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Artículos

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Factores sociodemográficos y clínicos relacionados con la progresión de la discapacidad en pacientes con esclerosis múltiple.

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Abstract:

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS), with variable prognosis, and significant social impact. The prevalence in Colombia was 7.52 per 100,000 inhabitants during 2013 and has increased by 60% from 2009 to 2013. **Objective:** identify the sociodemographic and clinical factors related to disability progression in MS. **Methodology:** A descriptive study with a cross-sectional analytical component was carried out using disability progression as the dependent variable. The medical records of 216 patients living within the Metropolitan Area of Valle de Aburrá, Antioquia, Colombia. **Results:** In the multivariate model, by adjusting the MS phenotype for the other variables, the following factors were associated with a greater likelihood of having disability progression: primary progressive (OR 3.246, 95% CI 1.294 - 8.145, P-value = 0.012); cerebellar complications (OR 2.498, 95% CI 1.186 - 5.265, P-value = 0.016); antidepressant drugs (OR 2.336, 95% CI 1.054 - 5.176, P-value = 0.037); the presence of other neurological diseases (OR 3.392, 95% CI 1.139 - 10.102, P-value = 0.028); and active lesions on magnetic resonance imaging (OR 2.162, 95% CI 1.042 - 4.485, -P = 0.038). Those with pathologies other than cardiovascular, metabolic, mental, autoimmune, or infectious diseases had a lower likelihood of disability progression (OR 0.138, 95% CI 0.024 - 0.799, P-value = 0.028). **Conclusions:** The results of the present work can serve as a starting point for monitoring patients, contributing to problem-solving, and improving the quality of life for people with this disease.

Keywords: disability, multiple sclerosis, disability progression, clinical predictors.

Resumen:

La esclerosis múltiple (EM) es una enfermedad desmielinizante crónica del sistema nervioso central (SNC), de pronóstico variable y con un impacto social significativo. La prevalencia en Colombia fue de 7,52 por 100.000 habitantes durante 2013 y ha aumentado en un 60% de 2009 a 2013. **Objetivo:** identificar los factores sociodemográficos y clínicos relacionados con la progresión de la discapacidad en la EM. **Metodología:** Se realizó un estudio descriptivo con componente analítico transversal utilizando la progresión de la discapacidad como variable dependiente. Las historias clínicas de 216 pacientes residentes en el Área Metropolitana del Valle de Aburrá, Antioquia, Colombia. **Resultados:** En el modelo multivariado, al ajustar el fenotipo de EM para las otras variables, los siguientes factores se asociaron con una mayor probabilidad de tener progresión de la discapacidad: primaria progresiva (OR 3,246, IC 95% 1,294 - 8,145, valor de p = 0,012); complicaciones cerebelosas (OR 2,498; IC del 95%: 1,186 - 5,265; valor de p = 0,016); fármacos antidepresivos (OR 2,336; IC del 95%: 1,054 - 5,176; valor de p = 0,037); la presencia de otras enfermedades neurológicas (OR 3,392, IC del 95% 1,139 - 10,102, valor de p = 0,028); y lesiones activas en la resonancia magnética (OR 2,162; IC del 95%: 1,042 - 4,485, -P = 0,038). Aquellos con patologías distintas de las cardiovasculares, metabólicas, mentales, autoinmunes o infecciosas tuvieron una menor probabilidad de progresión de la discapacidad (OR 0,138, IC del 95%: 0,024 - 0,799, valor de p = 0,028). **Conclusiones:** Los resultados del presente trabajo pueden servir como punto de partida para el seguimiento de los pacientes, contribuyendo a la resolución de problemas y mejorando la calidad de vida de las personas con esta enfermedad.

Palabras clave: discapacidad, esclerosis múltiple, progresión de la discapacidad, predictores clínicos.

Introduction

Multiple sclerosis (MS) is a chronic inflammatory, neurodegenerative disorder with a variable prognosis, high treatment cost, and significant social impact [1]. The behavior of MS is heterogeneous with different phenotypes, which makes its pathological characteristics and response to treatment variable [2,3]. Although a precise etiology is still unknown, genetic and environmental factors are thought to play a strong role in the onset and course of the disease [4,5]. At present, four clinical phenotypes are known: clinically isolated syndrome (CIS), relapsing-remitting MS (MSRR), secondary progressive MS (MSSP), and primary

progressive MS (MSPP) [5-7]. MS often presents with episodes of symptom exacerbation, known as outbreaks. Depending on their severity, they can cause temporary or permanent disability.. MS is one of the main causes of neurological disability in young adults between 20 and 40 years of age, with a higher prevalence in women [2,3].

Colombia is located on the equator and is considered to be an area of low MS prevalence. The first epidemiological registry of known cases was prepared by Vergara et al. in 1990 and described 133 cases in a Bogotá hospital in 1990 [8]. In 2000, Sánchez et al. carried out the first study using a capture-recapture methodology in five Colombian departments and found a prevalence of between 1.48 and 4.98 cases per 100,000 inhabitants, with a prevalence in Antioquia of 1.48 per 100,000 [9]. The last epidemiological study was carried out by Jiménez-Pérez et al., in which they evaluated government records from the years 2009 to 2013 and found a mean prevalence for this period of 7.52 per 100,000 inhabitants [10]. Antioquia has a rate of 6.82 per 100,000 inhabitants. Although different studies have shown lower rates and an association with genetic factors in the population [9,11-13].

Neurological disability associated with MS can be irreversible. For this reason, in clinical practice rating scales are used to measure disability and to assess progression over time. The most widely used method is the Expanded Disability Status Scale (EDDS), or the Kurtzke scale, which allows for the evaluation of the degree of functional limitation of the patient through eight functional systems [14,15]. Among the main functions affected are sensory, motor, cognitive, and visual [16]. MSRR is characterized by relapses or flare-ups, with acute clinical manifestations (24 hours to 30 days) and complete or partial recovery that can lead to disability accumulation [17,18]. There is currently no way to predict the factors that can influence the presentation of an outbreak, much less avoid them [19]. In the case of MSPP and MSSP, disability increases progressively, without relapses [20,21]. Despite how MS presents, most patients will end up with some degree of disability, which is progressive and irreversible [22-24]. This work aims to identify the sociodemographic and clinical factors related to the progression of disability in MS patients.

Methods

A descriptive study with a cross-sectional analytical component was carried out. The dependent variable was disability progression, defined as a steady increase between assessments of at least 0.5 points in the scale value over at least six months. Medical records of 216 patients who met the following inclusion criteria were included by the census of the period: confirmed diagnosis of MS according to McDonald's criteria; attendance at a reference site for follow-up of their disease between 2013 and 2020; having an Expanded Disability Status Scale (EDSS) score described in the medical record; and living within the Metropolitan Area of Aburrá Valley, Antioquia, Colombia.

Data collection variables and instruments

A Microsoft Excel database was created based on information from the medical records, which included variables on sociodemographic features of the population. Clinical features and areas with demyelinating lesions on magnetic resonance imaging (MRI).

Statistical analysis

Data were analyzed in Jamovi 1.6.16. Initially, an exploratory analysis of the data was carried out to detect data outliers. In the univariate analysis for the qualitative variables, absolute and relative frequencies were calculated; for the quantitative variables, their distribution was determined using the Shapiro Wilk test (normal or non-normal). Since the data were not normally distributed, medians and interquartile ranges were calculated. Independent variables were categorized according to their quantitative or qualitative nature and their distribution with the dependent variable (disability progression). For the quantitative variables,

the Mann-Whitney U test was used to compare with the dependent variable. Pearson's chi-square test was used to establish the relationship between qualitative variables. If less than 80% of the expected frequencies of each subcategory were greater than 5, the two-tailed Fisher's exact test was used. For each of the analyses, a significance was used for the hypothesis test (α) of 0.05, with a confidence interval of 95%, and a significant p-value of <0.05. A binary logistic regression was performed to determine the statistical association between the dependent variable, disability progression (Yes = 1, No = 0), and the factors associated with disability progression (independent variables).

Ethical considerations

This study was approved by the ethical review board at CES University and Neurological Institute of Colombia (sheet number RDGCOINVF05) where the research was developed.

RESULTS

Univariate analysis

Gender distribution was mostly women at 76.9%. The median age at diagnosis was 35 years of age (IQR 26.75-44 years) and 58.8% of the participants had a partner. Most of the patients had the RRMS phenotype at 75.5% and the PPMS phenotype at 14.4%, while the remaining 10% corresponded to the EMSP phenotype. Regarding comorbidities, 16.7% presented with metabolic disease, 9.3% with cardiovascular disease and in the same proportion neurological diseases, and 11.6% of patients presented with other types of diseases. Treatment of these comorbidities included 24.1% of the patients with antidepressants, 18.5% with analgesics, and 18.3% with drugs for cardiovascular disease (Table 1).

Table 1. Sociodemographic and clinical characteristics of patients with multiple sclerosis

TABLE 1
Sociodemographic and clinical characteristics of patients with multiple sclerosis

Variable	Categories	n	%
Sex	Woman	166	76.9
	Man	50	23.1
Age at diagnosis of MS (Me-IQR)		35	26.75-44
State of coexistence	With couple	89	41.2
	Single	127	58.8
Recurrent Remitting Multiple Sclerosis		163	75.5
Progressive Primary Multiple Sclerosis		31	14.4
Progressive Secondary Multiple Sclerosis		22	10
Comorbidities	Metabolic diseases	36	16.7
	Other diseases	25	11.6
	Cardiovascular diseases	20	9.3
	Neurological diseases	20	9.3
	Mental diseases	18	8.5
	Cancer	5	2.3
	Infectious diseases	4	1.9
	Autoimmune diseases	3	1.4
Treatments for comorbidities	Other drugs	55	25.5
	Antidepressants drugs	52	24.1
	Analgesic drugs	40	18.5
	Cardiovascular drugs	40	18.3
	Metabolic drugs	33	15.3
	Vitamin supplements	31	14.4
	Muscle relaxing drugs	16	7.4
	Hypoglycemic drugs	9	4.2
	Medications for gait	9	4.2
	Botulinum toxin	7	3.2

MS: multiple sclerosis. Me: medium. IQR: interquartile range.

Disability progression increased among 25% of the patients who participated during the study period. EDSS median was 1.5 (IRQ 0-5.6). Regarding the appearance of the initial symptoms of the disease until diagnosis, a median of 12 months (IRQ 6-48) was found. At the onset of the disease, there were clinical manifestations classified by the functional systems of the EDSS, among which the following stand out: cerebellar symptoms (21.1%); sensory symptoms (33.3%); or other symptoms (31.9%). Regarding complications caused by the disease as classified by the functional systems of the EDSS, 47.2% experienced alterations in vision, 44.4% had complications of cerebellar origin, and 17.1% presented sensitivity complications. Regarding magnetic resonance imaging, findings revealed that 78% had spinal injuries, 71.8% periventricular injuries, and 70.3% juxta-cortical injuries. The use of disease-modifying drugs is distributed as follows: 17.6% of patients have ever been prescribed interferon beta 1B; 14.8% natalizumab; 14.8% no disease-modifying treatment; and 10.6% teriflunomide.

Bivariate analysis

Supplementary Table shows the variables that had a statistically significant association with disability progression. Patients with the PPMS phenotype were 4.3 times more likely to have disability progression than were those who did not have the PPMS phenotype (OR 4.3, 95% CI 1.9 - 9.4, P-value = 0.001). Patients with the RRMS phenotype had 74% lower likelihood of progressing to disability (OR 0.26, 95% CI 0.1 - 0.5, P-value = 0.001). Men had 2.4 times the likelihood for disability progression than did women (OR 2.4, 95% CI 1.2 - 4.7, P-value = 0.015). In the analysis of age and disability progression, it was found that the medians of age, within the disability progression categories, differed significantly (P-value = 0.037) (Supplementary Table), with older age being more frequent among those who had progression of disability. Presence of initial sensitive symptoms (OR 0.42, 95% CI 0.2 - 0.9, P-value = 0.021), no complications (OR 0.0, 95% CI 0.0 - 0.5, value- P = 0.001), and the presence of other comorbidities (OR 0.2, 95% CI 0.1 - 1.0, P-value = 0.047) were associated with a lower probability of disability progression (Supplementary Table). Cerebellar complications (OR 3.6, 95% CI 1.9 - 7.0, P-value = 0.001), no treatment (OR 2.9, 95% CI 1.3 - 6.3, P-value = 0.009), use of cardiovascular drugs (OR 2.3, 95% CI 1.1 - 5.1, P-value = 0.031), use of antidepressant drugs (OR 2.5, 95% CI 1.3 - 4.9, P-value = 0.009), presence of other neurological diseases (OR 2.8, 95% CI 1.1 - 7.3, P-value = 0.035), and presence of active lesions on brain MRI (OR 2.0, 95% CI 1.1 - 3.9, P-value = 0.036) were all associated with a greater likelihood of disability progression.

Multivariate analysis

A binary logistic regression analysis was performed with significant variables to determine probability that patients experience disability progression. Table 2 presents the multivariate model for disability progression. Adjusting for the other variables, the PPMS phenotype (OR 3.246, 95% CI 1.294 - 8.145, P-value = 0.012), cerebellar complications (OR 2.498, 95% CI 1.186 - 5.265, P-value = 0.016), antidepressant drugs (OR 2.336, 95% CI 1.054 - 5.176, P-value = 0.037), the presence of other neurological diseases (OR 3.392, 95% CI 1.139 - 10.102, P-value =0.028), and active lesions on MRI (OR 2.162, 95% CI 1.042 - 4.485, P-value =0.038) were all associated with a greater likelihood of disability progression. By contrast, those with pathologies other than cardiovascular, metabolic, mental, autoimmune, or infectious had a lower likelihood of disability progression (OR 0.138, 95% CI 0.024 - 0.799, P-value = 0.028) (Table 2).

Table 2. Disability progression according to sociodemographic and clinical variables adjusted for other variables in patients with multiple sclerosis

TABLE 2
Disability progression according to sociodemographic and clinical variables adjusted for other variables in patients with multiple sclerosis

Predictor	Estimate	95% CI		I KNOW	Z	p	OR	95% CI	
Intercept	-2.308	-2.982	-1.634	0.344	-6.710	0.001	0.099	0.051	0.195
PP phenotype	1.178	0.258	2.097	0.469	2.509	0.012	3.246	1.294	8.145
Cerebellar complications	0.916	0.170	1.661	0.380	2.407	0.016	2.498	1.186	5.265
Antidepressant Drugs	0.848	0.052	1.644	0.406	2.089	0.037	2.336	1.054	5.176
Other diseases	-1.977	-3.729	-0.225	0.894	-2.211	0.027	0.138	0.024	0.799
Neurological diseases	1.221	0.130	2.313	0.557	2.194	0.028	3.392	1.139	10.102
Active lesions on MRI	0.771	0.041	1.501	0.372	2.070	0.038	2.162	1.042	4.485

OR: Odds Ratio. PP: progressive primary. MRI: magnetic resonance imaging. Final variables were statistically associated with the outcome variable according to HL criterion (p-value <0.25); next, the regression model was built, which had LR values Chi2 (6) = 39.06, P = 0.001, AIC = 207.214.

Discussion

Various studies have sought to contribute to the knowledge about MS by addressing sociodemographic, clinical, and biomarker aspects to predict the course of its pathology. Sociodemographic factors have been involved significantly in the development, prognosis, and clinical follow-up of patients with MS. According to the literature, MS is more prevalent in females than in males [25]. However, women have a better prognosis than men [26,27]. This result is evidenced in our study in that, even though the female population was 76.9%, the percentage of men who had progression of disability was 20.48%, while in women it was 38.0%. Regarding the age of diagnosis, studies indicate that pathology generally presents between 20 and 40 years of age (3.28-30) with a global average of 32 years of age [25]. On the other hand, in our study, the median age at diagnosis was 35 years of age and was associated with an increase of progression probability at an older age [31].

Regarding clinical factors, the literature indicates that the PPMS phenotype generates continuous progression of disability, which can lead to a higher score on the disability scale [32]. Another reported finding is that progressive phenotypes may experience greater compromise due to cortical lesions, and, therefore, may have greater disability progression and cognitive alterations [33]. Our findings show that this phenotype was represented by 14.4% of the patients and, of these, 51.6% had disability progression. The median time from symptoms until diagnosis was 12 months; however, little information is found in the literature in this regard. Since the presentation of symptoms must be analyzed in detail to generate a differential diagnosis and this process takes time, it is estimated that a person is diagnosed with this disease every five minutes [25].

MS has a wide variability in symptoms, which can lead to patients presenting with a diversity of clinical manifestations; in most cases, these manifestations will depend on the area of the CNS where demyelination is found [34,35]. Regarding the onset symptoms in our research, we found that 33.3% of patients presented with symptoms of sensory origin, based on the EDSS, which is consistent with findings in the literature [14]. These patients, in turn, had less progression of disability. The other important group of patients as those who presented other symptoms (31.9%), including different disorders that accompany the disease. In this regard, the evidence shows that the course of this disease in individual patients is variable and there is no specific consensus on initial symptoms [26,36].

Complications in MS patients significantly highlight the permanent damage that can occur. Of the patients included in our study, 44.4% had cerebellar complications and these patients experienced a 3.6 times greater likelihood of disability progression. Indeed, various other studies have also reported that these manifestations have been related to a more rapid progression of disease [36]. Therefore, these findings may

be helpful in understanding conversion from CIS to MS [37]. The group with neurological diseases had 2.8 times the possibility of disability progression. This has been previously documented as patients with these comorbidities have greater disease progression [2,38]. Diseases, such as epilepsy, have been correlated with progression in MS and the prevalence of seizures is higher in this patient population compared to the general population [38]. Other complications, such as migraine, may not only alter disease progression but also negatively impact the quality of life and, with it, daily activities [21]. Although rare in the literature, the association of Parkinson's disease and MS has been documented, which can lead to a greater accumulation of disability [39]. Stroke, being one of the most prevalent diseases in the world, may also have an impact on MS [40]. While it is reported that any type of comorbidity may impact disability in MS patients, our study shows that having comorbidities other than cardiovascular, metabolic, mental, autoimmune, or infectious diseases is associated with a lower likelihood of disability progression, it has been estimated that an additional pathology can increase disability by 13 to 18% in a patient with MS [41].

Regarding disease-modifying treatments, none of them was associated with progression of disability; however, a proportion of patients that progressed did have the PPMS phenotype and, therefore, disease-modifying drugs were only rarely used in this population [42,43]. In the group of patients who did not have disease-modifying treatment, a greater likelihood of progression was found, either due to the phenotype or due to non-compliance with the therapeutic regimen. Among the findings, patients with cardiovascular drugs showed a greater likelihood of disability progression; studies have shown an association between cardiovascular diseases and disability progression [44-47]. It is estimated that the prevalence of arterial hypertension among MS patients is in the range of 16-21%, and some 30% have been associated with metabolic syndromes [41]. Anxiety and depression are some of the most frequent comorbidities in MS [40]. It has been found that patients on antidepressant treatment have 2.4 times the likelihood of disability progression. This finding is debatable, because some of these patients may be depressed due to their clinical condition and, therefore, may be exposed to side effects from drugs that they are taking [48].

Concerning MRI studies, the presence of damage to white matter is important in the severity of the disease. It should be noted that these results must be taken into consideration objectively with the clinical assessment, since, depending on the affected brain area, there may be a greater or lesser degree of disability captured by the EDSS [49]. The most important finding is that patients with active lesions have twice the likelihood of disability progression [50,51]. In other studies, infra-tentorial lesions have been associated with the progression of disability. In our study, they were divided into lesions of the brainstem (38.3%) and cerebellum (39.2%); however, no statistical association with progression was found. This topic has been reviewed in the MAGNIMS consensus guidelines, as these types of lesions can account for the clinical evolution of this disease [52]. Spinal injuries have also been considered as prognostic factors in the evolution of this disease. However, such injuries were also not related to the progression of disability in our study population [53]. Studies have indicated that the topography and volume of lesions play an important role in disability. Since the greater the number of active lesions, the greater the progression, the appearance of new lesions on T2-weighted MRI could be an indicator of an increased risk of disability progression of up to 15-fold, even when no outbreaks have occurred [52].

In conclusion, MS is a disease with a high degree of complexity. All aspects of the patient's clinical condition must be evaluated individually to identify individual risk factors. The variables PPMS phenotype, cerebellar complications, antidepressant drugs, other diseases, neurological diseases, and active lesions made up the multivariate model. In accordance with the above, the results found in the present work can serve as a starting point for monitoring patients, contributing to problem-solving, and improving the quality of life for people with this disease. Further study of the relationship between neurological diseases and disability progression in MS remains important, since this may provide insight to rule out and/or try to

compensate for other underlying diseases that patients have and, thereby, achieve better management of MS. Our findings should help to make decisions in clinical practice. However, additional epidemiological studies and monitoring of the population are recommended.

Conflict of interests

The authors declare no conflict of interest in this article

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