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ORIGINAL ARTICLE

# Multiple sclerosis and neuromyelitis optica spectrum disorders in Argentina: comparing baseline data from the Argentinean MS Registry (RelevarEM)

Juan Ignacio Rojas[1,2] · Marina Alonso Serena[3] · Orlando Garcea[4] · Liliana Patrucco[1] · Adriana Carrá[5,6] · Jorge Correale[7] · Carlos Vrech[8] · Agustín Pappolla[1] · Jimena Miguez[1] · María L. Doldan[1,2] · Facundo Silveira[1] · Ricardo Alonso[4,9] · Leila Cohen[4] · Cecilia Pita[4] · Berenice A. Silva[4] · Marcela Fiol[7] · María I. Gaitán[7] · Mariano Marrodan[7] · Laura Negrotto[7] · María C. Ysrraelit[7] · Norma Deri[10] · Geraldine Luetic[11] · Alejandro Caride[12] · Edgar Carnero Contentti[12] · Pablo A. Lopez[12] · Juan Pablo Pettinicchi[12] · Celeste Curbelo[5,13] · Alejandra D. Martinez[5] · Judith D. Steinberg[5] · María E. Balbuena[14] · Verónica Tkachuk[14] · Marcos Burgos[15] · Eduardo Knorre[16] · Felisa Leguizamon[16] · Raúl Piedrabuena[17,18] · Susana del V. Liwacki[17,19] · Andrés G. Barboza[20] · Pedro Nofal[21] · Gabriel Volman[22] · Amelia Alvez Pinheiro[23] · Javier Hryb[24] · Dario Tavolini[25] · Patricio A. Blaya[26] · Emanuel Silva[27] · Jorge Blanche[28] · Santiago Tizio[29] · Fernando Caceres[30] · María Laura Saladino[30] · Gisela Zanga[31] · María E. Fracaro[32] · Gustavo Sgrilli[33] · Fátima Pagani Cassara[34] · Guido Vazquez[6] · Vladimiro Sinay[34] · María Laura Menichini[35] · Luciana Lazaro[9] · Lorena M. Cabrera[36,37] · Santiago Bestoso[38] · Pablo Divi[39] · Miguel Jacobo[39] · Eduardo Kohler[40] · Matías Kohler[40] · Diego Giunta[3] · Carolina Mainella[41] · Ruben Manzi[42] · Marcela Parada Marcilla[43] · Juan Pablo Viglione[44] · Ivan Martos[45] · Edgardo Reich[46] · Gustavo Jose[47] · Edgardo Cristiano[1,2] · Nora Fernández Liguori[9,48] · on behalf RelevarEM investigators

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## Abstract

The objective of this study was to describe and compare the baseline epidemiological data of multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) patients included in RelevarEM (Clinical Trials registry number NCT03375177).

### Methods

RelevarEM is a longitudinal, strictly observational MS and NMOSD registry in Argentina. Epidemiological and comorbidity data from MS and NMOSD patients were described and compared. For comorbidities, the Charlson comorbidity index (CCI) was used to calculate the burden at entry. CCI was stratified in 0 and ≥ 1 and described for the entire cohort.

### Results

A total of 1588 and 75 MS and NMOSD patients (respectively) were included. For MS patients, the mean age was 42 ± 7 years, female sex 65.3%, mean EDSS 2, and mean disease duration 8 ± 6 years. In NMOSD, the mean age was 40 ± 7 years, female sex 78.7%, mean disease duration 5 ± 3.5 years, and mean EDSS 2.5. The most frequent MS phenotype was RRMS in 82.4%. In MS, the CCI was 0 in 85.8.2% while ≥ 1 was in 14.2% of patients. Regarding phenotype stratification, CCI ≥ 1 was 3.9% in CIS, 13.5% in RRMS, 28.7% in SPMS, and 17.4% in PPMS ($p < 0.001$ between groups). In NMOSD, the CCI was 0 in 64% while ≥ 1 was in 36%. The MS/NMOSD ratio found was 21/1.

### Conclusions

This is the first analysis of the longitudinal Argentinean registry of MS and NMOSD describing and comparing conditions that contributes to provide reliable real-world data in the country.

✉ Juan Ignacio Rojas
rojasjuanignacio@gmail.com

Extended author information available on the last page of the article

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**Keywords** Multiple sclerosis · Neuromyelitis optica spectrum disorder · Registry · Epidemiology · RelevarEM

## Introduction

Multiple sclerosis (MS) is a chronic disease of the 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 [1–4].

Currently, there are several publications that deal with epidemiological aspects of MS throughout the world; nonetheless, despite this wealth of data, current knowledge of MS epidemiology in Latin America (LA) as well as Argentina is limited [1–4].

MS registries are essential tools for providing relevant information such as epidemiological aspects of the disease, safety issues, and treatment effectiveness [5, 6]. Recently, we presented the methodology behind RelevarEM, the first nationwide MS registry in Argentina and Latin America (Clinical Trials registry number NCT NCT03375177).

The objective of this study is to describe and compare the baseline epidemiological data of MS and neuromyelitis optica spectrum disorder (NMOSD) patients included in RelevarEM.

## Methods

RelevarEM is a longitudinal, strictly observational MS and NMOSD registry in Argentina [7]. 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 [7].

Any patient diagnosed with MS, a clinically isolated syndrome, a radiologically isolated syndrome, or an NMOSD defined by current validated diagnostic criteria (McDonald criteria 2005, 2010, and 2017 for MS [5, 8, 9] and Wingerchuk 2015 for NMOSD [6]) 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.

For the objective of this study, data regarding demographic and clinical characteristics of MS and NMOSD were obtained from the anonymized patient medical records (Fig. 1). For comorbidities, PIs use the Charlson comorbidity index (CCI) to calculate the comorbidity burden at registry entry [7].

## Statistical analysis

Analysis was performed using Stata version 10.1 [10]. Baseline characteristics of the cohort were reported in percentages for categorical data and in mean with standard deviation (SD) for the continuous data. For the comorbidity description, the CCI was stratified in 0 and ≥ 1 and described for the entire cohort as well as for the group stratified by age (< 20; 20–30; 30–40; 40–50; > 50 years) and by MS phenotype.

## Results

Up to 31 March 2019, 56 centers and 98 professionals distributed throughout Argentina have become part of the Registry. A total of 1588 and 75 MS and NMOSD patients (respectively) were included. For MS patients, the mean age was 42 ± 7 years (range 18–56) and female sex 65.3% (Table 1). MS phenotypes described were 82.4% relapsing-remitting MS; 5.5% secondary progressive MS; 4.2% primary progressive MS; and 6.5% clinically isolated syndromes. The mean EDSS of MS patients was 2 ± 1.5 (range 0–8), 82.4% of patients were under disease modifying treatment, and 14% were retired due to MS (Table 1). Regarding comorbidities in MS, CCI was 0 in 85.8.2% while ≥ 1 was in 14.2% of patients. When stratified by age, CCI ≥ 1 was 3.5% in patients less than 20 years; 5.9% in 20–29; 10.5% in 30–39; 13.9% in 40–49; and 23% in ≥ 50 years ($p < 0.001$ between groups) (Table 2). Regarding phenotype stratification, CCI ≥ 1 was 3.9% in CIS, 13.5% in RRMS, 28.7% in SPMS, and 17.4% in PPMS ($p < 0.001$ between groups).

For NMOSD patients, the mean age was 40 ± 7 years (range 31–53), female sex 78.7%, mean disease duration 5 ± 3.5 years, and mean EDSS 2.5 ± 3 [1–5, 7–9] (Table 1). A total of 97% of included NMOSD patients were tested with aquaporin 4 test, being positive in 56%. Almost 79% of patients were on specific treatment for NMOSD (rituximab 37%, mofetil mycophenolate 5.3%, azathioprine 37.3%). Almost 14.7% were retired due to the disease (Table 1). In NMOSD, the CCI was 0 in 64% while ≥ 1 was in 36%.

The female/male ratio was 1.88/1 and 1.2/1 in MS and NMOSD respectively while the MS/NMOSD ratio was 21/1.

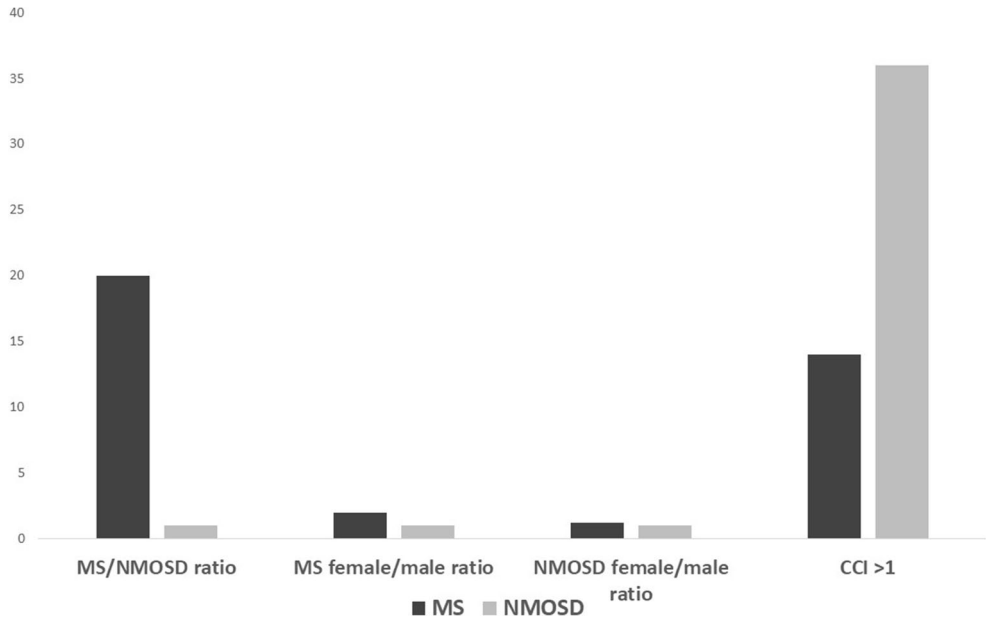


**Fig. 1** Demographic and clinical characteristics of MS and NMOSD. MS multiple sclerosis, NMOSD neuromyelitis optica spectrum disorder, CCI Charlson comorbidity index

**Table 1** Baseline characteristics of included MS and NMOSD patients

| | MS patients 1588 | NMOSD patients 75 | *p* value |
|---|---|---|---|
| Mean age (years), SD, (range) | 42 ± 7 (18–56) | 40 ± 7 (31–53) | 0.12 |
| Female sex, *n* (%) | 1037 (65.3) | 59 (78.7) | 0.23 |
| Female/male ratio | 1.88/1 | 1.2/1 | 0.03 |
| MS phenotype, *n* (%) | | | |
| CIS | 103 (6.5) | – | – |
| RRMS | 1308 (82.4) | – | – |
| SPMS | 87 (5.5) | – | – |
| PPMS | 67 (4.2) | – | – |
| RIS | 23 (1.4) | – | – |
| Mean disease duration, years (SD) | 8 ± 6 | 5 ± 7.9 | 0.18 |
| Aquaporin 4 test performed, *n* (%) | – | 73 (97) | – |
| Positive aquaporin 4 test, *n* (%) | – | 41 (56.2) | – |
| Negative aquaporin 4, test *n* (%) | – | 32 (43.8) | – |
| Techniques used for aquaporin 4 test | | 21 (28.6) | – |
| IFI, *n* (%) | | 1 (1.4) | – |
| ELISA, *n* (%) | | 51 (70) | – |
| Cell-based assessment, *n* (%) | | | |
| Patients under DMT or immunosuppression, *n* (%) | 1309 (82.4) | 59 (79) | 0.14 |
| Mean EDSS ± SD (range) | 2 ± 1.5 (0–8) | 2.5 ± 3 (1–8) | 0.32 |
| Working status | | | |
| Currently working, *n* (%) | 569 (35.8) | 28 (37.33) | 0.42 |
| Retired due to the disease, *n* (%) | 222 (14) | 11 (14.7) | 0.67 |
| MS/NMOSD ratio | 21/1 | | |

*MS* multiple sclerosis, *NMOSD* neuromyelitis optica spectrum disorder, *CIS* clinically isolated syndrome, *RRMS* relapsing-remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *PPMS* primary progressive multiple sclerosis, *RIS* radiologically isolated syndrome, *DMT* disease modifying therapy

**Table 2** Baseline comorbidity index in included MS and NMOSD patients

| | MS patients 1588 | NMOSD patients 75 | *p* value |
|---|---|---|---|
| CCI global | | | |
| 0 | 1363 (85.8%) | 48 (64%) | < 0.001 |
| ≥ 1 | 225 (14.2%) | 27 (36%) | 0.004 |
| CCI ≥ 1 stratified by age groups | | | |
| < 20 | 1/28 (3.5) | 4 (5) | 0.88 |
| 20–29 | 13/221 (5.9%) | 8 (10) | 0.63 |
| 30–39 | 46/438 (10.5%) | 11 (15) | 0.632 |
| 40–49 | 64/461 (13.9%) | 26 (35) | 0.003 |
| > 50 | 101/440 (23%) | 26 (35) | 0.006 |
| CCI ≥ 1 in CIS | 4/103 (3.9%) | – | – |
| CCI ≥ 1 in RRMS | 176/1308 (13.5%) | – | – |
| CCI ≥ 1 in SPMS | 25/87 (28.7%) | – | – |
| CCI ≥ 1 in PPMS | 16/67 (17.4%) | – | – |

*MS* multiple sclerosis, *NMOSD* neuromyelitis optica spectrum disorder, *CIS* clinically isolated syndrome, *RRMS* relapsing-remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis, *PPMS* primary progressive multiple sclerosis, *DMT* disease modifying therapy, *CCI* Charlson comorbidity index

## Discussion

This is the first analysis of the longitudinal Argentinean registry of MS. In this study, we describe 1588 MS patients and 75 NMOSD. The most frequent MS phenotype was RRMS (82.4%), and 9.7% were progressive forms of MS. A total of 82.4% of patients were under specific treatment for MS. Regarding comorbidities, we found a low CCI that was higher in progressive forms and older patients. Regarding NMOSD patients, most described were females, the aquaporin 4 test was positive in 56.2%, and 79% were on immunosuppression. In NMOSD patients, the mean EDSS was 2.5. It is important to mention that despite disability generally has been rated using the EDSS in NMOSD, the scale is insensitive to changes and modified scales are under development and validation to improve NMOSD patients follow up for future [11]. It is interesting to highlight the high percentage of NMOSD patients that fulfill the diagnostic criteria but are seronegative for aquaporin 4 test. A possible explanation could be provided by the technique used to assess the serum status. Although the majority was evaluated by cell-based technique, there is a high percentage that were evaluated by IFI, a technique with a low sensitivity. The MS/NMOSD ratio found was 21/1.

During the last decade, there has been a surge of interest in the epidemiology of MS in Latin America, and several investigations have begun to provide a reasonable estimate of the disease in the region. In a systematic review of the frequency of MS in Latin America, it was found that the incidence reported ranged from 0.15 to 3 cases per 100,000 person-years. Prevalence ranged from 0.75 to 38.2 cases per 100,000 inhabitants in 13 studies analyzed. However, no studies came from registries [7]. Recently, prevalence and incidence were described in certain regions of Argentina [2, 12–14]; however, scarce information about epidemiological aspects in large populations exist in the country.

In Argentina, some differences in frequency and distribution were previously reported when compared with North America and Europe [2, 14, 15]. In our current description, consistency with previous reports augments the evidence based on the previously observed differences [2]. The reasons for these differences are unknown; however, some studies strongly suggest that certain environmental and genetic factors may play a role [16, 17]. In the case of the former, increased solar exposure and subsequent vitamin D levels have been associated with a decreased risk of developing MS [16]. This may explain the increased risk observed in areas located at a greater distance from the equator [16]. It has also been proposed that improved hygiene, which partially explains the reduced rate of infections in western countries, is at the origin of increased incidence of allergic and autoimmune diseases [18]. Several factors contribute to this so-called hygiene hypothesis [18]. A striking association was initially described between hay fever and family size, as well as position in household in childhood [19]. Thus, the incidence of Chron's or atopic diseases is higher in first-born children who are not exposed in their infancy to the infections of siblings [19]. This social effect is observed in many areas of LAC and could be a factor involved in the low prevalence of autoimmune diseases observed in the region [18]. In addition, individual and collective hygiene, such as quality of drinking water and food, as well as vaccinations, might also contribute to explain differences in prevalence between LAC and the countries of Western Europe and North America [18, 19]. Regarding genetic factors, the Argentinean population is very heterogeneous, constituted by Caucasian and mestizos, a complex admixture of Caucasian and Amerindian [20–22].

No real-world observational studies are free from criticism, highlighting the difficulty of eliminating biases even with rigorous statistical analysis [23]. In our study, we describe the population and, consequently, risk bias analysis is 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 data obtained.

When compared with other international registries, we observed similar distribution in terms of MS phenotypes at registry starts (Table 3). The registries described in Table 3 show national and international registry collaborations. The methodology applied among them is quite similar, despite possible differences in the moment of implementation, and likely reinforces the fact that distribution of the MS phenotype is quite similar among the regions [2, 31–33]. We were not able to

**Table 3** Sample of major MS cohorts and registries underway

| | MSBase [24] | NYSMSC [25] | OFSEP [26] | Danish [27] | Swedish [28] | British Columbia [29] | Italian Registry [30] | RelevarEM [7] |
|---|---|---|---|---|---|---|---|---|
| Geographic catchment | Global | New York, some Northwestern Pennsylvania | France | Denmark | Swedish | British Columbia, Canada | Italy | Argentina |
| No. of active participants | 44,148 | 9650 | 58,000 | 25,000 | 14,500 | 10,000 | 44,636 | 1588 |
| Enrollment dates | 2004–present | 1996–present | 2011 (databases using the EDMUS started before) | 1956–present | 2001–present | 1980– present | 1990–present | 2018–present |
| MS type at registry start, % | RRMS 60.0; PPMS 10.0; SPMS 30 | RRMS 55.0; PPMS 9.0; SPMS 31; PRMS 5.0 | RRMS 58.0; SPMS 27.0; PPMS 15.0 | CDMS 84.4; possible MS 15.6 | RRMS 92.4; PPMS 7.6 | RRMS 87.6; PPMS 12.4 | RRMS 74; PPMS 6 | RRMS 82; PPMS 4.2; SPMS 5.5; |

*CDMS* clinically definite multiple sclerosis, *NYSMSC* New York State Multiple Sclerosis Consortium, *PPMS* primary progressive multiple sclerosis, *PRMS* progressive relapsing multiple sclerosis, *RRMS* relapsing-remitting multiple sclerosis, *SPMS* secondary progressive multiple sclerosis

compare the distribution of MS phenotypes in our registry with other Latin American registries.

In summary, this study provides updated information on epidemiological features of MS and NMOSD in Argentina. Patient registries gather valuable long-term patient information from the real world which are useful to a wide range of purposes (epidemiology, economic impact, healthcare access, and aspects concerning safety and effectiveness) [5, 6]. A wider use of MS disease registries in the region would be desirable in the near future in order to better understand the behavior of the disease in our region.

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## Compliance with ethical standards

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

**Conflict of interest** Authors declare no conflict of interest with the research done.

**Research involving human participants and/or animals** None.

**Informed consent** None.

**Ethical approval** None.

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## Affiliations

**Juan Ignacio Rojas[1,2] · Marina Alonso Serena[3] · Orlando Garcea[4] · Liliana Patrucco[1] · Adriana Carrá[5,6] · Jorge Correale[7] · Carlos Vrech[8] · Agustín Pappolla[1] · Jimena Miguez[1] · María L. Doldan[1,2] · Facundo Silveira[1] · Ricardo Alonso[4,9] · Leila Cohen[4] · Cecilia Pita[4] · Berenice A. Silva[4] · Marcela Fiol[7] · María I. Gaitán[7] · Mariano Marrodan[7] · Laura Negrotto[7] · María C. Ysrraelit[7] · Norma Deri[10] · Geraldine Luetic[11] · Alejandro Caride[12] · Edgar Carnero Contentti[12] · Pablo A. Lopez[12] · Juan Pablo Pettinicchi[12] · Celeste Curbelo[5,13] · Alejandra D. Martinez[5] · Judith D. Steinberg[5] · María E. Balbuena[14] · Verónica Tkachuk[14] · Marcos Burgos[15] · Eduardo Knorre[16] · Felisa Leguizamon[16] · Raúl Piedrabuena[17,18] · Susana del V. Liwacki[17,19] · Andrés G. Barboza[20] · Pedro Nofal[21] · Gabriel Volman[22] · Amelia Alvez Pinheiro[23] · Javier Hryb[24] · Dario Tavolini[25] · Patricio A. Blaya[26] · Emanuel Silva[27] ·**

**Jorge Blanche[28] · Santiago Tizio[29] · Fernando Caceres[30] · María Laura Saladino[30] · Gisela Zanga[31] · María E. Fracaro[32] · Gustavo Sgrilli[33] · Fátima Pagani Cassara[34] · Guido Vazquez[6] · Vladimiro Sinay[34] · María Laura Menichini[35] · Luciana Lazaro[9] · Lorena M. Cabrera[36,37] · Santiago Bestoso[38] · Pablo Divi[39] · Miguel Jacobo[39] · Eduardo Kohler[40] · Matías Kohler[40] · Diego Giunta[3] · Carolina Mainella[41] · Ruben Manzi[42] · Marcela Parada Marcilla[43] · Juan Pablo Viglione[44] · Ivan Martos[45] · Edgardo Reich[46] · Gustavo Jose[47] · Edgardo Cristiano[1,2] · Nora Fernández Liguori[9,48] · on behalf RelevarEM investigators**

1 Servicio de Neurología, Hospital Italiano de Buenos Aires, Perón 4190, CABA, Buenos Aires, Argentina

2 Centro de Esclerosis Múltiple de Buenos Aires, Buenos Aires, Argentina

3 Área de Investigación en Medicina Interna, Hospital Italiano de Buenos Aires, CABA, Argentina

4 Centro Universitario de Esclerosis Múltiple, Facultad de Medicina – UBA, Hospital Dr. J. M. Ramos Mejía, CABA, Argentina

5 Sección de Enfermedades Desmielinizantes, Hospital Británico, CABA, Argentina

6 Fundación Favaloro/INECO, CABA, Argentina

7 Departamento de Neurología, FLENI, CABA, Argentina

8 Departamento de Enfermedades desmielinizantes, Sanatorio Allende, Córdoba, Argentina

9 Sanatorio Güemes, CABA, Argentina

10 Centro de Investigaciones Diabaid, CABA, Argentina

11 Instituto de Neurociencias de Rosario, Santa Fe, Argentina

12 Unidad de Neuroinmunología, Departamento de Neurociencias, Hospital Alemán de Buenos Aires, CABA, Argentina

13 Policlínico Municipal Sofia T. de Santamarina, Buenos Aires, Argentina

14 Sección de Neuroinmunología y Enfermedades Desmielinizantes, Servicio de Neurología, Hospital de Clínicas José de San Martín, CABA, Argentina

15 Servicio de Neurología, Hospital San Bernardo, Salta, Argentina

16 Hospital de Agudos, Dr. Teodoro Álvarez, CABA, Argentina

17 Clínica Universitaria Reina Fabiola, Córdoba, Argentina

18 Instituto Lennox, Córdoba, Argentina

19 Servicio de Neurología, Hospital Córdoba, Córdoba, Argentina

20 Hospital Central de Mendoza, Mendoza, Argentina

21 Hospital de Clínicas Nuestra Señora del Carmen, San Miguel de Tucumán, Tucumán, Argentina

22 Hospital Presidente Perón de Avellaneda, Buenos Aires, Argentina

23 Hospital San Martín, Paraná, Entre Ríos, Argentina

24 Servicio de Neurología, Hospital Carlos G Durand, CABA, Argentina

25 INECO Neurociencias Oroño - Fundación INECO, Rosario, Santa Fe, Argentina

26 Neurocomp, Trelew, Chubut, Argentina

27 Predigma - Centro de Medicina Preventiva, Posadas, Misiones, Argentina

28 IRNEC (Instituto Regional de Neurociencias), San Miguel de Tucuman, Argentina

29 Hospital Español de la Plata, Buenos Aires, Argentina

30 INEBA, Institute of Neuoscience Buenos Aires, Buenos Aires, Argentina

31 Unidad asistencial César Milstein, CABA, Argentina

32 Clinica el Castaño, San Juan, Argentina

33 Axis Neurociencias, Bahía Blanca, Buenos Aires, Argentina

34 Instituto de Neurociencias, Fundación Favaloro/INECO, CABA, Argentina

35 Sanatorio Británico, Rosario, Santa Fe, Argentina

36 Servicio de Neurología, Hospital Militar Central, CABA, Argentina

37 Hospital Militar Campo de Mayo, CABA, Argentina

38 Servicio Neurología, Hospital Escuela José F. de San Martín Corrientes, Corrientes, Argentina

39 RIAPEM (Red Integral Asistencial al Paciente con Esclerosis Múltiple), Santiago del Estero, Argentina

40 Fundación Sinapsis Santa Rosa, Santa Rosa, La Pampa, Argentina

41 Hospital Español de Rosario, Rosario, Argentina

42 Sanatorio Pasteur, Catamarca, Argentina

43 Servicio de Neurología, Clínica Bazterrica, Buenos Aires, Argentina

44 Clinica Regional del Sud, Río Cuarto, Córdoba, Argentina

45 Clinica San Jorge. Ushuaia. Tierra del fuego, Ushuaia, Argentina

46 Servicio de Neurologia, Hospital Municipal Dr. Julio Mendez, Buenos Aires/Centro de Neurociencias Universidad Maimonides, Buenos Aires, Argentina

47 Sección de enfermedades desmielinizantes, Servicio de Neurología, Hospital Padilla, Tucumán, Argentina

48 Hospital Enrique Tornú, Buenos Aires, Argentina