

Why this is not multiple sclerosis: a case based approach

Quando não é esclerose múltipla: abordagem baseada em casos

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ABSTRACT

Objective: To present a case series of patients previously diagnosed as multiple sclerosis (MS) which were later confirmed as an alternative diagnosis, and describe the clinical and paraclinical signs that led to this change. **Method:** Nine patients are described. We reviewed the patient's clinical chart, magnetic resonance images (MRI) and cerebrospinal fluid. **Results:** There was a mean of three typical symptoms of MS and four clinical red flags per patient. MRI red flags were found in 88,9% of all referrals, with a mean of 3 encountered per patient. **Conclusion:** We identified that, not only the misdiagnosed patients did not fulfill MS diagnosis criteria, but also how the described red flags are a useful tool in the differentiation of MS from other diseases. This data is important for guiding future diagnosis, especially for general clinicians and neurologists, which directly interfere with the patient's management, treatment, prognosis and quality of life.

Keywords: multiple sclerosis, diagnosis, clinical, MRI red flags.

RESUMO

Objetivo: Apresentar uma série de casos de pacientes previamente diagnosticados como esclerose múltipla (EM) que tiveram um diagnóstico final alternativo, e descrever os sinais clínicos e paraclínicos que levaram à esta mudança. **Método:** Nove pacientes encaminhados para confirmação diagnóstica de EM. Revisamos os prontuários, imagens de ressonância magnética (MRI) e líquido cefalorraquidiano. **Resultados:** Houve uma média de três sintomas típicos de EM e quatro sinais de alerta por paciente. Sinais de alerta de ressonância magnética foram encontrados em 88,9% dos casos, com média de 3 por paciente. **Conclusão:** Identificou-se que, não só os pacientes com diagnóstico incorreto não cumprem critérios de diagnóstico, mas também como os sinais de alerta já descritos são uma ferramenta útil na diferenciação de EM de outras doenças. Esta informação é importante para orientar a assertividade diagnóstica, especialmente para os clínicos e neurologistas gerais, com interferência direta no tratamento, prognóstico e qualidade de vida do paciente.

Palavras-chave: esclerose múltipla, diagnóstico, clínico, ressonância magnética.

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 communities^{1,2}. 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.

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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^{8,9,10}. 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^{11,12}. 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^{11,12,13}.

The European MAGNIMS group defined, by consensus meetings, MRI red flags in the setting of clinically suspected MS, which suggest alternative diagnosis when present¹³. 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 MS¹². 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 Paulo¹⁴. 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 symptoms¹⁴, 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^{12,13,14}.

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^{15,16}. 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^{11,12,13}. 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 (3.3%) 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 pursuit 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.

Patient ID	Age at first symptom	Sex	First symptom	Clinical Course (progressive x relapsing)	Age at MS diagnosis (suspicion) at UNIFESP	Age at first diagnosis evaluation	Therapies before diagnostic definition	Final diagnosis	Therapies after diagnosis definition
1	36 years	F	Aggression outbreaks, left hand stiffness, hypoesthesia of the lower limbs and sudden bilateral amaurosis	Relapsing	38 years	43 years	Methylprednisolone pulse therapy; interferon beta-1a	Multiple cerebral emboli due to atrial mixoma	Suspension of interferon beta-1a
2	53 years	F	Somnolence, tremor and left side weakness	Progressive within weeks	53 years	53 years	Levodopa	Yellow fever vaccine associated encephalitis	Prednisone
3	21 years	F	Paresthesia, walking difficulty and sensory ataxia	Relapsing, single episode	21 years	21 years	Methylprednisolone sodium succinate	Syringomyelia	None
4	27 years	M	Paresthesia and limb weakness	Relapsing	27 years	27 years	Prednisone	NeuroBehçet	Prednisone, pulse IV methylprednisolone, IV cyclophosphamide and tocilizumab
5	29 years	F	Blurred vision, walking difficulty	Relapsing	29 years	38 years	Methylprednisolone IV pulse therapy, interferon beta-1b, Interferon beta-1a, paroxetine Vitamin B12	Susac syndrome or Primary CNS vasculitis	Prednisone and pulse IV cyclophosphamide
6	39 years	F	Lower back and thoracic pain, difficult walking	Progressive	39 years	41 years	Vitamin B12	Polyneuropathy and myelopathy due to severe nutritional deficiency	Parenteral nutrition, copper, zinc, iron and B12 supplementation
7	35 years	M	Visual and hearing loss, cognitive impairment and ataxia	Relapsing-Progressive	35 years	35 years	Pulse IV methylprednisolone, fingolimod and prednisone	Susac syndrome	Prednisone, azathioprine and pulse IV cyclophosphamide
8	36 years	M	Headache, hemiparesis and partial motor seizure	Progressive	36 years	36 years	Oral steroids	Primary CNS lymphoma (under review)	Dexamethasone and hematological consultation
9	33 years	F	Headache and visual loss	Progressive	33 years	33 years	None	Mitochondrial disorder (under review)	Sent for the Neuromuscular unit for evaluation

MS: multiple sclerosis; CNS: central nervous system.

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

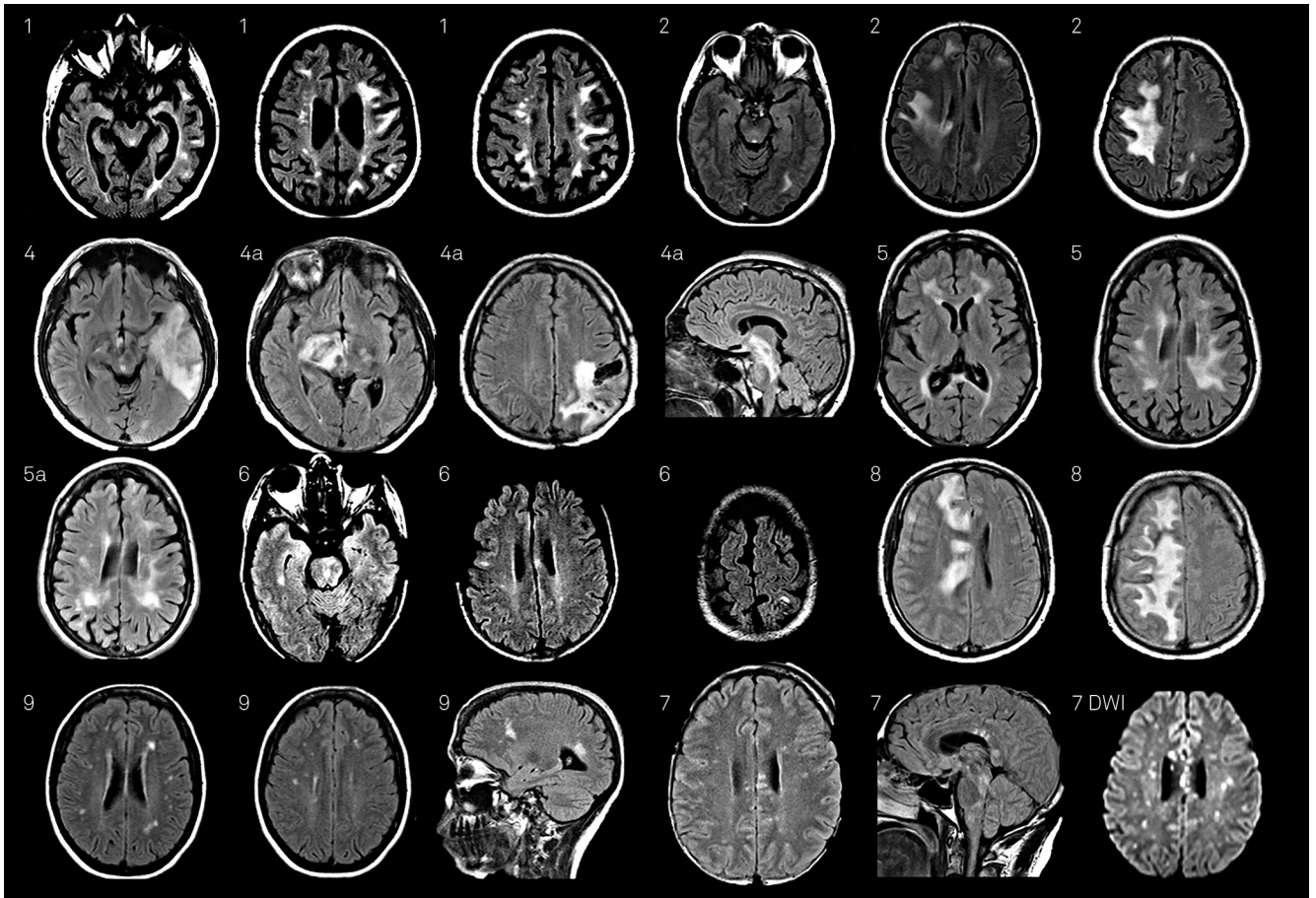
Patient ID	Typical MS symptoms	Clinical Red Flags	Final diagnosis	CSF cells (cell/mm ³)	CSF OCB	Paraclinical red flags	MRI judged typical for MS*	Barkhof-Tintoré DIS**	Barkhof-Tintoré DIS***	Swantón DIS***	Swantón DIT***	MRI Red Flags ****
1	Limb weakness, hypoesthesia, neurogenic bladder	Cardiac disease, thrombotic events, seizure, sudden bilateral painful amaurosis, aggression outbreaks, early cognitive decline with dysarthria.	Multiple cerebral emboli due to atrial mixoma	1.0	NA	Atrial mixoma Branch retinal artery occlusion on ophthalmologic evaluation Normal brain biopsy	-	+	+	-	-	Absence of temporal horn lesion, infratentorial and spinal cord lesion. Most lesions are subcortical
2	Limb weakness, paresthesia, urge incontinence, spasticity	Myalgias, anxiety, somnolence, abrupt onset, onset after age 50	Yellow fever vaccine associated encephalitis	1.0	NA	Brain biopsy with atypical inflammatory infiltrate and white matter with gliosis	-	+	+	-	-	Absence of temporal horn lesion, infratentorial and spinal cord lesion. Most lesions are large and subcortical, all enhance at the same time
3	Limb weakness, paresthesia, sensory ataxia	Normal neurological evaluation	Syringomyelia	1.2	NA	Normal visual evoked potentials	-	+	+	-	-	Lesion compatible with syringomyelia. No lesions on brain MRI.

Continue

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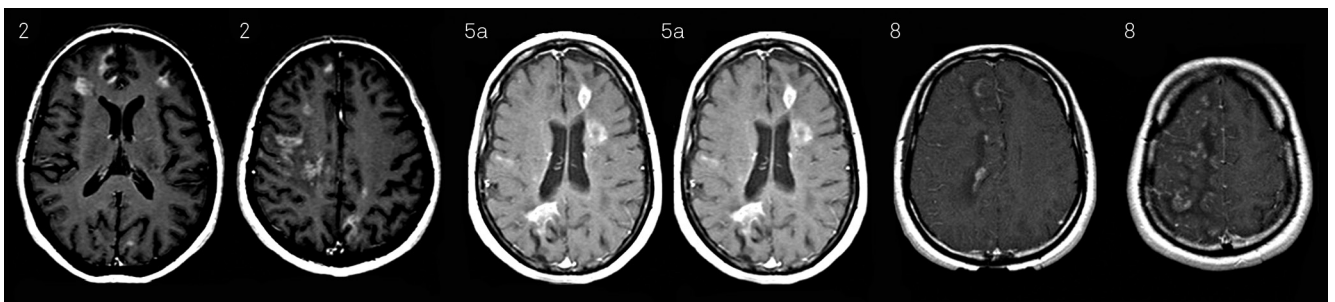
4	Limb weakness, paresthesia, diplopia, hypoesthesia	Seizure, Headache, mucosal ulcers, aggression, early dysarthria and dysphagia	NeuroBehçet	Up to 250.0 cell/mm ³ with neutrophil predominance	NA	CSF pleocytosis	-	+	+	+	+	Absence of spinal cord lesion. Most lesions are large and subcortical or large 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, amyotrophy, 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 audologic 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 collum). ** 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, 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 literature¹¹³.



Numbers correspond to same patient on Table 1; images with letters are from the same patients at different time points. All are FLAIR images except image 7 DWI, which is a diffusion weighted image. Note that only patient 6 presents typical periventricular (including temporal horn) and justacortical multiple sclerosis lesions, all other images present at least one red flag as presented on Table 2.

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



Numbers correspond to the same patients on Table 1 and exact same imaging time point as on Figure 1. Note that these images present a contrast enhancement pattern not typical for MS, thus representing red flags as discussed on Table 2.

Figure 2. T1 post gadolinium MRI from patients 2, 5 and 8.

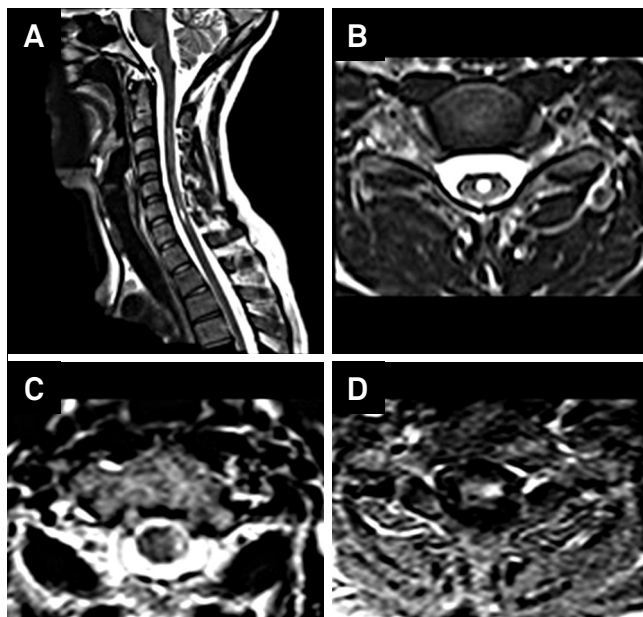
aggression outbreaks, treated with pulse IV methylprednisolone and interferonbeta-1a. One year later she presented acute speech disturbances, right hemiparesis, vision loss and cognitive decline. She had been operated for a left atrial mixoma at 29 years-old.

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



A: Sagittal T2 image disclosing central lesion without edema; B: axial T2 image disclosing this same lesion to be an enlargement of the central spinal canal (this lesion does not enhance); C: axial T2 image disclosing typical multiple sclerosis lesion in the lateral funiculus; D: axial T1 post gadolinium disclosing enhancement of the lesion shown in C.

Figure 3. Spinal cord images from patients 3 (top) and 6 (bottom).

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 occasionally 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 were 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 hyperreflexia, 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 injuries¹⁷, 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 angiogram 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 MS¹². According to Miller's classification¹², 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 MS⁸ and not specifically described in Miller's classification¹², 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 consideration¹². 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 life¹⁸. 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 technique¹⁹ and the presence of imaging red flags can give important diagnostic hints¹³. 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 time⁸, and the correlation with the patient's clinical symptoms^{13,20,21}. This last item is very important, since only MRI abnormalities are, up to date, no sufficient to establish one's diagnosis of MS, as neither Barkhof-Tintoré nor Swanton Criteria are 100% specific^{21,22}. 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 disease⁸, 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.

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