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The differential diagnosis of multiple sclerosis: classification and clinical features of relapsing and progressive neurological syndromes

Abstract In the absence of pathognomonic clinical features or a definitive laboratory test, multiple sclerosis (MS) remains ultimately a diagnosis of exclusion. Accurate diagnosis is increasingly important with available disease modifying therapy. Unfortunately the rate of misdiagnosis remains around 5%–10%, indicating that 1 in 20 patients thought to have MS has, instead, a condition resembling MS. In this review we describe conditions that may be confused with MS because they can present as lesions disseminated in time, space, or both. Conditions often confused with MS may be inflammatory (systemic lupus erythematosus, Sjögren's syndrome, vasculitis, sarcoidosis, Behçet's disease), infectious (Lyme disease, syphilis, progressive multifocal leukoencephalopathy, HTLV-1 infection, herpes zoster), genetic (lysosomal disorders, adrenoleukodystrophy, mitochondrial disorders, CADASIL), metabolic (vitamin B12 deficiency), neoplastic (CNS lymphoma) and spinal (degenerative and vascular malformations) diseases. The key to the accurate diagnosis of MS is vigilance for atypical features, suggesting the possibility of an alternative diagnosis.

Key words Multiple sclerosis • Differential diagnosis • Relapsing/progressive neurological syndromes

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Introduction

This review focuses on the disorders that pose the greatest diagnostic difficulty or are most frequently considered in patients being evaluated for multiple sclerosis (MS) because they can present as lesions disseminated in time, space, or both.

Inflammatory conditions

Systemic lupus erythematosus

Neurological manifestations of systemic lupus erythematosus (SLE) include neuropsychiatric syndromes, seizures, aseptic meningitis, vascular events, movement disorders, cranial and peripheral neuropathies, transverse myelitis, and optic nerve involvement (optic neuritis, ischemic optic neuropathy, or chronic gradually progressive visual loss). SLE also may produce relapsing, multifocal neurological manifestations similar to those of MS. Magnetic resonance imaging (MRI) of the brain reveals atrophy, white matter lesions (more often subcortical), and involvement of the cortex and deep gray structures. Analysis of cerebrospinal fluid (CSF) reveals oligoclonal bands (OB) and increased IgG index. The diagnosis is based on systemic manifestations, positive serology, and high titer of antinuclear antibodies (ANA) and of other auto-antibodies (low titer reflects systemic immune dysregulation in MS) [1].

Sjögren's syndrome

Neurological manifestations of Sjögren's syndrome include peripheral neuropathy (axonal sensorimotor polyneuropathy, mononeuritis multiplex, or sensory ganglionopathy), cerebral vasculitis, aseptic meningitis,

myopathy, acute transverse myelitis and acute optic neuropathy [2]. Cranial MRI shows white matter lesions. CSF analysis reveals OB and increased IgG index. Diagnosis is based on systemic manifestations (sicca syndrome and rheumatic manifestations), serology (abnormal ANA, SS-Ro, SS-La), and the demonstration of inflammatory foci on minor salivary gland biopsy.

Vasculitis

Systemic vasculitides such as polyarteritis nodosa or Wegener's granulomatosis are rarely difficult to distinguish from MS. Amore difficult diagnostic distinction is between MS and isolated angiitis of the central nervous system (IACNS) [3]. Neurological manifestations of IACNS include relapsing or progressive focal or multifocal cerebral manifestations, relapsing or progressive myelopathy, brainstem manifestations, cognitive impairment, headache and meningeal signs. Cranial MRI reveals patchy foci of increased signal in periventricular, deep, and subcortical white matter. Involvement of gray matter structures out of proportion to white matter and, when larger vessels are involved, infarcts point to cerebral vasculitis. Vascular or meningeal enhancement is prominent. On CSF analysis, there is normal or increased protein and prominent pleocytosis. The diagnosis is based oncerebral angiography (characteristic multifocal segmental narrowing of medium-sized arteries) and parenchymal/meningeal biopsy.

Sarcoidosis

Sarcoidosis is a chronic, relapsing inflammatory disorder characterized by non-caseating granulomata in multiple organs, in particular the lungs. Neurological manifestations of sarcoidosis are cranial neuropathies, aseptic meningitis, meningovascular involvement, hypothalamic dysfunction, intracranial mass lesions, mononeuropathy multiplex, inflammatory optic neuropathy, abnormalities of eye movements, myelopathy, and multifocal cerebral or brainstem involvement. Cranial MRI reveals prominent meningeal enhancement, hypothalamic involvement, hydrocephalus, enhancing mass lesions, and multifocal white matter lesions even in the periventricular white matter. On CSF analysis, there is marked increase in protein, marked pleocytosis, and hypoglycorrachia (different from MS), or modest increased protein, moderate pleocytosis, and evidence of intrathecal antibody synthesis (similar to MS). Diagnostic workup includes sedimentation rate, serum angiotensin-converting enzyme (ACE) [4], pulmonary function testing with diffusion capacity, gallium scan, computed tomography (CT) of the chest to look for hilar adenopathy, ophthalmologic evaluation for retinal/uveal/conjunctival involvement and biopsy of an involved tissue.

Behçet's disease

Neurological manifestations of Behçet's disease include focal meningoencephalitis involving the brainstem, cerebrovascular syndromes, seizures, acute encephalopathy, cranial neuropathies, optic neuritis, myelopathy, long tract motor signs, and ataxia following a relapsing or progressive course [5]. MRI exam shows multiple patchy foci of increased signal predominantly in the brainstem but also in cerebral white matter, deep gray matter structures, cerebellum, optic nerves, and spinal cord. Acute lesions enhance with Gd. There is no predilection for the periventricular white matter and more prominent involvement of the brainstem and basal ganglia. Analysis of CSF reveals lymphocytic pleocytosis, increased protein and oligoclonal bands. The diagnosis is based on the presence of additional features (e.g. oral and genital ulceration, skin lesions, and uveitis).

Infections

Lyme disease

Neurological manifestations of Lyme disease include meningitis, cranial neuropathy, radiculoneuritis, peripheral neuropathy, encephalomyelitis, and encephalopathy. Encephalomyelitis may cause relapsing or progressive multifocal central nervous system (CNS) symptoms and signs. MRI shows foci of abnormal signal in the cerebral white matter [6], and CSF analysis reveals intrathecal IgG synthesis and oligoclonal bands. The diagnosis of Lyme disease is based on the presence ofother systemic manifestations (erythema migrans plus concomitant arthritis and cardiac manifestations) and/or unequivocal evidence of *Borellia burgdorferi* (Bb) infection in the nervous system, either by the demonstration of intrathecal anti-Bb antibody production (elevated CSF Lyme antibody index) or of the Bb organism by antigen or nucleic acid assays.

Syphilis

Neurological manifestations of syphilis are atypical clinical presentations such as acute monocular loss of vision and progressive, multifocal manifestations including cognitive impairment, chronic optic neuropathy, long tract motor signs, sensory loss, ataxia, and progressive myelopathy.

Cranial MRI shows multifocal lesions in the cerebral white matter, and CSF analysis indicates prominent OB. The diagnosis is made by a positive outcome on the Venereal Disease Research Laboratory (VDRL) standard serological test for syphilis.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by JC virus (JCV) that occurs exclusively in patients with impaired cellular immunity due to immunosuppressive therapy or acquired immunodeficiency syndrome (AIDS) [7]. Neurological manifestations of PMLare visual field defects or cortical blindness, motor abnormalities, cognitive impairment, altered personality, ataxia, or dysarthria. Cranial MRI shows lesions of the white matter (periventricular, corpus callosum), gray-white junction, and gray matter that are high-intensity on long repetition time (TR) images and low intensity on T1-weighted images. There is no enhancement following Gd administration. Results of CSF analysis are usually normal. Diagnosis requires brain biopsy and detection of JCVnucleic acid (by polymerase chain reaction) in brain specimens, CSF, or peripheral blood lymphocytes clinical.

HTLV-1 infection

Neurological manifestations of infection with human T-cell leukemia virus (HTLV-1) are progressive thoracic myelopathy with predominantly upper motor neuron involvement in the legs, mild sensory disturbances, and bowel and bladder dysfunction; this combination of symptoms has been termed HTLV-1-associated myelopathy (HAM) [8]. Spinal cord MRI reveals atrophy of the thoracic cord with or without abnormal increased signal and faint Gd enhancement. Cranial MRI shows normal or scattered, punctate foci of increased signal in the peripheral white matter. Prominent OB and other indicators of intrathecal immunoglobulin synthesis are found on CSF analysis. HTLV-1 titer should be included in the diagnostic workup of patients with progressive myelopathy, especially when primary progressive MS is a consideration.

Herpes zoster

Herpes zoster represents a spontaneous reactivation of varicella-zoster virus (VZV) infection in sensory neurons of sensory ganglia following previous varicella (chickenpox). Neurological manifestations of the disease include occasional involvement in the region of the CNS projections of the sensory neurons producing myelitis (spinal roots) [9], encephalitis or cerebral angiitis (trigeminal nerve), or a brainstem syndrome involving any of the cranial nerves. VZV-related myelitis may follow a relapsing or progressive course. CSF exam reveals mononuclear cell infiltrate and increased IgG index or OB. Diagnosis is made by detection of VZVDNAin CSF or of antibodies to VZVin serum.

Metabolic and genetic disorders

Vitamin B12 deficiency

Neurological manifestations of vitamin B12 deficiency include a combination of cervical myelopathy (initially predominantly involving the posterior columns and later the lateral columns) and peripheral neuropathy, so-called myeloneuropathy, optic neuropathy, cognitive impairment, and fatigue [10]. Neurological and hematological manifestations may occur separately. MRI demonstrates abnormalities in the cerebral white matter resembling those of MS, but the CSF is normal. Demonstration of macrocytic anemia or hyper-segmented polymorphonuclear leukocytes makes the diagnosis. Increased serum methylmalonic acid and homocysteine levels are useful metabolic indicators of cobalamin deficiency.

Lysosomal disorders

Lysosomal disorders that mimic MS have been previously reviewed in detail [11].

Metachromatic leukodystrophy(MLD) is an autosomal recessive disorder resulting from a defect in the lysosomal enzyme arylsulfatase A. MLD can begin at any age, and has late-onset or adult forms. Neurological manifestations of MLD are prominent cognitive decline (in adults), optic atrophy, nystagmus, spastic weakness, gait disturbance, urinary dysfunction and peripheral neuropathy. Cranial MRI shows diffuse and symmetric abnormality of the cerebral white matter. MLD is diagnosed by the demonstration of deficient arylsulfatase Aactivity in leukocytes or cultured fibroblasts.

Fabry's disease is an X-linked recessive disorder caused by defective activity of the lysosomal enzyme alpha-galactosidase. The onset of symptoms in males usually occurs before adolescence, but onset in the second or third decade has been reported. Neurological manifestations of the adult-onset form include ischemia or recurrent strokes linked to multifocal small vessel occlusion. The diagnosis is based on the presence of angiokeratomas and corneal dystrophy and

on the demonstration of deficient leukocyte alpha-galactosidase activity.

*Krabbe's disease*is an autosomal recessive disorder resulting from deficient activity of galactocerebrosidase. Atypical and late-onset forms have been reported. Neurological manifestations in the adult are cognitive dysfunction, weakness, tremor, ataxia, dysarthria and nystagmus; peripheral nerve manifestations are usually not prominent. Diagnosis requires the determination of leukocyte or fibroblast galactocerebrosidase activity.

Adrenoleukodystrophy

X-linked adrenoleukodystrophy (ALD) is a peroxisomal disorder characterized by abnormalities of CNS myelin, adrenal dysfunction, and accumulation of very long chain fatty acids in the blood and tissues. Adrenomyeloneuropathy is the most common form of ALD in adults. Neurological manifestations of ALD include slowly progressing myelopathy in men beginning in the third decade of life associated with depression, impotence, and sometimes adrenal insufficiency. Approximately 10%–15% of female heterozygotes have symptoms similar to those described for men and frequently are misdiagnosed as having MS. Brain MRI shows cerebral demyelination starting in the frontal white matter and spreading to the occipital white matter over several months. ALD is diagnosed by the demonstration of increased serum levels of very long chain fatty acids.

Mitochondrial disorders

The mitochondrial cytopathies are a clinically heterogeneous group of multisystem disorders due to a variety of genetic defects affecting mitochondrial metabolism [11]. These disorders demonstrate a maternal inheritance pattern. Because the mitochondrial disorders frequently cause incomplete syndromes, the inheritance pattern may be obscured. Neurological manifestations include combined central and peripheral neurological involvement (neuropathy or myopathy), recurrent encephalopathy, vascular-type headaches, stroke-like episodes with good recovery, sensorineural hearing loss, myoclonus, episodic nausea and vomiting, pigmentary retinopathy in combination with optic atrophy, and basal ganglia calcification. Abnormalities in the cerebral white matter are seen on MRI. Diagnosis is based on evidence of cardiomyopathy or cardiac conduction abnormalities, diabetes, and increased serum lactate levels.

Leber's hereditary optic neuropathy (LHON) is the mitochondrial disorder most often mistaken clinically for MS. LHON is characterized by acute or subacute optic neuropathy in males with onset typically between the ages of 10 and 30 years. Neurological manifestations of LHON are ataxia and spastic weakness.

CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

CADASILresults from mutations in the notch3 gene on chromosome 19p13. Pathologically, it is characterized by a widespread microangiopathy affecting small arterioles 100–400 μm in diameter with thickening of the media produced by deposition of eosinophilic, granular, electron-dense material of unknown origin. CADASILcan easily be misdiagnosed as MS [12]. The prominent family history of headache also distinguishes CADASILfrom MS, but de novo mutations in the notch3 gene producing CADASIL have been reported [13]. Thus, the family history may be negative. Neurological manifestations of CADASILinclude relapsing, multifocal neurological manifestations similar to those of MS. Cranial MRI shows abnormalities in cerebral white matter, lack of involvement of the corpus callosum or cerebellum, involvement of deep gray structures and external capsule, and presence of lacunar infarcts. The CSF is normal or there are pleocytosis and OB. Diagnosis of CADASILrequires brain, skin or muscle biopsy. Genetic testing for CADASILbased on a blood specimen has recently become commercially available.

Clinically defined genetic disorders

Hereditary degenerative disorders such as Freidreich's ataxia, other hereditary ataxias, olivopontocerebellar atrophies, and hereditary spastic paraparesis sometimes can be mistaken for MS, particularly the primary progressive form. The prominent family history (particularly for the autosomal dominant disorders), lack of MRI findings, and normal CSF exam distinguish them from MS.

CNS lymphoma

The most common neoplasm to be mistaken for MS is CNS lymphoma. CNS lymphoma usually is unifocal but often may be multicentric [14]. MRIfindings of CNS lymphoma may look similar to those of MS, but the involvement of gray matter structures is out of proportion to that of the white matter. Additionally, persistent Gd-enhancement (particularly if there is a prominent component of enhancement along blood vessels) and continued enlargement of lesions strongly suggest a lymphocytic neoplasm. The CSF analysis

shows cytologically abnormal lymphocytes, non-specific abnormalities of protein or pleocytosis. Biopsy is necessary for diagnosis.

Spinal diseases

Spinal vascular malformations anddegenerative spinal diseases

The spinal vascular malformations most often mistaken for MS are dural arteriovenous fistulas and true malformations. Neurological manifestations include thoracic myelopathy, with an acute, relapsing, or progressive course [15]. MRI exam shows patchy increased signal within the spinal cord on long TR images. The spinal cord may be focally enlarged. There may be no Gd-enhancement or mild, heterogeneous enhancement. CSF analysis may be normal or reveal a mild pleocytosis or mildly elevated proteins; rarely is the protein level markedly increased. There are no findings of intrathecal antibody production. Diagnosis requires selective spinal angiography.

Severe cervical spondylosis may also mimic MS and have neurological manifestations that include polyradiculopathy with motor and sensory symptoms in the arms and myelopathic manifestations in the legs. The course is relapsing or progressive. Cranial MRI detects non-specific changes in the periventricular white matter. The CSF has an increased protein concentration. Spinal cord MRI is used for diagnosis.

Conclusions

The clinician must be vigilant for features atypical of MS, indicating that an alternative diagnosis needs to be considered. Warning signs are: (1) onset of symptoms before age 20 or after 50 years, (2) prominent family history, (3) atypical course (gradually progressive course from onset particularly in a young patient or with manifestations other than a myelopathy), (4) abrupt development of symptoms, (5) unifocal manifestations, (6) neurological manifestations unusual for MS, (7) associated systemic manifestations, (8) normal results on MRI, CSF, and evoked potential studies, and (9) atypical response to treatment (lack or rapid response to corticosteroids or disease-modifying treatments). Although these features do not rule out the diagnosis of MS, they indicate that extra care must be taken in making the diagnosis.

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