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Pediatric multiple sclerosis lesion burden and activity on magnetic resonance imaging: a retrospective and comparative study with a population of adult patients (COMPARE-MS)

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Atividade e carga lesional em ressonância magnética na Esclerose Múltipla pediátrica: estudo retrospetivo e comparativo com uma população de doentes adultos (COMPARE-MS)

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ABBREVIATURE LIST

AOMS – Adult-onset Multiple Sclerosis

CHUC – Centro Hospitalar e Universitário de Coimbra

CNS – Central Nervous System

DMT – Disease Modifying Therapy

EDSS – Expanded Disability Status Scale

FLAIR – Fluid-attenuated inversion recovery

Gd – Gadolinium

Gd+ – Gadolinium-enhanced

HPC – Hospital Pediátrico de Coimbra

HUC – Hospital Universitário de Coimbra

MRI – Magnetic Resonance Imaging

MS – Multiple Sclerosis

NEDA – No Evidence of Disease Activity

POMS – Pediatric-onset Multiple Sclerosis

T1 WI – T1 weighted image

T2 WI – T2 weighted image

ABSTRACT

Background: Pediatric-onset Multiple Sclerosis (POMS) may contrast with adult-onset MS (AOMS), mostly due to its more prominent inflammatory character. With the development of new effective disease modifying therapies (DMT) for relapsing-remitting multiple sclerosis (RRMS), which target the peripheral immune system, the No Evidence of Disease Activity (NEDA-3) status is being beheld as an outcome measure/overall goal for treatment.

Objective: We aimed to determine differentiating features between POMS and AOMS, at diagnosis and after 1 year under DMT, and compare between these two groups the proportion of patients reaching the NEDA-3 status, the relative contribution of each NEDA parameter and NEDA baseline predictors.

Methods: We analyzed and compared medical data regarding 15 POMS patients ≥8 and <18 years old with 15 AOMS patients ≥18 and <55 years, with the diagnosis of RRMS established at the Centro Hospitalar e Universitário de Coimbra (CHUC), according to the McDonald's 2010 criteria, with ≥1 year under DMT and with available magnetic resonance imaging (MRI) scans at diagnosis and 1 year after DMT initiation. Patients were paired according to gender and DMT in use. Demographical, laboratorial, clinical and imaging features were collected, and the NEDA-3 status was assessed. Logistic regression was carried out to determine which baseline characteristics were associated with NEDA-3 status after 1 year under DMT. We considered statistically significant a value of $p<0.05$.

Results: We found a statistically significant difference between groups in the number of T2 weighted image (T2 WI) diffuse lesions/with poorly defined borders ($p=0.015$). The mean Expanded Disability Status Scale (EDSS) score after 1 year under DMT was lower in the POMS group (1.6±0,8) compared to the AOMS group (2.3±0.8; $p=0.032$). Compared to patients under Natalizumab, patients under Interferons as DMT of choice presented a 12 time-fold higher probability of not achieving the NEDA-3 status ($p=0.029$).

Conclusion: Our findings support the need for an aggressive treatment approach in POMS patients, inclusively with 2nd line DMT, since this group is prone to experience long-term high disability levels.

KEYWORDS: Pediatric multiple sclerosis; magnetic resonance imaging; lesion burden; no evidence disease activity; disease modifying therapy.

RESUMO

Introdução: A Esclerose Múltipla de início em idade pediátrica (POMS) pode contrastar com a Esclerose Múltipla de início na idade adulta (AOMS), principalmente devido ao seu caráter inflamatório mais proeminente. Com o desenvolvimento de novas terapêuticas modificadoras de doença (DMT) eficazes no tratamento da Esclerose Múltipla tipo Surto-Remissão (RRMS), que têm como alvo o sistema imunitário periférico, o estado de ausência de evidência de atividade de doença (NEDA-3) tem sido visto como uma meta/objetivo global no tratamento.

Objetivo: Determinar caraterísticas diferenciadoras entre a POMS e AOMS ao diagnóstico e 1 ano após o início de DMT e comparar entre estes dois grupos de doentes a proporção que atinge o estado de NEDA-3, a contribuição relativa de cada parâmetro constituinte do NEDA e quais as variáveis ao diagnóstico que predizem este estado.

Métodos: Analisámos e comparámos os dados de 15 doentes com POMS com ≥8 e <18 de idade e 15 doentes com AOMS com ≥18 e <55 anos de idade, com diagnóstico de RRMS estabelecido no Centro Hospitalar e Universitário de Coimbra (CHUC), de acordo com os critérios de McDonald's 2010, com ≥1 ano sob DMT e com ressonância magnética disponível ao momento do diagnóstico e 1 ano após o início de DMT. Os doentes foram emparelhados de acordo com o género e tipo de tratamento em curso. Foram colhidas as caraterísticas demográficas, laboratoriais, clínicas e imagiológicas e foi avaliado o atingimento ou não do estado de NEDA-3. Foi usada a regressão logística para determinar quais as caraterísticas ao momento do diagnóstico que se associaram ao estado de NEDA-3 após 1 ano sob DMT. Consideramos estatisticamente significativo um valor de $p<0.05$.

Resultados: Foi encontrada uma diferença estatisticamente significativa entre grupos no número de lesões difusas com bordos mal definidos ponderadas em T2 (T2 WI) ($p=0.015$). A média da pontuação na *Expanded Disability Status Scale* (EDSS) após 1 ano sob DMT foi mais baixa nos doentes com POMS (1.6±0.8) comparativamente aos doentes com AOMS (2.3±0.8; $p=0.032$). Comparativamente aos doentes sob tratamento com Natalizumab, os doentes sob interferão beta apresentaram uma probabilidade 12 vezes superior de não atingir o estado de NEDA-3 ao fim de 1 ano ($p=0.029$).

Conclusão: Os resultados deste estudo reforçam a necessidade de uma abordagem terapêutica agressiva em doentes com POMS, podendo tal inclusivamente cursar com a prescrição de fármacos de 2ª linha, tendo em conta que este grupo de doentes está propenso a atingir altos níveis de incapacidade a longo prazo.

PALAVRAS CHAVE: Esclerose múltipla pediátrica; ressonância magnética; carga lesional; ausência de evidência de atividade da doença; terapêuticas modificadoras de doença.

INTRODUCTION

Multiple Sclerosis (MS) is a neurodegenerative chronic inflammatory 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 is not yet clearly proved in clinical practice.

The No Evidence of Disease Activity (NEDA-3), based on (i) no relapses, (ii) no evidence of magnetic resonance imaging (MRI) disease activity defined as the presence of gadolinium-enhanced lesions (Gd+) or new/enlarged T2 WI and (iii) no disability progression, defined as ≥1 point in the Expanded Disability Status Scale (EDSS) score, has been beheld as an outcome measure and as the overall goal for treatment in relapsing-remitting MS.[6,7]

In previous studies, 34% of patients treated with pegylated interferon beta-1a (ADVANCE study[8]) at 48 weeks, and 37% of patients treated with Natalizumab for 2 years (AFFIRM study[9]) achieved the NEDA-3 status. In a recent study, associating baseline characteristics to the NEDA-3 status in fingolimod-treated patients with RRMS, the risk of not achieving the NEDA-3 status was associated with a higher EDSS score at diagnosis and with a higher relapse rate in the year prior to treatment start.[7]

In this study, we intend to compare the clinical and imaging features of the pediatric MS population with relapsing-remitting multiple sclerosis (RRMS) with an adult population with the same clinical phenotype, both diagnosed at the Centro Hospitalar e Universitário de Coimbra (CHUC), at the time of diagnosis and after 1 year under DMT. This way, we aim 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.

METHODS

Study design and participants

This is an observational, retrospective, unicentric study.

We queried the Pediatric Neurology and Demyelinating Diseases consultations of the Hospital Pediátrico de Coimbra (HPC) and the Demyelinating Diseases consultation of Hospital Universitário de Coimbra (HUC) of CHUC databases, for all POMS patients ≥8 and <18 years at diagnosis and for AOMS patients ≥18 and <55 years at diagnosis, both groups with RRMS diagnosed according to the McDonald's 2010 criteria, established at the CHUC, under DMT for ≥1 year and with available MRI scans at the time of diagnosis (baseline MRI) and 1 year after DMT (control MRI).

We found 15 POMS patients who fulfilled these criteria who 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). Both groups of patients were analyzed and compared at the time of diagnosis and 1 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 established;
c) Laboratory information: presence/absence of oligoclonal bands;
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 of diameter, number of T1 WI-hypointense lesions (black holes) and number of Gd+ lesions.

Additionally, the following data concerning 1 year after DMT were collected:

a) Clinical characteristics: number of relapses (annualized relapse rate), EDSS score, and the NEDA-3 status;
b) MRI features: number of T2 WI-bright juxtacortical, periventricular, intracallosal, cerebellar and brainstem lesions, total number of T2 WI-bright lesions, new T2

WI-bright lesions, percentage of cases with reduction ≥50% in the 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 of diameter, number of T1 WI-hypointense lesions (black holes) and number of Gd+ lesions.

The MRI scans were performed in various imaging centers, but all with a magnetic field strength of 1.5T. 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 gadolinium 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 following parameters: 1) *no relapses* defined as absence of new symptoms or signs persisting for at least 24 hours, in the absence of concurrent illness; 2) *no evidence of MRI disease activity*, defined as absence of Gd+ or new/enlarged T2 WI lesions; and 3) *no disease progression*, defined as absence of an EDSS score increase of ≥1 point from baseline EDSS. Patients lacking data were categorized as no NEDA-3, if at least one of the demanding 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 1 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.

We used the independent t-test for the comparison between quantitative variables: EDSS at diagnosis, EDSS after 1 year under DMT, number of relapses prior to diagnosis and number of relapses in 1 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 3 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 correlation between NEDA-3 status achievement and variables at diagnosis. We considered statistically significant a value of $p<0.05$.

RESULTS

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

Table I – Demographic, baseline clinical and laboratory characteristics of both POMS and AOMS groups.

		POMS (n=15)	AOMS (n=15)	p value
DEMOGRAFIC CHARACTERISTICS				
Gender	Male	(n=8) 26.7%		
	Female	(n=22) 73.3%		
Race	Caucasian	(n=30) 100%		
Mean age at diagnosis		14.9 ± 2.1	36.2 ± 7.3	
CLINICAL CHARACTERISTICS				
Number of relapses prior to diagnosis	0	(n=12) 80%	(n=11) 73.3%	1
	1	(n=2) 13.3%	(n=4) 26.7%	
	2	(n=1) 6.7%	-	
Relapse topography prior to diagnosis	Medulla	(n=1) 33.3%	-	0.143
	Optic Nerve	(n=1) 33.3%	-	
	Brainstem	(n=1) 33.3%	(n=1) 25.0%	
	Hemispheric	-	(n=3) 75.0%	
Mean EDSS score		1.7 ± 0,9	2.3 ± 0.8	0.055
Treatment modality	1st line DMT	(n=10) 66.7%		
	Interferon beta	(n=5) 33.3%		
	Glatiramer acetate	(n=5) 33.3%		
	2nd line DMT	(n=5) 33.3%		
	Natalizumab	(n=5) 33.3%		
LABORATORY DATA				
Presence of CSF oligoclonal bands		(n=8) 53.3%	(n=11) 73.3%	0.214

All patients analysed were Caucasian. We included 8 (26.7%) males and 22 (73.3%) females and the mean age at diagnosis was 14.9 (± 2.1) years old for POMS and 36.2 (± 7.3) years old for AOMS patients.

We found no statistically significant difference in the number of relapses prior to diagnosis and their topography in between groups. The majority of both POMS (80.0%) and AOMS (73.3%) patients presented no relapses prior to diagnosis. From those patients who presented relapses prior to diagnosis, no POMS patient presented hemispheric relapses and no AOMS patient presented the medulla and optic nerve as relapse topography. The mean EDSS score at the time of diagnosis was tended to be lower on POMS comparing to AOMS patients, but without statistically significant difference between groups. Regarding treatment modality, 2/3 of the patients were under 1st line DMT (1/3 under interferon beta formulations and 1/3 under glatiramer acetate), while 1/3 were under a 2nd line drug (Natalizumab). Fewer POMS patients presented positive oligoclonal bands in the cerebrospinal fluid, when compared to AOMS patients, though that not reached a statistically significant difference.

The MRI features at diagnosis are listed in Tables II, III and IV and illustrated in the graphics from Figure 1 for POMS patients and Figure 2 for AOMS patients.

The MRI T2 WI features are shown in Table II. Concerning the total number of T2 WI lesions, although distributed throughout the lesion number categories, 40.0% of POMS (n=6) patients presented >10-20 lesions and 42.9% of AOMS (n=6) presented with >30 lesions. We did not find a tendency or a statistically significant difference between groups concerning T2 WI ovoid lesions with well-defined borders. Regarding the number of T2 WI lesions ≥1 cm of diameter, the majority of POMS patients present either absence of this type of lesions (n=8, 53.3%) or 1-5 lesions (n=6, 40.0%) while most AOMS patients present 1-5 lesions (n=9, 64.3%). 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%), whereas the percentages of AOMS patients appear more distributed in the lesion number categories.

Table II – MRI features of T2 WI lesions at diagnosis and comparison between groups.

		POMS (n=15)	AOMS (n=14)[1)]	p value
MRI FEATURES AT DIAGNOSIS – T2 WI LESION CHARACTERISTICS				
Total number of T2 WI lesions	1-5	-	(n=1) 7.1%	0.251
	>5-10	(n=4) 26.7%	(n=3) 21.4%	
	>10-20	(n=6) 40.0%	(n=1) 7.1%	
	>20-30	(n=3) 20.0%	(n=3) 21.4%	
	>30	(n=2) 13.3%	(n=6) 42.9%	
T2 WI ovoid lesions with well-defined borders	1-5	(n=1) 6.7%	(n=5) 35.7%	0.116
	>5-10	(n=5) 33.3%	(n=4) 28.6%	
	>10-20	(n=5) 33.3%	(n=3) 21.4%	
	>20-30	(n=4) 26.7%	(n=1) 7.1%	
	>30	-	(n=1) 7.1%	
T2 WI diffuse lesions with poorly defined borders	Absence	(n=4) 26.7%	(n=2) 14.3%	**0.015**
	1-5	(n=9) 60.0%	(n=3) 21.4%	
	>5-10	(n=1) 6.7%	(n=1) 7.1%	
	>10-20	-	(n=4) 28.6%	
	>20-30	(n=1) 6.7%	(n=2) 14.3%	
	>30	-	(n=2) 14.3%	
T2 WI lesions ≥1 cm of diameter	Absence	(n=8) 53.3%	(n=4) 28.6%	0.301
	1-5	(n=6) 40.0%	(n=9) 64.3%	
	>5-10	(n=1) 6.7%	(n=1) 7.1%	

[1)] **AOMS (n=14)** owed to the presence of unquantifiable MRI lesions in 1 patient.

The MRI T1 WI and Gd+ lesions are displayed in Table III. We found no statistically significant differences between groups. Concerning the number of T1 WI lesions, while the majority of POMS patients presents with 1-5 lesions (n=9, 60.0%), the percentages of AOMS patients are distributed throughout all the lesion number categories considered. About the number of Gd+ lesions, both groups present either absence of lesions or 1-5 lesions.

Table III – MRI T1 WI lesions and Gd+ lesions at diagnosis and comparison between groups.

		POMS (n=15)	AOMS (n=14)[1)]	p value
MRI FEATURES AT DIAGNOSIS – T1 WI CHARACTERISTICS				
Number of T1 WI lesions	Absence	(n=1) 6.7%	(n=1) 7.1%	0.115
	1-5	(n=9) 60.0%	(n=4) 28.6%	
	>5-10	(n=3) 20.0%	(n=4) 28.6%	
	>10-20	(n=1) 6.7%	(n=2) 14.3%	
	>20-30	(n=1) 6.7%	(n=2) 14.3%	
	>30	-	(n=1) 7.1%	
Number of Gd+ lesions[2)]	Absence	(n=7) 46.7%	(n=6) 50.0%	1
	1-5	(n=7) 46.7%	(n=5) 41.7%	
	>5-10	(n=1) 6.7%	(n=1) 8.3%	

[1)] **AOMS (n=14)** due 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 because of unknown reason).

The T2 WI location distribution is shown in Table IV. We also did not find any statistically significant difference between both groups. Concerning the cerebellar and brainstem lesion locations, most patients from both groups present either absence of lesions, or with 1-5 lesions. About the number of T2 WI juxtacortical and intracallosal lesions, most patients from both groups present 1-5 lesions. Regarding the number of T2 WI periventricular lesions, while the majority of POMS (n=8, 53.3%) patients presents with >5-10 lesions, the distribution of AOMS patients seems to be more equally distributed throughout the lesion number categories considered.

Table IV – MRI T2 WI lesions location at diagnosis and comparison between groups.

		POMS (n=15)	AOMS (n=14)[1)]	p value
MRI FEATURES AT DIAGNOSIS – T2 WI LESION LOCATION				
Number of T2 WI juxtacortical lesions	Absence	(n=1) 6.7%	-	0.216
	1-5	(n=10) 66.7%	(n=8) 57.1%	
	>5-10	(n=4) 26.7%	(n=4) 28.6%	
	>10-20	-	(n=1) 7.1%	
	>30	-	(n=1) 7.1%	
Number of T2 WI periventricular lesions[2)]	1-5	(n=5) 33.3%	(n=4) 30.8%	0.137
	>5-10	(n=8) 53.3%	(n=2) 15.4%	
	>10-20	(n=2) 13.3%	(n=4) 30.8%	
	>20-30	-	(n=2) 15.4%	
	>30	-	(n=1) 7.7%	
Number of T2 WI intracallosal lesions[3)]	Absence	(n=3) 20.0%	(n=3) 25.0%	1
	1-5	(n=12) 80.0%	(n=8) 66.7%	
	>5-10	-	(n=1) 8.3%	
Number of T2 WI cerebellar lesions	Absence	(n=7) 46.7%	(n=7) 50.0%	0.798
	1-5	(n=8) 53.3%	(n=5) 35.7%	
	>5-10	-	(n=2) 14.3%	
Number of T2 WI brainstem lesions	Absence	(n=8) 53.3%	(n=7) 50.0%	0.959
	1-5	(n=6) 40.0%	(n=6) 42.9%	
	>5-10	(n=1) 6.7%	(n=1) 7.1%	

[1)] **AOMS (n=14)** owed to the presence of unquantifiable MRI lesions in 1 patient.

[2)] **AOMS (n=13)** due 1 AOMS patient presenting confluent/diffuse lesion distribution.

[3)] **AOMS (n=12)** due to 2 AOMS patients presenting with confluent/diffuse lesion distribution.

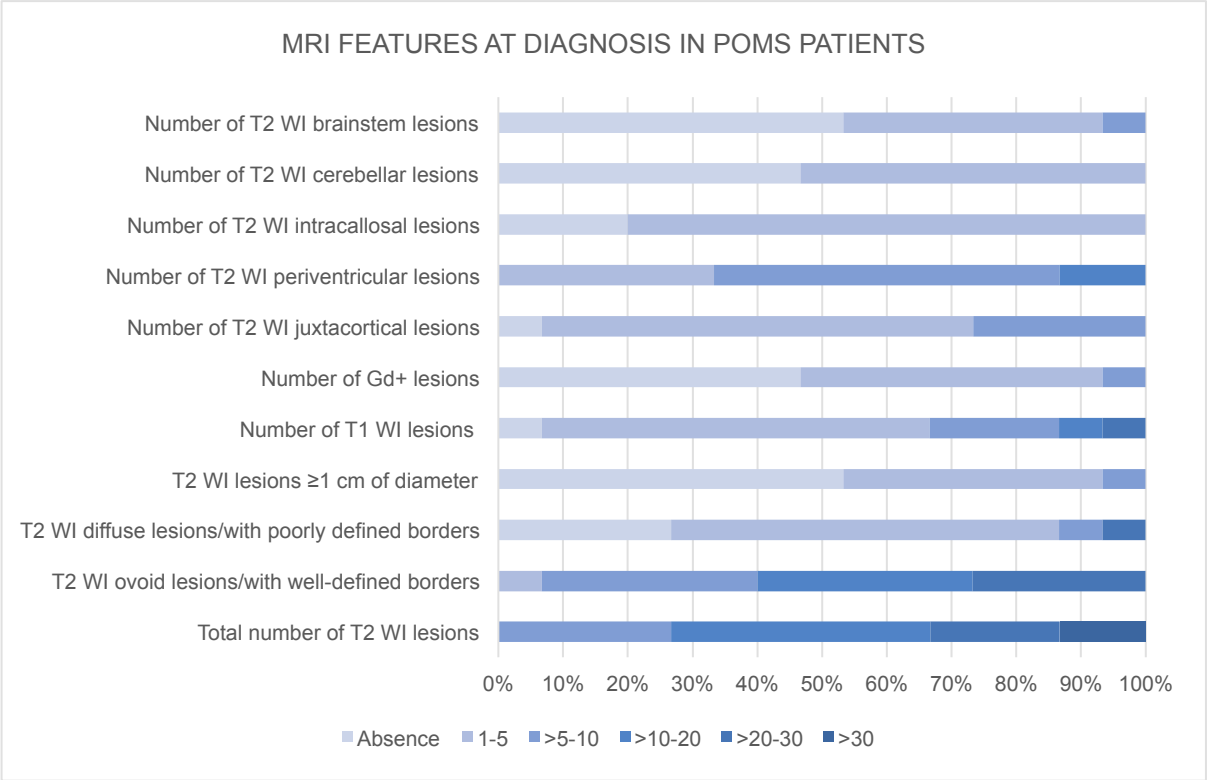

Figure 1 – MRI features at diagnosis in POMS patients.

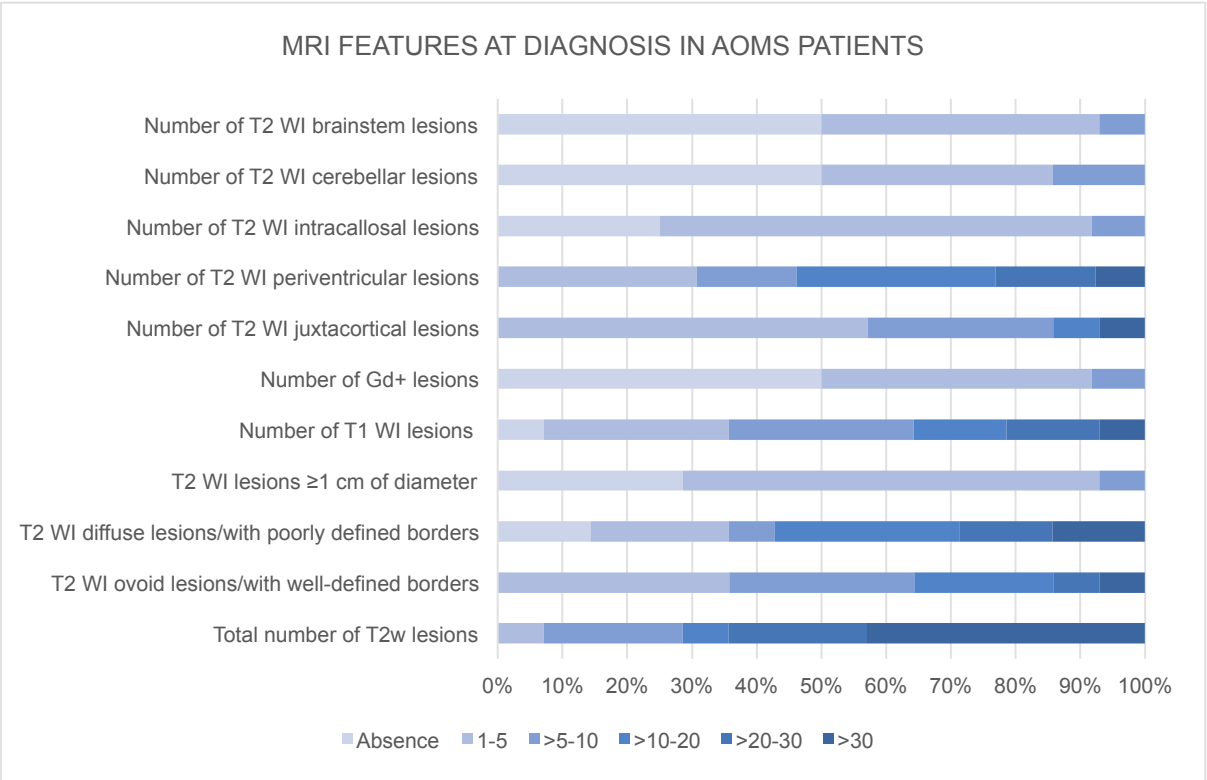

Figure 2 – MRI features at diagnosis in AOMS patients.

Clinical characteristics after 1 year under DMT and comparison between groups are listed in Table V. Most patients both from POMS (n=10, 66.7%) and AOMS (n=12, 80.0%) groups were relapse-free during 1 year under DMT. Four (26.7%) POMS and 3 AOMS (20.0%) patients presented 1 relapse, and from both groups, only 1 POMS patient presented an amount of 3 relapses while under DMT. We did not find a statistically significant difference between groups in the number of relapses during 1 year under DMT. The mean EDSS score after 1 year under DMT was lower in the POMS group, compared to the AOMS group, with statistically significant difference (p=0.032).

Table V – Clinical characteristics after 1 year under DMT and comparison between groups.

		POMS (n=15)	AOMS (n=15)	p value
CLINICAL CHARACTERISTICS AFTER 1 YEAR UNDER DMT				
Number of relapses/ 1 year	0	(n=10) 66.7%	(n=12) 80.0%	0.098
	1	(n=4) 26.7%	(n=3) 20.0%	
	3	(n=1) 6.7%	-	
Mean EDSS score		1.6 ± 0,8	2.3 ± 0.8	**0.032**

The MRI features 1 year after DMT are listed in Tables VI, VII, VIII and IX and illustrated in the graphics from Figure 5 for POMS patients and Figure 6 for AOMS patients.

The MRI features of T2 WI lesions 1 year after DMT and comparison between groups are listed in Table VI. In the total number of T2 WI lesions, both groups appear distributed in several number categories. From both groups, only 1 POMS patient presented no 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 the MRI feature analyses at diagnosis (Figure 3), with a higher percentage of POMS patients with absence of this type of lesion (n=5, 33.3%) and with 1-5 lesions (n=8, 53.3%), whereas the percentages of AOMS patients appear more distributed in the lesion number categories.

There is a statistical tendency in the number T2 WI ovoid lesions with well-defined borders, although without statistically significant difference 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 present 1-5 lesions

(n=4, 30.8%) and >5-10 lesions (n=6, 46.2%). Relatively to the number of T2 WI lesions ≥1 cm of diameter, both groups present either absence of lesions or 1-5 lesions.

Table VI – MRI features of T2 WI lesions 1 year after DMT and comparison between groups.

		POMS (n=15)	AOMS (n=13)[1)]	p value
MRI FEATURES AFTER 1 YEAR UNDER DMT – T2 WI LESIONS CARATERISTICS				
Total number of T2 WI lesions	Absence	(n=1) 6.7%	-	0.414
	1-5	-	(n=1) 7.7%	
	>5-10	(n=2) 13.3%	(n=2) 15.4%	
	>10-20	(n=4) 26.7%	(n=1) 7.7%	
	>20-30	(n=4) 26.7%	(n=3) 23.1%	
	>30	(n=4) 26.7%	(n=6) 46.2%	
T2 WI ovoid lesions well-defined borders	Absence	(n=1) 6.7%	-	0.056
	1-5	(n=1) 6.7%	(n=4) 30.8%	
	>5-10	(n=2) 13.3%	(n=6) 46.2%	
	>10-20	(n=5) 33.3%	(n=1) 7.7%	
	>20-30	(n=5) 33.3%	(n=1) 7.7%	
	>30	(n=1) 6.7%	(n=1) 7.7%	
T2 WI diffuse lesions poorly defined borders	Absence	(n=5) 33.3%	(n=1) 7.7%	**0.004**
	1-5	(n=8) 53.3%	(n=3) 23.1%	
	>5-10	(n=1) 6.7%	(n=2) 15.4%	
	>10-20	-	(n=4) 30.8%	
	>20-30	-	(n=1) 7.7%	
	>30	(n=1) 6.7%	(n=2) 15.4%	
T2 WI lesions ≥1 cm of diameter	Absence	(n=8) 53.3%	(n=5) 38.5%	0.476
	1-5	(n=7) 46.7%	(n=8) 61.5%	

[1)] **AOMS (n=13)** owed to the presence of unquantifiable MRI lesions in 1 patient and impossibility of access to control MRI in another.

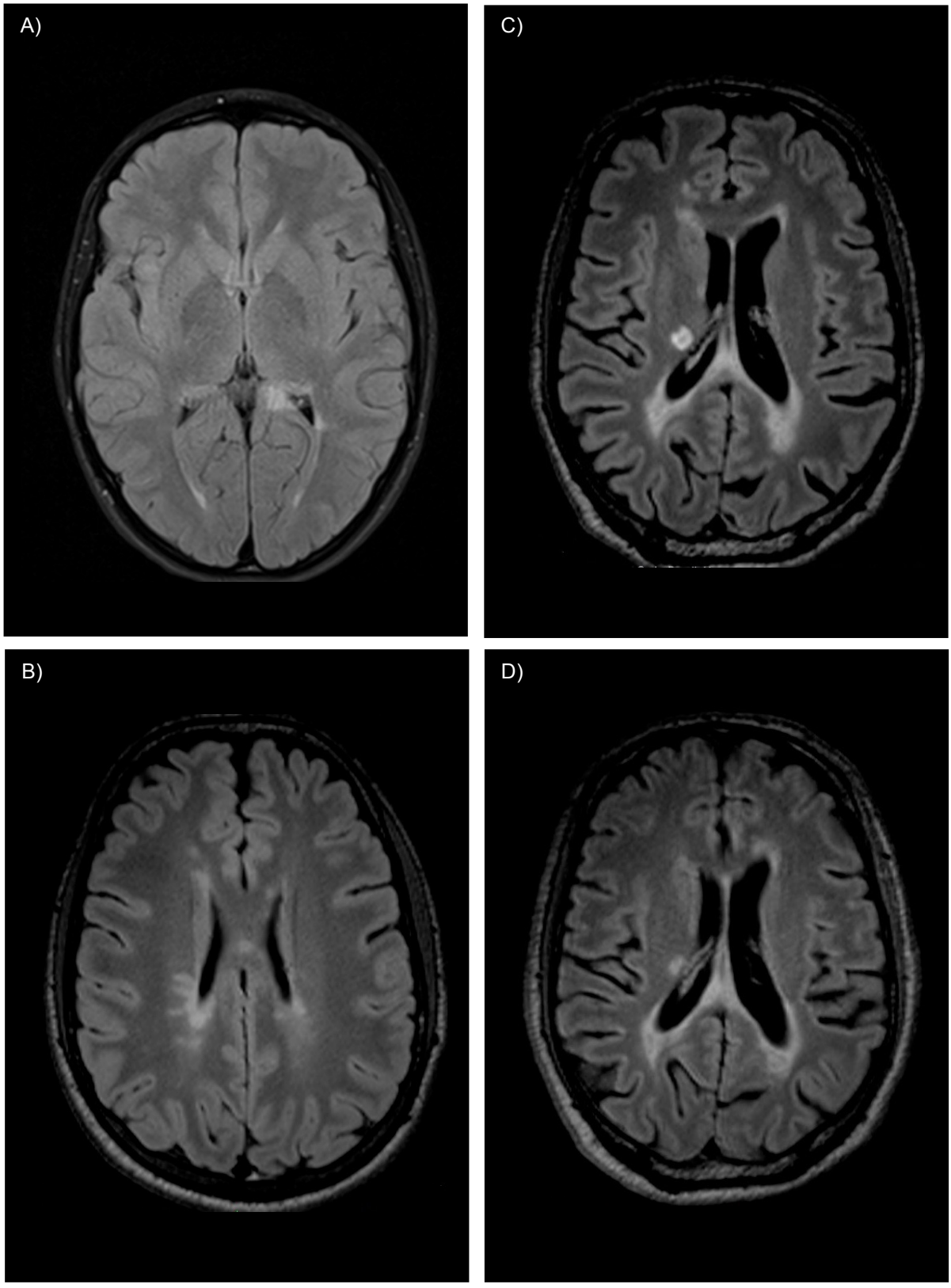

Figure 3 – T2 WI FLAIR axial images of diffuse lesions with poorly defined borders. MRI scan of a 16-year-old girl (A) and from a 14-year-old boy (B) at diagnosis. MRI scan from 51-year-old man at diagnosis (C) and 1 year after DMT (D).

The MRI T1 WI and Gd+ lesions 1 year after DMT are presented in Table VII. We found no statistically significant difference between groups in these two imaging features. Concerning T1 WI number of lesions, the percentage of patients from both groups appears spread between all categories of lesion number considered. Relatively to the number of Gd+ lesions, in both groups the majority of patients presents without Gd+.

Table VII – MRI T1 WI lesions and Gd+ lesions 1 year after DMT and comparison between groups.

		POMS (n=15)	AOMS[1)] (n=13)	p value
MRI FEATURES AFTER 1 YEAR UNDER DMT – T1 WI AND GD+ LESIONS				
Number of T1 WI lesions	Absence	(n=2) 13.3%	(n=1) 7.7%	0.282
	1-5	(n=7) 46.7%	(n=4) 30.8%	
	>5-10	(n=2) 13.3%	(n=3) 23.1%	
	>10-20	(n=3) 20.0%	(n=2) 15.4%	
	>20-30	-	(n=2) 15.4%	
	>30	(n=1) 6.7%	(n=1) 7.7%	
Number of Gd+ lesions[2)]	Absence	(n=11) 78.6%	(n=10) 90.9%	0.525
	1-5	(n=2) 14.3%	(n=1) 9.1%	
	>5-10	(n=1) 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.

The new T2 WI lesions and percentage of patients with reduction of ≥50% on T2 WI lesion number 1 year after DMT is displayed in Table VIII. Regarding the new T2 WI lesions on MRI, the majority of patients from both groups present either absence of new lesions or 1-5 lesions. From both groups, only 1 POMS patient presented a reduction of ≥ 50% on the number of T2 WI lesions (Figure 4).

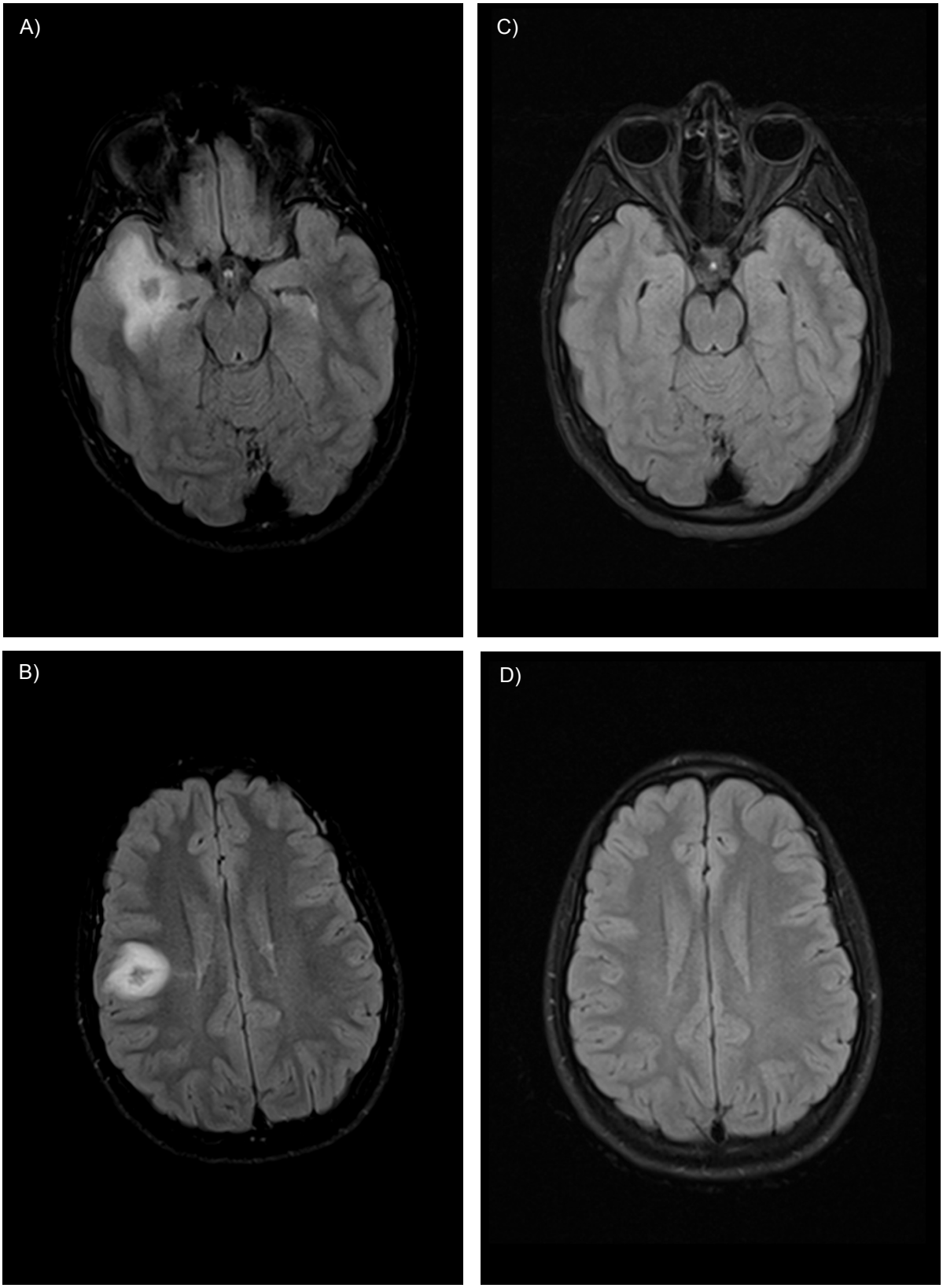

Figure 4 – Images from a 13-year-old girl with MS. T2 WI FLAIR axial images at diagnosis showing 2 diffuse lesions with poorly defined borders each with ≥1 cm of diameter (A, B). Axial FLAIR images 1 year after DMT showing complete resolution of the lesions identified in the MRI scan at diagnosis (C, D).

Table VIII – MRI new T2 WI lesions and reduction of ≥ 50% on T2 WI lesion number 1 year after DMT.

		POMS (n=15)	AOMS (n=13)[1)]	p value
MRI AFTER 1 YEAR UNDER DMT – T2W NEW AND REDUCTION OF ≥ 50% ON LESION NUMBER				
Number of T2 WI new lesions	Absence	(n=6) 40.0%	(n=8) 61.5%	0.188
	1-5	(n=5) 33.3%	(n=4) 30.8%	
	>5-10	(n=2) 13.3%	(n=1) 7.7%	
	>10-20	(n=1) 6.7%	-	
	>30	(n=1) 6.7%	-	
Reduction ≥50% on T2 WI lesion number		(n=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.

The MRI T2 WI lesions location 1 year after DMT and comparison between groups is shown in Table IX. The percentage of patients with periventricular lesions, in both groups, appears spread between all categories of lesion number considered. Concerning the cerebellar and brainstem lesion locations, most patients from both groups present either absence of lesions or 1-5 lesions. Regarding the intracallosal and juxtacortical lesions, the majority of patients from both groups presents with 1-5 lesions. We found no statistically significant difference between groups in lesion location after 1 year under DMT.

Table IX – MRI T2 WI lesions location 1 year after DMT and comparison between groups.

		POMS (n=15)	AOMS (n=13)[1)]	p value
MRI FEATURES AFTER 1 YEAR UNDER DMT – T2 WI LESION LOCATION				
Number of T2 WI juxtacortical lesions	Absence	(n=1) 6.7%	-	0.229
	1-5	(n=10) 66.7%	(n=7) 53.8%	
	>5-10	(n=3) 20.0%	(n=4) 30.8%	
	>10-20	(n=1) 6.7%	(n=1) 7.7%	
	>30	-	(n=1) 7.7%	
Number of T2 WI periventricular lesions[2)]	Absence	(n=1) 6.7%	-	0.151
	1-5	(n=6) 40.0%	(n=3) 25.0%	
	>5-10	(n=4) 26.7%	(n=3) 25.0%	
	>10-20	(n=3) 20.0%	(n=3) 25.0%	
	>20-30	-	(n=2) 16.7%	
	>30	(n=1) 6.7%	(n=1) 8.3%	
Number of T2 WI intracallosal lesions[3)]	Absence	(n=3) 20.0%	(n=2) 18.2%	0.682
	1-5	(n=12) 80.0%	(n=8) 72.7%	
	>5-10	-	(n=1) 9.1%	
Number of T2 WI cerebellar lesions	Absence	(n=7) 46.7%	(n=7) 53.8%	1
	1-5	(n=8) 53.3%	(n=5) 38.5%	
	>5-10	-	(n=1) 7.7%	
Number of T2 WI brainstem lesions	Absence	(n=8) 53.3%	(n=6) 46.2%	0.909
	1-5	(n=5) 33.3%	(n=6) 46.2%	
	>5-10	(n=2) 13.3%	(n=1) 7.7%	

[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)] **AOMS (n=12)** due 1 AOMS to confluent or diffuse lesion distribution.

[3)] **AOMS (n=11)** due to 2 AOMS patients presenting with confluent/diffuse lesion distribution.

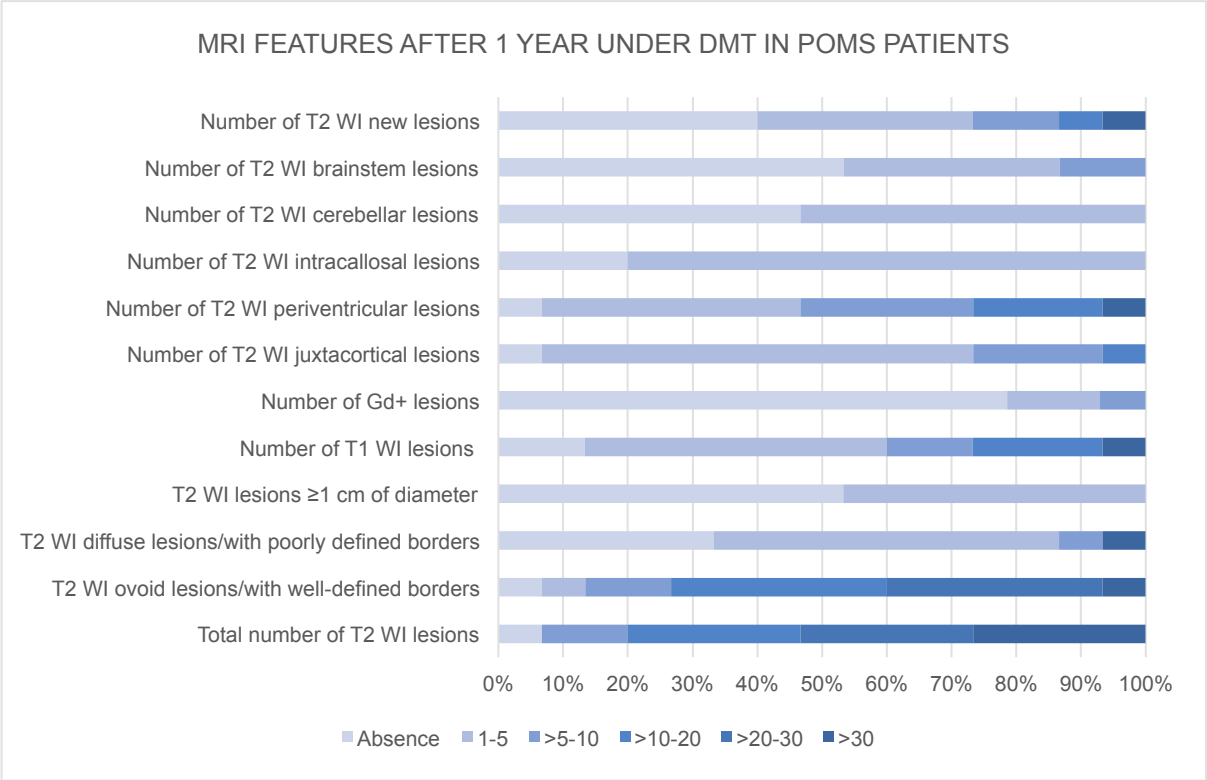

Figure 5 – MRI features after 1 year under DMT in POMS patients.

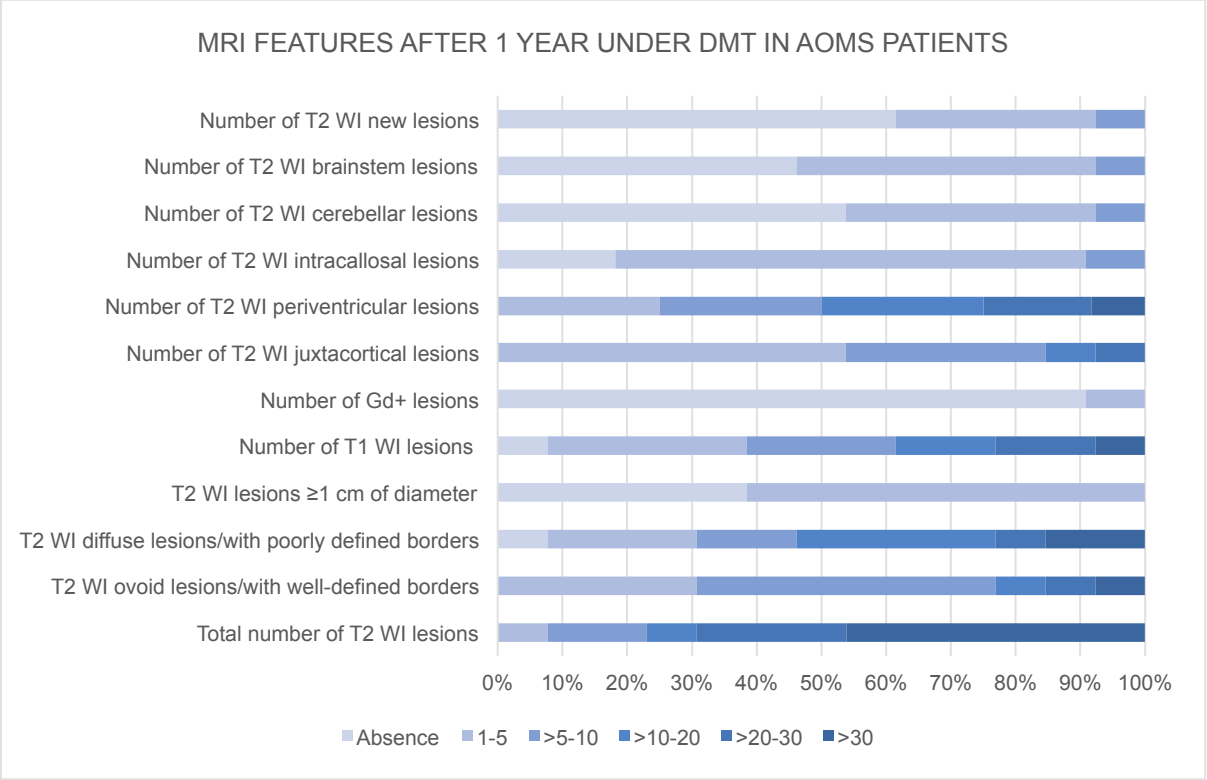

Figure 6 – MRI features after 1 year under DMT in AOMS patients.

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 Table X and in Figure 7 for POMS and in Figure 8 for AOMS patients.

Table X – NEDA-3 status and its 3 composite variables.

		POMS	AOMS	p value
NEDA-3				
NEDA-3 status achievement POMS (n=14)[1)] AOMS (n=11)[2)]		(n=4) 28.6%	(n=4) 36.4%	1
Composite variables	No relapses POMS (n=15) AOMS (n=15)	(n=10) 66.7%	(n=12) 80.0%	0.682
	No evidence of MRI disease activity POMS (n=15) AOMS (n=11)[2)]	(n=6) 40.0%	(n=6) 54.5%	0.692
	No disability progression[3)] POMS (n=13) AOMS (n=13)	(n=13) 100%	(n=11) 84.6	0.480

[1)] **POMS (n=14)** due to lack of information that enable the evaluation of absence of clinical disability progression.

[2)] **AOMS (n=11)** since the NEDA-3 status determination was not possible, owed to lack of data that enabled the evaluation of absence of MRI disease activity – 1 patient lacked a control MRI, 1 patient with unquantifiable MRI lesions and 2 patients who lacked a T1 WI scan with Gd contrast.

[3)] **POMS (n=13)** due to absence of data on the EDSS score at diagnosis of 2 patients and **AOMS (n=13)** due to lack of EDSS score at diagnosis in 1 patient and EDSS score after 1 year under DMT in another.

We found no statistically significant differences in between groups either in the NEDA-3 status achievement, nor on its 3 individual components. The NEDA-3 status was achieved by around a third of both POMS and AOMS patients. On 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 evidence of disease activity. Furthermore, we found that, compared to patients under Natalizumab, patients who were under Inteferon beta as DMT of choice presented a 12 time-fold higher probability of not achieving the NEDA-3 status (p=0.029). The model was statistically significant (p=0.002) and explained 68% of the variability in whether one would not achieve the NEDA-3 status. We did not find any other statistically significant correlation between the NEDA-3 status achievement and demographic, clinical, laboratory or MRI features present at diagnosis.

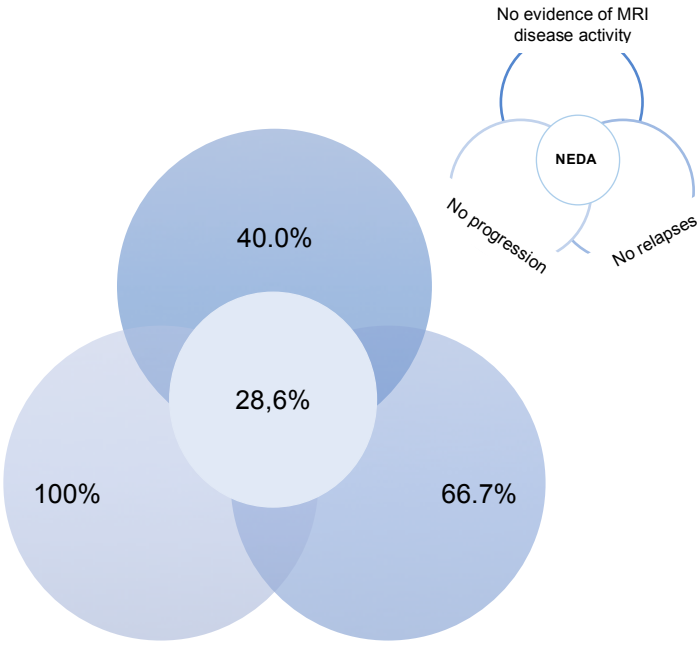

Figure 7 – NEDA-3 status and its 3 components in POMS group.

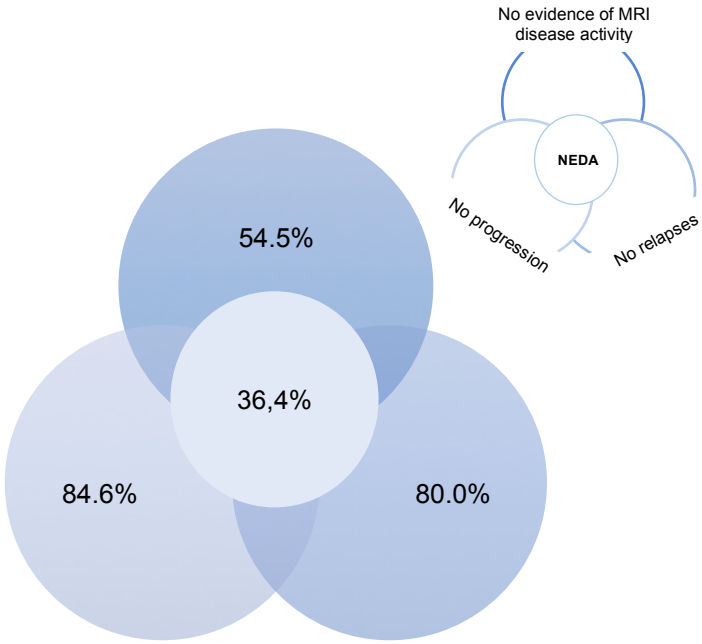

Figure 8 – NEDA-3 status and its 3 components in AOMS group.

DISCUSSION

The gender distribution of POMS patients showed a greater number of female patients affected. Since the mean age at diagnosis was 14.9 (± 2.1), the female preponderance is consistent with a prior Portuguese study and the international literature that states that the increased female preponderance in RRMS starts after puberty.[10,11]

Studies show that 40-50% of POMS patients present positive CSF oligoclonal bands, which is less than in AOMS patients.[3] Our findings are consistent with these results. The mean EDSS score at diagnosis was higher in AOMS patients compared to POMS patients, both at diagnosis (not statistically significant) and after 1 year under DMT (p=0.032), which is due to a slower disease progression in POMS compared to AOMS.[3]

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

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. Also, studies show that on follow-up MRI scans, POMS patients tend to have more new T2 WI and Gd+ lesions.[10,12] In our study, we did not find a tendency or a statistically significant difference between groups, which can be due to the fact that late-onset POMS tends to have a more similar to AOMS' MRI phenotype, than early-onset POMS (age <11 years old). Still, regarding MRI features, we found a statistically significant difference between groups in the number of T2 WI diffuse lesions with poorly defined borders, both at diagnosis and 1 year after DMT, with POMS patients evidencing fewer lesions than AOMS patients. This is a surprising 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 <11 years old and may vanish during disease course.

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 is reached. Although we were expecting a greater percentage of POMS patients reaching the NEDA-3 status, taking into account that DMT target the peripheral immune system and that POMS presents a greater underlying inflammatory burden than AOMS,[13] we did not find a statistically significant difference 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. Also, studies indicate that approximately 50% of AOMS achieve the NEDA-3 status after 2 years of follow-up, which can explain our lower percentage compared to these studies.[14]

Though relapses are more frequent in POMS than AOMS, our groups presented no statistically significant difference in the number of relapses during 1 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 2 neurologic episodes was estimated in 2.0 years.[3]

Regarding the "no evidence of MRI disease activity", there were no differences found between our two groups. This can be partly due both to the fact that there were also no differences in the number of relapses during 1 year under DMT[15] and by the short follow-up time. Furthermore, that could also explain the similar results between both groups in the NEDA-3 parameter "no disability progression".

In our study, we found that, compared to patients under Natalizumab as DMT, patients who were under Inteferon beta presented a 12 time-fold higher probability of not achieving the NEDA-3 status. This finding might be due to an increased efficacy of 2nd line DMT compared to 1st line DMT.

Our study encountered several 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. 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 amount 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.

CONCLUSIONS

The ultimate goal of treating MS patients is to prevent disability. Compared to patients under Natalizumab as DMT, patients who were under Interferon beta presented a higher probability of not achieving the NEDA-3 status. This information suggests that treatment with more effective drugs (such as Natalizumab) may lead to a better disease control in the early onset of the disease, supporting the need for an aggressive treatment approach in POMS patients, since this group is prone to experience high disability levels in the long term.

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