MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Epilepsy as a predictor of disease progression in multiple sclerosis

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Multiple Sclerosis Journal

2022, Vol. 28(6) 942–949

DOI: 10.1177/13524585211046739

Abstract

Background: Epilepsy development during the course of multiple sclerosis (MS) is considered to be the result of cortical pathology. However, no long-term data exist on whether epilepsy in MS also leads to increasing disability over time.

Objective: To examine if epilepsy leads to more rapid disease progression.

Methods: We analyzed the data of 31,052 patients on the German Multiple Sclerosis Register in a case–control study.

Results: Secondary progressive disease course (odds ratio (OR) = 2.23), age (OR = 1.12 per 10 years), and disability (OR = 1.29 per Expanded Disability Status Scale (EDSS) point) were associated with the 5-year prevalence of epilepsy. Patients who developed epilepsy during the course of the disease had a higher EDSS score at disease onset compared to matched control patients (EDSS 2.0 vs 1.5), progressed faster in each dimension, and consequently showed higher disability (EDSS 4.4 vs 3.4) and lower employment status (40% vs 65%) at final follow-up. After 15 years of MS, 64% of patients without compared to 54% of patients with epilepsy were not severely limited in walking distance.

Conclusion: This work highlights the association of epilepsy on disability progression in MS, and the need for additional data to further clarify the underlying mechanisms.

Keywords: Multiple sclerosis, epilepsy, seizures, disease progression, prognosis

Date received: 14 May 2021; revised: 7 August 2021; accepted: 22 August 2021

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Introduction

Different immunological and degenerative processes in gray and white matter lead to clinical relapses and persistent disability in multiple sclerosis (MS).[1–3] Gray matter alterations can be visualized with magnetic resonance imaging[4,5] enabling in vivo observation of the temporal progression of the disease[6,7] and its association with clinical symptoms and long-term disability.[8,9] As epilepsy is seen as a cortical network disorder,[10,11] gray matter pathologies presumably also increase the risk of epileptic seizures in MS.[12,13]

The largest studies so far focusing on MS and epilepsy suggest a correlation between epilepsy in MS and disease duration and disability,[14,15] but no data exist that identify whether epilepsy in MS also impacts on disability progression over time. Here, we analyzed a large cohort of MS patients whose details were taken from the German Multiple Sclerosis Register (GMSR), which contains data on more than 30,000 patients. Based on the register, we looked at risk factors associated with epilepsy and compared clinical characteristics at the onset of MS as well as long-term progression rates between patients with and without epilepsy.

Materials and methods

Study cohort

This analysis was based on the GMSR. The GMSR is a national database established in 2001 by the German MS Society (DMSG, Bundesverband e.V.).[16–18] The complete list of the GMSR consortium can be found in Supplementary Table 1. All patients on the register have provided their written informed consent. All data were collected in accordance with the Declaration of Helsinki, and the registry has received ethical approval by the local independent ethics committees.

Table 1. Patients' demographic and disease-related characteristics.

	All GMSR patients meeting study inclusion	Epilepsy during course of disease (last 5 years)	No epilepsy (last 5 years)
n	*n* = 31,052	*n* = 633	*n* = 30,419
Females (%)	71.4% [70.9–71.9]	69.2% [65.4–72.8]	71.4% [70.9–71.9]
Progressive onset (%)	4.9% [4.7–5.2]	4.4% [2.9–6.4]	4.9% [4.7–5.2]
∅-Age onset	33.1 (±10.7)	30.8 (±10.4)	33.2 (±10.7)
∅-Time to diagnosis	1.7 (±4.0)	2.0 (±4.6)	1.7 (±4.0)
∅-Age (last visit)	47.2 (±12.4)	48.8 (±12.1)	47.1 (±12.4)
High school graduation (%)	35.8% [35.3–36.4]	28.5% [24.7–32.7]	36.0% [35.4–36.6]
DMT (%)	71.9% [71.4–72.4]	67.8% [63.9–71.4]	72.0% [71.5–72.5]
Relapses (last 12 months)	0.13 (±0.42)	0.15 (±0.44)	0.13 (±0.41)

DMT: disease-modifying therapy.
DMT was assessed during the last visit.
Percentages are given along with 95% Clopper–Pearson confidence intervals, otherwise mean (±standard deviation).

Based on an export from the GMSR (January 2021, 33,174 patients), a cohort of patients was defined with at least one record of epilepsy. Patients with missing information were excluded, leaving 31,052 remaining patients of whom 633 had both MS and epilepsy documented within the past 5 years.

For the long-term comparison, only patients with complete data sets at disease onset (date of onset, disease course, and clinical characteristics) were included, resulting in a cohort of 550 patients with MS and epilepsy (MSE+) and 27,295 MS patients without epilepsy (MSE−). Detailed and complete disease-modifying treatment history (including absence of treatment) was available in a subcohort of 10,636 patients.

Statistical analyses

Group characteristics and comparisons between MS patients with epilepsy and MS patients without epilepsy were analyzed at last follow-up (last entry into database). Evaluation of epilepsy was presented as a 5-year prevalence estimation, that is, whether patients had a report of epilepsy within the last 5 years.

Variables of interest to detect associations with epilepsy were age at onset, current age, sex, time to diagnosis, Expanded Disability Status Scale (EDSS) score, disease course, symptoms at onset, symptoms at last visit, disease-modifying drugs (DMDs), and education. Univariate and multivariate logistic regression models were used to estimate associations with patients' baseline, disease, and treatment characteristics. Furthermore, group comparisons were performed on cohorts matched by sex, age at onset, and current age to adjust for baseline inequalities, based on a 10:1 matching to MSE+ (550 MSE+: 5500 MSE−). Clinical characteristics were compared at two time-points—symptoms at onset and at last reported visit.

For the comparison on disease progression, EDSS scores were longitudinally collected from each patient over the period of the first 15 years of disease duration. EDSS scores and related attainment of disability level milestones 4.0 and 6.0 were interpolated using generalized additive regression models for binomial data. Descriptive analyses were performed using R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, including the packages: optmatch_0.9–13, compareGroups_4.4.1, mgcv_1.8-31, ggplot2_3.3.0, and beeswarm_0.2.3), and statistical inference (i.e. confidence intervals) was carried out at a (descriptive) 5% type I error level.

Data availability

Anonymized data will be made available on request by any qualified investigator under the terms of the registries' usage and access guidelines and subject to informed consent of the patients.

Results

Demographics, prevalence

The demographics and characteristics of the GMSR cohort and the total MS-epilepsy cohort are summarized in Table 1. No statistical differences between both groups could be obtained according to sex and disease course, whereas age of onset was significantly earlier in MS patients with epilepsy compared to the whole cohort.

Table 2. 5-Year prevalence by disease course (latest visit).

	N	*N* (Epi)	% [95% CI]
CIS	497	4	0.80 [0.22–2.05]
RRMS	23,187	394	1.70 [1.54–1.87]
SPMS	4737	176	3.72 [3.20–4.29]
PPMS	2037	41	2.01 [1.45–2.72]
Total	31,052[a]	633[a]	2.04 [1.88–2.20]

CI: confidence interval; Epi: epilepsy; CIS: clinical isolated syndrome; RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis.
[a]The difference to the total number of patients was due to the indeterminable disease course (e.g. was in the transitional phase between RRMS and SPMS) in $N = 594$ and N (Epi) $= 18$ patients.

At the last reported visit, 83.5% of the MS patients with epilepsy had received anticonvulsive treatment, another 3.0% had received both pharmacological and non-pharmacological treatment, 0.7% had received only non-pharmacological treatment, and 12.9% had received no specific treatment.

In the GMSR, 2.0% of patients had at least one recorded entry of epilepsy in the 5-year interval prior to their last visit (633 out of 31,052). There was a significant difference in the 5-year prevalence of epilepsy between disease courses ($p < 0.001$), which was the highest for secondary progressive multiple sclerosis (SPMS, 3.7%) and the lowest for clinical isolated syndrome (CIS, 0.8%) (see Table 2).

Predictive factors for 5-year epilepsy prevalence

The 5-year prevalence of epilepsy significantly increases with age (Figure 1(a)), disease duration (Figure 1(b)), and EDSS score (Figure 1(c)), each $p < 0.001$. Univariate logistic regression models including age, disease duration, EDSS, disease course, and sex score showed associations between epilepsy and age (per 10 years: odds ratio (OR) = 1.12, 95% confidence interval [1.05, 1.19]), disease duration (per 10 years: OR = 1.40 [1.30, 1.50]), EDSS score (per point: OR = 1.29 [1.24, 1.33]), disease course (reference relapsing remitting multiple sclerosis (RRMS), SPMS: OR = 2.23 [1.86, 2.67], PPMS: OR = 1.19 [0.85, 1.62]) whereas male sex (OR = 1.11 [0.94, 1.32]) was only moderately associated with the prediction of epilepsy. In the multivariate logistic regression analysis, only disease duration (per 10 years: OR = 1.28 [1.15, 1.42]) and EDSS (per point: OR = 1.30 [1.24, 1.37]) remained significant, but not age, disease course, and sex.

To analyze the association with DMDs, multivariate logistic regression estimation was also performed in a subcohort of 10,636 patients. In this model, both time from disease onset to first treatment (within 10 years of disease duration) as well as exposure time to DMDs (as a percentage relative to a patient's disease duration) were not associated with epilepsy prevalence significantly (time to first treatment per year: OR = 1.00 [0.95, 1.05]; relative exposure time to disease duration per 10%: OR = 1.05 [1.00, 1.10]).

Group comparison between MS patients with epilepsy (MSE+) and matched controls without epilepsy (MSE−)

The cohort for the group and long-term comparison consisted of 550 MS patients with at least one record of epilepsy during the evaluated period of in mean 17.6 years. Compared with MSE− patients ($n = 5500$), MSE+ patients were more likely to have brainstem, motor and cerebellar symptoms, bladder dysfunction, and depression at onset of MS (see Table 3). Compared with MSE− patients, mean EDSS score in MSE+ patients in the first year of the disease was significantly higher (MSE+ 2.0; MSE− 1.5, $p < 0.001$). Furthermore, 91% of MSE+ patients had an EDSS score <4.0, and 95% <6.0 at onset, compared to 95% (EDSS score <4.0, $p = 0.07$) and 99% (EDSS score <6.0, $p = 0.001$) of MSE− patients.

In addition, at the last visit, MSE+ patients were more likely to show symptoms in each dimension: spasticity, ataxia, fatigue, pain, bladder dysfunction, bowel dysfunction, sexual dysfunction, cognitive dysfunction, depression, eye movement dysfunction, dysarthria, and dysphagia (see Table 3). Furthermore, employment status was lower and mean EDSS score was higher in MSE+ patients at the last reported visit.

Comparison of progression between patients with and without epilepsy (MSE+ vs MSE−)

A detailed analysis of EDSS progression over a 15-year period post-onset of MS revealed that MSE+ patients had a significantly higher EDSS score, as shown in Figure 2. Mean EDSS score after 15 years for MSE+ patients was 4.0, compared to 3.2 for MSE− patients ($p < 0.001$). Furthermore, the proportion of MSE+ patients with EDSS scores <4 and <6 was significantly lower after 15 years compared to the proportion of MSE− patients (EDSS score <4.0: MSE+ 54%, MSE− 64%; $p = 0.012$ and EDSS score <6.0: MSE+ 74%, MSE− 85%; $p < 0.001$).

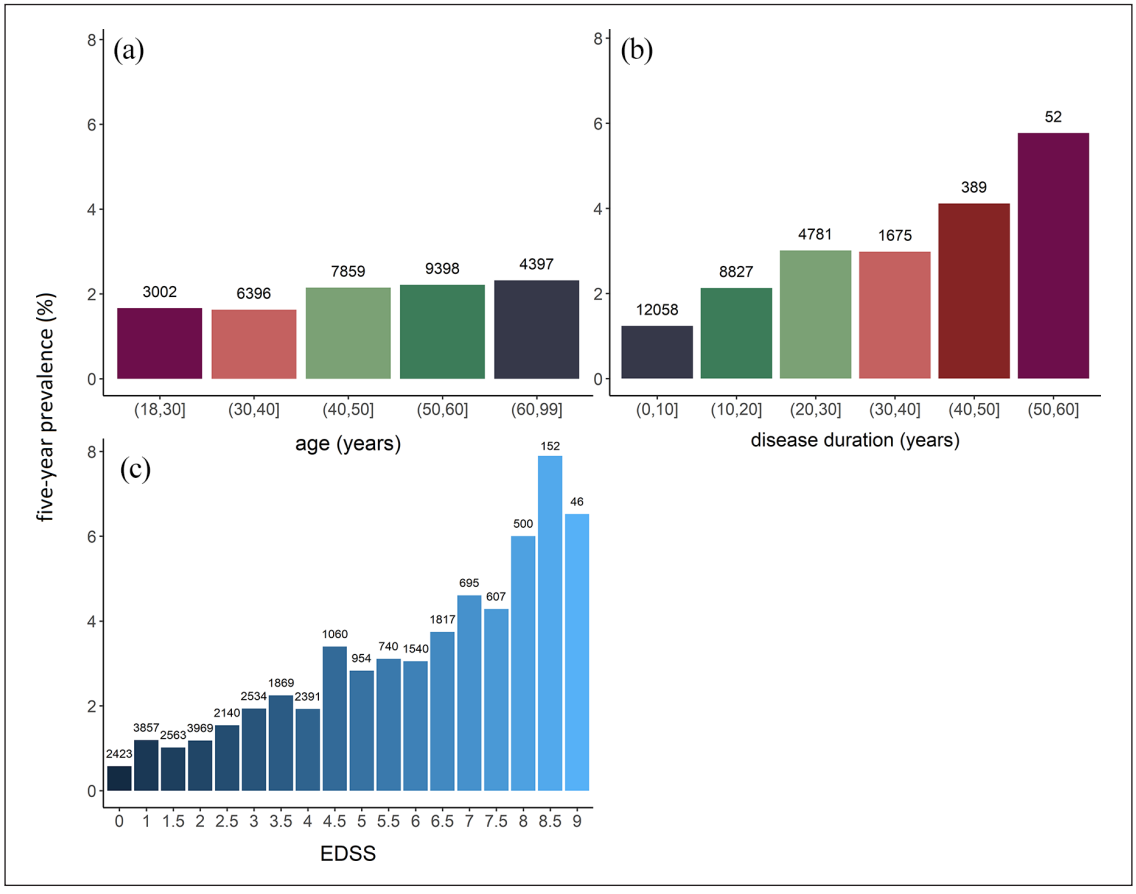

Figure 1. The 5-year prevalence of epilepsy in strata by age (a), disease duration (b), and EDSS (c). Sample sizes (*N*) are given per subgroup.
EDSS: Expanded Disability Status Scale.

Discussion

We analyzed one of the largest cohorts of MS patients worldwide to investigate risk factors for developing epilepsy across the term of the disease and to compare patients with and without epilepsy, to determine if epilepsy would be a risk factor for higher disability shortly after onset of the disease, at long-term follow-up, and for faster disease progression over time. We were able to (1) confirm the previously reported risk factors of age, disease duration, and overall disability for epilepsy in MS, (2) show that MSE+ patients were already more disabled in the first year of MS, and (3) show that MSE+ patients had faster MS progression compared to MSE− patients over a period of up to more than 17 years.

In the largest study so far, Burman and Zelano[14] analyzed data from 14,545 Swedish MS patients with a cumulative incidence of epilepsy in MS of 3.5%, and 5-year prevalence of 1.7%. In our data set of more than 30,000 patients, the 5-year prevalence was only slightly higher at 2.0%, and comparable to the ranges reported for prevalence in other studies.[19,20]

Our results are in line with previous data that have also shown a correlation between EDSS, age, and disease duration with epilepsy.[14,21] All data underline the strong association between clinical disability and risk of epileptic seizures in MS.

Here, we demonstrated for the first time that patients with MS and epilepsy already show a higher degree of clinical disability in the first year of MS. This finding may indicate a pre-existing higher degree of structural alterations in MS patients who develop epilepsy. In addition, clinical differences between groups were evident in neuropsychiatric domains (particularly depression) as well as brainstem, motor, cerebellar, and autonomic domains. The association between cortical pathology and increasing disability[5,6,9] as well as epileptic seizures[13,22] suggests that MS patients who later develop epilepsy may have more disseminated cortical pathology from early disease stages onward. These differences may in turn lead to more rapid progression of disability compared to MS patients without epilepsy, resulting in significantly

Table 3. Group differences between MSE+ and MSE−.

	MSE+ ($n = 550$)	MSE− (matched 10:1, $n = 5500$)	*p*-value
Symptoms at onset			
Visual	42%	42%	0.85
Brainstem	31%	21%	<0.001
Motor	48%	41%	0.008
Cerebellar	32%	23%	0.001
Sensible	54%	57%	0.19
Bladder dysfunction	14%	8%	<0.001
Bowel dysfunction	3%	3%	0.58
Sexual dysfunction	4%	3%	0.46
Depression	21%	13%	<0.001
Brainstem	49%	40%	<0.001
Symptoms at last visit			
Spasticity	50%	37%	<0.001
Ataxia	47%	31%	<0.001
Fatigue	62%	55%	0.001
Pain	36%	28%	0.001
Bladder dysfunction	51%	38%	<0.001
Bowel dysfunction	15%	10%	<0.001
Sexual dysfunction	17%	10%	<0.001
Cognitive dysfunction	46%	28%	<0.001
Depression	37%	23%	<0.001
Eye movement dysfunction	22%	14%	<0.001
Dysarthria	21%	7%	<0.001
Dysphagia	12%	4%	<0.001
Walking impairment	72%	56%	<0.001
Other	12%	6%	<0.001
Employment status	40%	65%	<0.001
EDSS	4.4 (±2.3)	3.4 (±2.2)	<0.001
Disease duration (years)	17.6 (±10.7)	17.5 (±10.7)	0.95

MSE+: multiple sclerosis patients with epilepsy; MSE−: multiple sclerosis patients without epilepsy; EDSS: Expanded Disability Status Scale.
Data are given by percentages and chi-square tests as well as mean (±standard deviation) and *t*-tests.

increased impairment in each functional system and significantly lower employment status at the last visit. Interestingly, the largest difference between MSE+ and MSE− patients in affected domains was shown for cognitive dysfunction (47% vs 28%), which might again be explained by a higher amount of cortical pathology in MSE+ patients. These hypotheses need to be followed up for confirmation in future studies using additional parameters (e.g. brain imaging).

The differences in disability were assessed up to 15 years after onset of MS, with a mean EDSS score of 3.2 in MSE− patients, which is close to common definitions of "benign" MS,[23] compared to 4.0 in MSE+ patients. Similarly, MSE+ patients met the EDSS milestones 4.0 and 6.0 to a greater extent. In a study by Catenoix et al.,[24] 67 MS patients with epilepsy achieved an EDSS score of 6.0 earlier than MS patients without epilepsy. In addition, a Norwegian study demonstrated significantly earlier conversion from RRMS to SPMS in 19 MS patients with epilepsy.[20] We confirmed and extended the significant impact of epilepsy on each clinical dimension and long-term disability. Furthermore, the difference on the EDSS between MSE− and MSE+ increases over time, with a difference of 0.5 EDSS points at MS onset (1.5 vs 2.0) to 0.8 EDSS points after 15 years (3.2 vs 4.0) to 1.0 EDSS points at last reported entry (3.4 vs 4.4), suggesting that epilepsy in MS may drive disease progression, as known, for example, in

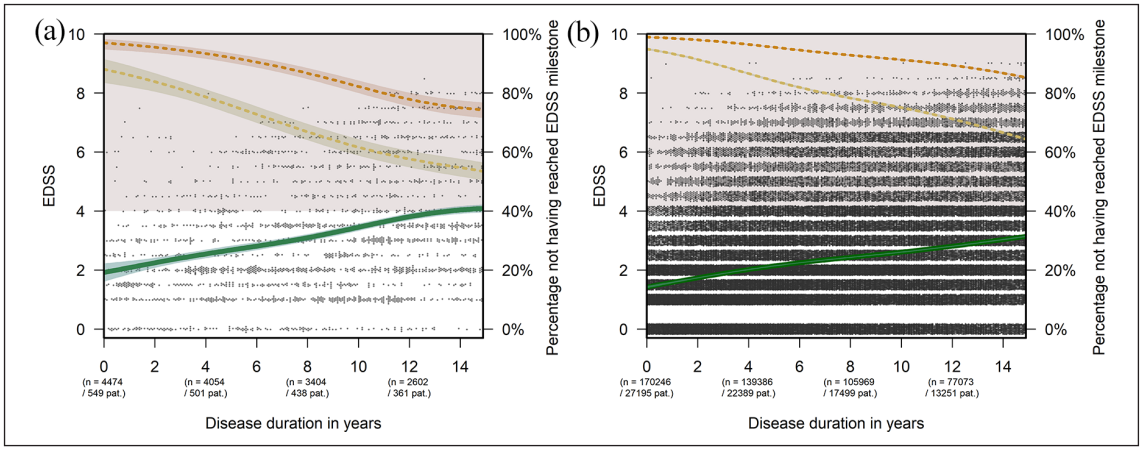

Figure 2. Long-term comparison between MSE+ (a) and MSE− (b). The solid line shows the interpolated mean EDSS of patients (left *y*-axis). The dotted lines show the percentage of patients who have not reached EDSS milestones of 4 (yellow) and 6 (orange; right *y*-axis). For some patients, EDSS was missing ($N = 1$ (MSE+), 126 (MSE−)).
EDSS: Expanded Disability Status Scale.

Alzheimer's dementia.[25] Our data are also in line with a recent study that revealed an increased mortality rate for MS patients with epilepsy,[26] emphasizing that epilepsy is a marker for negative long-term disease outcome.

Several limitations of register-based studies should be considered. As data collection is performed in multiple centers, additional heterogeneity may occur, and missing values may induce some degree of bias if these are not completely random. In addition, epilepsy is recorded on the register without further information about the frequency of epileptic seizures or about alternative causes as well as any imaging parameter. However, this cohort represents the largest real-world data set on this topic so far, and the information has been provided by neurologists specializing in MS.

Nevertheless, these data are not sufficient to understand the pathophysiological processes of epilepsy in MS. In vivo imaging studies suggest the causal role of cortical lesions,[13] which is in line with the hypothesis of epilepsy as a cortical network disorder.[10] Further studies will be needed to determine whether these network changes are due to inflammatory or neurodegenerative components and, even more importantly, if they represent permanent damage or may still be amenable to therapeutic interventions.

We have emphasized the important negative role of epilepsy in clinical disease severity at onset, as well as in its progression over time. We believe that our data underline the need for a better understanding of the interaction between epileptic seizures and MS. Future studies will be needed to determine if this association is dependent on different competing causes[27] or disease characteristics, and if it is also detectable between frequency of epileptic seizures and rate of disease progression, and to further clarify its underlying structural or functional pathology.

Acknowledgements

The authors thank all members of the German Multiple Sclerosis Register consortium. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.G. received honoraria and travel reimbursements for attending meetings from Biogen, Celgene, Merck Serono, Novartis, Roche, Sanofi Genzyme, and Teva. His research is funded by the German Ministry for Education and Research (BMBF), Merck Serono, and Novartis. None resulted in a conflict of interest. D.E. has nothing to disclose. F.v.P. obtained honoraria for speaking engagements from Desitin, EISAI, UCB, BIAL, Arvelle Therapeutics, Angelini Pharma, Zogenix, and GW Pharmaceuticals and was part of the speakers' bureau of Desitin, EISAI, UCB, BIAL, Arvelle Therapeutics, Angelini Pharma, Zogenix, and GW Pharmaceuticals. None resulted in a conflict of interest. A.S. has no personal pecuniary interests to disclose, other than being the lead of the German MS Registry, which receives funding from a range of public and corporate sponsors, recently

including The German Innovation Fund (G-BA), The German MS Trust, the German MS Society, Biogen, Celgene (Bristol Myers Squibb), Merck Serono, Novartis, Roche, and Sanofi Genzyme. None resulted in a conflict of interest. P.S.R. has received honoraria for consultancy/speaking from AbbVie, Almirall, Alexion, Biogen, Merck, Novartis, Roche, Sandoz, and Sanofi Genzyme, and has received research grants from Amicus, Biogen, Merck, and Roche. None resulted in a conflict of interest. U.K.Z. received honoraria and travel reimbursements for attending meetings from Alexion, Almirall, Bayer Health Care, Celgene, Sanofi Genzyme, Merck Serono, Novartis, Roche, and Teva. His research is funded by the German Ministry for Education and Research (BMBF), the German Ministry for Economy (BMWi), the Deutsche Forschungsgemeinschaft (DFG), and the European Union (EU). None resulted in a conflict of interest.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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