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Argentine Patagonia: prevalence and clinical features of multiple sclerosis

MO Melcon¹, L Gold², A Carrá³, F Cáceres², J Correale⁴, E Cristiano⁵, N Fernández Liguori⁶, O Garcea⁷, G Luetic⁸, M Kremenchutzky⁹ for the Patagonia Multiple Sclerosis Research Project

There are few studies reporting multiple sclerosis prevalence rates in the Buenos Aires region, Argentina (latitude 34°S) (between 12–18.5/100 000 inhabitants), and no studies have been performed in the larger region between parallels 36° and 55°S. The aim of this study is to determine the prevalence rates and clinical features of multiple sclerosis in residents of the Argentine Patagonia. Four cities from the region were selected for this study, giving a sample population of 417 666 inhabitants (~24% of the total Patagonia population). 1st March 2002 was determined as prevalence day. Patients were ascertained using multiple case-finding methods. The point prevalence rate was 17.2/100 000 (17.2 age-adjusted to the world population). Prevalence rates were higher for women than for men, 22.1 versus 12.2/100 000 inhabitants (21.4 versus 12.7 sex-adjusted to the world population). The study population was mainly of European descent and mestizoes. Clinical features were similar to those reported in other countries. This study shows that Argentine Patagonia is a medium-risk area with no south–north gradient between parallels 55° and 36°S. The Patagonia population shows recent internal migration that makes it difficult to determine whether the exposure to potential risk factors has been long enough to modify the disease incidence. *Multiple Sclerosis* 2008; 14: 656–662. <http://msj.sagepub.com>

Key words: Argentine Patagonia; clinical features; multiple sclerosis; prevalence

Introduction

Multiple sclerosis (MS) is a complex disease with an unknown etiology and without specific biological markers. Age and symptom variety at baseline, the broad spectrum of its clinical presentations and the unpredictable course of the disease present challenges when designing community-based epidemiological studies. The use of different information sources [1,2] and the participation of MS-trained neurologists are required for the case-finding procedure and to obtain reliable prevalence estimates.

Very few studies report MS prevalence rates (between 12–18.5/100 000 inhabitants) in the region of Buenos Aires, Argentina (latitude 34°S) [3,4]. Our study was conducted in the Argentine Patagonia where there is a peculiar pattern of migratory movements, geographical features and latitude gradient. The relationship between latitude and MS prevalence and the natural resistance of selected ethnic groups to the development of MS have already been described [5–8].

The purpose of the Patagonia Project: Multiple sclerosis in the southernmost part of South America [9] was to determine prevalence rates and clinical

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features of MS in the residents of Argentine Patagonia.

Methods

Study area and population

Argentine Patagonia is a region of South America that extends south from the Colorado River (latitude 36°S) to the Magellan Strait (latitude 55°S). The total surface area of Patagonia is 1 768 165 km²; this amounts to 47% of the total Argentine territory. The cities of Neuquén, Trelew, Río Gallegos and Ushuaia were specifically chosen because of their geographical distribution with a latitude gradient that could reflect regional variations in the incidence of MS (Figure 1). Also, there is a greater population density in urban areas because of the arid, cold and dry climate of the region (200 mm rain/year), with poor and plain flora [10] that make it difficult for people to live in the more rural areas outside the cities.

Argentine Patagonia has a total population of 1 733 494 [11] inhabitants which amounts to 4.8% of the total Argentine population. The number of residents from the selected cities (the study area) is 417 666, representing a sample of approximately

24% of the total Patagonian population. Residents have free access to healthcare services at the regional hospitals located in each city. The approximate number of general practitioners (GPs) for the entire study area is 391, i.e. one GP/1000 inhabitants. Each city has a regional hospital with about 700 beds.

Sources of case ascertainment

Definite and potential cases of MS were identified from the following sources: (1) all neurologists in the area, (2) GPs, (3) MS clinics, (4) MS Society membership listing, (5) all hospitals, (6) chronic-care facilities and (7) media announcements, lay referrals and information provided by family members.

We contacted all neurologists residing in the study area, one in Ushuaia, three in Río Gallegos, four in Neuquén, and three neurosurgeons in Trelew. As there are very few neurologists in the Patagonia region, we also contacted GPs. They were requested to search their records for patients with potential or confirmed MS. We obtained a list of MS patients from the MS clinics in the large hospitals in Buenos Aires who were living in the study area and referred to the clinics for a second opinion (from both GPs and neurosurgeons). The National MS Society in Buenos Aires provided us with a list of registered patients with MS living in the Argentine Patagonia. Provincial and regional healthcare systems provided access to their lists of patients with possible/definite diagnosis of MS. At the local hospital, medical records were reviewed. We also invited patients with MS to enroll in our study through announcements in the media.

Data collection was performed in two phases: Phase 1 for screening and Phase 2 for clinical evaluation. The screening instrument was similar to that used by the study neurologists, but included additional information about quality of life, treatment compliance, withdrawals and the use of complementary and alternative medicine.

In Phase 1, all potential MS cases identified through the different ascertainment sources completed the screening instrument. Informed consent was signed by the patient or a caregiver and the study neurologists. In those cases where the patient was no longer available or had died after 1 March 2002, the forms were completed by a close family member and the corresponding health professional.

In Phase 2 we performed a neurological evaluation to confirm diagnosis. Two MS-trained neurologists were assigned to examine the patients in each selected city. To be included in the study, patients were required to meet Poser's criteria of MS [12]. We excluded other myelin-related conditions (e.g.

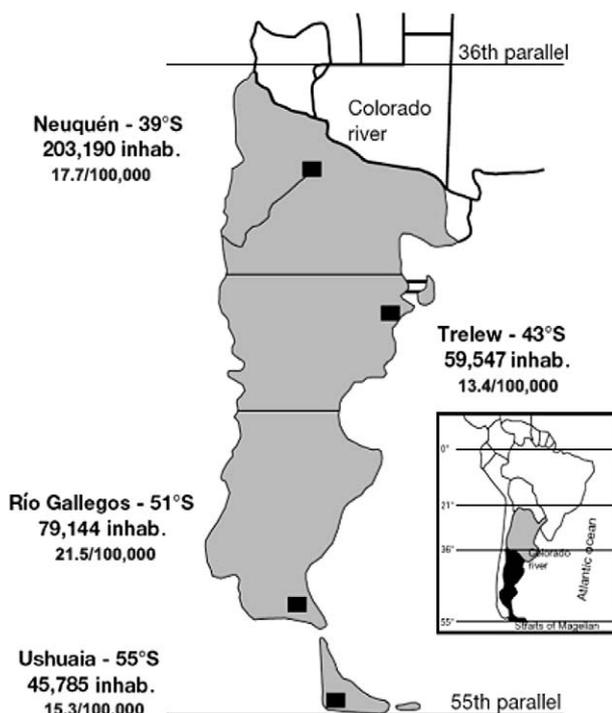


Figure 1 Map showing the location of Patagonia within Argentina and South America and showing the four study cities including latitude, population and prevalence per city.

clinically isolated syndrome (CIS), acute disseminated encephalomyelitis, Devic's neuromyelitis optica, isolated optic neuritis, acute transverse myelitis). We used the commonly applied international clinical categories to define the course of MS [13].

The study neurologists performed the neurological examinations and completed a specially designed data form that included personal/demographic information, a neurological profile/exam (including clinical, paraclinical and disability data) and specific and symptomatic treatments.

Statistical analysis

This survey was designed as a descriptive study. The prevalence of MS was determined as point-prevalence and defined as the number of patients living with MS on 1st March 2002 (prevalence day) per 100 000 inhabitants in the study area. Only those cases with disease onset on or before this day were included. The date of onset was defined as the date of the first MS-related symptom and was determined retrospectively. Individuals were only eligible if they had been permanent residents of their communities for at least 2 years prior to prevalence day. Prevalence rates were calculated using the 2001 census [11]. We calculated the age- and sex-specific prevalent figures. All results were age- and sex-adjusted to the Argentine standard population and to the world standard population for comparison among studies performed in different countries [11,14,15].

Results

The fieldwork stage of this study began in March 2002 and was completed in September 2003. The total target population in the selected cities was 417 666 people.

In Phase 1, a total of 140 patients with a probable diagnosis of MS were identified using different sources. A total of 101 (72.1%) of these 140 cases were permanent residents of the study area. Of these 101 patients, five were not examined in Phase 2 (three died and two were unavailable for clinical examination). However, complete medical documentation of these patients was obtained to confirm MS. A total of 96 (95%) patients underwent neurological examination in Phase 2, of whom five had CIS, one had acute disseminated encephalomyelitis and two had Devic's neuromyelitis optica.

Most MS-prevalent cases were obtained from neurology practices, MS clinics and the National MS Society (93%), all in Buenos Aires. Local neurology records provided 57 (79.2%) cases and MS clinics 19 (26.4%) cases, 12 of which were dupli-

cates, which led to 64 patients with MS out of a total of 72 (88.9%). The MS Society identified 15 (21%) cases, only three (4.2%) of which were not in any other sources, and the remaining 12 cases were also duplicates. This led to 67 (93.0%) MS cases. Media announcements and lay referrals provided eight (11.1%) cases, and family members a further 12 (16.7%) cases. Three (4.2%) and one (1.4%) cases respectively were not identified by other sources, leading to a total of 71 out of 72 cases (98.6%). Chronic-care facilities contributed only one (1.4%) case. A total of 39 (54.2%) cases were identified solely by local neurologists (Figure 2).

We identified 72 patients, 47 (65.3%) women and 25 (34.7%) men, who fulfilled Poser's diagnostic criteria for MS. A total of 70 (97%) patients had clinically definite MS and two (3%) patients had laboratory-supported MS. The crude-point prevalence rate for the four cities was 17.2/100 000 (16.9/100 000 age-adjusted to the Argentine population and 17.2/100 000 age-adjusted to the world population).

The prevalence rates were higher for women than for men, 22.1 versus 12.2 per 100 000 inhabitants. The sex ratio was approximately 1.7:1. Results were adjusted by age and sex according to the Argentine and world standard populations (Tables 1 and 2).

The mean age at prevalence day was 41.55 (range 16–62) years, the mean age at clinical onset was 29.26 (range 9–58) years and the mean age at diagnosis was 35 years. The median disease duration was 12.33 years for the examined group (range 0–

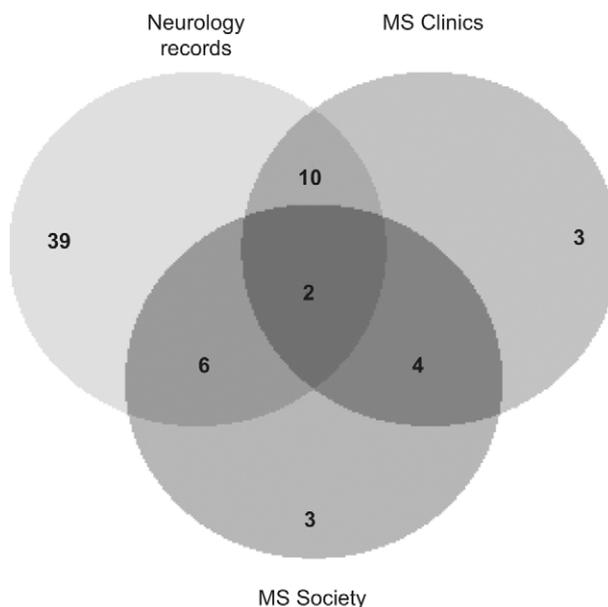


Figure 2 Number of cases exclusively identified by only one source and those identified by multiple sources.

Table 1 Age- and sex-specific prevalence of all MS cases in Patagonia, 1 March 2002

Age (years)	Men		Women		Both sexes	
	Number of cases (population)	Prevalence ^a	Number of cases (population)	Prevalence ^a	Number of cases (population)	Prevalence ^a
All MS cases from the four cities						
0–14	0 (65 800)	0.0	0 (64 109)	0.0	0 (129 909)	0.0
15–24	3 (37 337)	8.0	1 (37 138)	2.7	4 (74 475)	5.4
25–34	2 (30 524)	6.6	12 (32 781)	36.6	14 (63 305)	22.1
35–44	7 (28 623)	24.4	15 (30 187)	49.7	22 (58 810)	37.4
45–54	7 (21 512)	32.5	15 (22 361)	67.1	22 (43 873)	50.1
55–64	6 (12 310)	48.7	4 (12 826)	31.2	10 (25 136)	39.8
≥65	0 (9360)	0.0	0 (12 798)	0.0	0 (22 158)	0.0
Total	25 (205 466)	12.2	47 (212 200)	22.1	72 (417 666)	17.2
Adjusted rate ^b						
	Argentine	12.4		21.1		16.9
	World	12.7		21.4		17.2

^aCases per 100 000 inhabitants.

^bArgentine and world standard population [11,14].

43 years). The average expanded disability status scale score was 3.8. The disease course took the form of relapsing–remitting MS (75%), secondary progressive MS (15%) and primary progressive MS (10%). A total of seven (9.7%) patients had disease onset before the age of 16 years and three (4.2%) patients after the age of 50 years. Based on our prevalence data and on disease duration, the annual incidence rate was approximately 1.4 cases per 100 000.

The most common initial symptoms according to the questionnaire completed by the patients were blurred vision (20.8%), diplopia (8.3%), paresthesias or sensory loss (22.2%), weakness in one or more limbs (19.4%), gait disturbances (11.1%), impaired balance (4.2%), paralysis (4.2%), weakness, pain or paresthesias in the face (2.8%), bladder disturbances (4.2%) and others (2.8%).

In the year of disease onset, 17 (23.6%) patients were diagnosed with MS and 30 (41.6%) patients were diagnosed during the first 2 years after the onset of disease. A total of 68 (94.4%) patients had magnetic resonance imaging (MRI), 32 (44.4%) patients had MRI plus evoked potentials and six (8.3%) patients had MRI plus cerebrospinal fluid (CSF) test. Of the 72 MS prevalence cases, 46 (63.9%) patients were on disease-modifying drugs.

The study population was mainly of European descent and mestizoes. We found that 26% of the grandparents and 3% of parents came from Europe, indicating that a larger number of patients had first-generation, Argentine-born parents. A total of 30 (41.7%) of the identified patients were born and raised in Argentine Patagonia. Of the 42 (58.3%) patients who were not born in Patagonia, 90% migrated to the south from Argentine territory;

Table 2 Sex-specific MS prevalence in the four Patagonian cities, 1 March 2002

City (Latitude)	Men		Women		Both sexes	
	Number of cases (population)	Prevalence ^a	Number of cases (population)	Prevalence ^a	Number of cases (population)	Prevalence ^a
Neuquén (39°S)						
Total	16 (98 909)	16.2	20 (104 281)	19.2	36 (203 190)	17.7
Adjusted rate ^b						
	Argentine	16.6		17.8		17.2
	World	16.8		18.0		17.5
Trelew (43°S)						
Total	2 (43 984)	4.5	10 (45 563)	21.9	12 (89 547)	13.4
Adjusted rate ^b						
	Argentine	4.6		22.0		13.5
	World	4.6		22.4		13.8
Rio Gallegos (51°S)						
Total	5 (39 338)	12.7	12 (39 806)	30.1	17 (79 144)	21.5
Adjusted rate ^b						
	Argentine	12.6		27.2		19.9
	World	12.9		27.6		20.2
Ushuaia (55°S)						
Total	2 (23 235)	8.6	5 (22 550)	22.2	7 (45 785)	15.3
Adjusted rate ^b						
	Argentine	11.6		26.0		18.3
	World	12.0		32.0		18.8

^aCases per 100 000 inhabitants.

^bArgentine and world standard population [11,14].

only 10% of the patients came from Chile and other countries. The prevalence of familial MS in first-degree relatives was 2.8%. There were no twins among the subjects of this study.

Regarding the age of migration, 35% of the patients migrated before the age of 15 years. Of the 42 patients who were not born in Patagonia, 13 (31%) had symptoms before migrating and three (23%; two men, one woman) were diagnosed with MS before moving to the south.

Discussion

The design of this community-based MS survey had significant challenges and difficulties such as the long distances between cities, adverse weather conditions and the peculiar migration trends of the Patagonia region during the past 40 years. No single method is likely to identify all cases. An adequate methodology selection would depend on the country and the community where the survey is carried out and also on the efficiency of case-finding methods.

Methodological problems

Successful case-finding requires that individuals with MS is accurately diagnosed or is at least a suspected MS case, and then that such individuals are identified by that specific search [16]. Our results could be influenced by the availability of and access to: (1) healthcare facilities, (2) neurologists and/or MS-trained neurologists, (3) diagnostic procedures (e.g. MRI, CSF analysis) and (4) the information gathered by the investigators.

Even when we used several case-finding methods to determine the prevalence of MS [2,16,17] we consider that there may be underdiagnosed cases. In our study, the most important source of information is the neurology practice. However, because there are not only very few (only eight in the whole study area) but also no neurologists in one of the study cities, there may be a chance of underestimation of prevalence rates.

Geographic distribution

This study showed that Patagonia is a medium-risk area with no south–north gradient between parallels 55° and 36°S. Another major finding was an MS prevalence of 17.2/100 000 inhabitants. This is probably a conservative estimate as some patients may have been omitted despite our efforts. For example, some patients may not have been included if they were not permanent residents of

the study area (residing there for at least 2 years before the start of the study).

Recent reviews on the epidemiology of MS in Latin America report a low–medium prevalence [18]. Epidemiological studies performed south of the equator also showed that there is no south–north gradient between latitudes 55° and 23°S, and between longitudes 71° and 47°W. In Sao Paulo, Brazil (latitude 23°S, longitude 53°W), Callegaro, *et al.* [19] reported a prevalence of 15/100 000; in Santiago, Chile (latitude 33°S, longitude 71°W), a recent study showed a prevalence of 11.7/100 000 (see [20]); in Montevideo, Uruguay, (latitude 34°S, longitude 56°W), Ketzoian, *et al.* [21] found a prevalence of 20.9/100 000; and in Buenos Aires, Argentina (latitude 34°S, longitude 58°W), the prevalence was between 12 and 18.5/100 000 (see [3,4]). These regions are essentially medium-prevalence areas.

Study population

Patagonia was originally inhabited by the native tribes of the Onas, Yaganes, Araucanians (today called Mapuches) and mainly by the Tehuelche. Archaeological evidence found in the south of Argentina and Chile reveals that the first inhabitants could have arrived approximately 10 000 years ago, when the level of the waters in Magellan's Strait did not separate the island from the continent. The Tehuelche indigenous group ('the Patagonian giants') was the major autochthonous group of this vast region.

Long-term establishments began in 1850. The first immigrants that lived in Patagonia between 1850 and 1914 were English, Chilean (most Chileans have both Spanish and Araucanian background; others only have unmixed European descent), French, German, Italian, Polish, Scottish, Spanish, Welsh and Yugoslavian. In 1895, the total Patagonian population was 29 243 inhabitants and, between 1914 and 1920, only 17% were Argentines.

During the 1960s there was rapid demographic growth due to migratory movements from neighboring countries and from other Argentine provinces. In this last migration, people's ancestors were mostly born in Argentina, Chile, Italy and Spain and mostly represented by European and mixed ethnic backgrounds with different levels of education, social status and health-related issues. The median annual growth rate observed during 1991–2001 was 19.9 in Neuquén, 14.7 in Trelew, 21.1 in Rio Gallegos and 38.2 in Ushuaia per 1000 inhabitants [11].

Epidemiological studies of MS conducted during the last decade showed that genetic susceptibility plays a more important role than geography and latitude in determining MS prevalence [8,15,22].

Furthermore, several potential risk factors (e.g. climate, infections) may act together in a genetically susceptible individual to cause the disease [23]. However, our population shows a recent internal migration movement that makes it difficult to determine whether the exposure has been long enough to modify the incidence of the disease. Of the 58% of patients who were not born in Patagonia, 90% migrated to the south from the north and centre of Argentina.

Could men and women with a confirmed diagnosis of MS have migrated? In our survey, 13 (31%) patients who were not Patagonia-born showed symptoms before migrating, three of whom (two men, one woman) had a mild disability with a diagnosis of MS before moving to the south. It is possible that persons with moderate-to-severe MS-related disability do not migrate in search of a job to places with an extreme climate and far from their places of origin.

The number of cases identified by each data source has important implications for future MS population-based studies in Argentine Patagonia. Even when results show that neurologists provided the highest number of prevalent cases, we consider it important to include other case-finding sources and to have the active participation of MS-trained neurologists.

In conclusion, we consider that future case-control studies should focus on the environmental exposure and genetic factors that may provide further information to finally reveal the etiology of MS, not only in our region, but also in the rest of Latin America.

Conflicts of interest

The authors have no conflicts of interest.

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