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ARTICLE

Late onset multiple sclerosis: concerns in aging patients

Esclerose múltipla de início tardio: atenção a uma população que envelhece

Claudia Beatriz de Campos Lotti[1], Acary Souza Bulle Oliveira[1], Denis Bernardi Bichuetti[1], Isac de Castro[2], Enedina Maria Lobato Oliveira[1]

ABSTRACT

Late onset multiple sclerosis (LOMS) is when the first symptom starts after 50 years of age, representing 4.5% of multiple sclerosis (MS) patients. This study describes the clinical characteristics of patients with LOMS followed at a specialized MS center in São Paulo. Data was obtained from medical records of 742 patients with MS. The LOMS frequency was 4.18%, median age at onset was 54 years and the predominant disease course was primary progressive (64.3%). The patients reached the disability landmarks of EDSS grades 3.0, 6.0 and 7.0 in the following proportion and time: EDSS 3.0: 77.42% of patients in 3.7 years; EDSS 6.0: 58.06% in 5.1 years and EDSS 7.0: 32.26% in 5.7 years. The comparative analysis with a matched control group of patients with early onset MS showed that late onset, associated with a progressive course, were predictors of reaching EDSS 3.0 and 6.0 in a shorter time.

Keywords: aging; epidemiology; multiple sclerosis; disease progression.

RESUMO

Esclerose múltipla de inicio tardio (EMIT) caracteriza-se pelo início de sintomas aos 50 ou mais anos de idade, representando 4,5% dos pacientes com esclerose múltipla (EM). Este estudo descreve as características clínicas de pacientes com EMIT acompanhados num centro de EM em São Paulo. Dados foram obtidos através de análise de prontuário de 742 pacientes com EM. A frequência de EMIT foi de 4,18%, a mediana da idade de início foi de 54 anos e a forma clínica predominante a primariamente progressiva (64,3%). Os pacientes atingiram os marcos de incapacidade EDSS 3, 6 e 7 nas respectivas proporções e tempo: EDSS 3.0, 77,42% de pacientes em 3.7 anos; EDSS 6.0, 58,06% em 5.1 anos e EDSS 7.0, 32,26% em 5.7 anos. A análise comparativa a um grupo controle de jovens com EM, mostrou que o início tardio associado a forma primariamente progressiva foram preditores para atingir EDSS 3 e 6 num período menor.

Palavras-chave: envelhecimento; epidemiologia; esclerose múltipla; progressão da doença.

Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system that predominantly affects young adults between 20 and 40 years of age. Therefore, an uncommon form of MS is one in which symptoms start at 50 plus years of age, called late onset multiple sclerosis (LOMS)[1,2,3,4,5,6,7,8]. It accounts for 1.4% to 9.9% of the MS population in different countries[2,4,5,7,9,10,11,12].

On average, LOMS represents roughly 4.5% of the MS population[2,4,5,7], it has a female preponderance[1,2,4,7,12], its initial presentation is monosymptomatic, with a motor or cerebellar symptom, and the most common clinical course is primary progressive[4,13,14].

The progression to disability in LOMS has previously been attributed to disease duration time[15], to clinical form[2], gender[8], and older age at the time of the patient's first examination[13]. The later onset has been associated with a greater possibility of reaching Expanded Disability Status Scale (EDSS) grade 6.0 in a shorter period[16].

Vascular disease of the central nervous system and cervical spondylotic myelopathy are the main differential diagnoses, due to a higher prevalence at this age and possible similar symptoms[1,4,13,17,18]. Because of previous co-morbid conditions and higher odds of T2-hyperintense lesions on magnetic resonance imaging (MRI) of elderly patients[7,13,19], there is a delay in diagnosis that can reach three to five years in almost 40% of LOMS patients[7,14,20].

There is scanty literature concerning what influences the presentation and progression to disability in this age group, and few papers compare this population with young MS adults.

The purpose of this study is to describe the demographic, clinical and laboratory characteristics of patients with LOMS

[1]Universidade Federal de São Paulo, Departamento de Neurologia, São Paulo SP, Brasil;

[2]Universidade de São Paulo, Faculdade de Medicina, Disciplina de Nefrologia, São Paulo SP, Brasil.

Correspondence: Claudia Beatriz de Campos Lotti; Universidade Federal de São Paulo, Departamento de Neurologia; Rua Botucatu, 740; 04023-900 São Paulo SP, Brasil; E-mail: claudiabclotti@gmail.com

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followed at the MS center of the Neurology Department of the Federal University of São Paulo.

METHODS

The Neuroimmunology Clinic of the Federal University of São Paulo is a specialized center for the treatment of patients with MS and other demyelinating diseases. It has maintained a database with information on clinical status, laboratory tests, radiological evaluation and treatment of all patients under follow up, since 1994. Data for this retrospective cohort study was obtained from the medical records of 742 patients with MS.

The LOMS patients were defined by the occurrence of the first MS symptoms after age 50, meeting either Poser's or the McDonald criteria, depending on the current diagnostic criteria at the moment of their first appointment. According to the current diagnostic criteria, neuromyelitis optica patients were excluded from the analysis.

Information gathered from their clinical records included: demographic characteristics; disease onset and duration; follow-up time; onset, first and last visit symptoms and signs; EDSS scores in the first and last visit; disease course; number of relapses, progression index; MRI data, cerebral spinal fluid (CSF) and evoked potential findings.

Additionally, LOMS patients were compared to a young onset MS (YOMS) control group, matched according to sex and clinical form, in a 2:1 proportion. For this analysis, nine LOMS patients with a follow-up of less than 12 months were excluded.

This study was approved by the local institutional ethics committee (IRB) and registered under number 256958.

Statistical analyses

Continuous variables were tested for normality with the Kolmogorov-Smirnov and Shapiro Wilk tests and the values are expressed as median and percentiles 25 and 75. The categorical data are presented as absolute values and percentages and were tested using Pearson's $\chi 2$ test and Fisher's exact test, if applicable.

Nonparametric data was compared using the Mann-Whitney U test for two independent samples.

Discrimination of variables was calculated by a receiver operator characteristic curve (ROC curve) utilizing the area under the curve and asymptotic significance. Some continuous variables were categorized through the ROC curve. The cutoff points were calculated using the value with the best sensitivity and specificity.

The Kaplan-Meier model with log-rank test was applied at times, to obtain EDSS values.

A cox proportional model was used to determine predictive factors for reaching specific EDSS milestones and the hazards ratios were calculated.

Statistical significance was considered with $p \leq 0.05$ and the analyses were performed using SPSS 19.0.

RESULTS

LOMS population

Of the 742 patients with MS, 31 were LOMS patients, representing a percentage of 4.18%. The gender distribution was 2.1 females to 1 male patient, of whom 19 were Caucasian, three were Afro-descendant, two were of mixed ethnicity and there was no information on seven patients. The median age of initial symptoms was 54, 22 patients (71%) were between 50 and 55 years old, and only two patients were over 60 years old, which is referred to as very late onset MS.

The initial neurological presentation was motor impairment in 54.8% and cerebellar involvement in 29.0%, sensory impairment and brainstem symptoms in 19.4% each, visual in 16.1% and vesical dysfunction in 3.2% A multi-topographic involvement was described in 38.7%, and the most frequent combination was motor and cerebellar.

Three patients did not have enough information to define their clinical course, therefore they were excluded from the LOMS population analysis. Of the remaining 28 patients, 64.3% were primary progressive and 35.7% relapsing-remitting. In our study, there were no secondary progressive cases of LOMS.

The median follow-up period was 2.2 years and 3.1 years for primary progressive multiple sclerosis (PPMS) and relapsing-remitting multiple sclerosis (RRMS), respectively, while median disease time was of 9.2 for PPMS and 4.9 years for RRMS. Considering the RRMS patients, 70% had their second relapse less than a year after the first symptom. The median EDSS scores on the first and last evaluation for the RRMS group was 2.0 on both visits, and for the PPMS group was 2.0 at the initial visit and 7.0 on the last visit. Patients with LOMS reached the disability landmarks of EDSS 3.0, 6.0 and 7.0 in the following proportion and time: EDSS 3.0: 77.42% of patients in 3.7 years; EDSS 6.0: 58.06% in 5.1 years, and EDSS 7.0: 32.26% in 5.7 years (Tables 1 and 2). Of the 31 patients, three deaths

Table 1. Demographic and clinical data of the late onset multiple sclerosis patients with well-defined disease course.

Clinical course	RRMS		PPMS	
	n	(%)	n	(%)
Gender				
Female	7	70.0	11	61.1
Male	3	30.0	7	38.9
Ethnicity				
Caucasian	5	71.4	12	80.0
African descendent	1	14.3	2	13.3
Mixed ethnicity	1	14.3	1	6.7
	Median	(25–75)	Median	(25–75)
Time				
Age of onset	54	(52–54)	54	(51–57)
Disease duration (years)	4.9	(4.0–7.9)	9.2	(3.3–11.6)
Follow-up time (months)	37.5	(21.8–56.7)	25.8	(12.1–76.1)
Time to reach EDSS 3 (years)	3.8	(1.4–7.3)	3.8	(1.0–4.1)

RRMS: relapsing remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis; n: number of patients; EDSS: expanded disability status scale.

occurred during the follow-up: one from gastrointestinal bleeding, one myocardial infarction and one unknown cause.

Descriptions of brain MRI scans were compatible with MS in all patients. Sixteen of them had descriptions of spinal cord MRIs, of which nine (56.3%) had one or more lesions. Only 11 patients had their CSF analyzed, of which 54.5% had oligoclonal bands. Only six had visual evoked potential studies, with altered potentials in five (83.3%).

Table 2. EDSS milestones of the 31 late onset multiple sclerosis patients, despite disease course.

Variable	Median	(25%–75%)
First visit EDSS	3	(2.5– 6.0)
Last visit EDSS	6.5	(2.5–8.0)
Time in years to EDSS 3	3.7	(0.7– 5.9)
Time in years to EDSS 6	5.1	(2.9–8.7)
Time in years to EDSS 7	5.7	(3.5–10.5)
	n	%
Reached EDSS 3	24	77.40
Reached EDSS 6	18	58.1
Reached EDSS 7	10	32.30

EDSS: expanded disability status scale; n: number of patients.

LOMS versus YOMS

Twenty-two LOMS patients were compared to 44 patients with YOMS, whose initial symptom had started between 20 and 40 years of age.

We found no significant statistical difference between initial symptoms or functional system reported by either group on initial or final evaluation. The predominant initial symptom in RRMS patients was brainstem in the LOMS (44%) and sensitive in the YOMS (39%), while patients with the progressive form in both groups had predominantly motor symptoms.

The progression index (calculated by dividing the EDSS score by the disease duration time) was worse in the LOMS patients, more clearly seen in the PPMS group, 0.55 versus 0.74, for younger and older onset respectively. The annual relapsing rate was higher in the younger group (median of 0.7 versus 0.51). Neither of these differences had statistical significance (Tables 3 and 4).

Table 3. Young onset relapsing-remitting multiple sclerosis group comparison to the late onset relapsing-remitting multiple sclerosis group.

RRMS (age onset)	< 50 YORRMS		≥ 50 LORRMS		Mann-Whitney
	Median	(25%–75%)	Median	(25%–75%)	p-value
Disease duration (years)	5.6	(3.4–9.5)	5.4	(4.2–7.9)	0.980
Follow up (months)	36.7	(23.7–68.1)	44.1	(28.3–56.7)	0.940
EDSS-First Visit^{+}	2.0	(1.0–2.5)	2.0	(1.5–3.5)	0.668
EDSS-Last Visit^{++}	2.0	(1.0–2.0)	2.5	(2.0–3.0)	0.176
Total number of relapses	3.0	(3.0–5.0)	3.0	(2.0–4.0)	0.298
Time in months from 1^{0} to 2^{0} relapse	11.1	(6.1–25.4)	8.1	(2.0–22.3)	0.322
Time from onset to initial evaluation (months)	12.2	(7.6–49.5)	15.1	(6.9–37.7)	0.980
Annual relapse rate	0.7	(0.34–1.05)	0.51	(0.48–0.68)	0.253
Progression Index	0.3	(0.25–0.34)	0.4	(0.23–0.54)	0.616
Time to reach EDSS 3 (years)	4.6	(2.7 -7.0)	3.8	(1.4–7.3)	0.628
Time to reach EDSS 6 (years)	5.6	(2.9–9.5)	5.4	(4.2–8.7)	0.999
Time to reach EDSS 7 (years)	5.6	(3.4–9.5)	5.4	(4.2–8.7)	0.999

RRMS: relapsing-remitting multiple sclerosis; YORRMS: Young onset relapsing-remitting multiple sclerosis; LORRMS: late onset relapsing-remitting multiple sclerosis; EDSS: expanded disability status scale.

Table 4. Young onset primary progressive multiple sclerosis group comparison to the late onset primary progressive multiple sclerosis group.

PPMS (Age onset)	< 50 YOPPMS		≥ 50 LOPPMS		Mann-Whitney
	Median	(25% - 75%)	Median	(25% - 75%)	p-value
Disease Duration (years)	13.5	(8.7–16.5)	7.2	(3.3–11.6)	0.021
Follow up (months)	86.1	(67–124.1)	25.8	(16.1–76.1)	0.005
EDSS-First Visit^{+}	3.5	(3.0–6.0)	3.0	(3.0–4.0)	0.219
EDSS-Last Visit^{++}	6.5	(6.5–8.0)	7.5	(6.5–8.0)	0.691
Time from onset to initial evaluation (months)	49.3	(30.3–73.6)	49.0	(27.7–49.6)	0.452
PI (Progression Index)	0.55	(0.43–0.81)	0.74	(0.63–1.83)	0.058
Time to reach EDSS 3 (years)	3.0	(2.1–4.1)	3.1	(0.9–4.1)	0.711
Time to reach EDSS 6 (years)	6.8	(4.6–10.5)	5.5	(2.8–8.7)	0.324
Time to reach EDSS 7 (years)	9.0	(8–14.3)	7.3	(4.3–11.6)	0.168

PPMS: primary progressive multiple sclerosis; YOPPMS: young onset primary progressive multiple sclerosis; LOPPMS: late onset primary progressive multiple sclerosis; EDSS: expanded disability status scale; n: number of patients.

The median time to reach EDSS 3.0, 6.0 and 7.0 for the older RRMS patients was 3.8, 5.4 and 5.4 years, respectively, and in the younger group was 4.6, 5.6 and 5.6 years. In the PPMS group, the older patients reached EDSS grades 3.0, 6.0 and 7.0 in 3.1, 5.5 and 7.3 years, while the young patients reached these landmarks in 3.0, 6.8 and 9.0 years, respectively (Figure). The three EDSS milestones were reached in less time in the LOMS group compared to the YOMS, but there was no statistical significance (Tables 3 and 4).

The cox regression models were applied to find the predictive factors for reaching the EDSS grades 3.0 and 6.0 in a shorter time. We observed that patients who were 50 years and older and the ones with a primary progressive form, reached EDSS grades 3.0 and 6.0 significantly earlier. These variables were co-dependent (Table 5).

All patients had brain MRI scans that fulfilled dissemination in time and space, compatible with an MS diagnosis at first visit. Spinal MRI was performed in four patients with late onset RRMS, but did not show any spinal cord abnormalities, in contrast to the young group, in which 90% of the scans showed MS lesions. Conversely, within the PPMS patients, spinal inflammatory lesions were found in both age groups at the same proportion. We observed that the positivity of oligoclonal bands in spinal fluid was much higher in the younger group (Table 6).

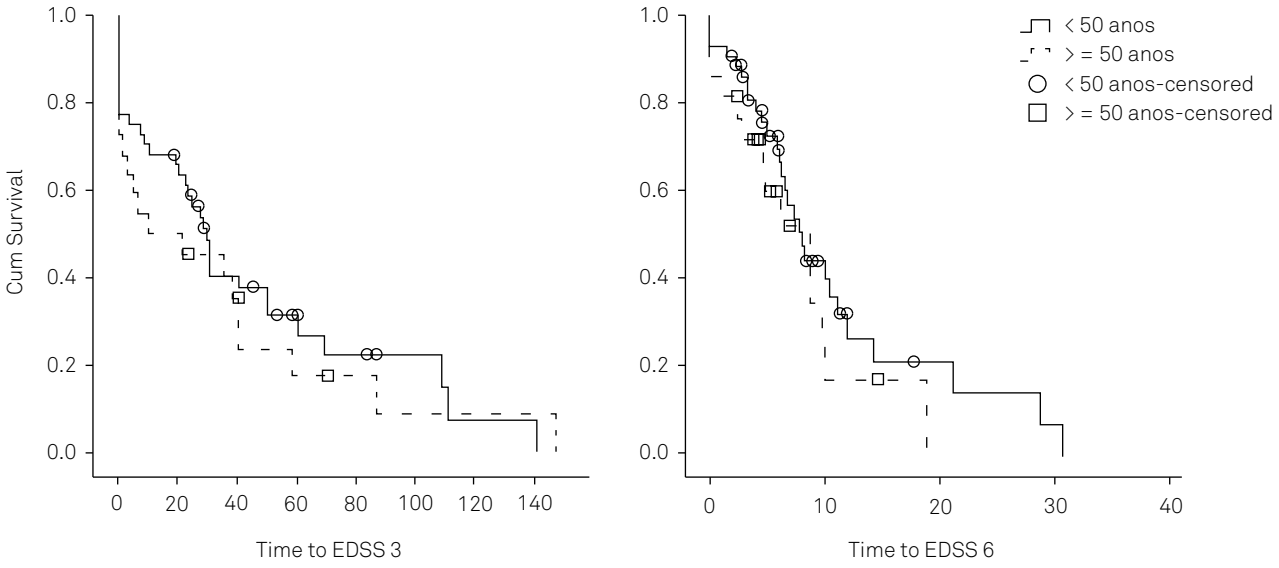
DISCUSSION

The population of Brazilian LOMS patients described in this retrospective cohort seems to be very similar to previously-published LOMS descriptions. We observed the same frequency of 4.18%, among patients with MS[2,3,4,5,7]; a female predominance of 2.1:1[1,2,4,7,12,14], a Caucasian preponderance[12]; a similar age of onset[2,4,7,11,14] and a higher percentage of the primary progressive form, that reached up to 83% in some descriptions[1,2,4,7,9,11,14,17,21].

Interestingly, very late onset MS (defined as the first symptom at 60 years or above), represented 0.27% of our cohort. This figure is lower when compared to other series, which reported a prevalence of 0.45% to 1.33%[2,3,5,9,12,17]. A possible explanation for this finding is the fact that Brazilians may die of other causes before a diagnosis of MS can be made, or since MS is not a common disease in Brazil, the correct diagnosis might be delayed or never made. The few papers that report this age range, emphasize that they have the same clinical characteristics of LOMS patients, but with a larger delay in diagnosis[17,22,23]. In the future with the aging world population and easier access to MRIs, very late onset MS may be more frequently described[24].

Concerning disease duration, late onset PPMS had a median duration time twice as long as late onset RRMS. Conversely, when it comes to follow-up time, the opposite occurs – late onset RRMS patients have a slightly longer follow-up history (3.13 versus 2.15 years). This could be explained by the longer time it usually takes to diagnose the progressive form, with a clear delay from initial symptom to first appointment at the MS clinic (4.12 years versus 1.15 years with the RRMS patients), as seen in Tables 4 and 5. The delay in diagnosis of the primary progressive form of LOMS has been observed by other authors, and may be justified by the fact that other diseases such as vascular disease of the central nervous system and cervical spondylotic myelopathy have a higher prevalence at this age and may present with similar symptoms[7,13,14]. Our short follow-up time may be due to the delay in patients being referred to a specialized MS center, and because of abandonment of the follow-up.

Similar to previously-described series, we observed a higher frequency of motor and cerebellar symptoms[2,9,11,12,13,14,25,26] and



Highlights: 1) This is the first Latin American study of demographic and clinical characteristics of patients with Late Onset Multiple Sclerosis (LOMS) followed at a specialized multiple sclerosis (MS) center in São Paulo; 2) LOMS frequency was 4,18% of all multiple sclerosis patients; 3)Comparative analysis with a matched control group of patients with young onset MS showed that the late onset associated with a progressive course were predictors of reaching EDSS 3.0 and 6.0 in a shorter time.

Figure. Kaplan-Meier estimates of time to reach EDSS 3 and 6 in LOMS and YOMS patients.

a high percentage of initial multifocal involvement[4,7] especially compared to young adults with MS[10]. A possible explanation is an association of the primary progressive form with a multifocal presentation. Such an hypothesis is corroborated by a study performed exclusively with late onset RRMS patients that reported a multifocal presentation in only 11% of patients[25].

In our cohort, we observed that 70% of the patients with late onset RRMS had the second relapse in less than a year, in spite of presenting with a low annual relapse rate. Different studies reported a similar low annual relapse rate in the late onset RRMS group, compared to the young onset RRMS group, in spite of a shorter interval between the first and second relapse. This low annual relapse rate in older patients could be attributed to a more inflammatory disease in young patients[1,3,12,18,23,27,28]. Recovery after the first relapse is better in younger patients and the chances of full recovery after a relapse decreases by 1% for each year older the patient is at onset[9,25]. This could explain why late onset RRMS patients acquire sustained severe neurological disability in a short period of time.

Regarding disability, 25.8% of LOMS patient were already at EDSS 6.0 at their first appointment at the MS clinic, and on final examination, the progressive form showed worse outcomes, concurring with previous series (Tables 4 and 5)[2,20,27,29]. In RRMS, the median time for LOMS patients to reach EDSS 3.0, 6.0 and 7.0 was almost identical to the younger group. On the other hand, for PPMS, the time to reach EDSS 6.0 and 7.0 was longer for the young group compared to LOMS, and the progression index diverged between LOMS and the younger group, 0.74 and 0.55, respectively, as seen in other studies[4,11,14,17,27]. These findings had no statistical significance, probably due to our small sample. We were able to significantly demonstrate that the late disease onset, as well as the primary progressive form, are predicting factors for reaching EDSS 3.0 and 6.0 in a shorter time, as two co-dependent variables, and similar to studies published[1,2,11,12,18,27,29]. Reaching disability milestones in a shorter period does not infer worse prognosis, considering that LOMS reached these at ages five to 11 years later than the young adults[2,18]. Some authors state that disability is influenced by the age at which the patient was first evaluated, thus patients older than 50 years, tend to have the same disabilities, regardless of the age of disease onset[13,15,28].

In our LOMS population, oligoclonal bands proved not to assist in the MS diagnosis. Only five out of the 10 LOMS patients were oligoclonal band positive. This lower percentage compared to previous series[1,7,14,17,18] is possibly due to differences in laboratory techniques or to the disease period in which the test was done. However, our finding is in agreement with the hypothesis that older patients have lower levels of inflammatory and neurodegenerative biomarkers in their CSF[30]. Spinal MRI seems to be an important additional diagnostic tool in LOMS patients who usually show signs of microangiopathy on brain MRI. We observed that 50% of the 12 LOMS patients submitted to spinal MRI had lesions, thus helping to differentiate between MS and vascular diseases[11,14,18]. Our study demonstrated that spinal MRI may be a helpful diagnostic tool only in the primary progressive LOMS group, in which we found 75% of clusters with lesions shown in spinal MRI, a high percentage, as expected in this clinical course[6,11,18].

Clearly, there are limitations to our study. It is a description of a small population based on a retrospective review of medical records. It covers 20 years and the changes in diagnostic criteria may have introduced a bias in the comparison of the different groups of patients. Nonetheless, it is the first Latin America description of a LOMS population and we demonstrated its similarities to other cohorts previously described. The LOMS patients represent almost 5% of the MS population, and it is important to better understand its characteristics, pattern of disability progression and disease-modifying factors, such as treatment. Further studies are warranted, especially to determine how age influences the clinical course, treatment response and permanent neurological disability.

Table 5. Cox proportion regression to find the predictive factors for reaching the EDSS 3 and 6 in a shorter time.

Variables of the equation*	p-value	Hazard Ratio	Confidence interval	
			95% Low	95% High
EDSS 3.0				
Clinical course	< 0.0001	3.923	2.003	7.683
Age of onset	< 0.0001	0.083	0.020	0.345
EDSS 6.0				
Clinical course	< 0.0001	6.687	2.365	18.909
Age of onset	0.002	0.036	0.004	0.308

*Variables adjusted by Gender; EDSS: expanded disability status scale.

Table 6. Spinal fluid analysis for the presence of oligoclonal bands in both disease courses, and the description of altered (presence of one or more lesions) or normal spinal MRI in both disease courses.

Variable	Age of onset	< 50		≥ 50		Pearson Qui-Square
		n (N)	%	n (N)	%	p-value
OCB in RRMS	Presence	5 (9)	56	3 (4)	75	0.506
Spinal MRI in RRMS	Altered	9(10)	90	0 (4)	0	0.001
OCB in PPMS	Presence	4 (4)	100	2 (6)	33	0.035
Spinal MRI in PPMS	Altered	6 (8)	75	6 (8)	75	0.999

N: total of patients submitted to the exam described in the first column; n: number of patients with alteration of the exam; OCB: Oligoclonal bands; MRI: Magnetic resonance imaging; RRMS: relapsing-remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis.

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