

# Central and peripheral demyelination

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## ABSTRACT

Several conditions cause damage to the inherently normal myelin of central nervous system, peripheral nervous system or both central and peripheral nervous system and hence termed as central demyelinating diseases, peripheral demyelinating diseases and combined central and peripheral demyelinating diseases respectively. Here we analysed and focused on the etiology, prevalence, incidence and age of these demyelinating disorders. Clinical attention and various diagnostic tests are needed to adequately assess all these possibilities.

**Key words:** Central and peripheral demyelination, demyelination, dysmyelination

## Introduction

The term demyelination describes a pathologic process of destruction of myelin-supporting cells, that is, oligodendrocytes and schwann cells in the central and peripheral nervous system, respectively and/or the myelin lamellae with relative preservation of axons.<sup>[1]</sup> Hence intrinsically normal myelin is destroyed. This needs to be differentiated from dysmyelination where there is a genetic defect related to the synthesis and turnover of myelin membranes which leads to deterioration of white matter ('leukodystrophy') of the brain and sometimes also the peripheral nerves.<sup>[2,3]</sup>

Depending on the primary site of demyelination in the nervous system it is divided into central demyelination involving the central nervous system and peripheral demyelination affecting the peripheral nervous system.

Central demyelinating diseases include:

### Inflammatory demyelination

The diseases which fall under this category are: Multiple sclerosis: Interaction of multiple genetic and environmental causes this most common form of

demyelinating disease, which is evident by its marked geographical variation in the prevalence being below 5/100,000 in many areas of Africa, South America and Asia to over 100/100,000 in Europe and North America. Women are affected more than men and age of presentation is between 15 and 55 years.<sup>[4]</sup>

Acute-disseminated encephalomyelitis (ADEM): About three-quarters of cases in this category are post-infectious and post-immunization encephalomyelitis because of T-cell hypersensitivity reaction due to top receding or concomitant infection that is most commonly viral like measles, mumps, rubella, varicella-zoster, Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus, hepatitis A or B, Coxsackie virus, influenza A or B, human immunodeficiency virus (HIV), human T-cell lymphotropic virus-1 (HTLV-1). Sometimes the culprit is bacterial infection like *Mycoplasma pneumoniae*, *Campylobacter jejuni*, *Leptospira*, group A *Streptococci*, *Borrelia*, *Chlamydia*, *Legionella*. Vaccines such as diphtheria-tetanus-polio, rabies, hepatitis B, measles, mumps, smallpox, rubella, Japanese B encephalitis, pertussis, influenza cause post-vaccination ADEM. Some drugs like Etanercept, Botulinum Toxin Type A, Adalimumab, Eculizumab, Lansoprazole, Oxcarbazepine, gonadotropins etc., also rarely cause ADEM.<sup>[4,5]</sup> However, it is possible that there may be no history of preceding illness or any event. The incidence of ADEM is about 0.8/100 000/year. It can affect any age group.<sup>[4,6]</sup>

Acute hemorrhagic leucoencephalitis (AHL): This is a hyper acute variant of ADEM preceded by viral or *M pneumoniae* infection. Some drugs like anti-tubercular

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10.4103/0976-3147.127887

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drugs,<sup>[7]</sup> inhalational anesthetic agents like isoflurane and desflurane<sup>[8]</sup> and various conditions like ulcerative colitis, Crohn's disease and septicemia are also associated with this. As with ADEM in some cases there is no obvious precipitant.<sup>[4]</sup>

### Osmotic demyelination syndromes

Osmotic stress and disruption of the blood-brain barrier (BBB) can cause acute demyelinating process, which if involves the pons is known as central pontine myelinolysis (CPM) and is called extrapontine myelinolysis (EPM) if other locations of the central nervous system are affected. The causes include alcoholism, malnutrition, hypoxic-ischemic states, deep burns, intensive care treatment, and metabolic disorders like uremia, prolonged diuretic use, dialysis, diabetes and liver transplantation. Other less common causes are psychogenic polydipsia, burns, post-pituitary surgery, post-urolurgical surgery/gynecological surgery, especially if involving glycine infusions. It can occur in all age groups and is a relatively uncommon disease.<sup>[9]</sup>

### Viral demyelination

Progressive multifocal leukoencephalopathy (PML): JC papovavirus (JCV) is acquired in childhood or adolescence and can cross the BBB to reach the central nervous system causing progressive multifocal leukoencephalopathy (PML). This is due to the direct destruction of oligodendrocytes by the virus and is associated with immunosuppressed conditions like abnormalities in cell-mediated immunity and patients on immunosuppressive drug therapy and also with antibody-based regimens given to autoimmune-disease patients like multiple sclerosis and Crohn's disease. This is a rare disease.<sup>[1]</sup>

Subacute sclerosing panencephalitis (SSPE): Several years after initial measles virus infection it is caused by the destruction of neurons, glial cells and oligodendrocytes and evokes a strong immune response. The estimated incidence of SSPE worldwide is 1 per million. It affects mainly children and young adults with average age being 5 to 15 years and mean age being 9 to 10 years. Boys are affected more than girls.<sup>[1,10]</sup> Though it hardly occurs in the developed countries because of mandatory immunization in children, SSPE is still common in resource-limited countries.

Peripheral demyelinating diseases include:

### Guillain-Barré syndrome

This is an acute-onset immune-mediated disease in which two-third of the cases is preceded by infections like *Campylobacter jejuni*, cytomegalovirus (CMV), *Mycoplasma*

*pneumonia*, Epstein-Barr virus, and influenza virus. The epitopes on the surface of peripheral nerves are similar to the epitopes on the surface of these infectious agents resulting in molecular mimicry. Various conditions like surgery, vaccination and parturition have also been associated with GBS. Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) is the most common form of GBS. Miller Fisher syndrome (MFS) in which there is activation of anti-GQ1b and anti-GT1a antibodies is the most recognizable variant of GBS. The estimated incidence for GBS is 1 to 2 per 100,000 population. Men and women are equally affected and can occur at any age.<sup>[11]</sup>

### Chronic inflammatory demyelinating polyradiculoneuropathy

This is an acquired demyelinating syndrome in which myelin sheaths of the peripheral nervous system are targeted. There are multiple triggers which evoke both the cellular immunity (T-cell activation) and humoral immunesystem (immunoglobulin and complement deposition on myelinated nerve fibers). The clinical variants of CIDP include the Lewis-Sumner syndrome also known as multi-focal acquired demyelinating sensory and motor neuropathy (MADSAM), sensory-predominant CIDP, distal acquired demyelinating sensory neuropathy (DADS) without IgM paraprotein, and CIDP with central nervous system involvement. The estimated prevalence of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) varies from 1.9 to 7.7 per 100,000. CIDP can affect all ages but older males are more commonly affected with a progressive disease course whereas it is relapsing-remitting in younger patients.<sup>[12,13]</sup> The gold standard treatment is steroids. However, plasma exchange and IVIg mode of treatment is recommended in subjects who fail to respond to steroids or have severe adverse effects with steroids.<sup>[14,15]</sup>

### Paraproteinemic demyelinating neuropathy

A paraprotein is an immunoglobulin molecule produced by a monoclonal plasma cell expansion (monoclonal gammopathy). So PDN refers to those neuropathies with a monoclonal gammopathy or paraprotein. Monoclonal gammopathy of uncertain significance (MGUS) is the condition in which an underlying causative disease is not evident. Typically PDN affects men in sixth to eighth decade and with age the prevalence of MGUS increases. Two broad categories are IgM PDN (associated with IgM antibodies to the myelin-associated glycoprotein (anti-myelin-associated antibodies) and IgG or IgA PDN (no specific antibody has been consistently associated).<sup>[16-18]</sup>

### Charcot marie tooth type 1 and type X

Charcot Marie Tooth (CMT) is the most common cause of hereditary neuropathy. The most common form is CMT1a, which is caused by duplication of the gene on chromosome 17 for peripheral nerve myelin protein 22 (PMP22). CMTX is second most common form of CMT caused by a mutation of the GJB1 gene for connexin 32 on the X-chromosome causing demyelinating neuropathy mainly in males. The reported incidence of CMT is 10 in 100000.<sup>[19,20]</sup>

### Copper deficiency

Copper deficiency leads to deficiency of many copper containing metalloenzymes such as superoxide dismutase (SOD), which is essential to protect damage against oxidative resulting in CNS demyelination.<sup>[21]</sup>

### Combined central and peripheral demyelination

Although rare but there are various case reports in which both central and peripheral nervous system are involved. Acute combined central and peripheral inflammatory demyelination,<sup>[22]</sup> MS with idiopathic inflammatory-demyelinating neuropathy,<sup>[23]</sup> simultaneous GBS and ADEM in pediatric population<sup>[24]</sup> and cerebral involvement in children with acute and relapsing polyneuropathy<sup>[25]</sup> are some of the cases reported in the past where both central and peripheral demyelination is evident by clinical features and various diagnostic tests. Combined central and peripheral demyelination in chronic autoimmune hepatitis has now been reported in a 52-year-old male having both chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and central pontine myelinolysis (CPM).<sup>[26]</sup> This case report further supports this distinctive clinical entity of combined central and peripheral demyelination.

The diagnostic tests used are MRI of brain, spinal roots, brachial plexus, lumbosacral plexus, cauda equina, brachial plexus and other nerve regions. Electrodiagnostic testing like nerve conduction studies, cerebrospinal fluid analysis, brain, and nerve biopsy, laboratory studies may help to confirm the diagnosis.<sup>[12]</sup>

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**How to cite this article:** Mehndiratta MM, Gulati NS. Central and peripheral demyelination. *J Neurosci Rural Pract* 2014;5:84-6.  
**Source of Support:** Nil. **Conflict of Interest:** None declared.