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ARTICLE

Multiple sclerosis starting before the age of 18 years: the Brazilian experience

Esclerose múltipla com início antes dos 18 anos de idade: a experiência brasileira

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ABSTRACT

Multiple sclerosis (MS) starting in childhood and adolescence poses a challenge for diagnosis and management of the disease. The aim of the present study was to assess the characteristics of early onset MS in Brazilian patients. Methods: Retrospective data collection from specialized MS units. Results: From 20 MS units in 11 Brazilian states, 117 cases of MS starting before the age of 18 years were collected. These patients had an average of 10 years of disease duration, still typically with low disability and one relapse every 2.5 years. The mean age for disease onset was 13.7 years. Conclusion: The present study introduces a large series of Brazilian cases of pediatric MS. Although some patients presented a very severe form of MS, on the whole the group of patients with MS starting in childhood or adolescence presented a relatively mild form of this disease in Brazil.

Keywords: multiple sclerosis, children, adolescents, pediatrics.

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RESUMO

Esclerose múltipla (EM) com início na infância e adolescência constitui um desafio para o diagnóstico e manejo da doença. A proposta do presente estudo foi avaliar as características da EM de início precoce em pacientes brasileiros. Métodos: Coleta de dados retrospectiva de arquivos de unidades especializadas em atendimento da EM. Resultados: A partir de 20 unidades de EM de nove estados brasileiros, foram coletados 117 casos de EM com início antes dos 18 anos de idade. Estes pacientes tinham uma média de 10 anos de duração da doença, de maneira geral apresentavam pouca incapacidade , com um surto a cada dois anos e meio. A média de idade no início da doença era 13,7 anos. Conclusão: O presente estudo apresenta uma grande série de casos brasileiros de EM pediátrica. Embora alguns pacientes tenham apresentado forma grave de EM, de maneira geral o grupo de pacientes cuja EM iniciou-se na infância ou adolescência apresentou uma forma relativamente leve da doença no Brasil.

Palavras-chave: esclerose múltipla, crianças, adolescentes, pediatria.

Multiple sclerosis (MS) is a chronic inflammatory and degenerative neurological disease that typically affects young adults. MS usually appears between the ages of 20 and 40 years, and an early start of MS (<18 years old) is relatively uncommon[1]. Diagnosis and management of these patients require special attention[2–5]. Few case series on the epidemiology and characteristics of MS starting in childhood and adolescence have been published in the world. Except for four papers[6–9], other publications have presented fewer than 100 cases each in their series[10–23].

When MS in Brazilian children and adolescents is considered, it is possible that some aspects are different from MS of European, Asian, North African, and North American counterparts. In Brazil, children have a more mixed genetic background, more frequent infestations by helminths, and high sun exposure since early life. These are genetic and environmental factors that may positively affect MS development and evolution. The present study aimed to better understand the epidemiological profile of early-onset MS in Brazilian patients. A specific database was set up to collect data from patients with MS whose disease started before the patient reached his/her 18th birthday.

METHOD

The present study was approved by the Ethics Committee of Universidade Metropolitana de Santos, SP, under number CAAE 13499913.7.0000.5509. Further approvals were obtained from institutions participating in the study that required additional submission to their Ethics Committees. No public, governmental, or private financial support was received for creating this database and for preparing this paper.

Brazilian neurologists and neuropediatricians caring for patients with MS were invited to participate in the study. The study was based on the medical records of patients under the care of the physicians sending the information. A specific file with demographic and clinical information on each patient was sent to the authors, and data collection took place between October and December 2012. Only cases with complete information were included in the analysis. Cases resembling acute disseminated encephalomyelitis, neuromyelitis optica (NMO), or spectrum disorders of NMO (NMO-SD) were excluded from this assessment.

All cases fulfilled McDonald's diagnostic criteria, revised for the pediatric population[3], and the recommendations of the expert consensus for diagnosing pediatric MS[24]. No cases of demyelinating diseases other than MS were included in the present study. Disability was assessed using the Expanded Disability Scale Score (EDSS)[25] and the clinical presentations of MS were defined as relapsing–remitting, secondary progressive, and primary progressive[26].

Statistical analysis was carried out using Student's *t*-test for continuous data, and Fisher's exact test and the chi-square test for categorical data. Whenever correlations were required, Pearson's correlation test was used. However, due to the characteristics of the study, many results are presented only in a descriptive manner.

RESULTS

Data were collected from 20 MS units in different cities in 11 Brazilian states. Together, these MS units had 2290 MS patients registered and 125 of them (5.5%) presented MS starting before the age of 18 years. A summary of the demographic and clinical data on these patients is presented in Table 1.

The average age at the time of disease onset was 13.7±3.4 years (range 4–17 years). In 19 patients (15%) the disease started when they were children, i.e. before reaching 11 years of age (onset of MS ranging from 4 to 10 years of age; mean 7.7±2.0 years). In the remaining 108 patients (85%) the disease started after 11 years of age. In this group of older children the age of onset of the disease was 14.8±1.6 years (range 11–17 years). For the purpose of most analyses in this study, these two age groups were considered to be a single group of patients with MS starting in childhood or adolescence.

The total group consisted of 38 boys and 87 girls (1:2.3), and their ethnic background was either Caucasian (57 cases, 45.6%) or African descent (68 cases, 54.4%). There were no cases of children or adolescents descended from Asians or

indigenous ancestors. All the children were born between the latitudes of 7° 9′ 28″ south and 30° 2′ 77″ south. At present, the average age of these patients is 23.3±9.3 years.

Despite an average age of 13.7 years for disease onset, confirmation of MS was only possible at an average age of 15.7±6.2 years. The initial presenting sign or symptom was most frequently multifocal (30 cases), involving the brainstem in 11 cases and/or the cerebellum in eight cases. When these occur separately, the most frequent presentations were sensory symptoms (22 cases), brainstem involvement (18 cases), cerebellar signs (17 cases), optic neuritis (16 cases), motor signs (16 cases), and spinal cord disease (three cases). Three cases were atypical, with one case of mental confusion, one of seizure, and one of hemianopsia. Motor presentation was either pyramidal (10 cases) or extrapyramidal (6 cases).

At the time of writing, 117 cases were in the form of relapsing–remitting MS, while six cases were secondary progressive MS. Two children died during the course of the disease.

The patients had suffered from MS for an average of 10.5±8.4 years and their current EDSS was, on average, 1.96±2.24. There was a moderate correlation between disease duration and degree of disability assessed by EDSS (r=0.519). It is of interest to note that EDSS≥6.0 was significantly associated with MS starting before age 11 years (Fisher's exact test p=0.011). The average disease duration for patients with EDSS≥6.0 in the present group was 23.3±17.6 years. The disease duration among the more disabled patients was significantly longer (p=0.0009) than that of patients currently with EDSS≤6.0.

Ninety-eight patients had normal intelligence and were currently doing well in school, whereas 11 patients were reported to have excelled at school. Fourteen patients presented moderate difficulties at school, but had not failed. Four of these required additional private tuition. Two patients had been attending special schools for the disabled and were having great difficulties with their education.

At the time of writing, with an average of about 10 years of MS duration, the patients had experiences an average of 4.2±2.4 disease relapses (median=4). Twelve patients presented 10 or more relapses during their disease. There was no correlation between disease duration and number of relapses (r=0.229) or disability and number of relapses (r=0.240).

Disease progression among patients who started MS in childhood (≤10 years) was compared with progression among those with MS starting later in childhood (≥11 years). Patients starting MS before age 11 years presented EDSS=1.5±2.8 after 5.5 years of disease duration. Those starting the disease after 11 years of age presented EDSS=1.0±2.0 after 14 years of disease duration (p=0.51).

Regarding treatment, 113 patients were currently receiving immunomodulatory and/or immunosuppressive medications for MS. There were 10 patients who for a variety of reasons were not treated, but mainly because they (and their families) did not want MS drug treatment. The remaining two patients died during the course of the disease.

The therapeutic options for these patients were extremely variable and are summarized in Table 2. Forty-one patients (32.8% of the total sample) were on their second or third different therapeutic scheme because of failure or intolerance.

All patients had received at least one pulse of corticosteroids during the course of the disease. Seven patients had been diagnosed with depression and were receiving antidepressants. Among other drugs used by the patients were sildenafil and baclofen, both for rare and specific cases. Use of physiotherapy and hydrotherapy was reported by 15 patients (12% of the cases).

There were no cases of other immunological diseases diagnosed among the patients of this group. Three patients had other cases of MS in the family (the mother of one patient and the cousin of two different patients).

Table 1. Demographical and clinical characteristics of 125 patients with multiple sclerosis starting before the 18th birthday.

	n=125
Age of onset	13.7±3.4 (range 4–17) years 15% started MS before completing 11 years 85% started MS after 11th birthday
Gender	38 males, 87 females
Ethnicity	Caucasians, n=57 African descent, n=68
Initial presentation	Multifocal, n=30 Sensitive symptoms, n=22 Brainstem signs, n=18 Cerebellar signs, n=17 Optic neuritis, n=16 Spinal cord signs, n=3 Atypical, n=3
Disease duration	10.5±8.4 years
Present EDSS	1.96±2.24 (range 0–10)
Relapses	4.2±2.4 during the disease Annual relapse rate=0.34±0.27

EDSS: expanded disability scale score.

DISCUSSION

While the present database does not represent the whole of Brazil, it covers a large geographical region incorporating several states and many professionals working in MS units in this country. There is no national database for registration of MS and other demyelinating diseases, and two previous Brazilian case series have reported on specific areas of the country[16,22]. The present study is the first large national series of cases of MS starting in childhood or adolescence.

The percentage of early-onset MS cases in Brazil, namely 5.5% of all MS cases, is in accordance with the worldwide literature[9], although some authors reviewing the subject consider it to be below 5%[4]. The present study did not analyze the

Table 2. List of medications currently in use for multiple sclerosis in 113 patients. Eleven patients were not using any drugs and two patients had died at the time of this assessment.

Medication in use	Number of cases
Glatiramer acetate	39
Interferon beta 1a 22 or 44 μg	21
Interferon beta 1a 30 μg	17
Interferon beta 1b 250 μg	12
Natalizumab	9
Azathioprine	3
Azathioprine + glatiramer acetate	3
Azathioprine + interferon beta 1a 22 or 44 μg	3
Fingolimod	2
Immunoglobulin (monthly)	2
Cyclophosphamide + glatiramer acetate	1
Corticosteroids (monthly)	1

prevalence of childhood and adolescence MS in the different regions of the country. The numbers are too small to reach conclusions and, therefore, only the prevalence of earlier onset MS in relation to later onset MS can be discussed. The analyses on these data did not taken into consideration environmental or genetic factors that might influence the findings.

The overall results from the present study showed that those patients who started MS before the age of 18 years were not severely disabled after the average disease duration of 10 years. Other authors have remarked that MS in childhood typically predicts a favorable short- to medium-term prognosis[27], which can account for the relatively low degree of disability among our patients. In fact, after suffering from MS for 30 years, 50% of these children are likely to enter the secondary progressive phase of the disease[27]. The patients in our cohort also had a good history of schooling, no associated diseases, and about one relapse every 2.5 years. Although isolated cases in our series progressed in a severe manner, the vast majority of the Brazilian patients starting MS before the age of 18 years were not particularly complicated cases. Theories that may account for the better disease course among Brazilian children and adolescents with MS include those relating to helminthic infections in childhood[28], sunlight exposure[29], and the typical national mixed race genetic background[30].

Finally, the rich variety of signs and symptoms of MS presenting during childhood and adolescence needs to be thoroughly known and understood by pediatricians[31]. Delays in diagnosing and treating these patients may negatively affect the disease course, and close monitoring of these patients by neurologists and neuropediatricians is very important. The average typical delay of 2 years to obtain the diagnosis of MS in our population of youngsters needs to be decreased in the near future.

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