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Clinical study

Aggressive multiple sclerosis in Argentina: Data from the nationwide registry RelevarEM

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ABSTRACT

The objectives of the present study were to describe the frequency of aggressive multiple sclerosis (aMS) as well as to compare clinical and radiological characteristics in aMS and non-aMS patients included in RelevarEM (NCT 03375177).

Methods: The eligible study population and cohort selection included adult-onset patients ($\geq$18 years) with definite MS. AMS were defined as those reaching confirmed EDSS $\geq$ 6 within 5 years from symptom onset. Confirmation was achieved when a subsequent EDSS $\geq$ 6 was recorded at least six months later but within 5 years of the first clinical presentation. AMS and non-aMS were compared using the $\chi 2$ test for categorical and the Mann-Whitney for continuous variables at MS onset and multivariable analysis was performed using forward stepwise logistic regression with baseline characteristics at disease onset.

Results: A total of 2158 patients with MS were included: 74 aMS and 2084 non-aMS. The prevalence of aMS in our cohort was 3.4% (95%CI 2.7–4.2). AMS were more likely to be male ($p = 0.003$), older at MS onset ($p < 0.001$), have primary progressive MS (PPMS) phenotype ($p = 0.03$), multifocal presentation ($p < 0.001$), and spinal cord as well as infratentorial lesions at MRI during disease onset ($p = 0.004$ and $p = 0.002$, respectively).

Conclusion: 3.4% of our patient population could be considered aMS. Men, patients older at symptom onset, multifocal presentation, PPMS phenotype, and spinal cord as well as brainstem lesions on MRI at clinical presentation all had higher odds of having aMS.

1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS), pathologically featured by the presence of multiple inflammatory lesions that progress in time and that lead to significant disability in most affected patients 20 or 30 years after disease onset [1,2]. Despite this, the actual rate of progression and disability accumulation varies considerably between patients and studies [3,4].

Regarding epidemiological aspects of MS in Latin America, a systematic review found that the incidence reported ranged from 0.15 to 3 cases per 100,000 person-years and the prevalence ranged from 0.75 to 38.2 cases per 100,000 inhabitants in 13 studies analyzed [5]. Recently, prevalence and incidence were described in certain regions of Argentina, describing a prevalence rate of 20 to 40 cases per 100,000 inhabitants while the incidence reported was of almost 3 new cases per 100,000 inhabitants per year [5–8].

Aggressive MS (aMS) describes a form of the disease with a rapid progressive course leading to significant disability in multiple neurologic systems or even death in a relatively short time after onset [3,4,9]. Despite there being no consensus on the exact definition of aMS [9], several studies performed during the last years have tried to better identify and understand the frequency and distribution as well as the progression and treatment response in order to determine more accurately which patients with aMS would most benefit from higher-efficacy, higher-risk treatments [3,4]. Those studies are mainly set in North America and scarce data of aMS comes from other regions.

Recently, we presented the methodology behind RelevarEM, the first nationwide MS registry in Argentina and Latin America (NCT03375177) [10,11]. The registry collects Information about MS and neuromyelitis optica spectrum disorders (NMOSD) patients regarding demographics, comorbidities, EDSS, relapses, treatments MRI and CSF findings [10].

The objectives of the present study were to describe the frequency of aMS as well as to compare clinical and radiological characteristics in aMS and non-aMS patients included in RelevarEM.

2. Methods

RelevarEM is a longitudinal, strictly observational MS and NMOSD registry in Argentina [10,11]. It is open to all practicing neurologists and MS specialists and their teams across the country. The registry tracks the outcomes of routine clinical practice of patients with MS and NMOSD in a web-based platform that allows researchers to register and follow-up their patients. The primary objective of the registry was to create an MS physician network in Argentina that captures pragmatic and relevant information from MS patients in terms of clinical and demographic aspects [10,11].

Any patient diagnosed with MS, a clinically isolated syndrome (CIS), a radiologically isolated syndrome, or an NMOSD defined by validated diagnostic criteria (for MS and NMOSD) [12,13] can be entered into the registry. To ensure the correct use of the diagnostic criteria for MS and NMOSD in each center, the executive committee invited all MS centers and physicians involved in the

care of affected patients in Argentina. To reduce the possibility of bias in the selection, each participating physician was required to include all patients seen in their practice or clinic.

2.1. Study population, cohort selection and variables included

For the objective of this study, data regarding demographic and clinical characteristics of MS were obtained from anonymized patient medical records at disease onset. The eligible study population and cohort selection included adult-onset patients ($\geq$18 years) with definite MS included in the registry between August 2018 and March 2020. AMS patients were identified from this source population and were defined as those reaching confirmed EDSS $\geq$ 6 within 5 years from symptom onset [3,4]. Confirmation was achieved when a subsequent EDSS $\geq$ 6 was recorded at least six months later but within 5 years of the first clinical presentation. Patients with aMS as well as non-aMS must have had at least 5 years of follow-up since disease onset to be included. Disease onset was defined as the detection of the first sign/symptom that suggested CNS demyelination in the optic nerves, brainstem, spinal cord or other regions, and which was not attributable to other diseases [14]. The clinical presentation of the disease was classified as monofocal or multifocal presentation [14]. The magnetic resonance imaging (MRI) used for the baseline analysis was the MRI performed during the disease onset.

2.2. Statistical analysis

Baseline characteristics of the cohort were reported in percentages for categorical data and in median and interquartile range (IQR) for continuous data. Characteristics of aMS and non-aMS cohorts were then compared using the $\chi 2$ test for categorical and the Mann-Whitney for continuous variables at MS onset. Finally, a multivariable analysis was performed using forward stepwise logistic regression with baseline characteristics at disease onset and risk of aMS during follow-up.

Once aMS were identified (dependent variable), a stepwise logistic regression analysis was performed between dependent variable adjusted by age, sex, mean age at disease onset, MS disease course, clinical presentation at onset, oligoclonal bands at CSF and MRI abnormalities at disease onset. Forward and backward stepwise analyses were conducted using the Wald statistic as a criterion, with P = 0.05 for entry and P = 0.10 for removal. The analysis of the data was done through Stata 15 software.

3. Results

Up to 31 March 2020, 56 centers and 98 professionals distributed throughout Argentina have become part of the registry. A total of 2158 patients with MS were included: 74 AMS and 2084 non-aMS. The prevalence of aMS in our cohort was 3.4% (95%CI 2.7–4.2%). Mean age at disease onset for aMS was 42 ± 5 years vs. 31 ± 4 years for non-aMS, and mean follow-up time for aMS and non-aMS was 8 ± 2.5 and 12 ± 4.3 years, respectively. Almost 82% of aMS were currently retired from work due to the disease vs. 33.4% in non-aMS patients. The remainder of the descriptive variables in aMS and non-aMS patients are described in Table 1. Regarding treatment, 36.5% in aMS vs. 6% in non-aMS were currently in monoclonal antibodies treatment (p < 0.001) (Table 2). In the regression analysis, patients with aMS were more likely to be male (p = 0.003, older at MS onset (p < 0.001), have primary progressive MS (PPMS) phenotype (p = 0.03), multifocal presentation (p < 0.001), and spinal cord as well as infratentorial lesions at MRI during disease onset (p = 0.004 and p = 0.002, respectively) (Table 1 and Fig. 1).

4. Discussion

This is the first analysis of the longitudinal Argentinean registry regarding aMS. By exploring the database retrospectively, we identified that 3.4% of our patient population could be considered as having aMS. We also identified specific patient characteristics associated with the presence of aMS. Men, patients older at symptom onset, multifocal presentation, PPMS phenotype, and spinal cord as well as brainstem lesion on MRI at clinical presentation all had higher odds of having aMS.

Our study is in line with previous research. Menon et al. described the demographic and clinical characteristics of patients with aMS in British Columbia, Canada [3]. By applying three definitions (**Definition 1**: confirmed Expanded Disability Status Scale (EDSS) $\geq$ 6 within 5 years of MS onset; **Definition 2**: confirmed EDSS $\geq$ 6 by age 40; and **Definition 3**: secondary progressive MS within 3 years of a relapsing-onset course), authors found a

Table 1
Baseline characteristics of aMS and non aMS.

	aMS (n = 74)	Non aMS (n = 2084)	p	OR (95%CI)
Number of patients and %	74 (3.4)	2084 (96.4)	–	–
Mean age at disease onset, years ± SD	42 (5)	31 (4)	<0.001	1.76 (1.23–2.11)
Female gender, n (%)	37 (50%)	1390 (66.7%)	0.003	0.64 (0.54–0.86)
Mean follow-up time, years ± SD	8 (2.5)	9.5 (4.3)	0.18	–
Disease course				
Primary progressive course, n (%)	16 (22)	250 (12)	0.03	1.54 (1.13–1.76)
Relapsing course, n (%)	58 (78)	1834 (88)	0.01	0.76 (0.55–0.92)
Working status				
Currently working, n (%)	14 (18.9%)	1385 (66.6%)	<0.01	–
Retired due to the disease, n (%)	60 (81.1%)	699 (33.4%)	<0.01	-
Clinical presentation				
Monofocal, n (%)	27 (36.5)	1578 (75.7)	<0.001	0.86 (0.68–0.97)
Multifocal, n (%)	47 (63.5)	489 (23.5)	<0.001	1.46 (1.18–2.11)
Unknown, n (%)	-	17 (0.8)	-	-
Positive OB in CSF, n (%)	67 (91%)	1771 (85)	0.23	1.07 (0.78–1.22)
MR abnormalities at clinical presentation				
Infratentorial lesions, n (%)	63 (85.1%)	1362 (65.6%)	0.002	1.21 (1.04–1.42)
Spinal cord lesions, n (%)	62 (82.7%)	1183 (56.7%)	0.004	1.33 (1.16–1.97)
Positive Gadolinium lesions, n (%)	40 (55.1%)	1078 (51.7%)	0.32	1.06 (0.87–1.32)

aMS = aggressive multiple sclerosis; SD = standard deviation; OB = oligoclonal bands; CSF = cerebro spinal fluid

Table 2
Treatment at disease onset and Current status in aMS and non aMS.

	aMS (n = 74)	Non aMS (n = 2084)	p-value
At disease onset			
Injectables, n (%)	17 (23.5)	719 (34.5)	0.05
Orals, n (%)	44 (59.5)	1094 (52.5)	0.23
Monoclonal antibodies, n (%)	6 (8)	42 (2)	<0.001
No treatment, n (%)	7 (9)	229 (11)	0.58
Current status			
Injectables, n (%)	4 (5)	500 (24)	<0.001
Orals, n (%)	33 (45)	1146 (55)	0.01
Monoclonal antibodies, n (%)	27 (36.5)	127 (6)	<0.001
No treatment, n (%)	10 (13.5)	311 (15)	0.11
Current EDSS, SD	6.5 (6–7)	2 (1–4)	<0.001

EDSS = expanded disability status scale; SD = standard deviation; aMS = aggressive multiple sclerosis

frequency of 4% to 14% aMS in the entire MS population [3], and they identified specific patient characteristics associated with the presence of aMS: men, older at symptom onset, and presenting with PPMS had greater odds of developing aMS [3]. In another study performed by the same group that included aMS, authors examined how the disease progressed in the aMS cohort of British Columbia, Canada [4]. For that analysis, authors used only one definition of aMS (EDSS $\geq$ 6 within 5 years from onset). After including 225 aMS for the analysis, the proportion of patients who showed a disease progression during the first years was 57.8% and only 1 out of 10 aMS showed any improvements in disability, indicating that the disability may be non-reversible. In that study, the odds of worsening increased with disease duration (adjusted odds ratio = 1.36; 95%CI 1.22–1.52) and the presence of PPMS (vs relapsing-onset) MS (AOR = 1.85; 95% CI = 1.01–3.38) [4].

There is no consensus on the definition of aMS. Such an absence likely explains the dearth of studies that explicitly describe this extreme disease presentation. In our work, we chose Definition 1 used in the Menon et al. study where analysis demonstrated no single definition criterion "superior" to others and provided a well-defined timeline that prevents misclassification.

Currently, there is much evidence that supports the importance of early treatment in MS to avoid disease progression and disability outcomes [2]. MS damages the entire brain and begins from the onset of the disease [15–20]. Results from randomized, controlled trials in populations with CIS and relapsing MS have clearly shown that they provide a reduction in disease activity in terms of radiological activity, clinical relapses and disability progression [21–26]. There is also much information from observational studies demonstrating that early treatment could control disease activity in many patients and avoid disease progression [27–29].

Considering that not all patients have the same prognosis and that there are currently more than 13 treatments for the disease, an appropriate knowledge of drug mechanisms of action, a correct identification of negative prognostic factors, and the accurate evaluation of the benefits and risks of the different treatments have all become highly relevant in making the best therapeutic decisions [2]. An individualized approach for targeting a treatment for each particular patient with MS has enabled neurologists to provide more effective and safer drug prescriptions [2,30–32]. As a consequence, the prompt identification of these patients could have important therapeutic implications, especially if a drug or other

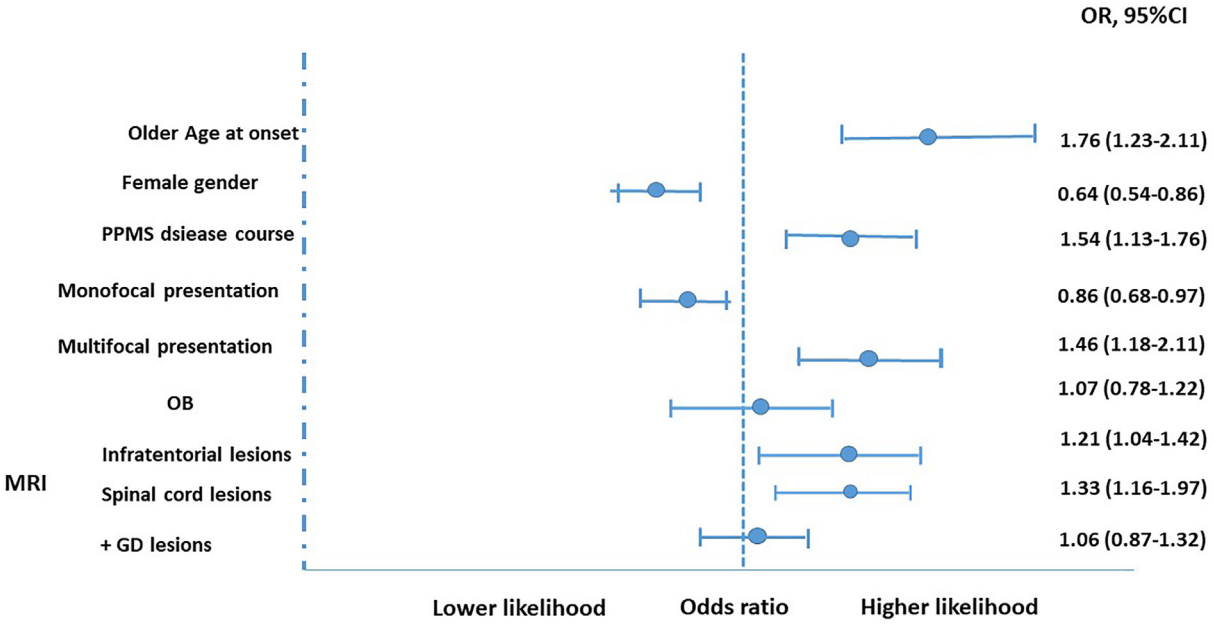

Fig. 1. Association between patient characteristics at baseline and aMS in the cohort. aMS = aggressive multiple sclerosis; OB = oligoclonal bands; CSF = cerebrospinal fluid, GD = gadolinium, PPMS = primary progressive multiple sclerosis.

intervention were to become available that could significantly delay the progression of the disease.

Our study had certain limitations. Based on previous studies, we believe that in Argentina there are about 6000 patients with MS [6]. In our study, we included more than 2,000 patients, and while the registry is nationwide, some patients were not included. This could generate the possibility of measurement bias. Although we had no information about the yearly evolution of the disease from onset, we did have a picture of how the disease begins and the status of patients since the entry to the registry. Therefore, information on how the disease behaves year by year is currently lacking. Finally, we were unable to examine other potential important outcomes such as cognition, quality of life, employment or other biomarkers which would be useful to include in future studies.

In conclusion, we have identified a prevalence of aMS of 3.4% (IC95 2.7–4.2%) of aMS patients in the Argentinean registry. Factors associated with aMS at disease onset were males, older age at disease onset, PPMS phenotype and the presence of spinal cord and brainstem lesions at clinical presentation. Replication of findings in other longitudinal, largely natural history data sets would be of value. A wider use of MS disease registries in the region would be desirable in the near future to better understand the behavior of the disease in our region.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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