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Pediatric multiple sclerosis: descriptive analysis of a Demyelinating Disorders Consultation

Esclerose Múltipla em idade pediátrica: análise descritiva da consulta de doenças desmielinizantes

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Pediatric multiple sclerosis: descriptive analysis of a Demyelinating Disorders consultation

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Indice

Abstract 3
Resumo 4
Background 5
Materials and Methods 7
Results 9
Discussion 16
Conclusion 19
Acknowledgements 19
References 20

Abstract

Background: Multiple Sclerosis (MS) is a chronic, inflammatory and demyelinating disease of central nervous system (CNS) and plays a role in non-traumatic neurological disability in young adults. In some cases, clinical manifestations have pediatric onset, which requires a particular approach. The main objective of this research paper is to provide a detailed biodemographical and clinical characterization of the pediatric-onset MS population that has been accompanied at our centre, since 2010.

Materials and Methods: We performed a retrospective, observational and unicentric study. We included data of patients' records with MS diagnosis confirmed before 18 years of age, according to current diagnostic criteria, since 1st January 2010.

Results: In a group of 32 patients, 30 (73.3% female gender) fulfilled the inclusion criteria, with mean age at diagnosis of 15.5±2.2 years and median value of Expanded Disability Status Scale (EDSS) score at diagnosis of 1.5±0.9. All the cases had a diagnosis of Relapsing-Remitting MS and in 43.3% optic nerve involvement was the first clinical manifestation. A concomitant immune-mediated disease was found in 10 patients (26.7%) and a positive familiar history MS in 20%. At time of diagnosis, 50% presented gadolinium enhancement lesions in magnetic resonance imaging (MRI) and the study of cerebrospinal fluid revealed positive oligoclonal bands in 85.7%. Interferon beta-1a was the first treatment option in the majority of the patients (30%) but, in 20%, the first therapeutic option was natalizumab. In a mean follow-up of 4.1±2.5 years, treatment change was made in 67.9% of cases. EDSS of last visit had a mean of 1.4±0.6.

Conclusion: This study provides new data coming from our pediatric-onset MS population and our results are in line with the most recent published sources. Besides allowing an important descriptive analysis of this population characteristics, so far, this study also provides a window of opportunity for further prospective analyses. Early diagnosis is very important to increase pharmacological control and functional impairment outcomes.

Keywords: Multiple sclerosis, children, demyelinating diseases.

Resumo

Introdução: A Esclerose múltipla (EM) é uma doença crónica, inflamatória e desmielinizante do sistema nervoso central, constituindo a principal causa de incapacidade neurológica não traumática no adulto jovem. Existem casos em que os sintomas têm início em idade pediátrica, revestindo-se a sua abordagem de algumas particularidades. O objetivo principal deste estudo é a caracterização biodemográfica e clínica detalhada da população com o diagnóstico de EM estabelecido antes dos 18 anos de idade, no nosso centro, desde 2010.

Materiais e Métodos: Realizou-se um estudo observacional e retrospetivo, unicêntrico. Recolheram-se, por consulta do processo hospitalar, dados de doentes com o diagnóstico de EM estabelecido antes de cumpridos os 18 anos, de acordo com os critérios vigentes, desde 1 de Janeiro de 2010.

Resultados: Incluíram-se 30 doentes (73,3% do género feminino), com idade média ao diagnóstico de 15,5±2,2 anos e valor médio da pontuação na Escala Expandida do Estado de Incapacidade (EDSS) na mesma altura de 1,5±0,9. Todos tinham o diagnóstico de EM surto-remissão e em 43,3% a primeira manifestação resultou do envolvimento do nervo óptico. Identificou-se doença imunomediada concomitante em 10 doentes (26,7%) e história familiar de EM em 20%. No momento do diagnóstico, 50% apresentavam lesões com realce por gadolínio na RM-CE e 85,7% dos que realizaram punção lombar tinham bandas oligoclonais. O interferão beta-1a foi o imunomodulador de primeira linha mais utilizado (30%), mas 20% dos doentes iniciaram tratamento com natalizumab. Após um seguimento médio de 4,1±2,5 anos, foi necessária modificação terapêutica em 67,9% dos casos, sendo o EDSS médio na última avaliação de 1,4±0,6.

Conclusão: Este estudo permitiu obter dados consistentes, a partir da coorte de doentes com EM de início em idade pediátrica, concordantes com a informação mais recentemente publicada. Para além de permitir uma análise descritiva das características desta população, este estudo abre uma janela de oportunidade para estudos futuros, de natureza prospetiva. O diagnóstico precoce é muito importante, para o estabelecimento de uma estratégia farmacológica que permita otimizar os resultados funcionais.

Palavras-chave: Esclerose Múltipla, crianças, doenças desmielinizantes.

Background

Multiple Sclerosis (MS) is a chronic, inflammatory demyelinating disease of the central nervous system (CNS), leading to a progressive loss of capacities and being an important cause of non-traumatic neurological disability in young adults.[1,2] Although more frequent in the young adult population, around of 10% of MS cases have an early-onset,[1] usually during adolescence and defining what is known as pediatric-onset MS.[2] The female:male ratio in this condition is around 3.3:1 to 4.5:1,[2,3] higher than the 2.3:1 ratio in adult-onset MS.[4] In Portugal, MS prevalence is around 0.06%[5] but there is very scarce information about the prevalence of pediatric MS.

Pediatric MS has been increasingly recognized to have some distinctive features, with a more inflammatory component, with higher relapse rates but with slower progression than adult-onset MS, the latter possibly due to a higher degree of neuroplasticity, in children. However, in many cases moderate-to-severe disability is reached at a younger age.[1] Optic nerve and spinal cord involvement are the most frequent initial presentations in pediatric MS.

The diagnosis in childhood can be challenging since there are several pathologies with similar clinical features, namely infections (particularly acute disseminated encephalomyelitis that can be related to a post-infectious condition), systemic inflammatory diseases or inherited metabolic diseases. Diagnosis is currently based on the International Pediatric Multiple Sclerosis Study Group (IPMSSG) criteria, which incorporate the 2010 McDonald criteria. The applicability of the recent 2017 McDonald criteria in the diagnosis of children is still being studied.[6,7,8,9]

Nevertheless, early diagnosis in pediatric MS is essential to consider the opportunity of early initiation of disease-modifying treatments (DMTs) and to prevent physical and cognitive sequelae.[2]

The classic first-line treatment for pediatric MS is interferon-beta or glatiramer acetate.[10] A recent study revealed that newer DMTs, as natalizumab, dimethylfumarate and fingolimod, are often used in pediatric MS with similar short-term safety, tolerability, and side effect profiles as in adults.[10]

Despite the recent advances in the knowledge on pediatric MS, more information is clearly needed, as it would lead to a better understanding of the disease. One example could be to study the impact of environmental and genetic factors in MS. Viral exposures, mainly Epstein-Barr virus (EBV), obesity and sexual hormones have been described as

risk factors for MS and the impact of physical exercise on measures of disease activity and severity has also been studied. Children may be considered as the ideal disease models to test for the possible implications of these environmental factors on disease pathophysiology.

The main objective of this study is a biodemographical and clinical characterization of patients with pediatric onset of MS, followed at the Demyelinating Disorders consultation of the Pediatric Hospital (Centro Hospitalar e Universitário de Coimbra). We also aim to explore the possible effect of eventual environmental factors in measures of disease activity.

Materials and Methods

Study Design

We performed an observational, retrospective and unicentric study.

This study was approved by the National Commission for Data Protection and by the Ethics Committee of our institution (Centro Hospitalar e Universitário de Coimbra).The study followed the principles of the Declaration of Helsinki, national legislation for clinical research and good clinical practice (ICH-GCP).

Population

We included patients with a confirmed diagnosis of MS established in pediatric age (<18 years-old), according to the 2012 IPMSSG and the 2010 McDonald criteria, followed at the Centro Hospitalar e Universitário de Coimbra between January 2010 and December 2018.

We excluded patients without subsequent follow-up or in which an alternative diagnosis was found during follow-up.

Procedures

After signing an informed consent document, we collected data from clinical records and by telephone call, including:

1) Biodemographical characteristics: birth date, gender, educational level, current body mass index (BMI), menarche age (for female patients), family history of MS and practice of physical exercise (current, at the time of the last appointment and/or in the past, i.e. any physical exercise previous to last appointment);

2) Clinical data: age at first clinical manifestation and at MS diagnosis, first clinical manifestation, phenotype classification of disease, Expanded Disability Status Scale (EDSS) score at diagnosis and in the last consultation, past medical and surgery history, current and past DMTs (drug, duration of the treatment and reason for discontinuation), other current treatments, number of relapses and treatment of relapses;

3) Complementary exams results: first magnetic resonance imaging (MRI), presence of anti-myelin oligodendrocyte glycoprotein (MOG) or anti-aquaporin 4 (AQP4) antibodies, visual evoked potentials, presence of oligoclonal bands in the cerebrospinal fluid (CSF) and presence of antibodies against Cytomegalovirus (CMV) and EBV.

We defined physical exercise as any body movement generated by the contraction of skeletal muscles that raises energy expenditure above resting metabolic rate, which is planned, structured, and repetitive (more than 3 times per week).

Relapse was defined as the existence of new neurological symptoms or signs, in the absence of concurrent disease. Different relapses were defined by an interval of time greater than 30 days between them.

Statistical analysis

We performed a descriptive analysis of clinical and biodemographical characteristics. Qualitative variables were displayed as absolute value and percentage, and quantitative variables as mean±standard deviation, minimum and maximum.

The normality of the variables was assessed using the Kolmogorov-Smirnov (KS) test for physical exercise in childhood, actual physical exercise and number of relapses, and the Shapiro-Wilk (SW) test for menarche age, age of diagnosis and number of relapses in female patients.

A Mann-Whitney U test was performed to evaluate the correlation between the number of relapses and current or past physical exercise.

The analysis of a possible correlation between menarche age and age of diagnosis was assessed by the Spearman coefficient. All analysis were performed with IBM SPSS® statistics 25 software.

Results

We included 32 patients, from which 2 were excluded due to the absence of subsequent follow-up.

Our sample (n=30) had a mean diagnosis age of 15.4±2.2 years and the time between first clinical manifestation and diagnosis was 0.4±0.7 years (Table 1). The female:male ratio was 2.75:1. Positive familiar history for MS was found in 6 patients (20%). Mean follow-up time was 4.1±2.5 years and a patient died during follow-up for reasons unrelated to MS.

Table 1. Biodemographical characteristics

	N	**Mean±SD (min; max)**
Age at diagnosis	30	15.4±2.2 y (9 y;17 y)
Age at first clinical manifestation	30	15.0±2.4 y (9y;17y)
IMC at last visit (Kg/m^2)	27	21.0±2.5 (16.4;26.5)
Menarche age	21	12.7±1.4y (11y;16y)
	n (%)	
Female gender	22 (73.3%)	
Family history of MS	6 (20.0%)	
Past physical exercise	9 (30.0%)	
Current physical exercise	6 (20.0%)	

Abbreviations: y: years; min: minimum value; max: maximum value; SD: standard deviation

We noticed actual physical exercise practice in 6 patients (20.0%) and past physical exercise habits in 9 (30.0%).

Regarding the seasonal distribution of patients' birth, 11 (36.6%) were born during the autumn months (September, October and November), 8 (26.7%) during the winter (December, January and February), 8 (26.7%) in the spring (March, April and May) and 3 (10.0%) during the summer (June, July, August) (Figure 1).

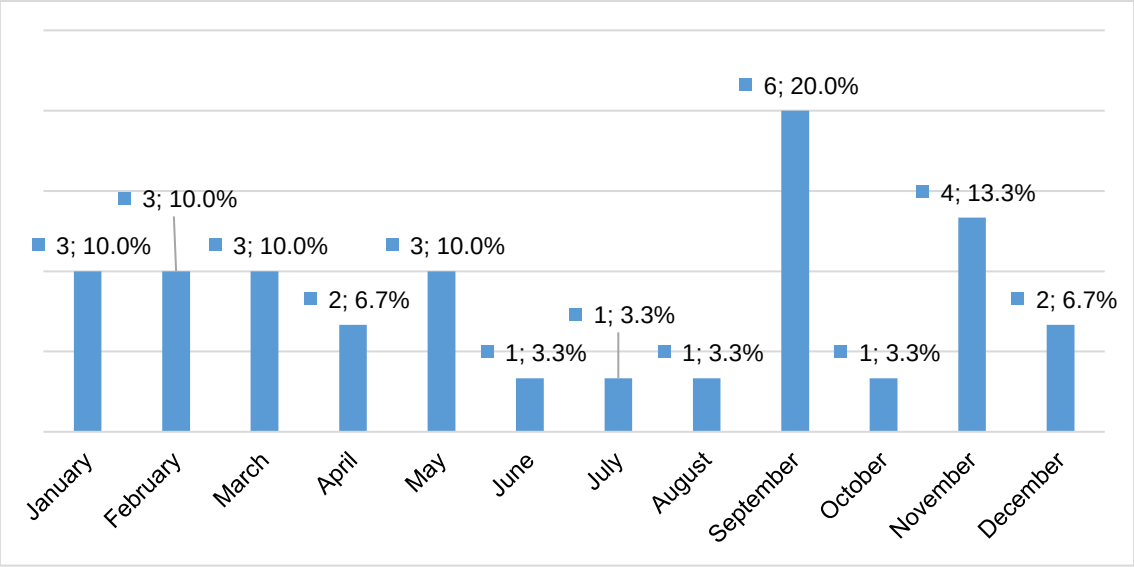

Figure 1. Birth months

Educational level is described in table 2. However, 26 patients did not finish their studies yet.

Table 2. Educational level

	n (%)
Elementary school	3 (10.0%)
High school	10 (33.3%)
Technical and professional course	5 (16.7%)
University degree	10 (33.3%)
Unknown	2 (6.7%)

We reported the past medical history according to immune system-related diseases, since this was defined as our specific goal (Figure 2). As it can be seen, more than 25.0% of patients are also diagnosed with a different immune-mediated condition. Fourteen patients (46.7%) of our group had other regular medical treatments: as vitamin D in 12 (85.7%), complex B vitamins in 9 (64.3%), magnesium in 2 (14.3%), montelucast in 1 (7.1%), diazepam in 1 (7.1%), amantadine hydrochloride in 2 (14.3%), escitalopram in 1 (7.1%) and omeprazole in 1 (7.1%) patients.

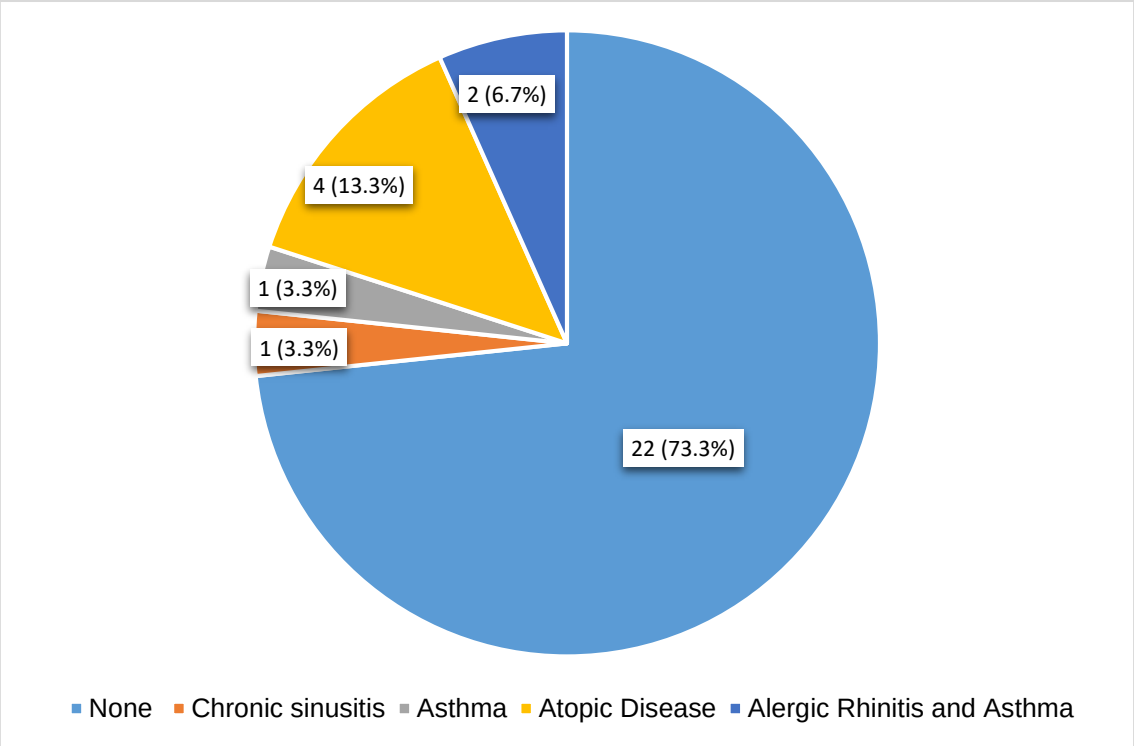

Figure 2. Concomitant immune-mediated diseases

Involvement of the optic nerve or of the spinal cord were the most common first clinical manifestations, occurring in 43.3% and 40.0% of the patients, respectively (Figure 3). One patient had a cortical presentation, the first clinical manifestation being a focal seizure, presenting with right head deviation and left upper limb tonic posture.

The mean EDSS at diagnosis was 1.7±0.9 (minimum 1 and maximum 3.5).

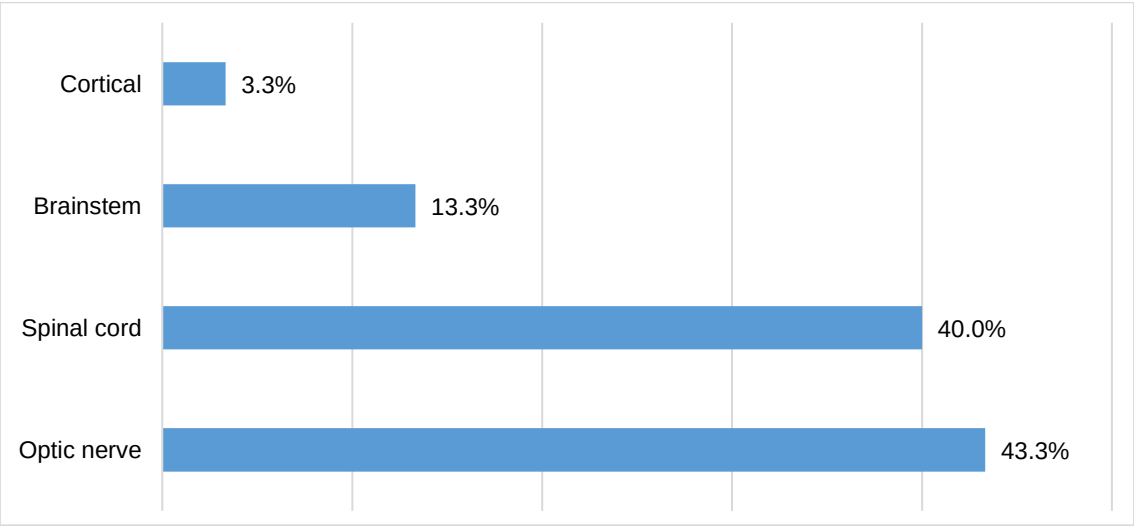

Figure 3. First clinical manifestation according to topographical classification

During initial diagnostic workup, all of the patients performed brain MRI and 14 (46.7%) spinal cord MRI; dissemination in space (DIS) and dissemination in time (DIT) criteria were found in 18 (60.0%) and DIS criteria only in 9 (30.0%) (Table 3). Lumbar puncture was performed in 21 (70.0%) patients and oligoclonal bands were present in 18 (85.7%) of them. Electroencephalogram was performed in one patient with a paroxysmal event previously described.

Table 3. MRI results at the time of diagnosis

	n (%)
DIS	9 (30.0%)
DIS and DIT	18 (60.0%)
Gd+	15 (50.0%)
No criteria for MS diagnosis	3 (10.0%)

Abbreviations: DIS: Dissemination in space; DIT: dissemination in time; Gd+: gadolinium enhancement lesions

During follow-up, serologic tests were performed for EBV (n=11) and CMV (n=12). Immunity was confirmed for CMV in 5 cases (41.7%) and for EBV in 10 (90.9%). Anti-MOG and anti-AQP4 antibodies were studied in two patients, with negative results. Visual evoked potentials were performed in two patients, both with optic neuritis at presentation, with an increase of latency period in one patient and a normal result in the other.

A DMT was initiated in 28 patients (93.3%) (Figure 4). One patient did not start DMT due to a personal option and other due to a medical team decision. The first choice in the most cases was interferon beta-1a (30%).

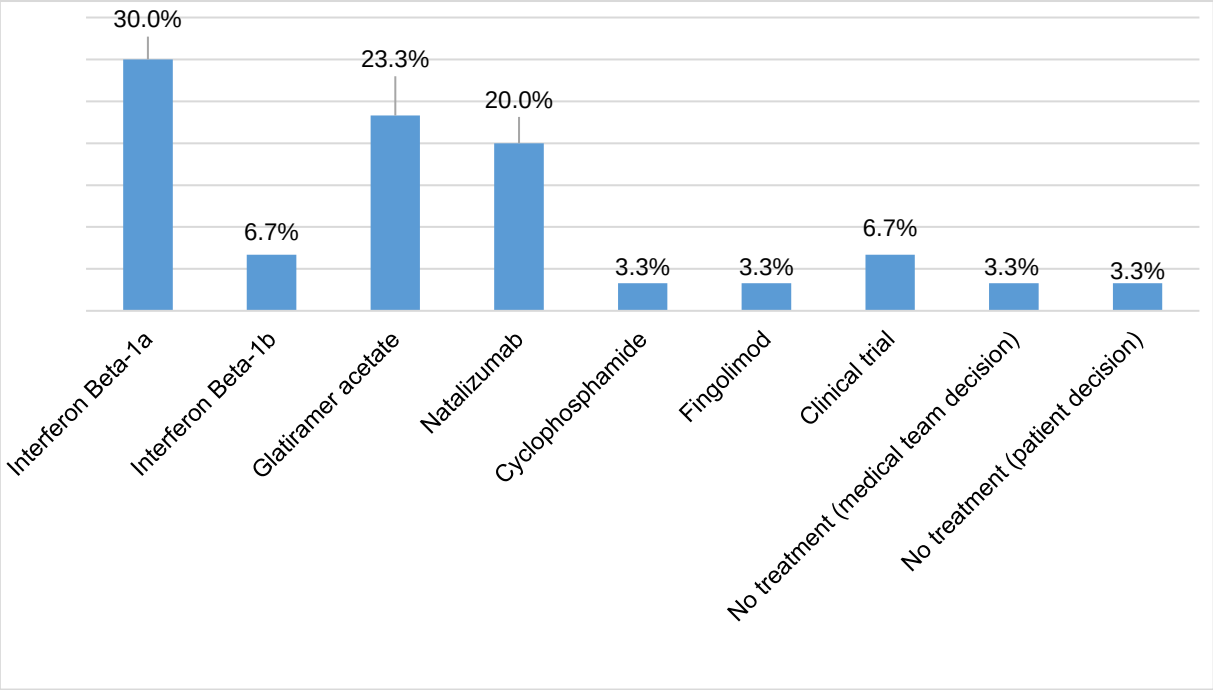

Figure 4. First DMTs used

Treatment with DMT was changed during follow-up in nineteen patients (67.9%).The most common reason for treatment discontinuation was ineffectiveness: 65.2% of cases (Table 4).

Table 4. Use of DMTs during follow-up

DMT	Mean duration of use, m, (SD)	Reason for discontinuation, n (%)
Natalizumab	27.0 (23.0)	Ineffectiveness, 2 (50.0%) Side effects, 1 (25.0%) Personal choice, 1 (25.0%)
Interferon beta-1a	30.2 (17.7)	Ineffectiveness, 3 (60.0%) Personal choice, 2 (40.0%)
Glatiramer acetate	18.6 (11.4)	Ineffectiveness, 5 (62.5%) Side effects, 3 (37.5%)
Interferon beta-1b	24.7 (14.3)	Ineffectiveness, 3 (100%)
DMT	**Duration of use,m**	**Discontinuation reason, n (%)**
Dimethylfumarate	9.0	Side effects, 1 (100%)
Cyclophosphamide	12.0	Ineffectiveness, 1 (100%)
Fingolimod	1.0	Ineffectiveness, 1 (100%)

Abbreviations: m: months; SD: standard deviation; n: number of patients.

Natalizumab was used in 4 patients, interferon beta-1a in 5, glatiramer acetate in 8 and interferon beta-1b in 3. Dimethylfumarate, fingolimod and cyclophosphamide were discontinued in just one patient (each), for that reason the results were presented in duration of use (in months), instead of mean and standard deviation.

Current DMTs are presented in Figure 5 (n=29, because one of the patients died – cause not related to MS). At this moment, none of our patients is under treatment with glatiramer acetate.

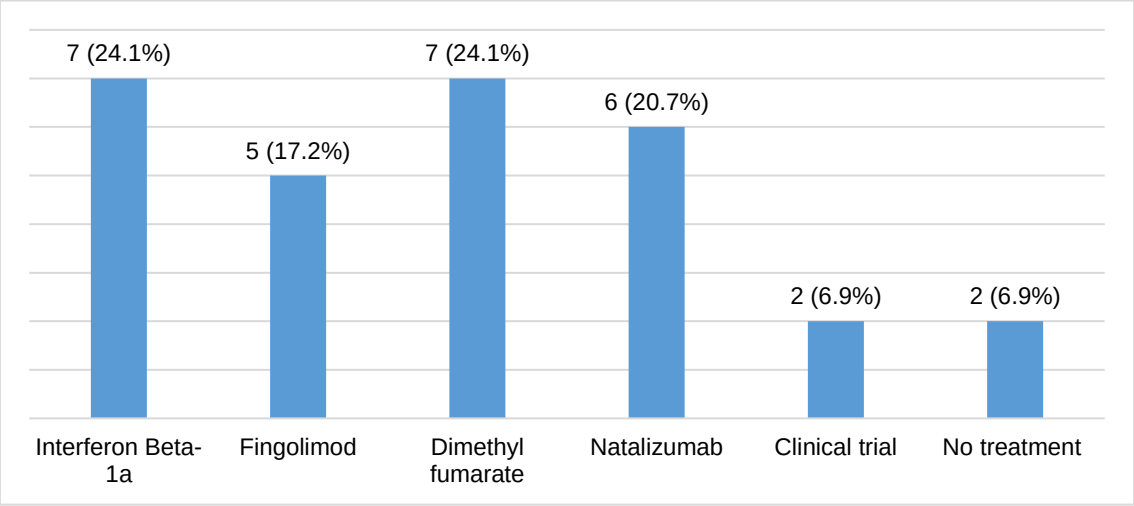

Figure 5 – Current DMTs in use for pediatric-onset MS in our centre

The mean follow-up time was 4.1±2.5 years and the mean number of relapses during follow-up was 2.2±1.4. The majority of the relapses involved the spinal cord (40%) or the optic nerve (32.3%) (Figure 6).

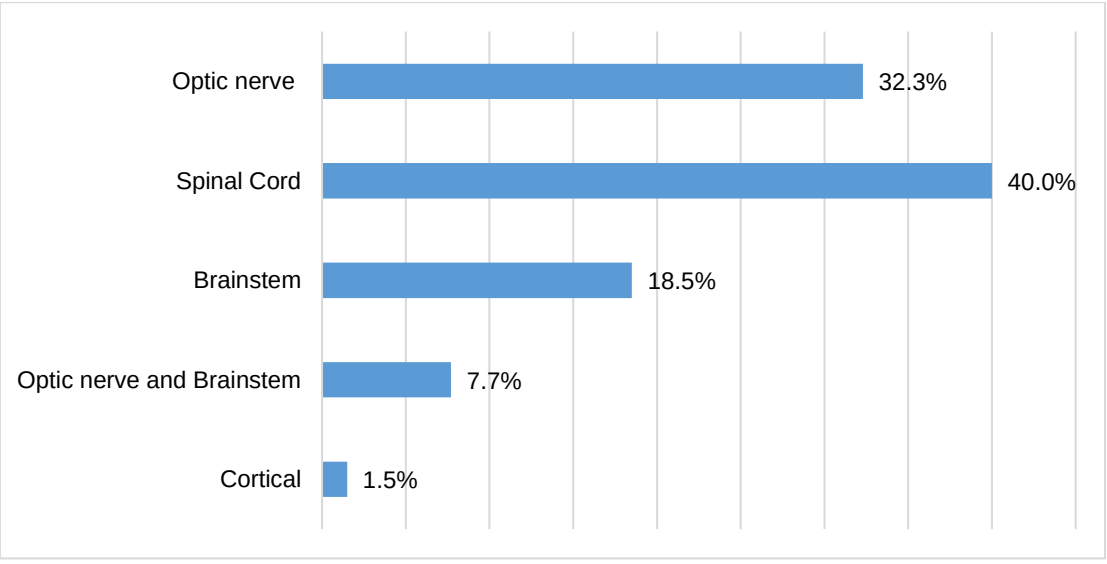

Figure 6. Topographical classification of relapses occurring during treatment

Treatment choice for relapses was mainly intravenous methylprednisolone (78.5%), with a typical regimen of 500-1000 mg, once daily, for 3-5 days. Intravenous Immunoglobulin and plasmapheresis were used in 1 case (1.5%). In 13 relapses (20.0%) no specific treatment was done.

The mean EDSS score at last visit was 1.4±0.6 (minimum 0 and maximum 3).

No correlations were found between past physical exercise and number of relapses, current physical exercise and number of relapses ($p>0.05$), neither, menarche age and age of diagnosis in female patients ($p>0.05$).

Discussion

We described a cohort of patients with pediatric-onset MS. The mean age of diagnosis and female predominance were in accordance with previous studies in the Portuguese pediatric population (15.4±2.2 years vs 16.1 years and 73.0% vs 72.0%).[5] Our patients had a higher prevalence of positive family history for MS (20.0% vs 6-13.5% in international studies and 2% in Portuguese studies).[5]

Vitamin D defect has been associated with more susceptibility to MS, including in pediatric patients, although the reasons are still not fully understood. Interestingly, approximately two thirds of our patients were born during autumn-winter months, further supporting hypothetical seasonal changes in MS susceptibility.[8]

The mean age of menarche in our cohort was 12.7 years, similar to general caucasian population in the USA (around 12.8 years), not supporting the role of hormonal factors in the early-onset of the disease.[11]

Concomitant immune-mediated diseases affecting the respiratory system were very frequent in our cohort, emphasizing the very practical notion of aggregation of immune-mediated diseases in susceptible individuals, requiring assertive and regular clinical control.

The majority of the patients had a concomitant treatment with multivitamins, vitamin D (85.7%), complex B vitamins (64.3%) and magnesium (14.3%). The use of these oligoelements in children with MS is not consensual, especially if their true deficit is not demonstrated. Nevertheless, this aspect emphasizes the high sensitivity of families to diet issues and vitamin supplementation.

The first clinical manifestation involved the optic nerve in 43.3% and the spinal cord in 40%, in agreement with previous reports.[9] Initial MRI study of brain and spinal cord supported the diagnosis with DIS and DIT criteria in 60% of the cases, leading to an early diagnosis and a short time between first clinical manifestation and effective diagnosis.

Oligoclonal bands were also an important part of the diagnostic workup and were present in the majority of the cases (85.7%), albeit in an inferior value than the one reported in adult onset of MS (98%).[5] Serology for EBV, a factor often associated with the risk for MS, was positive in 90.9% of the patients that were tested, supporting the association since an early age. However, due to its high prevalence in the general population, results must be interpreted with caution. Differently, serology for CMV was positive in only 41.7% of the patients tested.[12]

In our cohort, of a total of 30 patients, 28 initiated DMTs for MS. The patient that did not initiate the DMT for personal option, had the diagnosis at 17 years and by Portuguese law, an adolescent above the age of 16 years has the autonomy to decide.

Treatment of pediatric MS also carries significant challenges, as the degree of evidence is lower than in adults, mainly due to a lower number of randomized controlled trials in the pediatric population. The first choices in the most cases was interferon beta-1a (30%) and glatiramer acetate (23.3%), in accordance with the existent literature.[10] Cyclophosphamide was used in an induction scheme, followed by Interferon-beta, in a patient with an early aggressive disease, prior to natalizumab availability.

During the follow-up (mean 4.1±2.5 years), nineteen patients (67.8%) had to change in their treatment and the most common reason for treatment discontinuation was ineffectiveness. After classic first-line DMTs, natalizumab was the choice in 20% of the cases and there is evidence for that selection, since recent studies revealed that the most commonly used newer DMTs included natalizumab.[10]

Natalizumab and Interferon-beta were discontinued due to personal choice in 25% and 40% of the cases, respectively, because the patients did not tolerate an injectable treatment, a common problem and fear, in a young population. Hypersensitivity reactions were a side effect associated with natalizumab, glatiramer acetate and dimethylfumarate.

Current treatment choices in our population show an increase in the use of Dimethylfumarate (23.3%, a drug that was not used as a first choice) and Fingomolid (16.7%). Natalizumab maintained the same percentage, Interferon beta-1a decreased to 23.3% and Cyclophosphamide was not used again. There were 2 patients without treatment, the same ones who did not start treatment initially.

The mean relapse number was 2.2±1.4 during a mean time of follow-up of 4.1±2.5 years. The majority of the relapses involved the optic nerve (32.3%) or spinal cord (40.0%), similar to what was observed in the initial manifestation, but the involvement of brainstem increased to 18.5% of the cases. Treatment of relapses was usually methylprednisolone, but in 18.5% of the cases no treatment was done, usually in relapses with mild symptoms without immediate medical evaluation.

Progression of the disease, as measured by the difference between the mean first and last EDSS scores, was minimum and, despite a relatively short follow-up time, this

supports the notion that progression in pediatric MS is less significant than in the adult condition.

This study has some limitations due to its retrospective and unicentric nature. Also, the relatively small number of patients included does not allow a robust association analysis for the different variables. However, it was the first to deeply describe the characteristics of such a specific cohort of MS patients, also allowing to set the basis for a future prospective registry, that is being started at our centre and that aspires to be generalized to all the national territory.

Conclusion

Our study provides new data for biodemographical and clinical characteristics in pediatric MS, among a population of individuals regularly follwed at a specific Demyelinating Disorders Consultation, in a tertiary hospital centre. Our results support previous findings, namely regarding a more inflammatory profile of disease, but possible mechanisms associated with MS onset at pediatric ages are still unknown. The findings in this mainly descriptive analysis can lead to additional prospective investigations to increase the knowledge in this disease.

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Conflict of interests

The authors declare no financial or other conflicts of interest regarding the topics covered in this work.

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