Diagnostic Delay of Multiple Sclerosis in a Portuguese Population

Atraso no Diagnóstico de Esclerose Múltipla numa População Portuguesa

ARTIGO ORIGINAL

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ABSTRACT

Introduction: Multiple sclerosis is a chronic inflammatory disease, in which a diagnostic delay could reduce the available therapeutic options. Therefore, it is important to monitor the time to diagnosis and understand factors that may potentially reduce it. The objective of this study was to determine the time between the first symptoms and the diagnosis of multiple sclerosis and which factors may contribute to a diagnostic delay.

Material and Methods: Cross-sectional multicenter study, with retrospective data analysis, conducted in five tertiary Portuguese hospitals. Patients were consecutively selected from each local multiple sclerosis patients´ database. Sociodemographic and initial clinical data were collected through a questionnaire. Date of final diagnosis and multiple sclerosis classification was obtained from clinical files.

Results: A total of 285 patients were included with mean age at diagnosis of 36 years. The median time between first clinical manifestation and multiple sclerosis diagnosis was nine months (IQR 2 - 38). Diagnostic delay was associated with an older age ($p < 0.001$; $r = 0.35$), motor deficit at onset [26.5 months (IQR 4.5 - 56.5); $p = 0.0005$], higher number of relapses before diagnosis ($p < 0.001$; $r = 0,626$), first observation by other medical specialty [11 months (IQR 2 - 48); $p < 0.001$], prior alternative diagnosis [20 months (IQR 4 - 67.5); $p < 0.001$] and primary progressive subtype [37 months (IQR 25 - 64.5); $p < 0.001$]. The most significant delay occurred between the initial symptom and neurological observation.

Discussion: A significant delay occurred between initial symptoms and the diagnosis of multiple sclerosis, reflecting the need to increase awareness of this entity and its diverse symptom presentation.

Keywords: Age at Onset; Delayed Diagnosis; Multiple Sclerosis; Referral and Consultation

RESUMO

Introdução: A esclerose múltipla é uma doença inflamatória crónica na qual um atraso no diagnóstico poderá reduzir as opções terapêuticas, sendo importante monitorizar o tempo até ao diagnóstico e compreender os fatores que potencialmente o reduzam. Foi objetivo deste estudo determinar o tempo entre os primeiros sintomas e o diagnóstico de esclerose múltipla e quais os fatores que podem contribuir para o atraso no diagnóstico.

Material e Métodos: Estudo multicêntrico transversal retrospetivo, realizado em cinco hospitais portugueses. Os doentes foram selecionados, consecutivamente, a partir de bases de dados locais. Os dados sociodemográficos e clínicos iniciais foram adquiridos através de questionário individual. A data do diagnóstico final e a classificação da esclerose múltipla foram obtidas por consulta do processo clínico.

Resultados: Foram incluídos 285 doentes com média de idade ao diagnóstico de 36 anos. A mediana do tempo entre a primeira manifestação clínica e o diagnóstico foi de nove meses (IQR 2 - 38). O atraso no diagnóstico foi associado a idade avançada ($p < 0,001$; $r = 0,35$), défice motor inicial [26,5 meses (IQR 4,5 - 56,5), $p = 0,0005$], maior número de surtos previamente ao diagnóstico ($p < 0,001$; $r = 0,626$), primeira observação por outra especialidade médica [11 meses (IQR 2 - 48); $p < 0,001$], diagnóstico prévio alternativo [20 meses (IQR 4 - 67,5); $p < 0,001$] e esclerose múltipla primária progressiva [37 meses (IQR 25 - 64,5), $p < 0,001$]. O atraso mais significativo ocorreu entre o primeiro sintoma e a observação por neurologista.

Discussão: Ocorreu um atraso significativo entre o primeiro sintoma e o diagnóstico de esclerose múltipla, refletindo uma necessidade de maior acuidade na identificação dos seus principais sintomas.

Palavras-chave: Diagnóstico Tardio; Encaminhamento e Consulta; Esclerose Múltipla; Idade de Início

INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating and immune-mediated inflammatory disease of the central nervous system (CNS). The diagnosis of MS is based on international consensus criteria requiring evidence of dissemination of lesions both in time and space.[1,2]

MS has a pre-clinical period during which it is possible

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to detect the presence of demyelinating lesions by magnetic resonance imaging (radiologically isolated syndrome).[3] In about 90% of patients, the natural progression of MS follows sequential stages, namely subclinical disease, clinical isolated syndrome, relapsing-remitting and progressive forms.[4] Inflammation plays an important pathogenic role, especially in the early stages, thus being the main target for currently available treatments.[5,6] Disease-modifying therapies improve short-term outcomes, but their long-term effects are not yet established.[7] Nevertheless, there is evidence that these treatments are indeed improving the prognosis of MS.[8,9] In this context, arguments for an early treatment are reinforced, especially in high-risk patients,[10] increasing the need for an early diagnosis.

Diagnostic delay could reduce the available therapeutic options and the opportunity for early intervention,[3,11] which may result in irreversible sequelae.[4] Moreover, as MS global costs increase with disease severity,[12] an early diagnosis could also mitigate the economic burden of MS. Consequently, monitoring the time to diagnosis and understanding causes for delays is an important feature when managing MS patients.

The guidelines from the National Institute for Health and Clinical Excellence (NICE) recommend a timeline of 6 weeks from referral to a neurology consultation, and further 6 weeks until any necessary investigation is completed.[13,14] Nevertheless, diagnostic delay is a common problem across several countries,[3,11,15] and the reported time from symptom onset to diagnosis vary from 21.5 weeks[14] to 7 years.[3,11,16,17]

Disease-related or local factors could partly explain this delay. Regarding the former, they are mainly due to difficulties in recognizing the disease, for instance when clinical or radiological features are atypical.[18,19] Local factors such as different cultures or health care systems (including access to magnetic resonance imaging - MRI) can explain differences across countries. In this sense, it is important to understand which factors are associated with diagnostic delay and how these influences the disease prognosis.[16]

The aims of this study are to determine the time between the first clinical manifestation and MS diagnosis and which factors may contribute to a diagnostic delay in a cohort of Portuguese MS patients.

MATERIAL AND METHODS

A cross-sectional multicentre study, with retrospective data collection, was conducted in five tertiary hospitals, located in different regions of Portugal. Written informed consent was obtained from all patients. The ethics committee of each centre approved the study protocol.

Eligible patients were adult (aged ≥ 18 years) with clinical isolated syndrome (CIS) or MS (according to revised McDonald criteria)[1] diagnosed between January 2010 and December 2015. Patients were consecutively selected from each local MS patients´ database and all eligible patients were invited to participate in the study by letter and phone call. Sociodemographic and initial clinical data were collected through a questionnaire, including: age, gender, education, age and date (month and year) of disease onset, initial symptom, first diagnosis (neurological *versus* other), initial medical assessment (neurology consultation *versus* other medical specialty), number of relapses before diagnosis and date of the first neurological evaluation. Further data were collected from patients' medical records, including date of final diagnosis and MS classification: CIS or relapsing-remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS).

Patients were asked to characterise and to date the initial symptom, which was only considered if consistent with a relapse (occurrence of a new neurological deficit or worsening of a prior one, lasting at least 24 hours and separated from the previous event for at least one month). When there was a discrepancy with medical records, the patients' answers were assumed for the analysis.

The primary endpoint was to determine time between the first clinical manifestation and CIS/MS diagnosis (diagnostic delay). The secondary endpoint was to determine the possible influence of sociodemographic and clinical factors on the time to diagnosis.

Statistical analyses

All analyses were performed using SPSS (*Statistical Package for the Social Sciences*) version 20 (Chicago, IL). Descriptive statistics were used to describe continuous variables. Categorical variables were presented as numbers and percentages.

Chi Square test or Fisher's exact test was used for comparison between categorical variables. The association between two quantitative variables was performed through Pearson correlation coefficient or Spearman correlation coefficient (depending on the data distribution). Multivariable logistic regression analysis was used to determine factors that could be considered as independent predictors of diagnosis delay. Only variables presenting a correlation to the outcome ($p < 0.05$) were included as potential predictors, with the exception of the first specialty observation. *P* value < 0.05 was considered as statistically significant for all tests.

RESULTS

In this study, 285 patients with MS were included, the vast majority with RRMS/CIS forms (n=251; 88%). The sociodemographic, clinical characteristics and data concerning the process of diagnosis are presented in Table 1. Most patients were female (67.4%; female/male ratio: 2.06), the median age was 40 years (range: 21 to 75 years), and the median age at diagnosis was 36 years (IQR 26.5-45.0).

The median time between first clinical manifestation and MS diagnosis was 9 months (IQR 2-38), without significant differences between sex ($p = 0.809$). The median time between first symptom and neurological observation was 5 months (IQR 0-28), afterwards the median time until diagnosis was 0 months (IQR 0-2). We found a positive correlation between the age at diagnosis and the diagnostic delay ($p < 0.001$; r = 0.350).

Table 1 – Sociodemographic and clinical characteristics

	Total (n = 285)	Median diagnosis delay in months (IQR)	*p*-value
Sex, n (%)			
Men	93 (32.6%)	8 (1 – 41)	0.809[a]
Women	192 (67.4%)	9 (2 – 36)	
Age, n (%)			
Current age	40 (30.5 - 49.0)		
Age at diagnosis	36 (26.5 - 45.0)		
Time variables (months)			
Since first symptom to diagnosis		9 (2 – 38)	
Since first symptom to neurological observation		5 (0 – 28)	
Since neurological observation to diagnosis		0 (0 – 2)	
Academic degree, n (%)			
1 - 4 years	19 (6.7%)	28 (1 – 57)	0.157[a]
5 - 6 years	19 (6.7%)	8 (3 – 61)	
7 - 9 years	51 (17.9%)	12 (3 – 30)	
10 - 12 years	74 (26.0%)	13 (3 – 41)	
Higher education	122 (42.8%)	4 (1 – 35)	
Initial assessment, by medical specialty, n (%)[b]			
Neurology	83 (32.2%)	3 (0 – 13)	
General Practitioner	78 (30.2%)	18 (4 – 58)	
Ophthalmology	33 (12.8%)	4 (1 – 28)	< 0.001[c]
Orthopaedics	17 (6.6%)	8 (4 – 36)	
Neurosurgery	16 (6.2%)	32 (4 – 63)	
Internal Medicine	14 (5.4%)	4 (1 – 15)	
Otorhinolaryngology	9 (3.5%)	11 (1 – 83)	
Others	8 (3.1%)	-	
MS Classification			< 0.001[a]
RRMS/CIS	251 (88%)	7 (1 – 33)	
SPMS	8 (3%)		
PPMS	26 (9%)	37 (25 – 64.5)	

[a] Mann-Whitney non-parametric test.
[b] Percentages were calculated considering 258 patients (patients with information regarding initial medical assessment).
[c] Non-parametric test (Mann–Whitney) comparing initial medical assessment by Neurology *vs* other medical specialties (3 *vs* 11 months, $p < 0.001$).
Diagnostic delay was defined as the time between patient´s first symptom and MS diagnosis.

Patients who were first examined by a neurologist presented a statistically significant shorter time to diagnosis compared to those observed by another medical specialty (3 months (IQR 0-13.3) *vs* 11 months (IQR 2-48); $p < 0.001$). Twenty-seven patients (9.5%) did not seek medical assistance after appearance of the first clinical symptoms. No statistically significant differences were observed between academic qualifications and time to diagnosis ($p = 0.157$).

Regarding the initial clinical symptoms (Table 2), sensory changes were the most frequent (39.0%), followed by cranial nerve disturbance (26.0%), motor deficit symptoms (21.0%), ataxia (13.3%) and psychiatric symptoms (0.7%). Cranial nerve disturbance was the presentation leading to an earlier diagnosis. Patients presenting with motor deficit (n = 60) had the longest diagnostic delay ($p < 0.001$); in this group, 17 patients were first observed by a neurologist and 8 did not seek medical assistance after appearance of the first clinical symptoms.

A total of 128 (44.9%) patients had a prior alternative diagnosis and a statistically significant longer time to MS diagnosis: 20 (IQR 4-67.5) months *vs* 5 (IQR 1-22) months for those without a prior alternative diagnosis ($p < 0.001$). The correlation between the number of relapses and the time to diagnosis was positive and statistically significant ($p < 0.001$; r = 0.626).

Regarding MS classification, patients with RRMS/CIS/SPMS had a statistically significant shorter time to diagnosis when compared to those with PPMS: 7 (IQR 1-33) months *vs* 37 (IQR 25-64.5) months, respectively ($p < 0.001$).

Finally, multivariable logistic regression demonstrated that motor symptoms at onset (odds ratio [OR]: 0.344), prior incorrect diagnosis (OR: 0.378) and age (OR: 0.948) were

Table 2 – Initial symptoms and first diagnosis

	Total (n = 285)	Diagnosis delay in months (IQR)	*p*-value
Onset symptom, n (%)			
Sensory disturbance	111 (38.9%)	7 (2 – 26)	
Cranial nerve disturbance (including optic neuritis)	74 (26.0%)	3.5 (0 – 27.5)	
Motor deficit	60 (21.1%)	26.5 (4.5 – 56.5)	< 0.001[a]
Ataxia	38 (13.3%)	11 (2.75 – 33)	
Psychiatric	2 (0.70%)	-	
Number of relapses before the first, n (%)			
None	111 (38.9%)		
One	111 (38.9%)		
Two	34 (12.0%)		
More than two	29 (10.2%)		
Other diagnoses prior to MS diagnosis, n (%)			
No	157 (51.1%)	20 (4 – 67.5)	
Yes	128 (44.9%)	5 (1 – 22)	
Orthopaedics	36 (28.1%)		
Psychiatric	30 (23.4%)		
Neurosurgical	14 (10.9%)		
Ophthalmologic	13 (10.1%)		< 0.001[b]
Otorhinolaryngologic	10 (7.8%)		
Other Neurologic	5 (3.9%)		
Vascular	2 (2.3%)		
Others	17 (13.3%)		

[a] Kruskal-Wallis non-parametric test
[b] Mann-Whitney non-parametric test
[c] Percentages were calculated considering 128 patients (patients with prior alternative diagnosis information).

independently associated with MS diagnostic delay (Table 3). Simple linear regression showed that for each year of age at diagnosis, an increase of 1.326 months in time to diagnosis is expected.

DISCUSSION

In our study, the median time between the first clinical manifestation and MS diagnosis was 9 months. The most significant delay occurred between the first symptom and neurological observation; after this, the median time to diagnosis was 0 months. In addition, we identified several factors that could contribute to this delay in our patients.

Patients' age at diagnosis significantly influenced the diagnosis delay, with older patients presenting a longer time to diagnosis. We hypothesize that this was mainly due to an age-related broader differential diagnosis of MS: osteoarthritis may impair motor function and gait, brainstem symptoms such as vertigo may be attributed to vertebrobasilar ischemic attacks,[20] bladder dysfunction can be seen as a consequence of prostatic hypertrophy or weakness of pelvic floor muscles in women, and optic neuritis may be interpreted as ischemic optic neuropathy.[21] Moreover, with age, brain MRI may disclose some vascular white matter changes, further contributing to some difficulties regarding diagnosis.[22]

Like in other studies,[3] the most significant delay was between the time of first symptom and the first neurological evaluation. Almost one third of patients were first examined by a neurologist, a factor that was associated with a significant decrease in the diagnostic delay when compared to an initial observation by another medical or surgical specialist ($p < 0.05$).

Although we cannot completely determine where the delay occurred, this may be due to an under recognition of MS by other medical specialties, the time taken by the patient to seek medical attention and/or a difficult access to specialty appointments.

It is known that diagnostic errors are common and underemphasized, but they are also challenging to detect and dissect.[23] Like some other diseases, MS is often difficult to diagnose early in its course and there are several diseases and syndromes that may mimic this condition. Furthermore, several studies suggest that an important reason for MS diagnostic delay is the non-recognition of some of the symptoms, often resulting in misdiagnosis.[24,25] Our study shows that almost half of the patients received an incorrect prior diagnosis and this led to a longer delay on MS diagnosis. This is probably explained by the "multi-symptom" nature of this disease, which renders the diagnosis difficult, especially for those who are not closely acquainted with it.

Table 3 – Logistic regression for lower time until diagnosis (≤ 9 months)

	Initial model			Optimized model		
	OR	**95% CI for OR**	***p*-value**	**OR**	**95% CI for OR**	***p*-value**
Age at diagnosis (years)	0.953	0.930 – 0.977	< 0.001	0.948	0.926 – 0.972	< 0.001
Symptoms						
1 - Cranial nerves disturbance	Ref.					
2 - Motor	0.422	0.185 – 0.961	0.040	0.344	0. 158 – 0. 747	0.007
3 - Sensitive	0.625	0.327 – 1.197	0.156	0.616	0.321 – 1.183	0.146
4 - Ataxia	0.461	0.196 – 1.081	0.075	0.441	0.188 – 1.036	0.060
6 - Psychiatric	0.887	0.052 – 15.260	0.934	0.933	0.054 – 16.043	0.962
Diagnosis						
Incorrect diagnosis	0.394	0.235 – 0.662	< 0.001	0.378	0.226 – 0.632	< 0.001
Correct diagnosis	Ref.					
MS type						
PPMS	0.379	0.096 – 1.497	0.167	-	-	-
CIS/RRMS/SPMS	Ref.			Ref.		
***p*-value**		-			< 0.001	
Hosmer and Lemeshow test		-			0.212	
Overall percentage		-			67.0%	

OR: odds ratio; 95% CI for OR: 95% confidence interval for the odds ratio; Ref: category *versus* the one is making comparisons

From a clinical point of view, sensory symptoms, cranial nerve disturbance (including optic neuritis), motor deficit and ataxia were the most common onset symptoms. The difference between the diagnostic delay according to the onset symptom was statistically significant, which reflects that some onset symptoms immediately prompt the diagnosis, as observed by those with a cranial nerve disturbance presentation. Interestingly, motor deficits have a considerable long diagnostic delay, fitting previous reports.[11,26] In our study, only a minority of patients with a motor deficit presentation (28%) were first observed by a neurologist, which could explain part of this delay.

Lastly, we verified a longer time to diagnosis in patients with PPMS when compared with RRMS, which is consistent with previous reports.[11] PPMS is characterized by a gradual change in terms of disability, typically lacking relapses, making it harder to be recognized. Moreover, patients are usually older at onset and a progressive paraparesis is a common presentation, which widens the differential diagnosis.[22,27]

This study has some limitations. First, data collection was mainly based on patients' answers. Although asking for past neurological events is crucial while performing a suspected MS clinical history with implication in the diagnostic criteria,[1] the recollection of the exact date may be subjected to a memory bias. This poses a particular problem in patients with "benign" MS, in whom relapses can happen with several years apart and only a mild disability is seen, or in PPMS due to its absence of attacks. We tried to mitigate this by comparing patients´ answers to medical records and inquired back if any discrepancies were detected.

Another drawback is that we did not systematically evaluate the presence of other coexisting diseases, which may also contribute to a delay in the diagnosis of MS.[16] Previous studies have shown that comorbidity and lifestyle factors are associated with longer time between symptom onset and diagnosis.[16] First, pre-existing disease, or adverse effects of medications used to treat it, can conceal new symptoms, or the patient can attribute new symptoms to the known disease which has already been diagnosed. Second, the physician must also acknowledge that the new symptom is not attributable to a pre-existing disease and that it demands further diagnostic testing. Finally, the diagnostic test results must be interpreted correctly, again with the potential risk of failure in cases where pre-existing disease complicate this interpretation.[16,17]

We considered sample size a strength of this study, since MS prevalence in Portugal is 46.3/100,000 inhabitants,[28] affecting about 5000 people. Moreover, we included centres located in some of the main demographic regions of Portugal and we thoroughly reviewed the major clinical and sociodemographic factors presented by our patients that could impact the aim of the study.

In conclusion, the complexity of MS poses several diagnostic difficulties. Neurologists who specialize in MS together with their multidisciplinary teams, are ideally placed to establish the diagnosis of MS and guide its management. However, significant delays still occur between noticing the first symptoms and the final diagnosis of MS, in part due to a misinterpretation of patients´ complains. Although the future development of reliable MS biomarkers would facilitate the diagnosis and thereby reduce its delay, it is necessary to increase awareness of this entity and its diverse symptom presentation, especially among patients and other medical specialties apart from Neurology.

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PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication. Patient consent obtained.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest for this manuscript.

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