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Multiple sclerosis in Latin America: A different disease course severity? A collaborative study from the MSBase Registry

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Abstract

Limited data suggest that multiple sclerosis (MS) in Latin America (LA) could be less severe than in the rest of the world. The objective was to compare the course of MS between LA and other regions.

Methods: Centers from 18 countries with >20 cases enrolled in the MSBase Registry participated. Patients with MS with a disease duration of >1 year and <30 years at time of EDSS measurement were evaluated. The MS Severity Score (MSSS) was used as a measure of disease progression. Comparisons among regions (North America, Europe, Australia and LA), hemispheres and countries were performed.

Results: A total of 9610 patients were included. Patients were from: Europe, 6290 (65.6%); North America, 1609 (16.7%); Australia, 1119 (11.6%); and LA, 592 (6.1%). The mean MSSS in patients from LA was 4.47 ± 2.8, 4.53 ± 2.8 in North America, 4.51 ± 2.8 in Europe and 4.49 ± 2.7 in Australia. Mean MSSS in the northern hemisphere was 4.51 ± 1.6 compared to 4.48 ± 1.9 in the southern hemisphere. No differences were found for MSSS among hemispheres ($p = 0.68$), regions ($p = 0.96$) or countries ($p = 0.50$).

Conclusions: Our analyses did not discover any difference in mean MSSS among patients from different regions, hemispheres or countries.

***Keywords*:** Multiple sclerosis, South America, MSSS, disease progression

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Introduction

Multiple sclerosis (MS) is an inflammatory and degenerative demyelinating disease of the central nervous system (CNS).[1,2] It represents the most common inflammatory condition of the CNS and is the second cause of disability among young adults and middle-aged people in industrialized countries.[3,4]

Many population-based studies have identified geographical differences in incidence, prevalence and disease prognosis between regions that could be conditioned by environmental, genetic and ethnic factors.[3,5,6]

In Latin America (LA), there is strong evidence that the frequency of MS is lower than in Europe and North America.[6,7] In terms of disease progression, limited evidence suggests that MS patients in LA may have a more benign course in comparison with European and North American patients.[8]

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However, there are not enough studies from different areas of LA to allow comparisons between the disease progression among regions.[6,7]

Given these suggestive but unconfirmed results, we sought to compare MS course between LA and other regions of the world, using the Multiple Sclerosis Severity Score (MSSS) scale and data derived from the MSBase Registry.

Methods

The MSBase Registry is a strictly observational clinic-based database established in July 2004 for sharing, tracking and evaluating outcome data in MS.[9] Investigators aim to include either all patients or all newly diagnosed patients in the database. Data are collected in each participating center by a standardized database management system (iMed),[10] and anonymized datasets are then periodically uploaded to the MSBase server.[10] The objectives, methods and operational details of the MSBase project have previously been described by Butzkueven et al. (2006).[9]

Global MSSS, which is derived from the analysis of Expanded Disability Status Scale (EDSS) distributions of nearly 10,000 untreated patients enrolled in 17 European MS centers, represents a median decile rank of each EDSS grade in a population of patients with similar disease durations.[9] The MSSS is an indicator of the relative rate of disability progression, rather than of disability per se, and is therefore a more suitable measure for comparing disease progression in different MS populations than EDSS.[9] The MSSS may be used to compare disease progression in a local MS patient population against the untreated European MS population from which the original Global MSSS Table has been derived, or to compare subpopulations of interest within a local population.[11] MSSS scores were assigned unambiguously to any patient with EDSS from 0 to 9.5 and disease duration of 1–30 years, by referencing the MSSS Table in Roxburgh et al. (2005).[11] The table in Roxburgh et al. provides an algorithm used to derive the Global MSSS ensuring that, for any given year, scores increase with higher values for EDSS. For example, an individual with symptoms for 10 years and an EDSS score of 4 has a Global MSSS score of 5.28. Another patient with symptoms for 20 years and the same EDSS score would have a Global MSSS score of 2.99. A program is available for download from http://www-gene.cimr.cam.ac.uk/MSgenetics/GAMES/MSSS that calculates Global and Local MSSS values.[11]

Data extracted from MSBase in March 2011 comprised longitudinal clinical data of 15,670 patients from 55 MS centers in 18 countries. All individuals fulfilling MS Poser or McDonald criteria with a disease duration of >1 year and <30 years at the time of EDSS measurement were evaluated. In patients not suffering a relapse in the previous three months, the most recent EDSS was used to calculate the MSSS. To ensure the quality of analyzed data, only information from centers with at least 20 active records was used, as stipulated in the study protocol. The MSSS was used as a measure of disease progression. Comparisons among regions (North America, Europe, Australia and LA), between hemispheres and between countries were performed using the MSSS in univariate and multivariate analyses (linear regression analysis) accounting for age, clinical course, latitude and specific treatment used for MS and duration (beta interferon, glatiramer acetate, fingolimod and natalizumab). Origin of patients included was determined by country of birth. Latitude was stratified for the analysis in three large groups of countries: those belonging to the northern (N) area (83 degrees N and 45 degrees N), intermediate area (45 degrees N to 35 degrees N) and southern (S) area (12 degrees S and 55 degrees S).

The Stata software package, version 10 was used.[12] All p values were two tailed; $p < 0.05$ was considered significant.

Ethics statement

The MSBase Registry was approved by the Melbourne Health Human Research Ethics Committee and by local ethics committees in all participating centers (exemptions being granted according to applicable local laws and regulations). If required, written informed consent was obtained from enrolled patients.[9]

Results

A total of 9610 patients from a total of 15,670 fulfilled the inclusion criteria. Almost 94% had relapsing–remitting MS, 2.2% primary progressive MS, and 3.8% a secondary progressive form of MS. The distribution of patients from each country is displayed in Table 1.

The mean MSSS of the study cohort was 4.5 ± 2.8. There were 6290 patients from Europe (65.6%), 1609 from North America (16.7%), 1119 from Australia (11.6%) and 592 (6.1%) from LA (Tables 2 and 3). The mean MSSS in patients from LA was 4.47 ± 2.8, 4.53 ± 2.8 in North America,

Table 1. List of countries divided into three latitude areas.

Country	N	%	% RRMS	% under DMD
Northern (83 degrees N to 45 degrees N)				
Belgium	66	0.7	98	93
Canada	1561	16.2	95	90
Denmark	286	3	93	92
Germany	153	1.6	90	93
Netherlands	1480	15.4	89	88
United States of America	48	0.5	95	93
Intermediate (45 degrees N to 35 degrees N)				
Cuba	22	0,2	100	89
France	25	0.3	94.4	92
Italy	2541	26.5	93	90
Mexico	67	0.7	94	89
Portugal	156	1.6	88	91
Spain	1280	13.3	95	93
Turkey	303	3.2	89	89
Southern (12 degrees S and 55 degrees S)				
Argentina	503	5,2	93	90
Australia	1119	11.6	94	93
Total	**9610**	**100**	**94.3**	**91**

N: North; RRMS: relapsing–remitting multiple sclerosis; DMD: disease-modifying drug; S: South.

Table 2. Distribution of patients by region.

Region	*N*	%
Latin America	592	6.1
North America	1609	16.7
Europe	6290	65.6
Australia	1119	11.6
Total	9610	100

Table 3. Distribution of patients by hemisphere.

Hemisphere	*N*	%
Northern hemisphere	7899	82.2
Southern hemisphere	1711	17.8
Total	9610	100

4.51 ± 2.8 in Europe and 4.49 ± 2.7 in Australia. The mean MSSS in the northern hemisphere was 4.51 ± 1.6 compared to 4.48 ± 1.9 in the southern hemisphere (Table 4). No differences were found between the MSSS among hemispheres ($p = 0.68$), regions ($p = 0.96$) or between countries ($p = 0.50$) when analyses were adjusted in multivariate analysis by MS disease course, latitude, specific treatment for MS and by age (Table 4).

Discussion

This is the first study that compares the disease progression among regions with a confirmed difference in MS frequency.

The analyses of disease progression did not identify any differences in MSSS among patients from different regions, hemispheres or countries.

This analysis was facilitated by the availability of a large international database with shared demographic and clinical information collection that allows an increase in the external validation of results.[9]

A previous study of the New York State Multiple Sclerosis Consortium Database (NYSMSC) used the MSSS to compare disease progression between African American and white American MS populations in New York. It found that African Americans have a more rapidly disabling disease progression when compared with white American patients, even after adjusting for age, sex, disease duration, subtype and other variables.[13] Although we used a similar methodology to compare populations, the objective was in this case different, our study being the first of its kind to analyze differences in disease progression by region.

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Table 4. MSSS comparisons among hemispheres and regions.

	Northern hemisphere		Southern hemisphere		*p*
MSSS (mean ± SD)	4.51 ± 1.6		4.48 ± 1.9		0.68
	Latin America	North America	Europe	Australia	*p*
MSSS (mean ± SD)	4.47 ± 2.8	4.53 ± 2.8	4.51 ± 2.8	4.49 ± 2.7	0.96

MSSS: Multiple Sclerosis Severity Score.

A possible limitation of our study is the tool used to analyze disease progression (MSSS). There is an inherent uncertainty in dating disease onset in MS, which often has a prolonged subclinical phase,[13] as well as reliance on the self-reporting of patients for the estimate of disease duration. The previous could be viewed as a weakness of the MSSS.[11] The example provided in the Methods section clarified how this uncertainty could create a limitation of the tool used. Another suggested limitation of the MSSS is that since this tool is based in part on the EDSS, it may not provide any clear advantage over the EDSS in practical application.[13] However, the MSSS incorporates two factors that are not taken into account by raw EDSS scores: duration of disease and the expected change in the EDSS over time. For that reason the MSSS should be considered as a measure of the relative rate of disability accumulation in MS, rather than of disability per se, hence providing complementary information to EDSS regarding patient disease severity.[13] In both this and previous studies that have used this methodology the MSSS has been a useful tool in the comparison of disease progression among populations as there is no a priori reason to assume that subclinical phase or recall bias preferentially affects one group more than another. For this reason typical applications of the MSSS were suggested for use in various epidemiologic studies that correlate disease progression among populations with different family members with MS and in studies of genetic association where disease progression is compared between groups with different alleles at a particular locus.[13] It is also important to remember the difference in the amount of patients included per country; however, in this study clinical variables were adjusted for, in order to avoid the possibility of bias. Finally, another bias to consider is that the ascertainment bias given by the kind of patients included could not represent the cases originated in the population. However, all cases followed by study centers were included.

This study was designed to analyze the hypothesis of a milder disease progression in regions with less-frequent MS cases in comparison with regions with more prevalent MS cases by using the MSSS. We found no differences between hemispheres or regions in the disease progression of MS patients analyzed by using the MSSS scale to perform the comparisons required.

This study represents a first step in understanding why LA MS patients have a different risk of developing MS but a similar disease progression in comparison with European and North American patients. Future studies will help to elucidate our initial findings.

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