Why this is not multiple sclerosis: a case based approach
Quando não é esclerose múltipla: abordagem baseada em casos

Zaira Fernanda Martinho Nicolau1, Enedina Maria Lobato de Oliveira2, Denis Bernardi Bichuetti2

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disease that affects the central nervous system (CNS) and is the most frequent cause of non-traumatic neurologic disability in young and middle-age adults in specific communities1,2. The first symptoms usually appear between 20 and 40 years of age, affects more frequently women than men3, and has a greater incidence at the extremes of latitude4.

Early symptoms of MS are probably due to axonal demyelination, which leads to the slowing or blockade of neural conduction; and the resolution of the inflammatory edema associated to partial or total remyelination causes symptoms regression in the early years of the disease5. Most patients have a relapsing-remitting clinical course that can evolve to a secondary progressive phase within 15 to 20 years, and 15% present a slowly progressive disease without relapses6. Since some of the disease’s symptoms are not specific and MS occurs at an age range that overlaps other autoimmune diseases, its differential diagnosis includes systemic and neurologic inflammatory conditions such as Lupus, Sjogren, Behcet and Susac’s syndrome, to name a few, specific infectious diseases (HIV, hepatitis B and C and HTLV associated myelopathy), some metabolic and degenerative diseases, and, sometimes, primary and secondary neoplasms of the CNS, specially in progressive courses7.

1Universidade Federal de São Paulo, Sao Paulo SP; Brazil; 2Universidade Federal de São Paulo, Disciplina de Neurologia, Sao Paulo SP; Brazil.
Correspondence: Denis Bernardi Bichuetti; Disciplina de Neurologia - UNIFESP; Rua Botucatu, 740; 04023-900 São Paulo SP; Brasil; E-mail: bichuetti@unifesp.br
Conflict of interest: There is no conflict of interest to declare.
Disclosures: Bichuetti DB has received speaking/consulting honoraria from Bayer Health Care, Biogen Idec, Merck Serono, Genzyme-Sanoﬁ and TEVA and had travel expenses to scientiﬁc meetings sponsored by Bayer Health Care, Merck Serono and TEVA. Oliveira EML has received speaking/consulting honoraria from Bayer Health Care, Biogen Idec, Merck Serono, Genzyme-Sanoﬁ and TEVA and had travel expenses to scientiﬁc meetings sponsored by Bayer Health Care, Merck Serono and TEVA. Nicolau ZFM has nothing to disclose.

Received 30 April 2015; Received in final form 25 July 2015; Accepted 13 August 2015.
The hallmark for any MS diagnostic criteria is the identification of CNS lesions disseminated in time and space, i.e., occurring in more than one site in different moments of one’s lifetime, and this can be achieved with a combination of clinical and paraclinical exams. A conceptual and objective framework for performing the differential diagnosis of MS does not exist, furthermore it can change from site to site, as infections and inflammatory diseases have different prevalence around the world. Red flag is a term that denotes clinical or paraclinical signs that do not correspond to common MS findings, and can be divided into MRI and clinical red flags.

The European MAGNIMS group defined, by consensus meetings, MRI red flags in the setting of clinically suspected MS, which suggest alternative diagnosis when present. By the same methodology, and international data-driven and consensus-based diagnostic approach, presented a list of major, intermediate and minor clinical symptoms (neurological or not) that should raise suspicion against the diagnosis of MS. All clinician caring for patients with MS must know and use these consensus statements to guide appropriate clinical, radiological, and/or laboratory tests that should be done to exclude alternative diagnoses to MS and guide adequate treatment.

The aim of this study was to analyze the clinical and paraclinical features of patients that were initially diagnosed with MS, but whom in fact had an alternative disease. This information is important to assist clinicians with cases of atypical MS clinical presentations, in which the treatment and prognosis depends upon a correct formulation of the diagnosis.

METHOD

The Neuroimmunology Clinic of the Universidade Federal de São Paulo (UNIFESP) is a public tertiary care center focused on caring for patients with multiple sclerosis and other demyelinating diseases, established in 1994, and located at Hospital São Paulo. From 1994 to 2014 the clinic has evaluated 1,599 patients, including 988 with MS and 116 with neuromyelitis optica; the remaining 495 patients (31% of all) harbored an alternative diagnosis. This last group comprises patients with vascular disease of the CNS, metabolic disorders, non-demyelinating inflammatory disease, infectious diseases, systemic clinical diseases, psychiatric or psychogenic disorders and functional symptoms, that were first diagnosed or suspected to have MS and sent for our evaluation and follow-up. Some of these patients had obvious signs and symptoms against MS, but some demanded extra investigation to have a final and proper diagnosis established.

We selected patients sent for evaluation and follow up at the clinic with a previously stated diagnosis of MS, which were reviewed by the staff and had an alternative final diagnosis and the exclusion of MS as the cause of their signs and symptoms, seen consecutively from 2010 to 2013. Patients with a clear evidence of exclusively vascular disease of the CNS (i.e., with more than 50 years old and classic vascular risk factors), patients that presented with predominant peripheral nervous system symptoms, psychological or psychiatric disease and metabolic or hormonal disorders were excluded from this study due to an obvious alternative diagnosis, thus not representing a diagnostic challenge. Patients with a final diagnosis of neuromyelitis optica were also excluded from this analysis, as they have a very distinct presentation to MS. We reviewed each patient’s clinical chart, MRI of the brain and spinal cord and cerebrospinal fluid (CSF) analysis to conduct a descriptive study of the signs and symptoms that led to an initial diagnosis of MS and further present each case’s red flags that signaled the alternative diagnosis, based on previously published consensus statements. When available, treatment options for each case are also described.

All patients included in this study took part in a prospective registry of inflammatory and demyelinating disease ongoing in our unit that was approved by the institutional ethic committee and each patient signed an informed consent form.

RESULTS

Nine patients that fulfilled the study’s inclusion and exclusion criteria are described in this study (Table 1).

Clinical data

The mean age of symptom’s onset was 34 years, six (66.7%) patients were female and three (33.3%) were male. Patients had been previously told they had MS for a mean of two years (Table 1). There was a mean of three typical symptoms and four clinical red flags per patient (Table 2).

MRI data

All patients had their MRI performed more than one time except patient six. The scans (Figures 1 to 3) were evaluated by the clinic’s staff and neuroradiology team at each appointment and classified according diagnostic criteria for MS and the presence of radiological red flags (Table 2).

Patient case examples

The patients’ summaries illustrate their chronological symptoms progression and conduct held to pursue the correct diagnosis after the suspicion that the case was not MS. Each patient’s final diagnosis is also organized in Tables 1 and 2.

Patient 1

At age 38 presented an acute episode of hypoesthesia, tetraparesis, sudden bilateral amaurosis, seizure and...
**Table 1. Demographic and clinical characteristics of the analyzed patients.**

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age (years)</th>
<th>Sex</th>
<th>First symptom</th>
<th>Clinical Course (progressive x relapsing)</th>
<th>Age at first symptom</th>
<th>Sex</th>
<th>Age at first evaluation at UNIFESP (years)</th>
<th>Therapies before diagnostic definition</th>
<th>Final diagnosis</th>
<th>Therapies after diagnostic definition</th>
<th>MS: multiple sclerosis; CNS: central nervous system.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>F</td>
<td>F</td>
<td>Relapsing</td>
<td>36</td>
<td>F</td>
<td>43</td>
<td>Methylprednisolone pulse therapy, interferon beta-1a</td>
<td>Multiple cerebral emboli due to atrial mixoma</td>
<td>Prednisolone</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>F</td>
<td>F</td>
<td>Relapsing</td>
<td>53</td>
<td>F</td>
<td>53</td>
<td>Levodopa, Yellow fever vaccine associated encephalitis</td>
<td>Susac syndrome</td>
<td>Prednisolone</td>
<td>Prednisolone, cyclophosphamide, and tocilizumab</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>F</td>
<td>F</td>
<td>Relapsing</td>
<td>21</td>
<td>F</td>
<td>21</td>
<td>Methylprednisolone sodium succinate</td>
<td>Syringomyelia</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>M</td>
<td>M</td>
<td>Relapsing</td>
<td>27</td>
<td>M</td>
<td>27</td>
<td>Methylprednisolone pulse therapy, interferon beta-1a</td>
<td>Vascular injury due to nutritional deficiency</td>
<td>Prednisolone</td>
<td>Prednisolone, IV methylprednisolone, IV cyclophosphamide, and tocilizumab</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>F</td>
<td>F</td>
<td>Relapsing</td>
<td>29</td>
<td>F</td>
<td>38</td>
<td>Methylprednisolone pulse therapy, interferon beta-1a</td>
<td>Susac syndrome</td>
<td>Prednisolone</td>
<td>Prednisolone, pulse IV cyclophosphamide</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>F</td>
<td>F</td>
<td>Relapsing</td>
<td>39</td>
<td>F</td>
<td>41</td>
<td>Vitamin B12, Polyneuromyopathy and myelopathology due to severe nutritional deficiency</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>35</td>
<td>M</td>
<td>M</td>
<td>Relapsing</td>
<td>35</td>
<td>M</td>
<td>35</td>
<td>Methylprednisolone pulse therapy</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>36</td>
<td>M</td>
<td>M</td>
<td>Relapsing</td>
<td>36</td>
<td>M</td>
<td>36</td>
<td>Methylprednisolone pulse therapy</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>F</td>
<td>F</td>
<td>Relapsing</td>
<td>33</td>
<td>F</td>
<td>33</td>
<td>None</td>
<td>Mithocondrial disorder</td>
<td>None</td>
<td>Mithocondrial disorder</td>
</tr>
</tbody>
</table>

**Table 2. Clinical, laboratory, MRI characteristics and red flags.**

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Typical MS symptoms</th>
<th>MS-CIF</th>
<th>Clinical Red Flags</th>
<th>C-SFOB</th>
<th>Paraclinical red flags</th>
<th>MR Red Flags***</th>
<th>MRI Flagged for MS*</th>
<th>Clinical Red Flags</th>
<th>Paraclinical Red Flags</th>
<th>MR Red Flags***</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Limb weakness, hypoesthesia, neurogenic bladder</td>
<td>1.0</td>
<td>NA</td>
<td>1.0</td>
<td>NA</td>
<td>1.0</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Limb weakness, hypoesthesia, neurogenic bladder</td>
<td>1.0</td>
<td>NA</td>
<td>1.0</td>
<td>NA</td>
<td>1.0</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Limb weakness, hypoesthesia, neurogenic bladder</td>
<td>1.0</td>
<td>NA</td>
<td>1.0</td>
<td>NA</td>
<td>1.0</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Zaira Fernanda Martinho Nicolau et al. Why this is not multiple sclerosis
| Limb weakness, paresthesia, diplopia, hypoesthesia | Seizure, Headache, mucosal ulcers, aggression, early dysarthria and dysphagia | NeuroBehçet | Up to 250.0 cell/mm³ with neutrophil predominance | NA | CSF pleocytosis | - | + | + | + | + | Absence of spinal cord lesion. Most lesions are large and subcortical or large and in the brainstem.

5 | Limb weakness, fatigue, gait ataxia, sensory loss, spasticity | Extrapyramidal features, retinopathy, early and severe dysarthria, early cognitive impairment and abrupt onset | Susac syndrome or Primary CNS vasculitis | 13.0 | Presence | Rethynopathy Brain biopsy with necrotizing vasculitis | - | + | + | + | + | Absence of temporal horn lesion and infratentorial lesion. Most lesions are large and subcortical.

6 | Limb weakness, pain, spasticity | Polyradiculopathy, myopathy and muscle pain, myotrophy, past medical history of gastric bypass surgery | Polyneuromyopathy and myelopathy due to severe nutritional deficiency | 2.0 | NA | Anemia, low serum vitamin D, iron, copper and zinc | + | + | - | + | + | No

7 | Gait ataxia, spasticity, sensory loss, tetraparesis, urinary incontinence | Retinopathy, hearing loss, cutaneous involvement, early severe cognitive impairment and dysarthria | Susac syndrome | 2.0 | Absence | Skin biopsy with leukocytoclastic vasculitis, hearing loss on audiologic evaluation, elevated CSF protein (114mg/dL) | - | - | - | - | - | Punctiform lesions, diffusion restriction and lesions restricted to the corpus callosum (snowball lesions)

8 | Hemiparesis, sensory loss, spasticity | Headache, seizure, thrombotic events, progressive severe early hemiparesis | Primary CNS lymphoma (under review) | 9.0 | NA | Brain biopsy not typical of MS with atypical lymphocytic infiltrate | - | - | - | - | - | Exclusively unilateral hemispheric lesion

9 | Depression, vertigo | Headache, hearing loss, bilateral ptosis | Mitochondrial disorder (under review) | 1.0 | NA | - | - | - | + | - | Absence of temporal horn lesion, infratentorial and spinal cord lesion. Most lesions are small, round and scarce in the subcortical white matter.

MS: multiple sclerosis; CSF: cerebrospinal fluid; OCB: oligoclonal bands; CNS: central nervous system; NA: not analyzed; DIS: dissemination in space; DIT: dissemination in time; NA: not available. * Brain lesions were judged typical if most of them were periventricular, ovoid, larger than 3mm and perpendicular to the corpus callosum. If present, spinal cord lesion were judged typical if extending within less than 2 vertebral bodies and occupying only one spinal cord compartment (lateral, anterior or dorsal colom). ** Modified Barkhof-Tintoré criteria was used as per McDonald 2005 diagnostic criteria. DIS (3 out of 4): at least one lesion with enhancement or 9 total lesions, 3 periventricular, 1 justacortical or one infratentorial or spinal cord lesion. DIT: any new lesion. *** Swanton criteria was used as per McDonald 2010 diagnostic criteria. DIS: more than one lesion in more than one topography (periventricular, justacortical, brainstem and spinal cord). DIT: enhancing or nonenhancing lesions in the same scan or any new lesion. **** As judged by the staff according to current literature. 
aggression outbreaks, treated with pulse IV methylprednisolone and interferon-beta-1a. One year later she presented acute speech disturbances, right hemiparesis, vision loss and cognitive decline. She had been operated for a left atrial mixoma at 29 years-old.

After evaluation, her MRI lesions were judged to be of vascular origin (Figure 1) and her visual loss due to branch retinal artery occlusion. Her mixoma had recurred and she was sent for surgery for lesion removal; a brain biopsy excluded CNS vasculitis and demyelinating lesion, thus confirming the diagnosis multiple cerebral emboli due to atrial mixoma.

**Patient 2**

At age 52 presented an episode of somnolence for 24h followed by progressive left hemiparesis, tremor and urinary incontinence two weeks after being vaccinated for yellow fever and travelling to Costa Rica. Her MRI (Figures 1 and 2) disclosed large lesions with patchy enhancement even three

---

**Figure 1.** Brain MRI from patients described on Table 1.

**Figure 2.** T1 post gadolinium MRI from patients 2, 5 and 8.
months after vaccination. A brain biopsy was performed to discard CNS vasculitis, which disclosed mild inflammatory reaction. She was treated with IV and oral steroids with symptom’s improvement, although, remained with mild neurological impairment on follow up, but without further clinical or MRI activity. Her final diagnosis remained a possible post vaccine acute demyelinating encephalomyelitis or vaccine encephalitis.

**Patient 3**

At age 24 presented left arm and legs paresthesia associated with mild sensory ataxia with progressive onset within a few days; she was an athlete of the handball university team. Her first MRI was judged to be compatible with demyelinating lesion and she was treated with pulse IV methylprednisolone with moderate improvement. She remained with occasional upper limb paresthesia but presented no other symptoms three years later. Her MRI was reviewed and the lesion was concluded to be a cervical syringe (Figure 3).

**Patient 4**

At age 29 presented right progressive hemiparesis within weeks and partial motor seizure. A parietal mass lesion was operated and biopsy disclosed an inflammatory demyelinating lesion (Figure 1). On the following 10 months he presented recurrent episodes of left hemiparesis and somnolence with a brainstem and internal capsule lesion. Also, two episodes of fever and meningitis with neutrophils predominance but aseptic cultures, treated with steroids and antibiotics. His past medical history was reviewed and disclosed recurrent oral ulcers since he was a teenager, but no genital ulcers. His final diagnosis is a severe presentation of Neuro Behçet. He has failed immunosuppression with cyclophosphamide and tocilizumab and has currently been initiated on infliximab.

**Patient 5**

At age 29 presented acute painful bilateral blurred vision, arm and lower leg weakness, treated with steroids and started on interferon beta, which she used for nine years. On the subsequent years she presented recurrent episodes of neurological impairment, including dysarthria, dysphagia, hearing loss, ataxia and spasticity, all with sudden onset, leaving her with moderate to severe neurological impairment. Although she presented oligoclonal bands in the CSF and mild CSF pleocytosis on repetitive analysis; her MRI and clinical history where reviewed and judged not typical for MS. She was started on pulse IV cyclophosphamide but presented a new episode of multiple neurological deficits with increased number of brain lesions (Figure 1 and 2, image 5a). A brain biopsy was performed to rule out lymphoma and confirmed the diagnosis of necrotizing CNS vasculitis.

**Patient 6**

At age 39 she started a progressive course of muscle weakness and pain, muscle spasms and subtle left eye vision loss. Two years later she was bedbound, could not sustain herself seated without help, moderate tetraparesis but with mild hypereflexia, absence of Babinski sign, normal sensory exam, severe muscle pain on palpation and a Kwashiorkor physical appearance. She had performed a gastric bypass surgery 5 years before the symptoms started and was using only intramuscular vitamin B12 replacement therapy. Although her MRI (Figures 1 and 3) was judged compatible to MS, there were many clinical red flags (Table 2). Indeed, an extensive investigation disclosed multiple nutritional deficits and she improved with vitamin replacement therapy. One month later she presented moderate improvement, had mild muscle pain, could stand up with help and had resolution of generalized edema. Multiple nutritional deficiencies are known to cause central and peripheral neurologic injuries \(^1\), still, the patient was sent for further follow-up and MRI exams.

**Patient 7**

At age 35 presented progressive visual and hearing loss, cognitive difficulties, tetraparesis, gait ataxia and urinary incontinence for 3 months, associated to livedo reticularis. At first evaluation he was on prednisone associated to fingolimod for presumed MS. His complimentary investigation disclosed signs of systemic vasculitis and laboratory and MRI exams not compatible with MS (Table 2). He was started on pulse IV cyclophosphamide and later switched...
to oral azathioprine; 2 years later he presented mild cognitive deficit and moderate gait spasticity. Retinal angiography was normal, but only performed after intense immunosuppression.

**Patient 8**

At age 36 presented progressive left hemiparesis, headache and partial motor seizures. His MRI disclosed an extensive right side lesion with patchy enhancement (Figures 1 and 2) that presented marked improvement with IV steroids. He had a brain biopsy that disclosed normal results, but the lesion recurred upon steroids withdrawal. A second biopsy performed after a month without steroids was suggestive of central nervous system T cell lymphoma and he was sent for hematological evaluation and treatment.

**Patient 9**

This patient was referred to us at age 33 due to abnormal findings on MRI. She referred progressive visual loss since 16 years old due to Stargardt disease (juvenile onset macular degeneration, also present in her brother), depression, bilateral hearing loss and hypothyroidism. She was born to consanguineous parents (first degree cousins) and upon examination it was noted bilateral ptosis but no diplopia. She was sent to the neuromuscular unit for mitochondrial disease evaluation, which was considered the cause of her MRI lesions.

**Red flags in the diagnostic process**

MRI red flags were found in 89% of these referrals, with a mean of three red flags per patient, and only patient six presented typical MS lesions fulfilling imaging criteria. Clinical red flags can be rated as being of major, intermediate or minor significance in suggesting an alternative diagnosis to MS. According to Miller’s classification, there were a total of 37% major, 13% intermediate and 8% minor clinical red flags among these patients. Other atypical symptoms, which are described as any non typical symptoms in the guideline from the International Panel on the diagnosis of MS and not specifically described in Miller’s classification, totaled 42% of all red flags.

**DISCUSSION**

The presence of neurologic symptoms compatible with MS, which can be mostly unspecific, or even radiological features common in this disease, should not be enough to narrow the clinician diagnoses hypothesis to only MS. To establish a correct diagnosis it is essential that the physician combine the patient’s detailed past medical history, clinical findings, physical examination, MRI, laboratory tests and also take the known red flags into consideration. Patients with a misdiagnosis may be injured by the use of inadequate therapies and consequently do not receive a proper management, declining ones clinical condition and quality of life. The knowledge of the clinical course of MS and its clinical and paraclinical red flags are important since similar symptoms are reported in other diseases, such as neuromyelitis optica and acute disseminated encephalomyelitis, and even other inflammatory and vascular diseases, as depicted in this series.

Paraclinical tests are valuable tools for the diagnosis process of MS. MRI of the brain and spinal cord is the most sensitive investigational technique and the presence of imaging red flags can give important diagnostic hints. The analysis of the MRI images should be meticulous and include the presence of specific characteristics, such as periventricular location with ovoid shape and perpendicular to the corpus callosum, dissemination in space and time, and the correlation with the patient’s clinical symptoms. This last item is very important, since only MRI abnormalities are, up to day, no sufficient to establish one’s diagnosis of MS, as neither Barkhof-Tintoré nor Swanton Criteria are 100% specific. For instance, patient six had a compatible MRI, but when analyzed together with her clinical aspects, the diagnosis of MS was doubted.

The same thought should be held when analyzing the CSF. The presence of oligoclonal bands (OCB), which is common in patients with MS, should not be taken solely into consideration if specific clinical aspects of the disease are not present. Patient five had OCB bands, but her clinical symptoms were not clearly of MS, which lead to investigations that resulted in an alternative diagnosis. The CSF can thus add useful information about inflammatory and immunological alterations in patients with clinical presentation or radiological findings that are not typical of the disease, but should also never be valued without paying attention to the patient’s clinical presentation and MRI.

A whole-patient clinician approach is the most important attitude held by the physician, who should organize his medical reasoning by merging the clinical and paraclinical features, along with the proper identification of red flags, to succeed in diagnosing MS correctly. Isolated all these features are important, but their real significance is achieved only when they are analyzed together.

The limitations of our study are those of an observational cohort, thus not performed in a controlled setting. Furthermore, it was conducted within a western South-American population tertiary care hospital, thus the same study might yield distinct results or present other differential diagnosis if performed in other settings. Our aim is to expose to physicians faced with cases that appear to be MS that the existing guidelines on diagnosis of MS and the known red flags should be followed to perform an accurate diagnosis and minimize the chance of making a mistaken diagnosis and treatment, as this is important for each patient’s management, treatment, prognosis and quality of life.


