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Predictors of therapeutic failure in multiple sclerosis: a Brazilian center's experience.

Preditores de falha terapêutica na esclerose múltipla: experiência de um Centro de Referência Brasileiro

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RESUMO

Objetivo: Traçar o perfil de pacientes com EM que vivenciaram FT e, posteriormente, identificar preditores de FT. **Métodos:** Os prontuários de 289 pacientes foram revisados retrospectiva e longitudinalmente. Os pacientes foram divididos em dois grupos (população-alvo [1º grupo, TF ≥ 1, n = 46] e controle [2º grupo, sem FT, n = 46]); os grupos foram comparados. **Resultados:** Houve diferenças significativas entre os grupos em termos de diagnóstico, pulsoterapia/1ª recaída, número de medicamentos administrados, gravidade dos sintomas iniciais, sequelas de incapacidade, características de imagem, número de recaídas nos dois primeiros anos de EM e taxa de recaída anual. O 1º grupo tem chance aumentada de 18,5% de desenvolver pior prognóstico (EDSS > 4,0). Os piores prognósticos foram associados ao sexo masculino e idade de diagnóstico ≥ 30 anos. **Conclusão:** Em comparação com os controles, 46 pacientes na população-alvo tinham pelo menos um FT (16,6%), com risco aumentado (2x) de esclerose múltipla progressiva secundária, depressão e incapacidade aumentada (2x). As características iniciais da doença, bem como a taxa de recaída anual, podem ser um indicador precoce de FT.

Palavras-chave: Esclerose múltipla; Falha terapêutica; Progressão da doença; Comorbidades; Risco;

ABSTRACT

Objective: To trace the profile of patients with MS who experienced TF and, subsequently, identify TF predictors. **Methods:** The medical records of 289 patients were reviewed retrospectively and longitudinally. The patients were divided into two groups (target population [1st group, TF ≥ 1, n = 46] and the control [2nd group, without TF, n = 46]); the groups were compared. **Results:** There were significant differences between the groups in terms of diagnosis, pulse therapy/1st relapse, number of drugs administered, severity of initial symptoms, disability sequelae, imaging characteristics, number of relapses in the first two years of MS, and annual relapse rate. The 1st group has an increased chance of 18.5% of developing a worse prognosis (EDSS > 4.0). The worst prognoses were associated with male sex and a diagnosis age of ≥ 30 years. **Conclusion:** Compared to the controls, 46 patients in the target population had at least one TF (16.6%), with an increased risk (2x) of secondary progressive multiple sclerosis, depression, and increased disability (2x). The initial features of the disease, as well as the annual relapse rate, can be an early indicator of TF.

Keywords: Multiple sclerosis; Therapeutic failure; Disease progression; Comorbidity; Risk;

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INTRODUCTION

Multiple sclerosis (MS) is one of the main causes of disability in young patients (SILVA *et al.*, 2019), affecting the physical, psychosocial, and economic aspects of their lives, with a direct impact on their quality of life (TAUIL *et al.*, 2018). There are more than 2.5 million cases of MS worldwide (BROWNE *et al.*, 2014), and in Goiás, Brazil, the estimated prevalence is 22.4/1000000 inhabitants (RIBEIRO *et al.*, 2019).

Currently, MS is treated with several disease-modifying drugs (DMDs). The following DMDs are available and used in Brazil: Betainterferon, Glatiramer, Teriflunomide, Difumarate, Fingolimod, Natalizumab, Ocrelizumab, Alentuzumab, Cladribine, and Oftamumab. The treatment of MS is funded by the federal government, due to the high cost of DMDs, and made available free of charge to patients diagnosed with MS, according to the Protocol Clinic and Therapeutic Guidelines for Multiple Sclerosis, established by the Coordination of Management of Clinical Protocols and Therapeutic Guidelines (CONITEC) (COHEN *et al.*, 2020; MONTALBAN *et al.*, 2018).

With these various therapeutic options, a therapeutic failure (TF) algorithm is needed to establish a suboptimal response to minimize the risk of disease progression (BRASIL, 2019; FREEDMAN et al., 2013). Although several studies have discussed and established the criteria for TF (BRASIL, 2021; FREEDMAN *et al.*, 2013; RÍO *et al.*, 2014; HYUN *et al.*, 2015; FROTA; MENDES; VASCONCELOS, 2016; RÍO; RUIZ-PEÑA, 2016; RÍO; RUIZ-PEÑA, 2016; SORMANI *et al.*, 2016), there are still discussions and questions about this topic in the literature. This idea is reinforced by the significant progression of MS associated with the occurrence of TF (FROTA; MENDES; VASCONCELOS, 2016). Furthermore, it is well known that Brazil has a high rate of miscegenation (46.7% mestizos) (IBGE, 2010), that the population of Goiás (Midwestern of Brazil) is derived from the miscegenation of three major ancestral groups – 3% Native Americans, 83.7% Europeans and 13.3% Afro-descendants (MONTALBAN *et al.*, 2018); and this genetic inheritance may influence the incidence and progression of MS (ALVES; SANTOS; DINIZ, 2022; GIGONZAC; CRUZ, 2013). Although it is not one of the current study's objectives to assess the influence of miscegenation of the Brazilian population on MS, the use of general criteria for therapeutic failure in a miscegenated population is questionable. Thus, further studies are needed to elucidate TF predictors to help in the early and efficient identification of patients who will require medication adjustment to optimize treatment.

This study aimed to trace the profile of patients with MS in a Brazilian center (Midwestern Brazil) and then identify TF predictors that can effectively provide an early indication of patients who will need a medication adjustment.

METHODS

This is a retrospective longitudinal study conducted at the Reference Center for Demyelinating Diseases of Goiás, Brazil (CRIEM), and it was approved by the Research Ethics Committee of the Faculty of Medicine of the Federal University of Goiás (Opinion No.: 2,674,085). Written informed consent was obtained from the research participants before data collection.

The present study considered the following as inclusion criteria: the diagnosis of multiple sclerosis according to the McDonald 2017 criteria and consent to participate in the study. Patients with other demyelinating diseases were excluded. Between July 2018 and February 2020, the medical records of 289 CRIEM patients diagnosed with MS were reviewed and divided into two groups: group 1 (target population, all patients who had at least one TF during treatment, n = 48) and group 2 (control population, non-probabilistic sampling of 241 patients who did not experience TF, n = 48). Considering the homogeneity of the group of 241 patients with multiple sclerosis, and who did not have a therapeutic treatment during treatment, the random selection of a sample of 48 patients from this group is representative.

McDonald (2017) (THOMPSON *et al.*, 2018) and Brazilian Academy of Neurology (2016) criteria were considered for the diagnosis of TF in MS: (a) Relapse criterion – a clinical relapse (moderate quality of evidence), (b) Kurtzke's Expanded Disability Status Scale (EDSS) criterion: sustained and confirmed deterioration by one point on the EDSS after six months if baseline is score below than 6.0 or worsening by 0.5 points if baseline score is greater than 6.0 (moderate-quality evidence), and (c) Neuroaxis MRI criteria – active lesions, i.e., new/increased T2 lesions (2 lesions or more) or contrast-enhancing lesions (moderate-quality evidence) (FROTA; MENDES; VASCONCELOS, 2016). Patients who met at least two of the TF criteria during a 12-month period on drug treatment were diagnosed with therapeutic failure.

A standardized research questionnaire was completed with information recorded in medical records on the clinical-epidemiological lives of MS patients, from the first symptom suggestive of MS to the end of data collection (02/2020). Test results

(attached to medical records) and patient interviews provided additional information on incomplete medical record filling. After selecting samples from the target and control groups according to the inclusion criteria and considering the exclusion criteria (records with inconsistent information marking discontinuation or interruption of treatment or death of the patient), the final sample was 46 patients (95,83% of the target population) for the first group and 46 patients for the second group. With a sample size of 46 in each group, our study can detect effect sizes of $\delta \geq 0.76$ with a probability ≥ 0.95, assuming a two-sided detection criterion that allows for a maximum Type I error rate of a=0.05. (ALGERMISSEN; MEHLER, 2018).

The groups' clinical and epidemiological characteristics were compared, including sex, race/skin color, age, late diagnosis, treatment time, number and degree of relapses, pulse therapy, clinical status, EDSS, neuroaxis magnetic resonance results, and, number of drugs used.

Statistical analyses were performed using the Jamovi 1.6 statistical package (The Jamovi project, Sydney, Australia). Descriptive statistics are presented as counts, proportions, means and standard deviations or medians, where appropriate. The Anderson-Darling's test was performed to test the normality of continuous variables. Normally distributed data were analyzed using Student's t-test, whilst non-normally distributed data were analyzed using the Mann-Whitney's U-test. Where appropriate, Welch's t-test was also used. Pearson's chi-square test was used where appropriate. Correlation with TF was assessed using Spearman's correlation analysis with Bonferroni's correction. The significance level for all analyses was 5% ($p < 0.05$).

RESULTS

Clinical-epidemiological characteristics

The epidemiological characteristics of the 1st and 2nd groups were similar. Regarding diagnosis, the progression rate to the secondary form of MS was 36.9% higher in the 1st group when compared to the 2nd group (Table 1).

Table 1: Clinical-demographic profile of patients in the 1st group (n = 46) and 2nd group (n = 46)

	1st Group			2nd Group			
	Mean ± SD	**Median**	**Minimum-Maximum**	**Mean ± SD**	**Median**	**Minimum-Maximum**	**P**
Age	**35.7 ± 9.91**	**35.5**	12 – 52	**37.4 ± 13.7**	**36.5**	9 – 61	0.499
	N	**%**		**N**	**%**		
Gender							0.809
Male	12	26.1		11	23.9		
Female	34	73.9		35	76.1		
Race							0.672
White	18	39.1		20	43.5		
Non-white	28	60.9		26	56.5		
Diagnosis							**0.00026**[a]
SPMS	26	56.5		9	19.6		
RRMS	20	43.5		37	80.4		

[a]Statistically significant ($p < 0.05$)
RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; SD, standard deviation; N, absolute frequency; %, relative frequency
Source: Author of present work

The main comorbidities were depression, hypertension, and smoking (Table 2).

Table 2: Comorbidities of patients in the 1st group (n = 46) and 2nd group (n = 46)

	1st Group		2nd Group	
Comorbidities	**N**	**%**	**N**	**%**
Hypertension	**13**	**19.0**	**12**	**18,2**
Smoking	**7**	**10.0**	**10**	**15,2**
Diabetes	3	4.0	3	4,5
Thyroid changes	5	7.0	9	13,6
Heart disease	4	6.0	4	6,1
Depression	**35**	**51.0**	**16**	**24,2**
Herpes	1	1.0	2	3,0
Fibromyalgia	0	0.0	3	4,5
Psoriasis	0	0.0	1	1,5
Personality disorder	0	0.0	1	1,5
Trigeminal neuralgia	0	0.0	5	7,6

N, absolute frequency; %, relative frequency.
Source: Author of present work

In the 2nd group, 28 patients (60.9%) experienced more than one relapse, compared to 46 patients (100%) in the 1st group who had two or more relapses.

Additionally, only in the target population was a significant positive correlation found between age at diagnosis equal to or greater than 30 years and EDSS at first relapse ($p = 0.037$); the worst prognoses were associated with this age group (ARR reduction of 0.22, but an increase in mean final EDSS of 0.3).

In the 1st group, the mean incidence of TF was 2.03, with a maximum of four and a minimum of one failure per patient, over a treatment period of 3 to 37 years. In the 2nd group, medication was changed by nine (19.6%) patients within a treatment period of 1 to 24 years due to adverse reactions ($p<0.001$) (Table 3).

Table 3: Comparison of the clinical characteristics of the 1st group (N = 46) and the 2nd group (N = 46)

Variable	1st Group			2nd Group			
	Mean ± SD	**Median**	**Minimum - Maximum**	**Mean ± SD**	**Median**	**Minimum -Maximum**	**P**
Time of illness (years)	16.2 ± 7.67	16	3.0 – 40.0	13.1 ± 7.86	13.5	1.0 – 45.0	0.052[a]
Late diagnosis (months)	27 ± 51.4	2	1.0 – 240	16.1 ± 41.0	1	1.0 – 240	**0.039[a]**
No. of relapses/before diagnosis	1.70 ± 0.89	1.5	1.0 – 5.0	1.3 ± 0.66	1	0.0 – 3.0	**0.034[a]**
Number of relapses in the first 2 years of the disease	1.67 ± 0.76	1.5	1.0 – 3.0	1.3 ± 0.51	1	1.0 – 3.0	**0.008**[b]
Treatment time (years)	14.0 ± 13.5	13.5	3 – 37.0	11.7 ± 5,56	13.0	1.0 – 24.0	0.125[c]
ARR/pt	0.34 ± 0.3	0.3	0.04 – 1.7	0.06 ± 0.08	0	0.0 – 0.2	**< 0.001**[b]
No. of drugs	3.0 ± 0.9	3	2.0 – 5.0	1.24 ± 0.52	1	1.0 – 3.0	**< 0.001**[a]

Late diagnoses (months), time elapsed, in months, between the first outbreak and the diagnosis of the disease; No., number; Treatment time (years), period after diagnosis, which comprises the period in which the patient is under drug treatment; ARR/pt, annual relapse rate after initiation of treatment; SD, standard deviation; [a] Mann-Whitney U test, [b]Welch's t-test. [c]Student's t-test. Statistically significant ($p < 0.05$)
Source: Author of present work

Characterization of therapeutic failure

Compared with the 2nd group, significant evidence of faster MS progression was observed in the 1st group during the treatment period (Tables 4 and 5).

Table 4: Characterization of therapeutic failure according to the following criteria: number of relapses, severity of relapses, mean number of pulse therapy, EDSS level of the first and last relapses, and increase in MRI lesions and positive gadolinium lesions (1st Group, n = 46 and 2nd Group, n = 46)

	1st Group	2nd Group	Total	P	1st Group	2nd Group	Total	p
Relapses degree	**First relapse n (%)**			**<0.001** [a]	**Last relapse n (%)**			**<0.001**[a]
No Disability/Mild Disability	5 (10.9)	32 (69.6)	37 (40.2)	***	7 (15.2)	8 (17.4)	15 (16.3)	ns
Moderate Disability	35 (7.1)	12 (26.1)	41 (51.1)	***	14 (30.4)	17 (37.0)	31 (33.7)	ns
Severe/profound Disability	6 (13.0)	2 (4.3)	8 (8.7)	ns	25 (53.3)	3 (6.5)	28 (30.4)	***
NI					0 (0.0)	18 (39.1)	18 (19.6)	
MRI				**<0.05**[a]				**<0.05**[a]
>T2	27 (58.7)	9 (19.6)	36 (39.1)		20 (43.5)	13 (28.3)	33 (35.9)	***
>T2 and Gd+	18 (39.1)	37 (80.4)	55 (59.8)		6 (13.0)	17 (36.9)	23 (25.0)	***
Gd+					14 (30.4)	0 (0.0)	14 (15.2)	ns
NIPP	1 (2.2)	0 (0.0)	1 (1,1)		6 (13.0)	0 (0.0)	6 (6.5)	***
NI					0 (0.0)	16 (34.8)	16 (17.4)	ns

	1st Group			2nd Group			
	Mean ± SD	**Median**	**Minimum - Maximum**	**Mean ± SD**	**Median**	**Minimum-Maximum**	**p**
No. relapses/pt	3.5 ± 1.53	3.5	1 – 6.0	0.63 ± 0.9	0	0.0 – 4.0	**< 0.001**[b]
Pulse No./pt	3.4 ± 1.57	4	0 – 6.0	0.6 ± 0.8	0	0.0 – 3.0	**<0.001**[b]
EDSS first relapse	3.32 ± 1.16	3	1.5 – 6.5	2.84 ± 0.86	3,0	1.5 – 4.5	0.061[c]
EDSS last relapse	4.78 ± 1.61	4.5	2.0 – 8.0	3.7 ± 0.79	4.0	1.5 – 5.0	**<0.001**[c]
Final EDSS	4.12 ± 1.96	4	1.0 – 8.0	2.3 ± 1.18	2.0	0.0 – 5.0	**<0.001**[c]

EDSS, Kurtzke's Expanded Sustained Disability Scale; Degree of relapses, severity of relapses; No Disability/Mild Disability (0 – 2,5); Moderate Disability (3,0 – 4,0); Severe/profound Disability (4.5 – 9.5); NI, No relapse;EDSS first relapse, EDSS value on relapse; EDSS last relapse, EDSS value on relapse; MRI = Magnetic Resonance; >T2, lesions in T2; >T2 and Gd+, lesions on T2 and lesions with gadolinium contrast (T1); Gd+, lesions with gadolinium contrast (T1); NIPP, progressive disease without image changes; Number of relapses/pt, number of relapses after initiation of treatment; No. pulse/pt, number of pulse therapies after starting treatment; Final EDSS, EDSS value at study completion, in the absence of relapse; n, absolute frequency; %, relative frequency; [a]Pearson's chi-square test; [b]Welch's t-test; [c]Mann-Whitney U test ns, no significant statistic; Significant Post-Hoc test, * denotes P values between 0.05 and 0.01, ** denotes P values between 0.01 and 0.001, and *** denotes P values < or = 0.001.
Statistically significant ($p < 0.05$)
Source: Author of present work

In terms of EDSS, a patient with FT, in 1st group, was 18.5% more likely to have a worse prognosis (EDSS > 4.0) than a patient in the 2nd group. In the target population, 45.6% of patients had a final EDSS > 4.0, compared with only 4.3% in the 2nd group.

In the 1st group, a comparison of final mean EDSS between males (4.7) and females (3.9) showed that MS was 1.2 times more likely to have a worse prognosis in

males than in females. In the 2nd group, there was no difference between the sexes in terms of final mean EDSS (2.3 for both sexes).

In addition, a more severe clinical prognosis at 1st relapse was observed in the 1st group than in the 2nd group (Table 5).

Table 5: Clinical characterization of therapeutic failure in the 1st and last relapse: clinical picture, absence and presence of pulse therapy, relapse recovery criteria, relapse symptoms

	1st Group		2nd Group		Total		P	1st Group		2nd Group		Total		P
	First relapse n (%)							Last relapse n (%)						
Clinical Condition							**0.004**[a]							0.667[a]
Monosyn	9	(19.6)	22	(47.8)	31	(33.7)		8	(17.4)	6	(21.4)	14	(18.9)	
Polysyn	37	(80.4)	24	(52.2)	61	(66.3)		38	(82.6)	22	(72.6)	60	(81.1)	
Pulse							**<0.001**[a]							0.427[a]
No	2	(4.3)	27	(60.0)	29	(31.9)		10	(21.7)	4	(14.3)	14	(18.9)	
Yes	44	(95.7)	18	(40.0)	62	(68.1)		36	(78.3)	24	(85.7)	60	(81.1)	
Recovery							0.599[a]							0.586[a]
Partial	38	(82.6)	36	(78.3)	74	(80.4)		43	(93.5)	27	(96.4)	70	(94.6)	
Total	8	(17.4)	10	(21.7)	18	(19.6)		3	(6.5)	1	(3.6)	4	(5.4)	
Symptoms							0.229[b]							**0.039**[b]
Cerebellar	19	(18.4)	12	(14.6)	31	(16.8)		27	(25.0)	6	(8.0)	33	(18.0)	*
Motor	38	(36.9)	21	(25.6)	59	(31.9)		30	(27.8)	30	(40.0)	60	(32.8)	Ns
Neuritis	13	(12.6)	19	(23.2)	32	(17.3)		11	(10.2)	10	(13.3)	21	(11.5)	Ns
Sensory	18	(17.5)	18	(22.0)	36	(19.5)		17	(15.7)	15	(20.0)	32	(17.5)	Ns
Stem	15	(14.6)	12	(14.6)	27	(14.6)		23	(21.3)	14	(18.7)	37	(30.2)	Ns

Monosyn, monosymptomatic; Polysyn, polysymptomatic; Pulse, pulse therapy; Sensory, paresthesias; Motor, pyramidal; Stem, nystagmus, dysarthria, dysphagia or other cranial nerves; n, absolute frequency; %, Relative frequency; [a]Mann-Whitney U test; [b]Pearson's chi-square test; ns, no significant statistic; Significant Post-Hoc test, * denotes P values < 0.01, ** denotes P values < 0.001, and *** denotes P < 0.001.
Statistically significant ($p < 0.05$).
Source: Author of present work

The correlation analysis revealed a significant correlation between total TFs and age at diagnosis ($r = 0.439$; $p = 0.002$), number of relapses/post-treatment ($r = 0.465$; $p = 0.001$), annual relapse rate (ARR)/post-treatment ($r = 0.297$; $p = 0.045$), number of pulse therapies/post-treatment ($r = 0.480$; $p = 0.001$), number of drugs administered ($r = 0.967$; $p = 0.00$), and final EDSS ($r = 0.311$; $p = 0.036$). However, when applying the Bonferroni's correction (alpha corrected = 0.0042), the ARR/post-treatment and final EDSS showed no significant correlation with the overall TFs.

DISCUSSION

Despite the clear importance of early diagnosis and treatment, there is still no consensus on how to define and monitor patients' responses to MS treatments (FROTA; MENDES; VASCONCELOS, 2016; GASPERINI *et al.*, 2019; TROJANO *et al.*, 2017; VARGAS; TYOR, 2017). Therefore, our findings provide important predictors of TF associated with MS progression.

As observed in this study, individual characteristics such as gender, age, and initial manifestation of the disease, as well as disease subtype (CCATES, 2017) contribute to loss of response to treatment (TF) and consequently to the prognosis of MS, as reflected in the degree of disability (HEGEN; BSTEH; BERGER, 2018; RIO; RUIZ-PEÑA, 2016).

In the target population, the likelihood of secondary progression, which is associated with a worse prognosis, was 18.5% higher (EDSS > 4.0 in 45.6% of patients. Secondary progression rate = 36.9%) than in the control group, with an increase in the final mean EDSS of 1.82. A previous study revealed an even higher degree of disability associated with MS secondary progression (EDSS ≥ 4.0 in most patients) (SKOOG *et al.*, 2012). Without treatment, SPMS affects approximately 50% of MS patients 10 years after diagnosis (BRASIL, 2019). If the patient undergoes treatment, progression of the disease is delayed (the risk of progression is 6.4% at 10 years and 24.2% at 20 years) (CREE *et al.*, 2016; KIM *et al.*, 2019); however, in this study, no significant reduction in progression was observed in cases of occurrence of FT, in the 1st group. (HEGEN; BSTEH; BERGER, 2018; JOKUBAITIS *et al.*, 2016). It can be inferred that the prediction of secondary progression with an increasingly worse prognosis is greater in patients with TF, which may reduce their average life expectancy (currently around 30 years) than in patients without TF (CCATES, 2017).

Although the disease and a greater number of relapses are associated with female sex (FROTA; MENDES; VASCONCELOS, 2016), an increased risk of a worse prognosis is observed in the male sex (VUKUSIC; CONFAVREUX, 2007). Thus, our findings of the final mean EDSS of the patients (1st group) in this study showed that the odds of MS progressing to a worse prognosis were 1.2 times greater in males than in females. A previous study reported more significant results (4.6 times higher) than this study (DAMASCENO *et al.*, 2013).

Another factor associated with FT and consequent disease progression that was evident in our study was diagnosis at an advanced age. Compared with younger patients,

patients with FT, who were 30 years or older at the time of diagnosis, had an ARR reduction of 0.22 but a severity increase of 0.3 in the final mean EDSS and a positive correlation with the first relapse mean EDSS ($p < 0.05$), supporting the possibility of an age-related degenerative component (LERAY et al., 2010; VASCONCELOS et al., 2012; VASCONCELOS et al., 2020).

In addition, our results confirmed previous observations (LERAY et al., 2010; VASCONCELOS et al., 2012) that a higher relapse rate in the early stage of MS, i.e. in the first two years of the disease, could increase the likelihood of treatment failure ($p = 0.008$) and the risk of progression. However, once the progressive phase is reached, the influence of relapses disappears (LERAY *et al.*, 2010), i.e. in our study there was a lower risk of relapse as the population aged, but with a slow and continuous progression of disability, which was also demonstrated in a cohort study that reported a reduction in ARR from 0.29 to 0.015 during the disease period (SKOOG *et al.*, 2012).

There is evidence that late diagnosis (delay in treatment since the onset of the disease) may indicate TF and rapid progression from MS to its more progressive form (FROTA; MENDES; VASCONCELOS, 2016; RÍO; RUIZ-PEÑA, 2016; KIM *et al.*, 2019). Our results also show the influence of late diagnosis ($p = 0.039$) and the number of relapses before diagnosis/beginning of treatment ($p = 0.034$) on the evolution of MS to its more progressive form associated with TF in the population studied. This is thought to be due to difficulties in accessing treatment, highlighting the importance of socioeconomic and cultural characteristics in the prognosis of MS (BARIN *et al.*, 2020; COHEN *et al.*, 2020).

It is also important to note that factors such as comorbidities, as well as environmental and genetic characteristics of each patient, are also related to disease progression, including the occurrence of TF (FROTA; MENDES; VASCONCELOS, 2016; VASCONCELOS *et al.*, 2012).

Depression was the most common comorbidity in both groups with 2.19 times greater risk in the target population than in the control population (51% in the first group and 24.2% in the second). These results are consistent with other studies, which ranged from 27% to 58.5% (BRASIL, 2020; PEREIRA *et al.*, 2021; SISTEROLLI-DINIZ *et al.*, 2012; TAUIL *et al.*, 2018). Depression is thought to occur due to the lack of a cure for MS, TF, and feelings of impotence, and some cases (16.6%) may lead to suicide (CERQUEIRA *et al.*, 2015; TAUIL *et al.*, 2018). In this study, depression was not indicative of TF, but it worsened with the onset of TF. Therefore, it is important that

depression is treated psychotherapeutically and pharmacologically in patients with MS to improve their quality of life, especially if they are affected by TF (BRASIL, 2020).

There is a high degree of miscegenation in Brazil. Therefore, brown people, similar to black people, may carry the HLA haplotypes, which increases their probability of developing MS. It has been estimated that there are up to 30.7/100,000 inhabitants within Brazil (MONTALBAN *et al.*, 2018). There were a considerable number of non-white patients (brown or black) in both the 1st and 2nd groups of the study, suggesting the influence of genetic factors on the occurrence and development of MS, as reported in previous studies (FROTA; MENDES; VASCONCELOS, 2016; GIANFRANCESCO *et al*., 2018; VASCONCELOS, *et al*., 2012).

With regard to the criteria for TF established by the Brazilian Association of Neurology in 2016, including the number of relapses ($p < 0.001$), the degree of relapse, i.e. the severity of symptoms ($p < 0.001$), consequences of disability clustering (final EDSS, $p < 0.001$) and initial imaging characteristics (Neuroaxis magnetic resonance 1st relapse, $p < 0.001$), the target group had a higher risk of disease progression than the control group.

Our studies confirm the findings of previous studies identifying the highest rate of relapses and lesions using gadolinium contrast as predictors of treatment failure (JOKUBAITIS *et al.*, 2016; SORMANI *et al.*, 2016). A higher number of relapses ($r = 0.465$; $p = 0.001$), ARR/post-treatment ($r = 0.297$; $p = 0.045$) and initial imaging characteristics in the target population were associated with the occurrence of TF and consequently with the high final mean EDSS (4.12) of the patients.

At 1st relapse, the disease manifested more aggressively in the 1st group (a 0.5-point increase in EDSS due to the difference in initial mean EDSS between the groups; a 2.9-fold increase in the number of moderate/severe/profound relapses; 1.5 times - polysymptomatic clinical presentation; 2.4 times - need for pulse therapy). Therefore, our results confirm that the initial manifestation of the disease may indicate the occurrence of TF (FROTA; MENDES; VASCONCELOS, 2016).

The initial aggressive manifestation of MS, as evidenced by the initial symptoms (1st relapse, 36; 90% motor and 18.40% cerebellar) in the 1st group, was indicative of TF. This explains the greater accumulation of residual deficits in the 1st group (an increase of 1.5 points on the EDSS due to a difference of 1.65 in the final mean EDSS between groups), which mainly affected motor (27.8 %) and cerebellar (25.0%) functions compared with the 2nd group (Table 3).

There was no difference in post-relapse recovery between groups, indicating the efficacy of pulse therapy (methylprednisolone or combined with mitoxantrone, given regularly) on MS progression (ÖZAKBAŞ *et al.*, 2019). However, we reiterate the need for early identification of TF to avoid the worsening of patient's clinical condition.

Our study showed that 48 (16.6%) out of 289 patients with MS failed treatment. These patients could have a more active and progressive disease, which can be detected early by the initial characteristics of the disease (age at diagnosis over 30 years, late diagnosis, number of relapses in the first two years of the disease, severity of relapses and disability sequelae) and annual rate of relapses. Identifying predispositions to TF will guide neurologists in the early diagnosis of TF, delaying the progression of the disease and reducing the incidence of new relapses.

The study had the following limitations: the sample size and the fact it was a retrospective study with data collected from medical records. Considering that MS is a rare disease and that the above-mentioned criteria for TF require a follow-up of at least 12 months for the diagnosis of TF; the main limitation of this study is that the data were collected from medical records. To overcome these limitations, we chose to use TF as a composite and persistent endpoint to capture the change in treatment, as stated in the protocol. To minimize this limitation, interviews were also carried out and the results of patient exams were analyzed.

CONCLUSION

Our findings showed that the presence of TF in MS is associated with female sex, but the worst prognoses were associated with male sex and a diagnosis age of ≥ 30 years. When compared to the control group, 16.6% of patients who had at least one TF may have an increased risk of developing SPMS (2x), depression (2x), and disability (2x). This can be avoided by early diagnosis of TF, following the predictors of therapeutic failure reported in this study: the initial characteristics of the disease (diagnosis age equal to or greater than 30 years, late diagnosis, number of relapses in the first two years of disease, severity of relapses, disability sequelae) and the annual rate of relapses.

Authors Contributions

Conceptualization, Santos, FBC; methodology, Santos, FBC; validation, Guimarães, VC, Diniz, DS, Alves, CS; formal analyzis, Juliano, RF, Moraes, JB;

investigation, Santos, FBC; resources, Santos, FBC, Alves, CS; data curation, Juliano, RF; writing—original draft preparation, Santos, FBC; writing review, Moraes, JB, Alves, CS, Guimarães, VC; writing editing, Santos, FBC, Moraes, JB; supervision, Diniz, DS; project administration, Diniz, DS and Santos, FBC.

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Declaration of Conflict of Interest

The authors declare no competing interests regarding this publication.

REFERENCES

ALGERMISSEN, J.; MEHLER, D. M. A. May the power be with you: are there highly powered studies in neuroscience, and how can we get more of them? *Journal of Neurophysiology*, v. 119, n. 6, p. 2114–2117, 1 jun. 2018.

ALVES, C. S.; SANTOS, F. B. C.; DINIZ, D. S. Correlation between Amerindian ancestry and neuromyelitis optica spectrum disorders (NMSOD) among patients in Midwestern Brazil. *Arquivos de Neuro-Psiquiatria*, v. 80, n. 5, p. 497–504, maio 2022.

BARIN, L. *et al.* How do patients enter the healthcare system after the first onset of multiple sclerosis symptoms? The influence of setting and physician specialty on speed of diagnosis. *Multiple Sclerosis Journal*, v. 26, n. 4, p. 489–500, abr. 2020.

BRASIL. MINISTÉRIO DA SAÚDE. SECRETARIA DE CIÊNCIA TECNOLOGIA INOVAÇÃO E INSUMOS ESTRATÉGICOS. *Relatório de Recomendação: Protocolo Clínico e Diretrizes Terapêuticas da Esclerose Múltipla. Nº 582*. Disponível em: <http://conitec.gov.br/images/Relatorios/2021/20210409_Relatorio_Recomendacao_582_PCDT_EMRR.pdf>. Acesso em: 13 maio 2021.

BRASIL. SECRETARIA DE ATENÇÃO ESPECIALIZADA À SAÚDE. SECRETARIA DE CIÊNCIA TECNOLOGIA E INSUMOS ESTRATÉGICOS. MINISTÉRIO DA SAÚDE. *Portaria Conjunta nº 7, de 3 de julho de 2019*. Disponível

em: <http://conitec.gov.br/images/Protocolos/PCDT-Esclerose-Mltipla.pdf>. Acesso em: 5 maio 2021.

BROWNE, P. *et al.* Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology*, v. 83, n. 11, p. 1022–1024, 9 set. 2014.

CCATES - CENTRO COLABORADOR DO SUS: AVALIAÇÃO DE TECNOLOGIAS E EXCELÊNCIA EM SAÚDE. *Ocrelizumabe para o tratamento da esclerose múltipla*. *Universidade Federal de Minas Gerais (UFMG)*. Belo Horizonte: [s.n.], 2017.

CERQUEIRA, A. C. DE *et al.* Risk factors for suicide in multiple sclerosis: a case-control study. *Jornal Brasileiro de Psiquiatria*, v. 64, n. 4, p. 303–306, dez. 2015.

COHEN, J. A. *et al.* Leveraging real-world data to investigate multiple sclerosis disease behavior, prognosis, and treatment. *Multiple Sclerosis Journal*, v. 26, n. 1, p. 23–37, jan. 2020.

CREE, B. A. C. *et al.* Long-term evolution of multiple sclerosis disability in the treatment era. *Annals of Neurology*, v. 80, n. 4, p. 499–510, 13 out. 2016.

DAMASCENO, A. *et al.* Prognostic indicators for long-term disability in multiple sclerosis patients. *Journal of the Neurological Sciences*, v. 324, n. 1–2, p. 29–33, 2013.

FREEDMAN, M. S. *et al.* Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*, v. 40, n. 3, p. 307–323, 23 maio 2013.

FROTA, E. R. C.; MENDES, M. F.; VASCONCELOS, C. C. F. *Recomendações no Tratamento da Esclerose Múltipla e Neuromielite Óptica*. 2. ed. São Paulo: Editora Omnifarma LTDA, 2016.

GASPERINI, C. *et al.* Unraveling treatment response in multiple sclerosis. *Neurology*, v. 92, n. 4, p. 180–192, 22 jan. 2019.

GIANFRANCESCO, M. A. *et al.* Genetic risk factors for pediatric-onset multiple sclerosis. *Multiple Sclerosis Journal*, v. 24, n. 14, p. 1825–1834, dez. 2018.

GIGONZAC, T. C. V.; CRUZ, A. D. DA. *Caracterização genética da população do estado de Goiás baseada em marcadores STRs autossômicos e do cromossomo*. 2013. 71 f. UFG, 2013.

HEGEN, H.; BSTEH, G.; BERGER, T. 'No evidence of disease activity' - is it an appropriate surrogate in multiple sclerosis? *European Journal of Neurology*, v. 25, n. 9, p. 1107-e101, set. 2018.

HYUN, J.-W. *et al.* Utility of the Rio Score and Modified Rio Score in Korean Patients with Multiple Sclerosis. *PLOS ONE*, v. 10, n. 5, p. e0129243, 26 maio 2015.

IBGE - INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA. *Síntese de indicadores sociais: Uma análise das condições de vida da população brasileira*. . Rio de Janeiro: IBGE. , 2010

JOKUBAITIS, V. G. *et al.* Predictors of long-term disability accrual in relapse-onset multiple sclerosis. *Annals of Neurology*, v. 80, n. 1, p. 89–100, jul. 2016.

KIM, S.-H. *et al.* Real-World Effectiveness of Disease-Modifying Therapies in Korean Patients with Relapsing Multiple Sclerosis. *Journal of Clinical Neurology*, v. 15, n. 1, p. 20, 2019.

LERAY, E. *et al.* Evidence for a two-stage disability progression in multiple sclerosis. *Brain*, v. 133, n. 7, p. 1900–13, 2010.

MONTALBAN, X. *et al.* ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. *Multiple Sclerosis Journal*, v. 24, n. 2, p. 96–120, 20 fev. 2018.

ÖZAKBAŞ, S. *et al.* Monthly pulse methylprednisolone therapy is effective in preventing permanent disease progression in secondary progressive multiple sclerosis. *Noropsikiyatri Arsivi*, v. 56, n. 2, p. 115–8, 2019.

PEREIRA, A. C. DE O. DO C. *et al.* Avaliação da qualidade de vida e depressão em pacientes com esclerose múltipla em Juiz de Fora / Evaluation ok quality of life and depression in patients with multiple sclerosis in Outside Judge. *Brazilian Journal of Health Review*, v. 4, n. 2, p. 7830–7840, 9 abr. 2021.

RIBEIRO, T. A. G. J. *et al.* Prevalence of multiple sclerosis in Goiânia, Goiás, Brazil. *Arquivos de Neuro-Psiquiatria*, v. 77, n. 5, p. 352–356, maio 2019.

RÍO, J. *et al.* Evaluating the response to glatiramer acetate in relapsing–remitting multiple sclerosis (RRMS) patients. *Multiple Sclerosis Journal*, v. 20, n. 12, p. 1602–1608, 12 out. 2014.

RÍO, J.; COMABELLA, M.; MONTALBAN, X. Predicting responders to therapies for multiple sclerosis. *Nature Reviews Neurology*, v. 5, n. 10, p. 553–560, out. 2009.

RÍO, J.; RUIZ-PEÑA, J. L. Short-term suboptimal response criteria for predicting long-term non-response to first-line disease modifying therapies in multiple sclerosis: A systematic review and meta-analysis. *Journal of the Neurological Sciences*, v. 361, p. 158–167, fev. 2016.

SILVA, C. B. DA *et al.* Qualidade de Vida dos Portadores de Esclerose Múltipla. *ReBIS*, v. 1, n. 3, p. 54–9, 2019.

SISTEROLLI-DINIZ, D. *et al.* Functional impairments in white matter syndrome of neuropsychiatric systemic lupus erythematosus are similar to those observed in patients with multiple sclerosis. *Arquivos de Neuro-Psiquiatria*, v. 70, n. 10, p. 769–73, 2012.

SKOOG, B. *et al.* A representative cohort of patients with non-progressive multiple sclerosis at the age of normal life expectancy. *Brain*, v. 135, n. 3, p. 900–11, 2012.

SORMANI, M. P. *et al.* Assessing response to interferon-β in a multicenter dataset of patients with MS. *Neurology*, v. 87, n. 2, p. 134–140, 12 jul. 2016.

TAUIL, C. B. *et al.* Suicidal ideation, anxiety, and depression in patients with multiple sclerosis. *Arquivos de Neuro-Psiquiatria*, v. 76, n. 5, p. 296–301, maio 2018.

THOMPSON, A. J. *et al.* Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet Neurology*, v. 17, n. 2, p. 162–173, fev. 2018.

TROJANO, M. *et al.* Treatment decisions in multiple sclerosis — insights from real-world observational studies. *Nature Reviews Neurology*, v. 13, n. 2, p. 105–118, 13 fev. 2017.

VARGAS, D. L.; TYOR, W. R. Update on disease-modifying therapies for multiple sclerosis. *Journal of Investigative Medicine*, v. 65, n. 5, p. 883–891, jun. 2017.

VASCONCELOS, C C F *et al.* Long-term MS secondary progression: Derivation and validation of a clinical risk score. *Clinical Neurology and Neurosurgery*, v. 194, p. 105792, jul. 2020.

VASCONCELOS, C C F *et al.* African Ancestry Is a Predictor Factor to Secondary Progression in Clinical Course of Multiple Sclerosis. *ISRN Neurology*, v. 2012, p. 410629, 2012.

VUKUSIC, S.; CONFAVREUX, C. Natural history of multiple sclerosis: risk factors and prognostic indicators. *Current Opinion in Neurology*, v. 20, n. 3, p. 269–274, jun. 2007.