ARTICLE

Prevalence of multiple sclerosis in key cities of Brazil: a study in Passo Fundo, Southern Brazil

Prevalência de esclerose múltipla em cidades-chave do Brasil: um estudo em Passo Fundo, no sul do Brasil

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ABSTRACT

Background: To improve the comparability of multiple sclerosis (MS) prevalence across Brazilian regions, the Brazilian Committee for Treatment and Research in MS has implemented a standardized approach to assess the prevalence of the disease in five key cities, which were deemed representative of their regions in terms of socio-geographical features and where in-person revision of each case was feasible. **Objective**: To report the point-prevalence of MS in Passo Fundo, one of the key cities in Southern Brazil. **Methods**: We sought to identify all MS patients who were living in Passo Fundo on July 1st, 2015. The primary source for case ascertainment was records from the offices of neurologists and neurosurgeons practicing in the city. Multiple secondary sources were used to maximize identification of cases. All patients underwent in-person review of the diagnosis by a panel of neurologists with experience in MS. **Results**: We identified 52 MS patients living in Passo Fundo on July 1st, 2015. The point-prevalence rate for MS was 26.4/100,000 population (95% confidence interval, 19.7 to 34.6/100,000). Among the MS cases, 42 (80.8%) were female, for a sex ratio of 4.2:1. Forty-six cases (88.5%) were categorized as relapsing-remitting MS, and the remaining 6 cases, as secondary progressive MS (11.5%). Other epidemiological and clinical features were comparable to national and international MS populations. **Conclusions**: The prevalence of MS in Passo Fundo is one of the highest reported in Brazil so far. Studies in other key Brazilian cities, using the same methodology, are currently being carried out.

Keywords: Multiple Sclerosis; Prevalence; Epidemiology.

RESUMO

Introdução: Para melhor comparar a prevalência de esclerose múltipla (EM) nas diferentes regiões do Brasil, o Comitê Brasileiro para Tratamento e Pesquisa em Esclerose Múltipla implementou uma abordagem padronizada para avaliar a prevalência da doença em 5 cidades-chave, consideradas representativas de suas regiões em termos de características sociogeográficas e nas quais seria viável revisar cada caso pessoalmente. **Objetivos**: Descrever a prevalência pontual de EM em Passo Fundo, uma das cidades-chave, localizada no Sul do Brasil. **Métodos**: Buscamos identificar todos os pacientes com EM que viviam em Passo Fundo no dia 1° de julho de 2015. A fonte primária para identificação de casos foi os registros de consultórios de neurologistas e neurocirurgiões da cidade. Múltiplas fontes secundárias foram usadas para maximizar a identificação de casos. Todos os pacientes tiveram o diagnóstico revisado pessoalmente por um painel de neurologistas com experiência em EM. **Resultados**: Identificamos 52 pacientes com EM que viviam em Passo Fundo em 1° de julho de 2015. Assim, a prevalência pontual bruta de EM foi 26,4/100.000 habitantes (intervalo de confiança de 95%, 19,7 a 34,6/100.000). Entre os casos de EM, 42 (80,8%) eram mulheres, (razão de sexos: 4,2:1). Quarenta e seis casos (88,5%) foram categorizados como EM remitente-recorrente, e os 6 casos restantes como EM secundariamente progressiva (11,5%). As demais características epidemiológicas e clínicas foram comparáveis a populações de EM internacionais. **Conclusões**: A prevalência de EM em Passo Fundo é uma das maiores já relatadas no Brasil. Estudos em outras cidades-chave brasileiras, usando a mesma metodologia, estão em andamento.

Palavras-chave: Esclerose Múltipla; Prevalência; Epidemiologia.

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INTRODUCTION

The prevalence of multiple sclerosis (MS) reported in Brazil varies widely across regions[1], which may be due to genetic and environmental diversity as well as to methodological differences across studies. To improve comparability, the Brazilian Committee for Treatment and Research in Multiple Sclerosis (BCTRIMS) has implemented a standardized approach to assess the prevalence of MS in five key cities, which were deemed representative of their regions in terms of socio-geographical features and where personal revision of each case was feasible. The rationale, purposes, and general methods of this initiative are described elsewhere[2]. In the present study, we aimed to report the point prevalence of MS on July 1st, 2015 in Passo Fundo, one of the key cities, which is located in Rio Grande do Sul state, Southern Brazil.

METHODS

In order to identify all patients living in Passo Fundo with an established diagnosis of MS on the prevalence day (July 1st, 2015), we invited all adult and pediatric neurologists and neurosurgeons who were practicing in the city to provide data regarding MS cases under their care, as a primary source for case ascertainment. Secondary sources included the database of the Municipal Department of Health, which provides disease-modifying therapies for nearly all MS patients, the membership list of the local MS patient association, and

advertisements on radio and television so that MS patients could self-refer to the research team. The present study received ethics approval from the Research Ethics Committee of Federal University of Minas Gerais (study number 666650).

Case ascertainment took place between October and December 2015, using the strategy shown in Figure 1. Patients ascertained from different sources were considered overlaps if they had identical names. All potential cases were reviewed in-person on December 12th 2015 by a panel of neurologists with experience in MS (ACF, BCR, DLV, JB, and MALP). The assessment included demographic data, history of MS, neurological examination, and results of magnetic resonance imaging (MRI), cerebrospinal fluid examination, and other paraclinical tests. MS was diagnosed according to the modified McDonald criteria (2010)[3] and categorized according to the phenotypes proposed by Lublin *et al*, modified in 2013[4]. We did not aim to include patients with clinically isolated syndromes (CIS). Disability was assessed by means of the Expanded Disability Status Scale (EDSS)[5].

Cases in which the diagnosis of MS could not be confirmed by the examining panel and MS patients whose diagnosis had been established after July 1st, 2015 were discarded. Patients who were alive on July 1st, 2015 and deceased afterwards, before the study date, were included, provided there was consistent evidence supporting the diagnosis of MS.

An official estimate for the Passo Fundo population size in 2015 was obtained from the Brazilian Institute of Geography and Statistics (IBGE)[6]. Further information on the composition of the local population, such as age, gender, and ethnic
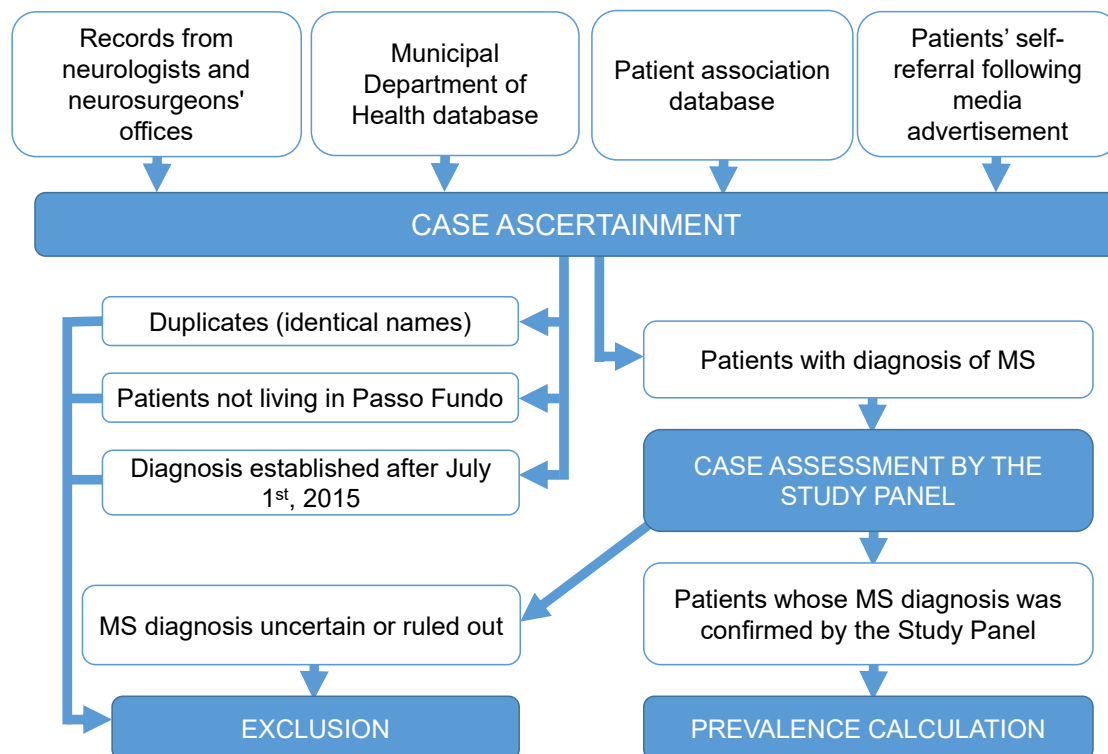

Figure 1. Case ascertainment in the multiple sclerosis prevalence study in Passo Fundo.

distribution, was only available from IBGE's 2010 census (the latest), and not for the year 2015[7]. Similarly, the latest survey of healthcare resources, also from the IBGE, dated back from 2009[8]. Geographical and socioeconomic information about Passo Fundo was collected from an online atlas[9].

We calculated the point-prevalence rate for July 1st, 2015 and estimated the 95% confidence intervals (95% CI) with the method proposed by Schoenberg[10]. Reporting of the present study was done in accordance to the Standards of Reporting of Neurological Disorders (STROND) guidelines – Application to MS[11].

RESULTS

Area and population

Passo Fundo is located at 28º 15' South latitude and 52º 24' West longitude (Figure 2), 680 meters above sea level[9]. The climate is humid subtropical (Köppen climate classification: Cfa)[9]. Both urban and rural environments are comprised in a total area of 783,421 square kilometers[9].

The population of Passo Fundo on July 1st, 2015 was 196,739[6]. Based on data from the 2010 census, 97% of the people lived in the urban area, and the majoritarian ethnic groups were Caucasian (83%) and mixed ancestry (14%)[8]. The latter comprises mostly individuals of mixed Caucasian and African ancestry. The Municipal Human Development Index (MHDI), also from 2010, was 0.776 (classified as high)[8].

In 2009, there were 86 outpatient facilities (including public clinics and private practices), 7 inpatient care facilities (totaling 974 beds), and 8 MRI scanners[8]. As of 2015, there were 24 adult and pediatric neurologists and neurosurgeons practicing in the city (unpublished data). Universal medical insurance coverage was available for all residents in Passo Fundo, by means of the Brazilian public healthcare system and/or private insurance companies.

Case ascertainment and assessment

Among the 24 adult and pediatric neurologists and neurosurgeons practicing in Passo Fundo at the study date, only one declined the invitation to collaborate with case ascertainment.

Fifty-two potential MS cases were identified, after exclusion of duplicates, subjects not living in Passo Fundo, and patients whose diagnosis of MS had been established after the prevalence day. All patients were alive on the study date and were contacted by the study team. All patients were able to attend the in-person review of diagnosis.

Prevalence

We identified 52 MS patients who were living in the city of Passo Fundo on July 1st, 2015, which yielded a point-prevalence of 26.4/100,000 population (95% CI, 19.7 to 34.6/100,000).

Epidemiological and clinical features

Epidemiological and clinical features of the MS patients living in Passo Fundo on the prevalence day are described in Table 1. Among the 52 MS cases, 42 (80.8%) were female, for a sex ratio of 4.2:1. The median age on the prevalence day was 40 years (range, 19 to 76 years). Regarding ethnicity, there were 51 (98.1%) Caucasians and 1 (1.9%) mixed ancestry individual (Caucasian/African).

Map created using SimpleMappr®, available at https://www.simplemappr.net.
Figure 2. Location of Passo Fundo, in Rio Grande do Sul state, Southern Brazil.

Table 1. Epidemiological and clinical features of MS patients living in Passo Fundo on the prevalence day (July 1st, 2015).

MS cases (n=52)	
Gender	
Female	42 (80.8%)
Male	10 (19.2%)
Age at prevalence day	
Median	40 years
Range	19 – 76 years
Ethnicity	
Caucasian	51 (98.1%)
Brown	1 (1.9%)
Age at MS onset	
Median	34.5 years
Range	14 – 66 years
MS phenotype	
Relapsing-remitting	46 (88.5%)
Secondary progressive	6 (11.5%)
EDSS score	
Median (range)	2.0 (0 – 9.5)
Current DMT	
Fingolimod	13 (25.0%)
Glatiramer acetate	2 (3.8%)
Interferon beta-1a, IM	16 (30.8%)
Interferon beta-1a, SC	1 (1.9%)
Interferon beta-1b	3 (5.8%)
Natalizumab	6 (11.5%)
None	11 (21.2%)

DMD: disease-modifying therapy; EDSS: Expanded Disability Status Scale; IM: intramuscular; MS: multiple sclerosis; SC: subcutaneous.

Forty-six cases (88.5%) were categorized as relapsing-remitting MS, and the remaining 6 cases as secondary progressive MS (11.5%). No patients with primary progressive MS were identified in Passo Fundo on the prevalence day.

The median age at disease onset was 34.5 years (range, 14 to 66 years). In 4 (7.7%) out of the 52 patients, the onset had been before the age of 18 years. Information on EDSS was available for 49 patients: the median score was 2.0 (range, 0.0 to 9.5). Sixteen patients (30.8%) were receiving intramuscular interferon beta-1a, 13 (25.0%) fingolimod, 6 (11.5%) natalizumab, 6 (11.5%) other disease-modifying therapies, and 11 (21.2%) were off treatment.

DISCUSSION

We found that the prevalence rate of MS in Passo Fundo is 26.4 cases per 100,000 population. To our knowledge, there are no previous estimates of MS prevalence in this city. However, this rate is comparable to that of Santa Maria, a city with similar socio-demographic features, located around 200 kilometers far from Passo Fundo, where the prevalence rate of MS was reported at 27.2 per 100,000 population[12]. No other studies reporting MS prevalence rates in Rio Grande do Sul state were found.

We selected Passo Fundo as a key city for prevalence study in Brazil due to several reasons. First of all, it can be assumed that its population is representative of the general population of Rio Grande do Sul state, both in terms of ethnic/genetic background and environmental exposures. In addition, the health resources available locally are good and have rendered Passo Fundo a reference in Neurology for many neighboring cities. On the other hand, the population size under 200,000 maximizes the chance of ascertaining and personally reviewing all MS cases.

The possibility for under-ascertainment of cases is the main limitation of this study. The main reason would be the delay between the initial symptoms of MS and establishing a formal diagnosis, which can take several months or years, either because of criteria-related issues (some patients are initially diagnosed with CIS, which we have not included in our study, some simply do not fulfill the criteria for either CIS or MS) or due to healthcare-related issues (e.g. delays in suspecting the diagnosis in the primary care setting, referring for specialized consultation, or completing the diagnostic workup).

Additionally, some patients may have been missed if they were not on regular follow-up and/or treatment, were followed-up only by general practitioners or specialists other than neurologists and neurosurgeons, were followed-up in other cities despite living in Passo Fundo, and/or were getting their medications from a source other than the public health system. However, the chances of missing MS patients were minimized by the use of multiple health system-based data sources, in addition to community-targeted strategies such as media advertisements.

On the other hand, it might be speculated that some people with significant MS-related disability originally living in smaller, neighboring cities eventually end up moving to Passo Fundo due to the greater availability of health resources, which could lead to some degree of prevalence overestimation, but likely not enough to overcome the previously mentioned underestimating factors. Therefore, we believe that the prevalence rate reported in the present study should be regarded as the *minimal* prevalence of MS in the city.

Yet, the prevalence of MS in Passo Fundo is among the highest reported in Brazil so far. A systematic review of studies investigating the prevalence of MS in several Brazilian cities found rates between 1.4 (in Recife, Northeast Brazil) and 27.2 per 100,000 population (in Santa Maria, Southern Brazil), with 80% of the studies reporting rates between 4.3 and 18.1 per 100,000 population[1]. In line with the study from Santa Maria, the present study corroborates that Rio Grande do Sul,

the southernmost state in Brazil, has the highest prevalence of MS in the country, which could be due to genetic and environmental factors.

Studies on the interethnic admixture of the Rio Grande do Sul population have reported genetic contributions mainly from Europeans (63-94%), in whom MS is far more prevalent, versus only 4-30% from Amerindians and 2-7% from Africans[13,14], whereas the genetic contributions of the latter groups are higher in most of the other Brazilian states. The positive association between latitude and MS prevalence may also account for the higher prevalence in Passo Fundo (and Rio Grande do Sul state as well) in comparison to other Brazilian regions, especially because such association is particularly relevant for populations of European descent[15,16].

Interestingly, the MS female-to-male ratio of 4.2:1 in Passo Fundo exceeds that reported for the neighboring city of Santa Maria (2.7:1)[12] and for the Americas as a whole (2.6:1)[17]. This excess is unlikely to result from unbalanced gender distribution in the general population across these areas, since the proportion of females in Passo Fundo (52.4%) is similar to that of Santa Maria (52.6%) and Brazil as a whole (51.0%), based on the 2010 census[7]. Median age at MS onset, distribution of phenotypes and proportion of pediatric cases in Passo Fundo are roughly similar to national[18] and international data[17].

Unfortunately, we were not able to provide exact age-, sex- and ethnic group-adjusted prevalence rates, which would facilitate subsequent comparability between cities, as the data required for these analyses (age, sex and ethnic group composition of the Passo Fundo population in 2015) are not available in IBGE information systems.

In conclusion, this study shows that the prevalence rate of MS in Passo Fundo, Southern Brazil on July 1st, 2015 was 26.4 per 100,000 population and corroborates that Rio Grande do Sul, the southernmost state in Brazil, has the highest prevalence of MS in the country. Studies in other Brazilian key cities, using the same methodology to ensure comparability of prevalence rates across different regions of the country, are currently being carried out.

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