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ORIGINAL ARTICLE

Prognostic impact of epileptic seizures in multiple sclerosis varies according to time of occurrence and etiology

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Abstract

Background and purpose: Epileptic seizures occur more often in patients with multiple sclerosis (MS) than in the general population. Their association with the prognosis of MS remains unclear. This study was undertaken to evaluate whether epileptic seizures may be a prognostic marker of MS disability, according to when the seizure occurs and its cause.

Methods: Data were extracted from a population-based registry of MS in Lorraine, France. Kaplan–Meier curves and log-rank tests were used to compare the probability of different levels of irreversible handicap during the course of MS in patients who experience epileptic seizures or do not, according to the chronology and the cause of the first epileptic seizure.

Results: Among 6238 patients, 134 had experienced at least one epileptic seizure (2.1%), and 82 (1.2%) had seizures secondary to MS. Patients with epileptic seizure as a first symptom of MS (14 patients) had the same disease progression as other relapsing–remitting MS patients. Patients who developed epileptic seizures during the course of MS (68 patients) had a higher probability of reaching Expanded Disability Status Scale = 3.0 (p =0.006), 6.0 (p =0.003), and 7.0 (p =0.004) than patients without an epileptic background. Patients with a history of epileptic seizures unrelated to MS also had a worse prognosis than patients without an epileptic background.

Conclusions: Epileptic seizures might be viewed as a "classic MS relapse" in terms of prognosis if occurring early in MS, or as a marker of MS severity if developing during the disease. Epileptic diseases other than MS may worsen the course of MS.

KEYWORDS
EDSS, epidemiology, epileptic seizure, multiple sclerosis, prognosis

INTRODUCTION

The prevalence of epileptic seizures during multiple sclerosis (MS) is estimated at between 0.9% and 10.8% [1–9], whereas the prevalence of epilepsy in the general population is evaluated at approximately 0.5%–0.8% [10]. Even if an epileptic seizure is not considered to be a classic event in MS, it has been shown that they can be the only symptom of relapse [11, 12], sometimes the first relapse of MS, before the first classic MS event. They can also appear after MS onset, in association with the accumulation of lesions in the brain tissue

and neurodegeneration [13]. On the other hand, patients with MS could also have epileptic seizures related to another etiology, that is, a comorbidity, sometimes existing for years before MS onset (e.g., idiopathic generalized epilepsy). Basically, patients with MS and epileptic seizures can be classified according to the relationship between MS and epileptic seizures, and in the case of seizures related to MS, according to the time of occurrence of the first epileptic seizure and the first classic MS event.

Studies have shown that the occurrence of epileptic seizures in MS patients is associated with disease progression, worse cognitive performance, and poorer prognosis with a faster progression toward severe handicap [13–16]. However, these simple associations could be qualified by the characterization of epileptic seizures in terms of time of occurrence and relationship to MS, as stated above.

Our aim was to evaluate the prognosis of MS patients with epileptic seizures depending on their relationship with MS and the time of their first occurrence if related to MS (first occurrence before or after the first classic MS event). We used a population-based registry containing the history of a large population of MS patients with a long-term follow-up including disability evaluation at all examinations, and intercurrent events such as epileptic seizures before or during MS.

MATERIALS AND METHODS

Population

Patients were identified through the Registre Lorrain de la Sclérose en Plaques (ReLSEP). The ReLSEP is an exhaustive certified registry of MS patients that was created in 1996 [17] and that includes almost all the patients diagnosed with MS in the Lorraine region (France). This registry is filled in prospectively with data from neurologists, rehabilitation centers, and the French Hospital Information System and the Health Insurance System databases. The following information is collected: demographic data, date of the first symptoms (first classic MS event if a diagnosis of MS is retained), disease history, treatments, magnetic resonance imaging (MRI), biological tests, intercurrent medical events (such as epileptic seizures), and evaluation of irreversible disability with the Expanded Disability Status Scale (EDSS) at all examinations [18]. More than 90% of all patients with MS in Lorraine were registered in the ReLSEP in 2008, and this proportion has increased since the multiplication of sources [19]. All these data are then anonymized and used in the standardized European Database for Multiple Sclerosis (EDMUS) system [20]. All the patients gave their informed consent. Data collection was approved by the French National Commission for Data Protection and Liberties (CNIL No. 913001–2014.01.06). Data were extracted on 1 February 2019.

Onset of MS was defined as the date of the first MS event in a patient's life: relapse in the case of relapsing onset MS (Ro-MS), progression in the case of progressive onset MS (Po-MS). EDSS scores were determined by the referring neurologist. Every score used was confirmed at least once within 3 months. To this end, we used the EDMUS impairment scale adapted from the disability status scale, an estimation of the irreversible EDSS score (with integer values from 0 to 10). For reasons of simplification, the term "EDSS" is used.

Inclusion criteria

In the current study, we included all patients in the ReLSEP. Patients who had experienced at least one epileptic seizure at any moment during their lives that was recorded in EDMUS constituted the cases, and patients without a known history of epileptic seizure were the controls. An expert neurologist (M.Se.) reviewed the patient's medical information present in the original file (medical history, MRI, electroencephalogram [EEG]) to check its reliability. If the occurrence of an epileptic seizure was confirmed, the expert neurologist (M.Se.) determined the etiology of the seizure (genetic, structural, metabolic, etc.). If no alternative etiology was found, the epileptic seizures were considered to be "possibly related to MS." The time of occurrence of the first seizure according to the first classic MS event in the case of seizures possibly related to MS was also determined.

We described the use of disease-modifying treatments (DMTs) during the MS course. Some of these treatments were considered to be "platform therapies" of moderate efficacy and to have limited effects on disability accrual in MS, whereas others, usually named "high active DMTs," are proven to be more efficient regarding this outcome [21]. Then, we identified patients treated at least once with highly active treatments: natalizumab, mitoxantrone, cyclophosphamide, anti-CD20 agents, or fingolimod.

Groups of patients with epileptic seizures

Patients with at least one epileptic seizure related to MS or of unknown etiology and whose first seizure occurred after a classic MS event were included in the AFTER group. Seizures could have been considered an MS symptom independent of relapses, such as symptoms of progression. For these patients, onset of MS was defined as the date of the first classic MS event.

Patients with at least one epileptic seizure related to MS or of unknown etiology and occurring before any classic MS event were included in the BEFORE group. The onset of MS was the date of the first epileptic seizure, as epileptic seizures might be the symptom of true MS relapse [6, 22].

Patients with at least one epileptic seizure before or after the first classic MS event but with a clearly defined etiology (genetic, structural, metabolic, etc.) not related to MS were included in the "nonrelated" (NR) group. In this case, the onset of MS was defined as the date of the first classic MS event.

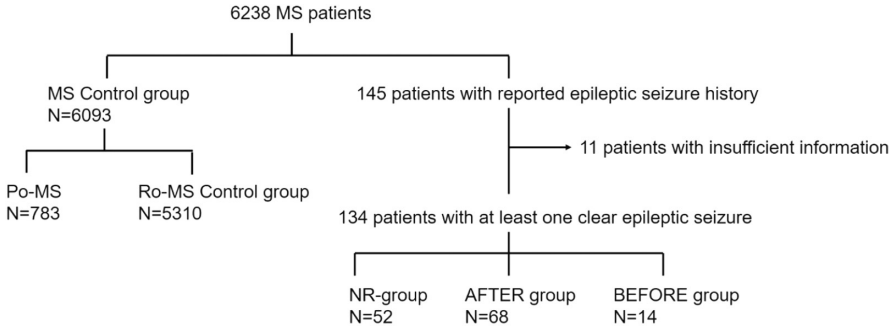

FIGURE 1 Flow chart. MS, multiple sclerosis; Po-MS, progressive onset MS; Ro-MS, relapsing onset MS

Control groups

For the NR and AFTER groups, the control patients (MS control group) were all other MS patients in the registry without a history of epileptic seizures regardless of the phenotype of MS (Ro-MS or Po-MS). For the BEFORE group, the control patients were restricted to patients with Ro-MS (Ro-MS control group), as the first MS event in this group was the first epileptic seizure, an acute event by nature, more suggestive of a relapse than the onset of progression. In the control groups, the baseline was defined as the onset of MS, that is, the date of the first symptom attributed to MS.

Statistical analysis

Quantitative data are expressed as mean and SD, or as median values (minimum–maximum), and categorical variables by percentages.

To compare the quantitative characteristics between groups, the nonparametric Kruskal–Wallis test was used because of group sizes. Percentage comparison was done using chi-squared or Fisher exact test when theoretical assumptions were not satisfied.

The probability of reaching EDSS = 3.0, 6.0, and 7.0 in each group was described with the Kaplan–Meier estimator and compared to controls by using log-rank tests. Baseline was the onset of MS in each group. Kaplan–Meier curves for the BEFORE group for EDSS = 6.0 and 7.0 were not performed because of an insufficient number of patients reaching the outcome. We also determined Kaplan–Meier estimators of the risk of occurrence of a further MS event after baseline for the BEFORE group versus the Ro-MS group. Additionally, we conducted sensitivity analysis when appropriate, as described in the Results section.

We also used Kaplan–Meier estimators with the date of birth to control for an age effect in the probability of reaching the EDSS outcomes for the BEFORE group versus Ro-MS, the AFTER group versus MS, and the NR group versus MS.

Finally, we performed a univariate Cox regression with the occurrence of the second MS event and EDSS = 3.0, 6.0, and 7.0 as time-dependent variables. Baseline was the first MS event. The variable of interest was the group (BEFORE vs. controls, AFTER vs. controls, NR vs. controls) after matching one patient of the groups with epileptic seizure (BEFORE, AFTER, NR) with five patients of their related control groups. Patients were matched on their age at disease onset, sex, and MS type at disease onset.

For all analyses, a p-value < 0.05 was considered statistically significant. Statistical analyses were done with SAS 9.4 software (SAS Institute).

RESULTS

From 1 January 1991 to 1 February 2019, a total of 6238 patients with MS were included in the ReLSEP. Of these, 145 had a reported history of epileptic seizures. Eleven patients were excluded from all descriptions and analyses because of missing data. Among the remaining 134 patients with a clear history of epileptic seizure (2.1%), 52 had epileptic seizures not related to MS (NR group, 0.8%), 68 patients presented at least one epileptic seizure related to MS or of unknown etiology that first occurred after the first classic MS event (AFTER group, 1.1%), and 14 patients presented at least one epileptic seizure due to MS or of unknown etiology occurring before the first classic MS symptom (BEFORE group, 0.2%; see Figure 1). Among these 14 patients, five presented a clear association between a cortical MS plaque and the clinicoelectrical pattern of the epileptic seizure (seizure related to MS) and nine had a seizure of unknown etiology but possibly related to MS.

The MS control group included 6093 patients, 5310 with Ro-MS (87.1%; Ro-MS control group) and 783 with Po-MS (12.9%). All patients are described in Table 1.

BEFORE group

Patient characteristics are reported and compared in Table 1. The annual rate of EDSS increase during follow-up was similar in both groups, as well as the use of highly active DMT during the MS course.

Among the patients of the BEFORE group, 10 presented a classic MS event in the 2 years following their first epileptic seizure, and two had such an event >2 years after the seizure. Seizures were focal in seven patients (50.0%) and seemingly generalized tonic–clonic in five (35.7%). The onset was unknown in two patients (14.3%). Three patients had a recurrence of epileptic seizures during follow-up.

There was no difference in the probability of a second MS event after baseline between the 14 patients of the BEFORE group and

TABLE 1 Comparison of baseline characteristics between the BEFORE group and Ro-MS control group

Characteristic	Ro-MS control group, *n* = 5310	BEFORE group, *n* = 14	*p*[a]	Ro-MS and Po-MS control group, *n* = 6093	AFTER group, *n* = 68	*p*[b]	NR group, *n* = 52	*p*[c]
Gender, *n* (%)			0.77[d]			0.93[d]		0.93[d]
Female	3919 (73.8%)	10 (71.4%)		4361 (71.6%)	49 (72.1%)		35 (67.3%)	
Male	1391 (26.2%)	4 (28.6%)		1732 (28.4%)	19 (27.9%)		17 (32.7%)	
Age at first MS event, years			0.27[e]			<.001[e]		0.51[e]
Mean (SD)	31.3 (9.90)	28.8 (10.54)		32.7 (10.72)	27.0 (8.3)		33.3 (9.48)	
Minimum–median–maximum	4–30.0–72	15–24.5–50		4–31.0–72	12–26.0–56		16–33.0–57	
MS types at first MS event, *n* (%)			NA			0.71[d]		0.04[d]
Relapsing onset MS	5310 (100%)	14 (100%)		5310 (87.1%)	61 (89.7%)		40 (76.9%)	
Progressive onset MS	0	0		783 (12.9%)	7 (10.3%)		12 (23.1%)	
EDSS at first MS event			0.161[e]			0.414[e]		0.065[e]
Mean (SD)	1.2 (0.53)	1.0 (0.00)		1.4 (0.78)	1.4 (0.84)		1.7 (0.10)	
Minimum–median–maximum	0–1.0–6	1–1.0–1		0–1.0–7	0–1.0–4		0–1.0–7	
Time from first MS event to end of follow-up, years			0.23[e]			<.001[e]		0.84[e]
Mean (SD)	16.7 (11.5)	13.1 (10.6)		16.7 (11.3)	24.8 (10.3)		15.9 (9.0)	
Minimum–median–maximum	0–15.0–69.0	2.3–8.3–34.8		0–15.1–69.0	3.8–25.8–50.1		2.8–13.6–40.4	
MS types at end of follow-up, *n* (%)			1.00[d]			<.001[d]		0.03[d]
Relapsing MS	3502 (66.0%)	9 (64.3%)		3502 (57.5%)	16 (23.5%)		26 (50.0%)	
Progressive MS	1808 (34.0%)	5 (35.7%)		2581 (42.5%)	52 (76.5%)		26 (50.0%)	
EDSS at end of follow-up			0.51[e]			<.001[e]		<.003[e]
Mean (SD)	3.2 (2.3)	2.8 (2.1)		3.6 (2.4)	5.7 (2.5)		4.5 (2.3)	
Minimum–median–maximum	0–2.0–9	1–2.5–7		0–3.0–10	1–6.0–9		1–4.0–9	
Annual rate of EDSS increase from MS onset to end of follow-up			0.76[e]			<.001[e]		<.001[e]
Mean (SD)	0.12 (0.20)	0.10 (0.10)		0.14 (0.22)	0.19 (0.14)		0.23 (0.20)	
Minimum–median–maximum	0–0.08–5.8	0–0.08–0.3		0–0.10–5.8	0–0.17–0.9		0–0.19–1.10	
MS treatment, *n* (%)								
Treated for at least 3 months by a DMT during follow-up	4289 (80.8%)	9 (64.3%)	0.16[d]	4824 (79.2%)	56 (82.4%)	0.65[d]	46 (88.5%)	0.12[d]
At least one highly active DMT	2818 (53.1%)	9 (64.3%)	0.44[d]	3238 (53.1%)	44 (64.7%)	0.07[d]	37 (71.2%)	0.01[d]

Abbreviations: DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; NA, not applicable; NR, nonrelated; Po-MS, progressive onset MS; Ro-MS, relapsing onset MS.

[a]First MS event for the BEFORE group: first epileptic seizure; for the Ro-MS control group: first relapse.

[b]AFTER group and Ro-MS and Po-MS control groups.

[c]The NR group and Ro-MS and Po-MS control groups.

[d]Chi-squared and Fisher exact test.

[e]Kruskal–Wallis test.

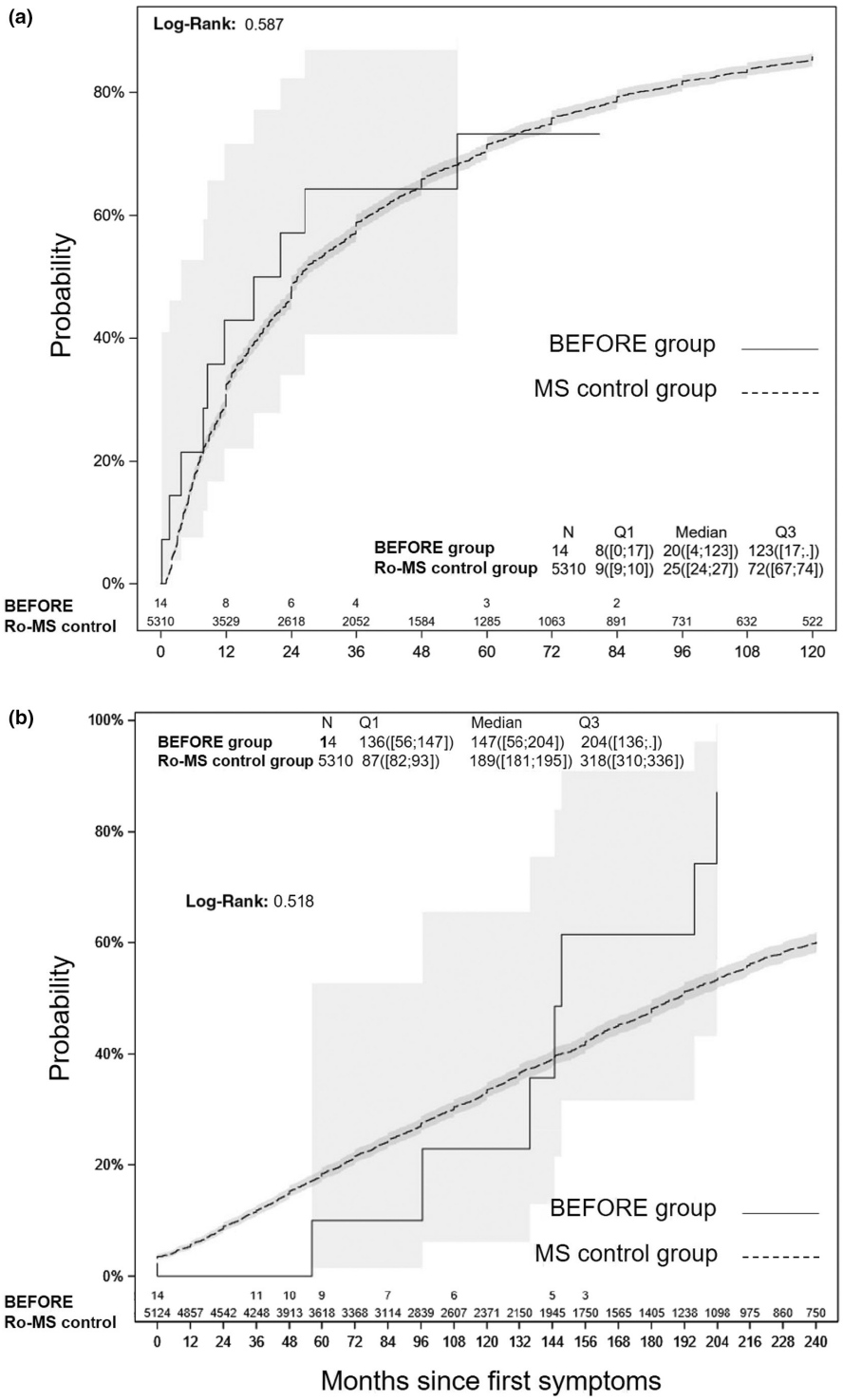

FIGURE 2 (a) Kaplan–Meier curves of the probability of the second relapse after the first multiple sclerosis (MS) event in the BEFORE group (baseline: first epileptic seizure) and the relapsing onset MS (Ro-MS) control group (baseline: first relapse). (b) Kaplan–Meier curves of the probability of Expanded Disability Status Scale (EDSS) = 3.0 after the first event of MS (same groups, same definitions of baselines). The number of control patients at baseline in B is less than the total number of Ro-MS control patients, because some of them were EDSS > 3.0 at baseline. The median survival time to the second relapse was 1.7 years (95% confidence interval [CI] = 0.3–10.3) in the BEFORE group, and 2.1 years (95% CI = 2.0–2.3) in the control Ro-MS group. The median time to reach EDSS = 3.0 was respectively 12.3 years (95% CI = 4.7–17.0) and 15.8 years (95% CI = 15.1–16.3)

their controls ($p = 0.59$; Figure 2a). There was no difference in the risk of reaching EDSS = 3.0 between the two groups ($p = 0.52$; Figure 2b).

As the relationship between MS and the seizure was doubtful in some cases, we decided to conduct sensitivity analyses using the first classic MS event (i.e., after the first epileptic seizure) as

baseline in patients who experienced a classic MS event during their follow-up. The log-rank test found no significant difference with the Ro-MS group concerning the occurrence of a second MS event ($p = 0.72$) or of EDSS = 3.0 ($p = 0.06$; curves not shown).

The additional Kaplan–Meier estimators with the date of birth in each group as baseline found no difference in the risk of the occurrence of EDSS = 3.0 ($p = 0.27$; curves not shown). Cox regression with matched data did not find any increased risk of a second MS event and EDSS = 3.0 in the BEFORE group (hazard ratio [HR] = 1.14, 95% confidence interval [CI] = 0.59–2.21, $p = 0.70$ and HR = 1.34, 95% CI = 0.64–2.80, $p = 0.44$, respectively).

AFTER group

The AFTER group included 68 patients. They were younger at their first MS relapse and had a higher annual rate of EDSS increase during their MS course. They were more likely to present a progressive MS form at last follow-up but had a longer follow-up (Table 1).

The median time between the first MS event and the first epileptic seizure was 14.7 years (±10.0). When epileptic seizures occurred, seven patients (10.3%) had Po-MS, 32 (47.1%) had Ro-MS, and 29 (42.6%) were in the secondary progressive phase. Seizures were focal in 18 patients (26.5%), seemingly generalized tonic–clonic in 40 patients (58.8%), and unknown in 10 patients (14.7%). Thirty-three patients had a recurrence of epileptic seizures, whereas eight had no further epileptic seizures. The recurrence status was unknown for 27 patients.

Patients reached EDSS = 3.0, 6.0, and 7.0 significantly faster than the MS control group ($p = 0.006$, $p = 0.003$, and $p = 0.004$, respectively; Figure 3).

Using date of birth at baseline led to the same results ($p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively; curves not shown). Cox regression with matched data found an increased risk of EDSS = 3.0 (HR = 1.43, 95% CI = 1.12–1.82, $p = 0.004$), 6.0 (HR = 1.78, 95% CI = 1.35–2.35, $p < 0.001$), and 7.0 (HR = 1.59, 95% CI = 1.11–2.29, $p = 0.012$).

NR group

The NR group included 52 patients. Forty-one (78.8%) had an idiopathic generalized epilepsy, and 11 (21.2%) had a structural etiology other than MS. Among those 11 patients, three had vascular disease (two arteriovenous malformation and one cerebrovascular thrombosis), two with tumoral disease (one meningioma and one glioma), four with metabolic or toxic etiology (one on alcohol withdrawal, one an iatrogenic event, and one due to fever), and two secondary to encephalopathy. Patients of the NR group had a higher mean EDSS at last follow-up, despite a nonsignificantly different duration of follow-up and a higher annual rate of EDSS increase since disease onset, and were significantly more likely to present a progressive form at their first MS event and at last follow-up (Table 1).

Most patients presented their first seizure before their first classic MS symptom (37, 71.2%), with a mean time between the first MS symptom and the first seizure of 15.8 years (±10.1). Thirteen patients (25%) presented their first seizure after a first classic MS symptom, with a mean time of 7.6 years (±7.0). The date of the first seizure was unknown for the two remaining patients.

Patients in the NR group reached an irreversible handicap stage (EDSS = 3.0, 6.0, and 7.0) significantly faster than the control patients ($p < 0.001$, $p = 0.05$, $p = 0.006$, respectively; Figure 4a–c). As a substantial proportion of patients in the NR group had already reached EDSS = 3.0 at baseline (12/52, 23.1% vs. 725/6093, 11.9% in the control group), we excluded patients with EDSS ≥ 3.0 at baseline from analysis. The NR group still showed significantly faster worsening than the control group (log-rank test, $p = 0.006$).

Sensitivity analysis with date of birth as baseline of the Kaplan–Meier estimators found similar results, with a higher probability of reaching EDSS = 3.0, 6.0, and 7.0 in patients with epileptic seizure of the NR group ($p < 0.001$, $p = 0.042$, $p = 0.021$, respectively; curves not shown). Cox regression with matched data did not find a statistically significant higher risk of EDSS = 3.0 (HR = 1.28, 95% CI = 0.93–1.77, $p = 0.13$), 6.0 (HR = 1.11, 95% CI = 0.78–1.57, $p = 0.58$), or 7.0 (HR = 1.44, 95% CI = 0.87–2.41, $p = 0.16$).

DISCUSSION

Our main results are the following: (i) patients who have an epileptic seizure of unknown etiology before their first classic MS event have the same disease prognosis as other Ro-MS patients; (ii) patients with an epileptic seizure related to MS or of unknown etiology after the diagnosis of MS have a worse prognosis than other MS patients, with a higher probability of EDSS worsening; and (iii) patients with an epileptic seizure with an identified etiology other than MS have a worse prognosis than other nonepileptic MS patients in terms of EDSS worsening.

In our large cohort, we identified only 14 patients who had an epileptic seizure suggestive of the first MS event (BEFORE group). This is especially true concerning the five patients for whom links can be made between a cortical plaque found on MRI and clinicoelectrical patterns. The inability of MRI to indicate a cortical plaque, which is common without dedicated MRI sequences such as double inversion recovery, has already been described [23]. We conscientiously reviewed the EEG and clinical history for each of these 14 patients throughout their follow-up, and neither the referring neurologist nor our team found an etiology other than MS in these nine patients. We decided to group these patients together with patients with an epileptic seizure indisputably related to MS. Although it is not certain that these seizures were related to MS, we assumed that the lack of an alternative diagnosis despite our investigations and after years of follow-up constituted a good indication in favor of MS being responsible for the onset of the epileptic seizures. The patients were, however, very similar to the entire group of Ro-MS patients without a history of epileptic seizure, in terms of age at onset, sex ratio, DMT use, and course of MS. The risk of

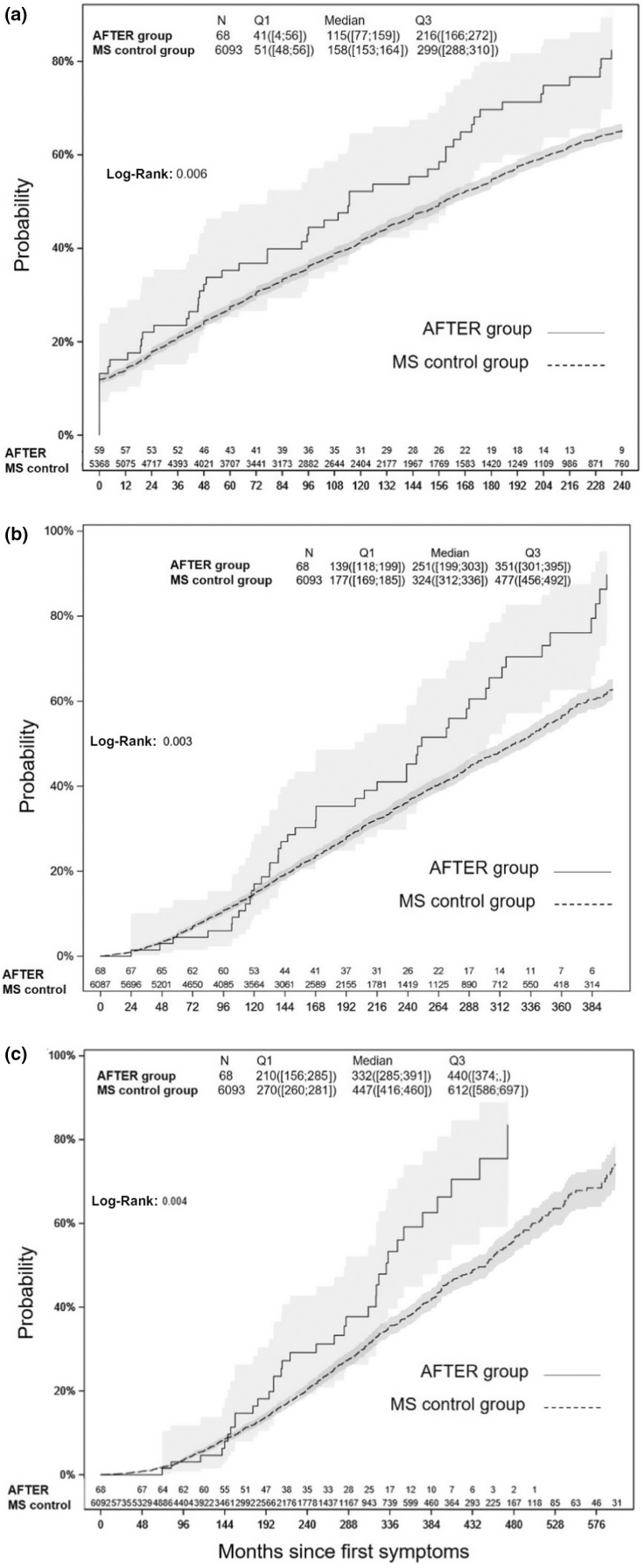

FIGURE 3 Kaplan–Meier curves of the probability of Expanded Disability Status Scale (EDSS) = 3.0 (a), EDSS = 6.0 (b), and EDSS = 7.0 (c), for the AFTER group and multiple sclerosis (MS) control group, after the first event of MS. The number of patients at baseline might be less than the total number of patients of a group, because patients already having presented the outcome at baseline are excluded. The median time to reach the different stages of EDSS, for the AFTER group and MS control group, were respectively 9.6 years (95% confidence interval [CI] = 6.4;13.3) and 13.2 years (95% CI = 12.8;13.7) for EDSS = 3.0, 20.9 years (95% CI = 16.6;25.3) and 27.0 years (95% CI = 26.0;28.0) for EDSS = 6.0, and 27.7 years (95% CI = 23.8;32.6) and 37.2 years (95% CI = 34.7;38.3) for EDSS = 7.0

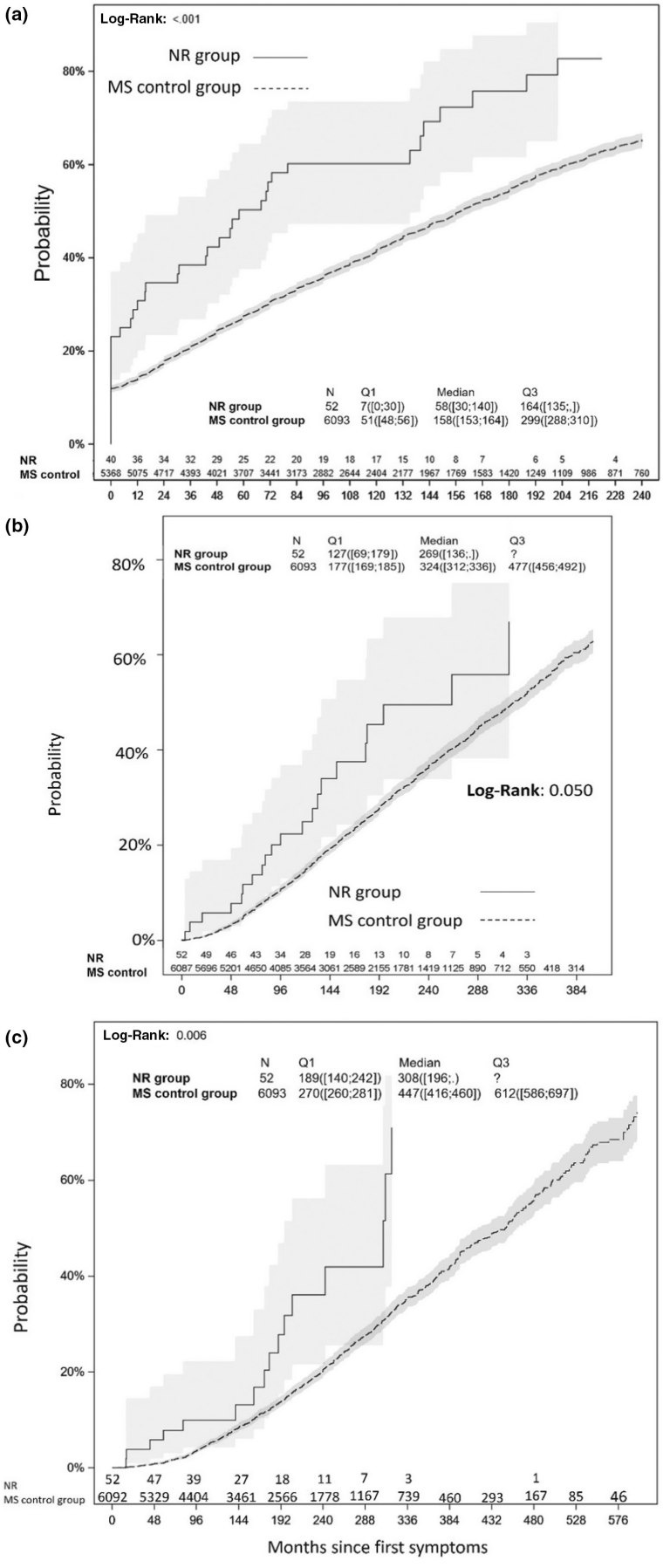

FIGURE 4 Kaplan–Meier curves of the probability of Expanded Disability Status Scale (EDSS) = 3.0 (a), EDSS = 6.0 (b), and EDSS = 7.0 (c), for the nonrelated (NR) group and multiple sclerosis (MS) control group, after the first event of MS. The number of patients at baseline might be less than the total number of patients of a group, because patients already having presented the outcome at baseline are excluded. The median time to reach the different stages of EDSS, for the NR group and MS control group, were respectively 4.8 years (95% confidence interval [CI] = 2.5–11.7) and 13.2 years (95% CI = 12.8–13.7) for EDSS = 3.0, 21.9 years (95% CI = 11.3–.) and 27.0 years (95% CI = 26.0–28.0) for EDSS = 6.0, and 25.7 years (95% CI = 16.3–.) and 37.2 years (95% CI = 34.7–38.3) for EDSS 7.0. Upper limit of confidence interval was not calculated for NR group - EDSS 6.0 and 7.0 because of a small number of patients.

irreversible EDSS or further MS event is not significantly different between Ro-MS patients without epileptic seizure and BEFORE patients. This indicates that starting the disease with this particular symptom is not a marker of a worse prognosis. As we had no dedicated imaging data, conclusions about cortical pathology are limited, especially because other works have shown that early widespread cortical lesions are associated with worse prognosis, in terms of both EDSS worsening and cognitive deterioration [15, 24, 25]. We can hypothesize that, in our 14 patients, the lesion responsible for the early seizure was highly focal and did not affect the future course of MS.

Patients in the AFTER group had a worse prognosis than those in the MS control group despite a similar use of DMT in these groups. Interestingly, the follow-up duration of patients in the AFTER group was longer, possibly because of a younger age at MS onset (mean = 27.0 years vs. 32.7 years in the control group). This might have increased the chances of developing epileptic seizures during the MS course, especially epileptic seizures secondary to late cortical neurodegeneration [26]. The mean time between the first MS event and the first epileptic seizure was long, approximately 14 years, and 53% of the patients in this group had the progressive form of MS when the epileptic seizure occurred, indicating that MS disease was already advanced. Consequently, these results strongly suggest that epileptic seizures in patients in the AFTER group were a marker of disease severity, rather than the cause of the disease severity. It is feasible that patients in the AFTER group had more severe cortical involvement, explaining both the epileptic seizures and the more rapid EDSS worsening. Severe and multifocal cortical involvement has been associated with epileptic seizures during MS course, with faster reduction of gray matter fraction, confirmed on MRI [27]. Cortical involvement is also a hallmark of progression in MS disease, with advanced neurodegeneration and severe handicap [28].

Finally, we identified 52 patients who had an epileptic seizure with a clearly identified etiology other than MS. These patients had a significantly worse prognosis than the MS control group in terms of handicap. Of note, Cox regressions based on matched data failed to show this higher risk. We assume that Cox regressions are less sensitive than log-rank tests; the matching procedure led to a dramatic reduction in the number of patients [29]. Studies have shown that the occurrence of psychiatric, musculoskeletal, and vascular comorbidities increases disability in MS patients [30–32]. Therefore, our results are in accordance with these findings, the neurological disease responsible for the seizures being considered a comorbidity of MS [33]. The underlying explanation has not yet been elucidated, but local inflammation and/or cortical atrophy enhanced by epileptic seizures could play a role and could also explain why there are more progressive MS forms at the first classic MS event.

One of the main limits of our study is that we might have underestimated the proportion of epileptic seizures in our cohort. The ReLSEP is mainly focused on collecting data about MS. Even if medically relevant events in the MS patients are prospectively collected, atypical events such as epileptic seizures could have been missed. Moreover, information about seizure etiology might be incomplete, as well as data about their recurrence and their treatment that might have impacted the further disability scores in our patients. Information about MRI in the registry are imprecise, and we were not able to assess the association between seizures and MS. However, our proportion of 2.1% is in the range of previous studies [1–9]. In this line, 11 patients had been identified as potentially epileptic by checking the MS database, but we were unable to determine the precise nature of the events that would qualify them as epileptic by investigating their medical files. We therefore excluded them. We assume that the impact of this was limited, as they are no more than 7.6% of the eventual cohort of patients with epileptic seizures. Another limit is that we do not have information about the patients' epilepsy-related handicap for the NR group, so we cannot be sure that EDSS worsening is related to MS or to a patient's epileptic history. Finally, we should keep in mind that the small number of patients in the BEFORE group ($n = 14$) limits the power of our comparisons and analysis.

CONCLUSIONS

The prognosis of MS in patients with epileptic seizures depends on the time between the first epileptic seizure and the first classic MS event, and on the relationship between MS and epileptic seizures. For some patients, an epileptic seizure can be considered the first symptom of MS, in which case the disease course is similar to other Ro-MS patients. On the other hand, patients with an epileptic seizure secondary to formerly diagnosed MS or with a second disease responsible for epileptic seizures have a worse prognosis. Other studies, including imaging data and measuring the extent of the cortical lesions in MS patients with epileptic seizures and controls, are warranted.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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