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ARTICLE

Evaluation of diagnosis and treatment practices of Brazilian neurologists among patients with multiple sclerosis

Avaliação das práticas de diagnóstico e tratamento de pacientes com esclerose múltipla por neurologistas brasileiros

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ABSTRACT

Background: Recent changes to the diagnostic criteria for multiple sclerosis (MS) and new medications have had a major impact on the way in which specialists manage the disease. **Objective**: To investigate factors considered by Brazilian neurologists in managing MS, and to identify how these contribute to diagnosis and treatment. **Methods**: Potential participants were selected by a steering committee (MS experts who developed this survey). Only MS specialists were included in the study (neurologists who had completed a neuroimmunology fellowship or who were treating more than 30 MS patients). Links to the online questionnaire were distributed between March 2019 and January 2020. This questionnaire was composed of sections with hypothetical MS scenarios. **Results**: Neurologists from 13 Brazilian states responded to the survey (n = 94). In the clinically isolated syndrome (CIS) scenario, the respondents agreed to treat patients with a high risk of MS diagnosis, whereas in the radiologically isolated syndrome (RIS) half of the respondents opted not to treat, even among high-risk patients. In cases of low-activity relapsing-remitting MS (RRMS), the choice of treatment was distributed among interferon beta, glatiramer acetate and teriflunomide, which were changed to fingolimod and natalizumab, as RRMS severity increased. The topics in which disagreement was found included practices regarding use of disease-modifying therapy (DMT) for pregnant patients and the washout

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period required for some DMTs. **Conclusions**: This study enabled identification of areas of agreement and disagreement about MS treatment among Brazilian neurologists, which can be used to update future protocols and improve patient management.

Keywords: Multiple Sclerosis; Neurologists; Diagnosis; Clinical Decision-Making; Immunotherapy.

RESUMO

Introdução: Mudanças recentes dos critérios diagnósticos e nos tratamentos para Esclerose Múltipla (EM) promoveram um grande impacto na maneira com que os especialistas manejam a doença. **Objetivos**: Investigar fatores considerados no manejo de pacientes com EM, por neurologistas brasileiros, bem como identificar como estes contribuem para o diagnóstico e o tratamento da doença. **Métodos**: Participantes foram selecionados pelo Comitê Organizador (especialistas em EM responsáveis por desenvolver a pesquisa). Apenas especialistas em EM foram incluídos (neurologistas com *fellowship* em neuroimunologia ou que atendem, atualmente, mais de 30 pacientes com EM). Os links de acesso a um questionário foram distribuídos entre março de 2019 e janeiro de 2020, o qual consistia em cenários hipotéticos referentes à EM. **Resultados**: Neurologistas de 13 estados brasileiros responderam à pesquisa (n=94). No cenário de Síndrome Clínica Isolada, os participantes concordaram em tratar pacientes com alto risco de diagnóstico de EM no futuro, resultado não encontrado nos casos de Síndrome Radiológica Isolada, no qual metade dos participantes optaram por não tratar, mesmo em casos de alto risco. Nos casos de EM Remitente-Recorrente de baixa atividade, a escolha para tratamento foi interferon beta, acetato de glatirâmer ou teriflunomida, sendo trocado para fingolimode e natalizumabe quando de aumento da gravidade. Discordâncias foram encontradas referentes ao uso de medicações durante a gestação e seus períodos de *washout*. **Conclusões**: Este estudo identificou concordâncias e discordâncias entre neurologistas brasileiros sobre EM, as quais podem ser auxiliares nas futuras atualizações de protocolos, visando melhorar o manejo dos pacientes.

Palavras-chave: Esclerose Múltipla; Neurologistas; Diagnóstico; Tomada de Decisão Clínica; Imunoterapia.

INTRODUCTION

Multiple sclerosis (MS) is the most common inflammatory disease of the central nervous system (CNS), characterized by variable clinical and pathological manifestations[1,2]. It is responsible for a large personal and socioeconomic burden, since it affects people in an economically active age group[3].

Diagnosing MS can be a challenging process, as there is no single test that confirms the disease[4,5]. In addition, the management of MS has changed rapidly over recent years, and new oral, intravenous and injectable medications for disease treatment have been approved[4,6]. These changes to MS therapy have had a major impact on the way in which medical specialists manage the disease. In most cases, there is agreement between experts in response to clinical cases presented to them, but some variability regarding the question of disease management has been observed[7].

The aim of this study was to provide an insight into the factors considered by Brazilian neurologists in managing MS, and to identify how these factors contribute to diagnosis and treatment, including the choice of most appropriate medication for each case.

METHODS

MS expert neurologists in eleven Brazilian states were selected by a steering committee that was composed of a representative member from each state. This committee was tasked with the role of selecting potential survey respondents, based on their membership of regional and national MS organizations. Links to the online survey questionnaire were distributed to potential respondents over the period from March 2019 to January 2020. The participant group consisted of MS experts (neurologists who had completed a neuroimmunology fellowship or who were currently treating more than 30 patients with MS). The respondents were self-selected, based on their willingness to participate in the survey.

The survey was developed and reviewed by members of the steering committee and was based on a similar survey produced by Fernandez et al., 2017[7]. The online questionnaire comprised 11 sections of questions evaluating management of the diagnosis, treatment and follow-up among patients with MS. It considered multiple hypothetical scenarios, including radiologically isolated syndrome (RIS), clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), MS in childhood and MS in pregnancy. The exclusion criteria consisted of refusal to participate in the survey and failure to answer at least 90% of the questionnaire. ***General agreement*** was defined by the steering committee as a level of agreement among the responses to a single question of 75% or greater. The current article addresses the sections regarding RIS, CIS, RRMS and MS in pregnancy, and the remaining topics will be discussed in a further study.

All participants were fully informed about the study and explanations were given regarding data confidentiality and the possibility of abandoning the study at any point in time. Signed informed consent was obtained prior to completion of the questionnaire. The study was approved by the Research Ethics Committee of PUCRS.

Data were captured online using the web application REDCap, with categorical data presented using counts and

percentages. The data were processed and analyzed using the Statistical Package for the Social Sciences software (SPSS, version 25.0; SPSS Inc, Chicago, Illinois, USA).

RESULTS

The online questionnaire link was received by 156 neurologists who are experts in MS. A total of 94 accessed the survey, among whom 76 responded fully. The number of respondents, categorized according to the Brazilian state in which they practice, is illustrated in Figure 1. Most of the participants were working in tertiary-level referral and teaching centers, that are reference centers for MS; had more than 20 years of experience of treating MS patients (34.9%); and reported that 26-50% of all their patients had MS (38.5%), with a total frequency of 10 to 49 MS patient appointments per month (53.9%). The majority of the respondents (56%) re-evaluated stable MS patients at six-monthly intervals.

Radiologically isolated syndrome (RIS)

A 28-year-old woman was evaluated following complaints of headache and underwent brain magnetic resonance imaging (MRI). The examination revealed T2/FLAIR hyperintense lesions in the central nervous system consistent with dissemination in space, in accordance with to the 2017 McDonald diagnostic criteria for MS[5]. Her physical examination and previous medical history was normal.

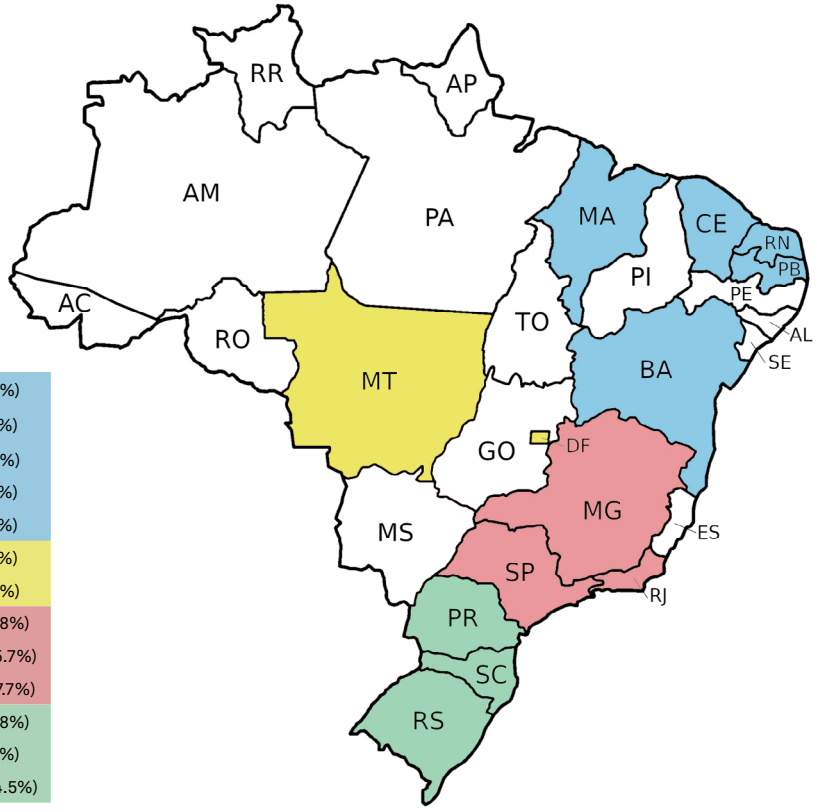
Most respondents indicated that they would not initiate disease-modifying therapy (DMT) at this time (96.3%). There was agreement on the need to perform a lumbar puncture (80.3%) and spinal cord MRI (81%) on the patient. If the spinal cord examination revealed hyperintense T2/FLAIR lesions suggestive of MS, 40.2% of the respondents would then initiate DMT.

There was agreement on the need to perform a follow-up MRI (97.6%), within a six-month interval (51.2%). After the follow-up period, some respondents would initiate DMT if the MRI showed one new or enlarging T2/FLAIR lesion (56.3%), one or more gadolinium-enhancing (Gd+) lesion (84.6%) or a clinical symptom suggestive of disease activity (100%).

Clinically isolated syndrome (CIS)

A previously healthy 26-year-old woman presented at an emergency department with hypoesthesia of the left foot, which progressed to both lower limbs and, after three days, presented a T10 sensory level. Physical examination was compatible with partial myelitis.

Most respondents agreed to perform an MRI of the brain (91.4%), cervical spinal cord (92.6%) and dorsal spinal cord (98.8%), as well as agreeing to carry out a lumbar puncture (97.5%). The majority of the respondents opted not to order evoked potential examinations, while almost two thirds of them (64%) agreed to request aquaporin-4 and myelin oligodendrocyte glycoprotein (MOG) antibody tests. The respondents were almost unanimous (92.6%) in deciding not to



Region	State	
Northeast	Bahia (BA)	N=2 (2.4%)
	Maranhão (MA)	N=1 (1.2%)
	Ceará (CE)	N=4 (4.8%)
	Rio Grande do Norte (RN)	N=1 (1.2%)
	Paraíba (PB)	N=1 (1.2%)
Central-West	Mato Grosso (MT)	N=1 (1.2%)
	Distrito-Federal (DF)	N=2 (2.4%)
Southeast	Minas Gerais (MG)	N=9 (10.8%)
	Rio de Janeiro (RJ)	N=13 (15.7%)
	São Paulo (SP)	N=23 (27.7%)
South Region	Paraná (PR)	N=9 (10.8%)
	Santa Catarina (SC)	N=5 (6.0%)
	Rio Grande do Sul (RS)	N=12 (14.5%)

Figure 1. Survey responses according to Brazilian state.

treat the patient with DMT if the investigative examinations revealed partial myelitis only. They further agreed (97.5%) to perform a follow-up MRI, which would need to be within an interval of three months (53.1%) or six months (40.7%).

In another scenario, instead of myelitis, the same patient presented to the emergency department with typical unilateral optic neuritis. Brain MRI revealed hyperintense T2/FLAIR lesions consistent with demyelinating lesions. There was strong agreement regarding the following situations: 62.8% of neurologists would initiate DMT if cerebrospinal fluid (CSF) demonstrated oligoclonal bands and MRI showed spatial dissemination; 72.8% would consider treatment only in CIS patients with high risk of conversion to MS; and 85% would treat if MRI also revealed brain Gd+ lesions, thus demonstrating dissemination in time. Around half of the respondents (54.3%) would consider initiating therapy if the patient presented with other less specific clinical symptoms, such as cognitive changes or fatigue.

When asked about DMTs for CIS treatment, some neurologists (38.3%) opted for interferon (IFN) beta-1a SC as first choice, glatiramer acetate (GA) as second choice (31.3%) and teriflunomide as third choice (24.4%) therapy. All results for the treatment choices are illustrated in Table 1.

Table 1. Treatment choices for MS patient scenarios.

DMT	CIS			Naïve RRMS			RRMS	
	First choice n (%) (N = 81)	Second choice n (%) (N = 81)	Third choice n (%) (N = 78)	First choice n (%) (N = 77)	Second choice n (%) (N = 77)	Third choice n (%) (N = 76)	First [a] modification n (%) (N = 79)	Second [b] modification n (%) (N = 80)
No treatment	3 (3.7)	2 (2.5)	2 (2.6)	3 (3.9)	2 (2.6)	2 (2.6)	-	-
Alemtuzumab	–	–	–	–	–	–	1 (1.3)	3 (3.8)
Azathioprine	–	–	–	–	–	–	–	–
IFNb 1a IM	6 (7.4)	4 (5.0)	5 (6.4)	5 (6.5)	5 (6.5)	1 (1.3)	–	–
IFNb 1a SC	31 (38.3)	15 (18.8)	4 (5.1)	23 (29.9)	11 (14.3)	10 (13.2)	6 (7.6)	1 (1.3)
IFNb 1b SC	2 (2.5)	4 (5.0)	5 (6.4)	1 (1.3)	5 (6.5)	2 (2.6)	-	2 (2.5)
Cladribine	–	–	–	–	–	1 (1.3)	1 (1.3)	4 (5.0)
Cyclophosphamide	–	–	–	–	–	–	–	–
Fingolimod	5 (6.2)	8 (10.0)	10 (12.8)	4 (5.2)	12 (15.6)	12 (15.8)	22 (27.8)	15 (18.8)
DMF	12 (14.8)	11 (13.8)	15 (19.2)	21 (27.3)	11 (14.3)	10 (13.2)	11 (13.9)	3 (3.8)
GA	17 (21.0)	25 (31.3)	11 (14.1)	10 (13.0)	16 (20.8)	12 (15.8)	5 (6.3)	2 (2.5)
Mitoxantrone	–	–	–	-	-	-	-	-
Natalizumab	–	2 (2.5)	3 (3.8)	1 (1.3)	4 (5.2)	7 (9.2)	20 (25.3)	48 (60.1)
Ocrelizumab	–	–	4 (5.1)	1 (1.3)	2 (2.6)	3 (3.9)	13 (16.4)	1 (1.3)
Rituximab	1 (1.2)	–	–	–	–	–	–	1 (1.3)
Teriflunomide	4 (4.9)	9 (11.3)	19 (24.4)	8 (10.4)	9 (11.7)	16 (21.1)	–	–

CIS: clinically isolated syndrome; DMF: dimethyl fumarate; DMT: disease-modifying therapy; GA: glatiramer acetate; IFNb: interferon beta; IM: intramuscular; RRMS: relapsing remitting multiple sclerosis; SC: subcutaneous. aTwo clinical relapses during the past six months resulting in residual disability; MRI revealing multiple non-enhancing T2/FLAIR lesions in the brain, brainstem and spinal cord; but no atrophy and no T1 black holes. bIncluding atrophy and multiple T1 black holes.

Relapsing-remitting MS (RRMS)

RRMS, treatment-naïve

A 24-year-old man, recently diagnosed with RRMS, sought medical attention to initiate therapy. His neurological examination was normal and brain MRI imaging demonstrated five hyperintense T2/FLAIR lesions, with no Gd+ lesion. Spinal cord MRI was normal.

In this scenario, most respondents agreed to perform lumbar puncture (89.5%) and initiate DMT (87.8%). Similarly to the CIS treatment choices, the highest percentage of respondents chose first-line injectables as their first and second options: IFN beta-1a SC (29.9%) and GA (20.8%), respectively. The third choice was teriflunomide (21.1%). The respondents generally agreed (67.5%) to perform a follow-up MRI within a six-month interval.

Modification of the initial RRMS patient case to present a more severe scenario (two clinical relapses in 12 months and emergence of new T2/FLAIR lesions and Gd+ lesions) resulted in the choice of first-line treatment for first therapy modification changing to fingolimod (27.8%). When the case severity was increased further (emergence of black holes and atrophy on MRI imaging), natalizumab (32.5%), ocrelizumab (22.8%) and alemtuzumab (26.6%) were the treatment options for first, second and third choice, respectively, in the

second therapy modification. All results for the treatment choices are illustrated in Table 1.

RRMS in pregnancy

A 30-year-old woman, diagnosed with RRMS and undergoing treatment with DMT, became pregnant. No agreement was seen between the respondents regarding management of DMT in this scenario. Some (53.7%) opted to discontinue therapy, while others chose to maintain DMT until confirmation of the pregnancy (54.4%) and yet others chose to maintain therapy during pregnancy (26.7%).

The respondents choosing to maintain DMT during pregnancy selected the following specific drugs: GA (81.1%) and IFN (52.3%), which was similar to the finding when they were asked about treatment in breast-feeding (GA 59%; IFN 36.5%).

RRMS and disease therapy

The respondents were asked to indicate the minimum number of clinical relapses and new MRI lesions in a 12-month period that would prompt them to suggest a change in DMT (Table 2). Almost half (49.3%) considered one or two new or enlarging T2/FLAIR lesions to be sufficient reason for therapeutic change, while 68.4% would recommend change if one Gd+ lesion was present. In addition, around half of the neurologists (55.3%) would alter DMT if one clinical relapse occurred within the previous 12 months. Table 3 illustrates the drug preference for each DMT change.

The respondents were asked if they would apply a washout period for specific DMTs. There was general agreement (72.6-86.3%) that a washout period should be applied for alemtuzumab, cladribine, cyclophosphamide, mitoxantrone, natalizumab, fingolimod, ocrelizumab and rituximab, while there was less agreement (50-54.3%) in relation to azathioprine, dimethyl fumarate and teriflunomide. Few respondents (4.2-5.6%) would indicate a washout period for IFN and GA.

DISCUSSION

The present study examined the diagnosis and treatment practices adopted by Brazilian neuroimmunology specialists, through application of a structured questionnaire presenting multiple MS patient scenarios. Evaluation of their answers highlighted several areas of agreement among the respondents, mainly relating to diagnosis, investigation and patient follow-up practices. These areas of agreement are detailed in Table 4.

Considering the RIS scenario, most respondents agreed not to initiate DMT for a patient with T2/FLAIR brain lesions only on MRI. The number choosing to treat RIS patients increased as other abnormalities appeared in complementary tests, such as spinal cord lesions or Gd+ lesions, or after a follow-up period, with the appearance of relapse symptoms. Expert recommendations by De Stefano *et al.*[8] have suggested that there is a lack of current evidence to support treatment in individuals with RIS, even when the findings suggest that there is a high risk of conversion to MS. However, Freedman *et al.*[9] emphasized that the reasons for initiating DMT in RIS patients were usually related to MRI findings, such as spinal cord lesions, high lesion load and Gd+ lesions. In some ways, this was compatible with the opinions of our respondents and to the findings of Yamout *et al.*[10], who considered treatment among RIS patients at high risk of clinical conversion to MS: aged under 37 years, male gender and with the presence

Table 2. Clinical and radiological characteristics over a 12-month period that would prompt a suggestion for change of DMT.

	Number of participants n (%) (N = 76)
Number of clinical relapses	
1	42 (55.3)
2	34 (44.7)
3	–
4 or more	–
Number of new or enlarging T2/FLAIR lesions on MRI	
1-2	37 (49.3)
3-4	30 (40.0)
5-8	1 (1.3)
9 or more	–
Number of Gd+ lesions on MRI	
1	52 (68.4)
2	17 (22.4)
3 or more	7 (9.2)

DMT: disease-modifying therapy; Gd+: gadolinium-enhancing; MRI: magnetic resonance imaging.

Table 3. DMT of choice for most neurologists considering treatment modification.

Current DMT	First choice in treatment modification	n (%) (N = 76)
Alemtuzumab	Ocrelizumab	35 (46.1)
Azathioprine	DMF	17 (22.4)
IFNb 1a IM	DMF	38 (50.0)
IFNb 1a SC	DMF	39 (52.0)
IFNb 1b SC	DMF	37 (48.7)
Cladribine	Ocrelizumab	31 (42.5)
Cyclophosphamide	DMF	26 (34.2)
Fingolimod	Natalizumab	57 (75.0)
DMF	Fingolimod	43 (56.6)
GA	DMF	35 (47.3)
Mitoxantrone	Ocrelizumab	17 (23.3)
Natalizumab	Ocrelizumab	39 (52.7)
Ocrelizumab	Alemtuzumab	27 (37.0)
Rituximab	Alemtuzumab	26 (35.6)
Teriflunomide	DMF	38 (52.1)

DMF: dimethyl fumarate; DMT: disease-modifying therapy; GA: glatiramer acetate; IFNb: interferon beta; IM: intramuscular; SC: subcutaneous; DMT: disease-modifying therapy

Table 4. Areas of agreement between participating neurologists.

Clinical situations	Areas of agreement
RIS	LP, brain and spinal cord MRI are ancillary tests for RIS investigation. DMT should not be initiated if T2/FLAIR lesions alone are seen in brain MRI, and a follow-up MRI should be requested in six months. DMT should be considered if the follow-up examination demonstrates any Gd+ lesion or if the patient presents any clinical symptom suggestive of relapse.
CIS	LP, brain and spinal cord MRI are ancillary tests for CIS investigation. DMT should not be initiated if the only abnormality in the investigative examination is partial myelitis or optic neuritis, and a follow-up MRI should be requested in three or six months. DMT should be considered in CIS patients with high risk of conversion to MS. DMT should be considered if MRI demonstrates Gd+ lesions (unless the topography is the optic nerve). In case of optic neuritis, DMT should be initiated if the MRI and CSF demonstrate spatial dissemination and oligoclonal bands, respectively.
RRMS	LP is an ancillary test for RRMS investigation. DMT should be initiated for a treatment-naïve patient with mild disease (few hyperintense lesions on T2/FLAIR, no Gd+ lesions and low annual rate of clinical relapse), preferably a first-line therapy (injectable or oral drugs), and a follow-up MRI should be requested in six months. An increase in case severity (atrophy, black holes, new lesions on MRI, or two or more clinical relapses in 12 months) saw a preference for switching therapy to a more effective DMT, such as third-line or fourth-line intravenous drugs. The only DMT more broadly indicated for continuation during pregnancy is GA.
Therapeutic management	DMT switching should be considered in situations of occurrence of 1-2 clinical relapses, 1-5 new or enlarging T2/FLAIR lesions, or a minimum of one Gd+ lesion on MRI, in a 12-month period. A wash-out period is considered for some DMT escalation, such as to alemtuzumab, cladribine, cyclophosphamide, mitoxantrone, natalizumab, fingolimod, ocrelizumab and rituximab. No wash-out period is needed for IFN and GA treatments.

CIS: clinically isolated syndrome; CSF: cerebrospinal fluid; DMT: disease-modifying therapy; GA: glatiramer acetate; Gd+: gadolinium-enhancing; IFN: interferon; LP: lumbar puncture; MRI: magnetic resonance imaging; RIS: radiologically isolated syndrome; RRMS: relapsing-remitting multiple sclerosis.

of spinal cord lesions. Furthermore, a United States consensus[11] showed similar agreement to our study with regard to initiating DMT in RIS patients who showed Gd+ lesions on MRI (80% vs. 84.6%). A study by Fernandez *et al.*[7] noted that the decision to treat a RIS patient was dependent on the type, number and location of lesions on follow-up MRI examinations, especially if there were new Gd+ or spinal cord lesions.

Strong agreement was seen between the Brazilian neurologists regarding investigation of patients with a first neurological symptom suggestive of CIS, by performing LP and

MRI. The 2017 updated McDonald diagnostic criteria for MS defined some changes, such as positive OCB in CSF, to replace the criteria of dissemination of lesions in time, so as to allow a diagnosis of MS if this is associated with MRI demonstration of spatial dissemination[5]. However, although respondents showed that they were in favor of requesting LP and MRI in this scenario, only a little more than half appeared to be up-to-date regarding these changes in diagnostic criteria, since only 62.8% would initiate DMT if the CSF demonstrated positive OCB and MRI showed spatial dissemination.

About 70% of the respondents considered initiating DMT only in CIS patients with high risk of conversion to MS, which is similar to the Brazilian protocol recommendations[12,13]. The Brazilian Academy of Neurology (ABN) and the Brazilian Committee for Treatment and Research in Multiple Sclerosis (BCTRIMS) endorse the idea of initiating DMT only in patients with high-risk CIS (one or more typical T2/FLAIR lesions on MRI, clinical presentation and MRI lesion suggestive of CNS demyelination). In a European study[7], the majority of the respondents indicated starting DMT for CIS cases if there were one or more brain Gd+ lesions, three or more new or enlarging brain T2/FLAIR lesions or at least one spinal cord lesion. Currently, the DMTs that have demonstrated efficacy in CIS are IFN, cladribine, GA and teriflunomide[14-18]. These are the four first-line therapies recommended by the Brazilian guidelines and the European Academy of Neurology for treating high-risk CIS patients[12,13,19]. In contrast, the American Academy of Neurology consensus makes a less aggressive recommendation, in which serial imaging at least annually for the first five years and close follow-up are suggested, rather than initiating DMT in CIS patients[20]. Data from Fernandez *et al.* showed choices similar to those of our respondents, in which almost 40% opted to initiate IFN beta-1a SC, 30% opted for GA and almost 25% chose teriflunomide[7].

Analysis on the responses regarding treatment-naïve RRMS patients also revealed that these same three therapies were the ones most cited, such that almost 30% of the respondents opted for IFN beta-1a SC, followed by GA and teriflunomide. These DMTs, together with DMF, have also been recommended by two Brazilian consensus papers[12,13], in cases without concerns for high levels of disease activity[21-24]. It is important to emphasize that most Brazilian patients receive their treatment from the state. Therefore, neurologists all over the country must follow a national protocol designed by the Ministry of Health[13]. Currently, only first-line medications can be initiated for MS patients, regardless of disease activity level.

When considering RRMS, however, a tendency is seen towards a change in therapy to a more effective drug when signs of increased disease activity become evident. Almost 30% of the respondents in the present study opted to switch treatment to fingolimod when presented with the scenario of a patient with previously controlled disease who has now experienced two clinical relapses in a 12-month period and has exhibited new T2/FLAIR and Gd+ lesions on a brain MRI. Furthermore, when the brain MRI of this same patient demonstrated atrophy and T1 black holes, which are signs of more aggressive disease, the respondents opted to switch DMTs again to natalizumab, ocrelizumab or alemtuzumab, in order of preference. This practice is corroborated by guidelines developed by the ABN and BCTRIMS[12], in which higher potency drugs like fingolimod, natalizumab, alemtuzumab, ocrelizumab and cladribine[25-29] should be considered for patients who meet the criteria for aggressive RRMS or present poorer prognostic factors. In the previously mentioned European study[7], there was a tendency to use natalizumab at an earlier stage in such cases, even at the first sign of worsening condition.

In considering patient follow-up, most respondents opted to request an MRI within a six-month interval after DMT initiation. This practice is similar to what has been reported from other studies conducted in Europe, Canada and the United States, in which MRIs are recommended every six months over the course of one or two years for patients with recently diagnosed RRMS, and after each DMT change[7,30].

Areas of disagreement in treatment practice were also identified. About 60% of these Brazilian neurologists opted to test for anti-aquaporin-4 and anti-MOG antibodies after a first neurological symptom suggestive of demyelinating disease. However, this might be a more recommended practice, since neuromyelitis optica spectrum disease (NMOSD) and MOG antibody disease are important differential diagnoses in CIS[31]. In addition, a lack of agreement among the respondents was noted regarding DMT use in patients wishing to become pregnant, in terms of whether or not its use should be continued during the planning stage, until pregnancy confirmation, or during the course of pregnancy. European, American and Brazilian consensuses have indicated this practice needs to be individualized according to disease activity. Ideally and if possible, however, DMT use should be discontinued before conception, although there is only scarce evidence guiding this decision[12,19,20]. A European consensus[19] recommended that in situations of high risk of disease activity, use of IFN or GA should be considered until pregnancy has been confirmed. Continuation of therapy during pregnancy could also be considered in some specific cases: treatment with natalizumab throughout pregnancy could be considered after full discussion of the potential implications, as also could treatment with alemtuzumab, provided that a four-month interval from the last infusion until conception is strictly observed. According to the Brazilian consensus, GA is generally preferred over other DMTs[12].

A final area of disagreement identified was the washout period required for some DMTs. There was no consensus among the respondents regarding this practice for DMF and teriflunomide. In general, the proposed mechanism of action for DMF would not suggest the existence of any issues with rapid transition to another therapy. However, this has also

been shown to have a lymphopenic effect in some patients, which would explain the preference of most experts to perform a short washout period of 4 to 8 weeks in order to avoid possible risks[32]. In relation to teriflunomide, if a switch to an escalation treatment with natalizumab, fingolimod or alemtuzumab is required, a washout period through an accelerated elimination procedure is recommended[33].

Regarding the limitations of this study, the survey presented to respondents consisted of a set of typical scenarios seen among MS patients, which may not represent real-life situations and did not allow the neurologists to individualize their practices, as is often necessary and is done in relation to MS. In addition, some answers may have been influenced by real issues often faced by Brazilian neurologists, such as bureaucratic problems during drug dispensing and the financial challenges of patients using the public healthcare system.

This study enabled identification of areas of agreement among Brazilian neurologists regarding different scenarios that relate to patients with MS. There was notable agreement about most of the practices relating to diagnosis, treatment and follow-up of cases. Scenarios with less agreement and divergence of ideas were also highlighted. These results can be used to promote debate among Brazilian experts regarding those areas in which disagreement was found, with the goal of helping to update future protocols and improve patient management.

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