Pediatric Neurology 94 (2019) 48–54

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Pediatric Multiple Sclerosis in Rio de Janeiro: Secondary Progression and Disability

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ARTICLE INFO

Article history:
Received 4 March 2018
Accepted 23 December 2018
Available online 31 December 2018

Keywords:
Multiple sclerosis
Secondary progression
Pediatric multiple sclerosis
Expanded Disability Status Scale
Epidemiology

ABSTRACT

Background: The onset of multiple sclerosis (MS) in 2% to 10% of cases occurs prior to 18 years of age. Early age onset appears to affect some aspects of multiple sclerosis. The objective of our study was to evaluate the prevalence, the clinical and demographic characteristics, and the disease progression in a sample of pediatric multiple sclerosis patients from a mixed population.

Methods: In a cross-sectional design, the prevalence, demographic characteristics, and initial clinical forms were compared between 75 cases of pediatric multiple sclerosis (PMS) and 689 adults with MS. Sixty-five PMS patients with complete data and 260 randomly selected adults with relapsing-remitting multiple sclerosis were compared. A Kaplan-Meier analysis was conducted to compare the age at and time to Expanded Disability Status Scale (EDSS) 3, EDSS 6, and secondary progressive multiple sclerosis (SPMS).

Results: A total of 9.8% of all MS cases with available data were PMS. All cases of PMS consisted of relapsing-remitting multiple sclerosis. Brazilians of African descent comprised 34.6% of the sample, and the female-to-male ratio was 2.4:1. At the first attack, motor alterations were more common. Benign forms were more common in PMS (84.6% versus 62.2%). Fewer PMS patients reached EDSS 6 (11.6% versus 25.4%) ($P = 0.0017$) and SPMS (11.1% versus 28.1%) ($P = 0.005$). PMS patients took longer to reach EDSS 3 ($P = 0.017$), EDSS 6 ($P = 0.001$), and SPMS ($P < 0.001$); however, they reached EDSS 3 earlier ($P < 0.001$).

Conclusions: In this mixed cohort, the prevalence of PMS was similar to that reported in other studies, and the pediatric patients had a more benign course than adults with MS.

Introduction

The onset of multiple sclerosis (MS) before 18 years of age is uncommon, and its clinical profile varies slightly from that found in adults. A greater number of attacks in the initial phases of the disease, better recovery, the finding of larger lesions by magnetic resonance imaging, and a more inflammatory cerebrospinal fluid profile are some of the characteristics that have already been described.[1–4] Survival studies conducted in predominantly Caucasian cohorts have shown slower transition to secondary progressive multiple sclerosis (SPMS) in pediatric MS patients, despite the greater degrees of disability at an earlier age.[5–9]

In areas where the prevalence of MS is considered low and the population is mixed, few data are available on the clinical characteristics of pediatric MS and its conversion to SPMS. Brazilian data on long-term disability in pediatric MS are still to be published. Conversely, survival studies have been conducted in adult Brazilians, and being of African descent is associated with a poorer prognosis insofar as conversion to SPMS is concerned.[10] In multiethnic North American cohorts, being of African descent was also associated with poorer prognosis and a greater risk of developing pediatric MS and other demyelinating diseases of childhood.[11,12] The objective of this study was to evaluate the prevalence of early onset, as well as the clinical and demographic characteristics and disease progression in a sample of pediatric MS patients from a mixed population such as that of Brazil.

Conflicts of interest: None.

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https://doi.org/10.1016/j.pediatrneurol.2018.12.015
0887-8994/

Methods

Patients

This cohort study included a retrospective, longitudinal analysis of clinical and demographic characteristics, as well as conversion to SPMS, in patients diagnosed with MS[13,14,15] and followed regularly at a referral center for the treatment of demyelinating diseases in the *Hospital Federal da Lagoa*, Rio de Janeiro, Brazil between March 1998 and November 2014. A total of 806 patients with a confirmed diagnosis of MS were identified. In 764 of these cases, demographic data and baseline clinical description were available and complete.

Data collection and analysis

Demographic and clinical data were collected and compared between two groups of MS patients, those whose first attack occurred before age 18 years and those in whom the first attack occurred after age 18 years. To analyze progression (time to disability and to SPMS), only patients with relapsing-remitting multiple sclerosis (RRMS), who had had the disease for greater than two years and for whom data on progression were complete were included. The pediatric MS patients were compared with randomly selected adult MS patients in the proportion of one to four.

Evaluation measurements

Demographic data of interest included sex, ethnicity, and age (in years) at the first clinical attack. The patients classified as being of African descent were those with phenotypical characteristics and confirmed African ancestry (three previous generations). The following clinical variables were collected: the number of attacks in one, two, and five years; whether recovery from the first attack was complete, partial, or the patient did not recover; the interval (in years) between the first two attacks; and the type of functional system (FS) affected in the first attack. Recovery from the relapse was considered full when the patient, 30 days or more after the onset of the relapse, exhibited no neurological signs and symptoms related to the relapse and improvement of the Expanded Disability Status Scale (EDSS) to the value documented prior to the relapse. In accordance with the number of systems affected, the patients were then classified as polysymptomatic if two or more FSs were affected and monosymptomatic when only one was affected.

The disease progression markers evaluated were the time between the first attack and the time to reach EDSS 3, time to EDSS 6, and time to SPMS.

We utilized standard definitions of benign or malignant MS to characterize better or worse disease evolution. The others evolved in an intermediate manner. The patients were classified as having the benign or malignant form of MS in accordance with the definitions established by Kantarci and Weinshenker[16] and Perini et al.[17] MS was considered benign when the EDSS score remained $\leq$3 after 10 years of illness and malignant when the EDSS score was $\geq$6 after five years of illness.[16,17]

The study end points were defined as follows: EDSS 3 referred to the presence of one FS grade 3 with others 0 or 1, or the presence of three FS grade 2 and others 0 or 1; EDSS 6 referred to the patient requiring intermittent or constant unilateral assistance with a crutch or cane to walk 100 m, or the presence of three or more FS grade 3 or one FS grade 5, with the others being of grade 2 or more. Disease progression was evaluated from the presence of progressive deterioration accompanied by an irreversible increase of at least 1 point or more in the EDSS scale over a period of at least six months, unassociated with the occurrence of attacks and of an irreversible nature. EDSS was recorded by a neurologist at baseline. Data based on the patients' age (in years) when reaching the end points were also collected.

An initial analysis consisted in describing the prevalence and demographic and clinical characteristics of the pediatric form of MS. At this stage of the study, all forms of MS were included. In the second analysis, the pediatric and adult forms of MS were compared. After univariate analysis, the demographic and clinical variables found to be statistically significant were included in a multiple analysis of the entire sample of patients with RRMS (both the adult and pediatric forms) to evaluate which prognostic factors could affect the end points evaluated.

Statistical analysis

The Statistical Package for the Social Sciences, version 13.0 for Windows, was used to construct the database and perform the statistical analyses. Measures of central tendency (medians, minimum and maximum values, and interquartile ranges) were used for the continuous variables whose distribution was not normal. The categorical variables were expressed as frequencies (%) and ratios. Fisher's exact test or Pearson's chi-square test was performed for comparison of categorical variables. The Mann-Whitney *U* test was used to compare continuous variables between groups. Kaplan-Meier survival curves were used to analyze the age at and the time to reach the different disability markers and conversion to SPMS. The log rank test was used to compare curves. In the univariate analysis, the median time in years until reaching EDSS 3, EDSS 6, and conversion to SPMS were calculated, as well as the patients' age when reaching these end points. In the survival analyses, means were used when the data presented normal distribution by the methods of Kurtosis, Skewness, and Kolmogorov-Smirnov. In other situations, medians were used. Significance was established at $P < 0.05$.

The Cox regression method was used in the multivariate analysis to identify the variables that conferred risk or protection with respect to the end points analyzed. Hazard ratios with 95% confidence interval (CI) were calculated.

Ethical aspects

The study was registered at Plataforma Brasil on August 20, 2013 and was approved by the internal review board of the Gaffrée and Guinle Teaching Hospital under reference CAAE: 18650513.6.0000.5258 (CEP/HUGG-UNIRIO). All the relevant ethical requirements were followed in the use of the patients' medical records.

Results

Prevalence of pediatric MS

Of the 764 MS patients, 75 (9.8%) fulfilled the requirements for inclusion in the pediatric group.

Demographic data and clinical forms of pediatric MS

The patients of non-African descent made up two-thirds of all cases. Disease onset occurred after puberty (from age 12 to less than 18 years) in most pediatric patients (82.7%), with a minority experiencing onset before age 10 years (four cases = 5.3%; 0.52% of the entire cohort). The majority were girls (70.7%), with a female-to-male ratio of 2.4:1. This ratio was inverted, however, in patients less than 12 years of age, in which males were more common (1.6 male to one female). After age 12 years, the predominance of

females was even higher (female-to-male ratio 3.4:1) ($P = 0.005$). In all the pediatric patients, the disease began as RRMS; however, in the final evaluation a greater proportion of male patients had converted to SPMS (Table 1).

Pediatric versus adult MS

Demographic aspects and the initial clinical form

There was no statistically significant difference in sex or ethnicity between the adult and pediatric MS patients. Primary progressive MS was not the initial form of the disease in any of the pediatric MS patients; however, its frequency was 10.0% in the adult cases of MS ($P = 0.010$) (data not shown).

Clinical aspects and progression

A total of 65 pediatric MS patients whose data on progression were complete were included in the longitudinal analysis and paired with 260 adult patients with RRMS and at least two years since onset of the disease. The clinical data and data regarding progression are shown in Tables 2 and 3, respectively.

Recovery from the first attack

Significantly more pediatric MS patients recovered from the first attack compared with the adult MS patients ($P = 0.036$): full recovery was achieved by 89.1% versus 74.7% and partial recovery was achieved by 7.8% versus 21.8%, respectively.

Number of attacks and the time interval between the first two attacks

There was no statistically significant difference between the pediatric and adult MS patients with regard to the interval between the first two attacks. In slightly over half of the pediatric cases, the interval between the first and second attacks was ≤2 years. The second attack occurred at three years or more after the first attack in 26 patients (44.1%). Three-quarters of them were female patients (n = 21, 53.8%) and a quarter were male patients (n = 5, 25.0%) ($P = 0.03$) (data not shown).

Functional systems

The monosymptomatic type was more common in both groups. In the pediatric MS patients, the most common initial alteration was pyramidal followed by sensory signs, whereas in adult MS sensory manifestations were more common than pyramidal signs. In the analysis according to sex, there was a statistically significant difference in the pediatric MS group, with sensory manifestations being more common in females (42.8%), whereas they were only the fourth most common type of manifestation in males (18.2%) ($P = 0.048$). In the adult MS patients, there was no difference between males and females with regard to the frequency of FSs affected (data not shown).

Treatment

Around 95% of the patients received some type of disease-modifying treatment and the median time until treatment was initiated was close to five years, with no statistically significant difference between the pediatric MS and adult MS groups (data not shown).

Disease profile

Benign and malignant forms

According to the classification of the benign form of MS, which considers a 10-year course of the disease, a significantly higher number of pediatric MS patients had this form of the disease in relation to the adult MS group (84.6% versus 62.2%; $P = 0.007$) (Table 3).

With respect to the frequency of patients who reached the end points evaluated in this study, EDSS 3 was reached by similar proportions of patients in the pediatric and adult MS groups (46.8% versus 49.6%); however, EDSS 6 was reached by a significantly greater proportion of adult MS patients compared with the pediatric MS patients (25.4% versus 11.3%). Conversion to SPMS was notably more common among the adult MS patients (28.1% versus 11.1%). Analysis of the time until reaching the disability markers and converting to SPMS and comparison between the adult and pediatric MS patients are shown in Table 3.

Pediatric MS patients took longer to reach EDSS 3 (median 19.0 years; 95% CI, 10.8 to 27.1) compared with the adult MS patients (median 13.0 years; 95% CI, 11.4 to 14.6) ($P = 0.01$) (Fig 1). On the other hand, the pediatric MS patients reached EDSS 3 at a much younger age (mean, 36.1 years; 95% CI, 32.1 to 40.1), 12 years earlier compared with the group of adult MS patients (mean, 48.3 years; 95% CI, 46.3 to 50.2) (Fig 2). The mean age for reaching EDSS 3 was significantly lower in the group of pediatric MS patients ($P < 0.001$). Likewise, the time until reaching EDSS 6 was also greater in the pediatric MS patients (median not reached for pediatric patients versus 25.0 years; 95% CI, 22.6 to 27.4; $P = 0.001$) (Fig 3). However, there was no statistically significant difference between the two groups with respect to the age at which EDSS 6 was reached. The

TABLE 1.
The Demographic and Clinical Profile of the Pediatric MS Patients

Characteristics	Total (n = 75)	Male (n = 22)	Female (n = 53)
Ethnicity, n (%)			
White	49 (65.3)	14 (63.6)	35 (66.0)
African descent	26 (34.7)	8 (36.4)	18 (34.0)
Age at onset (years), n (%)			
<10 years	4 (5.3)	2 (9.0)	2 (3.8)
10-11 years	9 (12.0)	6 (27.3)	3 (5.7)
12-17 years	62 (82.7)	14 (63.6)	48 (90.6)
Median (range)	15.0 (3.0-17.0)	14.0 (6.0-17.0)	15.0 (3.0-17.0)
RRMS clinical phenotype at onset, n (%)	75 (100)	22 (100)	53 (100)
Clinical phenotype at last follow-up, n (%)			
RRMS	69 (92.9)	19 (86.4)	50 (94.3)
SPMS	6 (8.0)	3 (13.6)	3 (5.7)

Abbreviations:
MS = multiple sclerosis
RRMS = relapsing-remitting multiple sclerosis
SPMS = secondary progressive multiple sclerosis

TABLE 2.
Comparison of the Clinical Data of Pediatric and Adult MS Patients

Characteristics	Pediatric MS (n = 65)*	Adult MS (n = 260)*	*P* Value
Sex, n (%)			0.053
Male	22 (33.8)	58 (22.3)	
Female	43 (66.2)	202 (77.7)	
Year of first attack, n (%)			0.780
<2000	37 (56.9)	143 (55.0)	
≥2000	28 (43.1)	117 (45.0)	
Ethnicity, n (%)			0.556
White	42 (64.6)	177 (68.1)	
Of African descent	23 (35.4)	82 (31.5)	
Recovery from first attack, n (%)			0.886
Total recovery	62 (96.9)	249 (96.5)	
No recovery	2 (3.1)	9 (3.5)	
Form of recovery, n (%)			**0.036**
Total recovery	57 (89.1)	192 (74.7)	
Partial recovery	5 (7.8)	56 (21.8)	
Did not recover	2 (3.1)	9 (3.5)	
Interval between first attacks, n (%)			0.581
≤2 years	33 (55.9)	155 (59.8)	
≥3 years	26 (44.1)	104 (40.2)	
Number of functional systems affected in the first attack, n (%)			0.896
Monosymptomatic	46 (71.9)	189 (72.7)	
Polysymptomatic	18 (28.1)	71 (27.3)	
Final EDSS			0.061
Median (IQR)	2.0 (1.0-3.5)	2.5 (1.5-6.0)	
Range	0.0-9.0	0.0-9.0	
Time since disease onset			0.224
Median (IQR) (years)	13.0 (6.0-18.0)	12.0 (7.0-21.0)	
Range	2.0-45.0	2.0-46.0	
Number of attacks in the first year			0.201
Median (IQR)	1.0 (1.0-1.0)	1.0 (1.0-2.0)	
Range	1.0-4.0	1.0-5.0	
Number of attacks in the first two years			0.561
Median (IQR)	1.0 (1.0-2.0)	1.0 (1.0-3.0)	
Range	1.0-6.0	1.0-5.0	

Abbreviations:
MS = multiple sclerosis
IQR = interquartile range
EDSS = Expanded Disability Status Scale
P value in bold is statistically significant.
* "n" varies as a result of missing data.

pediatric MS patients took 16 years longer than the adult MS patients to convert to SPMS (median 39.0 years versus 23.0 years; 95% CI, 18.8 to 27.2) (Fig 4). With respect to age at conversion to SPMS, there was no statistically significant difference between the groups (Table 3).

Risk factors for reaching the disability markers and converting to SPMS

After multivariate analysis, having the pediatric form of MS and not having recovered completely from the initial attacks were found to represent factors that affected the risk for all the end

TABLE 3.
Data on Disease Profile and Progression: Comparison Between Pediatric and Adult MS Patients

Data on Disease Profile and Progression	Pediatric MS (n = 65)*	(95% CI)	Adult MS (n = 260)*	(95% CI)	*P* Value
Malignant MS, n (%)	1 (1.8)		12 (5.4)		0.243
Benign MS, n (%)	33 (84.6)		112 (62.2)		**0.007**
Reached EDSS 3, n (%)	29 (46.8)		129 (49.6)		0.688
Time to EDSS 3 (years), median	19.0	10.8-27.2	13.0	11.4-14.6	**0.017**
Age at EDSS 3 (years), mean	36.1	32.1-40.1	48.3	46.3-50.2	**<0.001**
Reached EDSS 6, n (%)	7 (11.3)		66 (25.4)		**0.017**
Time to EDSS 6 (years), median	†	—	25.0	22.6-27.4	**0.001**
Age at EDSS 6, mean	50.8	46.1-55.6	59.8	56.9-62.7	0.607
Conversion to SPMS, n (%)	7 (11.1)		73 (28.1)		**0.005**
Time to SPMS (years); median	39.0	—	23.0	18.8-27.2	**<0.001**
Age at conversion to SPMS (years); mean	50.9	46.6-55.2	57.4	54.3-60.5	0.973

Abbreviations:
95% CI = 95% confidence interval
EDSS = Expanded Disability Status Scale
MS = multiple sclerosis
SPMS =secondary progressive multiple sclerosis
P values in bold are statistically significant.
* "n" varies as a result of missing data.
† Median not reached.

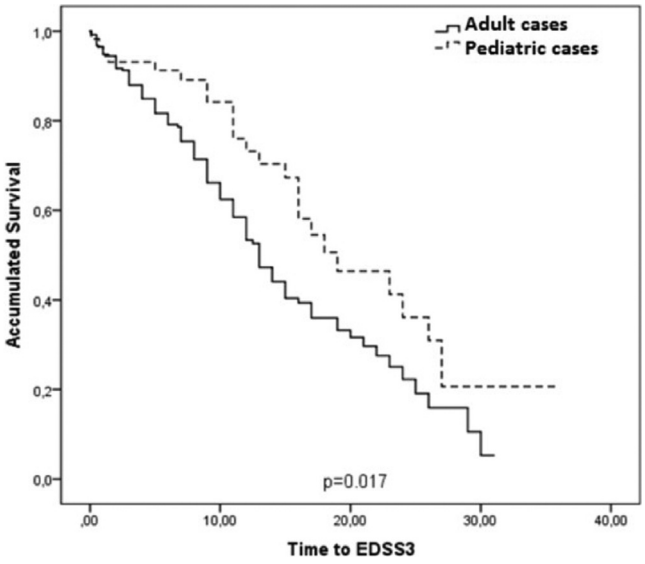

FIGURE 1. Kaplan-Meier analysis: time to EDSS 3 in pediatric MS patients compared with adult MS patients. EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

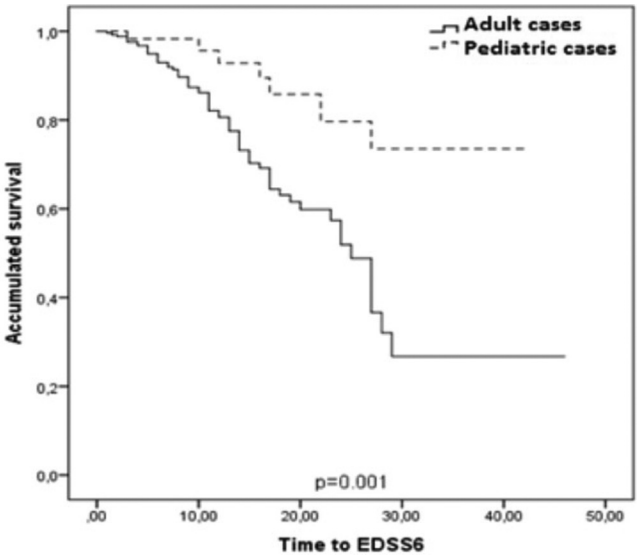

FIGURE 3. Kaplan-Meier analysis: time to EDSS 6 in pediatric versus adult MS cases. EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

points studied. Onset of the disease at age less than 18 years conferred protection against reaching EDSS 3, EDSS 6, and converting to SPMS. On the other hand, incomplete recovery represented a greater risk of all three end points. Being male represented a risk only with respect to reaching EDSS 3 and EDSS 6, whereas the occurrence of two attacks or more in the first year of the disease represented a risk with respect to reaching EDSS 6 and converting to SPMS. A short time interval between the first two attacks represented a risk regarding reaching EDSS 3 alone (Table 4).

Discussion

Studies of pediatric MS populations represent an opportunity to acquire more information about the disease in a phase that is closest to its biological onset. The prevalence of pediatric MS of 9.8% found in this study is high compared with the prevalence reported in European cohorts.[2,5,8,18–20] Higher frequencies have also been described in cohorts evaluated in Brazil and Italy[9,21] as well as in a multicenter study conducted in South America; the rate of pediatric MS was also slightly higher than in Europe and North America.[23] The cutoff age in most recent studies was 16 years.[6–9] Only one study included patients aged up to 18 years and compared disability and conversion to SPMS.[5]

The present sample originates from a specialist referral center for MS and this may explain the higher prevalence. Most patients experienced their first attack after 10 years of age, with rates up to 0.8% reported before this age in other studies, including a Brazilian study.[6,8,20,22,23] The disease at age less than 10 years occurred in only 0.52% of our sample.

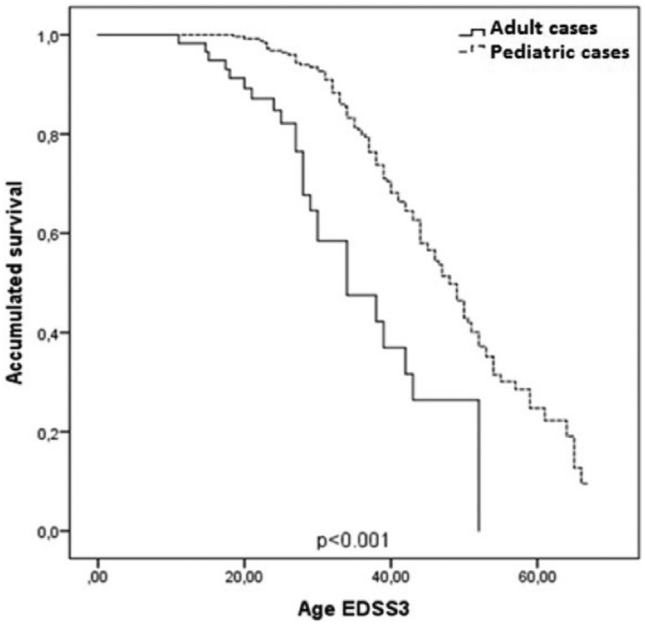

FIGURE 2. Kaplan-Meier analysis: age at EDSS 3 in pediatric versus adult MS cases. EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

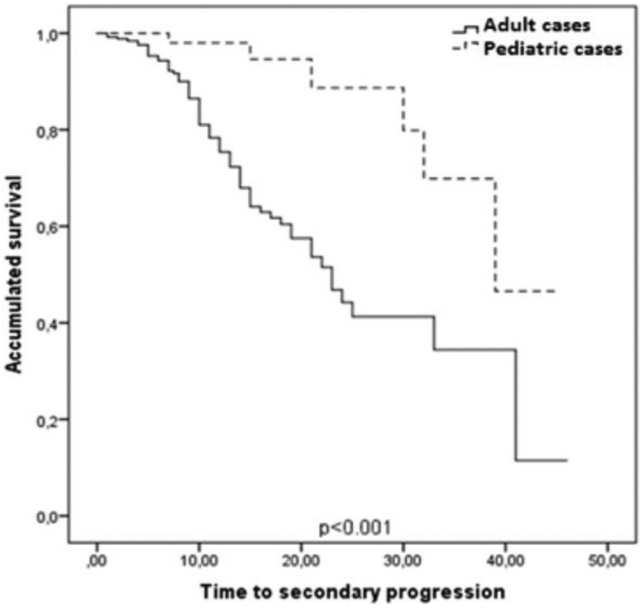

FIGURE 4. Kaplan-Meier analysis: time to conversion to SPMS in pediatric versus adult MS patients. MS, multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

TABLE 4.
Multivariate Survival Analysis Using Cox's Regression Model: Risk of Reaching EDSS 3 and EDSS 6 and of Converting to SPMS According to Demographic and Clinical Characteristics of the Disease

End Points	EDSS 3			EDSS 6			Secondary Progressive Stage		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Variables									
Being male	1.60	1.11-2.33	**0.01**	2.16	1.33-3.50	**0.002**	1.50	0.10-2.42	0.10
Incomplete recovery	2.80	2.10-3.72	**<0.001**	2.56	1.80-3.64	**<0.001**	2.15	1.50-3.10	**<0.001**
Short interval between first and second attack	1.60	1.16-2.25	**0.004**	1.37	0.87-2.14	0.17	1.30	0.78-2.10	0.34
≥2 relapses in first year	1.50	0.95-2.24	0.81	2.00	1.13-3.41	**0.02**	2.16	1.30-3.60	**0.003**
Pediatric multiple sclerosis patients	0.60	0.36-0.88	**0.01**	0.35	0.17-0.74	**0.006**	0.31	0.14-0.70	**0.003**

Abbreviations:
CI = confidence interval
EDSS = Expanded Disability Status Scale
HR = hazard rate
SPMS = secondary progressive multiple sclerosis

One-third of our pediatric MS patients and 45.6% of pediatric MS patients from São Paulo[24] were of African descent, reflecting the typical ethnic characteristics of the Brazilian population. The incidence of black children with MS in a USA study (Southern California) was even higher than in Caucasian and Hispanic children.[11] In a European study, 1.3% of the cases were of African descent.[5] In a Brazilian adult MS cohort, African ancestry was associated with poorer prognosis.[25] However, in the multivariate analysis, African descent was not associated with poor prognosis in our pediatric MS patients. With relation to gender, as in other previous studies, the usual predominance of females among patients with MS tends to be absent at earlier ages. In the subgroup of patients aged less than 12 years, there was a slight predominance of boys, whereas in the older group the female-to-male ratio was even higher than in the group of adults. These data corroborate the hypothesis that male sex hormones serve as a protective factor, whereas estrogens act on the immunopathologic mechanisms of MS, increasing predisposition to the disease after puberty.[26]

The present cohort consisted exclusively of the initial RRMS clinical form of the disease, with no cases of primary progressive MS, as previously described.[27] In pediatric MS, the predominant inflammatory characteristic may be reflected in the greater number of attacks, the shorter interval of time between attacks, albeit with a greater capacity for recovery because of a greater neuronal reserve, and the lesser participation of degenerative mechanisms.[1] Few studies have qualitatively analyzed recovery from initial attacks in pediatric MS. Here, recovery from the first attack was better in the pediatric MS population compared with the adults. Poorer results were found in a study of pediatric MS published when diagnostic and therapeutic resources were even more limited.[22] In more recent studies, younger patients in general recovered well from attacks, at least in the initial phases.[28–30]

The polysymptomatic here observed was similar to rates described by other authors.[9,19,24,31,32] Among pediatric MS patients, pyramidal signs were the most common, followed by sensory signs. In Latin American and Middle Eastern studies, motor involvement was also the most common,[7,21,33] whereas other studies found sensory signs to be the most common.[6,22,24] Stratification by gender shows that girls have more sensory signs at onset.

Investigators have been trying to identify a clinical phenotype or central nervous system topography preferentially affected in pediatric MS patients; however, data have been conflicting and no definitive conclusion can be drawn.[6,7,9,19–22,24,33,34]

Although the literature documents a greater number of attacks and a shorter interval between them during the initial phases of pediatric MS, this does not translate to greater long-term disability.[35] In studies in which disability and conversion to SPMS were compared between pediatric and adult MS cases, the time elapsed until the end points were longer in the pediatric MS group.[7,9] In our study, there was no difference in this respect between pediatric and adult MS. This divergent result from the literature should be analyzed in the light of the limitations of our study. Follow-up data were missing for a large number of patients and the retrospective analysis of the initial attack, especially in patients with a long follow-up period, could not always be recovered. A prospective study is needed.

Half the patients both in pediatric and adult MS groups reached EDSS 3 and only 10% of the pediatric cases reached EDSS 6, which represnets half of the rate found in the adults. In the study conducted by Boiko et al.,[6] 58% and 40% of the pediatric MS patients reached, respectively, EDSS 3 and EDSS 6. Like other studies,[6,7] time to EDSS 3 was greater in pediatric than in adult MS patients, but EDSS 3 was reached at earlier age in the pediatric form.

Although, the pediatric patients of the present study also took longer to reach EDSS 6 compared with adults; the age at the time of reaching this end point was similar. More robust cohorts consisting of more than 100 pediatric cases of MS permitted analysis of more severe end points, which are generally less common.[5,8] In those studies, pediatric MS patients took longer and reached greater degrees of disability (EDSS 6 to 8) at a younger age than the adults.

Our pediatric MS patients were 2.5 times less likely to have converted to SPMS compared with the adults, values close to those already reported (14% versus 24%).[9] Conversely, Boiko et al.[6] described a higher conversion to SPMS; and El-Salem and Khader[7] did not find differences between the groups.

The occurrence of benign MS remained questionable.[16] Recent studies have shown that even with the preservation of motor functions, there could be cognitive decline, fatigue, and depression.[36] The frequency of benign MS reported is extremely variable (from 5% to 64%).[37–39] The occurrence of benign MS among pediatric MS patients was 22.4% higher than in adults, and no pediatric MS patient fulfilled the criteria for malignant MS. Nevertheless, despite the low frequency of benign disease—based on the EDSS scale and disease duration—formal cognitive tests were not applied in our pediatric cohort. Because of this, we could not evaluate the benignity of the disease. Although in pediatric MS irreversible neurological damage may take longer to occur, patients reach severe disability at a young age when professional performance and social and family life are in full development, which does not in fact characterize a “benign” condition.

In addition to the small number of pediatric MS patients who had converted to SPMS in the present cohort, the time until this end point was longer compared with the adult group and also in relation to the times described in other studies. Our pediatric patients reached SPMS after 39 years of the disease, a time similar to that in

a previous study.[7] Other authors have reported a faster course until conversion to SPMS.[5,6,8,9]

In most of the published studies, pediatric MS patients converted to SPMS at a significantly younger age than adults with MS.[5,8,9] But in our study, there was no statistically significant difference between the age of the pediatric and adult MS patients at the time of conversion. One possible explanation for the differences in relation to the time until EDSS 6 and SPMS would be the physiopathology of the disability. Milder EDSS stages are generally the result of residual deficits from attacks and are more closely related to acute inflammatory aggression, because in the later phases of the disease, the degenerative process and axonal loss, which are closely linked to more advanced age, are prevalent. The fewer cases in this cohort, explained by the low prevalence of the disease in this setting, and also the few cases with more advanced disability and conversion to SPMS represent a limitation of this study. Another limitation of this study was the precision of the outcome measure; EDSS scores have an inherent variability, were performed by multiple examiners, and were obtained retrospectively from hospital charts.

In our mixed population and in caucasian populations, the pediatric patients represent fewer than 10% of the cases and, despite an early onset, these individuals take longer to become physically incapacitated and evolve with secondary progression.

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