follow-up of at least twelve months experienced only a single seizure and 59.6% had recurring seizures. 39% of patients with recurrent seizures were considered drug-resistant, with 9.7% experiencing status epilepticus. Seizure recurrence after a first seizure depended significantly on the MS subtype and was seen more often if the first seizure occurred simultaneously with a MS relapse than in the absence of a relapse.
**Conclusion** Our study shows a lower number of seizures and epilepsy in MS than previously reported. While a single seizure in MS usually has a good prognosis, relapse-associated seizures and established epilepsy in MS may not be as benign as previously assumed.

**Keywords** Epilepsy · Seizures · Multiple sclerosis · Epidemiology · Anticonvulsive treatment · Prognosis

## Abbreviations

CIS Clinically isolated syndrome
CNS Central nervous system

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| | |
|---|---|
| DMT | Disease-modifying therapy |
| ICD | International Classification of Diseases |
| MS | Multiple sclerosis |
| PPMS | Primary progressive multiple sclerosis |
| RRMS | Relapsing-remitting multiple sclerosis |
| SPMS | Secondary progressive multiple sclerosis |

## Introduction

Seizures are associated with various brain diseases, including multiple sclerosis [1]. Large registry studies have identified a threefold increase in seizure incidences in MS patients [2, 3]. One drawback of these studies is the reliance on disease classification codes, such as the codes of the International Classification of Diseases (ICD), which are primarily assigned for billing purposes and do not display clinical correlations. Extensive clinical data on patients is often not available, such that an alternative brain pathology may not be identified as the cause underlying seizures or epilepsy and as a consequence these events are falsely attributed to MS. Thus, the contribution of MS to the burden of seizures and epilepsy may be overestimated in these studies. Retrospective analyses and chart reviews show a seizure prevalence of 1.5–7.5% in MS patients [4–8]. The informative value of some of these studies is limited due to the small number of MS patients with only 250–500 patients included in the analysis [6–8]. Thus, there is an ongoing debate on the true prevalence of seizures and epilepsy in MS.

Besides the clarification of epidemiologic data, a more important issue is the prognosis of a single seizure or epilepsy in patients suffering from MS [9]. In previous studies, with a limited number of MS patients, the percentage of those classified as drug-resistant was low and varied from 7.5–16% [4, 7], suggesting a more benign course of epilepsy in patients with MS than is commonly seen in focal epilepsy, where pharmacoresistance is usually observed in up to one third of the patients [10, 11]. In contrast to this assumption, several studies have shown that the proportion of patients suffering from status epilepticus is high in MS patients with epilepsy (10–36%) [4, 12, 13] and is in the range of the general population with epilepsy where status epilepticus has been reported in 22% or 27% of patients, respectively [14, 15]. Given the prevailing uncertainties about the nature of seizures and epilepsy in MS, it is not surprising that up to now no clear consensus has been reached regarding the question if, given the presence of cerebral lesions in MS, a single seizure in MS patients should be interpreted as a proof of symptomatic epilepsy. And this raises a further important question: whether and when to administer anticonvulsive treatment. Additionally, it remains unclear if seizure recurrence depends on the MS subtype and on the timing of first seizure manifestation within the disease course. Since unnecessary anticonvulsive treatment as well as ongoing seizures severely impact the quality of life of MS patients [16] additional data is urgently needed.

We, therefore, investigated the following questions—relevant in day to day practice: What is the frequency of seizures and epilepsy in patients with MS? What is the prognosis of a single seizure or epilepsy in patients with MS? Does the MS subtype, present at the time of the first seizure, and the timing of seizure manifestation with respect to MS relapses influence the likelihood of seizure recurrence?

## Material and methods

We retrospectively screened all medical reports from the Department of Neurology, University Hospital Münster, from 01.03.2004 to 14.03.2017, by querying the data base of our electronic health record system and using the search terms "multiple sclerosis"/"MS", "inflammatory central nervous system disease", "clinically isolated syndrome"/"CIS", "relapsing–remitting multiple sclerosis"/"RRMS", "secondary progressive multiple sclerosis"/"SPMS", and "primary progressive multiple sclerosis"/"PPMS" in a stage one search. In the second stage, we screened for the search terms "seizure", "epilepsy", and "epilept*".[1] Finally, we manually identified all patients that had suffered at least one seizure. Patients were excluded if they had a comorbid condition that was likely to be the etiology underlying epilepsy, e.g. patients with a tumor, cortical stroke, or head trauma. In addition, patients with a first seizure occurring more than 5 years prior to the onset of MS (defined as the manifestation of the patient's first symptoms) were excluded as well, assuming that their epilepsy was unlikely due to MS, but due to an independent etiology. This 5-year cut-off was only applied, if the patients did not have positive evidence of MS disease manifestation such as a MRI scan suggestive of multiple sclerosis, or positive oligoclonal bands in the cerebrospinal fluid, i.e. radiologically isolated syndrome, at the time of first seizure manifestation. Patients in our cohort with a minimum of two seizures were defined as suffering from epilepsy. We chose this rather restrictive definition as there is currently no clear consensus about the significance of a single seizure in MS patients, who usually present with lesions on MRI.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA). Chi-Square tests were computed with the significance level set at $p < 0.05$.

[1] *Served as a wildcard character.

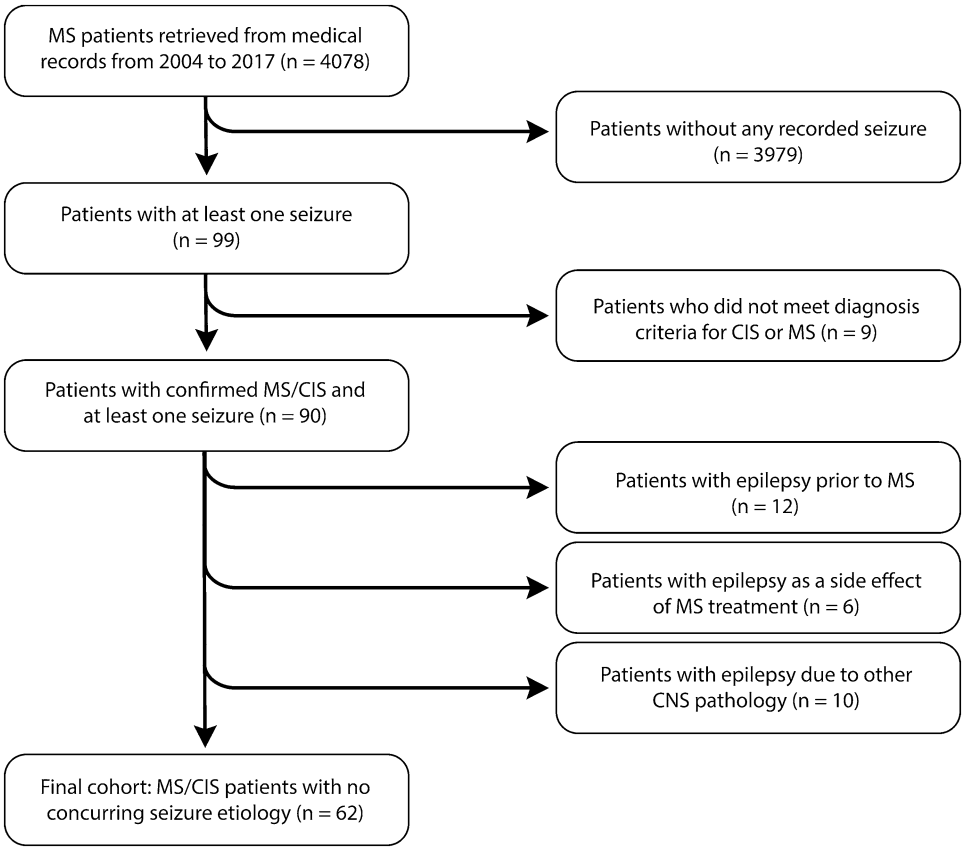


**Fig. 1** Flowchart summarizing the selection of patients that constitute our final patient cohort

## Results

### Search results and epidemiology of seizures and epilepsy in our cohort of MS patients

Our stage one search identified 4078 patients within the 13-year study period. Next, after the stage two search and manual screening, we were able to identify 99 patients who had experienced at least one seizure. Nine of these patients were excluded according to the McDonald criteria [17–19]. We excluded six patients who had seizures as a side effect of MS treatment: of these, three patients had cerebral vein thrombosis manifesting with seizures due to relapse treatment with high doses of steroids, two patients had progressive multifocal leukoencephalopathy secondary to natalizumab treatment, and one patient developed encephalitis associated with immunosuppression due to fingolimod. Ten further patients with an additional central nervous system (CNS) disease were excluded since the CNS disorder, rather than MS, was considered to be the primary cause of epilepsy after review by a board-certified neurologist and epilepsy specialist (SK). Another twelve patients were excluded, because the first seizure occurred at least 5 years prior to the onset of MS without further positive evidence of CIS or MS from magnetic resonance imaging or cerebrospinal fluid analyses, thus indicating an independent etiology of seizures (Fig. 1).

Thus, 90 patients with MS had at least one seizure yielding a prevalence of 2.2%. A total of 62 patients (1.5%) who had suffered at least one seizure were considered as attributable to MS in our final analysis. 38 patients (0.9%) suffered at least two seizures and thus fulfilled the diagnostic criteria of epilepsy.

### Demographic data and clinical characteristics

72.6% of the 62 patients were female. Median age at MS onset was 29 years and median age at MS diagnosis was 35.5 years. Three out of 62 patients (4.8%) had pediatric MS with a disease onset before the age of 16. The first seizure occurred at a median age of 40 years, with a median of 4 years after onset of MS and 3.5 years after MS diagnosis. There was a wide range of timing of initial seizure manifestation from 6 years before to 32 years after MS onset. Median follow-up after the first seizure occurred for 52 months (mean follow-up for 82 months). 52 patients had a follow-up for at least 12 months after the first seizure. At the time of the first seizure, 21 out of 37 patients with available data on disease-modifying therapy (DMT) had not received any MS treatment (Table 1).

**Table 1** Disease-modifying therapy (DMT) at seizure onset and last follow-up

| | At seizure onset (%) ($n=37$) | At last follow-up (%) ($n=62$) |
|---|---|---|
| No DMT | 21 (56.8) | 28 (45.2) |
| Interferon | 12 (32.4) | 8 (12.9) |
| Recurrent steroid pulses | 1 (2.7) | 10 (16.1) |
| Glatiramer acetate | 1 (2.7) | 4 (6.5) |
| Mitoxantrone | 1 (2.7) | 1 (1.6) |
| Azathioprine | 1 (2.7) | – |
| Dimethyl fumarate | – | 4 (6.5) |
| Fingolimod | – | 3 (4.8) |
| Alemtuzumab | – | 2 (3.2) |
| Natalizumab | – | 1 (1.6) |
| Rituximab | – | 1 (1.6) |

## Seizure recurrence depends on MS subtype

We speculated that the type of MS at the time of the first seizure might influence seizure recurrence. At the time of the first seizure, two out of 45 patients with available data on disease type, and with a follow-up of at least 1 year, were diagnosed with CIS (4%), 29 with RRMS (64%), nine with SPMS (20%), and five with PPMS (11%). Seizures recurred in 2/2 (100%) patients with CIS, 17/29 (58.6%) patients with RRMS, 1/9 (11%) patients with SPMS, and 4/5 (80%) patients with PPMS. There was a statistically significant difference in seizure recurrence depending on MS subtype [$\chi^2(2, n=43)=8.09, p=0.018$; chi square statistics for RRMS, SPMS and PPMS], with a high proportion of patients developing recurrent seizures in the groups with PPMS as the co-occurring type of MS at the time of the first seizure, and a relatively low proportion of patients in the group with SPMS.

## Seizure recurrence depends on association with MS relapse

Data on the association of the first seizure with a relapse were available for 24 patients. Relapses were defined as MS-associated neurological deficits which last for a minimum of 24 h. 11/24 patients (46%) experienced their first seizure and a relapse simultaneously. All of them had a clinical follow-up of at least 1 year. Seizures recurred in 6/11 patients (55%). In contrast, 13 patients suffered their first seizure without a relapse. Of those, ten patients had a follow-up of at least 1 year, and, interestingly, only one patient (10%) developed recurring seizures, whereas the other nine patients remained seizure-free. There was a statistically significant difference in the development of recurrent seizures, which was more likely if the first seizure occurred simultaneously with a relapse than if the first seizure manifested independently of a relapse [$\chi^2(1, n=21)=4.68, p=0.031$]. The proportion of patients treated with anticonvulsants after the first seizure did not differ significantly between the two groups [$\chi^2(1, n=21)=0.019, p=0.890$]. The majority of patients were started on anticonvulsants after the first seizure independent of whether the first seizure occurred simultaneously with a relapse (8/11 started on anticonvulsants) or independent (7/10 started on anticonvulsants).

## Prognosis and treatment in MS patients with a single seizure

21/52 patients (40.4%) with a follow-up of at least twelve months had a single seizure only. Seven of these 21 patients received anticonvulsive monotherapy with levetiracetam at the last follow-up. 13/21 patients (61.9%) did not receive anticonvulsive therapy. Interestingly, of these 13 patients, eight had a history of anticonvulsive therapy that had been successfully stopped, four had never received treatment without seizure recurrence, and for one patient the history of anticonvulsive treatment was not known. For another patient, data on anticonvulsive therapy was not available at the last follow-up.

## Prognosis and treatment in patients with recurring seizures

31/52 patients (59.6%) with a follow-up of at least twelve months had suffered more than one seizure. 17 of these patients (54.8%) were seizure-free for at least 1 year prior to the last follow-up (six without anticonvulsive treatment, nine on monotherapy and two on dual combination), while 13/31 (41.9%) had at least one seizure during the last year (four on monotherapy, six on dual combination, three on triple combination). 12/31 patients (38.7%) were pharmacoresistant according to the International League Against Epilepsy (ILAE) definition [20]. For one patient data on seizure frequency was not available at the last follow-up.

Status epilepticus occurred in six out of 62 patients (9.7%). All of these patients were suffering from epilepsy with recurring seizures. Five of these patients had a follow up of at least 1 year, whereas for one patient, no follow-up data was available. All five patients were not seizure-free at the last clinical follow-up despite anticonvulsive combination therapy. One patient, who had not experienced self-limited seizures before, suffered a de-novo status epilepticus.

## Discussion

### Epidemiology of epilepsy and seizures in MS patients

In our large cohort of 4078 MS patients, 1.5% of patients suffered one and 0.9% at least two seizures, i.e. were diagnosed with epilepsy, with a median of 4 years after onset of MS. These figures were derived after the exclusion of patients with unconfirmed MS diagnosis, and the exclusion of patients with epilepsies due to other causes. The onset of seizures which was reported to occur within the first decade of MS disease in the literature ($6.8 \pm 6.1$ years) was also early in our study [21, 22]. However compared to the literature, the proportion of patients with single seizures is relatively small in our cohort. A recent meta-analysis calculated a seizure prevalence of 3.1% among MS patients [23]. In contrast, the proportion of patients with epilepsy in our MS cohort does not exceed prevalence in the general population [10]. However, data on the prevalence of epilepsy in our patients' age group suggests a prevalence of 0.3–0.8%, which is in fact slightly lower than the prevalence of epilepsy in our MS cohort [24]. One explanation for the higher number of patients with MS and seizures in previous work, and thus the discrepancy to our study, is the reliance on diagnosis codes in registry- and nationwide cohort-studies, which do not systematically take CNS comorbidities as a cause for epilepsy into account [2, 3]. In fact, other studies using a similar approach as ours revealed lower incidences of seizures and/or epilepsy, similar to our work [4, 5]. But the data remains debatable, since there are studies with a comparable approach to ours that yielded higher rates of seizures and epilepsy in patients with MS [7, 25].

Nevertheless it is interesting to note that studies with rather small ($\leq$ 80) and high numbers (1420–5041) of patients tend to report high (3.8–10.8%) and low percentages (0.5–2.5%) of cases with epilepsy, respectively, thereby clearly assigning our findings to the latter group [3, 26, 27]. Another explanation for the discrepancy may be that in some studies with similar study design the patient cohorts dated back to the 1990s, when older DMTs such as interferons, glatirameracetate, azathioprine, and steroids were applied. It is very likely that in the period that was covered by our retrospective study (2004–2017) a relevant proportion of patients was treated with newer DMTs. One may speculate that newer DMTs may influence epileptogenesis. Moreover, recent studies have established that molecular pathways which are targeted by some newer DMTs—such as the Nrf2 pathway targeted by dimethylfumarate—are important in suppressing the development of seizures and epilepsy [28].

### Prognosis of a first seizure in MS

There is an ongoing debate regarding the prognosis of seizures in MS and whether and when to start anticonvulsive treatment after a single seizure. Typically, in an individual without any neurological comorbidity, anticonvulsive treatment may not be initiated after a single seizure if electroencephalography or magnetic resonance imaging do not demonstrate evidence for a higher risk of seizure recurrence. In our cohort, 40.4% had a single seizure only. Four of these 21 patients never received anticonvulsive therapy and eight patients successfully stopped medication. Unfortunately, we could not provide data for unsuccessful withdrawal of medication.

In a prospective study of the general population, Bell and colleagues found a recurrence risk of 61% after the first seizure, yielding a similar number of seizure-free patients as in our cohort [29]. In a recent national registry study from Sweden, Mahamud and colleagues did not find an increased risk of seizure recurrence for MS patients with a first seizure, although there was a trend to a higher risk in SPMS versus RRMS patients [9]. This finding is in contrast to our data, which showed a significantly lower recurrence risk of seizures in SPMS—although our study was limited by the low number of SPMS patients. Nevertheless epileptic seizures as symptoms of MS relapses have been described before and were found to be around 40% in some studies [30]. The relatively high chance of remaining seizure-free after a first seizure would argue against an immediate initiation of anticonvulsant medication with potential side effects.

It is still unclear whether seizure recurrence after a first seizure depends on the association between the index seizure and the MS relapse. Spatt and colleagues argued that a relapse-associated first seizure could be interpreted as an acute symptomatic seizure [31], comparable to acute symptomatic seizures due to other brain pathologies. Hence, it should not prompt immediate treatment with anticonvulsant drugs. In our 24 patients with data available regarding the circumstances of the first seizure, we observed that 55% of patients with their first seizure in the setting of a relapse went on to develop epilepsy. In contrast, only 10% of patients with their first seizure not associated with a relapse developed epilepsy. Thus, our data indicate that a relapse-associated seizure may not necessarily have a benign prognosis. Because of the small number of patients, our findings should, however, be interpreted with caution.

### Prognosis of recurring seizures in MS

When focusing on those patients with at least two seizures fulfilling the diagnostic criteria of epilepsy, the number of seizure-free patients (54.8%) is lower than in the general epilepsy population. Thus, we did not find epilepsy in our MS

patients to have a more benign prognosis than in the general population. The majority of those patients with uncontrolled seizures received dual or triple anticonvulsive combination therapy, so we would not assume that our patients received inadequate or overly cautious medication.

Status epilepticus has been described to occur in MS patients with epilepsy [4, 12, 13] and was seen in 10–36% of patients. In contrast, in our cohort status epilepticus occurred in only 9.7% of patients, a proportion that is smaller than the proportion of patients at risk of status epilepticus in the general epilepsy population, which is around 22% or 27% [14, 15]. All our patients suffering status epilepticus developed chronic epilepsy and none of them was seizure-free at the last follow-up. Therefore, anticonvulsive treatment should be initiated and optimized in all patients with an episode of status epilepticus.

### Limitations

Due to the retrospective nature of our study, there remains the risk of overreporting of seizures, as non-epileptic events such as convulsive syncope may be mistaken for a seizure and reported as such. Additionally, seizures may be underreported, especially if they occur only once or in the setting of an acute illness. We believe the risk of underreporting to be low in our study, since all patients underwent a careful interview by neurologist specialists (and some by epileptology specialists) and most patients were seen on a regular basis over many years which should prevent loss of information. As a single center study based on a MS specialist clinic, patients with a more severe MS disease course may be overrepresented, although one may argue that in this case epilepsy prevalence would not have been as low as we found it. As the availability of magnetic resonance imaging data at the time of the first seizure was limited in our cohort, we could not analyze the size and distribution of cortical lesions, which are associated with physical disability and cognitive impairment [32], and their influence on seizure recurrence in our cohort of MS patients, so this point remains uninvestigated in our cohort.

## Conclusion

The frequency of seizures and epilepsy attributable to MS appears lower than previously implicated. A single seizure in MS may have a good prognosis and may argue for a watchful strategy but there is a relevant seizure recurrence risk if seizures coincide with a relapse. In addition, epilepsy attributable to MS does not seem to be more benign than epilepsy due to other etiologies given that relevant proportion of MS patients develop drug-resistant epilepsy.

**Author contributions** SK, SGM and JK conceived the study and defined the concept, SK and LL statistically analyzed and interpreted the data and wrote the initial draft of the manuscript. JK revised the manuscript for intellectual content and together with LL prepared the figures for the manuscript. SG performed the database query. SGÜ, SK, LL and JK screened the clinic letters and collected the data. SGM, TB, CEE, GM, HW, NM advised on the study concept and interpreted some of the data. All authors contributed to the concept of the work and writing the manuscript, critically discussed the data and approved the version to be published.

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## Compliance with ethical standards

**Conflicts of interest** Prof. S. G. Meuth has received honoraria for lecturing, travel expenses for attending meetings and financial research support from Almirall, Amicus Therapeutics GmbH Deutschland, Bayer Health Care, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Serono, Novartis, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis, Chugai Pharma, QuintilesIMS und Teva. Dr. J. Krämer received honoraria for lecturing from Biogen, Novartis, Mylan and Teva, and financial research support from Sanofi Genzyme. Prof. H. Wiendl has received honoraria for lecturing and travel expenses for attending meetings from Actelion, Alexion, Biogen, Cognomed, F. Hoffmann-La Roche Ltd., Gemeinnützige Hertie-Stiftung, Lundbeck, Merck Serono, Novartis, Roche Pharma AG, Sanofi-Genzyme, TEVA, WebMD Global, for scientific advisory boards/steering committees from Biogen, Evgen, MedDay Pharmaceuticals, Merck Serono, Novartis, Roche Pharma AG, Sanofi-Genzyme, and compensation for serving as a consultant for Abbvie, Actelion, Biogen, Immunic AG, Novartis, Roche, RxMx, Sanofi-Genzyme, and research support from German Ministry for Education and Research (BMBF), Deutsche Forschungsgesellschaft (DFG), Else Kröner Fresenius Foundation, European Union, Fresenius Foundation, Hertie Foundation, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies (IZKF) Muenster and RE Children's Foundation, PML Consortium, Swiss MS Society, Biogen GmbH, GlaxoSmith-Kline GmbH, Roche Pharma AG, Sanofi-Genzyme. Dr. S. Kovac has received honoraria for lecturing and advising from Sanofi Genzyme and Esai. Dr. L. Langenbruch has received honoraria for lecturing Eisai. S. Güler and S. Geßner have no competing interests. Dr. N. Melzer has received honoraria for lecturing and travel expenses for attending meetings from Biogen Idec, GlaxoSmith Kline, Teva, Novartis Pharma, Bayer Healthcare, Genzyme, Alexion Pharmaceuticals, Fresenius Medical Care, and Diamed and has received financial research support from Euroimmun, Fresenius Medical Care, Diamed, Alexion Pharmaceuticals, and Novartis Pharma. Prof. C. E. Elger has received honoraria from UCB, Desitin, BIAL, and Eisai, and grants from the Deutsche Forschungsgemeinschaft (DFG) and the Bundesministerium für Bildung und Forschung (BMBF). Dr. G. Möddel has received honoraria for lecturing and travel expenses from UCB Pharma, Eisai, Desitin, and Electrical Geodesics Inc. (EGI). Prof. T. Budde has received grants from Deutsche Forschungsgemeinschaft (DFG), the Bundesministerium für Bildung und Forschung (BMBF), Biogen and Bayer Healthcare.

**Ethical standards** Informed consent was not obtained because of the retrospective nature of the study.

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