Descriptive profile of multiple sclerosis starting until the age of 16 in the reference center of the state of São Paulo

Perfil descritivo de esclerose múltipla com início até os 16 anos nos pacientes de um centro de referência do estado de São Paulo

Perfil descriptivo de esclerosis múltiple con inicio hasta los 16 años de edad en los pacientes del centro de referencia del litoral de la provincia de são paulo

Yára Dadalti Fragoso[1], Joseph Bruno B. Brooks[2], Tiago Martins dos S. Leal[3]

ABSTRACT

Objective: To describe the profile of patients with multiple sclerosis starting at or before the age of 16 in the coastal region of the state of São Paulo, Brazil.

Cases description: Retrospective analysis of the characteristics of patients who presented the initial episode of multiple sclerosis at or before the age of 16. There were nine girls and four boys in this situation (7.1% of the total population with multiple sclerosis in such area). The average age at diagnosis was 13.9 years old (ranging from 8 to 16), and the current average age is 19.5 years old (12 to 28). The initial presentation was: ataxia (four cases), optic neuritis (two), cortical motor (two), cortical sensitive (two), dystonia (two), and spinal cord multiple sclerosis (one). All patients started with the relapsing-remitting form of the disease, and two of them now present a secondary progressive course.

Comments: Multiple sclerosis with onset at or before the age of 16 needs to be properly registered and discussed among pediatricians, neurologists, and neuropediatricians. Very few doctors have good knowledge about this condition, and delay in diagnosing and treating may have devastating consequences for the future of these children and adolescents.

Key-words: multiple sclerosis; children; adolescents; nervous system.

RESUMO

Objetivo: Descrever o perfil de pacientes com esclerose múltipla iniciada até os 16 anos de idade no litoral do estado de São Paulo, Brasil.

Descrição dos casos: Análise retrospectiva das características dos pacientes que tiveram o episódio inicial de esclerose múltipla até os 16 anos. Nesta situação encontravam-se nove meninas e quatro meninos (7,1% da população total de esclerose múltipla da região). A idade média por ocasião do diagnóstico foi de 13,9 anos (variação entre 8 e 16), sendo a média atual de 19,5 anos (12 a 28). A apresentação inicial da doença foi: ataxia (quatro casos), neurite óptica (dois), motora cortical (dois), sensitiva cortical (dois), distonia (dois) e esclerose múltipla medular (um). Todos os pacientes iniciaram com a forma remitente-recorrente da esclerose múltipla e dois deles, atualmente, apresentam a forma progressiva secundária.

Comentários: A esclerose múltipla com início até os 16 anos precisa ser adequadamente registrada e discutida entre pediatras, neurologistas e neuropediatras. Poucos médicos têm bom conhecimento desta condição e a demora no diagnóstico e no tratamento pode ter consequências devastadoras para essas crianças e adolescentes.

Palavras-chave: esclerose múltipla; crianças; adolescentes; sistema nervoso.

Instituição: Departamento de Neurologia, Faculdade de Medicina, Universidade Metropolitana de Santos (Unimes), Santos, SP, Brasil
[1]Mestre e Doutora em Medicina pela Universidade de Aberdeen; Professora Titular de Neurologia da Unimes, Santos, SP, Brasil
[2]Neurologista pela Academia Brasileira de Neurologia; Médico Especialista do Centro de Referência em Esclerose Múltipla da DRS-IV, Santos, SP, Brasil
[3]Pediatra no Departamento de Neuropediatria do Hospital Guilherme Álvaro; Médico do Centro de Referência em Esclerose Múltipla da DRS-IV, Santos, SP, Brasil

Endereço para correspondência:
Yára Dadalti Fragoso
Rua da Constituição, 374 – Vila Nova
CEP 11015-470 – Santos/SP
E-mail: yara@bsnet.com.br

RESUMEN

Objetivo: Describir el perfil de los pacientes con esclerosis múltiple iniciada hasta los 16 años de edad, en la región del litoral de la provincia de São Paulo, Brasil.

Descripción de los casos: Análisis retrospectivo, a partir de los registros médicos, de las características de los pacientes que tuvieron episodio inicial de esclerosis multiple hasta los 16 años de edad. Fueron nueve muchachas y cuatro muchachos en esta situación (7,1% de la población total de esclerosis multiple en la región). El promedio de edad en el momento del diagnóstico fue de 13,9 años (variación 8–16), siendo el promedio de edad actual de 19,5 años (12–28). La presentación inicial de la enfermedad fue ataxia (4 casos), neuritis óptica (2 casos), motora cortical (2 casos), sensitiva cortical (2 casos), distonía (2 casos) y esclerosis multiple medular (1 caso). Todos los pacientes iniciaron con la forma remitente-recurrente de la esclerosis multiple y dos de ellos ahora presentan la forma progresiva secundaria.

Comentarios: esclerosis multiple con inicio hasta los 16 años de edad necesita ser adecuadamente registrada y discutida entre pediatras, neurólogos y neuropediatras. Pocos médicos tienen buen conocimiento de esta condición y la demora en el diagnóstico y tratamiento pueden tener consecuencias devastadoras para estos niños y adolescentes.

Palabras clave: esclerosis múltiple; niños; adolescentes; sistema nervioso.

Introduction

Multiple sclerosis (MS) is being diagnosed in children and adolescents with ever-increasing frequency[1]. However, knowledge about the subject has not grown at the same rate and there is a lack of studies describing the profile of MS cases in childhood and adolescence. There have been no clinical trials of drugs that modify the disease conducted specifically with children and so observations are generally based on retrospective reviews of case series[2]. To date, the effects of pharmacological treatment of MS have only been adequately investigated in the context of adult MS. Algorithms for diagnosis and treatment of children with MS are only now beginning to be developed by the majority of research teams[3-6].

In Brazil, the general recommendation is to follow the guidelines for diagnosis and treatment that have been proposed by groups in other countries, since only one study of early-onset MS conducted in Brazil has been published[7]. With the exception of that study, which was conducted in the Northeast of Brazil, little is known about the disease in Brazilian children and adolescents in terms of clinical presentation, clinical course, resulting disability, patients' compliance with treatment or how it is managed. The objective of this study is to contribute to knowledge about MS with onset by 16 years, presenting data from 13 patients currently being treated at a specialist MS clinic in coastal São Paulo state, Brazil.

Case descriptions

This study was approved by the Ethics Committee at the Universidade Metropolitana de Santos, SP, under protocol number 017/11.

There are 182 MS patients registered at the MS referral center serving the coastal region of São Paulo state and 13 of them had onset by 16 years of age. Data on these patients were obtained from medical records and then each patient was invited to attend an extra consultation in case there was a need to request details that were not provided in medical records. Disability was assessed using the Expanded Disability Status Scale (EDSS)[8]. This is a classic measure used to assess disability in MS, varying from zero (normal) to ten (death from MS).

The clinical forms of the disease have been classified by Lublin & Reingold[9] as relapsing remitting MS (RRMS), secondary progressive MS (SPMS) or primary progressive MS (EMPP). The majority of MS cases have onset as the RR form[9] and progress to a secondary form over the course of several years. The RRMS form is characterized by demyelination attacks, indicative that the disease is active.

Drugs that have been shown to modify the course of the disease for these patients include glatiramer acetate (Copaxone®) and interferon beta (1b subcutaneous [Betaferon®], 1a subcutaneous [Rebif®], or 1a intramuscular [Avonex®]). These medications are provided to all MS patients living in Brazil by the country's Ministry of Health through its program for provision of special-use medications and high-cost medications.

Data were extracted by the authors and input to an Excel spreadsheet before conducting what is an essentially descriptive analysis of the findings. Where statistical analyses proved necessary, Student's t test and tests of correlation were applied, respecting a 95% confidence interval and adopting $p \leq 0.05$ as the cutoff for significance.

The results are summarized in Table 1. There were nine girls and four boys with diagnoses of MS confirmed by the age of 16. Mean age at diagnosis was 13.9 years (range: 8–16). Mean age at the time of interview was 19.5 years

Table 1 - Demographic and clinical data on 13 patients with multiple sclerosis whose disease started at or before the age of 16 years. Disability was assessed using scores from the expanded disability status scale (EDSS)[8], ranging from zero (normal) to 10 (death due to the disease)

Sex	Age at diagnosis	Current age	Initial clinical presentation	disability degree at diagnosis	Number of attacks	Current disability degree	Compliant with treatment
M	8	12	Ataxia	0	7	5	Yes
F	12	13	Cortical stimuli-sensitive, multifocal	0	3	0	Yes
F	13	14	Dystonia	0	2	0	Yes
M	14	23	Cortical motor, multifocal	0	7	4.5	Não
F	14	15	Dystonia	0	3	0	Yes
F	14	24	Cortical motor, multifocal	0	3	1	Yes
F	14	24	Ataxia	1	8	8	Não
M	14	23	Spinal cord	6	2	2.5	Yes
F	14	15	Ataxia	0	2	0	Yes
M	15	23	Cortical stimuli-sensitive	0	3	1	Não
F	15	17	Optic neuritis	0	4	2	Yes
F	16	22	Optic neuritis	0	12	4	Yes
F	16	28	Ataxia	0	5	4	Yes

M: male; F: female

(12–28). The most common initial presentations were ataxia (4 cases), optic neuritis (2 cases), motor cortical manifestations (2 cases), stimuli-sensitive cortical manifestations (2 cases), dystonia (2 cases) and spinal cord damage (1 case). All patients initially presented with RRMS and at the time of writing two patients had developed progressive forms of the disease, both classified as having SPMS.

Mean EDSS score at the time of diagnosis was 0.54 and after 6 years' follow-up mean EDSS was 2.46. Over this period, patients suffered a mean of 4.7 attacks. Nine patients had good compliance with treatment. Patients who had always been treated by the same physician, patients who had been treated with one drug and patients who had good compliance with treatment had better clinical progression. Initial mean EDSS among these patients was 1.2 and after a mean follow-up period of around 6 years, their mean EDSS was 0.9. Patients who changed physicians and drugs more than once had a mean EDSS of 4.5 at the time of writing, compared with their initial score of 0.5. One case in particular had low treatment compliance, used all available treatments (both in Brazil and overseas) and had markedly worse progress (initial EDSS was 0 and current EDSS is 8, after ten years of MS). Patients who did not comply with treatment and changed physician were 1.92 times more likely to have unfavorable clinical progression, over the period studied (95%CI 0.39–9.60).

Discussion

The prevalence of MS in the city of Santos, SP, has been estimated at 15.54/100,000 inhabitants[10]. Although this calculation only applies to the city of Santos itself and not to neighboring areas, it is not expected that regional prevalence differs greatly from this figure. The number of diagnosed cases currently registered at the MS referral center for the coastal region of São Paulo state is 182 patients, 7.1% of whom were diagnosed by the age of 16. This percentage of early-onset MS cases (before 18) is comparable with the figure of 10% reported by Tenenbaum in a recent review[5], to the 3–10% reported by Ghezzi[4] and to the 10% observed in Recife, Brazil[7]. This means that, if the prevalence observed in the cities of Santos and Recife were to be reproduced throughout Brazil, there would be from 2,000 to 3,000 children with MS in our country. This alone is sufficient justification for creating national guidelines for the diagnosis and treatment of these children and adolescents.

It is notable that although the prevalence of MS in the overall Brazilian population is relatively low compared with other countries, there appears to be the same percentage of very young patients.

The ratio of girls to boys in our population was 1.5:1, which is similar to a sample described by Ferreira[7]. On the other hand, there was a clear predominance of cerebral symptoms among the initial MS presentations of the children and adolescents in

this study (30.7%), whereas Ferreira observed a predominance of motor symptoms at the point the disease took hold (38.7%).

Differential diagnosis of MS at this early age is different from its equivalent for older people and the current recommendations for precise diagnosis are a revised version of the McDonald criteria and were published in 2010[11]. Whether or not these criteria are entirely applicable in Brazil is a question that has yet to be answered. Once a diagnosis has been made, there is no reason for delaying treatment[5]. This study has provided a new perspective, since patients who maintained the same physician and the same medication enjoyed better results.

It could be argued that the better results in these cases were the result of less aggressive forms of the disease. It is possible that patients who suffer more frequent attacks tend to consult other physicians and change medications hoping to achieve better results. However, the number of attacks was similar for the two groups ($p=0.27$). It is necessary to consider a larger number of cases before drawing conclusions, but it does appear that early diagnosis and treatment and persevering with both physician and treatment lead to better results among these patients. This point may be particularly important when it is the parents of children and adolescents with MS who evaluate treatment success, since they may have unrealistic expectations.

Early diagnosis and treatment of MS are equally important for adults, children and adolescents[12]. This is a disease with a clinical course of progressive disability and the drugs available to treat it are only capable of delaying the disability: they cannot cure the disease. Furthermore, while they are more evident with newer therapeutic agents, both the older drugs and the newer ones used to treat MS have adverse events profiles that should be taken into account [13]. Despite the possibility discussed earlier of there being thousands of children with MS in Brazil, our country does not have specific treatment recommendations. This failure is not limited to Brazil; there are very few parts of the world that do have specific guidelines for pediatric MS[2,14] at a time when new and powerful drugs are being released onto the market. In truth, Brazil does not yet have a database for recording cases from which we could learn more by monitoring our child MS patients.

Appropriate treatment and good compliance[15] are crucial to changing the devastating course of MS and improving patients' quality of life[16,17]. Unless pediatricians are aware of the possibility of MS with onset during childhood and adolescence they cannot not be in a position to suspect this diagnosis. The objective of this article was to alert the pediatric community to the condition. One suggestion for increasing correct diagnosis is to include specific training courses on noninfectious chronic inflammatory diseases in medical residencies[18].

Finally, it was not possible to conduct any analyses with relation to the relative therapeutic success of glatiramer acetate and the different interferon beta formulations because the case series was too small.

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