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REVIEW

Inflammatory demyelinating disease of central nervous system in clinical practice

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Abstract

The diagnosis and treatment of central nervous system (CNS) idiopathic inflammatory demyelinating diseases have been recurrently reviewed over the past two decades. In this group of diseases, Multiple Sclerosis (MS) is the most frequent CNS pathology. However, MS diagnosis requires a systematic exclusion of alternative diagnoses. Our objective with this review is to help standardize and optimize the use of actual diagnosis criteria of inflammatory demyelinating diseases of the CNS, in clinical practice. Its focus is on exclusion of potential MS mimics, differentiating between MS and non-MS idiopathic inflammatory demyelinating conditions, as well as in the diagnosis of common initial isolated clinical syndromes.

Keywords: Multiple sclerosis, Differential diagnosis, Red flags.

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Introduction

Diagnostic criteria for inflammatory demyelinating diseases (IDDs) of the central nervous system (CNS) have developed over the past 10 years. The capacity to make an accurate diagnosis in this group of diseases as early as possible is important for patient management, counseling, and optimal therapy. Multiple Sclerosis (MS) is the most frequent CNS pathology of the group of IDDs, but MS diagnostic criteria emphasize that an alternative explanation for the clinical presentation must be considered and excluded before a diagnosis of MS can be made. So is important to consider other inflammatory diseases before the diagnosis of MS is made in a neurological clinically isolated syndrome (CIS) or in autoimmune inflammatory syndrome.

Three broad categories of diseases should be considered in the differential diagnosis work-up of CNS disease suggestive of IDDs: non-IDDs with symptoms and signs that may mimic IDDs; MS and spectrum of idiopathic inflammatory demyelinating diseases of the CNS; and IDDs associated to other autoimmune diseases. Non-IDDs include patients who have an infectious, neoplastic, congenital, metabolic or vascular disease with clinical similar presentations of patients with IDDs. In non-MS IDDs, the spectrum of idiopathic inflammatory demyelinating diseases of the CNS encompasses, MS variants, neuromyelitis optica spectrum disorders (NMOSD) and acute disseminated encephalomyelitis (ADEM). In the third group of other IDDs, IDDs associated at other autoimmune diseases, connective tissue diseases, are the most frequent mimickers of MS, because demyelinating syndromes may occur as the first manifestations before the systemic features.

In this paper, we first discuss the recent diagnosis criteria for the most frequent IIDs, and then we discuss specific cases that illustrate the clinical practice.

Multiple sclerosis: diagnosis

MS is a chronic immune-mediated inflammatory disease that affects the CNS and is the most frequent cause of non-traumatic neurological disability in young and middle-age adults in specific communities [1, 2]. Histologically, perivenular inflammatory lesions (consisting of mononuclear infiltrations) that are evident in the earlier phases of the disease, resulting in demyelinating plaques, are the pathological hallmark of MS [3]. Although the autoimmune hypothesis in the base of the pathological process of the disease is supported by concrete clinical data—such as the efficacy of immunomodulatory treatments—the initial stimulus, which provoke the immune-mediated cascade, remains unknown [4]. Environmental, genetic and infectious factors with interaction between them appear to play important roles in MS pathogenesis [5, 6]; however, MS is not a homogeneous disease and presents several distinct immunopathological profiles that are translated in the different MS clinical subtypes (e.g. relapse-remitting MS, progressive MS) [7]. MS symptoms are usually characterized by loss of motor and sensory function, that results from immune-mediated inflammation, demyelination and subsequent axonal damage [8]. Clinically, most MS patients experience recurrent episodes (relapses) of neurological impairment [9]. The first symptoms usually appear between 20 and 40 years of age and the disease affects women more frequently than men. In the natural history of MS, most patients have a relapsing-remitting clinical course that can progress to a secondary progressive phase within 15 to 20 years; and 15% of patients present a slowly progressive disease without relapses (progressive MS) [9–11].

CIS, the most frequent type of MS clinical presentation, is a first acute or subacute episode of neurological symptoms, with presumed inflammatory demyelinating lesion in the CNS; CIS lasts more than 24 hours and occurs in the absence of fever or infection [12]. These clinical event can be monofocal if the clinical features were referable to a single CNS lesion (CIS is generally monofocal) but in 10–15% of cases the event can also be multifocal if the clinical features could be attributed to more than one CNS site [13]. The four most common CIS syndromes seen at presentation in the MS diagnosis process include those affecting the optic nerve [optic neuritis (ON)], spinal cord (myelitis) brain stem/cerebellum and cerebral hemispheres [12]. **Table 1** presents the more frequent inaugural clinical CNS events with presumed inflammatory demyelinating cause in which is fundamental to distinguish MS from the other spectrum of idiopathic IDDs of the CNS.

After a CIS, the time to onset of a relapse, which corresponds to the diagnosis of clinically definite MS (CDMS), varies from several months to more than 10 years [14, 15]. In the phase of CIS the capacity to make an accurate diagnosis in crucial: although CIS is typically the first MS episode, it is important to consider the principal differential diagnosis that can mimic MS disease [16]. Achieving a prompt diagnosis of MS is essential, namely because the availability of disease-modifying treatments is growing, and these drugs are thought to be particularly effective in the early phases of the disease [16, 17]. But, to this point, no single test—including tissue biopsy—can provide a definite diagnosis of MS. So MS diagnostic criteria, have been modified and systematic reviewed in the last years as new evidence and expert recommendations have emerged [18–20]. The hallmark for 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 [18]. This definition can be achieved with a combination of clinical and paraclinical exams, which is the base of 2010 McDonald criteria [19].

Additionally, the diagnostic criteria require exclusion of alternative diagnoses that can mimic MS either clinically or radiologically. In formal terms, the diagnosis can

Table 1. Inaugural clinical CNS event with presumed inflammatory demyelinating cause: optic neuritis, acute myelitis, encephalopaty.

Clinical events	Typical of MS diagnosis	Red flag to MS diagnosis—other demyelinating disease
Optic neuritis (ON)		
Clinical	– Unilateral ON; partial and mainly central visual blurring; pain on eye movement; normal disc or mild disc swelling	– Bilateral ON; altitudinal visual defect – Optic chiasm involvement
MRI	– Unilateral short-length lesions of optic nerve (increased T2 signal, gadolinium enhancement, and optic nerve swelling) – Disease dissemination in space (by involvement of at least two of five areas of the CNS) and dissemination in space	– Bilateral optic nerve involvement – Posterior nerve predominance (extension into the optic chiasm) – Extensive lesions of the optic nerve (more than half of its length)
Other paraclinical studies	– CSF positive OGBs – Rare CSF pleocytosis (≤50 cells/μL) – CSF protein: mildly elevated (<100 mg/dL) – Visual evoked potentials: prolonged P100 latencies and normal amplitudes	– Positive AQP4–IgG test – CSF negative OGBs – CSF pleocytosis (neutrophils and eosinophils) – CSF protein: often elevated (>100 mg/dL) – Optical coherence tomography: greater retinal nerve fiber layer thinning (not usually in MS-ON eyes)
Acute Myelitis		
Clinical	– Partial spinal cord syndrome	– Complete spinal cord syndrome, with paralysis below the level of the lesion and loss of sphincter control
MRI	– 1 vertebral segment long or less, occupying peripheral white matter tracts such as the dorsal columns	– Intramedullary MRI lesion extending over 3 contiguous segments (LETM) and extension of a cervical lesion into the brainstem (characteristic of NMOSD) – Lesion involvement in the central gray matter and associated with cord swelling, central hypointensity on T1-weighted sequences, and enhancement following IV gadolinium administration
Other paraclinical studies	– CSF positive OGBs – Rare CSF pleocytosis (≤50 cells/μL) – CSF protein: mildly elevated (<100 mg/dL)	– Positive AQP4–IgG test, CSF negative OGBs – CSF pleocytosis (neutrophils and eosinophils) – CSF protein: often elevated
A encephalopathic event		
Clinical	– New non-encephalopathic event occurs three or more months after a first encephalopathic event – Relapsing disease that occurs beyond a second encephalopathic event (first diagnosis as ADEM)	– Polysymptomatic presentation: monophasic ADEM – Two episodes consistent with ADEM separated by three months but not followed by any further events: multiphasic ADEM – Symptomatic Cerebral Syndrome with NMOSD-typical brain lesions (with Positive AQP4–IgG test: NMO diagnosis)
MRI	– New MRI findings consistent with revised radiologic criteria for dissemination in space – Presence of black holes, two or more periventricular lesions (high sensitivity for MS diagnosis)	– Multiple bilateral T2-enhancing supratentorial white matter lesions, usually large (>1–2 cm) and one or more lesions with gadolinium enhancement; – Longitudinal extensive lesions in spinal MRI – Lesions in the thalamus and basal ganglia – Brainstem lesions (in ADEM are more often located in the midbrain and are more often bilateral and symmetrical)
Other paraclinical studies	– CSF positive OGBs – Rare CSF pleocytosis (≤50 cells/μL) – CSF protein: mildly elevated (<100 mg/dL)	– Usually CSF negative OGBs – CSF pleocytosis (neutrophils and eosinophils) – CSF protein: often elevated

be made based on clinical presentation alone, but MRI should be done to support clinical diagnosis and rule out other disorders; associated with laboratory investigation ,which are fundamental to excluded to exclude non-MS pathologies [21, 22]. Cerebrospinal fluid (CSF) can add useful information about inflammatory and immunolog-

ical alterations in patients with clinical presentation or radiological findings similar to MS and allow the exclusion of MS mimickers (namely infectious and neoplastic conditions) [23, 24]. A typical CSF (i.e. a positive CSF for MS diagnosis) analysis result is the increase in immunoglobulin concentrations and 2 or more oligoclonal bands (OCBs), which is seen in more than 90% of the MS patients [25]. In primary progressive MS that require one year of disease progression, McDonald criteria highlight a positive CSF for diagnosis [19]. So, to establish a correct diagnosis it is essential that the physician combines the patient's detailed medical history, clinical findings, physical examination, MRI, laboratory tests and also take the known red flags into consideration. 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 [12].

The knowledge of the clinical course of MS and its clinical and paraclinical red flags are important since similar symptoms are reported in other non-MS IDDs, such as NMOSD, ADEM, and even other inflammatory diseases [26]. Paraclinical tests are valuable tools for the diagnosis of MS and MRI of the brain and spinal cord is the most sensitive investigational technique [27, 28]. European collaborative research network that studies MRI in multiple sclerosis (MAGNIMS) proposed MRI criteria to be applied in MS; MAGNIMS criteria are included in the most recent diagnostic criteria for MS, 2010 McDonald criteria (20).

Recent expert panel guideline papers have further reinforced the relevance of MRI in the context of differential diagnosis which included meticulous MRI image analysis with the presence of specific demyelinating lesions characteristics, dissemination in space and time, and the correlation with the patient's clinical symptoms [20, 28]. Typically MS lesions are hyperintense on T2-weighted, proton density or FLAIR imaging, and hypointense or isointense on T1 weighted imaging [29]. They are typically ovoid in shape, of small size (3–8 mm on average, although giant plaques may occur), located mainly in the periventricular white matter but are also common in the posterior fossa, spinal cord and in subcortical location. They tend to be perpendicular to the ventricles, involve the corpus callosum and U-fibers, and may enhance with Gd, especially during active inflammation, due to disruption of the blood brain barrier (BBB) [29, 30]. The perivascular orientation of MS lesions (i.e., the observation that most MS lesions develop around a vessel) is a potential tool for lesion and disease differentiation. By applying susceptibility-weighted imaging (SWI) techniques, it has been shown that the notion of a perivascular (perivenous) lesion orientation aids to differentiate MS lesions from focal vascular lesions: MS lesion shows a central vein suggestive of perivenous inflammation whereas the vascular lesions do not show a central vein [27].

In patients presenting with a CIS suggestive of MS, the 2010 revision of the McDonald criteria allow for the first time the diagnosis of MS based on one single MRI scan showing dissemination in space and in time (a simultaneous presence of non-enhancing and non-symptomatic contrast-enhancing lesions) [19].

According to the 2010 McDonald criteria for MS diagnosis, dissemination in space can be established with at least one T2 lesion in at least two of four locations characteristic of MS: one or more juxtacortical lesion, one or more periventricular lesion, one or more infratentorial lesion, and one or more spinal cord lesion [19]. In 2016 the MAGNIMS proposed an increase in the number of lesions necessary to confirm involvement of the periventricular area from one to three, and to add an additional cardinal CNS location, the optic nerve [20]. So, actually, MRI criteria to establish disease dissemination in space can be shown by involvement of at least two of five areas of the CNS as follows: three or more periventricular lesions; one or more infratentorial lesion; one or more spinal cord lesion; one or more optic nerve lesion; one or more cortical or juxtacortical lesion [20]. In the last review of MAGNIMS, MRI criteria for disease dissemination in time can remain unchanged and according to the 2010 McDonald criteria, disease dissemination in time can be established by the following: presence of at least one new T2 or gadolinium enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI; or the simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time [20].

Although follow-up brain MRI is well established for demonstration of dissemination in space and in time, the value of repeated spinal cord imaging to establish the MS diagnosis is uncertain, but the presence of demyelination lesion in the spinal cord is crucial in the differentiation of MS pathology from ischemic small vessel disease [28]. Also in the last expert panel guidelines a new definition is recommend: no distinction needs to be made between symptomatic and asymptomatic MRI lesions to establish dissemination in both space and time [19, 20].

In primary progressive MS identical dissemination in space criteria should be used in the diagnosis, with use of CSF testing for confirmation [19, 20].

Non-enhancing T1-hypointense lesions (black holes) in MRI are chronic lesions characterized by severe axonal damage and the presence of this lesion in patients with a CIS is indicative of an already-established MS disease process [29]. 2016 MAGNIMS consensus guidelines reinforce that the presence of non-enhancing black holes should not be considered as a potential alternative criterion to show dissemination in time in adult patients with MS [20].

In those CIS patients not fulfilling the 2010 McDonald diagnostic criteria, follow-up MRI scans are necessary to eventually establish the MS diagnosis [20]. The interval between the baseline and follow-up scan is a matter of debate. Since 80% of the CIS patients with three or more brain lesions at baseline present with new T2 lesions after

3 months, a follow-up interval of 3–6 months has been recommended [28]. In the case of no dissemination in time at that time, a third scan could be done 6–12 months later. These time intervals may also apply to the incidental finding of typical MS lesions on MRI without evidence of clinical disease, radiologically isolated syndrome (RIS) patients [30]. In people with these clinically silent brain lesions consistent with MS, presence of oligoclonal bands, younger age (≤37 years), male sex, and abnormal visual evoked potentials were predictors of development of a first clinical attack [31]. Although MAGNIMS consensus guidelines recommend that people should not be diagnosed with MS on the basis of MRI findings alone [20]. Clinicians should be cautious in overemphasizing MRI findings without making a thorough clinical evaluation and careful differential diagnosis, as the MRI criteria by themselves do not distinguish between MS and other disorders that can cause similar changes in the brain, and are not sufficient to support a reliable diagnosis of MS [32]. This emphasizes again the importance of the principle of "no better explanation" in the diagnosis of MS.

Acute disseminated encephalomyelitis and multiple sclerosis: principal aspects in differential diagnosis

Acute Disseminated Encephalomyelitis (ADEM) is classical defined as a first multifocal and monophasic demyelinating, inflammatory clinical event mainly affecting children and mostly occurring after recent (2 weeks prior) viral or bacterial infections or more rarely after vaccinations [33]. An acute onset with polysymptomatic presentation (multifocal neurological deficits) usually occurs in ADEM, and is secondary to the involvement of multiple areas of the white matter, the gray matter and spinal cord [34, 35]. Encephalopathy, defined as a change in behavior (irritability or confusion) and/or in consciousness (lethargy, stupor, coma), is ADEM's prominent clinical feature [36]; other signs are described in various combinations that could be multifocal, such as hemiparesis, ataxia, dystonia, choreiform movements, aphasia, diplopia [36, 37]. Multiple cranial nerve involvement has been reported, especially optic nerves associated with optic disk edema and also signs of spinal cord involvement might be present, such as flaccid paralysis, constipation, or urinary retention [38].

The diagnosis of ADEM is a diagnosis of exclusion and suffers from the lack of a biological marker, accurate diagnosis solely based on the first clinical demyelinating event is very limited [39, 40]. Several factors may help in distinguishing ADEM from MS. Clinical presentations of encephalopathy, seizures, fever, headache, bilateral, optic neuritis, brainstem symptoms, and meningeal signs are reported to be statistically significantly more likely with a diagnosis of ADEM than MS. Children less than 10 years of age are more likely to have ADEM than MS at the time of an initial demyelinating event and a history of antecedent infection or vaccination is more frequently reported in ADEM cases [41].

Since the last revised diagnostic criteria proposed by the International Pediatric MS Study Group (IPMSSG), ADEM is defined as a first polyfocal clinical demyelinating event with encephalopathy and abnormalities on MRI and does not match the criteria for dissemination in space and time for a MS diagnosis [37, 42]. Monophasic ADEM is the most frequent form occurring in 70–80% of cases. But, in the past decades a multiphasic form of ADEM has been recognized, however differentiating multiphasic ADEM from MS in these cases may be a diagnosis challenge [43, 44].

In 2013, IPMSSG provided clinical definitions to be used as guidelines for pediatric demyelinating diseases [42]. The definition of multiphasic ADEM was revised and is now defined as two episodes consistent with ADEM separated by three months but not followed by any further events [42]. The second ADEM event can involve either new or a re-emergence of prior neurologic symptoms, signs and MRI findings. Although relapsing disease following ADEM that occurs beyond a second encephalopathic event is no longer consistent with multiphasic ADEM but rather indicates a chronic disorder, the diagnosis of MS or NMO should be considered. A positive anti-aquaporin-4 IgG titer in the initially hypothesis of ADEM greatly facilitates this diagnosis of NMO [45, 46].

Since 2013, ADEM can be considered the first manifestation of MS [42]. MS diagnosis is considered if after the initial ADEM episode a second clinical event meets the following three requirements: is nonencephalopathic, occurs three or more months after the initial incident neurologic illness and is associated with new MRI findings consistent with revised radiologic criteria for dissemination in space [42].

In ADEM event lumbar puncture is usually performed to exclude an active meningoencephalitis [47]. CSF can be normal or show lymphocytic pleocytosis and increased level of proteins; also a important CSF finding is the absence of olygoclonal bands, typically presented in MS [43].

Also MRI in ADEM presents characteristics that can be differentiated from MS. The most common MRI finding is the presence of multiple bilateral T2-enhancing supratentorial white matter lesions, usually large (>1–2 cm) and one or more lesions with gadolinium enhancement; when the spinal cord is affected, longitudinal extensive lesions can appear in spinal MRI [48]. Brainstem lesions in ADEM are more often located in the midbrain and are more often bilateral and symmetrical [48]. In ADEM periventricular lesions are less common relative to MS but lesion number, usually less than two periventricular lesions [49]. Also, lesions in the thalamus and basal ganglia are more typical of ADEM than MS. The presence of persistent hypointense lesions in the white matter are infrequent in monophasic ADEM [50].

Some MRI aspects are important to predict progression to MS after a first demyelinating suggestive of ADEM event and the absence of a diffuse bilateral lesion

pattern, presence of black holes, two or more periventricular lesions, is reported to have the highest sensitivity for identifying those cases with an eventual diagnosis of MS after a first demyelinating attack [37].

Neuromyelitis optica and multiple sclerosis: principal aspects in differential diagnosis

A major development over the past two decades was the recognition of neuromyelitis optica (NMO; i.e. Devic's syndrome) as a special form of neuroinflammatory disorder of the central CNS [51]. Classical NMO is characterized by severe attacks of optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM) (52). NMO has unique clinical, imaging, laboratory, and pathological characteristics as well as a pathogenic mechanism that distinguishes it from MS.

The identification of an auto-antibody, NMO-IgG, the first biological marker found in patients with IIDD, with high specificity for NMO that was also present in partial NMO syndromes represented a important marker in the study of IIDD [53]. NMO-IgG was shown to bind selectively to the aquaporin 4 (AQP4) water channel, a transmembrane protein located in the astrocytic foot processes at the blood-brain barrier [51]. Positivity to the anti-AQP4 IgG antibody was included among the laboratory criteria for NMO for the fisrt time in 2006 [54].

The term NMO spectrum disorder (NMOSD) was developed to cover NMO and other CNS inflammatory diseases in which the NMO-IgG antibody was identified. The clinical and laboratory features of NMOSD differ from those found in MS and certain clinical presentations are particularly suggestive of NMOSD, allowing the differential diagnosis with MS. The core clinical characteristics necessary for NMOSD diagnosis, distinguishable from MS, implicate 1 of 6 CNS regions involvement, that are nest discussed [56]:

1. Optic nerve (optic neuritis-ON). ON can be simultaneously bilateral, involves the optic chiasm, causes an altitudinal visual defect, or causes a severe visual loss; in MRI bilateral optic nerve involvement, posterior nerve predominance (especially with extension into the optic chiasm), or extensive lesions of the optic nerve (more than half of its length) are all suggestive of NMOSD [56].

2. Spinal cord (acute myelitis). Acute myelitis in NMOSD requires intramedullary MRI lesion extending over 3 contiguous segments (LETM) and extension of a cervical lesion into the brainstem is characteristic of NMOSD [55]; these is the most specific neuroimaging characteristic of NMOSD and is very uncommon in adult MS. The extensive involvement of the cord, results in a complete spinal cord syndrome, with paralysis below the level of the lesion. Also, pain is a major myelitis signal in an NMOSD, also frequently accompanied by paroxysmal tonic spasms [57]. These clinical manifestations are different of the typical myelitis in MS, which most commonly presents with a partial spinal cord syndrome usually with more sensory symptoms [53]. In NMOSD lesions typically involve the central gray matter and may be associated with cord swelling, central hypointensity on T1-weighted sequences, and enhancement following IV gadolinium administration [58]. In contrast, MS cord lesions are usually about 1 vertebral segment long or less, occupy peripheral white matter tracts such as the dorsal columns [59]. Although the LETM pattern is characteristic of NMOSD, 7%–14% of initial and 8% of subsequent myelitis attacks in AQP4-IgG-seropositive patients do not meet the LETM definition and lesions of less than 3 segments can be also detected in NMOSD, because the MRI is performed early in the evolution of acute myelitis [60]. Also in clinical remission a LETM lesion may fragment into discontinuous lesions. It is also relevant to salient that some patients with progressive MS have coalescent cord lesions that can superficially suggest a LETM pattern [61]. Also LETM MRI pattern may also occur in patients with infectious, granulomatous, neoplastic/paraneoplastic diseases, spinal cord infarction and dural arteriovenous fistula [59].

3. Area postrema. Area postrema syndrome may occur in up to 43% of patients with NMOSD. Area postrema syndrome typically manifests by intractable hicups or nausea and vomiting. MRI study requires associated dorsal medulla/area postrema lesions (often bilateral) and characteristically contiguous with an upper cervical spinal cord lesion [62].

4. Brainstem. Acute brainstem syndrome is associated with periependymal brainstem lesions, typically in the periependymal surfaces of the fourth ventricle. The most common brainstem symptoms are vomiting, hiccups, oculomotor abnormalities and pruritus (12.4%), less commonly reported are hearing loss, facial palsy, trigeminal neuralgia, vertigo or vestibular ataxia other cranial nerve abnormalities [63].

5. Diencephalon. Acute diencephalic syndrome with hypersomnia/narcolepsy due to hypothalamic involvement is reported in the literature. In MRI are typically detected lesions involving the hypothalamus, thalamus, or periependymal surfaces of the third ventricle [64].

6. Cerebrum. In symptomatic Cerebral syndrome large hemispheric lesions may cause encephalopathy and lesions may have a tumefactive appearance [65]. NMOSD typical brain lesions are large, confluent, bilateral deep white matter lesions; or long diffuse, heterogeneous: edematous corpus callosum lesions (1/2 of the length of the corpus callosum or greater) [66, 67]. Involvement of the entire thickness of the corpus callosum may create an "arch bridge" appearance [67]. Long corticospinal tract lesions can also be detected in MRI, unilateral or bilateral, contiguously involving internal capsule and cerebral peduncle [67]. In these large hemispheric lesions that may cause encephalopathy, the presence of positivity to the anti-AQP4 IgG antibody is fundamental in the differ-

ential diagnosis with ADEM. Frequent brain lesions in acute NMOSD present in follow-up MRI persistent T1 hypointensity lesions, including some with cystic or cavitary features, most commonly in callosal and corticospinal tracts [67]. So, diagnostic criteria for NMOSD with AQP4-IgG: it is necessary at least 1 core clinical characteristic and positive test for AQP4-IgG using best available detection, with exclusion of alternative diagnoses.

In a group of NMOSD patients without AQP4-IgG or NMOSD with unknown AQP4-IgG status for the definite diagnosis it is necessary that at least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements [56]: at least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome, dissemination in space (2 or more different core clinical characteristics) and, additional MRI requirements are necessary. In the patients with acute ON diagnosis requires brain MRI showing normal findings or only nonspecific white matter lesions, or optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium enhancing lesion extending over 1/2 optic nerve length or involving optic chiasm; and in the patients with myelitis, MRI needs to show intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) or ≥3 contiguous segments of focal spinal cord atrophy [67].

The international panel for NMO diagnosis considered absence of CSF oligoclonal bands as supportive evidence for NMOSD. Also CSF pleocytosis (>50 leukocytes/mL, incidence approximately 35% in NMOSD) or the presence of neutrophils or eosinophils are particularly useful in distinguishing NMOSD from MS.

More work is required to subdivide AQP4-Ab-negative NMOSD limited forms, which are a particularly challenging diagnosis. These patients would benefit from early differential diagnosis between NMOSD and MS since they have distinct response to immunomodulatory therapy and distinct prognosis [68]. A serum myelin oligodendrocyte glycoprotein (MOG) antibody has been identified in some AQP4 negative patients and might define a distinct, probably milder form of NMO and help differentiating it from MS [69]. MOG-seropositive patients show a diverse clinical phenotype with clinical features resembling NMO (attacks confined to the spinal cord and the optic nerves) and MS with an opticospinal presentation (positive OCBs, brain lesions) [70]. But, actually MOG positive patients seem to represent a subgroup of adult patients with NMO, LETM and ON that have better outcome than those associated with AQP4-ab [71]. In those patients who are double negative (MOG and AQPA4), the accurate diagnosis may demand longitudinal follow-up. Diagnosis of AQP4-seronegative patients still represents a clinical challenge, as this remains a heterogeneous population that requires better description.

Idiopathic inflammatory demyelinating diseases and rheumatic diseases

It is well known that rheumatic diseases can be characterized by highly diverse central CNS involvement [72]. In patients with a relapsing-remitting or primary progressive course of these connective tissue diseases, CNS involvement may be indistinguishable from MS [73]. Cases presenting with an acute isolated neurological syndrome, such as transverse myelopathy (TM) and/or optic neuropathy, may pose a diagnostic problem since they can mimic MS clinically and radiologically. These may be the only early or even the first manifestations in systemic lupus erythematosus (SLE) and Sjogren's syndrome (SS), Behcet disease (BD) and antiphospholipid syndrome (APS), before the systemic features of the disease [74]. Patients may present demyelination areas in the white matter of the brain and spinal cord, which are difficult to differentiate from MS. Forms of white matter damage can be small punctuate MRI lesions (vasculopathy), extensive leucoencephalopathy, demyelinating plaques, lesions of optic nerves and the in the spinal cord [75].

Since the identification NMO-IgG auto-antibody that there is evidence that NMO-IgG seropositivity might be associated with organ-specific autoimmune diseases like SS, sarcoidosis, APS or SLE [76]. Suggesting that NMOSD occurring with other autoimmune diseases is a concurrent pathology and not a vasculopathy or other complications of the connective tissue diseases [77]. The discovery of NMO-IgG antibody allowed the identification of several diseases that previously were not considered as belonging to the field of NMOSD. So, in SLE, SS, APLS, CNS involvement particularly with optic nerve or spinal cord involvement it is important to consider the detection of anti-aquaporin-4 antibody, that supports the diagnosis of NMOSD [79]. The early recognition of NMOSD is an important prognostic factor in patients with these systemic autoimmunity and with recurrent transverse myelitis or/and optic neuritis [80]. Detection of the NMO-IgG may indicate the need for more aggressive immunosuppression to help avert potentially catastrophic episodes of myelitis or optic neuritis [81].

ON was been described in rheumatic diseases and has been documented with variable clinical presentations, ranging from acute retrobulbar neuritis to ischemic optic neuropathy and slowly progressive visual loss [82]. Although occurs in only 1 % of these patients, it has also been documented as a presenting sign in patients who later meet diagnostic criteria for rheumatic diseases, like SLE. In patients with SLE, the pathology with more cases reported in the literature with optic nerve involvement, a small-vessel microangiopathy contribute to a similar "ischemic" optic neuropathy but clinical features can discriminate between ischemic optic neuropathy and the ON seen in demyelinating syndromes [83]. In contrast to demyelinating ON, ischemic optic neuropathy causes

acute (less than 1 day), rather than subacute, loss of vision, and is associated with retro-orbital pain in less than 10% of cases and significant fundoscopic findings of peripapillary hemorrhages [84]. ON associated with SLE is often painless, subacute, and progressive, and commonly very severe, clinically characteristically distinguishably from MS [75, 76]. Alternative demyelinating syndromes associated with autoimunne systemic diseases, therefore, need to be considered if patient's pattern of ON was inconsistent with MS, but also inconsistent with ischemic optic neuropathy [85].

Spinal cord involvement has also been reported in patients with rheumatic diseases particulary in SLE and SS [86]. TM in SLE is infrequently reported, i.e., in only 1–2 % of patients with different types of onset described: a smoothly progressive onset with ascending neurological symptoms; a subacute, gradually progressive onset; and a hyperacute, catastrophic onset type (87). The prognosis is generally poor and depends on such factors as celerity of diagnosis, extent of spinal cord involvement, and prompt treatment. There are also case reports of SS with acute transverse myelopathy as the initial manifestation, but typical dorsal location with a well-defined border and homogeneous Gd-enhancement of MS lesions were not features of SS myelopathy [88]. In connective tissue disorders spinal cord involvement more frequent courses with longitudinally extensive myelitis (no predilection to dorsal spinal cord). [89]. Several reports indicate that there is a significant association between TM in SLE and the presence of aPL [90].

In connective tissue disorders with CNS involvement oligoclonal band analysis may be positive, in LES is positive in up to 50% of patients, although, interestingly and unlike MS, these changes can resolve with successful immunotherapy [85]. Also, patients clinically diagnosed with MS who are found to have significantly high levels of aPL, and patients clinically diagnosed with APS who are found to have subcortical white matter lesions on imaging studies [74, 75]. ANA is a high sensitivity but low specificity test for the diagnosis of SLE, for example 27% of MS patients have ANA positivity. ANA positivity in pSS was reported at a rate of 72.8% with the typically positivity to SS-A (Ro) and SS-B (La) but, anti-ds DNA is highly specific for SLE. Connective tissue diseases should be considered when ANA titers are high (>1:160) and persistent [85].

During follow-up, of patients with relapsing remitting clinical profile with neurological signs resembling MS but whose MRI findings never fulfilled the criteria for MS and that showed limited response to intravenous corticosteroids it is important screen for systemic symptoms unexpected in MS, like: arthritis, arthralgia, dry mouth and eyes, thrombosis, miscarriages/pregnancy morbidity, livedo reticularis, thrombocytopenia, Raynaud's phenomenon, photosensitivity, oral/genital ulcerations, uveitis, rash and gastrointestinal symptoms [91]. It is also necessary to check auto-antibody profile, sometimes this profile is screened several times and no seropositivity was detected, but this probably occurs due to the suppressive effect of repeated intravenous corticosteroid treatment [92]. It is important to consider that over several years in the close follow-up of these patients, repeated laboratory evaluations of vasculitic markers may reveal positivity, leading to the final definite diagnosis of rheumatic diseases.

So those patients who have possible MS diagnosis, but, incomplete response to steroid treatment and atypical radiological findings should be examined further for connective tissue diseases [92]. In addition, the immunomodulatory treatment of MS may potentially induce or aggravate vasculitic activity of these pathologies [75].

Conclusion

Three broad categories of diseases should be considered in the differential diagnosis work-up of CNS disease suggestive of MS: non-IDDs with symptoms and signs may mimic IDDs (including MS); non-MS IDDs (the spectrum of idiopathic inflammatory demyelinating diseases) and IDDS associated with other autoimmune diseases.

We resume clinical presentations that are typical and suggestive of MS and those that are atypical for MS, describing clinical and paraclinical red flags, that might conduct to an alternative diagnosis. However, we think that more prospective clinical studies are needed, with a particular attention to the relative prevalence of disorders in a specific geographic area or population, in order to establish diagnostic algorithms which can provide an accurate diagnosis for CNS syndromes suggestive of MS.

Abbreviations

ADEM: Acute disseminated encephalomyelitis; APS: Antiphospholipid syndrome; AQP4: Aquaporin4; BBB: Blood brain barrier; BD: Behcet disease; CDMS: Clinically definite multiple sclerosis; CIS: Clinically isolated syndrome; CNS: Central nervous system; CSF: Cerebrospinal fluid; IDD: Inflammatory demyelinating disease; IPMSSG: International Pediatric MS Study Group; LETM: Longitudinally extensive transverse myelitis; MOG: Myelin oligodendrocyte glycoprotein; MS: Multiple sclerosis; NMO: Neuromyelitis optica; NMOSD: neuromyelitis optica spectrum disorders; OCB: Oligoclonal bands; ON: optic neuritis; RIS: Radiologically isolated syndrome; SLE: Systemic lupus erythematosus; SS: Sjogren's syndrome; SWI: Susceptibility-weighted imaging; TM: Transverse myelopathy

Competing interests

The authors declare no conflict of interest.

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