Demyelinating Disorders of the CNS: Spectrum of Imaging Findings and Diagnostic Challenge

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Learning objectives

• To identify clinical and imaging patterns of demyelinating disorders

• Can MRI assist in characterizing and differentiating various CNS demyelinating disorders
Background

Inflammatory demyelination disorders of the CNS are a broad group of disorders that involve acute on chronic autoimmune destruction CNS neuroglia. These are relatively common in Caucasians compared to Asian and African-American populations. These disorders vary in terms of their epidemiology, pattern of disease presentation, pathology, imaging findings and prognosis.

Multiple Sclerosis (MS):

MS is the most common form of chronic demyelinating diseases of the CNS.

It has a lifetime incidence of 0.1% and is more common among siblings of affected patients (up to 25%) indicating the strong genetic component of the disease.\(^1,3\) The central hypothesis surrounding the pathophysiology of MS involves dysregulation of CD4 T lymphocytes.

There is evidence to suggest that Th1 and Th17 lymphocytes are involved in autoimmunity resulting in demyelination.\(^2\) While the precise genes have not been identified, polymorphic variations of CD58, IL7R and IL2Ra genes were correlated with MS.

Over 90% of patients with MS are females and the most common age of onset is between 21 and 30 years. Presenting complaints often include ataxia, reduced visual acuity, parasthesias, bladder and bowel dysfunction and depression.

There are four major clinical courses of MS which include clinically isolated syndrome (CIS) and RIS, relapsing remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS). Patients with CIS may be diagnosed with MS if they satisfy the 2017 McDonald MS diagnostic criteria.

No single diagnostic marker is present and hence the diagnostic criteria is required to make a diagnosis of MS. The only laboratory finding that is part of the criteria is the presence of CSF-specific oligoclonal bands. On MRI, demyelinating plaques are typically identified in the juxtacortical, periventricular, cortical or infratentorial regions or in the spinal cord. Optic nerve involvement is common.\(^4\)

Acute attacks are treated with intravenous methylprednisolone. Immunotherapies for relapsing and acute attacks include monoclonal antibody drugs, interferons and glatiramer acetate. Imaging is often used to assess response to treatment and monitor progression of disease.

There are many adverse effects of the treatment for MS. Some adverse effects include increased risk of miscarriage (interferon beta), Progressive Multifocal
Leukoencephalopathy (PML) due to activation of JC virus (natalizumab), urinary tract infections (VLA4 antagonists), Therapy Related Acute Leukemia (TRAIL) (mitoxantorone), arrhythmias (fingolimod) and thyroid autoimmunity (alemtuzumab) to name a few.5

Neuromyelitis Optica Spectrum Disorders (NMOSD):

NMO or Aquaporin 4 IgG (AQP4-IgG) positive Neuromyelitis Optica was first described in 1870 and was thought to be a subtype of MS. It was later identified as a separate entity due to its unique antibody status. The pathogenesis involves autoimmunity against astrocytes.

Although it is more common in Caucasian populations overall, it has a higher prevalence than MS in non-Caucasian populations. NMO can also be encountered in patients less than 18 years of age.

Patients may present with vision loss, complete acute spinal cord syndrome, intractable hiccups, nausea, narcolepsy and autonomic regulation.

It commonly involves the optic nerve and circumventricular organs, or structures located around the third and fourth ventricles.

Acute attacks are treated with intravenous methylprednisolone. Immunosuppressive therapy with eculizumab has shown to slow disease progression.

There is stepwise progression of the disease due to accumulation of plaques.

Similar to MS, MRI can be used to assess response to treatment in NMO.6,7

Myelin Oligodendrocyte Glycoprotein (MOG) encephalomyelitis:

MOG was initially identified as a form of atypical NMO. These cases for NMO had similar phenotypes to NMO but were AQP4-IgG negative. Later MOG -IgG was identified in a subset of patients with NMOSD. Thus, they were grouped along with NMO Spectrum Disorder (NMOSD). Further testing revealed a significant number of patients with MOG-IgG with similar phenotypes, clinical course and prognosis. The pathogenesis involves autoimmunity against oligodendrocytes in contrast to astrocytes in NMO.

MOG is frequently seen in children, while the above mentioned disorders are less common.

Patients present with recurrent optic neuritis (ON), myelitis and brainstem encephalitis, as well as with acute disseminated encephalomyelitis (ADEM)-like presentations.
Imaging plays a key role in identifying MOG because conventional treatments for MS and NMO are not effective in MOG-IgG disease.

Treatment of acute attacks involves IV methylprednisolone and IVIg. Immunosuppressive treatment is achieved best with rituximab, ocrelizumab and ofatumumab.

MOG disease also has a higher rate of relapse following cessation of steroid treatment for acute attacks.\textsuperscript{8,9,10}

**Mimics of Multiple Sclerosis:**

**Acute Disseminated Encephalomyelitis (ADEM):**

ADEM is a rare inflammatory disorder of the CNS which often follows bacterial or viral infections and less commonly vaccination. It usually occurs in children and is MOG-IgG positive in about 50\% of cases. ADEM has a lightly higher male preponderance compared to the above-mentioned disorders. Clinical presentation includes rapid onset altered level of consciousness, behavioral disturbance, ataxia, visual disturbance, seizures, focal neurological symptoms and nausea and vomiting. There is no unique antibody test associated with ADEM.

On MR, large lesions (>1 - 2 cm in size) are encountered in the supra and infratentorial white matter. Grey matter lesions include the basal ganglia and thalamus. Intramedullary lesions are seen in the spinal cord.

Treatment of acute attacks involves IV methylprednisolone. IVIg or plasmapheresis may be used if response to corticosteroids is not adequate. Long term immunomodulating drugs may not be necessary in most cases.

There is rapid partial resolution of the demyelinating lesions within 1-2 weeks. There may be a total resolution of symptoms and lesions in 6 - 12 months. Persistent neurological symptoms may be present in a small subset of people. For these patients, no therapy has been shown to be superior to another.\textsuperscript{11,12}

**Susac's Syndrome (SS)**

SS is a clinical disorder characterized by a triad of encephalopathy, sensorineural hearing loss and visual disturbance caused by branch retinal artery occlusion. The condition is very rare as there are only over 100 case reports for this disease. Although its pathophysiology is not clear, the occlusion is believed to be mediated by an autoimmune process affecting the small vessels. This is important to note as it is not a demyelinating disorder, however mimics demyelinating disorders.
It is commonly found in females between 20-40 years of age and quite often within the first year of pregnancy.

The clinical presentation includes symptoms like hearing loss, visual disturbance, urinary dysfunction, aphasia, cognitive impairment and headaches. Not all patients present with the triad described above. The MR findings of this disease are quite characteristic and are described below.

Treatment consists of initial high dose IV methylprednisolone followed by a course of tapering oral steroids. Cyclophosphamide has also shown some evidence of efficacy.

Over 50% of patients have irreversible damage and have residual symptoms, with a mild improvement seen in very few patients. Some patients may also relapse on treatment and may have further brain lesions despite therapy, indicating the need for further research into treatment for this disorder.\(^{16,17}\)
Imaging findings OR Procedure details

MRI features of demyelination:

Demyelinating lesions can be broadly classified into grey matter, white matter, optic nerve and spinal cord lesions.

White matter lesions are the most common lesions found in demyelinating disorders. These lesions appear hyperintense on T2WI. While this is a sensitive finding, it is hardly ever specific if taken in isolation. FLAIR sequences improve tissue contrast by suppressing the signal from CSF, making juxtacortical lesions easier to identify.

T1WI can initially appear normal, however in some patients the plaques appear hypointense. These lesions can be either acute or chronic and represent axonal injury.

Gadolinium based imaging can help distinguish between active and chronic lesions. These lesions can be homogenous, heterogenous or ring enhancing. Lesions that are seen on T2WI and T1WI that also show gadolinium enhancement are acute in nature. However, it is important to note that Gadolinium enhancement of white matter lesions may not completely correlate with clinical presentation as Gadolinium enhanced imaging is 5-10 times more sensitive at identifying active inflammatory lesions.

Grey matter lesions are classified into subcortical and cortical lesions. T2WI is relatively insensitive in identifying grey matter plaques. On T2WI, hypointensities of grey matter are observed, particularly in the subcortical grey matter. Double Inversion Recovery and FLAIR have a higher sensitivity compared to T2WI in identifying white matter lesions.

Spinal cord lesions are best visualized on T2WI and STIR/FSE sequences. Demyelinating lesions appear as hyperintense, however can be missed if are very small. Similar to white matter changes, T1 hypointensities can also be seen within the spinal cord.

Optic nerve involvement is best demonstrated with dedicated imaging of the optic nerve. STIR sequences play a role in facilitating identification of plaques over the optic nerve. Advanced imaging techniques like diffusion tensor imaging are also used in certain circumstances, however, provide no significant diagnostic advantage. Like white matter lesions, these plaques also demonstrate gadolinium enhancement.  

Features of demyelinating disorders on MRI:
Although there is cross-over among the different disorders, each disorder is associated with certain unique pattern of imaging findings.

In patients with MS, unilateral optic neuritis, short longitudinal cervical spinal cord lesions, periventricular (Dawson's fingers - Fig 1 and 2), juxtacortical and posterior fossa involvement is commonly seen. Optic neuritis in MS is typically unilateral, short and involves minor extension into the chiasm (Fig 3). The spinal cord lesions are short and hence are often missed. Involvement of the corpus callosum is seen in MS and is not seen in NMO. Ring and nodular Gadolinium enhancement of lesions is frequently seen (Fig 1).\(^1,14\) Sometimes, large tumor-like lesions can also be seen with MS. These lesions are known as tumefactive MS. These lesions are often atypical for MS and may appear to exert mass effect and also show ring enhancement. They can often be differentiated from CNS tumors by the presence of open ring enhancement directed towards the cortex which is not seen in tumors. They also demonstrate mixed T2-weighted iso and hyper intensity of enhanced regions, and absence of cortical involvement.\(^19\) Fig 4 and 5 show two cases of tumefactive MS. Fig 6 shows a case of widespread MS.

In NMSOD, bilateral optic nerve involvement including the chiasm, cervicothoracic spinal involvement and circumventricular organ involvement is seen. The lesions are frequently encountered at the cortico-subcortical junction. Large brainstem lesions may be seen. Spinal cord lesions are longitudinal and may also appear to exert mass effect. Cloud-like and periependymal patterns of gadolinium enhancement are seen in NMOSD.\(^15\) Fig 7, 8 and 9 show three separate cases of NMO involving the cerebrum, optic nerves and spinal cord respectively.

The imaging findings of MOG-IgG encephalomyelitis are not very consistently reported in literature due to it being a relatively newly identified disorder. Cerebral lesions are shown in Fig 10. In these patients, bilateral optic nerve involvement sparing the chiasm (Fig 11), conus medullaris and thoracolumbar spinal involvement, basal ganglia, thalamic and infratentorial lesions are commonly seen.\(^15\) Fig 12 shows cervicothoracic spinal cord involvement in a case of MOG-IgG encephalomyelitis.

ADEM commonly involves the cortical grey matter, deep white matter with periventricular sparing and thoracic spinal cord. Due to the large size of these lesions (especially spinal cord lesions), mass effect can be observed. All lesions tend to show simultaneous patchy gadolinium enhancement (Fig 13). In some cases, lesions are bilateral and symmetrical. There is rapid resolution of lesions which is not seen in the other demyelinating disorders.\(^3\)
The imaging findings of Susac's syndrome are characteristic of the disease. They include periventricular lesions and involvement of the corpus callosum, the latter is not seen in the above-mentioned demyelinating disorders. The callosal lesions are often of CSF density. Another characteristic of these lesions is that they do not enhance with gadolinium. On FLAIR, these lesions are of mixed density (Fig 14).
Fig. 1: An example of Dawson's fingers as seen on T1 (a) and FLAIR (c). The lesions are hyperintense on T2 (b) and show little to no enhancement on post contrast T1 (d).

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**Fig. 2:** An example of classic Multiple Sclerosis. Sagittal T1 (a) shows periventricular hypointense lesions suggestive of T1 black holes. The lesions appear hyperintense on T2 (b) and FLAIR (c). Post contrast T1 (d) imaging shows minimal enhancement.

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**Fig. 3:** Bilateral Optic neuritis in a case of Multiple Sclerosis. T2 (a), FLAIR (b) show bilateral optic nerve edema and retrobulbar fat stranding with enhancement on Post contrast (c) sequence

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**Fig. 4:** A case of tumefactive MS. Imaging appearances resembles a tumour. Hyperintense lesion in the parietal lobe on T2 imaging (a) and FLAIR (c), contrast enhancement on T1 imaging (b).

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**Fig. 5:** Tumefactive Multiple Sclerosis. T1 (A) imaging shows a hypointense lesion T2 (B) and FLAIR (C) images show a hyperintense lesion. Post contrast T1 (dD) study shows incomplete ring enhancement.

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Fig. 6: A case of widespread Multiple Sclerosis. Axial FLAIR (a) shows numerous hyperintense demyelinating plaques. One of these enhances on post contrast imaging (b). Sagittal imaging shows periventricular lesions on T2 (c) and FLAIR (d). Multiple longitudinal short segment lesions are seen on spinal T2 imaging (e). These changes are predominantly peripheral and dorsally located as seen on axial T2 WI.

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**Fig. 7:** Typical imaging findings in Neuromyelitis Optica Spectrum Disorder. Small demyelinating plaques are seen in the subcortical white matter. T1 (a) hypointense, T2 (b) and FLAIR (c) hyperintense lesions that show no contrast enhancement (d).

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**Fig. 8:** Bilateral optic neuritis in NMOSD. Long segment and proximal optic nerve involvement on T2FS images (a,b)

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Fig. 9: Spinal cord imaging in a case of NMOSD. Longitudinal plaques on T2WI (a) showing no contrast enhancement (b,e) that is centrally located and involves more than 50% of the cord area as seen on T2 (a,d),

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Fig. 10: Demyelinating lesions in MOG encephalomyelitis. Multiple small irregular parietal lobe lesions as seen on T1 (a), T2 (b), FLAIR (c) and post contrast T1 (d) imaging.

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**Fig. 11:** Optic neuritis as seen in MOG encephalomyelitis. T1 (a), T2 (b) and post contrast T1 (c) imaging reveal distal segment bilateral optic nerve enhancement.

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**Fig. 12:** Multiple short and long segment demyelinating lesions seen in the cervical (a) and thoracic (b) spinal cord in case of MOG demyelination.
Fig. 13: Demyelinating lesions in a case of adult onset ADEM. Multiple mass like white matter lesions seen on T1 (a), T2 (b) and FLAIR (c).

Fig. 14: MRI findings in a case of Sussac's disease. Numerous callosal lesions seen on FLAIR.
Fig. 15: A case of PML in a patient who was treated with natalizumab for Multiple Sclerosis

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Conclusion

Inflammatory CNS demyelination disorders have unique Imaging findings and correlate well with clinical presentation. Knowledge of imaging features, lab findings in each is essential for accurate diagnosis as it significantly alters patients' management and prognosis.
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