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The consequences of delayed diagnosis and treatment in persons with multiple sclerosis given autologous hematopoietic stem cell transplantation

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Abstract

Objectives: We have analyzed the association of delayed both diagnosis and treatment of persons with MS with the long-term results of patients given aHSCT.
Methods: Patients with MS referred to the HSCT-Mexico program were included in the study; in 103, detailed pre- and post-transplant evolution could be recorded. Two groups of patients were analyzed according to the time of evolution between the onset of symptoms and the definite diagnosis of MS: more than 8 months (delayed diagnosis, DD), or less than 8 months (non-delayed diagnosis, NDD). The progression of MS was assessed by changes in the expanded disability status scale (EDSS).
Results: The time elapsed between the onset of symptoms and the correct diagnosis was lower for the NDD group (1.55 vs. 35.87 months, $p<0.05$). Both groups of patients showed a similar EDSS score at diagnosis (1.5 vs. 1.5); however, the EDSS at the time of the transplant was higher in the DD group (4.5 vs. 3.0, $p=0.3$) and the response of the EDSS score to the transplant was significantly better for the NDD group, the last EDSS scores being 2.5 vs. 4.25 ($p=0.03$). Both groups of patients responded to aHSCT by diminishing the EDSS, but the response was significantly better in the NDD group.
Conclusions: These data indicate that both the pre-transplant progression of the disease and the response to aHSCT were significantly worse in the DD group. An early diagnosis and an early aHSCT intervention are critical for a good prognosis, in terms of lowering and stabilizing the motor disability in MS patients given autografts.

Keywords: multiple sclerosis; auto-HSCT; delayed diagnosis

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, autoimmune, and demyelinating disease. Its pathogenesis involves, autoimmune reactivity directed against myelin antigens in the central nervous system (CNS), resulting in an initial inflammatory phase, followed by an axonal and neurological degenerative process; it is one of the main causes of neurological disability in young adults, mostly aged between 20 and 40 years, with an increased worldwide incidence (2.1 per 100,000 persons/year) [1] since 2013 [2–4]. Factors that have been associated with developing MS, include family history, Caucasian race, vitamin D deficiency, gender, and infection with various pathogens like Epstein-Barr virus, human coronavirus 229E, human papillomavirus, Rubella, and others, each with its possible individual molecular mimic to a CNS antigen [1, 4–6]. Sensitive and specific laboratory tests, based on the detection of oligoclonal bands in cerebrospinal fluid, are now used as part of the initial diagnostic protocol guidelines and are part of the McDonald

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MS diagnostic criteria [3]. Other biomolecular markers, such as neurofilament light chain [7] or microRNA [8], have the potential to detect disease at an earlier stage.

It has been shown that a delayed MS diagnosis reduces the efficacy of available agents such as disease modifying therapy (DMT) and increases the cost in other alternatives or resources, such as autologous hematopoietic stem cell transplantation (aHSCT) [1, 5]. This results in increased long-term disability, and the need for lifetime support and management, which has a high socioeconomic impact [1–4, 9]. There are many factors related to a delayed MS diagnosis. Various authors have suggested that an important factor is low socioeconomic status or living in a low-income country, linked with a proinflammatory phenotype in childhood [4]. Low health literacy and economic factors create barriers to seeking appropriate medical and neurological evaluation, and to pursue the necessary imaging and laboratory tests required [7]. Other factors associated with a delayed MS diagnosis are related to disease onset later in life (≥40 years), nonspecific clinical manifestations (mainly motor deficiency, visual symptoms) [1, 5], and a higher number of relapses. Delayed specialty referral is associated with further disease progression and a worse prognosis. According to the National Institute for Health and Clinical Excellence guideline CG186, the time to specialist referral should not exceed 12 weeks; the guideline recommends a maximum interval of 6 weeks from clinical onset to first consultation and a maximum of 6 additional weeks until specialist neurological referral [1, 5, 9–11].

Some of the clinical manifestations at disease onset can lead to alternative diagnoses, which can also delay specialty referral and delayed or wrong initial medical/therapeutic interventions. The 2017 McDonald diagnostic criteria [3] have the main goal of establishing a diagnosis of MS at the time of the first clinical event, allowing earlier interventions and diminishing further complications due to the natural progressive course of the disease.

There are several pharmacological options to treat persons with MS, however aHSCT has proven to be an excellent option with beneficial results in roughly 80 % of patients [12–15]. Based on our 30 years of experience using aHSCT in 1,475 patients with MS in the *Centro de Hematología y Medicina Interna de Puebla, México*, we have shown that the procedure is feasible [16], safe [17, 18], useful [19] and associated with better results if no previous DMT is given to the patients [12].

In this study, we have analyzed the association of a delayed both diagnosis and treatment of MS within long-term results of patients given aHSCT as treatment. Our results indicate that an early diagnosis, but also early aHSCT intervention are critical for a good prognosis, in terms of lowering and stabilizing the motor disability in MS patients.

Materials and methods

Patients

Patients referred to the HSCT-Mexico program between March 2018 and February 2023 were included in the study. Individuals with all types of MS were included: relapsing remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS). Patients must have had a Karnofsky score [10] above 70 %, and an expanded disability status scale (EDSS) score of 8 or below, in the 2 weeks prior to transplantation. All patients went through a wash-out period of DMT for at least 3 months prior to aHSCT. All patients were informed of the procedure's characteristics, its possible complications, and all signed informed consent. All patients were given an aHSCT employing the "Mexican method", which uses high-dose cyclophosphamide and rituximab [18]. The study was approved by the Ethics Committee of the Clinica RUIZ (*Conbioetica* 21CEI00120130605, Registry No. 13 CEI 21 114 126). The protocol is registered in *ClinicalTrials.gov* identifier NCT02674217. Subjects were instructed to provide data of their neurologic evolution every 3 months post-transplant on special forms sent by e-mail, via Zoom, or in personal phone calls. A positive response included both improvement and stabilization of the EDSS score.

Study procedures

A cross-sectional, observational study was developed at the *Centro de Hematologia y Medicina Interna, Clínica Ruiz*, after meeting the inclusion and exclusion criteria; in which all eligible patients with MS were interviewed and examined by specialized neurologists. Different demographic data, complete clinical data, a complete neurological examination, including the EDSS score, and various radiological examinations results were collected. Initial clinical data, and sociodemographic information were collected through a virtual survey, including date of birth, place of birth, sex, initial clinical onset, date of initial symptoms, date of first medical consultation (neurological vs. general), initial diagnosis (MS vs. alternative diagnosis), date of first neurological evaluation, date of neurological confirmed MS diagnosis. Further data was collected from patients' medical records including the aHSCT date.

Statistical analysis of data

The IBM Statistical Package for Social Sciences version 25.0 was used for data analysis (Armonk, NY: IBM Corp). The qualitative variables were described using ratios and percentages. The Shapiro–Wilk test was used to confirm the normality of the distribution. Quantitative variables with normal distributions were reported using mean and SD, while those without normal distributions were described using median and interquartile ranges. The level of statistical significance was set at p=0.05. Diagnostic delay was analyzed as a dichotomous variable and classified as non-delayed diagnosis, NDD (diagnosed within the first 8 months) or a delayed diagnosis, DD (diagnosed beyond 8 months). We chose 8 months because it is the median time from the symptom's onset to the correct

diagnosis in this cohort. The delayed diagnosis was the considered outcome variable, and multivariate logistic regression analysis was employed to identify variables that can be regarded as independent predictors of diagnosis delay.

Results

Complete data of the post aHSCT evolution could be obtained in 103 patients with MS. Median age was 49 years, range 21–74. Sixty-five patients (63.1 %) were females and thirty-eight (36.2 %) were males. The mean age at onset was 35 years (range 14–64) years; in females 34.31 ± 10.2 and in males 36.87 ± 11.52. The mean age at diagnosis was 37.95 ± 11.02 (17–66) years. The duration of the MS in our cohort ranged from 1 month up to 46 years with a median duration of 10 years (IQR: 4–16). The most prevalent motor symptoms at onset were weakness in 48 patients (46.60 %), lower limb tingling in 38 (36.89 %), optic neuritis in 24 (23.30 %), urinary incontinence in 23 (22.33 %), loss of sense of touch in 21 (20.39 %), and other symptoms (see Table 1).

The median time from the onset of symptoms to a first neurological consultation was 8.1 months. Sixty-six patients (64.1 %) were initially diagnosed, according to the McDonald MS diagnostic criteria, with RRMS (40.8 %), and PPMS (21.4 %). For the 37 patients (35.9 %) with another prior diagnosis different from MS due to different initial onset manifestations (Table 2), the median time to MS diagnosis was 20.4 months, in which 31 patients were diagnosed with RRMS, 5 with PPMS, and 1 with SPMS. By the time the patients, with an early or a delayed diagnosis, went through their aHSCT, 52 (49.5 %) were diagnosed with RRMS, 28 (27.2 %) with SPMS, and 23 (22.3 %) with PPMS.

Two groups of patients with MS were analyzed according to the time of evolution between the onset of symptoms and the definite MS diagnosis: More than 8 months (delayed diagnosis, DD), or less than 8 months (non-delayed diagnosis, NDD): ages at diagnosis were statistically significant lower in the NDD than in DD (mean 34.38 vs. 41.32, p=0.01); the years of evolution of the MS were lower in the NDD group (median 7.35 vs. 12, p=0.045); the time elapsed between the onset of symptoms and the correct diagnosis was lower for the NDD (1.55 vs. 35.87 months, p<0.05) as well as the time between onset of symptoms and to the initial neurology consultation (median 1.03 vs. 12.43 months, p<0.05).

As far as the result of the transplant is concerned, both groups of patients showed a similar EDSS score at diagnosis (1.5 vs. 1.5, p=0.80); however, the EDSS at the time of the transplant was higher in the DD group (4.5 vs. 3.0, p=0.3) and, as a result, the response of the EDSS score to the transplant was significantly better for the NDD group, the last reported values for the EDSS being (2.5 vs. 4.25, p=0.03). Both groups of patients responded to aHSCT by diminishing the EDSS, but the response was larger in the NDD group, see Figure 1. These data indicate that the pre-transplant progression of the disease was worse in the DD group and that the response to the aHSCT was also worse in the DD group.

The analysis shows that there is a relation between the initial diagnosis (MS or other diagnostic) and the diagnostic

Table 1: Prevalence of the initial symptoms in the group of 103 patients with multiple sclerosis.

Symptoms	Patients (%)	Symptoms	Patients (%)
Weakness in lower limbs	48 (46.60 %)	Burning pain	8 (7.77 %)
Tingling in lower limbs	38 (36.89 %)	Fecal incontinence	8 (7.77 %)
Optic neuritis	24 (23.30 %)	Tinnitus	8 (7.77 %)
Urinary incontinence	23 (22.33 %)	Decreased visual acuity	7 (6.80 %)
Loss of sense of touch	21 (20.39 %)	Fatigue	7 (6.80 %)
Dizziness	19 (18.45 %)	Drop foot	6 (5.82 %)
Diplopia	18 (17.48 %)	Spasticity in upper limbs	5 (4.85 %)
Weakness in upper limbs	18 (17.48 %)	Gait disorders	4 (3.88 %)
Lhermite's sign	17 (16.50 %)	Dysphagia	3 (2.91 %)
Numbness	17 (16.50 %)	Dysarthria	3 (2.91 %)
Blurred vision	15 (14.56 %)	Hyperesthesia	3 (2.91 %)
Spasticity in lower limbs	14 (13.59 %)	Trigeminal neuralgia	2 (1.94 %)
Ataxia of limbs	10 (9.71 %)	Deafness	2 (1.94 %)
Headache	10 (9.71 %)	Depression	2 (1.94 %)
Migraine	9 (8.74 %)	Insomnia	1 (0.97 %)
Facial weakness	9 (8.74 %)	Brain fog	1 (0.97 %)

Table 2: Prior diagnosis in patients with a delayed diagnosis of multiple sclerosis.

Prior diagnosis	Patients, n (%)	Prior diagnosis	Patients, n (%)
Optic neuritis	5 (4.8 %)	Optic neuromyelitis spectrum disorder	1 (0.9 %)
Clinically isolated syndrome (CIS)	3 (2.9 %)	Iron deficiency	1 (0.9 %)
Transverse myelitis	3 (2.9 %)	Overreactive bladder	1 (0.9 %)
Stroke	2 (1.9 %)	Sialolithiasis	1 (0.9 %)
Depression	2 (1.9 %)	Sciatic nerve pinch	1 (0.9 %)
Herpes virus infection	2 (1.9 %)	Lyme disease	1 (0.9 %)
Fatigue	2 (1.9 %)	Prolapsed disc	1 (0.9 %)
Stress	2 (1.9 %)	Lower back pain	1 (0.9 %)
Guillain Barre	1 (0.9 %)	Spinal lesion	1 (0.9 %)
Trigeminal neuralgia	1 (0.9 %)	Tendon strain	1 (0.9 %)
Bell's palsy	1 (0.9 %)	No initial diagnosis	3 (2.9 %)

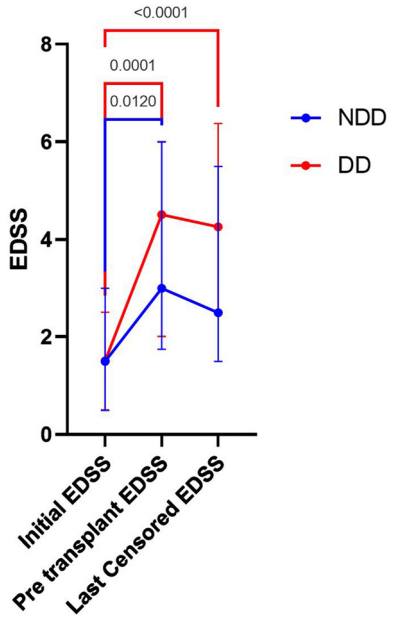

Figure 1: Changes in the expanded disability status scale (EDSS) score from first EDSS evaluation to last censored EDSS after autologous hematopoietic stem cell transplantation. Lines indicate patients who had evolutions of less (NDD, non delayed diagnosis) or more (DD, delayed diagnosis) than 8 months between the onset of symptoms and the diagnosis of multiple sclerosis.

delay ($p<0.05$). In this cohort we found no relation between gender and the diagnostic delay ($p=0.82$). Table 3 show all the variables compared between the two groups. As seen in Table 4, the logistic regression analysis showed that the variables age at diagnosis and misdiagnosis were independent predictors of MS diagnostic delay.

The NICE clinical guidelines for MS diagnosis (NG220) recommend a timeline of 6 weeks from the initial MS diagnosis to the first specialized referral [20], in our cohort, we found that in the NDD group, only 43 (86 %) accomplished the 6 weeks timely specialized reference, whereas 7 went through a delayed referral; as for the DD group, only 17 (32 %) patients went through a timely specialized referral, while the other 36 patients did not.

Table 3: Relation between diagnostic delay and different demographic and clinical parameters.

	DD (n=53)	NDD (n=50)	p-Value
Age at MS onset	36.3 ± 12	34.2 ± 9.2	0.32[a]
Age at diagnosis	41.3 ± 11.6	34.4 ± 9.2	0.01[a]
Years of disease	12 [5.7–16.5]	7.35 [1.9–16.1]	0.045[b]
Symptoms onset to diagnosis, months	35.9 [14.5–83.33]	1.5 [0.87–4.10]	0.00[b]
Symptoms onset to first neurologist consultation, months	12.4 [3.5–54.4]	1.0 [0.4–3.0]	0.00[b]
Initial EDSS	1.5 [0.5–2.5]	1.5 [0.5–3.0]	0.80[b]
Pre transplant EDSS	4.5 [2.0–6.0]	3.0 [2.0–6.0]	0.30[b]
Last censored EDSS	4.2 [2.5–6.0]	2.5 [1.5–6.0]	0.03[b]
Use of DMT prior to transplantation			
No DMT	17	13	0.50[c]
DMT	36	37	
Diagnosis to DMT, months	3.37 [1.43–27.43]	1.20 [0.53–4.73]	0.50[b]
Patients who accomplished the NG220 recommended time from the initial MS diagnosis to a specialized referral			
<6 weeks	17	43	00[c]
>6 weeks	36	7	
Gender			
Male	19	19	0.82[c]
Female	34	31	
Initial diagnosis			
Other	32	9	0.00[c]
MS	21	41	
Initial symptoms			
Motor symptoms	37	23	0.014[c]
Non-motor symptoms	16	27	
Continent of origin			
Asia	0	1	
Africa	2	0	
America	27	27	
Europe	24	18	
Oceania	0	4	

[a]T student. [b]Mann-Whitney. [c]Chi square. DD, delayed diagnosis (above 8 months); NDD, non-delayed diagnosis (less than 8 months); MS, multiple sclerosis; EDSS, expanded disability status scale.

Discussion

It is well known that there are many factors related to a delayed MS diagnosis [5]. This retrospective cohort study evaluated whether a delayed diagnosis is an important factor in determining an adverse prognosis in persons with MS treated with aHSCT.

In our cohort, the age at MS symptoms onset showed no difference between de DD and NDD groups. However, the mean age at diagnosis was statistically significant higher in the DD group (41.3 vs. 34.4 years), consequently, the interval between the symptoms onset to the diagnosis was higher in the DD group than the NDD group (median: 35.9 vs. 1.5 months). Our results may be comparable with those reported by different researchers: Ghiasian et al. reported a

Table 4: Univariate and multivariate logistic regression analysis for the parameters affecting diagnostic delay in the bivariate analysis.

	Univariate		Multivariate	
	p-Value	OR (95 % CI)	p-Value	OR (95 % CI)
Age at diagnosis	0.002	0.939 (0.903–0.977)	0.010	0.939 (0.896–0.985)
Initial diagnosis (MS, other)	0.000	6.942 (2.801–17.202)	0.000	0.128 (0.047–0.349)
Symptoms onset (motor, non-motor)	0.015	0.368 (0.164–0.827)	0.098	0.451 (0.176–1.159)
Age at MS onset	0.315	0.981 (0.946–1.018)		
Sex	0.821	0.912 (0.409–2.031)		

OR, odd's ratio; CI, confidence interval; MS, multiple sclerosis. Only variables with p<0.05 in the univariate analysis were included in the multivariate.

mean delay of 21.9 months in men and 16.9 in women from Iranian population [21]; Cárdenas-Robledo et al. reported a mean of 34.6 months from Colombian population [2]; Khedr et al. [22] reported a mean of 36.5 months from Egyptian population in their delayed diagnostic group [22]; Aires et al. reported a mean of 9 months from a Portuguese population [9]. In contrast to what Ghiasian et al. reported, we did not find a relationship between gender and the diagnostic delay.

Research has shown that the rate of progression of MS is higher in patients with polysymptomatic onset and motor disturbances [23, 24]. In our cohort the 70 % of patients in the group with delayed diagnosis had motor symptoms as the most common initial presenting symptom. This delay could be related to a lack of awareness of the diverse symptom presentation of MS, as well as a lack of knowledge and skills among physicians in diagnosing MS. Delays may represent delays in first seeking medical attention, or delays being seen by a neurologist. We observed that the median time to first neurologist consultation was significantly higher in the group with delayed diagnosis and only 68 (58 %) patients in our cohort were referred to a neurologist in less than 6 weeks after the initial diagnosis.

We have previously shown that, in persons with MS given aHSCT as treatment, prior exposure to DMT is associated with a worse long-term response to the transplant [12], and that the time between the diagnosis of MS and the aHSCT is also related with the post-transplant response [25]. These data suggests that the early use of aHSCT in the treatment of persons with MS is associated with a better chance of long-term response. We have now shown that, before the correct diagnosis of MS, the time elapsed between the onset of symptoms and the diagnosis of the neurological condition is also associated with the long-term response to the autograft. As shown in Figure 1, transplantation was able to stop the evolution of disability in both groups, since a decrease in the median EDSS score was observed; however, it is noteworthy that in the NDD, the response to aHSCT was better than in the DD group.

There are currently different types of DMTs that can slow the progression of MS. Most DMTs have a significant anti-inflammatory effect and have been shown to be most effective in early stages of MS [26]. At stages when inflammatory activity has decreased, it may be possible to discontinue DMT treatment. The difference between DMT and aHSCT is that aHSCT is designed to eliminate autoreactive lymphocytes and restart a new immune system in a non-inflammatory environment without costimulatory signals [27]. This could be the explanation for the significant improvement observed in our results: patients with a shorter evolution and without previous treatment with DMT should be in a more inflammatory stage than patients with a longer evolution of the disease and treated with DTM. This finding is consistent with the National Multiple Sclerosis Society's view that aHSCT may be a useful treatment option for people with MS who demonstrate substantial breakthrough disease activity (new inflammatory central nervous system lesions and/or clinical relapses) despite treatment with high efficacy DMT or have contraindications to high-efficacy DMTs and are younger than 50 years, with disease duration less than 10 years [28]. Prospective comparisons between aHSCT and highly effective DMTs are currently lacking. In the MIST trial, patients treated with aHSCT are reported to have less disease progression, however natalizumab was included in the comparator arm and the number of treated cases was small [13].

The best strategy to decrease MS diagnostic delay is to increase awareness of the need for rigorous neurological evaluation in individuals with MS-like symptoms accompanied by the appropriate application of MRI criteria [29]. In addition, teleconsultation and the use of cell phone applications could be a feasible and well-received care strategy for MS patients, allowing evaluations to be performed without the need for displacement [30, 31].

The main limitation of our study has to do with the size of the sample analyzed. Because it is a retrospective analysis, there are incomplete data or data that the patients did not provide clearly. In addition, all these patients are foreigners. This factor poses a challenge for the follow-up of their neurological evolution after transplantation, so that in some cases their post-transplantation neurological evolution is unknown.

The results of this work suggest that early diagnosis and treatment are crucial factor in determining disease outcomes in patients with MS and in the long-term results of the aHSCT provided this is elected as the therapeutic option. Not only an early MS diagnosis, but also an early aHSCT can lead to a better prognosis and decreased motor disability. aHSCT is now an important method to consider as a main treatment option in early MS-diagnosed patients.

Research ethics: The study was approved by the Ethics Committee of the Clinica RUIZ (Conbioetica 21CEI00120130605, Registry No. 13 CEI 21 114 126).
Informed consent: Informed consent was obtained from all individuals included in this study, or their legal guardians or wards.
Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: The authors state no conflict of interest.
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Data availability: The raw data can be obtained on request from the corresponding author.

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