Inflammatory Activity and Treatment Response in Pediatric Compared to Adult Multiple Sclerosis: A Pilot, Retrospective and Observational Study of the First Year After Diagnosis

Atividade Inflamatória e Resposta ao Tratamento na Esclerose Múltipla Pediátrica, em Comparação com o Adulto: Estudo Piloto, Retrospetivo e Observacional do Primeiro Ano Após o Diagnóstico

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Acta Med Port 2021 Jan;34(1):28-34 ▪ https://doi.org/10.20344/amp.13160

ABSTRACT

Introduction: Pediatric-onset multiple sclerosis may contrast with adult-onset multiple sclerosis, in terms of disease activity. We aimed to determine differentiating features between pediatric-onset multiple sclerosis and adult-onset multiple sclerosis, at diagnosis and after one year under disease modifying therapies, and analyse the attainment of the status of "No Evidence of Disease Activity" between groups.

Material and Methods: We analyzed demographical, laboratory, clinical and imaging features of patients with relapsing-remitting multiple sclerosis diagnosed at our center, according to the McDonald's 2010 criteria, with ≥ 1 year under disease modifying therapies and with available magnetic resonance imaging scans at diagnosis and one year after disease modifying therapies initiation. Patients were paired according to gender and disease modifying therapies in use. "No Evidence of Disease Activity" status was assessed, and differences were studied.

Results: Fifteen pediatric-onset multiple sclerosis (aged ≥ 8 and < 18 years) and 15 adult-onset multiple sclerosis (≥ 18 and < 55 years) patients were recruited. We found a statistically significant difference in the number of T2 weighted image diffuse lesions/with poorly defined borders (p = 0.015). The mean expanded disability status scale score after one year under disease modifying therapies was lower in the pediatric-onset multiple sclerosis group (1.6 ± 0.8) compared to the adult-onset multiple sclerosis group (2.3 ± 0.8; p = 0.032). Nevertheless, no differences were found regarding the percentage of cases achieving "No Evidence of Disease Activity" in either group.

Discussion: Although there is an empirical impression about the difference in inflammatory activity between pediatric-onset multiple sclerosis and adult-onset multiple sclerosis, it was not possible to corroborate it in our study. Nevertheless, this was an exploratory and retrospective analysis of a small sample of patients, identifying variables in which such differences appear to be most important.

Conclusion: Extensive studies of children, adolescents and adults with multiple sclerosis will be needed to categorize the clinical and radiological differences that allow the identification of drug response biomarkers in the early stages of the disease.

Keywords: Child; Magnetic Resonance Imaging; Multiple Sclerosis; Multiple Sclerosis, Relapsing

RESUMO

Introdução: A esclerose múltipla de início em idade pediátrica pode contrastar com a esclerose múltipla de início na idade adulta, em termos de atividade da doença. Pretendemos determinar características diferenciadoras entre esclerose múltipla de início em idade pediátrica e esclerose múltipla de início na idade adulta ao diagnóstico e um ano após o início de terapêuticas modificadoras da doença e analisar o atingimento do estado de "Ausência de Evidência de Atividade de Doença".

Material e Métodos: Analisámos as características demográficas, laboratoriais, clínicas e imagiológicas de doentes com esclerose múltipla surto-remissão diagnosticados no nosso centro, segundo os critérios de McDonald 2010, com ≥ 1 ano sob terapêuticas modificadoras de doença e com ressonâncias magnéticas disponíveis no diagnóstico e um ano após o início de terapêuticas modificadoras da doença. Os doentes foram emparelhados de acordo com o género e terapêuticas em uso. O estado de "Ausência de Evidência de Atividade de Doença" foi avaliado e as diferenças estudadas.

Resultados: Quinze doentes com esclerose múltipla de início em idade pediátrica (≥ 8 e < 18 anos de idade) e 15 com esclerose múltipla de início na idade adulta (≥ 18 e < 55 anos de idade) foram recrutados para este estudo. Encontrámos uma diferença estatisticamente significativa no número de lesões difusas/com bordos mal definidos ponderadas em T2 (p = 0,015). A pontuação média da escala expandida de incapacidade após um ano sob a respetiva terapêutica modificadora de doença foi menor no grupo esclerose múltipla de início em idade pediátrica (1,6 ± 0,8) em comparação com o grupo esclerose múltipla de início na idade adulta (2,3 ± 0,8;

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Recebido: 26 de junho de 2019 - Aceite: 11 de março de 2020 | Copyright © Ordem dos Médicos 2021

p = 0,032). Ainda assim, não se encontraram diferenças relativamente à percentagem de casos alcançando "Ausência de Evidência de Atividade de Doença" em ambos os grupos.
Discussão: Apesar de existir uma impressão empírica sobre uma diferença de atividade inflamatória entre a esclerose múltipla de início em idade pediátrica e a esclerose múltipla de início na idade adulta, não foi possível corroborá-la no nosso estudo. De qualquer modo, esta foi uma análise exploratória e retrospetiva de uma amostra pequena de doentes, em que identificámos as variáveis em que tais diferenças parecem ser mais importantes.
Conclusão: Estudos alargados de crianças, adolescentes e adultos com esclerose múltipla serão necessários para categorizar as diferenças clínicas e radiológicas que permitam identificar biomarcadores de resposta a fármacos, em fases precoces da doença.
Palavras-chave: Criança; Esclerose Múltipla; Esclerose Múltipla Recidivante-Remitente; Ressonância Magnética

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS).[1] Despite being mainly diagnosed in adults, it has been estimated that 3% - 10% of all cases correspond to pediatric patients.[2] Demographic, clinical and imaging features of pediatric-onset MS (POMS) may differ considerably to those of adult-onset MS (AOMS) patients,[3] particularly presenting a more inflammatory character than adult MS.[4] With new developments in disease modifying therapies (DMT), which target the peripheral immune system, the main objective has been to minimize the inflammatory course of the condition, in order to promote disease control and to prevent long term disability risks.[5] Therefore, it is expected that children and adolescents with MS under DMT present better treatment results than their adult counterparts. However, this hypothesis has not yet been clearly demonstrated in clinical practice.

The 'no evidence of disease activity' (NEDA-3), based on the absence of relapses, on the absence of evidence of magnetic resonance imaging (MRI) disease activity [defined as the absence of gadolinium-enhanced lesions (Gd+) or new/enlarged T2-weighted imaging (WI) lesions] and in lack of disability progression [defined as an increase of ≥ 1 point in the Expanded Disability Status Scale (EDSS) score], is considered an outcome measure and as the overall goal for treatment in relapsing-remitting MS (RRMS).[6,7] In fact, in recent studies, this has been a very focused and discussed variable.

In this pilot study, we intended to compare the clinical and imaging features of the pediatric MS population with RRMS diagnosed at our centre with an adult population with the same clinical phenotype, at the time of diagnosis and after one year under DMT. We thus aimed to identify the proportion of patients who reach the NEDA-3 status, the relative contribution of each NEDA-3 parameter and NEDA-3 clinical/imaging baseline predictors. We hypothesise a larger proportion of POMS patients reaching the NEDA-3 status, compared to the AOMS population.

MATERIAL AND METHODS

Study design and participants

This is an observational, retrospective and single-centre study, which has been approved by the local ethics committee and by the national data protection commission.

We searched the databases of the Pediatric Neurology and Pediatric Demyelinating Diseases consultation and of the Demyelinating Diseases consultation in Coimbra Hospital and University Centre, for POMS patients ≥8 and <18 years at diagnosis and for AOMS patients ≥ 18 and < 55 years at diagnosis, both groups with RRMS diagnosed in the hospital according to the McDonald 2010 criteria, under DMT for ≥ 1 year and with available MRI scans at the time of diagnosis (baseline MRI) and one year after DMT (control MRI). We found 15 POMS patients who fulfilled these criteria. These patients were thus paired with 15 AOMS patients who fulfilled the above criteria, according to gender and DMT in use (1st line: interferon beta and glatiramer acetate; 2nd line: natalizumab). After all patients signed an informed consent document, both groups were analyzed and compared at the time of diagnosis and one year after DMT initiation. Additionally, we performed a comparison within each group between these two moments in time.

Procedures

Baseline data were collected from all selected patients and included:

a) Demographic characteristics: gender, age at diagnosis and race;
b) Clinical characteristics: clinical phenotype of the disease, number of relapses prior to diagnosis and their topography, EDSS score and treatment modality;
c) Laboratory information: presence/absence of oligoclonal bands in cerebrospinal fluid (CSF);
d) MRI features: number of T2 WI-bright juxtacortical, periventricular, intracallosal, cerebellar and brainstem lesions, total number of T2 WI-bright lesions, T2 WI-bright ovoid lesions with well-defined borders, T2 WI-bright diffuse lesions with poorly defined borders, T2 WI-bright lesions with ≥ 1 cm in diameter, number of T1 WI-hypointense lesions (black holes) and number of Gd+ lesions.

Additionally, the following data concerning one year after DMT were collected:

a) Clinical characteristics: number of relapses (annualized relapse rate), EDSS score, and the NEDA-3 status;
b) MRI features: in addition to all the variables considered for the baseline, new T2 WI-bright lesions and the percentage of cases with reduction ≥ 50% in the total number of T2 WI-bright lesions were also evaluated at this time point.

The MRI scans were not always performed in the same imaging center, but all were obtained with a magnetic field strength of 1.5T and there was no intra-individual variability (with regard to the scanner used) throughout the study.

Each MRI examination included at least T2 WI, T2 WI FLAIR (fluid-attenuated inversion recovery) and T1 WI sequences. The number of Gd+ lesions was determined by comparison between pre and post contrast Gd administration in T1 WI sequences. We used the closest MRI scan available to the date of diagnosis and closest to 1 year after DMT, when the prior scans were not available.

NEDA-3 status

Qualifying for NEDA-3 required the parameters that were previously described. Patients lacking data were categorized as no NEDA-3, if at least one of the required NEDA parameters available for evaluation was not met.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 23.0. All variables are expressed as percentage of patients, except age at diagnosis and EDSS scores both at diagnosis and after one year under DMT, which are expressed as means (with standard deviation, SD). We categorized the number of MRI lesions as 'absence', '1 - 5', '> 5 - 10', '> 10 - 20', '> 20 - 30' and '> 30 lesions'. The statistical normal distribution of each variable was tested and, accordingly, parametric or non-parametric tests were implemented for comparisons between and within groups, with the necessary corrections. Bilateral alternative hypotheses were considered.

We used the independent t-test for the comparison between quantitative variables: EDSS at diagnosis, EDSS after one year under DMT, number of relapses prior to diagnosis and number of relapses in one year while under DMT in between groups. The chi-squared test was used to compare non-parametric nominal variables: relapse topography prior to diagnosis, treatment modality, presence of CSF oligoclonal bands, reduction ≥ 50% on T2 WI lesion number, NEDA-3 status and its three composite parameters. The Mann-Whitney test was used to compare non-parametric ordinal variables as MRI features between groups in each moment in time considered. Logistic regression analysis was performed to evaluate the association between NEDA-3 status achievement and variables at diagnosis. We considered a value of $p < 0.05$ statistically significant.

RESULTS

The demographic, baseline clinical and laboratory characteristics of both the POMS and AOMS groups are listed in Table 1.

The MRI features at diagnosis are listed in Table 2. We found no statistically significant differences between groups concerning the total number of T2 WI lesions, T2 WI ovoid lesions with well-defined borders, T2 WI ≥ 1 cm of diameter, number of T1 WI lesions and number Gd+ lesions. We found a statistically significant difference between groups in the number of T2 WI diffuse lesions with poorly defined borders ($p = 0.015$), with a higher percentage of POMS patients with absence of this type of lesion (n = 4, 26.7%) and with 1 - 5 lesions (n = 9, 60.0%).

Clinical characteristics after one year under DMT and comparison between groups are listed in Table 3. Most patients from both the POMS (n = 10, 66.7%) and AOMS (n = 12, 80.0%) groups were relapse-free during one year under DMT. We did not find a statistically significant difference between groups in the number of relapses during one year under DMT. The mean EDSS score after one year under DMT was lower in the POMS group, compared to the AOMS group, and that difference was statistically significant

Table 1 – Demographic, baseline clinical and laboratory characteristics of both POMS and AOMS groups [n (%)]

		POMS (n = 15)	AOMS (n = 15)	*p* value
Demografic characteristics				
Gender	Male	8 (26.7%)		
	Female	22 (73.3%)		
Race	Caucasian	30 (100%)		
Mean age at diagnosis (years)		14.9 ± 2.1	36.2 ± 7.3	
Clinical characteristics				
Number of relapses prior to diagnosis	0	12 (80%)	11 (73.3%)	
	1	2 (13.3%)	4 (26.7%)	1
	2	1 (6.7%)	-	
Mean EDSS score		1.7 ± 0.9	2.3 ± 0.8	0.055
Treatment modality	1st line DMT	10 (66.7%)		
	Interferon beta	5 (33.3%)		
	Glatiramer acetate	5 (33.3%)		
	2nd line DMT	5 (33.3%)		
	Natalizumab	5 (33.3%)		
Laboratory data				
Presence of CSF oligoclonal bands		8 (53.3%)	11 (73.3%)	0.214

Table 2 – MRI features at diagnosis and comparison between groups

		POMS (n = 15)	AOMS (n = 14)[1]	
MRI features at diagnosis		**n (%)**	**n (%)**	***p* value**
Total number of T2 WI lesions	1 - 5	-	1 (7.1%)	
	> 5 - 10	4 (26.7%)	3 (21.4%)	
	> 10 - 20	6 (40.0%)	1 (7.1%)	0.251
	> 20 - 30	3 (20.0%)	3 (21.4%)	
	> 30	2 (13.3%)	6 (42.9%)	
T2 WI ovoid lesions with well-defined borders	1 - 5	1 (6.7%)	5 (35.7%)	
	> 5 - 10	5 (33.3%)	4 (28.6%)	
	> 10 - 20	5 (33.3%(	3 (21.4%)	0.116
	> 20 - 30	4 (26.7%)	1 (7.1%)	
	> 30	-	1 (7.1%)	
T2 WI diffuse lesions with poorly defined borders	Absence	4 (26.7%)	2 (14.3%)	
	1 - 5	9 (60.0%)	3 (21.4%)	
	> 5 - 10	1 (6.7%)	1 (7.1%)	**0.015**
	> 10 - 20	-	4 (28.6%)	
	> 20 - 30	1 (6.7%)	2 (14.3%)	
	> 30	-	2 (14.3%)	
T2 WI lesions ≥ 1 cm of diameter	Absence	8 (53.3%)	4 (28.6%)	
	1 - 5	6 (40.0%)	9 (64.3%)	0.301
	> 5 - 10	1 (6.7%)	1 (7.1%)	
Number of Gd+ lesions[2]	Absence	7 (46.7%)	6 (50.0%)	
	1 - 5	7 (46.7%)	5 (41.7%)	1
	> 5 - 10	1 (6.7%)	1 (8.3%)	

[1] AOMS (n = 14) owed to the presence of unquantifiable MRI lesions in 1 patient.
[2] AOMS (n = 12), due to lack of Gd contrast administration in 2 patients (1 because of allergic reaction and 1 of unknown reason).

(p = 0.032).

The MRI features one year after DMT are listed in Table 4. From both groups, only one POMS patient presented no new T2 WI lesions. From the analysed variables, we found only one statistically significant difference between groups in the number of T2 WI diffuse lesions with poorly defined borders (p = 0.004), similarly to the findings in analyses of MRI features at diagnosis (Fig. 1). There was a trend for a difference in the number of T2 WI ovoid lesions with well-defined borders, although without statistically significant differences between groups (p = 0.056), with the highest percentages of POMS patients with > 10 - 20 lesions (n = 5, 33.3%) and >20 - 30 lesions (n = 5, 33.3%), while the highest percentages of AOMS patients presented 1 - 5 lesions (n = 4, 30.8%) and > 5 - 10 lesions (n = 6, 46.2%). We found no statistically significant differences between groups concerning the number of T1 WI lesions. As for the number of Gd+ lesions in both groups, they were not present in most patients. Only one POMS patient presented a reduction of ≥ 50% on the number of T2 WI lesions.

Regarding the NEDA-3 status, the percentage of patients who achieved this milestone and the individual analyses of its three composite parameters are shown in Fig. 2. We found no statistically significant differences between groups, either in the NEDA-3 status achievement, nor in its three individual components. The NEDA-3 status was achieved by around a third of both POMS and AOMS patients. In the POMS group, there was no disability progression in any case, while the AOMS group had slightly better results in both the number of relapses and lack of imaging

Table 3 – Clinical characteristics 1 year after DMT and comparison between groups [n (%)]

		POMS (n = 15)	AOMS (n = 15)	***p* value**
Clinical characteristics after one year under DMT				
Number of relapses/1 year	0	10 (66.7%)	12 (80.0%)	
	1	4 (26.7%)	3 (20.0%)	0.098
	3	1 (6.7%)	-	
Mean EDSS score		1.6 ± 0.8	2.3 ± 0.8	**0.032**

Table 4 – MRI features after one year under DMT [n (%)]

		POMS (n = 15)	AOMS (n = 13)[1]	*p* value
MRI features after one year under DMT				
Total number of T2 WI lesions	Absence	1 (6.7%)	-	0.414
	1 - 5	-	1 (7.7%)	
	> 5 - 10	2 (13.3%)	2 (15.4%)	
	> 10 - 20	4 (26.7%)	1 (7.7%)	
	> 20 - 30	4 (26.7%)	3 (23.1%)	
	> 30	4 (26.7%)	6 (46.2%)	
T2 WI ovoid lesions with well-defined borders	Absence	1 (6.7%)	-	0.056
	1 - 5	1 (6.7%)	4 (30.8%)	
	> 5-10	2 (13.3%)	6 (46.2%)	
	> 10 - 20	5 (33.3%)	1 (7.7%)	
	> 20 - 30	5 (33.3%)	1 (7.7%)	
	> 30	1 (6.7%)	1 (7.7%)	
T2 WI diffuse lesions with poorly defined borders	Absence	5 (33.3%)	1 (7.7%)	**0.004**
	1 - 5	8 (53.3%)	3 (23.1%)	
	> 5 - 10	1 (6.7%)	2 (15.4%)	
	> 10 - 20	-	4 (30.8%)	
	> 20 - 30	-	1 (7.7%)	
	> 30	1 (6.7%)	2 (15.4%)	
T2 WI lesions ≥1 cm of diameter	Absence	8 (53.3%)	5 (38.5%)	0.476
	1 - 5	7 (46.7%)	8 (61.5%)	
Number of Gd+ lesions[2]	Absence	11 (78.6%)	10 (90.9%)	0.525
	1 - 5	2 (14.3%)	1 (9.1%)	
	> 5 - 10	1 (7.1%)	-	
Number of T2 WI new lesions	Absence	6 (40.0%)	8 (61.5%)	0.188
	1 - 5	5 (33.3%)	4 (30.8%)	
	> 5 - 10	2 (13.3%)	1 (7.7%)	
	> 10- 2 0	1 (6.7%)	-	
	> 30	1 (6.7%)	-	
Reduction ≥ 50% on T2 WI lesion number		1 (6.7%)	-	1

[1] AOMS (n = 13) owed to the presence of unquantifiable MRI lesions in 1 patient and impossibility of access to control MRI in another.
[2] POMS (n = 14) and AOMS (n = 11) due to lack of Gd contrast administration in 1 POMS and 1 AOMS patients for unknown reason and 1 AOMS patient owed to allergic reaction.

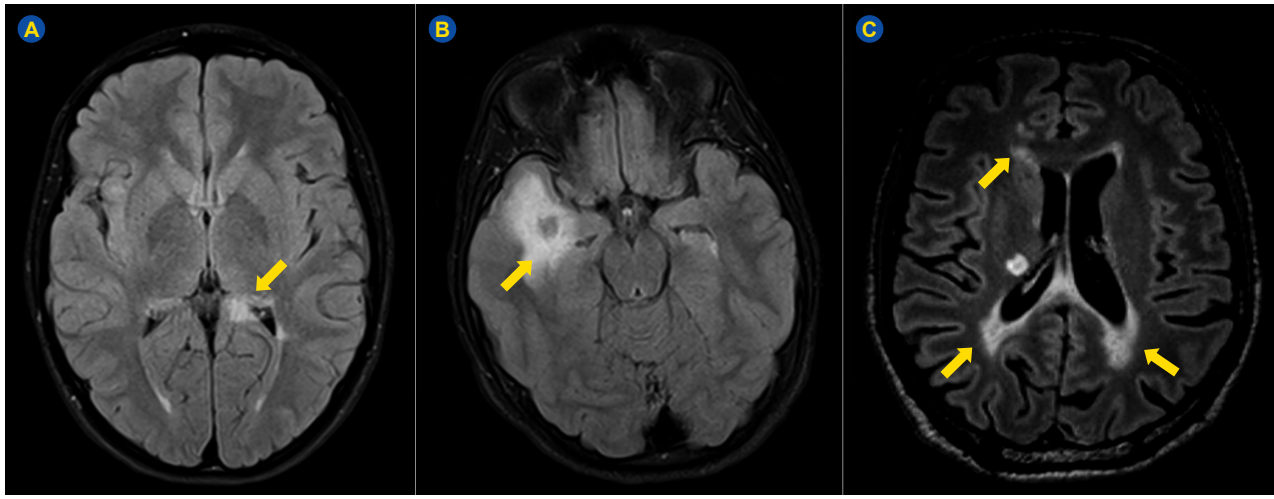

Figure 1 – T2 WI FLAIR axial images of diffuse lesions with poorly defined borders (arrows). MRI scan of a 16-year-old girl (A) and from a 13-year-old girl (B) at diagnosis. MRI scan from 51-year-old man at diagnosis (C).

evidence of disease activity.

DISCUSSION

In our study, we found no statistically significant differences between the POMS and AOMS groups regarding the number of relapses prior to diagnosis, which can be due to a correct application of MS diagnostic criteria and a decrease in the time between first symptom onset and diagnosis. Moreover, we did not find statistically significant differences between groups in relapse topography (data not shown), since late-onset POMS tends to resemble the typical neurologic syndromes of AOMS.[2]

The literature indicates that, at diagnosis, POMS patients present a greater total number of T2 WI lesions, with preference for infratentorial (brainstem and cerebellar) involvement and higher number of T1 WI and Gd+ lesions, compared to AOMS patients. Furthermore, studies show that in follow-up MRI scans, POMS patients tend to have more new T2 WI and Gd+ lesions.[8-10] In our study, we did not find a tendency or statistically significant differences between groups for these variables, which can be due to the fact that late-onset POMS tends to be more similar to the MRI phenotype of AOMS compared to early-onset POMS (age under 11 years old). We also found statistically significant differences between groups in the number of T2 WI diffuse lesions with poorly defined borders, both at diagnosis and one year after DMT, with POMS patients having fewer of these lesions compared to AOMS patients. This is an unexpected finding, since POMS patients tend to present larger (more inflammatory) lesions with poorly defined borders. This might be partly explained by the fact that these lesions are more frequent in patients aged under 11 years old. But it is also important to point out that this type of lesion in children is much more suggestive of other types of diagnosis, such as acute disseminated encephalomyelitis.

Studies on the natural history of MS suggest that in the early years of the disease, MS is rather inflammation-driven with a variable amount of time until an EDSS score of 3.0 is reached.[11] Although we were expecting a greater percentage of POMS patients reaching the NEDA-3 status, taking into account that DMT targets the peripheral immune system and that POMS presents a greater underlying inflammatory burden compared to AOMS,[12] we did not find statistically significant differences in the NEDA-3 status achievement between groups, which can be due to our small patient sample and partly to mean EDSS scores < 3, found in both groups. In addition, studies indicate that approximately 50% of AOMS achieve the NEDA-3 status after two years of follow-up.[13] Our short follow-up duration (12 months) can explain the lower percentage of AOMS patients reaching the NEDA-3 status compared with these studies. Nevertheless, it is important to note that POMS patients did not show any progression of disability (as measured by the EDSS score) throughout the study, although there were fewer children without relapses or MRI activity, when compared with the adult population. This only corroborates the inflammatory nature of the pediatric disease, although the repair capacity in the CNS (remyelination mechanisms, as an example) seems likely to be higher in children, to the point that there is no effective disability progression. Thus, NEDA-3 may not be sensitive enough to reflect this difference, which is very relevant in clinical practice. We might speculate on the possible benefit of NEDA-4 (in which data on brain atrophy would be added) in children and adolescents, but this will have to be objectively assessed and measured in future studies.[14]

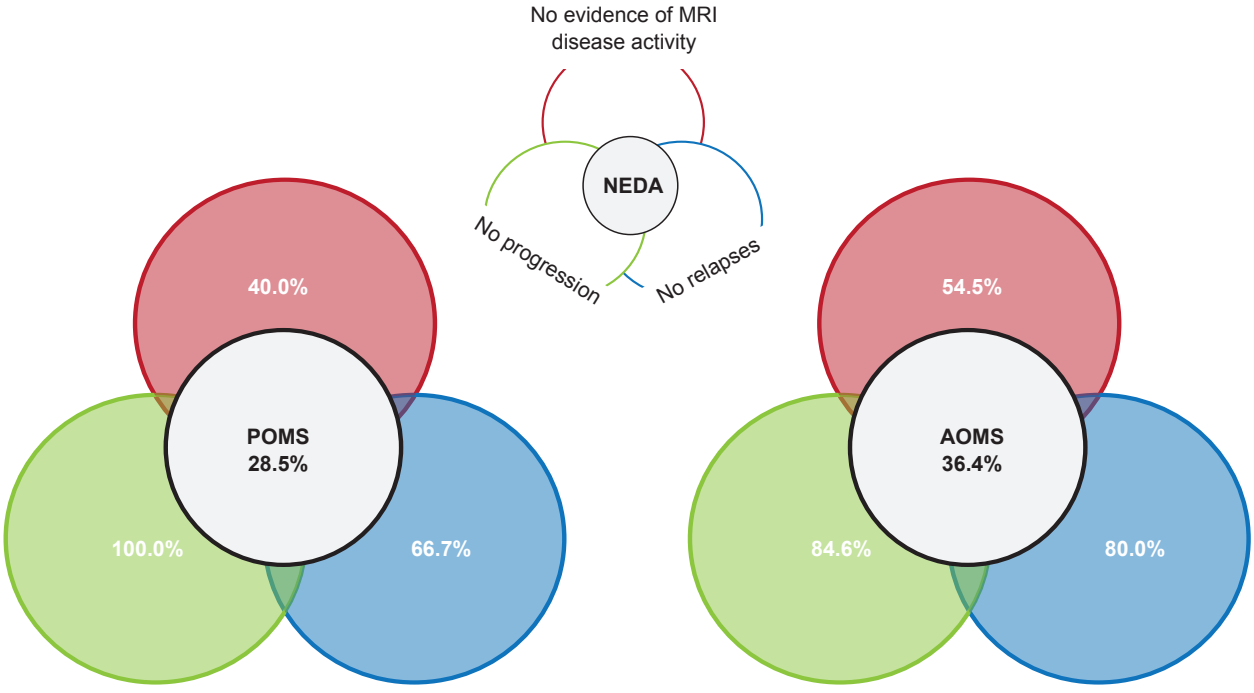

Figure 2 – NEDA-3 status and its three components

Even though relapses are more frequent in POMS than AOMS, our groups presented no statistically significant difference in the number of relapses during one year under DMT, including the NEDA-3 parameter "no relapses", which can be explained by DMT efficacy. On the other hand, this can also be due to our short follow-up time, since it is reported that the median time between the first two neurologic episodes in these patients was estimated in 2.0 years.[3]

Regarding the 'no evidence of MRI disease activity', no statistically significant differences were found between our two groups. This can be partly due both to the lack of differences in the number of relapses during one year under DMT[13] and to the short follow-up time.

Our study encountered some limitations mainly due to its retrospective design. Since many needed data were inaccessible, allied to the small number of pediatric MS patients and to some obstacles related to MRI reading, the statistical power of our analyses was restricted to 80%. Additionally, we considered the first MRI available closest to the date of diagnosis as the baseline MRI and, since different DMT take distinct times to achieve an appreciable effect, patients were under effective therapy for diverse amounts of time, which may influence our study's results. Another drawback that should be addressed is the short follow-up period (12 months) after DMT initiation, which in turn requires further effort to determine if the NEDA-3 status is sustained in a longer-term follow-up.

CONCLUSION

Our pilot study did not demonstrate a clear difference between POMS and AOMS among the various clinical and radiological variables that were considered, particularly regarding the use of NEDA-3 as a target. Nevertheless, despite the small magnitude of the differences found, the notion that the pediatric disease has a more marked inflammatory character cannot be excluded. This highlights the need for further clinical research in this area in order to develop markers that can more effectively measure the impact of different therapeutic options on the evolution of pediatric-onset MS.

ACKNOWLEGDEMENTS

The authors acknowledge the colleagues that contributed to the analyses and interpretation of the MRI features and the Laboratory of Biostatistics and Medical Informatics, in the Faculty of Medicine of the University of Coimbra, for the help and advice in statistical analysis.

PROTECTION OF HUMAN SUBJECTS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration issued by World Medical Association, and updated on 2013.

CONFIDENTIALITY OF DATA

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

FINANCIAL SOURCES

No funding was received for this research.

REFERENCES

1. Vollmer T, Huynh L, Kelley C, Galebach P, Signorovitch J, DiBernardo A, et al. Relationship between brain volume loss and cognitive outcomes among patients with multiple sclerosis: a systematic literature review. Neurol Sci. 2016;37:165-79.
2. Tenembaum SN. Pediatric multiple sclerosis: distinguishing clinical and MR imaging features. Neuroimaging Clin N Am. 2017;27:229-50.
3. Alroughani R, Boyko A. Pediatric multiple sclerosis: a review. BMC Neurol. 2018;18:27.
4. Chitnis T. Disease-modifying therapy of pediatric multiple sclerosis. Neurotherapeutics. 2013;10:89-96.
5. Kaunzner UW, Al-Kawaz M, Gauthier SA. Defining disease activity and response to therapy in MS. Curr Treat Options Neurol. 2017;19:20.
6. Giovannoni G, Turner B, Gnanapavan S, Offiah C, Schmierer K, Marta M. Is it time to target no evident disease activity (NEDA) in multiple sclerosis? Mult Scler Relat Disord. 2015;4:329-33.
7. Giuliani M, Logoteta A, Prosperini L, Hirsch MN, Pozzilli C. Baseline characteristics associated with NEDA-3 status in fingolimod-treated patients with relapsing-remitting multiple sclerosis. Mult Scler Demyelinating Disord. 2017;2:10.
8. Ruet A. Update on pediatric-onset multiple sclerosis. Rev Neurol. 2018;174:398-407.
9. Correia AS, Augusto L, Meireles J, Pinto J, Sousa AP. Pediatric multiple sclerosis in Portugal: a multicentre study. Acta Med Port. 2016;29:425-31.
10. Waubant E, Chabas D, Okuda D, Glenn O, Mowry E, Henry R, et al. Difference in disease burden and activity in pediatric patients on brain magnetic resonance imaging at time of multiple sclerosis onset vs adults. Arch Neurol. 2009;66:967-71.
11. Stangel M, Penner IK, Kallmann BA, Lukas C, Kieseier BC. Towards the implementation of 'no evidence of disease activity'' in multiple sclerosis treatment: the multiple sclerosis decision model.' Ther Adv Neurol Disord. 2015;8:3-13.
12. Gorman M, Healy B, Polgar-Turcsanyi M, Chitnis T. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. Arch Neurol. 2009;66:54-9.
13. Bigi S, Banwell B. Pediatric multiple sclerosis. J Child Neurol. 2012;27:1378-83.
14. Kappos L, De Stefano N, Freedman MS, Cree BA, Radue EW, Sprenger T, et al. Inclusion of brain volume loss in a revised measure of 'no evidence of disease activity' (NEDA-4) in relapsing-remitting multiple sclerosis. Mult Scler. 2016;22:1297-305.