The frequency and characteristics of MS misdiagnosis in patients referred to the multiple sclerosis centre of Catalonia

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Abstract

Background: Multiple sclerosis (MS) misdiagnosis may cause physical and emotional damage to patients.

Objectives: The objective of this study is to determine the frequency and characteristics of MS misdiagnosis in patients referred to the Multiple Sclerosis Centre of Catalonia.

Methods: We designed a prospective study including all new consecutive patients referred to our centre between July 2017 and June 2018. Instances of misdiagnosis were identified, and referral diagnosis and final diagnosis were compared after 1 year of follow-up. Association of misdiagnosis with magnetic resonance imaging (MRI) findings, presence of comorbidities and family history of autoimmunity were assessed.

Results: A total of 354 patients were referred to our centre within the study period, 112 (31.8%) with ‘established MS’. Misdiagnosis was identified in eight out of 112 cases (7.1%). MRI identified multifocal white matter lesions, deemed non-specific or not suggestive of MS in all misdiagnosed cases. Patients with MS misdiagnosis had more comorbidities in general than patients with MS (p = 0.026) as well as a personal history of autoimmunity (p < 0.001).

Conclusion: A low frequency of MS misdiagnosis was found in our clinical setting. Multifocal non-specific white matter lesions in referral MRI examinations and the presence of comorbidities, including a personal history of autoimmunity, seem to be contributing factors to misdiagnosis.

Keywords: Multiple sclerosis, misdiagnosis, magnetic resonance imaging, comorbidities

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Introduction

Multiple sclerosis (MS) has a wide spectrum of clinical manifestations, and the proper interpretation of the radiological findings may pose an actual challenge at the time of diagnosis. Neither highly specific nor sensitive biomarker for MS has been identified to date. Different disorders and conditions can mimic the radiological and/or clinical appearance of MS. Non-MS inflammatory demyelinating diseases such as Neuromyelitis Optica Spectrum Disorders (NMOSD) and disorders associated with anti–myelin oligodendrocyte glycoprotein (anti-MOG) antibodies and incidental and migraine-related white matter changes are the most common to mimic MS. Other possible sources of misdiagnosis also include infectious, metabolic and vascular diseases. Despite the current well-validated diagnostic criteria for MS, the occurrence of misdiagnosis remains a challenge with significant implications for patients, their families and the healthcare system.

Current evidence supports the benefits of an early diagnosis and disease-modifying treatment (DMT) onset seeking to reduce long-term disability. In given cases, this may lead neurologists to rush into a diagnosis of MS, hence constituting a factor playing a role in mistaken diagnosis. The latest revisions of the McDonald criteria have a strong focus on the role of magnetic resonance imaging (MRI), increasing its sensitivity though with low impact on specificity for...
MS diagnosis, making early diagnosis more likely.\textsuperscript{10} However, the degree of emphasis allocated to the role of MRI during the diagnostic process can also contribute to misdiagnosis by wrong interpretation of non-specific or non-inflammatory demyelinating lesions. The same is true for the application of the radiological criteria in patients with atypical clinical presentations and also in asymptomatic patients.\textsuperscript{5,11} For this reason, all criteria sets published to date, from Schumacher’s to McDonald’s, emphasized on the need to rule out any ‘other better explanation’ for the clinical scenario before making a definitive diagnosis of MS.\textsuperscript{11–13}

Several studies have described that, of all new patients with a suspicion of or established MS diagnosis referred to centres specializing in demyelinating disorders, 30\%–67\% did not have MS eventually.\textsuperscript{8,14} Unfortunately, around 50\% of such patients had initiated DMT at the time of determining the misdiagnosis, having exposed to possible secondary emotional and physical damage. Misdiagnosis is also associated with the clinical challenge of having to approach undoing of a diagnosis of MS. Through a cross-sectional Internet-based survey of MS specialists, most neurologists responded that reporting an ‘undiagnosis’ to a patient could be equally or even more challenging than confirming a new diagnosis of MS.\textsuperscript{15} However, most of the studies published on this issue were performed in the United States, and data from European centres on clinical and paraclinical factors contributing to misdiagnosis are scarce.

Therefore, the aim of this study was to determine the frequency and characteristics of MS misdiagnosis in patients referred to the Multiple Sclerosis Centre of Catalonia (Cemcat) and to assess the impact of clinical and MRI findings on the odds of misdiagnosis.

**Methods**

We designed an observational prospective study including all consecutive new patients referred to our centre between July 2017 and June 2018. Experienced MS specialist neurologists at Cemcat clinically evaluated each new patient at the first visit and again after 1 year of follow-up. Diagnoses at the first visit were assessed and reassessed at the last follow-up visit. Final diagnoses were then adjudicated by a validation team composed of three expert MS neurologists specially appointed from within the team. MRI imaging was evaluated and reported on by a neuroradiologist with over 20 years of experience in MS. Reasons for referral were classified into one out of five exclusive categories: (1) patients referred with ‘established MS’, (2) patients referred with ‘suspected MS’ or ‘to rule out MS’, to always include the term ‘MS’ in the referral form, (3) patients whose referral form included the term ‘demyelinating’, (4) patients whose referral form only mentioned ‘neurological signs or symptoms’ and (5) patients referred with a neurological diagnosis other than MS. For patients referred with an established diagnosis of MS, characteristics of first clinical manifestation (onset, duration and topography) were recorded. The availability of a pre-referral MRI scan was collected. We also recorded the site where MRI scan was performed (Vall d’Hebron Hospital Neuroradiology Section vs. elsewhere) and referring physician’s awareness of the MRI report. In addition, the performance of a pre-referral lumbar puncture (LP) was also considered. On the day of the first visit, family history of autoimmune diseases and data on autoimmune and general comorbidities were collected (Table 1).\textsuperscript{16} The validation team classified each patient’s diagnosis at the first visit and at the 1-year follow-up visit into one of three exclusive categories: (1) established MS, (2) suspected MS and (3) non-MS. To reach the category of established MS, we applied the fulfilment of the 2017 McDonald criteria after reasonable exclusion of alternative diagnoses. The category of suspected MS included patients with (1) typical clinical history of a demyelinating disease and absence of MRI/LP data supporting the diagnosis (clinically isolated syndrome) because of a normal or non-specific MRI, inconclusive MRI with presence of multifocal lesions not fulfilling MS criteria for dissemination in space (DIS) though suggestive of an inflammatory demyelinating disease or lack of paraclinical data due to MRI/LP not performed or unavailable at first visit and (2) patients presenting with a radiologically isolated syndrome (RIS), that is, presence of MRI findings meeting MS criteria in the absence of clinical symptoms. To formally include patients in the non-MS category, a combination of clinical manifestations and MRI not suggestive of MS was considered. In patients with a non-MS diagnosis, the following alternative diagnoses were recorded: isolated non-specific signs or symptoms, peripheral nervous system disease, non-inflammatory myelopathy, oncological disease, cerebrovascular disease, infectious disease, metabolic disorder, headache/migraine, non-MS inflammatory disease, non-inflammatory optic neuropathy, non-specific or non-inflammatory lesions in the MRI and functional neurological disorders, among others.

After establishing the final diagnosis at our centre, the frequency of misdiagnosis was assessed. Based on existing discrepancies between diagnosis at referral and final diagnosis, two groups were defined: (a)
patients with ‘established MS’ on the referral form whose diagnoses changed to non-MS and (b) patients with ‘established MS’ whose diagnoses changed to suspected MS. For both groups of patients, MRI findings were assessed and classified as follows: normal, non-specific/non-inflammatory lesions, suggestive lesions not fulfilling the McDonald MS criteria, and other. Instances of DMT use and the presence or absence of oligoclonal bands (OB) was also recorded. Aiming to gauge the influence on the misdiagnosis from family and personal history of autoimmune diseases and patient general comorbidities, the frequency of these factors was compared between patients with a final diagnosis of MS and patients with ‘established MS’ on the referral form that changed to non-MS. Finally, conditions most frequently misdiagnosed as MS were listed. All statistical analyses were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 22.0; IBM Corp., Armonk, NY, USA). The study received the approval of the local ethics committee, and all patients gave informed consent prior to their inclusion in the study.

Results

Diagnostic categories and availability of paraclinical examinations at first visit
From July 2017 to June 2018, 354 patients were referred to and had their first visit at Cemcat. Of these patients, 112 (31.6%) were referred with ‘established MS’ (category 1), 77 (21.8%) were referred with ‘suspected MS’ or ‘to rule out MS’ (category 2), in 47 (13.3%) only the term ‘demyelinating’ appeared on the referral form (category 3), in 105 (29.7%) only neurological signs or symptoms were described as the reason for referral (category 4) and 13 (3.7%) were referred with a diagnosis other than MS; category 5 (Table 2). In 86.6% (97/112) of patients in category 1, an MRI examination had been performed (85% in external MRI facilities) before assessment at the first visit to Cemcat, and in 72% of cases, the referring physician was aware of the MRI findings. In addition, an LP was performed before referral in 70.5% (79/112) of patients.

Frequency of MS misdiagnosis
At the time of the first visit, 19 out of 112 patients (16.9%) changed from the category ‘established MS’ (as per the referral form). Hence, 12/19 (63.1%) moved under the label of suspected MS and 7/19 (36.8%) under the label of non-MS. Reasons for change to suspected MS were having an inconclusive (n = 5), a normal/non-specific MRI (n = 1), lack of ancillary tests (n = 5) and absence of typical symptoms (RIS) (n = 1).

At the 1-year follow-up visit, after performing an MRI scan at our centre and/or reviewing the external MRIs by expert neuroradiologists, as well as after completing the aetiological study with an LP in selected cases, one out of those 12 patients that had...
Table 2. Diagnosis at first visit and at 1-year follow-up for all referred patients according to diagnosis on referral (n = 354).

<table>
<thead>
<tr>
<th>Diagnosis at referral</th>
<th>Diagnosis at first visit</th>
<th>Diagnosis at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Established MS (n = 137)</td>
<td>Suspected MS (n = 88)</td>
</tr>
<tr>
<td>Established MS (n = 112)</td>
<td>93 (83%)</td>
<td>12 (10.7%)</td>
</tr>
<tr>
<td>Suspected MS (n = 77)</td>
<td>25 (32.5%)</td>
<td>34 (44%)</td>
</tr>
<tr>
<td>Mention of ‘demyelination’ (n = 47)</td>
<td>13 (27.6%)</td>
<td>10 (21.3%)</td>
</tr>
<tr>
<td>Signs &amp; symptoms only (n = 105)</td>
<td>6 (5.7%)</td>
<td>31 (29.5%)</td>
</tr>
<tr>
<td>Diagnosis other than MS (n = 13)</td>
<td>0 (0%)</td>
<td>1 (7.7%)</td>
</tr>
</tbody>
</table>

MS: multiple sclerosis.

their diagnosis changed from 'established MS' to suspected MS received the diagnosis of non-MS, five patients received the diagnosis of established MS and six patients retained the label of suspected MS. All seven cases labelled as non-MS at the first visit remained as non-MS at the follow-up period. Hence, a total of eight cases were finally considered non-MS at the one year (8/112%–7.1%) visit, and 14 out of 112 patients (12.5%) had their diagnoses changed from ‘established MS’ to suspected MS or non-MS at the end of the study period (Table 3).

Out of these 14 patients, 9 (64%) had received or were on DMT. Considering only patients with a final diagnosis of non-MS (n = 8), the mean time during which they had carried the incorrect diagnosis of MS was 86.4 months (SD: 67.6). Six out of eight (75%) patients had been on treatment at the time of referral for 74.1 months (SD: 71.2).

Conditions most frequently misinterpreted as MS were cerebrovascular disease (2/8), migraine (2/8), functional neurological disorders (2/8), non-MS inflammatory demyelinating disease (1/8) and non-specific symptoms associated with non-specific findings on MRI (1/8).

MRI features and CSF findings
In six out of the eight patients whose diagnoses changed from ‘established MS’ to non-MS at 1 year, MRI scans had been reassessed by a local expert neuroradiologist in MS and multifocal white matter lesions were deemed non-specific and not suggestive of MS because of morphology/size (very small and non-ovoid white matter lesions), topography (mostly subcortical white matter without involvement of the Corpus Callosum, infratentorial area or spinal cord) and lack of enhancement after administration of gadolinium contrast. Those patients whose MRI rendered a final diagnosis of cerebrovascular disease (n = 2) showed diffuse and confluent hyperintensities of the white matter associated with chronic lacunar infaracts. Five out of the six cases (66.6%) whose diagnoses changed from ‘established MS’ to suspected MS had lesions suggestive of a demyelinating inflammatory aetiology (in four cases not fulfilling DIS and one case of RIS fulfilling DIS).

Regarding the cerebrospinal fluid (CSF) findings, in five out of the eight patients whose diagnoses had changed from ‘established MS’ to non-MS at 1 year, an LP had been performed prior to referral (one case with negative OB, two cases with unknown results and two cases of positive OB with no pattern specified). At our centre, the LP was repeated in three of the cases with unknown/inconclusive results and newly performed in two patients, with the absence of OB in all cases. Considering patients in whom diagnoses changed from ‘established MS’ to suspected MS, four out of six had the LP performed prior to referral (one case with negative OB, one case with unknown findings and two cases with positive OB with no pattern specified); in our centre, the LP was newly performed in one patient, with the absence of OB.

Family history of autoimmunity and comorbidities
Just one out of the eight (12.5%) patients who had their diagnoses changed from ‘established MS’ to
Table 3. Characteristics of patients with misdiagnosis of MS.

<table>
<thead>
<tr>
<th>Diagnosis at 1 year: non-MS</th>
<th>Age</th>
<th>Gender</th>
<th>First clinical manifestation</th>
<th>DMT onset pre-referral</th>
<th>Alternative diagnosis</th>
<th>MRI findings</th>
<th>Family autoimmunity</th>
<th>Autoimmune comorbidities</th>
<th>General comorbidities</th>
<th>Oligoclonal bands</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>Female</td>
<td>Atypical</td>
<td>Yes – IFN beta 1b</td>
<td>Non-specific symptoms</td>
<td>NS-NIL</td>
<td>No</td>
<td>No</td>
<td>Combination of CVFR</td>
<td>Unk</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>Female</td>
<td>Atypical</td>
<td>Yes – GA</td>
<td>Functional neurological disorder</td>
<td>NS-NIL</td>
<td>No</td>
<td>No</td>
<td>Anxiety-depression syndrome</td>
<td>Neg</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>Female</td>
<td>Atypical</td>
<td>No</td>
<td>Migraine headache</td>
<td>NS-NIL</td>
<td>No</td>
<td>Other</td>
<td>Migraine</td>
<td>Neg</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>Female</td>
<td>Atypical</td>
<td>Yes – GA</td>
<td>Migraine headache</td>
<td>NS-NIL</td>
<td>No</td>
<td>MS</td>
<td>Smoker</td>
<td>Neg</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>Male</td>
<td>Atypical</td>
<td>No</td>
<td>Non-MS ID</td>
<td>NS-NIL</td>
<td>No</td>
<td>Rheumatoid arthritis</td>
<td>Major depression</td>
<td>Neg</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>Female</td>
<td>Atypical</td>
<td>Yes – CT</td>
<td>Cerebrovascular disease</td>
<td>NS-NIL</td>
<td>No</td>
<td>Thyroid pathology</td>
<td>Chronic bronchitis/asthma</td>
<td>Neg</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>Female</td>
<td>Atypical</td>
<td>Yes – IFN beta 1b</td>
<td>Cerebrovascular disease</td>
<td>NS-NIL</td>
<td>No</td>
<td>Psoriasis</td>
<td>Combination of CVFR/migraine</td>
<td>Neg</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>Female</td>
<td>Atypical</td>
<td>Yes – IFN beta 1a</td>
<td>Functional neurological disorder</td>
<td>NS-NIL</td>
<td>No</td>
<td>Thyroid pathology</td>
<td>Anxiety-depression syndrome/smoker</td>
<td>NP</td>
</tr>
<tr>
<td>Diagnosis at 1 year: suspected MS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>21</td>
<td>Female</td>
<td>Typical</td>
<td>No</td>
<td>–</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
<td>Other diseases</td>
<td>Neg</td>
</tr>
<tr>
<td>10</td>
<td>43</td>
<td>Female</td>
<td>Typical</td>
<td>Yes – AZA</td>
<td>–</td>
<td>SL-NFMSC</td>
<td>No</td>
<td>Inflammatory bowel disease</td>
<td>Anxiety-depression syndrome/smoker</td>
<td>Unk</td>
</tr>
<tr>
<td>11</td>
<td>49</td>
<td>Female</td>
<td>Typical</td>
<td>No</td>
<td>–</td>
<td>SL-NFMSC</td>
<td>No</td>
<td>No</td>
<td>Smoker</td>
<td>Neg</td>
</tr>
<tr>
<td>12</td>
<td>58</td>
<td>Female</td>
<td>Typical</td>
<td>No</td>
<td>–</td>
<td>RIS</td>
<td>MS</td>
<td>No</td>
<td>Other oncological diseases</td>
<td>Pos (UP)</td>
</tr>
<tr>
<td>13</td>
<td>54</td>
<td>Female</td>
<td>Typical</td>
<td>Yes – GA</td>
<td>–</td>
<td>SL-NFMSC</td>
<td>No</td>
<td>No</td>
<td>Arterial hypertension</td>
<td>Pos (UP)</td>
</tr>
<tr>
<td>14</td>
<td>33</td>
<td>Male</td>
<td>Typical</td>
<td>Yes – IFN beta 1a</td>
<td>–</td>
<td>SL-NFMSC</td>
<td>No</td>
<td>Inflammatory bowel disease</td>
<td>Epilepsy</td>
<td>NP</td>
</tr>
</tbody>
</table>

DMT: disease-modifying treatment; MS: multiple sclerosis; non-MS ID: non-MS inflammatory disease; IFN: interferon; GA: glatiramer Acetate; CT: clinical trial; AZA: azathioprine; NS-NIL: non-specific-non-inflammatory lesions; SL-NFMSC: suggestive lesions but not fulfilling MS criteria; RIS: radiologically isolated syndrome; CVRF: cardiovascular risk factors; Unk: unknown; Neg: negative; NP: not performed; Pos: positive; UP: unknown pattern.
non-MS at 1 year had a family history of autoimmune diseases compared to 43/170 (25.3%) patients with a final diagnosis of established MS (p = 0.412). However, a higher percentage of autoimmune comorbidities (62.5% (5/8) vs. 13% (22/170), p < 0.001) and comorbidities in general (100% (8/8) vs. 64.7% (110/170), p = 0.026) were observed in patients whose diagnoses changed from ‘established MS’ to non-MS at 1 year compared with patients with a final diagnosis of established MS. Mostly autoimmune comorbidities found were thyroid pathology (2/8), psoriasis (1/8) and rheumatoid arthritis (1/8). Regarding general comorbidities, the most common were cardiovascular risk factors (4/8), mainly arterial hypertension, positive smoking status and combinations thereof; psychiatric disorders (3/8), mostly anxiety-depression syndrome and major depression and other neurological diseases (2/8), migraine being the most frequent.

Discussion
This study suggests that, even in the context of a low frequency of diagnostic errors occurring, the misinterpretation of radiological findings is an important contemporary factor contributing to misdiagnosis of MS. Comorbidities, including previous history of autoimmune diseases, also seem to be associated with MS misdiagnosis.

The frequency of patients’ diagnoses changing from ‘established MS’ to a final diagnosis of non-MS in our clinical setting (7.1%) was lower than results shown in previous studies. Kaisey et al. described the occurrence of misdiagnosis in 18% of all new patients referred with an established MS diagnosis at the Cedars-Sinai Medical Centre and the University of California, Los Angeles Medical Centre. In a retrospective review of medical records, Yamout et al. found a higher frequency of misdiagnosis (26%) when they considered patients referred with an established and suspected MS diagnosis and not only patients referred with a definite MS diagnosis. Recently, a study by Calabrese et al. found alternative diagnoses in 24.4% of patients referred with suspicion of a demyelinating disorder, in which the authors excluded all cases with an already established MS diagnosis. Before MRI was integrated into the MS diagnostic criteria, Poser et al. described an erroneous diagnosis of MS in 35% of cases. There are several aspects that could explain the discrepancy in misdiagnosis frequency between our results and the aforementioned studies. First, only 31.6% of all patients were referred to our centre with a diagnosis of ‘established MS’. This suggests that in the region of Catalonia most primary care physicians or community neurologists prefer to promptly refer patients with suspicion of a demyelinating disorder to MS reference centres as opposed to completing the diagnostic work-up and establishing the diagnosis at their own practice. Second, when approaching the analysis of misdiagnosis frequency, we considered two instances. On one hand, patients who changed from ‘established MS’ in the referral form to any other confirmed disorder, that is, non-MS, resulting in only 7.1% diagnostic errors. On the other hand, we assessed separately patients referred with ‘established MS’ who finally received a diagnosis of suspected MS at the 1-year follow-up visit. When we grouped both instances, considering all patients whose diagnosis of ‘established MS’ in the referral form was removed by the end of the study period, the misdiagnosis frequency (12.5%, 14/112) was closer to that reported in previous series. Finally, the fact that in our centre the final diagnosis was always reassessed by and assigned to the same validation team could have overcome certain discrepancies and biases caused by individual interpretation only, increasing the specificity or homogeneity of the diagnosis.

Considering the low frequency found in our study population (7.1%), when we attempt to extrapolate the frequency of misdiagnosis into the total Spanish population with MS of about 46,000 individuals (100 per every 100,000 inhabitants), then the number of misdiagnosed patients is estimated to be beyond 3000. Regardless of the frequency, the mean time during which our patients in our study carried a misdiagnosis of MS and received DMT, was longer than 6 years, leading to potential physical and/or psychological damage to patients as well as a high impact on the health care and pharmaceutical cost. Of note, one of these misdiagnosed patients had even been enrolled in a clinical trial for MS.

In spite of the difference in frequency, conditions most frequently misinterpreted as MS in our clinic were similar to those reported by other authors. These were mainly migraine, psychiatric disorders and non-specific MRI white matter findings. Furthermore, the frequency of DMT indication in the misdiagnosed patients (64%) was also in line with the frequency informed (60%–70%) in previous studies. Multifocal white matter lesions deemed non-specific and not suggestive of MS were reported in all patients whose diagnosis changed from ‘established MS’ to non-MS, pointing to the fact that MRI could be a strong contributor to MS misdiagnosis, especially when not considering clinical aspects or when the
accompanying symptoms are atypical as observed in the cases in our work and also when other supporting features are not considered.22–24 Yamout et al.18 found that the proportion of patients with a final MS diagnosis among those originally referred based on MRI findings was only 8%, as opposed to 75% of patients referred based on clinical symptoms or physical findings. In the cases that MRI findings are inconclusive, searching for spinal cord lesions could be helpful as they either do not occur or will have different characteristics in other diseases.25 In addition, assessing the presence of the central vein sign can successfully differentiate MS from non-MS white matter lesions with high sensitivity and specificity in selected cases.26,27

Obtaining a second opinion from an experienced neuroradiologist is also recommended.7 Finally, a ‘wait and see’ attitude within a short reassessment interval may be sometimes prudent in patients with atypical clinical presentations or atypical MRI findings, as new data may confirm or rule out MS diagnosis, thus avoiding moving into unnecessary and potentially harmful treatments.9,28

OB analysis in the CSF and serum, preferentially with isoelectric focusing and immunoblotting or immunofixation for IgG, can also be useful in doubtful cases.7,24 In our study, the LP was performed or repeated in most patients changing from ‘established MS’ to non-MS at the 1-year follow-up visit. OB were negative in all cases, thus confirming the misdiagnosis.

We also analyzed general and autoimmune comorbidities as well as family history of autoimmune diseases as possible contributing factors to misdiagnosis. Our results suggest that a personal history of autoimmunity and other comorbidities could lead to a diagnostic error. Much in the same line, Kaisey et al.17 also concluded that a personal history of autoimmune disease was significantly associated with misdiagnosis of MS while a family history of autoimmune or neurologic diseases was not. Given the fact that, as shown in several studies, MS frequently associates with other autoimmune diseases or the fact that individuals with an autoimmune disease have a higher risk of a co-occurring autoimmune disorder, the presence of this type of comorbidity may favour misdiagnosis.29 Similarly, general comorbidities, such as cardiovascular risk factors, migraine and even psychiatric disorders, are associated with the presence of white matter hyperintensities, which may contribute to misinterpreting MRI findings.30

This study has some limitations. First, we did not collect detailed clinical presentations of patients referred to our centre, making it impossible to detail which were the most commonly misinterpreted signs or symptoms. Second, the role of other complementary tests, such as visual-evoked potentials or optic coherence tomography, were not taken into account on analyzing the chances of misdiagnosis. Finally, the low frequency of misdiagnosis in our study reduced the opportunity to clearly identify other potential confounding factors at the time of diagnosis. Conversely, one of the strengths of this study is the fact that this is the first prospective study assessing the frequency of misdiagnosis in an MS referral centre in Europe. Each patient referred to our centre due to a probable demyelinating syndrome was initially evaluated by a trained neurologist, reviewed later by a non-variable team of MS-experienced neurologists who confirmed or dismissed the initial diagnosis, reducing the probability of misdiagnosis and adding validity to our study. Finally, MS-expert neuroradiologists reviewed all the MRI results from both external and internal MRI facilities.

In conclusion, although the present study found a lower frequency of diagnostic errors than previous reports, there is still a significant proportion of patients being misdiagnosed of MS. In this sense, although MRI plays a fundamental role in assessing demyelinating disorders, it may paradoxically also contribute to misdiagnosis by misinterpretation of non-specific or non-inflammatory demyelinating lesions or even as a consequence of applying the radiological diagnostic criteria in patients with atypical clinical presentations. In the face of such cases, strict adherence to the MS diagnostic criteria and further evaluation – including spinal cord imaging, use of additional MRI sequences, CSF analysis and continued clinical or radiological monitoring – are likely to ease the diagnostic process, thereby avoiding misdiagnosis and unnecessary sometimes costly and potentially harmful treatments. Presence of comorbidities and personal history of autoimmunity may also be associated to misdiagnosis. Future research is necessary to achieve more conclusive results.

Declaration of Conflicting Interest
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