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Season of birth as a risk factor for multiple sclerosis in Brazil

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ABSTRACT

Risk factors for development of multiple sclerosis (MS) are still a matter of debate. Latitude gradient, vitamin D deficiency and season of birth are among the most investigated environmental factors associated with the disease. Several international studies suggest that birth in spring is a substantial risk factor for MS. We investigated the season of birth as a potential risk for MS in different geographical regions of Brazil. We conducted a cross-sectional retrospective study with 2257 clinically definite MS patients enrolled in 13 Brazilian MS clinics in the south, southeast, and northeast regions of Brazil. Demographic and clinical data relating to date of birth and clinical features of the disease were collected and analysed, and subsequently compared with birth date among the general Brazilian population. The distribution of date of birth of MS patients showed an increase in spring and a decrease in autumn, with no difference being observed in the other seasons. In conclusion, season of birth is a probable risk factor for MS in most parts of Brazil. These findings may be related to the role that vitamin D plays in MS pathogenesis.

1. Introduction

Multiple Sclerosis (MS) is a chronic auto-immune neurological disease of unknown cause, generally progressive and characterised by inflammatory and demyelinating components, and by axonal loss [1]. It is believed that it arises from a combination of genetic predisposition with environmental factors that trigger the disease [2–5]. The risk factors for the onset of MS have not yet been fully defined. Degree of latitude [6–16], season of birth [2,3,17–24], vitamin D deficiency [25–27] and childhood infections [3,23,28–30] are the most studied environmental factors that may be associated with this disease.

Several international studies have suggested that a springtime birth would substantially increase the risk of an individual developing MS at some point in the future. The risk of developing MS in countries situated in the northern hemisphere is greater for those people born in May and less for those born in November [17,19–22,24]. This topic, however, has barely been researched in the southern hemisphere [18]. In addition, some studies have not confirmed these findings [31,32].

This research aims to study the season of birth as a risk factor for the development of MS in Brazil; the influence of place of birth in this association, seen in different geographic regions, and to correlate the frequency of birth month for MS patients with the birth rates for different months of the year in the Brazilian population as a whole.

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2. Materials and methods

A cross-sectional study was conducted of patients diagnosed with MS being followed at specialist centres for the treatment of the disease, located in three of the most prevalent and populous regions of Brazil, including four in the northeast, six in the southeast, and three in the south of the country. The regions of the south, and to a lesser degree, the southeast, typically have four well defined seasons. This is especially so in the south where it can become very cold, with significant reductions in exposure to sunlight in wintertime. The regions of the northeast, in contrast, have high temperatures and levels of sunlight exposure throughout the year, with the changes of season best defined by greater or lesser amounts of rainfall. Another important difference between these regions relates to demographic characteristics. In the south, especially in the states of Rio Grande do Sul (RS) and Santa Catarina (SC), 83.6% of the population are Caucasian, 15.6% are of African descent and 0.7% of other ethnicities (oriental and indigenous). In the northeast, however, especially in the state of Bahia (BA), there is a large predominance of inhabitants of African descent (76.7%), with only 23.0% being Caucasian and 0.3% other ethnicities [33].

Included in the study were patients with an MS diagnosis according to the McDonald criteria (2001) or the modified McDonald criteria (2005); or according to the Poser criteria (1983) (probable or definite MS, with or without laboratory support), for those patients monitored up till the year 2000 only, and that consulted within the last 25 years the services participating in this study (between 1985 and 2010).

The project was approved by the Research Ethics Committees of the participating institutions and consent was obtained from the participating centres for the use of data from the medical records. The information collected did not cause harm to patients.

Demographic and clinical data were collected in each region and analysed regarding date of birth and clinical features of the disease, and subsequently compared with date of birth among the general Brazilian population, as published by the Brazilian Institute of Geography and Statistics (IBGE) [34,35]. It is important to note that the frequency of births remained stable over the entire period under consideration, with a higher frequency of births in March and a smaller proportion in December in all states and regions of Brazil.

The data was entered in an Excel 2007 spread sheet and analysed using the statistics package SPSS for Windows, version 17. Categorical variables (dichotomous or polytomous) were described by frequencies, and the ordinals by medians and interquartile ranges. The quantitative variables were described by means and standard deviation. For the definition of birth date as a risk factor for MS, the chi-squared value was calculated comparing the distribution observed in patients with the expected distribution, which was based on either the proportion of births per month or per season of the Brazilian population as a whole, or by state or region studied.

3. Results

A total of 2257 patients were studied (78.6% with relapsing-remitting MS; 72.3% female; mean age 42.1 ± 12.4 years). The distribution of birth date of MS patients was compared with that of the entire Brazilian population, with an increase in the number of births of MS patients being seen in spring (October, November and December) and a decrease in autumn (April, May and June), with no difference being observed in the other seasons (Figs. 1 and 2). These alterations were most significant in the southeast region of Brazil and also, to a lesser extent, in the south. All regions showed a significant increase in the prevalence of births of people with MS in the springtime and a decrease in the autumn. In the southern region, there was also a reduction in the prevalence of births of individuals with MS in the wintertime, although to a lesser degree. The same also occurred in the northeast region in the winter and spring (Fig. 3).

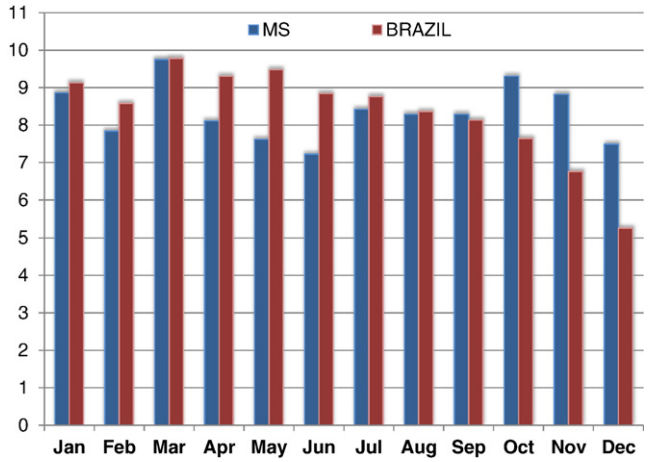

Fig. 1. Monthly distribution of births for patients diagnosed with multiple sclerosis, and for total births in Brazil.
Source: Information System on Live Births, Ministry of Health.

The seasonal difference in births was observed in all the states, regardless of ethnicity. Births in the spring showed an increased risk of MS onset, whereas births in the autumn had a lower risk, both in Bahia ($P < 0.001$), a state with a large predominance of African descendants, and in the southern region ($P < 0.001$), where Caucasians represent approximately 84% of the population. This relationship of season with the onset of MS was observed in both progressive and relapsing-remitting cases (Fig. 4).

4. Discussion

The occurrence of an association between birth month and the risk of developing a given disease over the course of a lifetime has been reported in many diseases, other than multiple sclerosis. Such an association has been reported in patients with schizophrenia, brain tumours, amyotrophic lateral sclerosis, epilepsy, Parkinson's disease, celiac disease, type 1 diabetes mellitus, Grave's hyperthyroidism and Hashimoto's thyroiditis [29,30]. Like MS, most of these diseases exhibit autoimmune and/or degenerative characteristics.

A pooled analysis of the risk of MS by birth month was performed based on studies from Canada, Great Britain, Denmark and Sweden ($n = 42{,}045$). This study involving patients born in the northern hemisphere showed a significant increase in the risk of developing MS for individuals born in May, as compared with those born in other months of the year, and some protection, or at least a reduction in risk, for those

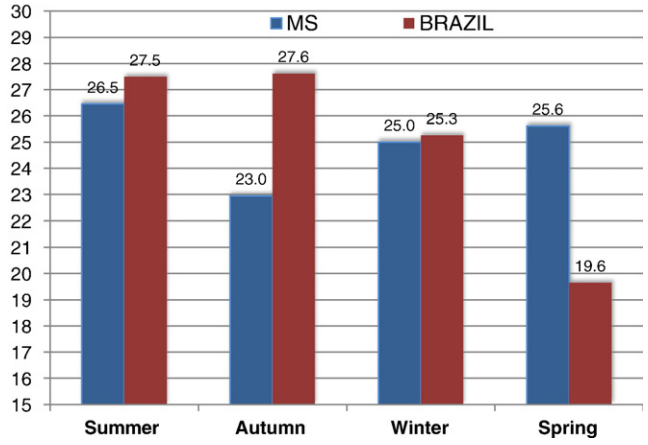

Fig. 2. Distribution by season of the year for patients diagnosed with multiple sclerosis, and for total births in Brazil.
Source: Information System on Live Births, Ministry of Health.

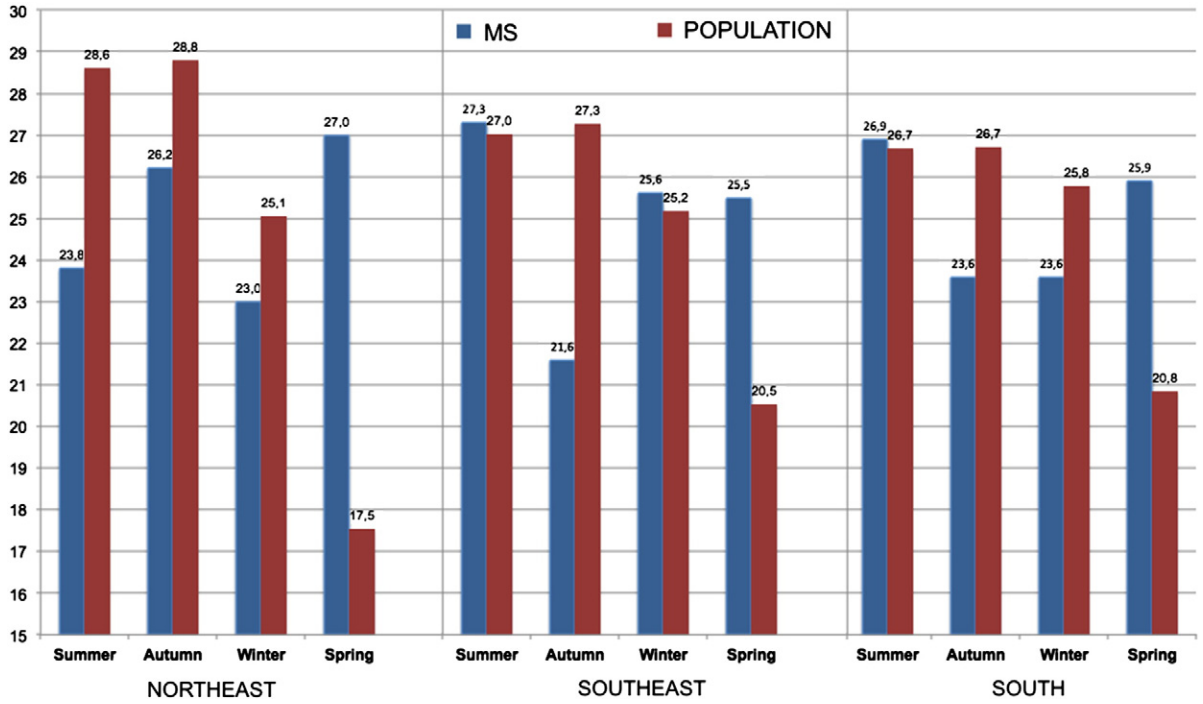

Fig. 3. Distribution by season of the year for patients diagnosed with multiple sclerosis, according to region in Brazil.

born in November. This relationship was higher in familial cases, suggesting genetic and environmental interactions linked to climate [4]. Salzer et al., 2010, found a higher prevalence in patients born in June, which would correspond with our findings of this being the month with the lowest prevalence, as the seasons are reversed in the two different hemispheres [29]. Other studies have also demonstrated the period of birth as an environmental factor related to future onset of MS, but linked to season rather than month. These studies suggest an increased risk for individuals born in spring or in late summer and a protection for those born in autumn or winter [3,23,29]. These findings are identical to ours, where a significant increase in the prevalence of MS took place in patients born during spring and a reduction for those born in the autumn.

It is believed that the best explanation for this data is that to be born in springtime gives rise to an environmental risk of developing MS in pregnancy, in the perinatal period or in the first months after birth. However, the factors involved in this association have not yet been fully explained. To date, three possible factors for the association between birth month and onset of MS have been proposed. The first proposed mechanism relates to the occurrence of infections during pregnancy and/or in the neonatal period, resulting from seasonal variations in the incidence of many infections [23,28,29]. Against this hypothesis is the fact that no infectious agent has yet been actually defined [3,23,29]. In addition, some studies suggest the period in which infectious processes could affect susceptibility to MS onset would in fact be during puberty and adolescence, and not the foetal period or early infancy [29,36]. On the other hand, some authors put forward that certain infections could serve as a protector rather than a trigger for MS. According to the hygiene hypothesis, the presence of childhood infections will modify the immune response, hindering

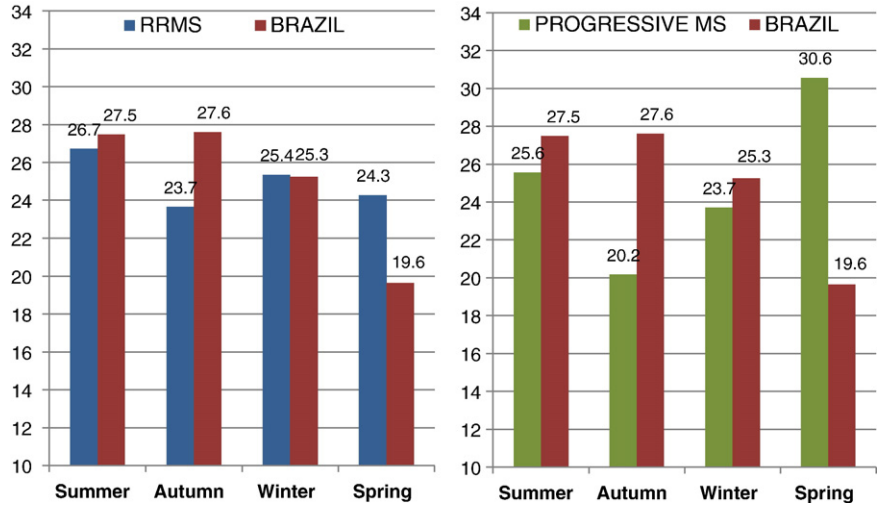

Fig. 4. Seasonal distribution of births for patients diagnosed initially with the relapsing-remitting (RRMS) or progressive form of multiple sclerosis, and for total births in Brazil. Source: Information System on Live Births, Ministry of Health.

the development of autoimmune disorders [3]. An additional possibility may relate to the fact that, in general, newborn babies go through a natural period of partial seclusion for some months after birth. This leaves them less exposed to the external environment and therefore, less susceptible to infections. This delay of outside exposure may be further extended for babies born in the spring as the colder weather of winter arrives by the time they reach 4 to 6 months of age. Consequently, those individuals born in spring may have a lower incidence of early infection, resulting in inadequate development of their immune system and, theoretically, leaving them more susceptible to autoimmune diseases in adulthood.

A second possible risk factor could be related to diet. A study of pregnant women conducted in New Zealand observed that diet and blood concentrations of nutrients vary depending on time period of the year and season. Thus, the ingestion of greater or lesser amounts of anti-oxidant agents could result in an increase in oxidative damage, both directly on neurons and the immune system [29,37]. The third hypothesis relates to vitamin D deficiency, secondary to reduced sun exposure during critical periods of gestation. Several authors have argued that vitamin D acts like a modulator of the immune system by promoting the differentiation of interleukin 10 (IL-10) with the production of regulatory T cells; by stimulating natural killer cells (NK) that prevent the onset of autoimmune diseases; by regulating osteopontin, a Th1 cytokine that increases the production of interferon-gamma and IL-12 and reduces IL10, and by blocking the production of IL-2 [16,29]. Stewart et al., 2007, found when studying untreated patients with relapsing–remitting MS and control individuals that an increase of IL-10 occurs in both groups during the summer, confirming the above findings [38]. Furthermore, vitamin D acts directly in regulating the expression of HLA-DRB1*1501[2,16], the gene locus known to be most related to an increased predisposition to developing MS [2]. It should be noted that it is not possible to exclude that these findings arise from other as yet unknown factors that may act earlier in pregnancy or just after birth [23,39,40].

An Australian study has suggested that the risk of MS is inversely related to the amount of UV radiation exposure during the first trimester of pregnancy [40]. In Canada, on the other hand, it was observed that the risk of fraternal twins developing MS is approximately twice that for siblings produced from the same parents but born at different times of the year. This suggests the occurrence of environmental factors during pregnancy and/or soon after birth. Moreover, studies with half-siblings have shown an effect which is exclusively maternal for the onset of MS, suggesting that the causal factor is more likely to be environmental rather than genetic [4]. Additionally, many studies have correlated high sun exposure in late childhood and high vitamin D levels in adulthood with a reduced risk of developing MS [24]. The fact that there were no differences between the regions and the states with distinct ethnic characteristics suggests that, in this case, the environmental factor is more important than the genetic factor.

During summer and early autumn, individuals are exposed to large amounts of UV radiation, even more so in a tropical country like Brazil. It is believed that this leads to an increase in the quantity of vitamin D provided in the late gestation period of the foetus for those babies born in the autumn. It is also known that it is towards the end of pregnancy that the peak of brain myelinisation is reached in the development and establishment of immunological memory [23,40]. Furthermore, authors have demonstrated that vitamin D deficiency during pregnancy, albeit temporary, causes permanent alterations in the adult brain [16,24]. This principally occurs due to a robust and consistent down-regulation of transcripts and proteins involved in cytoskeleton maintenance, molecular transport of organelles and synaptic plasticity. In addition, it is now well established that vitamin D regulates important brain-derived neurotrophic factors. Lastly, experimental studies have demonstrated that the withdrawal of vitamin D from the diet of pregnant rats results in a decrease in the expression of nerve growth factor in the brains of their offspring, both in the neonatal period and in adulthood [24]. These findings together suggest that it is likely that high levels of vitamin D at the end of the second and throughout the third trimester of pregnancy may protect against the future onset of MS [4,16]. This is consistent with the observations in our population, especially in the south, and less so in the southeast, where the seasons are well defined and with high levels of sun exposure throughout the summer and early autumn, interspersed by a significant reduction in temperature and sun exposure during the winter months.

5. Conclusions

Season of birth is a probable risk factor for MS in most parts of Brazil. These findings may be related to the role that vitamin D plays in MS pathogenesis. Further studies are required to clarify this issue.

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