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Incidence of multiple sclerosis in Chile. A hospital registry study

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Objective – To study the incidence of MS in Chile by examining the hospitalizations across all geographical regions of the country and to examine whether there is a correlation between these rates and the latitude or ultraviolet radiation. *Methods* – This is a descriptive study examining the national registry of hospitalizations because of MS (code G35 in ICD-10) from January 1, 2001, to December 31, 2006. Incidence rates were calculated by gender and geographical region and standardized to the world population estimated for 2010. *Results* – A total of 6857 hospitalizations were analyzed. There were 935 individuals; 63.9% were women. The mean incidence rate for 2002–2006 period was 0,90 (95% CI: 0.75–1.05). The annualized incidence rates for regions from North to South were as follows: I Tarapaca 0.54 (95% CI: 0.0–1.21), II Antofagasta 0,93 (0.10–1.75), III Atacama 1.07 (0.0–2.31), IV Coquimbo 0.63 (0.01–1.24), V Valparaiso 0.83 (0.38–1.27), VI O'Higgins 0.72 (0.14–1.30), VII Maule 0.52 (0.06–0.98), VIII BIO BIO 0.81 (0.41–1.21), IX Araucanía 0.43 (0.0–0.86), X Los Lagos 0.91 (0.35–1.46), XI Aysen 0.99 (0.0–2.98), XII Magallanes 3.54 (0.57–6.51), and XIII Metropolitana 1.10 (0.84–1.36). There were no significant correlations between hospitalization rates and latitude, except for region XII. UV radiation levels showed significant differences only for region XII. *Conclusion* – There is a moderate risk of MS in Chile. The southernmost region showed significantly higher incidence rates than those in the rest of the country (a cluster zone). We did not find any correlation between incidence rates and latitude or UV radiation.

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Introduction

Multiple sclerosis (MS) is the most common cause of non-traumatic neurological dysfunction in young adults (1, 2). The costs associated with MS are very high, including healthcare costs as well as the time, social, and personal costs involved in the care required by the patient.

The incidence of MS varies between 4.5 and 12 per 100,000 in Europe (3, 4). The prevalence varies between 47.2 and 86.3 cases per 100,000 individuals in the United States (5) and between 10 and 165 cases per 100,000 individuals in Europe (6). There are vast regions of the world where this information is not available (5). In Latin America, the prevalence obtained using different methodologies varies between 1.48 and 35.7 per 100,000 individuals (7–9).

MS is commonly accepted to have a higher prevalence in regions that are further away from the Equator, following a north–south gradient. This observation has led to hypotheses that try to explain the role of environmental factors in MS (10, 11). Given that continental Chile is a long, narrow country ranging from latitude 17° to 56°S (12), it is an ideal location to study such hypotheses.

Most of the patients with MS in Chile are hospitalized. Since 2001, magnetic resonance (MR) has been implemented by the public sector in the different geographical regions of Chile. The objective of this study was to assess the incidence of MS in Chile, based on hospitalized patients, focusing on the incidence for each region and any possible correlations with latitude and indexes of ultraviolet (UV) radiation.

Materials and methods

We used the Ministry of Health (MINSAL) national registry of hospitalizations from 2001 to 2006, corresponding to the G35 diagnostic category of the International Classification of Diseases (ICD-10). This compulsory registry encompasses both the private and public sectors who must fill a discharge diagnosis form; all of them are kept in a national register of hospitalizations. MS is priority pathology with guidelines for diagnosis, using Mac Donald (2005) criteria, and treatment, issued for neurologists (13) All patients have easy and equal access to neurological service irrespective of income and residence. Although it may take longer for some, within 6 years, all of them had been examined at least once by a neurologist.

The majority of the population is 'mestizo' by ethnic composition; 84% of mitochondrial haplogroups of the mixed population are of Amerindian origin, whereas the Y-chromosomes are mainly European. The female ancestors were mainly Amerindian, and the male ancestor, mainly European. The only exception with virtually sole European ancestry is the Magallanes region.

The unique 10-digit Chilean person identity code (RUN) allowed the identification of new cases of hospitalization for G35, even when patients had changed residence. The baseline year was 2001, and new patients were identified for each subsequent year.

Regional annualized incidence was defined as the mean number of new cases for G35 category for the period 2002–2006 in the numerator and the total 2004 population for each region in the denominator. The 95% confidence intervals (CI) were calculated for each region. The average rates were standardized to the 2010 estimated world population. The specific rates for age and gender in each region were calculated.

The annualized incidence rates for each region were correlated with the latitude of the center of that region (e.g., 20°S was taken as the corresponding latitude value for the Tarapacá region, located between latitudes 17°30′ and 21°38′, and 53°S for the Magallanes region, located between 48°36′ and 56°30′) (14). The same procedure was implemented for UV radiation, with the mean radiation (mW/m^2) of each region (years 2001–2006) being calculated from data from the Chilean Meteorological Center. For those regions lacking UV radiation registries, correlations were made with the UV radiation values from the closest neighboring areas, and linear regression between latitude and UV radiation was used to estimate the expected UV values.

The relationship between the latitude and UV radiation of the regions and their corresponding annualized incidence rates were studied using weighted regression analyses (using square root of number if incident cases in each region as weight), Microsoft Excel 2008 (© 2007 Microsoft Corporation, Redmond, WA, USA), and SPSS Statistics (SPSS Inc.; © IBM Corporation, Armonk, NY, USA).

Results

Six thousand eight hundred and fifty-seven files of patients admitted to hospitals with a diagnosis of MS were obtained. Six thousand three hundred and nine (92%) had an individualized RUN. There were 935 people with a diagnosis of MS. They were admitted a mean of 6.7 times over the 6 years of the study with a mean of 3 days $\pm$ 6.87 per hospitalization (range: 1–149 days). The mean age was 39 $\pm$ 12.03 years. Women accounted for 63.9% of the hospitalizations, with the ratio between men and women ranging from 1:1.6 to 1:2.2. The hospitalization increased between the ages of 25–49, reaching the highest rate between the ages of 35–39.

The regional annualized incidence rates are shown in Table 1. The number of new cases remained fairly constant (mean 147.20 $\pm$ 8.76 per years), and the average incidence rate for the period 2002–2006 was 0.90/100,000 (95% CI: 0.75–1.05). Women constituted the majority of the new cases for all the years in this study, doubling that of men in the years 2003 and 2005.

Table 1 Five years annualized incidence rate per 100.000 of multiple sclerosis, latitude, and UV radiation in Chile

Regions	N	Incidence rate (95% CI)	Latitude	UV radiation (mW/m^2)
I. Tarapacá	12	0.54 (0.0–1.21)	−20.00	2948.38
II. Antofagasta	28	0.93 (0.1–1.75)	−23.50	2767.25
III. Atacama	13	1.07 (0.0–2.31)	−27.50	2560.25
IV. Coquimbo	20	0.63 (0.01–1.24)	−30.75	2392.06
V. Valparaíso	63	0.83 (0.38–1.27)	−32.75	2288.55
Metropolitana	352	1.10 (0.84–1.36)	−33.50	2249.74
VI. O'Higgins	26	0.72 (0.14–1.3)	−34.50	2197.99
VII. Maule	23	0.52 (0.06–0.98)	−35.50	2146.24
VIII. Biobío	79	0.81 (0.41–1.21)	−37.00	2068.61
IX. Araucanía	23	0.43 (0. 0–0.86)	−38.50	1990.99
X. Los Lagos	47	0.91 (0.35–1.46)	−41.75	1822.80
XI. Aysén	6	0.99 (0.0–2.98)	−46.50	1576.98
XII. Magallanes	29	3.54 (0.57–6.51)	−53.15	1232.83
Chile	721	0.90 (0.75–1.05)		

Annualized incidence rates adjusted by sex and age to 2010 world population. There is statistical significance between total Chile rates and the I, IV, VI, IX XI, and XII regions ($P < 0.05$)

The Magallanes region had an annualized incidence rate that was significantly higher than the national average during the 6 years of the study, as much as four times higher than the rest of the country. The regional rates were significantly different from the national rates for the corresponding years. The annualized rate in the Metropolitan region was 1.10/100,000 (CI: 0.84–1.36).

The study of seasonal hospitalization trends showed the highest rates to be in the spring, with significant differences ($P < 0.05$) between the number of hospitalizations in the spring and summer for all years except 2001.

The relationship between the annualized incidence rates in the different regions and latitudes was not significant ($\beta = -0.04$, $P = 0.5$, 95% CI: −0.2 to 0.09). When the Magallanes region is included in the analysis, there is a significant inverse correlation between period incidence rate and latitude (6-year mean, $\beta = -0.31$, $P = 0.02$, 95% CI: −0.56 to −0.05). When the Magallanes region is excluded, the significance of this correlation is lost. A similar phenomenon was observed when the correlation between period incidence rate and UV radiation index was examined; it was only significant when the Magallanes region was included ($\beta = -0.006$, 95% CI: −0.008 to −0.005) (Fig. 1).

Discussion

The annualized incidence rate for 2002–2006 was 0.90 per 100,000. This incidence rate is similar to that obtained in a previous study that examined a fixed population within Chile. Barahona found a rate of 1.8 per 100,000 annually (9), and our results oscillate between 0.75 and 1.05 per 100,000. Values around 0.5 per 100,000 were observed in Panama (15) and 1.76–2.24 in Argentina (16, 17). However, these values may not be fully comparable because they were all obtained using different methodologies (16). There are several studies on the prevalence of MS in LA. Colombia (17, 18) has figures comparatively lower than those of Argentina (19) and Brazil (20).

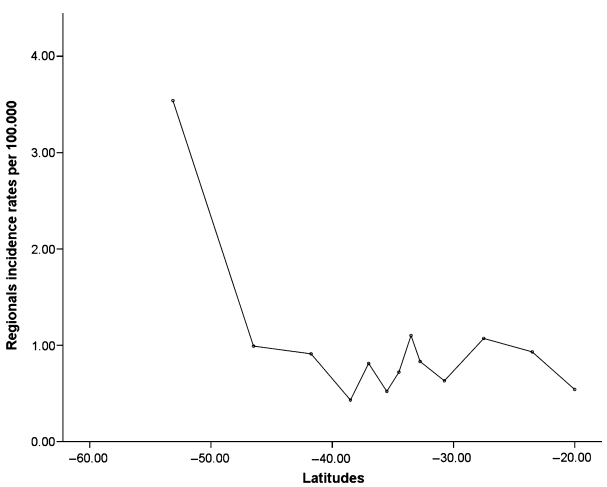

Figure 1. Regionals incidence rates and latitudes. There are no significant relations between regions rates and latitude if Magallanes (36° to 55°S) is excluded.

The hospitalization for MS in Chile increased until 2003. This could be related to the improvements in diagnosis because of the implementation of MR in the public sector and/or to the development of treatments (e.g., interferon and methylprednisolone) that require hospitalization for patients with MS.

The observation that patients between the ages of 30 and 39 had higher incidence rates is consistent with previous reports. Trelett et al. reported a higher incidence of relapses in patients between the ages of 20 and 50 (21). In addition, the higher prevalence in women is consistent with data obtained in international studies. In Argentina, Melcon et al. observed a rate of 12 per 100,000 for women and 7 per 100,000 for men in the Junin province (22). Similar results were observed in Brazil, with Callegaro reporting a rate of 20.1 in women and 8.5 in men (20).

The regional analysis of the average incidence showed significant differences between the regional and national rates, with Magallanes presenting the highest rates. The causes for the latter observation are not yet well understood, but they could include a better registry of patients and/or unknown environmental factors, given that this phenomenon was not correlated with latitude in the different Chilean regions. This lack of correlation between MS and latitude is consistent with the results of an Argentinean study carried out in the Patagonian region between the latitudes of 36° and 55°S (22).

The Magallanes region has a population with a high percentage of Croatian immigrants, who arrived during the nineteenth century. This area contains the largest ovine farms in the country. These immigrants consume much ovine meat, leading to a diet high in saturated fats. Another possible explanation for the differences observed in the Magallanes region is that the hospital infrastructure may be better in this area, thus attracting patients from neighboring regions such as Aysen. The higher frequency of Caucasian genes in this area may be a more important factor in the highest rate in the country.

Some regions such as Coquimbo and the Maule region had consistently low incidence rates. Despite having the proper diagnostic medical resources (e.g., MR and neurologists), these areas

had the lowest values in the country during the entire period of the study. These low rates could be related to an unknown environmental factor that provides some protection against MS. Magallanes continues to have the highest incidence, with values up to four times the national rate. Surprisingly, the incidence values were not significantly different across the 6 years examined and were actually all within the confidence intervals.

Kurtzke (23) has suggested the existence of geographical areas with distinct MS prevalences, with the prevalence increasing with the distance from the Equator. Santiago de Chile is located at latitude 33°S. A recent study by Koch-Henriksen et al., a meta-regression analysis, dismissed the notion of a latitudinal gradient in Europe and North America (24) and the latitudinal gradient for incidence is non-existent for the northern hemisphere. Some geographically close areas, however, have been shown to differ significantly in their MS prevalences (25). In addition, the regions of Mediterranean Europe, which had been previously considered to be areas of low prevalence, now appear to have a high prevalence (26).

There are also likely to be differences in the genetic susceptibility of certain populations to MS. The increase in prevalence with latitude has some obvious exceptions. MS has not been observed in Eskimos (Nunavut, north of Canada, latitude between 60° and 75°N) (25), Indians from North and South America, Australian aborigines, New Zealand Maoris, Hungarian gypsies (Central Europe, latitude 47°N), Pacific islanders, or ethnically pure lampoons (north Finland, in the Arctic Polar Circle, latitude 60°N) (26, 27). In addition, this disease is very rare in Japan (latitude 32–42°N), with a prevalence of 1–4 per 100,000 (28), as well as in China and Korea, and in African black population. These findings suggest that there is a genetic/racial bias in the susceptibility to MS. In this context, the prevalence of this disease among Caucasians is well known, particularly among the Scandinavian population (29). Nevertheless, MS has a low prevalence in the Caucasian populations in South Africa, which highlights the contribution of environmental factors and latitudes (30).

There are also differences between the northern and southern hemispheres that could affect the prevalence of MS. Very few studies have shown a latitude gradient in the southern hemisphere. The populated areas of this hemisphere, however, reach lower latitudes than in the northern hemisphere. The Cabo de Hornos is located at latitude 56°S, from which the large Drake Sea opens. Puerto Williams, the capital of the Chilean Antarctica, is the southernmost populated area on the planet, with latitude 55°S. Other such cities are Ushuaia, Argentina (54°S, 45,000 people), and Punta Arenas, Chile (53°S, 150,000 people). There are large territories north of these cities in this region that are either uninhabited or contain only a few villages with small populations. In contrast, the northern hemisphere contains seven cities with populations greater than 50,000 people located north of the Arctic Polar Circle. In addition, major cities, including Oslo at 60°N, Stockholm at 59°N, Copenhagen at 55°N, Berlin at 52°N, London at 51°N, Paris at 49°N, Montreal at 45°N, Toronto at 44°N, and New York at 40°N, are located at far latitudes. These observations highlight some of the large and obvious differences between the distribution and density of the population at different latitudes between the northern and southern hemispheres.

Similar seasonal variations in the prevalence and incidence rates were also observed in other reports, with increases in the spring. These findings could be explained by the low sun exposure during the winter (31).

The correlation of MS with UV radiation was also studied, with lower radiation exposure corresponding to a higher MS rate. This observation could be due to the changes in vitamin D levels, which decrease with lower UV radiation exposure (32). The analysis of geographical factors such as UV radiation and latitude, however, could be masking other environmental factors that also change as the location nears the Poles. For example, Gong proposed that the duration of daylight in a region could lead to the changes in the circadian rhythms, affecting the production of hormones that could modulate the immune system (33).

An important limitation of this study is the validity of the MS diagnosis. The MS diagnosis may not have been carried out using adequate criteria. Problems in the codification of information in the database can also reduce the internal validity of the research. However, the following suggest that the diagnosis used in our study was valid: the implementation of MR in the different regions, hospitalization at least once in the 6 years of the study in all patients, the individualized diagnosis of MS in the ICD-10, and the requirement of hospitalization for many patients to receive their treatment. A second limitation is the possibility that not all of the patients diagnosed with MS were hospitalized.

Conclusion

The average 2002–2006 annualized incidence of MS is 0.9 (0.75–1.05) for the whole of Chile, and

this estimate is based on the best possible and reliable data. The incidence of MS did not correlate with latitude and UV radiation. There is a cluster of MS in Magallanes region, which might be related to Caucasian genes and different nutritional behaviors.

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Conflict of interest

All authors have no conflict of interest.

References

1. Krokavcova M, Nagyova I, van Dijk JP et al. Mastery, functional disability and perceived health status in patients with multiple sclerosis. Eur J Neurol 2008;**15**:1237–44.
2. Rostásy K. Multiple sclerosis in children: Clinical, diagnostic, and therapeutic aspects. Int Rev Neurobiol 2007;**79**:269–79.
3. Joensen P. Multiple sclerosis incidence in the Faroe Islands 1986–2007. Acta Neurol Scand 2010;**121**:348–53.
4. Sumelahti M-L, Tienari PJ, Hakama M, Wikstrom J. Multiple sclerosis in Finland: incidence trends and differences in relapsing remitting and primary progressive disease courses. J Neurol Neurosurg Psychiatr 2003;**74**:25–8.
5. Noonan CW, Williamson DM, Henry JP et al. The prevalence of multiple sclerosis in 3 US communities. Prev Chronic Dis 2010;**7**:A12.
6. Pugliatti M, Rosati G, Carton H et al. The epidemiology of multiple sclerosis in Europe. Eur J Neurol 2006;**13**:700–22.
7. Corona T, Román GC. Multiple sclerosis in Latin America. Neuroepidemiology 2006;**26**:1–3.
8. Cristiano E, Patrucco L, Rojas JI. A systematic review of the epidemiology of the epidemiology of multiple sclerosis in South America. Eur J Neurol 2008;**15**:1273–8.
9. Luetic G. MS in Latin America. Int MS J 2008;**15**:6–11.
10. Beck CA, Metz LM, Svenson LW, Patten SB. Regional variation of multiple sclerosis prevalence in Canada. Mult Scler 2005;**11**:516–9.
11. Ahlgren C, Odén A, Torén K, Anderson O. Multiple sclerosis incidence in the era of measles-mumps-rubella mass vaccinations. Acta Neurol Scand 2009;**119**:313–20.
12. http://www.uchile.cl/?_nfpb=true&_pageLabel=conUrl&url=8035.
13. http://www.redsalud.gov.cl/portal/url/item/95542bbbc251eeb8e04001011f01678c.pdf
14. Biblioteca del Congreso Nacional del Chile. Chile, our country: Regions, 2010. http://siit2.bcn.cl/nuestropais/regiones.htm (accessed 22 February 2010).
15. Gracia F, Castillo LC, Benzadón A et al. Prevalence and incidence of multiple sclerosis in Panama (2000–2005). Neuroepidemiology 2009;**32**:287–93.
16. Cristiano E, Patrucco L, Giunta D et al. Incidence of multiple sclerosis in Buenos Aires: a 16 years health maintenance organization-based study. Eur J Neurol 2010;**17**:479–82.
17. Sánchez JL, Aguirre C, Arcos-Burgos OM et al. Prevalence of multiple sclerosis in colombia. Rev Neurol 2000;**31**:1101–3.
18. Toro J, Sarmiento OL, Díaz del Castillo A et al. Prevalence of multiple sclerosis in Bogotá, Colombia. Neuroepidemiology 2007;**28**:33–8.
19. Cristiano E, Patrucco L, Rojas JI et al. Prevalence of multiple sclerosis in Buenos Aires, Argentina using the capture-recapture method. Eur J Neurol 2009;**16**:183–7.
20. Callegaro D, Goldbaum M, Morais L. The prevalence of multiple sclerosis in the city of São Paulo, Brazil, 1997. Acta Neurol Scand 2001;**104**:208–13.
21. Tremlett H, Zhao Y, Joseph J, Devonshire V, Neurologists UC. Relapses in multiple sclerosis are age- and time-dependent. J Neurol Neurosurg Psychiatr 2008;**79**:1368–74.
22. Melcon MO, Gold L, Carrá A et al. Argentine patagonia: prevalence and clinical features of multiple sclerosis. Mult Scler 2008;**14**:656–62.
23. Kurtzke JF. A reassessment of the distribution of multiple sclerosis. Acta Neurol Scand 1975;**51**:137–57.
24. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol 2010;**9**:520–32.
25. Sadovnick AD, Ebers GC. Epidemiology of multiple sclerosis: a critical overview. Can J Neurol Sci 1993;**20**:17–29.
26. Vassallo L, Elian M, Dean G. Multiple sclerosis in southern Europe. Prevalence in malta in 1978. J Epidemiol Community Health 1979;**33**:111–3.
27. Ebers GC, Sadovnick AD. The geographic distribution of multiple sclerosis: a review. Neuroepidemiology 1993;**12**:1–5.
28. Kuroiwa Y, Igata A, Itahara K, Koshijima S, Tsubaki T. Nationwide survey of multiple sclerosis in Japan. Clinical analysis of 1,084 cases. Neurology 1975;**25**:845–51.
29. Poser CM. Viking voyages: the origin of multiple sclerosis? An essay in medical history. Acta Neurol Scand Suppl 1995;**161**:11–22.
30. Dean G. Annual incidence, prevalence, and mortality of multiple sclerosis in white South-African-born and in white immigrants to South Africa. Br Med J 1967;**2**:724–30.
31. Tremlett H, van der Mei IAF, Pittas F et al. Monthly ambient sunlight, infections and relapse rates in Multiple Sclerosis. Neuroepidemiology 2008;**31**:271–9.
32. Beretich B, Beretich T. Explaining Multiple Sclerosis prevalence by ultraviolet exposure: a geospatial analysis. Mult Scler 2009;**15**:891–8.
33. Gong X, Xie Z, Zuo H. A new track for understanding the pathogenesis of Multiple Sclerosis: from the perspective of early developmental deficit caused by the potential 5-ht deficiency in individuals in high-latitude areas. Med Hypotheses 2008;**71**:580–3.