REVIEW ARTICLE DOI: 10.15713/ins.bhj.75

# Update on multiple sclerosis mimics


## ABSTRACT

Several diseases mimic multiple sclerosis (MS) clinically as well as in magnetic resonance imaging (MRI) findings. Organ-specific autoimmune inflammatory diseases such as acute disseminated encephalomyelitis, neuromyelitis optica spectrum disorders, and myelin oligodendrocyte glycoprotein antibody disease have their own specific clinicoradiological features that help to differentiate them from MS. Connective tissue disorders, vasculitis, and sarcoidosis manifest with constitutional and systemic features. Presence of headache, seizures, movement disorders, psychosis and cognitive dysfunction, and distinct MRI findings also help to separate them from MS. Vascular diseases, infections, nutritional, metabolic, toxic, inherited, and degenerative disorders, and neoplastic and related diseases also have unique characteristics. Revision of McDonald's Diagnostic criteria for MS in 2017 has increased the sensitivity for diagnosis of MS. They should be applied to patients who present with clinical features compatible with MS and not those with atypical features. When applied to a patient with relevant clinical and MRI features, they carry a high degree of accuracy. Trying to fit a patient with atypical features into MS is likely to cause a misdiagnosis. Factors that need to be taken into account are the atypical clinical features, absence of dissemination in space and time, peripheral nervous system and systemic involvement, and morphology of MRI findings (not fitting into MRI criteria for MS), to be able to differentiate MS mimic from MS. On the one side, the clinician must acquire competence not to miss diagnosis of MS, as starting disease-modifying therapy (DMT) early has the best long-term prognosis. On the other side, one should not misdiagnose MS to avoid unnecessary psychological trauma of receiving diagnosis of a disabling disease and exposure to DMTs. The key is strict application of clinical and radiological criteria and being aware of the "red flags."


**Key words:** Multiple sclerosis mimic, White matter disease, Differentiating features, Red flags

## INTRODUCTION

Multiple sclerosis (MS) is the most common autoimmune inflammatory disorder of the central nervous system (CNS) characterized clinically by recurrent acute attacks (called relapses) and disability progression independent of relapses.[1] With the advent of many MS-specific disease modifying therapies, an accurate diagnosis is not only crucial to inform therapy but also to predict future disability.[2] Despite a better understanding of the pathogenesis of MS, we still lack a specific biomarker to confirm its diagnosis.[3] The consequence of misdiagnosis is grave as the natural history, course and treatment of MS mimics differ widely from MS.

Nearly a quarter of patients with MS-like clinical presentation harbor an alternate diagnosis, the most common ones being vascular diseases, migraine with atypical magnetic resonance imaging (MRI) lesions, and neuromyelitis optica spectrum disorders (NMOSD).[4] Predictors of alternative diagnosis were absence of cerebrospinal fluid (CSF)-specific oligoclonal bands (OCB), atypical MRI lesions, lack of dissemination in space, and normal visual evoked potentials (EPs).[4]

The following red flags should suggest a diagnosis other than MS.[5]

(i) Systemic and constitutional symptoms and signs including ulcers, arthritis, organ dysfunction, and abortions.
(ii) Neurological signs and symptoms outside the CNS such as peripheral neuropathy and myopathy.
(iii) Atypical CNS symptoms which include headache, meningeal signs, and extrapyramidal syndromes.
(iv) Atypical MRI findings such as longitudinally extensive myelitis, persistent enhancement of lesions beyond 3 months, hemorrhages within the lesions, hydrocephalus, and atypical lesion location (subcortical > periventricular and juxtacortical).

The important features of MS are briefly described for comparison with diseases mimicking MS.


Shripad S. Pujari[1], Sruthi S. Nair[2]

*[1]Department of Neurology, Deenanath Mangeshkar Hospital and Research Center, Noble Hospital, Pune, Maharashtra, India, [2]Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India*

**Corresponding Author:**
Shripad S. Pujari, Department of Neurology, Deenanath Mangeshkar Hospital and Research Center, Noble Hospital, Pune, Maharashtra, India.
E-mail: drshripadpujari@gmail.com

## CARDINAL FEATURES OF MS

MS presents with three types of symptoms, those due to relapses, progression of disability independent of relapses, and ancillary symptoms. Common relapses presentations include subacute unilateral optic neuritis (ON), partial myelitis, hemispheric (hemiparesis and sensory loss), and brainstem syndromes. Brainstem relapses are also archetype and are internuclear ophthalmoplegia, trigeminal neuralgia, hemifacial myokymia, and vertigo. Features of all relapses are prototype in MS, they are rarely severe and respond to intravenous methylprednisolone. Disability progression manifests commonly as impaired ambulation. Ancillary symptoms include Uhthoff's phenomenon, Lhermitte's phenomenon, fatigue, sphincter symptoms, sexual dysfunction, cognitive decline, and painful tonic spasms.[3]

MRI reveals white matter lesions, usually <1 centimeter (cm) in size, in four locations which are periventricular, juxtacortical/cortical, infratentorial, and in the spinal cord. Brain lesions appear finger like (called Dawson's fingers), located at the callososeptal interface, perpendicular to the lateral ventricles, involve the U fibers and the temporal lobes.[6,7] [Figure 1a-c]. During ON, MRI may be normal or show medium length altered signal intensity within the optic nerve. Brainstem lesions are small, perpendicular to the surface and located in the peripheral part of the brainstem. Spinal cord lesions are small, extend less than 2 vertebral segments [Figure 1d], perpendicular to the surface and eccentric (in the peripheral portion of the cord). CSF OCB is positive in more than 90% of Caucasians but only in 36% Asians in MS.[8,9] EPs also show evidence of demyelination in the form of delayed latencies even in areas which were never clinically affected.

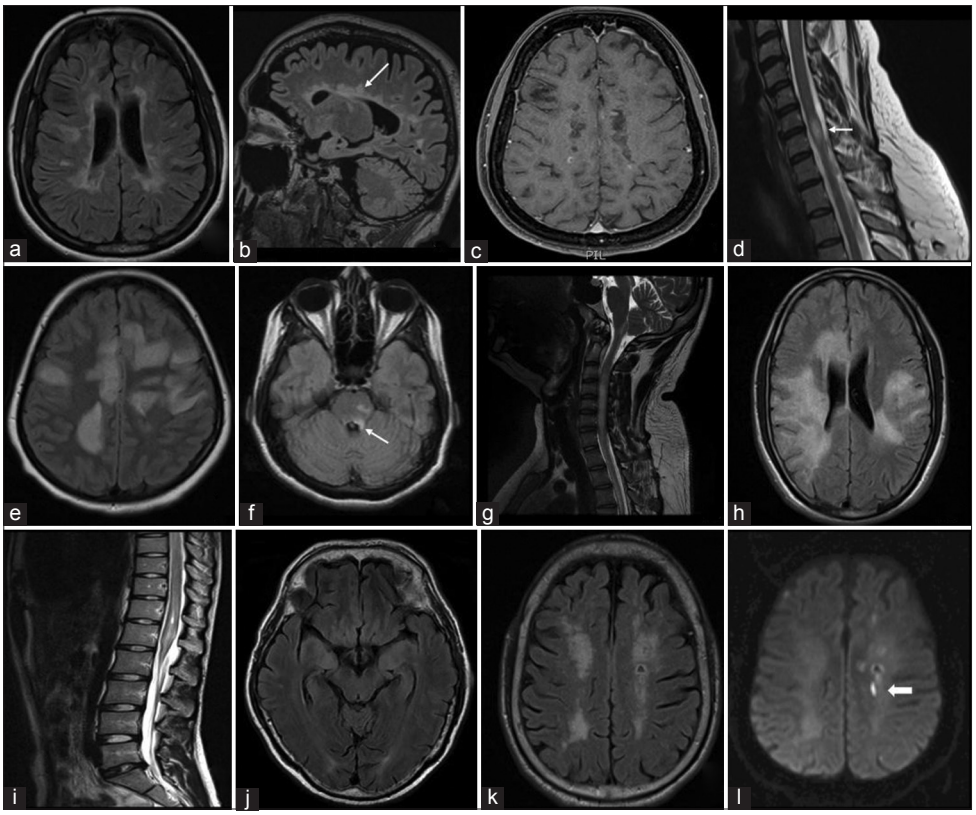


**Figure 1:** Magnetic resonance imaging in central nervous system-specific autoimmune diseases. (a-d) Multiple sclerosis. T2 fluid-attenuated inversion recovery (FLAIR) axial (a) and sagittal (b) sections showing multiple periventricular and juxtacortical lesions. Typical appearance is Dawson's fingers perpendicular to corpus callosum (arrow in b). T1 post-gadolinium axial section brain (c) showing open ring and nodular enhancing lesions and black holes. T2 sagittal section of spinal cord (d) with short segment "cigar-shaped" lesion at C6-7 level (arrow). (e) Acute disseminated encephalomyelitis. T2 FLAIR axial sections showing multiple large lesions with diffuse margins in white and gray matter. (f, g) Neuromyelitis optica spectrum disorder. Axial T2 FLAIR of brain shows hyperintense lesion abutting floor of fourth ventricle (arrow in f) and longitudinally extensive spinal cord lesion, hyperintense in T2, extending from C3 to C7 with cord expansion. (h, i) MOG antibody disease with large and diffuse white and gray matter hyperintensities in T2 FLAIR axial section (h) and spinal cord T2 hyperintensity involving conus-epiconus regions (i). (j) LGI1-positive autoimmune encephalitis with bilateral anteromedial temporal lobe hyperintensities with gyral expansion in T2 FLAIR sequences. (k,l) Primary angiitis of central nervous system. T2 FLAIR axial images show discrete and confluent subcortical white matter hyperintensities with lacunes (k), some of the lesions show diffusion hyperintensity (block arrow in L) and low ADC (not shown)

**Table 1:** Diseases which can mimic multiple sclerosis.[1,3]

| Category | Sub-category | Disease |
|---|---|---|
| Organ specific autoimmune disorders | | ADEM |
| | | NMOSD |
| | | MOGAD |
| | | CLIPPERS |
| | | GFAP astrocytopathy |
| | | Autoimmune encephalitis (AIE) |
| | | Primary angiitis of the CNS (PACNS) |
| Systemic autoimmune inflammatory diseases | Connective tissue diseases | SLE |
| | | Sjogren's syndrome |
| | | Systemic sclerosis |
| | Vasculitides | Polyarteritis nodosa (PAN) |
| | | Microscopic polyangiitis |
| | | Granulomatosis with polyangiitis angiitis (Wegener's granulomatosis) |
| | | Eosinophilic granulomatosis with polyangiitis (Churg Strauss Syndrome) |
| | | Temporal arteritis |
| | | Behcet's syndrome |
| | Granulomatous disease | Sarcoidosis |
| Miscellaneous immune disorders | Endocrine | SREAT |
| | Gastrointestinal | Inflammatory bowel diseases |
| | Multisystem | Thrombotic thrombocytopenic purpura |
| | Ophthalmological | Susac's syndrome |
| Vascular diseases | | Small vessel ischemia |
| | | Thrombo-embolism (shower of emboli) |
| | | CADASIL |
| | | APLA |
| | | Moyamoya disease |
| | | Spinal arteriovenous malformation |
| Infections | Viruses | PML, HTLV1, HIV, CMV, Chikungunya, other viral encephalitides |
| | Bacteria | CNS tuberculosis, Lyme disease, Neurosyphilis |
| | Protozoa and parasites | Toxoplasmosis, cysticercosis |
| Nutritional | | SACD- $B_{12}$/ Cu deficiency |
| | | Wernicke's encephalopathy |
| Metabolic | | Osmotic demyelination |
| | | PRES |
| Toxins and drugs | | Nitrous oxide myelopathy |
| | | Tobacco-alcohol ambylopia |
| | | Marchiafava Bignami disease |
| | | Methanol intoxication |
| | | Cassava poisoning |
| | | Lathyrism |
| Malignancy | | Gliomatosis cerebri |
| | | Lymphoma |
| | | Lymphomatoid granulomatosis |
| | | Paraneoplastic encephalitis and myelitis |
| | | Radiation induced encephalopathy |
| Genetic diseases | | Leucodystrophies |
| | | Mitochondrial disorders |
| | | HSP |
| Trauma | | Diffuse axonal injury (DAI) |
| Compressive | | Spondylotic myelopathy |
| | | Cervico-medullary junction anomalies |
| Degenerative | | Primary lateral sclerosis |
| Miscellaneous | | Migraine |
| | | Somatisation |
| | | Fibromyalgia |
| | | Hypoxic ischemic encephalopathy (HIE) |
| | | Perinatal hypoxia |

*(Contd...)*

**Table 1:** *(Continued)*

Abbreviations: ADEM- acute disseminated encephalomyelitis, APLA- Antiphospholipid antibody syndrome, CADASIL- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CLIPPERS - Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids, CMV- cytomegalovirus, CNS- central nervous system, GFAP- Glial fibrillary acidic protein, HIV- Human immunodeficiency virus, HSP- hereditary spastic paraplegia, HTLV-1- Human T-cell lymphotropic virus-1, MOGAD myelin oligodendrocyte glycoprotein antibody disease, NMOSD neuromyelitis optica spectrum disorders, PML- Progressive multifocal leuco-encephalopathy, PRES- Posterior reversible encephalopathy syndrome, SACD- subacute combined degeneration of spinal cord, SLE- Systemic lupus erythematosus, SREAT- Steroid responsive encephalopathy with autoimmune thyroiditis.

## DISORDERS THAT MIMIC MS

Categories of diseases with individual disorders that mimic MS are listed in Table 1. Each category and disease will be discussed with an effort to differentiate them from MS.

## DIFFERENTIATING FEATURES OF INDIVIDUAL DISEASES

### Organ-Specific Autoimmune Disorders

*Acute disseminated encephalomyelitis (ADEM)*

ADEM is an inflammatory demyelinating disease with the clinical features such as fever, encephalopathy, seizures, and meningismus that differentiate it from MS.[3,10] MRI shows multifocal patchy T2W and T2 fluid-attenuated inversion recovery hyperintense lesions involving corticomedullary junction of cerebral hemispheres, corpus callosum, brainstem, cerebellum, spinal cord, and, to a lesser extent, in the basal ganglia and thalami. The lesions involve both the gray and white matter, are usually more than 1 cm with poorly defined margins, and may or may not enhance on contrast administration [Figure 1e]. Enhancing lesions at times take form of an incomplete ring.[3,10]

ADEM is commonly monophasic, but occasionally, patients may develop a new attack after 3 months or more when it is termed multiphasic ADEM.[10]

*NMOSD*

Clinically, ON in NMOSD is commonly bilateral (either simultaneous or sequential), severe and responds poorly to treatment. MRI in ON is either normal or shows involvement of more than 50% of the length of the optic nerve (called longitudinally extending ON), optic chiasmal, and optic tract involvement. Myelitis involves three or more segments in 84% of patients, the signal intensity occupies the central portion of the cord, is associated with cord swelling, has lens-like contrast enhancement, cystic enlargement, and leaves behind cord atrophy.[11] Hemispherical lesions lack the criteria to satisfy MS, are larger than MS plaques, peri-ependymal, can be tumefactive, and many times follow the tract [Figure 1f and g]. Callosal lesions are thick and have an arch bridge appearance.[7] CSF OCB is negative in more than 75–86%.[11,12]

*Myelin oligodendrocyte glycoprotein antibody disease (MOGAD)*

Clinicoradiological manifestations of this disease overlap with NMOSD and MS but as the pathogenesis of this disease is different from both these disorders, it is now considered as a distinct entity.[13] Common manifestations are unilateral/bilateral ON, myelitis, brainstem syndromes, and cortical encephalitis. Pediatric MOGAD presents with ADEM in 60–70% of cases. Peri-ON is common in MOGAD ON, brain lesions can be ADEM-like or smaller in size, spinal cord lesions can be longitudinally extensive or short-segment transverse myelitis, posterior fossa lesions involve brainstem as more round with poorly defined borders, and middle cerebellar peduncle fluffy infiltrates [Figure 1h and i]. Encephalitic lesions involve cortex and leptomeningeal enhancement may be seen.[14,15]

*Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids*

This is a rare CNS inflammatory disease with punctate lesions predominating in pons, cerebellum, and spinal cord. This typically affects older patients (median 6$^{th}$ decade of life) with subacute presentation with gait ataxia, dysarthria, diplopia, facial sensory impairment, and vertigo with or without cognitive impairment and bipyramidal symptoms. Radiological signs are pathognomonic with multiple homogeneous nodular enhancement of size <3 mm and no mass effect. The region of T2 hyperintensity does not exceed the region of enhancement. It shows marked clinical and radiological response to corticosteroid therapy and recurrence on steroid withdrawal. Diagnosis is established with clinicoradiological criteria or neuropathological demonstration of dense T-cell infiltration.[16]

*Glial fibrillary acidic protein (GFAP) astrocytopathy*

This recently described CNS inflammatory disease presents with meningoencephalomyelitis. Headache, seizures, delirium, psychiatric symptoms, and tremors are common presentations in contrast to MS while optic neuropathy and partial myelitis may mimic MS. Peripheral neuropathy occurs in <5%. A minority of cases have coexistent autoimmune diseases and paraneoplastic association, particularly teratoma. MRI shows typical radial perivascular enhancement. CSF IgG antibody to GFAP is diagnostic. Symptoms generally respond to steroid, while nearly 20% relapse on withdrawal needing a long-term steroid-sparing therapy.[17]

*Autoimmune encephalitis*

Autoimmune encephalitis encompasses a group of diverse conditions with antibodies directed against neuronal intracellular, synaptic, and cell surface proteins. The classical clinical presentations are subacute onset of cognitive impairment, neuropsychiatric manifestations, and seizures with or without focal neurological deficits. These symptoms are distinct from MS although MRI brain could show multifocal MRI lesions in both. The lesions in autoimmune encephalitis are more commonly diffuse and involve both gray and white matter or predominantly gray matter [Figure 1j]. Post-contrast enhancement may be absent or may show gyral or patchy patterns. Extra-limbic multifocal lesions are common in anti-N-methyl-D-aspartate receptor encephalitis, anti-gamma amino butyric acid A (GABA-A) encephalitis, and anti-glutamic acid decarboxylase encephalitis.[18,19] Hashimoto encephalopathy (now called steroid responsive encephalopathy with autoimmune thyroiditis) is currently understood to be closely associated with autoimmune encephalitis. Cognitive impairment, seizures, and gait difficulty dominate the clinical picture and MRI may show multifocal periventricular and subcortical white matter lesions.[19] The role of antithyroid antibodies in the pathogenesis is poorly defined, though a marked response to steroid therapy is the rule.

*Primary angiitis of CNS (PACNS)*

PACNS is an organ-specific vasculitis with inflammation and destruction of CNS vessels. Clinical presentations range from headache, seizures, and acute focal deficits to encephalopathy and cognitive impairment. The most common lesions are infarcts which show diffusion restriction in the acute phase. Hyperintense lesions are also noted in subcortical white matter, deep gray matter, and cortical regions. These lesions vary from small punctate to diffuse mass-like lesions and may have associated bleeds [Figure 1k and l]. The typical corpus callosum lesions of MS are absent. Spinal cord disease is rare but occurs in 10%. Angiographic abnormalities (luminal narrowing and beading of cerebral arteries) are characteristic, but have low sensitivity and specificity.[20]

## SYSTEMIC AUTOIMMUNE INFLAMMATORY DISEASES

### Systemic Connective Tissue Diseases

They can present with CNS and peripheral nervous system manifestations. CNS disease can result from inflammation (meningitis, encephalitis, and myelitis), vessel diseases (vasculitis and venous thrombosis), or due to structural changes of the spine. Secondary manifestations which could be unrelated to vasculitis are also quite common and include headache, seizures, psychosis, movement disorders, confusional state, and cognitive dysfunction.[21]

Systemic lupus erythematosus (SLE) has myriad CNS manifestations, the most common being headache, mood disorders, cognitive dysfunction, stroke, and seizures. MRI may show features of vasculitis or inflammation. Small vessel disease manifests as white matter T2 hyperintensities, lacunes, and microhemorrhages while infarcts characterize small and large vessel disease. Large and diffuse lesions mimicking demyelination involve white matter and deep gray matter and result from inflammation [Figure 2a]. Peripheral neuropathy, inflammatory myopathy, and autonomic neuropathy may coexist with CNS disease. Autoantibodies specific to the disease should be sent for including antinuclear antibody, antibodies against double-stranded DNA, and lupus anticoagulant. Low complement levels correlate with inflammatory process.[6,21]

CNS manifestations are relatively uncommon with Sjogren's disease. Longitudinally extensive myelitis and ON in the context of primary Sjogren's syndrome often reflect coexistent NMOSD. Non-specific cerebral white matter lesions and focal inflammatory lesions can mimic MS [Figure 2b and c].[21] Diagnosis is suspected with history of dry eyes, dry mouth, and positive SS-A and/or SS-B antibodies.

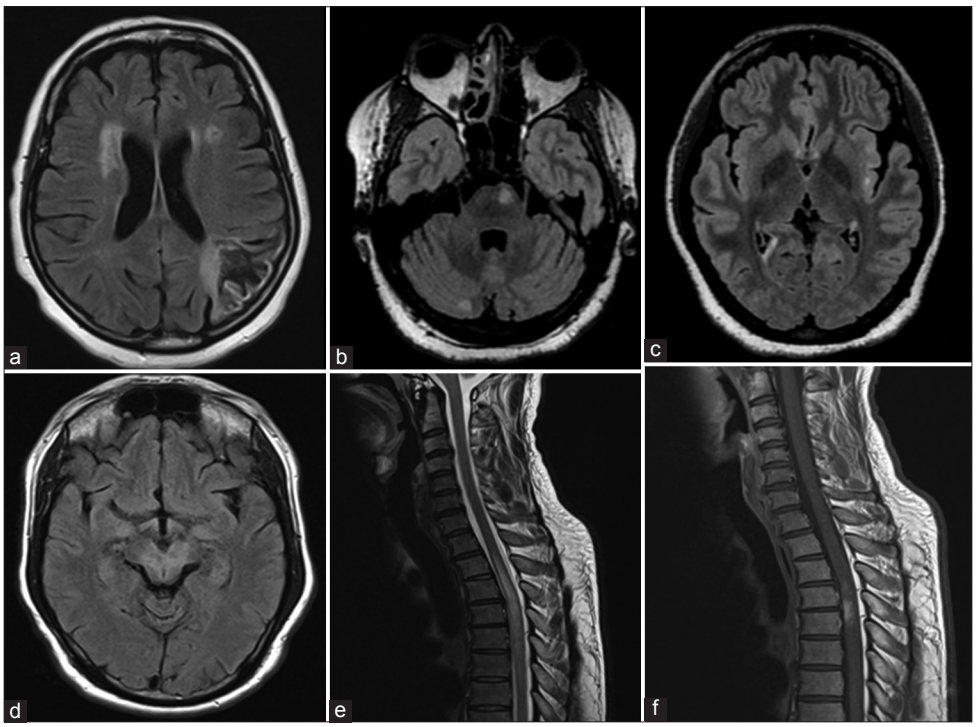


**Figure 2:** Magnetic resonance imaging (MRI) in systemic autoimmune diseases. (a) Systemic lupus erythematosus. T2 fluid-attenuated inversion recovery (FLAIR) axial image shows anterior deep white matter hyperintensities (right side more than left) and chronic infarct with gliosis in the left parietal lobe. (b,c) Sjogren's syndrome. Multiple discrete lesions in the right cerebellar hemisphere and ventral pons (b) and periventricular region and gray matter (c) in axial T2 FLAIR sections with nodular enhancement (not shown). (d) Behcet's disease. Axial T2 FLAIR hyperintensity diffusely involving midbrain, a location typical for the disease. (e,f) Sarcoid myelopathy. MRI spine sagittal sections show longitudinally extensive heterogeneous hyperintensity of thoracic cord from T1 to T7 (e) with enhancement in post-gadolinium T1 sequences (f)

### Primary Systemic Vasculitis

This term encompasses a host of diseases with inflammation of blood vessel walls resulting in ischemia and inflammatory damage to the end-organ. The main MS mimics among them are Takayasu arteritis, giant cell arteritis, and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Takayasu's arteritis leads to steno-occlusive disease of large vessels and neurological manifestations occur in nearly one-half of the patients. The symptoms range from vertigo and visual obscurations to ischemic strokes. Giant cell arteritis manifests as headache and acute-onset unilateral or bilateral visual loss due to anterior ischemic optic neuropathy. ANCA-associated vasculitis, particularly granulomatosis with polyangiitis, produces CNS manifestations due to vasculitis and granulomatous disease of meninges and parenchyma. Headache, cranial neuropathies, strokes, and venous thrombosis are the predominant presentations. Peripheral inflammatory markers, autoantibodies, and systemic disease help in establishing the diagnosis.[21]

### Behcet's Disease

Oral and genital ulcers, skin lesions, arthritis, positive pathergy test, HLA typing (HLA B51 association), and more common non-parenchymal neurological involvement in the form of cerebral venous sinus thrombosis or meningitis are characteristic features of Behcet's disease. Parenchymal inflammatory or vasculitic disease has a predilection for brainstem, with contiguous spread to thalamus and internal capsule [Figure 2d]. White matter lesions are more commonly subcortical than periventricular. Isolated myelitis and ON are rare.[21,22] Lesions of Behcet's disease may show the central vein sign similar to MS lesions.[6]

### Sarcoidosis

Sarcoidosis is a multisystemic disease affecting the lungs, skin, liver, lymph nodes, eyes, and nervous system. About 5–15% of patients have neurosarcoidosis. Preferential involvement of the meninges, optic nerves and chiasm, other cranial nerves (commonly facial nerves), pituitary and diencephalic region, and spinal cord is characteristic.[23] Punctate white matter lesions with enhancement can mimic MS. Sarcoid-associated myelopathy presents more commonly as a longitudinally extensive myelitis [Figure 2e and f], though short-segment tumefactive myelitis is described. Subpial origin and enhancement give rise to the "trident sign" in axial sections. The diagnosis is based on a consistent clinical and imaging syndrome and a positive biopsy showing non-necrotizing, well-organized granulomas.[23,24]

### Susac's Syndrome

A triad of encephalopathy, sensory neural hearing loss, and branch retinal artery occlusion results from an autoimmune arteriopathy of brain, retina, and inner ear. Similar to MS, young females are commonly affected.[25] The centrally located "snow ball" lesions in the body of corpus callosum are easily differentiated from the perpendicular Dawson's fingers of MS which abut the ventricular margin.[6] Restricted diffusion is also noted in the lesions. Extra-cerebral disease is demonstrated with fundus fluorescein angiography and audiometry.

## VASCULAR DISEASES

### Small Vessel Ischemic Disease

Small vessel disease is common in older patients and those with vascular risk factors. The two MRI manifestations are lacunar infarcts and subcortical white matter T2 hyperintensities. The lesions are located in the subcortical and periventricular cap regions, either discretely or as confluent lesions [Figure 3a]. They are differentiated from MS lesions by the sparing of U-fibers, corpus callosum and spinal cord, infrequent lesions in juxtacortical/cortical, inferior temporal and cerebellar locations, and lack of contrast enhancement of the lesions. Pontine hyperintensities are common in small vessel disease, but tend to be central compared to peripheral lesions in MS [Figure 3b]. Microbleeds and widening of Virchow-Robin spaces may coexist with vascular lesions.[7]

### Thromboembolic Disease

Acute, multifocal presentation, deficits, as well as infarcts in a vascular territory and presence of stroke risk factors are the cardinal features to be used to differentiate this disease from MS.[3,7]

### Antiphospholipid Antibody (APLA) Syndrome

APLAs are encountered in isolation or concomitant with connective tissue diseases, vasculitides, and infections. Although the primary disease mechanism is prothrombotic state leading to strokes, a variety of non-stroke manifestations includes headache, seizures, myelitis, chorea, and cognitive dysfunction. Primary APLA syndrome can present with an MS-like syndrome with visual and focal sensorimotor disease with relapses and remissions. MRI lesions in T2 also closely mimic MS though the smaller size, fewer number, and subcortical location favor APLA syndrome [Figure 3c and d]. The lesions in APLA syndrome also tend to disappear with anticoagulation and are less prone for asymptomatic accrual. APLAs may be positive in 2–88% of MS patients and hence need to be interpreted in tandem with the clinical-radiological signs.[26]

### Moyamoya Disease

Moyamoya disease is a rare progressive steno-occlusive cerebrovascular disease of the terminal internal carotid arteries which results in a rich collateral vascular network in the base of the brain. The latter is referred to as "moyamoya"

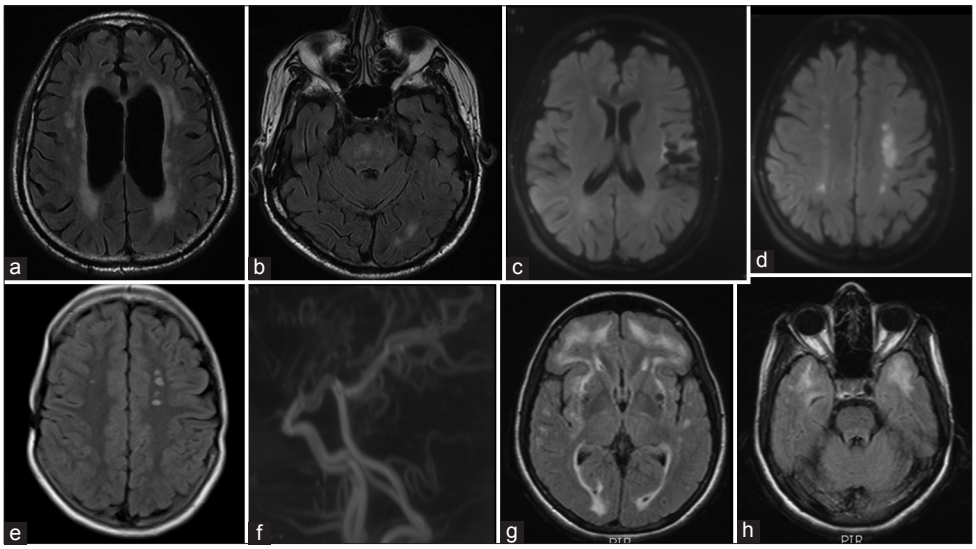


**Figure 3:** Magnetic resonance imaging in vascular diseases. (a,b) Cerebral small vessel disease. T2 fluid-attenuated inversion recovery (FLAIR) axial sections show discrete and confluent periventricular and subcortical lesions (a) and central pontine hyperintensities (b). (c,d) Antiphospholipid antibody syndrome. Chronic infarct with encephalomalacia left frontal lobe and chronic infarct right parietal lobe (c), deep subcortical white matter ischemic changes bilaterally, more on left (d). (e,f) Moyamoya disease. T2 FLAIR axial sections show discrete hyperintensities in deep watershed territory in bilateral subcortical white matter, more on left (e). MR angiogram TOF sequence lateral view shows non-visualization of bilateral supraclinoid internal carotid, middle cerebral, and anterior cerebral arteries with abundant collaterals (f). (g,h) Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Symmetric T2 FLAIR hyperintensities noted in periventricular white matter, centrum semi-ovale, external capsule, insular subcortex (g), and anterior temporal white matter (h)

vessels. Symptoms result from hemodynamic ischemia and are precipitated by hyperventilation. The infarcts may show typical (territorial, watershed, and lacunar) or atypical (gyral, non-territorial, and confluent lesions with cystic regions) patterns, the latter being more frequent.[27] Angiographic demonstration of the large vessel stenosis/occlusion and the typical "puff of smoke" appearance of collaterals are required for the diagnosis [Figure 3e and f].

### Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

The core clinical features of this genetic vasculopathy are migraine, recurrent strokes or transient ischemic attacks, neuropsychiatric symptoms, and cognitive dysfunction. Relative symmetry of the white matter lesions, specific involvement of temporal poles, and external capsules and subcortical infarcts help in differentiating from MS [Figure 3g and h]. Microbleeds in cortical and subcortical locations are common. Cortex, callosum, and extrapontine infratentorial regions are spared.[28] Mutations in *NOTCH3* gene confirm the diagnosis. An analogous condition called CARASIL can result from recessive mutations in high-temperature requirement A serine peptidase 1.[28]

## INFECTIONS

Many CNS infections show white matter lesions on MRI but clinical features, characteristic imaging findings, blood, and CSF tests often help to separate infections from MS. Certain infections which can have features simulating MS are discussed hereafter.

### Progressive Multifocal Leukoencephalopathy (PML)

PML is an opportunistic CNS infection caused by JC virus in patients with HIV infection and on immunosuppressive therapy. Natalizumab and fingolimod therapy in MS increases the risk for PML which makes this a particular concern for differentiation from a relapse of MS. It presents with subacute focal neurological deficit (weakness, cognitive dysfunction, ataxia, aphasia, or visual dysfunction) and seizures. The lesions are usually multifocal or confluent and confined to subcortex. The edge of the lesion shows diffusion restriction and enhancement is mild or absent [Figure 4a and b].[29] PML is generally progressive and fatal even with intervention.

### Human Immunodeficiency Virus (HIV) Encephalitis

Clinically, HIV encephalitis presents with gradually progressive cognitive decline without many focal signs. MRI shows diffuse, symmetrical white matter hyperintensities, sparing the U-fibers [Figure 4c] and without contrast enhancement, and atrophy out of proportion for patient's age.[7,30]

### Central Nervous System Tuberculosis (TB)

Multiple tuberculomas in MRI and optic neuropathy in CNS TB may mimic MS. Tuberculomas can be single or multiple

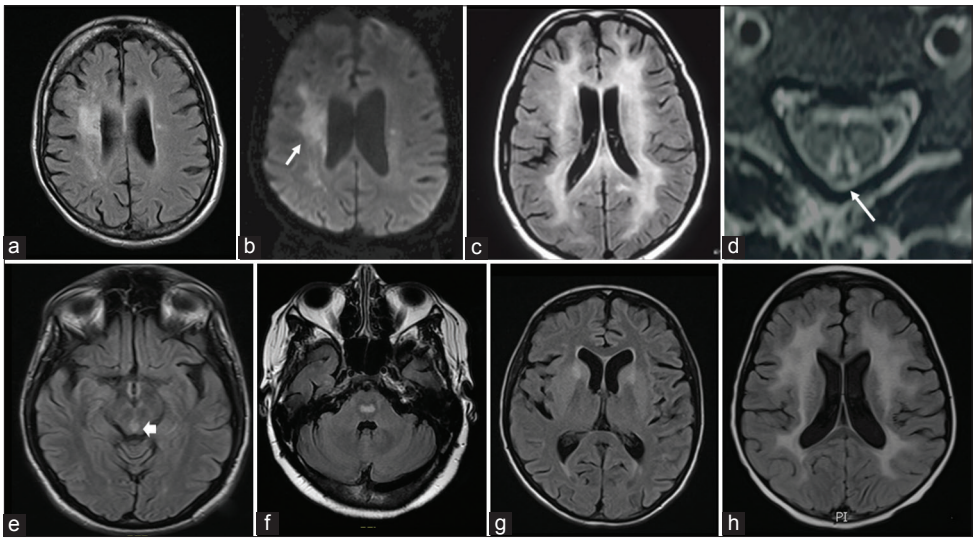


**Figure 4:** Magnetic resonance imaging in infectious, nutritional, and metabolic diseases. (a,b) Progressive multifocal leukoencephalopathy. Right subcortical and periventricular white matter hyperintensity with poorly defined borders in T2 fluid-attenuated inversion recovery (FLAIR) (a) with diffusion hyperintensity (arrow in b) and low ADC in the leading edge of the lesion (not shown). (c) HIV encephalopathy. Symmetric and diffuse periventricular and subcortical white matter hyperintensities in T2 FLAIR sequence. (d) Subacute combined degeneration of spinal cord. T2 axial section of cervical cord shows symmetric "wedge-shaped" hyperintensity involving the posterior columns (arrow). (e) Wernicke's encephalopathy. Symmetric hyperintensities of mammillary bodies and in the periaqueductal region (block arrow) in T2 FLAIR axial brain section. (f) Central pontine myelinolysis. Central hyperintensity in pons in T2 FLAIR with diffusion restriction (not shown). (g) Extrapontine myelinolysis. Symmetric T2 FLAIR hyperintensities of caudate, putamen, and globus pallidus. (h) Methotrexate-induced leukoencephalopathy. Symmetric T2 FLAIR hyperintensities of frontoparietal white matter extending to U-fibers

and can occur in any region of the brain. They are T2 hypo or hyperintense and show ring and nodular patterns of enhancement with or without conglomeration. Meningeal enhancement, thick exudates, and hydrocephalus can coexist with the parenchymal lesions. Tuberculous myelitis manifests as longitudinally extensive T2 hyperintensity with marginal enhancement and perilesional edema and coexists with arachnoiditis.[31]

### Lyme Disease

Lyme disease is an infectious inflammatory disease caused by the tick-borne spirochete *Borrelia burgdorferi*. It is endemic in North America and North Europe. Neurological manifestations are in the form of meningoencephalitis or meningoradiculoneuritis with involvement of facial and optic nerves and spinal nerve roots. The T2 hyperintensities on MRI have no specific characteristics and may enhance in the acute phase along with the leptomeningeal enhancement. Detection of bacterial antibodies in CSF is diagnostic.[30]

### Human T-Cell Lymphotropic Virus-1 HTLV-1-Associated Myelitis

HTLV-1 is transmitted sexually or through blood products or with intravenous substance abuse. It presents with progressive spastic paraparesis with pain and sphincter dysfunction. MRI may show white matter hyperintensities in the supratentorial region and spinal cord atrophy. Detection of HTLV-1 antibodies in CSF confirms diagnosis.[30]

### Neurosyphilis (NS)

Neurological manifestations are in the form of meningitis, meningovascular syphilis, meningomyelitis, tabes dorsalis, and progressive cognitive decline which markedly differ from typical MS relapses. MRI brain shows meningeal enhancement, vasculitic infarcts, and white matter hyperintensities which do not satisfy the criteria for MS. MRI spine may show longitudinally extensive myelitis with "candle gutter" appearance which is a feature of syphilitic myelitis.[32] Syphilis is a mimicker of many diseases and a high degree of suspicion has to be kept if you encounter manifestations as described above. Serum and CSF *Treponema pallidum* hemagglutination test, fluorescent treponemal antibody test, and venereal disease research laboratory test help establish the diagnosis.[30]

## NUTRITIONAL, METABOLIC, AND TOXIC DISEASES

### Vitamin B12 and Related Deficiencies

Vitamin $B_{12}$ deficiency leads to subacute combined degeneration (SACD) of spinal cord. Progressive symmetric posterior column signs and spastic paraparesis can mimic progressive MS. Cognitive and neuropsychiatric symptoms may also occur. MRI spine shows a typical symmetric longitudinal T2 hyperintensity of cervicothoracic dorsal columns seen on

axial images as "inverted V sign" [Figure 4d]. Confluent and reversible white matter hyperintensities may be noted on brain MRI.[33] Coexistent macrocytosis, neuropathy, and symmetric involvement should suggest Vitamin B12 deficiency. Folate and copper deficiency and nitrous oxide toxicity produce similar clinical syndromes.

### Wernicke's Encephalopathy

Acute thiamine deficiency produces a triad of encephalopathy, cerebellar ataxia, and oculomotor abnormalities or limited forms of these symptoms. Symmetric and specific involvement of thalami, mammillary bodies, periventricular region (around third ventricle), and periaqueductal region are noted in the MRI [Figure 4e].[34] An antecedent in the form of alcohol binge, recurrent vomiting, malnutrition, pregnancy, or renal failure is usually identified.

### Marchiafava-Bignami disease

Marchiafava-Bignami disease presents with subacute cognitive decline and is primarily a disease of corpus callosum. It may rarely involve the white matter, and when it does, it spares the U-fibers. Callosal lesions involve the body and genu in continuum and thickness unlike MS callosal lesions.[7]

### Osmotic Demyelination

Osmotic demyelination syndrome is an acute or subacute metabolic disease which comprises central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM). Patients present with quadriparesis and bulbar weakness or extrapyramidal dysfunction, commonly following hyponatremic encephalopathy and rapid correction. A symmetric trident-shaped T2 hyperintensity is noted in CPM [Figure 4f] whereas the lesions are more extensive involving cerebellum, basal ganglia, and cerebral white matter in EPM [Figure 4g].[35]

### Posterior Reversible Encephalopathy Syndrome (PRES)

PRES presents with headache, encephalopathy, seizures, and visual disturbances. It occurs in specific situations such as severe hypertension and eclampsia, after administration of certain medicines such as methotrexate [Figure 4h], cyclosporine, and tacrolimus.[36] MRI shows subcortical and cortical areas of T2 hyperintensities, predominantly affecting parieto-occipital areas, but frontal and temporal involvement may also be seen. They classically revert after offending agent is corrected/discontinued.[7]

## MALIGNANCIES

### Gliomatosis Cerebri and Other Neoplasms

Gliomatosis cerebri is an infiltrating glial tumor with contiguous involvement multiple brain lobes. Progressive focal deficits, seizures, and raised intracranial tension constitute the clinical picture. MRI shows diffuse and confluent T2 hyperintensities involving white and gray matter with expansion of the affected regions [Figure 5a]. Enhancement is variable.[37] Typical discrete lesions of MS and spinal cord lesions are not seen. Other mass lesions such as glioma and central nervous system lymphoma [Figure 5b and c] may rarely mimic MS.

### Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis is a multisystem lymphoproliferative disease considered to be a precursor for non-Hodgkin's lymphoma. Lung, skin, and CNS involvement, either as parenchymal or meningeal disease, are characteristic. Multifocal T2 hyperintense lesions ranging in size from punctate to mass-like which shows nodular, punctate, or linear enhancement and a very typical radial enhancement along vessels seen some patients. Meningeal and ring-like enhancement can also be noted.[38]

### Paraneoplastic Neurological Syndromes (PNSs)

PNSs include a group of immune-mediated disorders associated with malignancies mainly small cell lung cancer, breast, ovary, germ cell, lymphoma, thymoma, and monoclonal gammopathies. The classical CNS paraneoplastic presentations include paraneoplastic encephalomyelitis, limbic encephalitis, and opsoclonus myoclonus ataxia. The clinical presentations of these syndromes include subacute cognitive and behavioral changes and delirium and eye movement abnormalities. These presentations are hardly ever confused with MS. Paraneoplastic cerebellar degeneration, paraneoplastic myelitis, and cancer-associated retinopathy can mimic MS but their MRI findings do not bear a resemblance to MS. Paraneoplastic antibodies help confirm the diagnosis.[30]

### Radiation-Induced Encephalopathy (RIE)

RIE presents with subacute encephalopathy or progressive cognitive decline in a patient who has received radiotherapy. MRI shows confluent, relatively symmetrical hyperintensities [Figure 3d].[7,39]

## GENETIC DISEASES

### Leukodystrophies

Leukodystrophies have highly variable presentation and may manifest in childhood, adolescence, or adulthood. The clinical pointers which differentiate from progressive MS are very long duration of symptoms, positive family history, atypical symptoms (dystonia, marked cognitive dysfunction, and epilepsy), and peripheral neuropathy. MRI usually shows symmetric and confluent lesions with specific patterns of involvement (sparing of U-fibers, subcortical pattern, and anterior or posterior dominance) [Figure 5e and f] which argue against MS.[40]

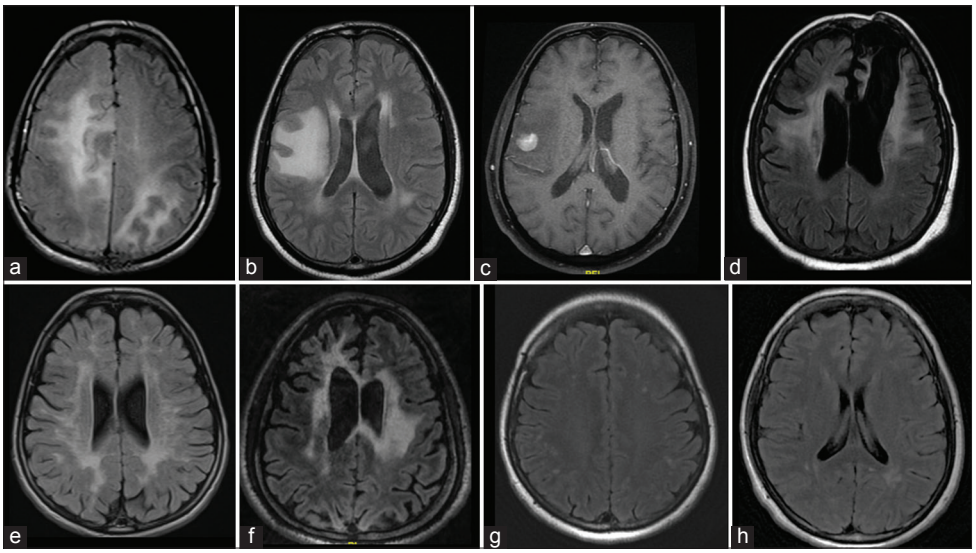


**Figure 5:** Magnetic resonance imaging in neoplasms, radiation encephalopathy, leukodystrophies, and migraine. (a) Gliomatosis cerebri. Asymmetric gray matter lesion involving adjacent subcortex with ill-defined borders and mass effect. (b,c) Central nervous system lymphoma. Asymmetric subcortical T2 fluid-attenuated inversion recovery (FLAIR) hyperintensity extending to cortex on right (b) with nodular contrast enhancement (c). (d) Radiation-induced leukoencephalopathy. Post-operative changes in the left frontal lobe with T2 FLAIR confluent periventricular and deep white matter hyperintensities of frontal lobes. (e) Metachromatic leukodystrophy. Symmetric frontoparietal white matter hyperintensities in T2 FLAIR relatively sparing U-fibers and tigroid appearance. (f) Adult onset leukodystrophy with axonal spheroids. Asymmetric periventricular, deep white matter, and corpus callosum hyperintensity in T2 FLAIR with diffusion restriction (not shown). (g,h) Migraine. T2 FLAIR discrete subcortical hyperintensities with no predilection for periventricular or juxtacortical regions or contrast enhancement

### Mitochondrial Diseases

Leber's hereditary optic neuropathy (LHON), mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), Leigh disease, and polymerase gamma (POLG)-related disease may mimic progressive MS.[40] Of particular interest is LHON which usually manifests as subacute and asymmetric visual loss in adolescents and young adults. The diagnosis can be made in the acute phase by the typical fundus picture of disc edema, increased vascularity, and tortuous blood vessels. However, optic atrophy is the common phenotype in the long term. Three point mutations of mitochondrial DNA which encodes complex I subunit of the respiratory chain account for more than 95% of the cases. An MS-like illness coexists with LHON at a frequency far more than population frequency suggesting an association between the two diseases. This phenotype is referred to as Harding's disease.[40]

## TRAUMA

### Diffuse Axonal Injury (DAI)

DAI occurs during trauma due to axonal shearing. It presents as rapidly progressive worsening of sensorium and MRI shows white mater hyperintensities in the gray-white matter interface, internal capsule, deep gray nuclei, upper brainstem, and corpus callosum.[7]

## MISCELLANEOUS

### Migraine with Atypical MRI Features

White matter abnormalities and infarct-like lesions can occur in migraine even in the absence of cerebrovascular risk factors. In combination with aura or non-specific symptoms, these lesions are often mistaken for MS. Topographic location and strict application of diagnostic criteria for MS help in differentiation. The lesions are discrete and subcortical in location, sparing the U-fibers and cortex [Figure 5g and h]. Spinal cord lesions and post-contrast enhancement are never seen.[6]

### Somatization and Fibromyalgia

Both these disease present with multitude of symptoms which may mimic MS but none of the symptoms fit into any classic relapse of MS. There are neither any objective signs confirming a relapse nor MRI findings suggestive of MS. CSF and VEPs are always normal. Strict adherence and application of MS clinical and radiological diagnostic criteria will prevent these misdiagnoses.[41]

## CERTAIN UNIQUE MIMICKERS OF PRIMARY PROGRESSIVE MS

Primary lateral sclerosis and hereditary spastic paraplegia (HSP) present with pure motor insidious onset gradually progressive spastic paraparesis. They are distinguished from

**Table 2:** Some peripheral disorders that can mimic multiple sclerosis

| Organ involved | Disease |
|---|---|
| Anterior horn cell | Motor neuron disease (MND) |
| Dorsal root ganglion | Ganglionopathies (Sjogren's, paraneoplastic, idiopathic) |
| Peripheral nerve disorders | Inflammatory neuropathies |
| | Vasculitic neuropathy |
| | Nutritional ($B_{12}$, folate deficiency) neuropathies |
| | Toxic (heavy metals, drugs) neuropathies |
| Neuromuscular junction disorders | Myasthenia gravis |

MS by virtue of absence of sensory manifestations and classical MRI features of MS. Presence of family history and genetic analysis is diagnostic for HSP.[3]

## LOWER MOTOR NEURON/PERIPHERAL MOTOR AND SENSORY DISORDERS MIMICKING MS

At times, lower motor neuron/peripheral nerve or dorsal root ganglion disorders can present with features that can be mistaken for MS. They are listed in Table 2. Presence of wasting, fasciculations, motor weakness, and sensory loss in the distribution of spinal segment or peripheral nerve presentation in the pattern of length-dependent peripheral neuropathy or mononeuropathy multiplex, fatigable weakness, and depressed or absent deep tendon reflexes are important findings pointing toward a peripheral lesion. Electromyography and nerve conduction studies will help confirm localization of the lesion.

## CONCLUSIONS

The mimics of MS are diverse with a wide range of clinical and radiological differential diagnosis. A systematic approach to clinical history and examination with a view to categorizing typical versus atypical presentations would go a long way in excluding many of the possibilities. Presence of systemic disease or symptoms, positive family history, and signs outside CNS are major red flags. Likewise, images should be specifically assessed to categorize the appearance as typical, atypical, or exclusionary for MS. Good quality of imaging with appropriate brain and spinal cord sequences with and without contrast is mandatory for the diagnosis. Ancillary investigations including serological and CSF studies should be applied when the diagnosis is in doubt. The recognition of MS from its mimics will avoid unnecessary and potentially harmful or futile therapies.

## REFERENCES


1. Wildner P, Stasiołek M, Matysiak M. Differential diagnosis of multiple sclerosis and other inflammatory CNS diseases. Mult Scler Relat Disord 2020;37:101452.
2. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, *et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-73.
3. Solomon AJ. Diagnosis, differential diagnosis, and misdiagnosis of multiple sclerosis. Continuum (Minneap Minn) 2019;25:611-35.
4. Calabrese M, Gasperini C, Tortorella C, Schiavi G, Frisullo G, Ragonese P, *et al*. "Better explanations" in multiple sclerosis diagnostic workup: A 3-year longitudinal study. Neurology 2019;92:e2527-37.
5. Miller DH, Weinshenker BG, Filippi M, Banwell BL, Cohen JA, Freedman MS, *et al*. Differential diagnosis of suspected multiple sclerosis: A consensus approach. Mult Scler 2008;14:1157-74.
6. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, *et al*. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: Practical guidelines. Brain 2019;142:1858-75.
7. Aliaga ES, Barkhof F. MRI mimics of multiple sclerosis. Handb Clin Neurol 2014;122:291-316.
8. Freedman MS, Thompson EJ, Deisenhammer F, Giovannoni G, Grimsley G, Keir G, *et al*. Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis: A consensus statement. Arch Neurol 2005;62:865-70.
9. Jena SS, Alexander M, Aaron S, Mathew V, Thomas MM, Patil AK, *et al*. Natural history of multiple sclerosis from the Indian perspective: Experience from a tertiary care hospital. Neurol India 2015;63:866-73.
10. Tenembaum S, Chitnis T, Ness J, Hahn JS, International Pediatric MS Study Group. Acute disseminated encephalomyelitis. Neurology 2007;68:S23-36.
11. Katz Sand I. Neuromyelitis optica spectrum disorders. Continuum (Minneap Minn) 2016;22:864-96.
12. Jarius S, Paul F, Franciotta D, Ruprecht K, Ringelstein M, Bergamaschi R, *et al*. Cerebrospinal fluid findings in aquaporin-4 antibody positive neuromyelitis optica: Results from 211 lumbar punctures. J Neurol Sci 2011;306:82-90.
13. Jarius S, Ruprecht K, Kleiter I, Borisow N, Asgari N, Pitarokoili K, *et al*, In cooperation with the Neuromyelitis Optica Study Group (NEMOS). MOG-IgG in NMO and related disorders: A multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. J Neuroinflammation 2016;13:280.
14. Pujari SS, Kulkarni RV, Nadgir DB, Ojha PK, Nagendra S, Aglave V, *et al*. Myelin oligodendrocyte glycoprotein (MOG)-IgG associated demyelinating disease: Our experience with this distinct syndrome. Ann Indian Acad Neurol 2021;24:69-77.
15. Netravathi M, Holla VV, Nalini A, Yadav R, Vengalil S, Oommen AT, *et al*. Myelin oligodendrocyte glycoprotein-antibody-associated disorder: A new inflammatory CNS demyelinating disorder. J Neurol 2021;268:1419-33.
16. Tobin WO, Guo Y, Krecke KN, Parisi JE, Lucchinetti CF, Pittock SJ, *et al*. Diagnostic criteria for chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). Brain 2017;140:2415-25.
17. Kunchok A, Zekeridou A, McKeon A. Autoimmune glial fibrillary acidic protein astrocytopathy. Curr Opin Neurol 2019;32:452-8.
18. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, *et al*. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2016;15:391-404.
19. Kelley BP, Patel SC, Marin HL, Corrigan JJ, Mitsias PD, Griffith B.

Autoimmune encephalitis: Pathophysiology and imaging review of an overlooked diagnosis. AJNR Am J Neuroradiol 2017;38:1070-8.
20. Hajj-Ali RA, Singhal AB, Benseler S, Molloy E, Calabrese LH. Primary angiitis of the CNS. Lancet Neurol 2011;10:561-72.
21. Dimberg EL. Rheumatology and neurology. Continuum (Minneap Minn) 2017;23:691-721.
22. Uygunoğlu U, Saip S, Siva A. Behçet's syndrome and nervous system involvement. Curr Neurol Neurosci Rep 2018;18:35.
23. Stern BJ, Royal W, Gelfand JM, Clifford DB, Tavee J, Pawate S, *et al*. Definition and consensus diagnostic criteria for neurosarcoidosis: From the neurosarcoidosis consortium consensus group. JAMA Neurol 2018;75:1546-53.
24. Murphy OC, Salazar-Camelo A, Jimenez JA, Barreras P, Reyes MI, Garcia MA, *et al*. Clinical and MRI phenotypes of sarcoidosis-associated myelopathy. Neurol Neuroimmunol Neuroinflamm 2020;7:e722.
25. Kleffner I, Dörr J, Ringelstein M, Gross CC, Böckenfeld Y, Schwindt W, *et al*. Diagnostic criteria for Susac syndrome. J Neurol Neurosurg Psychiatry 2016;87:1287-95.
26. Fleetwood T, Cantello R, Comi C. Antiphospholipid syndrome and the neurologist: From pathogenesis to therapy. Front Neurol 2018;9:1001.
27. Kim JS. Moyamoya disease: Epidemiology, clinical features, and diagnosis. J Stroke 2016;18:2-11.
28. Majersik JJ. Inherited and uncommon causes of stroke. Continuum (Minneap Minn) 2017;23:211-37.
29. Sahraian MA, Radue EW, Eshaghi A, Besliu S, Minagar A. Progressive multifocal leukoencephalopathy: A review of the neuroimaging features and differential diagnosis. Eur J Neurol 2012;19:1060-9.
30. Ömerhoca S, Akkaş SY, İçen NK. Multiple sclerosis: Diagnosis and differential diagnosis. Noro Psikiyatr Ars 2018;55:S1-9.
31. Trivedi R, Saksena S, Gupta RK. Magnetic resonance imaging in central nervous system tuberculosis. Indian J Radiol Imaging 2009;19:256-65.
32. Pujari SS, Kulkarni RV, Duberkar D, Nirhale S, Nadgir D, Dhonde P, *et al*. Neurosyphilis, a true chameleon of neurology. Ann Indian Acad Neurol 2021;24:566-72.
33. Reynolds E. Vitamin B12, folic acid, and the nervous system. Lancet Neurol 2006;5:949-60.
34. Zuccoli G, Pipitone N. Neuroimaging findings in acute Wernicke's encephalopathy: Review of the literature. AJR Am J Roentgenol 2009;192:501-8.
35. Howard SA, Barletta JA, Klufas RA, Saad A, De Girolami U. Best cases from the AFIP: Osmotic demyelination syndrome. Radiographics 2009;29:933-8.
36. Jewells VL, Latchaw RE. What can mimic multiple sclerosis? Semin Ultrasound CT MR 2020;41:284-95.
37. Ranjan S, Warren KE. Gliomatosis cerebri: Current understanding and controversies. Front Oncol 2017;7:165.
38. Tateishi U, Terae S, Ogata A, Sawamura Y, Suzuki Y, Abe S, *et al*. MR imaging of the brain in lymphomatoid granulomatosis. AJNR Am J Neuroradiol 2001;22:1283-90.
39. Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD. Radiation-induced brain injury: A review. Front Oncol 2012;2:73.
40. Weisfeld-Adams JD, Katz Sand IB, Honce JM, Lublin FD. Differential diagnosis of Mendelian and mitochondrial disorders in patients with suspected multiple sclerosis. Brain 2015;138:517-39.
41. Solomon AJ, Bourdette DN, Cross AH, Applebee A, Skidd PM, Howard DB, *et al*. The contemporary spectrum of multiple sclerosis misdiagnosis: A multicenter study. Neurology 2016;87:1393-9.

**How to cite this article:** Pujari SS, Nair SS. Update on multiple sclerosis mimics. Bombay Hosp J 2021;63(4):159-170.

**Source of support:** Nil, **Conflicts of interest:** None