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on behalf of RelevarEM investigators

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ORIGINAL ARTICLE

Clinical and demographic characteristics of primary progressive multiple sclerosis in Argentina: Argentinean registry cohort study (RelevarEM)

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Abstract

Background Primary progressive multiple sclerosis (PPMS) is an infrequent clinical form of multiple sclerosis (MS). Scarce information is available about PPMS in Latin America. The aim of this work is to describe the clinical and demographic characteristics of PPMS patients in Argentina.

Material and methods RelevarEM is a longitudinal, strictly observational registry in Argentina. Clinical and epidemiological data from PPMS patients were described.

Results There were 144 cases of PPMS. They represented 7% of MS patients. The mean age was 44.1 years. The female:male ratio was 1.08. The mean Expanded Disability Status Scale (EDSS) score was 5.5 and the mean disease evolution time was 10.6 years. Oligoclonal bands were found in 72.9%. At the time of diagnosis, magnetic resonance imaging showed spinal cord lesions in 82.6% and contrast-enhancing brain lesions in 18.1% of patients. Almost one third of patients were treated with a disease-modifying drug, and ocrelizumab was the most frequently used (55.8%).

Conclusions PPMS is an infrequent subtype of MS and its recognition is of the highest importance as it has its own evolution, treatment, and prognosis. The importance of our research resides in providing local data and contributing to a better understanding of PPMS and its treatment in Latin America.

Keywords RelevarEM · Primary progressive multiple sclerosis · Argentinean multiple sclerosis epidemiology

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating, and neurodegenerative disease that affects the central nervous system (CNS) with a variable evolution course. Its complex pathogenicity involves demyelination, axonal loss, and reactive gliosis, among other mechanisms [1]. It is the main non-traumatic cause of neurological disability in young adults, with a peak incidence between 18 and 50 years of age. In many countries, including Argentina, epidemiologic studies have observed a sustained rise in the incidence and prevalence of MS over the years [2]. The disease evolution clinical course led to the description of four excluding phenotypes: relapsing-remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), and progressive-relapsing (PRMS) [3]. Although this is a classification dating from 1996, it is still useful for discriminating between relapsing and progressing forms. Moreover, this classification is related to different clinical characteristics and pathophysiologic mechanisms, with neurodegeneration and axonal dysfunction, being the main pathologic processes acting in progressive forms [4]. Recently, prevalence and incidence were described

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in certain regions of Argentina. However, there is scarce information about epidemiological aspects in certain areas of the country. In Buenos Aires, for example, the estimated prevalence is 38.2 per 100,000 inhabitants (95% CI 36.1–41.2). An update, almost 20 years after the first report in the area, showed a significant increase in the previously published prevalence [5]. On the other hand, the prevalence in the Northwest Region of Argentina (NOA) is lower (23.8 cases per 100,000 inhabitants). [6] The first analysis of the longitudinal Argentinean registry of MS and NMOSD showed that in a group of 1588 MS patients, the most frequent MS phenotype was RRMS in 82.4%, followed by SPMS (5.5%) and PPMS (4.2%) [7].

Currently revised clinical MS phenotypes' classification maintained the distinction between multiple sclerosis with an attack onset versus a progressive course from onset [8]. In the 2017 revised McDonald criteria, the international panel supported the previous definitions of PPMS as "1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse." Additionally, they incorporated a further categorization in active or not (based on a recent clinical relapse or magnetic resonance imaging [MRI] lesion activity) and progressive or not (based on the clinical assessment of disability) [9]. The PPMS prevalence ranges from 10 to 20%, according to different series [10, 11]. From an epidemiological viewpoint, there have been reports that describe the existence of geographical incidence and prevalence variations, although most reports describe European and North American populations [12]. There is little information available describing the incidence, prevalence, and characteristics of MS in Latin America [2, 13–15]. With regard to PPMS, a recently published systematic review reported a prevalence in Latin America of 0.13 to 1.1 cases every 100,000 people [16]. Notably, no data was included from Argentinean studies as there are currently no local publications.

Considering the importance of having local epidemiological information, and with the aim of describing clinical and demographic characteristics of PPMS patients, we analyzed this subgroup in the national MS registry RelevarEM (National MS and NMOSD Argentinian Registry, clinicalTrials.gov Identifier: NCT03375177) [17]. The objective of this study is to describe and compare the baseline epidemiological data of PPMS patients included in RelevarEM.

Methods

RelevarEM is a longitudinal, strictly observational MS and neuromyelitis optica spectrum disorders (NMOSD) registry in Argentina. The registry is open to all practicing neurologists and to MS specialists and their teams across the country. It 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 physicians network in Argentina that captures pragmatic and relevant information from MS patients in terms of clinical and demographic aspects [17].

Any patient diagnosed with MS, a clinically isolated syndrome, a radiologically isolated syndrome, or an NMOSD defined by validated diagnostic criteria 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. Qualified centers and principal investigators were selected based on their experience in disease management (number of MS patients seen per year), the possibility to perform clinical and paraclinical procedures (oligoclonal bands on CSF, MRI exams, etc.), and activities involved in education and research in MS in Argentina [17]. To reduce the possibility of bias in the selection, each participating physician was required to include all patients seen in their practice or clinic.

For this research, all MS patients' data uploaded to RelevarEM until July 2019 were analyzed (n = 2.089). Patients with a diagnosis of NMOSD were excluded (n = 76). Patient's data came from 56 centers and 98 physicians distributed throughout Argentina, who were taking part in the Registry. Those with the diagnosis of PPMS were identified. Data regarding demographic and clinical characteristics of PPMS were obtained from the anonymized patient medical records. Relevant variables were selected for analysis considering their biological significance. Age, gender, city of residency, working status, and disability certificate were included as demographical variables. Clinical variables included were years since diagnosis, disability measured by EDSS score, clinical relapses, received treatments, presence of oligoclonal bands, and MRI characteristics. Patients were categorized as "active" PPMS (when having clinical relapses, new/enlarging T2 lesions, and/or contrast-enhancing lesions in MRI) or "not active" PPMS [8].

Statistical analysis

Categorical variables are expressed through frequency and percentage. Continuous variables are expressed as means and standard deviation (±). The t test or Pearson chi-square test was used for bivariate between-group comparisons. The IBM SPSS v.20 software (IBM Corp., NY, USA) was used, and the level of significance was conventionally set at 0.05.

Results

Of the 2089 registered patients, 144 had diagnosis of PPMS, rendering a 7% frequency. Demographic characteristics of

these patients are summarized in Table 1. The mean age at diagnosis was 44.1 years (± 10.71). The female/male ratio was 1.08. Regarding place of birth, 35% of the PPMS patients registered in RelevarEM were born in Buenos Aires Province, 29% in Buenos Aires City, 8% in Córdoba Province, and the remainder in other provinces. The mean disease evolution since diagnosis was 10.6 years (± 7.7) and the mean EDSS score was 5.5 (± 1.5), as illustrated in Fig. 1. There were no gender-associated statistical differences in years of disease evolution, EDSS score, or age at diagnosis ($p > 0.05$).

The mean EDSS score was statistically different ($t = -5.01$; $p < 0.05$) between patients with disability certificate ($n = 100$, EDSS score: 5.99 ± 1.2) and those without it ($n = 44$, EDSS score: 4.55 ± 1.7). No other differences (such as age at symptom onset or years of evolution) were found between those groups. With regard to working status, 65.3% ($n = 94$) were unemployed. These patients had a higher EDSS score when compared with employed patients ($t = -4.51$; $p < 0.01$) (Fig. 2).

Table 1 Clinical and demographic characteristics of PPMS patients in the RelevarEM registry

	PPMS ($n = 144$)
Females	74 (51.3%)
Age (years)	54.65 ± 11.01
Age at diagnosis (years)	44.04 ± 10.71
Years since diagnosis	10.61 ± 7.72
EDSS	5.5 ± 1.55
Unemployment	50 (34.7%)
Disability certificate	100 (69.4%)
Positive oligoclonal bands	105 (72.9%)
First MRI	
Contrast-enhancing lesion/s	26 (18.1%)
Medullary lesion/s	125 (86.8%)
Currently treated	43 (29.8%)
Treatment	
Beta-interferon	4 (9.3%)
Glatiramer acetate	4 (9.3%)
Fingolimod	4 (9.3%)
Dimethyl fumarate (DMF)	2 (4.6%)
Natalizumab	1 (2.3%)
Alemtuzumab	1 (2.3%)
Ocrelizumab	24 (55.8%)
Rituximab	1 (2.3%)
Other	2 (4.6%)

Data are expressed as mean ± standard deviation (continuous variables) or frequency and percentage (categorical variables). *PPMS* primary progressive multiple sclerosis, *MRI* magnetic resonance imaging

Concerning complementary studies, 72.9% of patients ($n = 105$) had positive oligoclonal bands. A vast majority ($n = 125$, 86.8%) also had spinal cord lesions. Brain contrast-enhancing lesions in the MRI at the time of diagnosis were present in 26 patients (18.1%). In reference to disease evolution, 45 patients (31.2%) were classified as "active" PPMS and 23 (16%) had at least one relapse during follow-up. The mean time from symptom onset to the first relapse was 41.8 months (SD 48.7). During the final 6 months of the study, 7.6% ($n = 11$) of patients had contrast-enhancing lesions and 2 patients had a clinical relapse. When comparing "active" and "inactive" patients, there were no statistically significant differences in gender ($p = 0.6$), EDSS score ($p = 0.7$), or age at symptom onset ($p = 0.9$).

Almost one third of patients (29.9%, $n = 43$) was being treated with a DMD; of these, 55.8% ($n = 24$) were using ocrelizumab, followed by parenteral drugs (18.6%, $n = 8$; such as beta-interferon and glatiramer acetate), as described in Table 1. No differences were found in the prescribed treatment for "active" and "not active" patients ($p = 0.08$). When comparing between treated and untreated patients, those under treatment had a lower EDSS score (5.7 ± 1.5 vs. 5.0 ± 1.4, $p = 0.01$) and shorter disease evolution (12.1 months ± 8.4 vs. 7.0 ± 3.8, $p < 0.01$) and were younger (56.2 years ± 11.1 vs. 51.0 ± 10.1, $p < 0.01$) than untreated patients.

Discussion

During the last years, several epidemiological reports regarding Latin America's MS patients have been published [12, 13]. In that context, RelevarEM was created and became the first observational registry of MS patients in Argentina, allowing a longitudinal record of epidemiological data [17].

Diagnosing PPMS is still a clinical challenge. The term "progressive" refers to a continuous neurological worsening during at least 6 to 12 months. Nevertheless, determining the exact date of symptom onset is usually challenging for both physician and patient [18]. Currently, diagnosis of PPMS is established in the presence of neurological worsening for at least 12 months, as well as with the concomitance of at least two of the following categories: brain MRI lesion, spinal cord lesions pointing to space dissemination, or pathological cerebrospinal fluid (CSF; presence of oligoclonal bands or high titers of CSF immunoglobulins) [9]. A Latin America consensus on the management of PPMS was published in 2018. Its main recommendation was the use of the 2017 McDonald criteria for diagnosis but minding the exclusion of regional diseases [19]. The identification of progressive forms of MS has recently come into focus since the Food and Drug Administration (FDA) approval of ocrelizumab as the first DMD effective for those phenotypes [20].

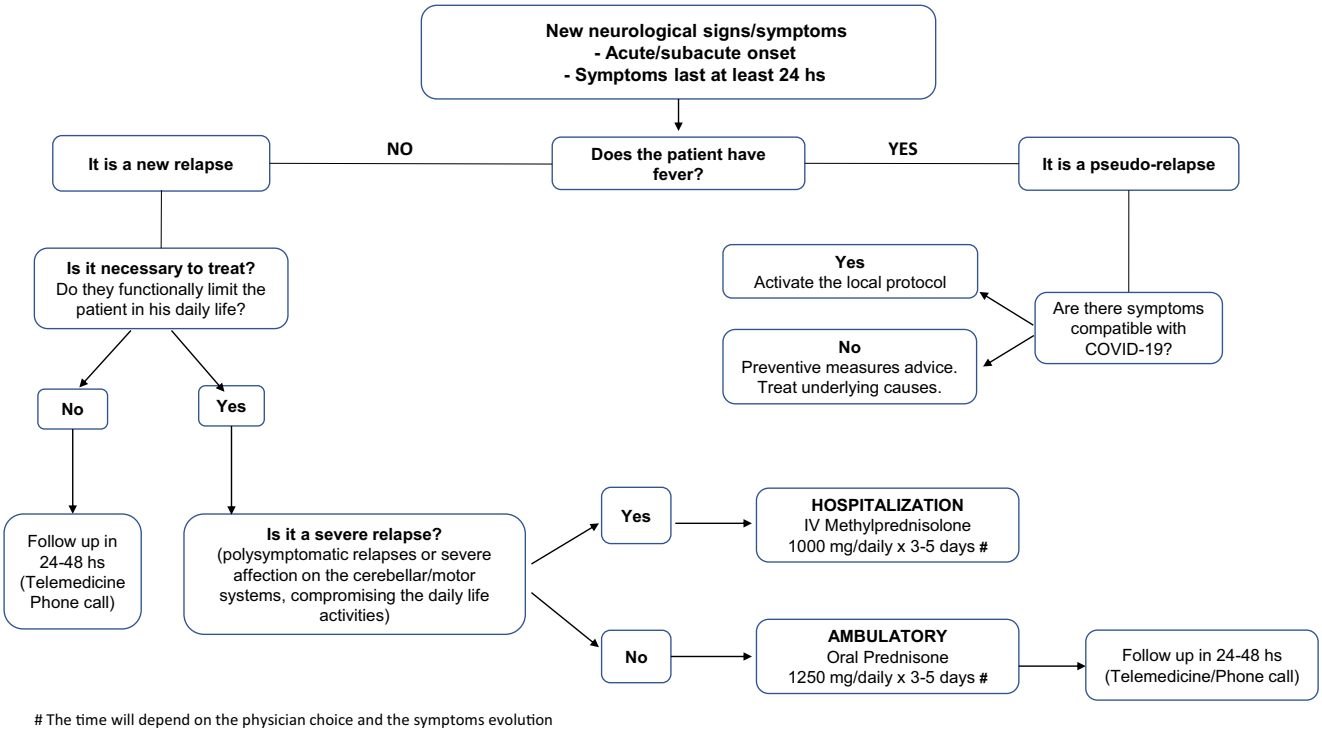

Fig. 1 Frequency of EDSS score in PPMS patients. PPMS, primary progressive multiple sclerosis; EDSS, Expanded Disability Status Scale

Regarding Latin America, different frequencies of PPMS have been reported. A systematic review published in 2018 analyzed the existing data of PPMS. Since most publications did not fulfill the inclusion criteria, they were able to include only 7 studies from the last 20 years [16]. They reported a PPMS prevalence in Latin America of 0.13 to 1.1 cases per 100,000 and, when considering the other subtypes, a frequency between 2 and 31%. Cuba and Brazil (Paraiba) were the countries with the greatest and fewest cases of PPMS reported, respectively. As previously mentioned, no Argentinean studies were included in the analysis. According to this study, the frequency and characteristics of PPMS found in our country are in line with epidemiological results published in Hungary [21], the USA [22], and Northern Ireland [23]. As previously reported, the frequency of PPMS was similar in both genders [24], although other studies have signaled a higher frequency in women [11, 25]. The mean age of symptom onset is also similar to those reported in other countries, with a mean onset between 37.3 and 43 years of age, which is markedly higher when compared with RRMS [11, 21]. The

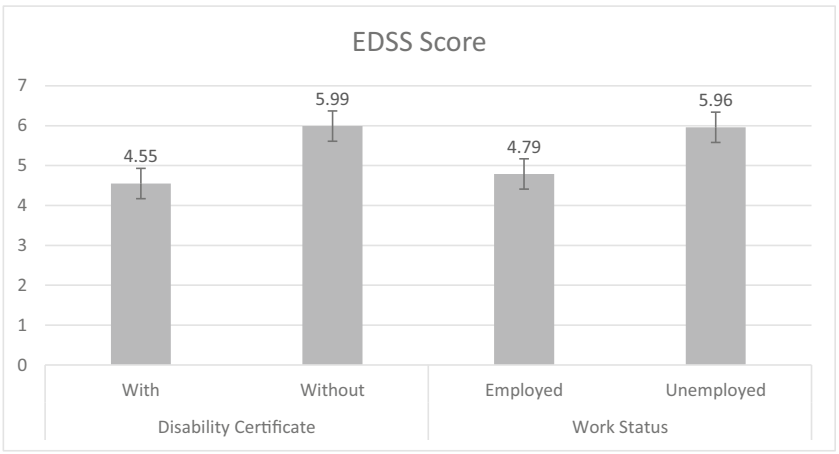

Fig. 2 EDSS score differences between patients with and without disability certificate and those with or without employment. EDSS, Expanded disability Status Scale

mean EDSS score found in the PPMS patients was also in line with previous studies [26]. One third of our patients had clinical (relapse) or radiological (contrast-enhancing or new/enlarging T2 lesions) activity. In 2014, a panel of experts proposed the subclassification of active and not active forms, aiming to distinguish patients that would most likely gain greater benefit from the new medication [8]. In our case, active PPMS patients were younger than not active patients but were no different when comparing disability or gender.

Working status is a very important characteristic in MS patients since unemployment is associated with emotional and economical hazards and diminishes both the patient and caregiver quality of life [27, 28]. In our cohort, more than half of PPMS patients were unemployed. This is markedly higher than the 16.5% in a recently reported Argentinean MS cohort, where most patients had the RRMS subtype [29]. High rates of unemployment in PPMS patients were also reported in an Iranian and a British study [11, 23]. We believe it is important to consider the demonstrated association of unemployment and the physical disability measured by the EDSS score [30]. In that regard, in our PPMS cohort, unemployed patients had higher EDSS scores than those with employment. Nevertheless, it is of paramount importance to recognize that the EDSS score is not the only reported variable associated to unemployment in MS patients, as local [31] and international [30] studies have also related it to cognitive impairment. Carnero Contentti et al. evaluated access to health services of 219 Argentinean MS patients and found that only half of MS patients had a disability certificate [29]. In Argentina, this certificate is important as it entitles the holder to certain benefits, access to facilities, and a guarantee of disability rights. Although the majority of our patients had a disability certificate, the remainder had an EDSS score higher than 4.5, posing a potential problem related to a restricted access to the needed health services for those patients.

Regarding the use of DMD, of the third of patients under treatment, half of them were being prescribed ocrelizumab. Ocrelizumab is a humanized monoclonal antibody and the first drug approved for the PPMS treatment. This drug acts mainly in B lymphocytes through an antibody-dependent cellular toxicity [32]. It is important to remember that until the development of ocrelizumab [32], there was no PPMS treatment approved by drug regulatory agencies [19, 33]. It is highly likely that this is the main reason for the diversity of drugs found being used among treated patients since the vast majority of them had begun their treatment in the pre-ocrelizumab era. Although being a retrospective and multicenter study, treatment criteria could not be evaluated. When comparing clinical and demographic characteristics between treated and untreated patients, those under treatment had a lower EDSS and shorter disease evolution and were younger than untreated patients. However, we found no significant differences when comparing "active" and "not active" patients.

The main relevance of this study is the lack of previous epidemiological reports in our area about PPMS patients. We consider that the results are representative of our country, as most neurologists and centers treating MS patients are active contributors of the database. We take into account that no real-world observational studies are free from criticism, and highlight the difficulty of eliminating biases, even with rigorous statistical analysis [34]. In our study, considering the qualified centers and principal investigators, risk of bias is probably low. It should also be noted that much of the effort of the project is dedicated to compliance with the necessary and required regulatory aspects as well as the use of various strategies that aim to increase the quality of the obtained data. Moreover, when compared with other international registries, we observed similar distribution in terms of MS phenotypes at registry starts [7]. The main limitation of this study is a retrospective analysis from a non-compulsory registry and, therefore, probably underestimation of the total number of patients. On the other hand, the identification of PPMS is often highly complex, so these patients may have a diagnostic error. Finally, access to paraclinical procedures (oligoclonal bands on CSF, MRI exams, etc.) are more restricted in some regions that others within Argentina. These restrictions could also influence epidemiological analysis by the selection or exclusion of certain centers based on the access to these exams.

In conclusion, as shown by international studies [12], every country has its own data regarding this devastating disease. Although information on the subject is increasingly available, the data from Latin America is still scarce. While PPMS is an infrequent subtype of MS, its recognition is of the highest importance as it has its own evolution, treatment, and prognosis. We report the clinical and demographic characteristics of PPMS patients in Argentina. Although our study has generalization limitations, as mentioned above, we believe that its importance resides in being the first local data report to contribute to a better understanding of PPMS and its treatment in Argentina.

Authors' contributions Ricardo Alonso and Orlando Garcea contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Ricardo Alonso, Cecilia Quarracino, Barbara Eizaguirre, and Leila Cohen. The first draft of the manuscript was written by Ricardo Alonso and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability Not applicable

Compliance with ethical standards The project was approved by the Ethics Committee of every principal investigator involved in the study.

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals None

Informed consent None

Ethical approval None

Disclaimer Those grants did not interfere in the development plan, variables, PI selection, patient information nor other aspects of the Registry.

Code availability Not applicable

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