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PEDIATRIC MULTIPLE SCLEROSIS

Analysis of clinical and epidemiological aspects according to National MS Society Consensus 2007

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Abstract – Objective: To describe the epidemiological and clinical characteristics of child/adolescence multiple sclerosis (MS). **Method:** According to a descriptive, cohort study, with comparison of groups, data of 31 cases of child/adolescent MS, diagnosed at State Reference Center for Demyelinating Diseases – Hospital da Restauração, Recife, Pernambuco, Brazil, from 1987 to July 2007, were analyzed. The variables were: sex, initial symptoms, time for diagnosis, time of disease onset (early childhood, later childhood and adolescence), time of follow-up, number of relapses, relapses index and disability. Using SPSS software, version 13.0, t Student and Mann-Whitney tests were performed, with significance level of 0.05. **Results:** There were 3 (9.7%) cases of early childhood MS, 9 (29%), of late childhood MS, and 19 (61.3%), of adolescence MS. The general sex rate female: male was 1.8:1, varying according to age of onset. The predominant deficits were motor (12; 38.7%) and brainstem/cerebellum (7; 22.5%) especially on subsequent relapses of relapsing/remitting form. Time for diagnosis and average relapses index were higher in early childhood than in adolescence class (p=0.049 and p=0.028, respectively). Disability was higher for primary and secondary MS, as well as for early childhood. **Conclusion:** Early childhood MS presents proper and different characteristics from adults, consisting in a difficult diagnosis that demands aid of expert neurologist on MS.

KEY WORDS: multiple sclerosis, classification, epidemiology, diagnose techniques and procedure.

Esclerose múltipla pediátrica: análise de aspectos clínicos e epidemiológicos de acordo com o Consenso de 2007 da Sociedade Americana de Esclerose Múltipla

Resumo – Objetivo: Descrever características epidemiológicas e clínicas de casos de esclerose múltipla (EM) de início precoce. **Método:** Em estudo descritivo, prospectivo, tipo coorte, com comparação de grupos, foram analisados 31 portadores de EM de início precoce, diagnosticados no Centro Estadual de Referência para Atenção a Pacientes Portadores de Doenças Desmielinizantes do Hospital da Restauração, Recife, Pernambuco, entre 1987 e julho de 2007. As classes ao primeiro surto foram: infantil precoce, infantil tardia e juvenil, e as variáveis: sexo; sintomas iniciais; tempo para diagnóstico, de doença e de seguimento; número de surtos, índice de recidivas e EDSS. Com o programa SPSS, versão 13.0, foram utilizados os testes t de Student e Mann-Whitney com nível de significância de 0,05. **Resultados:** Foram observados 3 (9,7%) casos de EM infantil precoce, 9 (29%), infantil tardia, e 19 (61,3%), juvenil. A razão geral de sexo feminino:masculino igualou-se a 1,8:1, variando segundo idade de início. Predominou comprometimento motor (12; 38,7%) e de tronco encefálico ou cerebelo (7; 22,5%), especialmente nos surtos subseqüentes da forma surto-remissão. O tempo para diagnóstico e o índice médio de recidivas foram maiores na infantil precoce que na juvenil (p=0,049 e p=0,028, respectivamente. O grau de incapacidade foi maior nas formas primária e secundária progressiva, assim como na infantil precoce. **Conclusão:** A EM na infância e adolescência apresenta características próprias, diferentes daquelas do adulto, constituindo-se em diagnóstico difícil, que exige auxílio de especialista em EM.

PALAVRAS-CHAVE: esclerose múltipla, classificação, epidemiologia, técnicas de diagnóstico e procedimento.

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The incidence of multiple sclerosis (MS) is higher among young adults and people of middle age. Disease onset in elderly has been well documented, but in childhood it was questioned during many years. Although the MS in childhood is well described, and the number of cases is increasing, the disease still raises doubts on frequency, nature and evolution[1]. Epidemiological studies identified that approximately 2% to 5% of patients present first symptoms before the age of 16, that is, in childhood or in adolescence[2]. The National MS Society Consensus considered that although pediatricians and child/pediatric neurologists are more alert to the possibility of MS in this age group, they are not able to establish this diagnosis due to the difficulties regarding the mimicry with diseases that are frequent in this population[2]. Diagnosis and treatment of childhood MS constitutes a challenge. Among the differential diagnosis with MS in paediatric group, are: acute disseminated encephalomyelitis, leucodystrophy and metabolic disorders and many other diseases. Regarding to acute disseminated encephalomyelitis, its first symptoms mimicries those of MS in a way that sometimes, in the first episode, it may be impossible to distinguish these two nosologic entities[2,3].

The most obvious consequence of this difficulty is the delay in MS identification and, therefore, in the institution of therapy, increasing the risk of disability. The studies of MS with paediatric patients are recent, when compared to those involving young patients or elderly. It means that paediatricians and child/pediatric neurologists, searching for better assistance to their patients, started to consult neurologists of the Reference Hospital to discuss the diagnosis, which was a challenge. Looking for evidence based on medicine on childhood MS, it was possible to detect lack of studies and, in addition, analysis limited to small samples. Only four studies were published between 1958 and 2005 with more than a hundred cases, all of them at geographic regions of high MS prevalence[4].

With this motivation, the aim of this study is to describe clinical and epidemiological characteristics of 31 cases of MS, diagnosed before 18 years old, with follow-up until 2007.

METHOD

According to a descriptive, cohort study, with comparison of groups, 31 patients with child/adolescence MS (median age equal to 11.68±4.71, varying from 1–18 incomplete years), among 310 MS patients, diagnosed and followed at the State Reference Centre for Demyelinating Diseases of Hospital da Restauração (CRAPPDD-HR), Recife, Pernambuco, Brazil, from 1987 to July 2007, were analyzed. No exclusion criteria were adopted, because the patients had been subjected to CRAPPDD-HR's routine, which included magnetic resonance image (MRI), cerebral spinal fluid (CSF) examination, visual evoked potential and other complementary tests to exclude diseases that could mimicry MS, during follow-up.

The identification of clinical forms followed McDonald criteria[5]. Study groups for comparison were classified by age at first relapse, as: early childhood, late childhood and adolescence, corresponding from zero to five years, six to 10 years and 11 to 18 incomplete years, respectively[6].

The analyzed variables were: sex, age at first symptoms attributed to MS, first symptoms, time elapsed between the first symptoms and diagnosis, duration of disease, duration of follow-up at CRAPPDD-HR, number of relapses, relapses index and assessment by Expanded Disability Status Scale (EDSS)[7]. The relapse rate was calculated by the ratio between number of relapses and duration of disease, expressed in years or fractions.

First symptoms of 2 (6.4%) patients were based on their and caregivers descriptions, and 29 (93.6%), on medical registrations since first symptoms.

Data for this research were obtained within CRAPPDD-HR computerized registration of clinical data, therapeutic and supplementary tests, generated in each quarterly consultation to MS patients.

Data were analyzed with Statistical Package for Social Sciences (SPSS) software, version 13.0, using absolute and relative frequencies distribution, mean, standard deviation and amplitude. Mann-Whitney test and t Student test were performed for comparison of means, in a significance level of 0.05, except for relapses number. Due to the identification of a male patient, with late childhood MS, who presented 46 relapses, one considered the median of relapses number for this analysis.

This study includes the CRAPPDD-HR Research Program on MS, registered at Research Ethics Committee involving human beings from Hospital da Restauração. All patients or caregivers signed a free informed consent term, at the first consult, after receiving information on the objectives of the CRAPPDD-HR Research Program on MS.

RESULTS

Among 31 analyzed patients, early symptoms attributed to MS were identified between zero and five years old (early childhood class) for 3 (9.7%) patients, between six and 10 years old (late childhood class) on 9 (29%), and from 11 to 17 years old (adolescence class) for 19 (61.3%).

The female:male ratio was equal to 1.8:1, with change following the classification as to the age at first relapse to: 3:0, 0.8:1 and 2.2:1, respectively for early childhood, late childhood and adolescence classes (Table 1).

Among initial symptoms, there was a predominance of motor impairment (12 cases, 38.7%) and brainstem/cerebellum (7 cases; 22.5%). A predominance of motor change was detected, regardless to age at first symptoms, with absence of optic neuritis and impairment of brainstem/cerebellum, in early childhood class. In late childhood, the most frequent symptoms were also motor or brainstem/

Table 1. Distribution of epidemiologic and clinical variables of 31 patients with child/adolescent MS – CRAPPDD-HR – Recife – Pernambuco – Brazil – 1987-2007.

Variables	Classification according to age of first relapse							
	Early childhood		Late childhood		Adolescence		Total	
	n	%	n	%	n	%	n	%
Gender								
Female	3	100	4	44.4	13	68.4	20	64.5
Male	–	–	5	55.6	6	31.6	11	35.5
Ratio female:male	3:0	–	0.8:1		2.2:1		1.8:1	
Initial symptoms								
Motor	2	66.7	4	44.4	6	31.6	12	38.7
Optic neuritis	–	–	1	11.1	5	26.4	6	19.4
Sensorial	1	33.3	1	11.1	4	21.0	6	19.4
Brainstem/cerebellum	–	–	3	33.4	4	21.0	7	22.5
Clinical forms and conversions								
CIS of brainstem to MS CD	–	–	1	11.1	–	–	1	3.2
RRMS	2	66.7	7	77.8	16	84.2	25	80.6
SPMS	–	–	–	–	2	10.5	2	6.5
RR SPMS	–	–	1	11.1	1	5.3	2	6.5
PPMS	1	33.3	–	–	–	–	1	3.2

CIS of brainstem to CDMS, clinically isolated syndrome of brainstem converted to clinically defined MS; RRMS, relapsing/remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; RR SPMS, relapsing/remitting multiple sclerosis converted to secondary progressive; PPMS, primary progressive multiple sclerosis.

cerebellum, different from adolescence class, in which optic neuritis and sensory symptoms were frequent (Table 1). None of patients or previous medical registrations referred conscience level impairment or seizures as initial symptoms.

Among 25 patients (80.6%, with relapsing/remitting form), 11 (44%) had association of motor symptoms and brainstem/cerebellum in subsequent relapses. Other symptoms included: headache (3 patients; 12%); paresthesia (1 case; 4%) and bladder or bowel dysfunctions (1 case; 4%).

Concerning to clinical forms and clinically isolated syndrome conversion to clinically defined MS, based on McDonald criteria[5], one case of late childhood MS had brainstem involvement as inaugural symptom. There was a predominance of relapsing/remitting form, regardless to age of onset. It must be emphasized that two cases of adolescence MS, on diagnose at CRAPPDD-HR, already presented secondary progressive form, while two other patients, one in late childhood class and another on adolescence, had the first diagnose as relapsing/remitting form and developed secondary progressive, during the clinical follow-up at this Centre. In early childhood class, there was one case of primary progressive form (Table 1).

Table 2 exposes data of patients follow-up. The differences in age of onset and disease duration were not considered, because they derived from the method used in this study to establish classes.

The median follow-up time was higher for adolescence class, when compared to the others, but the differences were not significant (p=0.386, p=0.168 and p=0.370, respectively for the differences between early and late childhood class, early childhood and adolescence and late childhood and adolescence) (Table 2).

The average time between first symptoms and MS definitive diagnosis was higher for early childhood class (25.66±8.62 years), decreasing on late childhood class (14.66±18.41 years) and adolescence class (4.89±3.57 years). Despite the differences among these averages, there was significance exclusively between early childhood and adolescence classes (p=0.049).

Comparing the three classes according to relapses, the adolescence class showed the lowest number. There was no significant difference on median number of relapses between classes, compared two by two (Table 2).

The relapses index average varied according to age of onset. It was lower for early childhood class (0.187±0.192 relapses/year), increased on late childhood (0.717±0.518 relapses/year), and reduced to 0.433±0.243 relapses/year on adolescence class. There was a significant difference exclusively between early childhood and adolescence classes (p=0.028) (Table 2).

Disability evolution, determined by the difference from EDSS of first consultation and EDSS of the last one, showed that early childhood class was more disabled than late childhood and adolescence, but the differences were not significant. Late childhood class was similar to adolescence, in this aspect (Table 2).

Table 2. Distribution of clinical variables of 31 patients with child/adolescent MS, related to time – CRAPPDD-HR – Recife – Pernambuco – Brazil – 1987-2007.

Variables related to time	Classification according to age of onset			Total	p value[2]
	Early childhood	Late childhood	Adolescence		
Age of onset (years)					–
Mean±sd[1]	3.33±2.08	7.44±1.33	15±1.86	11.68±4.71	
Minimum	1	6	11	1	
Maximum	5	10	17	17	
Time of disease (years)					–
Mean±sd[1]	28.33±8.50	18.67±20.12	9.84±4.21	14.19±12.71	
Minimum	22	1	2	1	
Maximum	38	52	18	52	
Time of follow-up (years)					0.386[3]
Mean±sd[1]	2.67±1.53	4.00±2.34	4.94±2.65	4.45±2.52	0.168[4]
Minimum	1	1	1	1	0.370[5]
Maximum	4	9	12	12	
Time for diagnose (years)					0.352[3]
Mean±sd[1]	25.67±8.62	14.67±18.42	4.89±3.57	9.74±12.27	0.049[4]
Minimum	18	0	1	0	0.152[5]
Maximum	35	48	12	48	
Number of relapses					0.641[3]
Median	3.0	4.0	3.0	3.0	0.742[4]
Q1–Q3	1.0–10.0	2.5–7.5	3.0–4.0	3.0–5.0	0.308[5]
Mean±sd[1]	4.67±4.73	8.78±14.14	3.63±1.61	5.23±7.86	
Minimum	1	1	2	1	
Maximum	10	46	8	46	
Relapse index (relapses/year)					0.028[3]
Mean±sd[1]	0.187±0.192	0.717±0.518	0.433±0.243	0.491±0.369	0.114[4]
Minimum	0.026	0.082	0.200	0.026	0.149[5]
Maximum	0.400	1.533	1.000	1.533	
Initial EDSS					0.562[3]
Mean±sd[1]	3.5±4.0	2.0±1.0	1.5±2.0	2.0±2.0	0.474[4]
Minimum	1.0	0.0	0.0	0.0	0.466[5]
Maximum	8.0	3.0	6.5	8.0	
EDSS at last visit					0.510[3]
Mean±sd[1]	3.0±4.5	2.0±2.5	2.5±3.0	2.5±3.0	0.757[4]
Minimum	0.0	0.0	0.0	0.0	0.517[5]
Maximum	8.0	7.0	8.5	8.5	

[1]mean±sd, mean±standard deviation; [2]p values of t Student test, analyzed at a significance level of 0.05, right tailed; [3]mean differences of early childhood and late childhood; [4]mean differences of early childhood and adolescence; [5]mean differences of late childhood and adolescence.

Disability grade was not related to class of onset, but to clinical form, restricting the greatest deterioration to primary progressive and secondary progressive forms.

DISCUSSION

Whereas CRAPPDD-HR had 310 MS patients registered and in attendance at the time of this research, early childhood, late childhood and adolescence classes accounted for 1.0%, 2.9% and 6.1% of patients, respectively, proving that the MS is rare in pediatric age. In France[8], in 2001, the percentage ranged from 0.4% to 5.6% of cases, of which 0.12% to 0.45%, before the age of ten. However, in 2004[9], in a cohort study, involving 168 children under 18 years old, with MS, the incidence ranged from 0.2% to 0.7% before 10 years old and 2.7% to 4.4 %, before the age of sixteen.

For early childhood class diagnosis, there was a minimum delay of more than 10 years, compared to adolescence class or even to late childhood and this result corroborated the statements of other authors[2,3] on the difficulty and challenge on diagnosing childhood and adolescence MS.

A single relapse is an event that requires an extensive investigation in adults. In children, this work-up should be even more meticulous due to atypical symptoms and a diversity of differential diagnosis to be signed, confusing child/pediatric neurologist, because MS diagnosis is an exclusion condition.

The possibility of MS in paediatric age is based on clinical, laboratory and image data, with which temporal and spatial evolution of lesions are identified, but one must consider that central nervous system (CNS) maturate process may be a confounding factor and neuroimaging criteria are not validated for this population[10].

In this study, it was observed that female:male ratio was lower than the adult ratio, found in the same centre, equal to 4.1:1[11]. Peña et al.[10], referring to paediatric age, reported ratio equal to 1:1, when symptoms began before ten years old, and 3:1, when after 12 years old. However, in this study, this result should be considered with caution due to the small number of cases, especially in early childhood class. Such comments are likely to change in greater series.

The sex ratio difference between adolescence and childhood suggests the influence of puberty hormonal factors on MS immune mechanism[8,10,12].

As for initial typical signs and symptoms, the predominance of motor impairment in all classes was lower than the one from Mikaeloff et al.[13] (74%, 75% and 66% for early, late childhood and adolescence classes, respectively). The more frequent initial atypical signs and symptoms, in childhood, may include headache, nausea, vomiting, fever, dizziness, conscious alteration, motor or sensory hemisyndromes and brainstem/cerebellum dysfunctions. This combination may suggest acute disseminated encephalomyelitis or meningoencephalitis diagnosis, but there is an important difference to be considered: 48.9% of children (or even 70%, in early childhood class[13]) have poly-symptomatic presentation against 12% of adults[14]. In our experience, the signs of motor or sensorial hemi-syndromes and brainstem/cerebellum dysfunctions can be frequent in this age group, but they are atypical, therefore their presence does not permit MS certain diagnosis.

Concerning to clinical forms, the most unusual was primary progressive, affecting 3.2% of cases. In adults, primary progressive and progressive with relapses forms represent 20% of cases, whereas among those under 18 years old is less than 7%[15] (or even equal to 2.6%), probably because inflammatory reactions predominate in children and adolescents[12].

Although most children and adolescents with MS relapsing/remitting form maintain mild disability, one should highlight the unpredictability of MS evolution. In four cases of secondary progressive form, there was fast impairment in less than 10 years, from mild disability (2 cases with EDSS equal to 3.0) to moderate (one case with EDSS equal to 4.0) or severe (one case with EDSS equal to 6.5).

Identifying that early childhood presented a relapse index significantly lower than late childhood class, we hypothesized that, at least in part, the fact is due to the immaturity of immune system, yet unable to respond proportionately to the aggression that MS represents to central nervous system. The difficulty of lymphocyte profiles to retaining immune information from protein changes, associated to the disease onset before the end of myelinization, may explain minor structural expression of lesions, in appearance, size and distribution[16]. Some authors also state that changes on MRI in that class are more atypical and the lesions are more confluent[10]. This hypothesis was not supported by other researches, so the statement should be taken as an attempt to explain the findings of this study, which may be confirmed by typing lymphocytes in CSF or peripheral blood.

Childhood MS neuroimaging characteristics include: involvement of deep gray matter, large lesions (especially in early childhood class) and extensive spinal cord lesions (myelitis). In adults, these spinal cord lesions are small. Moreover, in children's first relapse, MRI has low sensitivity (37%), which may hinder further the diagnostic[6].

As relapse rate is the result of the ratio between relapse number and time of disease, we could assume that the lowest index of early childhood class would derive from the greatest time of illness. If the logic was that, then late childhood class should present relapse index minor than the adolescence class, for the same reason, but this result was not found in the present study. Although late childhood class has greater disease duration, it showed higher relapse rate. This exercise of clinical reasoning may be criticized, but it has its value since the current knowledge about childhood MS is still scarce and any contribution can be an invitation to new researches.

Work at the Reference Centre for Demyelinating Diseases is filled with bonuses and sadness, especially when patients are diagnosed with multiple sclerosis. This research brings a gratifying data result. Patients, once diagnosed in CRAPPDD-HR, rarely do not join quarterly follow-up. This may be the explanation for a non significant disability evolution between initial assessment and the last visit, within a time interval equal to 12 years. However, it would be reckless to attribute lack of significance between these EDSS only to the activities of CRAPPDD-HR. One can also assume that MS course, beginning in childhood or in adolescence, may differ from that started

in adult, an answer that can only be achieved in the future, with a greater follow-up than this one now presented.

Among the questions related to MS childhood or youth, is the disease course. The involvement of CNS on these ages has been a worry for neurologists and paediatricians due to the risk of cognitive impairment, given CNS immaturity. Against this argument, we must oppose the CNS plasticity, characteristic of younger ages that can act as a protective factor for these deficits. This reflection calls to investigate temporal evolution of cognitive function of patients who begin MS earlier.

We found that childhood and adolescence MS presents different characteristics from those usually identified in adults, becoming a difficult and laborious diagnostic, which requires knowledge of diseases that can mimicry MS. This fact shows the importance of the Reference Centre for Demyelinating Diseases, because these professionals have clinical experience, allied to external evidences, published or debated in scientific meetings, which improve critical sense and facilitate particularly the challenge of diagnosing. This was a warning of Greenhalgh[17] view on the importance of evidence based medicine as the union of clinical experience to constant study of scientific publications. The article points out, to paediatricians and child/pediatric neurologists, the importance of being alert to the possibility of a MS diagnosis, seeking aid from experts on MS, because to confirm and to treat MS in childhood is a challenge.

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