Brain Medicine

OPEN

RESEARCH REPORT

The association of different acute manifestations of multiple sclerosis on functional outcome

João Pedro F. Gonçalves[1], Alex C.S. Figueiredo[1], Gabriel S.M. Nunes[1], Catarina S.T. de Araújo[1], Marivaldo Y.S. Leal[1,#], Luísa D.M. Aravena[1,#], Felipe A.B. Millard[1,#], and Pedro A.P. de Jesus[1,2]

[1]Biomorphology Department, Health Sciences Institute, Federal University of Bahia, Salvador, Bahia 40110-100, Brazil
[2]Cerebrovascular Division, Department of Neurology, Roberto Santos' General Hospital, Salvador, Bahia 40301-110, Brazil
[#]These authors contributed equally.

Corresponding Author: João Pedro Fernandes Gonçalves; Av. Reitor Miguel Calmon, S/N – Vale do Canela, Salvador – BA, 40110-100, Brazil
Phone: +55 (71) 98512-7890. E-mail: joaofernandes@ufba.br

Brain Medicine; https://doi.org/10.61373/bm024r.0073

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS), typically presenting in young adults (20–50 years old). Clinical manifestations are heterogeneous, depending on which part of the CNS demyelination occurs. Therefore, this study aims to assess whether different symptoms at first acute manifestation of MS are associated with worse functional outcomes. We enrolled all patients with a confirmed diagnosis of MS, regardless of the subtype, so long as it fulfilled the McDonald's 2017 criteria. A stepwise multiple linear regression model included statistically significant ($p < 0.05$) variables in the Mann–Whitney U test. A total of 195 patients with MS were included in the final analysis, of which 140 (78.5%) were female. Acute blurry vision, acute paralysis, acute hypoesthesia, autonomic syndrome, and Lhermitte's sign at disease outbreak were found to be associated with worse EDSS (Expanded Disability Status Scale) in univariate tests. In adjusted analysis, the independent predictors of worse EDSS were acute blurry vision (Beta = 0.183; $p = 0.010$) and autonomic syndrome (Beta = 0.219; $p = 0.003$). These results may help better understand the relationship between MS symptomatology, functionality, and patient prognosis, potentially assisting physicians in determining MS patient's initial treatment.

Keywords: Multiple sclerosis, prognosis, functional outcomes.

Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system (CNS), typically presenting in young adults (20–50 years old). MS affects around two to three times more women than men. There are 2.8 million people in the world living with MS, with a higher prevalence in North America and Europe. Clinical manifestations are heterogeneous since demyelination can happen in any part of the CNS (1). It may cause physical and cognitive impairment during the disease's development, such as fatigue and loss of self-efficacy. Therefore, MS provokes significant disability and harmfully affects patients' functional independence.

The current literature lacks studies regarding clinical factors associated with patients' personal experiences with the disease. Therefore, health professionals could direct care to minimize the impact of MS symptomology on the patient's life and improve functionality. Data regarding the effect of specific symptoms on functionality and outcomes are often controversial, for example regarding the effect of paralysis and hypoesthesia in functionality (2–4). Thus, this study aims to clarify the association between these clinical features and patients' functional outcomes, evaluated through the Extended Disability Status Scale (EDSS).

Table 1. Demographic and clinical characteristics of the study population, including data regarding clinical course, EDSS at admission, and number of relapses. The table also details the prevalence of symptoms at disease onset and their association with the EDSS in the univariate analysis

Variables		
Demographics		
Age (mean; sd)	39.89 (11.57)	
Sex		
Male	45 (28.2%)	
Female	140 (71.8%)	
Race		
Black	44 (22.6%)	
Mixed	90 (46.2%)	
White	58 (29.7%)	
Clinical characteristics		
Clinical course		
Relapsing-remitting	173 (88.7%)	
Primary progressive	19 (9.7%)	
Unknown	3 (1.6%)	
EDSS at admission (median, IQR)	2 (1–4)	
Number of relapses (median, IQR)	2 (1–4)	
Years since onset (median, IQR)	8 (5–13)	
Symptoms of onset		***p*-value**
Acute blurry vision	77 (39.5%)	<0.001
Acute blindness	17 (8.7%)	0.257
Acute paresis	122 (62.6%)	0.167
Acute paralysis	22 (11.3%)	0.021
Acute paresthesia	131 (67,2%)	0.139
Acute hypoesthesia	106 (54.4%)	0.005
Autonomic syndrome	71 (36.4%)	<0.001
Nausea	34 (17.4%)	0.656
Vomiting	22 (11.3%)	0.984
Ataxia	107 (54.9%)	0.471
Cranial nerves dysfunction	92 (47.2%)	0.993
Headache	93 (47.7%)	0.659
Lhermitte sign	57 (29.2%)	0.017

SD = Standard Deviation; IQR = Interquartile range.

Results

A total of 195 patients were diagnosed with relapsing-remitting (173 patients, 88.7%) and primary progressive MS (19 patients, 9.7%) and included in the final analysis. Three (1.6%) patients had the clinical course of MS that was still under investigation at admission to the study. A total of 140 patients were women (71.8%), and the average age was 39.89 ± 11.57 years. Their median EDSS at admission was 2 points (IQR 1–4) (Table 1). General information about the symptoms of the first acute manifestation of the disease is also described in Table 1.

An univariate analysis was performed using the symptoms of the first acute manifestation of the disease, as well as demographic information such as sex and age. From these, five variables showed statistically significant correlation with worse EDSS at admission, were they: acute blurry vision ($U = 3204.5$; $p < 0.001$; $r = -0.251$), acute paralysis ($U = 1326.5$; $p = 0.021$; $r = -0.165$), acute hypoesthesia ($U = 3444.5$; $p = 0.005$; $r = -0.204$), autonomic syndrome ($U = 2696.5$; $p < 0.001$; $r = -0.325$),

Received: 20 April 2024. Revised: 14 August 2024 and 6 September 2024. Accepted: 10 September 2024.
Published online: 24 September 2024.

Table 2. Multiple linear regression analysis showing the relationship between symptoms at onset and the EDSS. The table includes unstandardized (B) and standardized (Beta) coefficients, t-statistics, p-values, 95% confidence intervals, and odds ratios (OR) for each predictor

	Unstandardized Coefficients		Standardized Coefficients			95% Confidence Interval for B		
	B	Std. Error	Beta	T	*p*-value	Lower Bound	Upper Bound	Odds ratio (OR)
Acute blurry vision	0.891	0.341	0.183	2.614	0.010	0.219	1.563	1.201
Acute hypoesthesia	−0.013	0.018	−0.048	−0.706	0.481	−0.049	0.023	0.953
Acute paralysis	0.391	0.545	0.052	0.718	0.474	−0.683	1.465	1.053
Autonomic syndrome	1.088	0.364	0.219	2.991	0.003	0.371	1.806	1.245
Lhermitte sign	0.523	0.364	0.100	1.438	0.152	−0.194	1.240	1.105

Std. = Standard.

and Lhermitte sign ($U = 2617.5$; $p = 0.017$; $r = -0.181$). All variables showed a small effect size, excluding the autonomic syndrome, which showed a moderate effect size.

The linear regression model included the five variables that showed a correlation with the EDSS. The final model was statistically significant ($R^2 = 0.117$; $p < 0.001$), although with a low R^2, indicating poor model fit to data. Two variables were shown to be independent predictors of worse EDSS at admission: acute blurry vision (Beta = 0.183; $p = 0.010$; IC95% = 0.219–1.563; OR = 1.201) and autonomic syndrome (Beta = 0.219; $p = 0.003$; IC95% = 0.371–1.806; OR = 1.245). Therefore, patients with acute blurry vision or autonomic syndrome at presentation have, respectively, 20% and 24.5% more chance of developing worse functional status. The test statistics for each variable and the model are described in Table 2.

Discussion

This study highlights how some symptoms at diagnosis are associated with worse prognosis based on EDSS, such as acute blurry vision, acute paralysis, acute hypoesthesia, autonomic syndrome, and Lhermitte sign, although with a small effect size, except for autonomic syndrome, which showed a moderate effect size. In multivariate analysis, acute blurry vision and autonomic syndrome were shown to be independent predictors of worse prognosis.

As expected, all symptoms at first presentation associated with higher EDSS are evaluated by the scale, except for the Lhermitte sign. Lhermitte's sign typically presents in cervical spine lesions or low brainstem lesions (5). This could help to explain why this sign might be associated with worse outcomes while other brainstem signs (such as cranial nerve impairments) are not. A previous study tried to assess the correlation between Lhermitte's sign and prognostic factors but bared unfruitful results (6). However, the main difference between the presenting study and the previous is the moment when LS was present, which in the latter was in any moment of disease.

Acute blurry vision at presentation was considered to be an independent predictor of worse EDSS in our study. Besides visual acuity being evaluated in EDSS, blurry vision is a symptom directly related to possible affection in pathways, such as the optic nerve. Some studies have associated alterations in the retina and optic nerve, and even acuity, with worse functionally measured by EDSS (7, 8). This can be explained by the association of these features with central inflammation, which plays a significant role in the pathophysiology of MS (9). Furthermore, a study showed that increasing annual rates of atrophy of the inner retinal layers are associated with worsening ambulation, significantly increasing the EDSS score (10).

Our study defines autonomic dysfunction as urinary or fecal incontinence/retention. These symptoms are also correlated with spinal symptoms, which can also be associated with gait disturbances, pyramidal, and sensitive symptoms thus resulting in higher EDSS (11–14). Another important feature while interpreting this finding is that EDSS itself measures sphincteric dysfunction since it is a great cause of functional dependence, especially both fecal and urinary incontinence (15). Moreover, urodynamic dysfunction signs are associated with higher EDSS in previous studies (16–19). Alterations in the anal sphincter were not associated with differences in EDDS in previous studies (2). However, some older studies suggest an association of sphincter involvement with unfavorable prognosis (3).

The effects of acute blurry vision and autonomic dysfunction are not to be taken lightly. They showed 20% and 24.5% increased odds of worse functional outcomes, respectively. For instance, many clinical variables such as sex, age at onset, and family history of MS have no significant effect on functional outcomes. Moreover, known predictors such as the number of relapses have similar or even lower effect sizes on long-term disability (4).

Although hypoesthesia and paralysis were associated with worse EDSS in the univariate analysis, their effects were not significant in the multivariate analysis. As for hypoesthesia, this may be related to a possible relationship between hypoesthesia and dynamic postural control (20), maybe leading patients to subjectively associate hypoesthesia and ataxia. As ataxia is evaluated in the EDSS, the effect of hypoesthesia in the univariate analysis may be exaggerated by a possible correlation with ataxia. In a previous study, sensory symptoms did not affect long-term disability outcomes (4).

As for acute paralysis, the evidence supporting this finding is controversial in the literature (3, 4). We see it as counterintuitive since motor function is evaluated through the EDSS, and severe motor impairment has higher punctuation on the scale (15). Therefore, we expected patients with acute paralysis to have worse functional outcomes. More studies are needed to confirm or discard this correlation and to help understand why it may have happened.

In this setting, the findings of our study may potentially help physicians in defining initial disease-modifying therapies (21). For example, severe motor or cerebellar involvement is considered a criterion of severity of onset and worse prognosis. Therefore, these clinical features are taken into account when deciding on the initial therapy or changing to high-efficacy therapies. In the future, acute blurry vision and sphincteric involvement may further integrate recommendations in stratifying the risk of MS worsening, and for this reason, impact major clinical decisions.

Our study has some limitations. First, symptoms at onset are susceptible to memory bias since the patient may recall more severe symptoms than others. This is particularly important because it may erroneously overestimate or underestimate the frequency of specific symptoms. Therefore, the associations found in the study may not correspond perfectly to the daily basis clinical practice reality. Second, we only assessed sphincteric symptoms to characterize an autonomic syndrome. However, other symptoms related to dysautonomia are also described in MS. Other essential elements, such as the number of white matter lesions and locations, are not collected in this study. Also, the scale directly measures most symptoms that showed significant association with EDSS. For that reason, other functional status scales could enhance this analysis.

Despite these limitations, this study contributes significantly to investigations and understanding of MS progression. The only first acute manifestations of MS irrespectively correlated to worse functional outcomes were acute blurry vision and autonomic syndrome. Although some other symptoms were significantly associated with higher EDSS, such as acute paralysis, acute hypoesthesia, and Lhermitte sign, they were shown not to be independent predictors of worse functional outcomes, probably because of inevitable interactions with factors that had not been taken into account in the univariate analysis. For that matter, these results may help better understand the relationship between MS symptomatology and functionality and, in specific settings, may help the physician establish the patient's prognosis.

However, further studies, preferentially prospective cohorts from the time of diagnosis, are needed to help establish other potential predictors of worse functional outcomes. Also, following patients since the diagnosis and/or the first acute manifestation of the disease may mitigate the memory bias and potentially allow for objective neurological examination in this context. Furthermore, other models that better account for confounding variables, such as disease progression indicators (number of relapses, neuroimaging features), may provide a more reliable association. Interventional studies would also help explore possible interventions to mitigate the effect of these independent predictors of functionality.

Methods

Participants

From January 2019 to May 2022, all patients with confirmed diagnosis of MS based on the 2017 McDonald criteria were enrolled in a Neuroimmunology Diseases referenced center (22). Exclusion criteria were as follows: (1) later diagnosis of another neuroimmunology disease that better explained the symptoms; (2) disease relapse within 3 months before admission to the study; (3) incomplete information about demographic characteristics and clinical features of the first acute manifestation of MS.

Data Collection

General data included age, sex, disease duration (years since onset), total number of relapses, and EDSS score. The first acute manifestation of the disease variables included various symptoms, such as acute blurry vision, acute blindness, acute paresis, acute paralysis, acute paresthesia, acute hypoesthesia, autonomic syndrome (defined as acute bladder dysfunction or acute sphincter dysfunction), nausea, vomiting, ataxia, cranial nerves dysfunction, headache and Lhermitte sign (described as a shocking or tingling sensation that runs through the limbs or trunk during neck flexion).

The EDSS is the most used scale to quantify disability, clinical progression, and therapeutic efficacy in MS. It ranges from 0 (normal function and examination) to 10 (death). Between 1 and 10, the intervals are divided into 0.5 points. Scores bigger than 6 are associated with MS-related deficits, and the interval between 4 and 6 is highly influenced by deambulation (15).

Statistical Analysis

SPSS 26.0 statistical software (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to analyze whether the data were normally distributed. A univariate analysis using the Mann–Whitney U test was performed to assess the association between clinical and demographic features and worse functional outcomes. The Mann–Whitney U was used since our study deals with an ordinal dependent variable, the EDSS, and various dichotomous symptoms as independent variables. Effect sizes were estimated by the "*r*" statistics, derived from the z-value, in which a *r* below 0.3 is considered a small effect size, *r* between 0.3 and 0.5 is of medium effect size, and above 0.5 is considered a large effect size. A stepwise multiple linear regression model included statistically significant ($p < 0.05$) variables in the Mann–Whitney U test or those with clinical plausibility. Multicollinearity was tested and verified.

The sample size was estimated by the maximum possible number of independent predictors in the multivariate analysis, considering the variables used in the univariate analysis. The estimative was of 154 participants, based on 13 independent possible variables.

Study Approval

This study was approved by the Ethics Committee of the University Hospital Professor Edgard Santos, CAAE: 50819021.1.0000.0049. Informed consent was obtained from all participants before data collection. Data confidentiality is ensured by password-protected databases, which are only accessed by the authors responsible for the statistical analysis.

Data Availability

Data availability is restricted due to human subject involvement and is non-public. All data used in the analysis are available upon reasonable request to the corresponding author.

Author Disclosures

All contributors have confirmed that no conflict of interest exits.

Author Contributions

Manuscript: JPFG, GSMN, MYSL, LDMA, FABM
Idea: ACSF
Statistics: JPFG, CSTA, GSMN
Revision: CSTA, PAPJ

References

1. Ando H, Cousins R, Young CA. Understanding quality of life across different clinical subtypes of multiple sclerosis: a thematic analysis. Qual Life Res. 2022;31(7):2035–46. DOI: 10.1007/s11136-021-03041-7. PMID: 34822047
2. Marola S, Ferrarese A, Gibin E, Capobianco M, Bertolotto A, Enrico S, et al. Anal sphincter dysfunction in multiple sclerosis: an observation manometric study. Open Med (Wars). 2016;11(1):509–17. DOI: 10.1515/med-2016-0088. PMID: 28352843; PMCID: PMC5329875.
3. Langer-Gould A, Popat RA, Huang SM, Cobb K, Fontoura P, Gould MK, et al. Clinical and demographic predictors of long-term disability in patients with relapsing-remitting multiple sclerosis: a systematic review. Arch Neurol. 2006;63(12):1686–91. DOI: 10.1001/archneur.63.12.1686. PMID: 17172607.
4. Bsteh G, Ehling R, Lutterotti A, Hegen H, Di Pauli F, Auer M, et al. Long term clinical prognostic factors in relapsing-remitting multiple sclerosis: insights from a 10-year observational study. PLoS One. 2016;11(7):e0158978. DOI: 10.1371/journal.pone.0158978. PMID: 27391947; PMCID: PMC4938610
5. Kempster PA, Rollinson RD. The lhermitte phenomenon: variant forms and their significance. J Clin Neurosci. 2008;15(4):379–81. DOI: 10.1016/j.jocn.2007.05.002. PMID: 18280165
6. Beckmann Y, Özakbaş S, Bülbül NG, Kösehasanoğulları G, Seçil Y, Bulut O, et al. Reassessment of Lhermitte's sign in multiple sclerosis. Acta Neurol Belg. 2015;115(4):605–8. DOI: 10.1007/s13760-015-0466-4. PMID: 25841671
7. Mirmosayyeb O, Yazdan PanahM, Mokary Y, Ghaffary EM, Ghoshouni H, Zivadinov R, et al. Optical coherence tomography (OCT) measurements and disability in multiple sclerosis (MS): A systematic review and meta-analysis. J Neurol Sci. 2023;454:120847. DOI: 10.1016/j.jns.2023.120847. PMID: 37924591
8. Dolcetti E, Buttari F, Bruno A, Azzolini F, Gilio L, Di CaprioV, et al. Low-contrast visual acuity test is associated with central inflammation and predicts disability development in newly diagnosed multiple sclerosis patients. Front Neurol. 2024;15:1326506. DOI: 10.3389/fneur.2024.1326506. PMID: 38585351; PMCID: PMC10995923
9. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. Lancet. 2018;391(10130):1622–36. DOI: 10.1016/S0140-6736(18)30481-1. PMID: 29576504
10. Gernert JA, Böhm L, Starck M, Buchka S, Kümpfel T, Kleiter I, et al. Inner retinal layer changes reflect changes in ambulation score in patients with primary progressive multiple sclerosis. Int J Mol Sci. 2023;24(16):12872. DOI: 10.3390/ijms241612872. PMID: 37629053; PMCID: PMC10454007
11. Pou Serradell A, Roquer González J, Perich Alsina X. [Acute posterior cord lesions in multiple sclerosis. An MRI study of the clinical course in 20 cases]. Rev Neurol (Paris). 2000;156(12):1126–35. PMID: 11139729
12. Wang J, Zhang H, Lin J, Yang L, Zhao L, Du A. Atypical and delayed spinal cord MRI features of COVID-19-associated myelopathies: a report of four cases and literature review. Neurol Sci. 2024;45(5):1835–43. DOI: 10.1007/s10072-024-07351-9. PMID: 38430399; PMCID: PMC11021317
13. Presas-Rodríguez S, Grau-López L, Hervás-García JV, Massuet-Vilamajó A, Ramo-Tello C. Myelitis: differences between multiple sclerosis and other aetiologies. Neurologia. 2016;31(2):71–5. DOI: 10.1016/j.nrl.2015.07.006. PMID: 26383061
14. Araki I, Matsui M, Ozawa K, Takeda M, Kuno S. Relationship of bladder dysfunction to lesion site in multiple sclerosis. J Urol. 2003;169(4):1384–7. DOI: 10.1097/01.ju.0000049644.27713.c8. PMID: 12629367
15. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444–52. DOI: 10.1212/wnl.33.11.1444. PMID: 6685237
16. Nazari F, Shaygannejad V, Mohammadi Sichani M, Mansourian M, Hajhashemi V. The prevalence of lower urinary tract symptoms based on individual and clinical parameters in patients with multiple sclerosis. BMC Neurol. 2020;20(1):24. DOI: 10.1186/s12883-019-1582-1. PMID: 31952513; PMCID: PMC6966887
17. Bientinesi R, Coluzzi S, Gavi F, Nociti V, Gandi C, Marino F, et al. The impact of neurogenic lower urinary tract symptoms and erectile dysfunctions on marital relationship

in men with multiple sclerosis: a single cohort study. J Clin Med. 2022;11(19):5639. DOI: 10.3390/jcm11195639. PMID: 36233507; PMCID: PMC9570884
18. Wiedemann A, Kaeder M, Greulich W, Lax H, Priebel J, Kirschner-Hermanns R, et al. Which clinical risk factors determine a pathological urodynamic evaluation in patients with multiple sclerosis? an analysis of 100 prospective cases. World J Urol. 2013;31(1):229–33. DOI: 10.1007/s00345-011-0820-y. PMID: 22227822
19. Ineichen BV, Schneider MP, Hlavica M, Hagenbuch N, Linnebank M, Kessler TM. High EDSS can predict risk for upper urinary tract damage in patients with multiple sclerosis. Mult Scler. 2018;24(4):529–534. DOI: 10.1177/1352458517703801. PMID: 28367674
20. Dogru Huzmeli E, Duman T. Somatosensory impairments in patients with multiple sclerosis: association with dynamic postural control and upper extremity motor function. Somatosens Mot Res. 2020;37(2):117–24. DOI: 10.1080/08990220.2020.1753685. PMID: 32295464
21. Freedman MS, Devonshire V, Duquette P, Giacomini PS, Giuliani F, Levin MC, et al. Treatment optimization in multiple sclerosis: canadian ms working group recommendations. Can J Neurol Sci. 2020;47(4):437–55. DOI: 10.1017/cjn.2020.66. PMID: 32654681
22. Koch MW, Moral E, Brieva L, Mostert J, Strijbis EM, Comtois J, et al. Relapse recovery in relapsing-remitting multiple sclerosis: An analysis of the CombiRx dataset. Mult Scler. 2023;29(14):1776–85. DOI: 10.1177/13524585231202320. PMID: 37830451; PMCID: PMC10687796