Progression of Relapsing-Remitting Multiple Sclerosis despite the new era of treatments

Progressão da Esclerose Múltipla Remitente-Recorrente apesar da nova era de medicamentos.

Progresión de la esclerosis múltiple recurrente-remitente a pesar de la nueva era de las drogas.

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ABSTRACT

Objective. The present study aims to evaluate the conditions associated with the progression of Multiple Sclerosis (MS) and patients' dysfunctions. **Methods.** We perform a retrospective longitudinal analytical observational study in 46 patients with MS from a polyclinic in Rio de Janeiro, Brazil. We used the Expanded Disability Status Scale (EDSS) to rank the patients according to their disability and establish a correlation with risk factors, treatment, and time of disease. **Results**. Of 46 patients, 69.6% were female, and 67.4% were white. Patients with fewer functional systems affected at the beginning of the disease had a longer time for disease progression, according to EDSS. Low-efficacy drugs led to a high rate of discontinuation of the treatment. Patients who used a continuous treatment took longer to reach higher EDSS values than those who discontinued treatment. **Conclusion.** Despite the control of MS with high-effective drugs, there is still some disability for the patient. The factors that influenced the progression of the disability were: multiple symptoms at the beginning of the disease, more than 30 years old at the beginning of the MS, delay in diagnosis and initiation of treatment, among others.

Keywords: Multiple sclerosis, Disease progression, Therapeutics.

RESUMO

Objetivo. O presente estudo tem como objetivo avaliar as condições associadas à progressão de doença e disfunções dos pacientes com Esclerose Múltipla (EM). **Métodos**. Estudo observacional analítico longitudinal retrospectivo com 46 pacientes com EM de uma policlínica do Rio de Janeiro, Brasil. Foi utilizada a Escala de Incapacidade Funcional Expandida (EDSS) para classificar os pacientes de acordo com a incapacidade e estabelecer correlação com fatores de risco, tratamento e tempo de doença. **Resultados**. Dos 46 pacientes, 69,6% eram do sexo feminino e 67,4% eram brancos. Pacientes com menos sistemas funcionais afetados no início da EM levaram maior tempo para progressão da doença. Medicamentos de baixa eficácia foram associados a uma alta taxa de descontinuação do tratamento. Pacientes em tratamento contínuo levaram maior tempo para atingir valores mais altos de EDSS comparado com pacientes que descontinuaram o tratamento. **Conclusão**. Apesar do controle da EM com medicamentos de alta eficácia, os pacientes ainda apresentam alguma incapacidade. Os fatores que influenciaram a progressão da incapacidade foram: múltiplos sintomas no início da doença, mais de 30 anos no início da EM, atraso no diagnóstico e início do tratamento, entre outros.

Palavras-chave: Esclerose múltipla, Progressão de doença, Terapias.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS). It is characterized by episodes of focal deficit due to the involvement of the optic nerve, spinal cord, and brain. The location of demyelination determines the neurological manifestations[1-2]. The course of MS is relapsing-remitting (RRMS) at onset in 85% of cases[3]. The prevalence of MS varies considerably worldwide. In Brazil, there are regions of medium prevalence (between 5 and 30 cases per 100,000 population)[4].

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The most popular and widely used instrument to describe the clinical severity and functional deficits in MS is the Expanded Disability Status Scale (EDSS) of Kurtzke. EDSS consists of an ordinal rating system ranging from 0 (normal neurological status) to 10 (death due to MS). The determination of EDSS 4 – 6 is heavily dependent on aspects of walking ability[5].

Notable negative prognostic factors for MS, in general, include the onset of progressive disease, disability at 2 and 5 years, frequent relapses in the first years of disease, male gender, and a short interval between the first and the second attacks[6]. Race and ethnicity are also composite variable in disease presentation, severity, and progression[7]. Vaconcelos[8] et al. (2016) concluded that being of African descent was associated with a shorter time until reaching progression of MS in a study made in Rio de Janeiro (RJ), Brazil.

Although there are currently no treatments that promote remyelination or neural repair[9], the new era of treatment began with disease-modifying agents (DMTs) that have been approved for RRMS. DMTs decrease inflammation through several mechanisms and can be classified as low-, moderate- or high-efficacy drugs[10].

The Brazilian Ministry of Health provides freely for MS patients interferon-beta 1a (IFN-β -1a), interferon-beta 1b (IFN-β -1b), glatiramer acetate, teriflunomide, dimethyl fumarate, natalizumab, and fingolimod[11]. Despite the restricted drugs provided by the government, other DMTs are available.

This article aims to assess the factors that influenced the functional impairment of patients with MS and how the treatment influenced the progression of their disease.

MATERIALS AND METHODS

A retrospective longitudinal analytical observational study was performed with 46 patients from a polyclinic in RJ, Brazil. Participants were recruited in April 2020, and data were collected in April and May 2020. The inclusion criteria of the present study were patients in regular care, with a final diagnosis of relapsing-remitting MS defined according to the 2017 Revised McDonald Diagnosis Criteria and absence of suspicion of other CNS inflammatory diseases. And as exclusion criteria, patients with an uncertain diagnosis of MS and without regular care in the polyclinic.

Therefore, after the approval of the study by the Ethics Committee and all the Informed Consent Forms were signed and confidentiality was maintained by not identifying patients' names, we proceeded to a neurological physical examination, review of medical records, and interview of patients. Data were obtained based on the following questions: 1. Ethnicity; 2. Gender: male and female; 3. Date of Birth; 4. Age of the patient at the onset of the disease; 7. Year of onset of the disease; 8. Total time of illness; 9. Total time of illness at diagnosis; 10. Total disease time to start treatment and type/time of treatment; 11. Number and type of functional systems compromised at the beginning of the disease; 12. Time period to reach stages 3, 6, and 7.5 of the EDSS, and the current EDSS, all obtained by the authors or other physicians, according to medical records. 13. Number of attacks in the first and the fifth year of the disease. 14. Type of medication used and time of use/ failure reasons.

Disease progression was defined as an increase in EDSS that was sustained for six months or more, with no improvement or progressive worsening at each assessment. Therapeutic failure was defined by persistent or increase in the number or severity of attacks, a rise in the EDSS of one point when the initial EDSS is 3 to 5.5, or half point when the initial EDSS is 6 or more, or cognitive worsening that interferes with activities of daily living.

The initial clinical manifestations were categorized into functional systems (FS): pyramidal, cerebellar, sensitive, visual, brain stem, sphincter, and mental. The onset of the disease was defined according to the date of the first attack. The date defining the total duration of the disease was that of the patient's last interview.

The software R v 4.0.2 was used for the statistical analysis, initially applying the Shapiro-Wilk and Anderson-Darling normality tests, which showed that most variables followed a normal probability distribution. In this sense, the need to use non-parametric statistical methods of comparison was shown. Therefore, the Mann-Whitney

non-parametric statistical test was chosen to verify whether there is a difference between the categories of variables. The results were considered to have statistical significance when the p-value was equal to or less than 0.05.

RESULTS

The study included 46 patients, of which 15 were black and mixed race (brown), and 31 were white, 32 were women, and 14 were men. The lowest value of age in patients at the beginning of the disease was 12 years and the highest was 52 years. The global average age at the onset of the disease was 30.04 years. There is a slight tendency for whites (average age of disease onset 29.32) to start the disease at a younger age than blacks and mixed Race (average age of

disease onset 32.14), which is statistically significant (p=0,002).

The minimum and maximum total duration of the disease until the date of inclusion in the study was 1 and 28 years, respectively, with slightly shorter duration in people of black and mixed race. The duration of the disease from the beginning of the manifestations to the beginning of the treatment was observed from the same year of beginning until 21 years of illness; however, there was a patient who only underwent pulse therapy and did not have any more attacks despite not using any continuous treatment. As for the total duration of treatment, it varied from recent onset to 21 years, with a slightly higher average in men. Furthermore, there were 15 people with at least two attacks in the first year of the disease and 14 people with at least two attacks in the fifth year of the disease. Additional data are summarized in Table 1.

Table 1

Clinical and evolutionary characteristics according to sex and ethnic group.

Variable	Women	Men	p-value	White	Blacks and Mixed Race	p-value	Total (N=46)
Number of Patients	32	14	-	31	15	-	46
Average of disease duration until diagnosis (in years)	3.1	3.3	0.292	3.3	2.1	0.952	3.08
Average duration of illness (in years)	12.0	12.4	0.250	12.5	11.7	0.672	12.33
Average of the number of functional systems affected at the beginning of the disease	1.0	1.5	0.213	1.2	1.9	0.127	1.41
Average duration of illness until the start of treatment (in years)	4.4	4.0	0.416	4.6	3.4	0.952	4.38
Average total duration of treatment (in years)	7.0	8.2	0.108	7.7	7.7	0.279	7.62
Number of attacks in the first year							
≤1	25 (78.1%)	6 (42.9%)	<0.001*	20 (64.5%)	10 (71.4%)	<0.001*	-
≥2	7 (21.9%)	8 (57.1%)	<0.001*	11 (35.5%)	4 (28.6%)	<0.001*	-
Number of attacks in the fifth year							
≤1	22 (68.8%)	6 (42.9%)	<0.001*	20 (64.5%)	7 (50.0%)	<0.001*	-
≥2	7 (21.9%)	7 (50.0%)	<0.001*	8 (25.8%)	6 (42.9%)	<0.001*	-

* The results were considered to have statistical significance

The absolute numbers and frequencies of the different types of functional systems compromised at the onset of the disease are shown in Figure 1. The most affected functional system was the visual (25%), followed by the pyramidal and sensitive (21% both) and brain stem (19%). Only two patients had a mental disorder as an initial manifestation.

Women reached EDSS 3 in a shorter time compared to men, but in order to achieve EDSS 6, men took less time than women, and blacks and mixed-race individuals took longer than whites. Finally, to reach EDSS 7.5, men took more than twice as long to reach it compared to women, whereas blacks and mixed-race individuals also took twice as long to reach it, compared to whites. Additional data are summarized in Table 2.

In general, patients younger than 30 years old at the onset of the disease took longer to reach EDSS 3, 6, and 7.5, compared to patients aged 30 years or older at the onset of the disease, which was statistically significant for the time to reach EDSS 3. In general, patients with 1 Functional System affected at the beginning of the disease took longer to reach EDSS 3, 6, and 7.5, which was statistically significant for the time to reach EDSS 3. Additional data are summarized in Table 3.

Most patients take less than five years of disease until the beginning of treatment, of which 60.7% present current EDSS less than 3. Additional data are summarized in Table 4.

Functional Systems
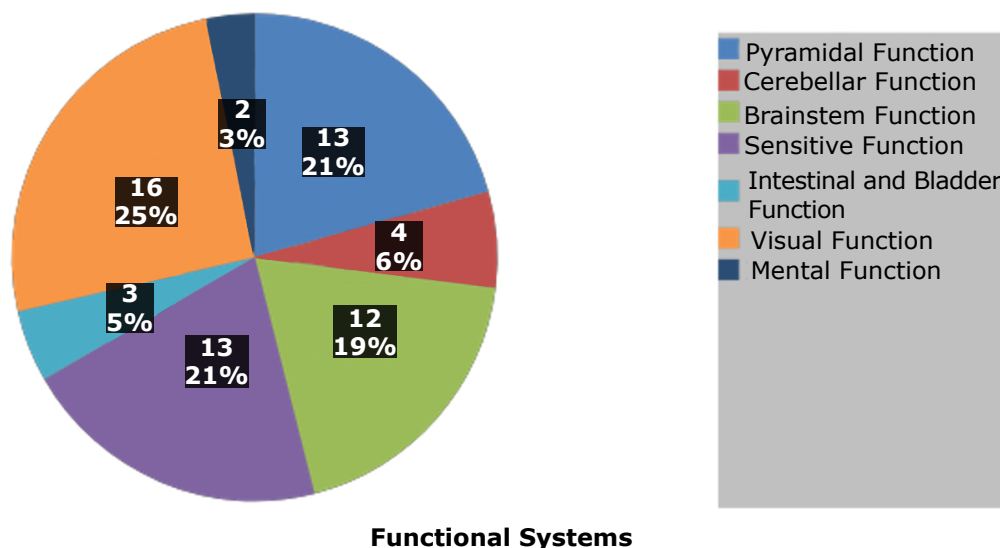
Figure 1: Frequency of functional systems compromised at the beginning of the disease

Table 2

Average time (in years) to reach EDSS degrees according to gender and ethnicity

Variable	Women	Men	p-value	White	African descent and Mixed Race	p-value
Time for EDSS 3	4.49	7.1	0.86	6.21	6	0.320
Time for EDSS 6	8.04	6.6	0.743	7.4	11.3	0.417
Time for EDSS 7.5	5	12.5	-----	5.25	14.5	-----
Number of patients who reached each EDSS at any given time						
EDSS 3	17	9	-	15	5	-
EDSS 6	9	4	-	8	3	-
EDSS 7.5	3	1	-	2	2	-

Note: Due to the insufficient sample, it was not possible to compute the p-value for the EDSS 7.5 reach time.

Table 3

Average time (in years) to reach EDSS degrees according to age group and the number of functional systems changed at the onset of the disease.

Variable	Age at onset		p value	No. of FS affected at onset		p value
	< 30 years	≥ 30 years		1 FS	≥ 2 FS	
Time to reach EDSS 3	8.5	2.8	<0.001*	7.3	3.3	<0.001*
Time to reach EDSS 6	9.0	5.1	0.118	8.8	7.8	0.793
Time to reach EDSS 7.5	9.6	1.0	-----	9.4	1.5	-----

Note: Due to the insufficient sample, it was not possible to compute the p-value for the EDSS 7.5 reach time.

Abbreviation: FS – functional system.

* The results were considered to have statistical significance

Table 4

Average value of the current EDSS according to the time of illness until the start of treatment.

Variables	Time of illness to start of treatment		p-value
	< 5 years	≥ 5 years	
Number of Patients	28	17	
Number of Patients with a current EDSS < 3	17	3	
Average value of the current EDSS	2.57	4.83	0.004 *

* The results were considered to have statistical significance

Patients who discontinued for ≤ 1 year (37 patients) had a lower current EDSS (average value 2.66) than patients who discontinued treatment for more than one year (seven patients with an average current EDSS value of 3.66). Furthermore, statistically significant results (p=0.038) were seen in the times to reach EDSS 3 and 6, in which patients who discontinued for > 1 year reached such EDSS with a shorter time (average of 6.1 years), compared to those who discontinued for ≤ 1 year (average 3.8 years).

The drugs used by the patients were grouped into three categories: 1) Low Efficacy Drugs: Subcutaneous interferon beta 1a; Intramuscular interferon beta 1a; Subcutaneous interferon beta 1b; Glatiramer Acetate; Teriflunomide, which were used 55 times in a total of 40 patients. 2) Medium Efficacy Drugs: Fingolimod Hydrochloride, and Dimethyl Fumarate, which were used 22 times in a total of 21 patients. 3) Highly-Effective Drugs: Natalizumab, Alemtuzumab, and Ocrelizumab, which were used 25 times in a total of 21 patients.

In general, it is observed that low-efficacy drugs were used by more patients and had a considerable number of therapeutic failures and adverse reactions. There was a significant reduction in the number of therapeutic failures in medically effective medications and even more so in highly effective medications, although the number of reasons for switching was higher in highly effective medications than in those with medium efficacy, as a result of the use of Natalizumab, which was suspended in eight patients, who met all the withdrawal criteria: use of the drug for more than two years, positivity for anti-JCV antibody and use of immunosuppressant in previous therapy. Additional data are summarized in Table 5.

Table 5

Absolute number of patients in use, average time of use (in years), and reasons for an exchange, by medication.

Variables	Number of Patients	Therapeutic Failure	Adverse reactions	Other Reasons for Withdrawal	Average Usage Time (years)
Subcutaneous interferon beta 1a	17	9	5	1	2.98
Intramuscular interferon beta 1a	14	10	1	1	2.71
Subcutaneous interferon beta 1b	5	2	1	1	4.73
Glatiramer Acetate	15	7	2	5	2.75
Teriflunomide	4	0	0	2	0.93
Fingolimod Hydrochloride	16	6	2	0	3.57
Dimethyl fumarate	6	1	0	0	3.33
Natalizumab	19	3	0	8	3.69
Alemtuzumab	5	0	0	0	2.4
Ocrelizumab	1	0	0	0	1

DISCUSSION

Despite the control of MS with drugs being more effective, there is still some dysfunction. Most patients have a minimum degree of disability regardless of the duration of the disease.

In the studied population, the demographic analysis showed a predominance of female patients (69.6%) and white ethnicity (67.4%). The average age at the onset of the disease found was 30.4 years. These demographic characteristics are similar to data found in other studies conducted in Brazil and worldwide[12-16]. The youngest age at diagnosis of MS in this study was 12 years old and the highest was 52 years old. In a study in Saudi Arabia in 2018, the lowest age for diagnosis was 9 years and the highest was 58 years[16]. The average time between the onset of the disease and the diagnosis was 3.08 years. Negreiros[4] et al. (2015), in Paraíba (Brazil), found a slightly longer time (3.9 years), and Skoog[17] et al. (2012) found a shorter time (2 years) in Switzerland.

Most patients had only one attack in the first year of illness and the fifth year of illness. Teixeira[14] (2011) has shown that the first two outbreaks of most patients occurred in the first three years (median time of 2.1 years). Damasceno[6] et al. (2013) concluded that the number of attacks within five and ten years of disease onset is associated with a slightly increased risk for EDSS 8. A Brazilian study demonstrated that the occurrence of two or more attacks in the first year of disease increases the chance of dysfunction due to MS in a shorter period[14].

The number of functional systems affected at the onset of the disease ranged from 1 to 5, with an average of 1.0 in females and 1.5 in males. The visual (25%), pyramidal (21%), sensitive (21%), and brainstem (19%) systems were the most affected. Teixeira[14] (2011) also highlighted the visual function as the functional system most affected at the beginning of MS. On the other hand, Ghezzi[18] et al. (2002) showed that the functional systems most often involved in the onset of the disease were pyramidal and brain stem (both in 28% of cases).

Patients aged 30 years or older at the onset of the disease had a shorter time for the disease to progress. Other studies have shown similar results[6,19]. Furthermore, patients with fewer functional systems affected at the beginning of the disease had a longer time for disease progression, according to EDSS. Vasconcelos[8] et al. (2016) and Hawkins[20] et al. (1999) have shown that polysymptomatic patients at the beginning of the disease have a worse prognosis. On the other hand, a study from Iran showed that the rate of dysfunction and disease progression, based on the EDSS, are the same in monosymptomatic and polysymptomatic patients[21].

The time between the onset of the disease and the beginning of treatment was around 4.38 years. Two studies from abroad found shorter time: Decard[22] et al. (2018) found an average time of 1.4 years in

Switzerland and Laffaldano[23] et al. (2018) from the international database on MS (MSBase) and database from Denmark, Sweden, Italy, and France, found an average time of 3.8 years. A Brazilian study found a longer time of 6.15 years[6]. In national studies, the time to start treatment was longer and this may be due to the difficulty of accessing treatments for MS in the Brazilian health system.

Most patients who started treatment before five years of illness had a current EDSS below 3.0. The time of diagnosis and the time to start treatment were identified as the most influential factors in the control of MS and the course of the disease. That is because it would limit inflammation and the possibility of degenerative damage[24]. Giovannoni[25] et al. (2016) explained that the sooner the pharmacological treatment is started, the greater the possibility of reducing the disease's subclinical activity, preserving brain volume and decreasing or preventing the progression of disability.

Regarding the impact of continuity of the treatment on the progression of MS, it was evidenced that patients who used it continuously took longer to reach higher EDSS values than those who discontinued treatment. Another study demonstrated that the interruption of treatment was correlated with the progression of disability and/or new attacks of the disease[26].

The lower the efficacy of the medication used, the higher the rate of therapeutic failure and adverse reactions, implying a change in treatment. Meyniel[26] et al. (2012) showed that the increase in disability, that is, the disease progression, is a significant fact for the discontinuation of subcutaneous and intramuscular interferon beta 1a, as well as Glatiramer Acetate. The rate of abandonment of treatment with these immunomodulators is higher in the first two years, reaching up to 25%[27-28]. In the present study, of the 55 times they were used, low-efficacy drugs had a therapeutic failure in 28 (50.9%), leading to discontinuation of the drug's use. Tilbery[27] et al. (2009) found in their research that both the loss of the drug's effectiveness and the exaggerated expectation are causes of this abandonment and/or exchange.

Highly-effective drugs showed a higher rate of other causes of discontinuation. This was due to the relationship between the use of Natalizumab (a highly-effective drug) and the positive status of the JC virus in some patients. The presence of this pathogen in patients that use Natalizumab for more than three years and had been treated previously with immunosuppressants shows a higher risk of developing Progressive Multifocal Leuko-encephalopathy – LEMP.[29] The prevalence of this virus in the population can reach 80%[30].

Some of the limitations of this research are related to data collection. With the start of the Covid-19 pandemic in March 2020, activities at the polyclinic were suspended. For this reason, some of the information was acquired via telephone interview and, therefore, the number of patients was reduced and statistical analysis could not be performed for some variables. Other challenges of this aspect were: establishing the chronology of events and being precise in the value of the old and current EDSS since this information depends on patient reports.

CONCLUSION

In conclusion, MS is a disease that affects several functional systems. The factors that influenced the progression of the disability were: multiple symptoms at the beginning of the disease; more than 30 years old at the beginning of the MS. Other aspects like the time until the diagnosis and the time until the start of treatment also influenced the disease control. The sooner the treatment started, the lower the current EDSS. The approach to these aspects is fundamental for implementing measures that identify patients with MS earlier. Furthermore, although low-efficacy drugs are the most widely used, it showed a higher rate of therapeutic failure or other reasons that led to drug discontinuation. While those of high and moderate effectiveness are used for a longer period but with a lower exchange rate. Discontinuation of treatment was directly related to the progression of disability, which means an increase in EDSS in less time. Therefore, the choice of medication and monitoring the patients to check the functionality of the therapeutic plan is of fundamental importance to avoid greater functional impairment and restrictions on the patient's life.

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