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FIVE KEY PRACTICE ASPECTS

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Demyelinating peripheral neuropathies

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Peripheral neuropathies can be categorised into demyelinating or axonal types based on electrophysiological criteria, or labeled as unclassified when electrophysiological findings are ambiguous. Demyelinating peripheral neuropathies exhibit distinct pathophysiological mechanisms, clinical features and investigation findings that set them apart from axonal neuropathies. This distinction is clinically significant as the underlying causes and treatment strategies differ. This article will briefly discuss five clinically relevant aspects of demyelinating peripheral neuropathies.

1. Demyelinating peripheral neuropathies are not so common

Most peripheral neuropathies are axonal in type, and are caused by a variety of aetiologies. As such, the majority of cases of peripheral neuropathy seen in everyday clinical practice are likely to be axonal neuropathies. In contrast, demyelinating peripheral neuropathies are less common and have relatively few underlying causes. (Table 1) Diagnosing a demyelinating peripheral neuropathy is important as it narrows down the differential diagnosis and increases the likelihood of finding an underlying treatable aetiology.[1]

2. Demyelinating neuropathies have different clinical presentations

Pattern recognition is helpful in the evaluation of peripheral neuropathy and provides important clues to the likely type of neuropathy. The initial assessment should include the symptom distribution (length dependent, length independent or multifocal) and the modality affected (motor, sensory, autonomic or a combination of these). The majority of peripheral neuropathies are length-dependent and sensory predominant. Length-dependent neuropathies are symmetric in distribution, with symptom onset in the lower extremities as terminal endings of the longest nerves are affected first. Sensory symptoms usually precede motor weakness, and symptoms gradually ascend along the lower limbs, and upper limb involvement is late in the disease course. Such length-dependent neuropathies are likely to be axonal in type.

In contrast, demyelinating peripheral neuropathies are usually length-*independent.* Both proximal and distal segments of limbs can be involved early in the course of disease, and proximal limbs are usually affected earlier and more than the distal limbs. This pattern of involvement is more suggestive of a poly-radiculo-neuropathy with proximal root involvement (e.g., GBS, CIDP). Motor weakness and global hypo/areflexia are more commonly seen.[2]

A predominantly motor neuropathy is more likely to be demyelinating (e.g., Guillain-Barre syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN)), whereas axonal neuropathies with predominant motor involvement (e.g., porphyria, lead poisoning) are rare.[1] Relative lack of muscle wasting in a weak muscle is more commonly seen in a demyelinating neuropathy.[1] Asymmetric distribution of symptoms and signs (e.g., multifocal CIDP,

MMN), multifocal acquired signs (e.g., multifocal CIDP, MMN, multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy [Lewis-Sumner syndrome)) and early upper limb involve-ment (e.g., multifocal CIDP, MMN, MADSAM neuropathy) are more common in demyelinating peripheral neuro-pathies.[1,3,4,5,6,7,8,9]

3. Most demyelinating neuropathies are immune-mediated

The majority of demyelinating neuropathies have an immune-mediated inflammatory pathophysiological basis. (Table 1) The key clinical features, investigation findings and response to treatment of the main immune-mediated inflammatory demyelinating neuropathies are summarised in Table 2. The underlying pathophysiological mechanisms differ between the different immune-mediated inflammatory demyelinating neuropathies and remain poorly understood. However, some of them have well documented associations with autoantibodies, and other immunological abnormalities have been variably described.

TABLE 1 Common demyelinating neuropathies

Demyelinating neuropathies
GBS
CIDP and CIDP variants
Other immune mediated – MMN, MADSAM neuropathy, DADS neuropathy
Paraproteinaemic neuropathies – POEMS syndrome, anti MAG neuropathy, CANDA, CANOMAG
Infections – diphtheria
Toxins – arsenic
Drugs – amiodarone
Inherited – Charcot Marie Tooth disease type1A, Refsum disease

GBS- Guillain-Barre syndrome; CIDP – chronic inflammatory demyelinating polyneuropathy, DADS – distal acquired demyelinating symmetric neuropathy; MADSAM – multifocal acquired demyelinating sensory and motor neuropathy; MMN – multifocal motor neuropathy; POEMS – polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome; MAG – myelin associated glycoprotein; CANDA – chronic ataxic neuropathy with disialosyl antibodies; CANOMAD – chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins and disialosyl antibodies

TABLE 2 Key features of immune-mediated demyelinating neuropathies

	GBS	CIDP	DADS neuropathy	MADSAM neuropathy	MMN
Disease course	Acute, monophasic, self-resolving	Chronic, usually relapsing or progressive; acute onset and monophasic course uncommon	Chronic, progressive	Chronic, progressive	Chronic, progressive

(Continued)

	GBS	CIDP	DADS neuropathy	MADSAM neuropathy	MMN
Key clinical features	Symmetrical proximal and distal weakness with or without sensory loss	Symmetrical proximal and distal weakness with or without sensory loss	Symmetrical distal sensory loss with or without weakness	Asymmetric, distal >proximal sensory loss & weakness, UL >LL; multifocal (in distribution of individual nerves)	Asymmetric distal weakness, UL>LL, without sensory loss; multifocal (in distribution of individual nerves)
Investigations					
NCS/EMG	Conduction block; symmetric demyelination, symmetric sensory abnormalities	Conduction block; symmetric demyelination; symmetric sensory abnormalities	Conduction block is uncommon; symmetric sensory abnormalities	Conduction block; asymmetric multifocal demyelination; asymmetric multifocal sensory abnormalities	Conduction block; asymmetric multifocal demyelination; sensory normal
CSF protein	elevated	elevated	elevated	elevated	usually normal
Other lab investigations	Anti-GM1, GM-2, GD1a, GD1b, GQ1b, GT1a antibodies – mainly in GBS variants		IgM monoclonal gammopathy; Anti-MAG antibodies		IgM anti GM-1 antibodies
Response to treatment					
Steroids	No	Good	Poor	Good	No; can worsen
IVIg	Good	Good	Poor	Good	Good
PLEX	Good	Good	Poor	Uncertain	Poor
Other		Azathioprine, cyclophospha-mide, MMF, cyclosporin			Rituximab, cyclophospha-mide

GBS – Guillain-Barre syndrome; CIDP – chronic inflammatory demyelinating polyneuropathy, DADS – distal acquired demyelinating symmetric neuropathy; MADSAM – multifocal acquired demyelinating sensory and motor neuropathy; MMN – multifocal motor neuropathy; UL – upper limbs; LL – lower limbs

Anti-ganglioside antibodies (anti-GM1, GM2, GD1a) are described in 40-60% patients with GBS.[7,10,11,12,13] Patients with acute sensori-motor neuropathy, which is the most common type of GBS, are usually seronegative for anti-ganglioside antibodies, and routine testing is not recommended in them.[7,10,11] Pure motor variants of GBS, such as acute motor axonal neuropathy (AMAN), are more strongly associated with anti-GM1 and anti-GD1a antibodies, with more than 80% of patients being found to be seropositive.[7,10] Anti-GM2 IgM antibodies are detected in patients with sensory-motor GBS following CMV infection, who tend to have severe sensory loss and an aggressive course.[7,] Anti-GQ1b antibodies are detected in up to 90% of patients with Miller-Fisher syndrome (MFS), MFS overlap syndromes and more than two-thirds of cases with Bickerstaff brainstem encephalitis.[7,10] Over half of patients with the pharyngeal-cervical-brachial variant of GBS have anti-GT1a antibodies.[7,10] Acute sensory ataxic neuropathy (ASAN) is associated with anti-GD1b and anti-GQ1b antibodies. [7,10]

Typical CIDP is not associated with autoantibodies, and the pathophysiology is not clear. An inflammatory process mediated by T- and B- lymphocytes, inflammatory cytokines and complement is postulated in typical CIDP.[7,10,14,15] However, several conditions considered to be CIDP variants are strongly associated with autoantibodies. High titres of IgM anti-GM1 antibodies are described in over 50% of patients with multifocal motor neuropathy (MMN).[3,5,6,9,10] Distal acquired demyelinating symmetric (DADS) neuropathy (now considered distal CIDP variant) is associated with an IgM monoclonal gammopathy. Up to 50-65% of patients with DADS neuropathy and an IgM monoclonal gammopathy have IgM antibodies directed against myelin associated glycoprotein (anti-MAG IgM antibodies), and anti-MAG neuropathy is now considered a distinct clinical entity.[4,7,10] Testing for anti-MAG antibodies is now recommended in all patients with a distal demyelinating neuropathy associated with an IgM monoclonal gammopathy.[4,10,16] Chronic ataxic neuropathy with disialosyl antibodies (CANDA) and the related CANOMAD (chronic ataxic neuropathy with ophthalmoplegia, M-protein, cold agglutinins and disialosyl antibodies) are demyelinating ataxic neuropathies associated with disialosyl antibodies such as anti-GD1b, GT1b, and GQ1b.[10]

Antibodies directed against cell adhesion molecules in the nodes of Ranvier and paranodal regions have been recently described in patients with a CIDP phenotype; these include antibodies against contactin 1 (CNTN1), contactin-associated protein 1 (Caspr1), and neurofascins (NF155, NF140, NF186). These patients present with an acute demyelinating neuropathy resembling GBS or acute CIDP.[7,10] They are now re-classified as a novel disease entity called' autoimmune nodopathy', distinct from CIDP. [4,7,10,17]

4. Demyelinating neuropathies have different investigation findings

Electrophysiological studies (nerve conduction studies (NCS), electromyography (EMG) and other tests) are an integral component of the evaluation of peripheral neuropathy, and are essential in distinguishing demyelinating neuropathies from axonal types. Electrophysiological criteria for the diagnosis of demyelinating peripheral neuropathies are clearly defined.[1,4,11,12,17,18] Diagnosis requires features suggestive of acquired demyelination in two or more motor nerves on NCS; key features are partial motor conduction block, prolonged distal latencies, slow conduction velocities, absent F waves or prolonged F wave latencies, abnormal temporal dispersion of the compound muscle action potential (CMAP) and prolonged CMAP potentials.[1,3,4,8,18] More sophisticated electrophysiological studies, such as the blink reflex, are useful when standard NCS/EMG tests are equivocal. As the blink reflex is mediated by the short trigeminal and facial nerves, it is preserved in length-dependent axonal neuropathies.[1]

Diagnosis of a demyelinating peripheral neuropathy on NCS/EMG should always lead to further evaluation for an underlying, potentially treatable cause. Albumino-cytological dissociation in CSF, characterised by elevated proteins (>45 mg/dL) with a minimal cellular reaction (<5 cells/mcL) is a hallmark of immune-mediated inflammatory demyelinating neuropathies, such as GBS, CIDP, and MADSAM neuropathy,[3,4,5,9,11,12,17,19] and is also seen in inherited demyelinating neuropathies such as Charcot-Marie-Tooth type 1A (CMT1A) neuropathy.[17] Other laboratory investigations include evaluation for paraproteins such as an IgM monoclonal gammopathy in DADS neuropathy and related anti-MAG neuropathy, and CANDA/ CANOMAD.[3,6,10] As described earlier, detection of autoantibodies is useful in diagnosing some of the immune-mediated demyelinating neuropathies such as MFS, other GBS variants, MMN, anti-MAG neuropathy and CANDA/ CANOMAD,[3,5,9,10] and is an evolving field.

Nerve imaging with MRI and nerve ultrasound is a valuable addition to the diagnostic work-up; they are useful in the evaluation of the proximal segments of peripheral nerves which are not usually well assessed in routine NCS/EMG. Nerve hypertrophy on ultrasound and MRI, and T2 hyperintensity and contrast enhancement on MRI, can be demonstrated in the proximal median nerves, cervical nerve roots, brachial or lumbosacral plexuses and cauda equina in immune-mediated demyelinating neuropathies such as CIDP and MMN.[5,6,9,18,19] Nerve biopsy shows characteristic segmental demyelination and remyelination, onion bulb formation and inflammatory infiltrates in a demyelinating

neuropathy,[19] but is not routinely indicated in the diagnostic work up. In anti-MAG neuropathy, deposition of IgM between myelin layers leads to a characteristic finding of widely spaced myelin lamellae on nerve biopsy.[7]

5. Demyelinating peripheral neuropathies are treatable neuropathies

As many demyelinating peripheral neuropathies have an immune-mediated pathophysiological basis, immuno-modulatory treatments are effective (Table 2).

GBS is a monophasic illness and responds well to intravenous immunoglobulin (IVIg) or plasma exchange (PLEX), but not to steroids.[9,11-13] CIDP, in contrast, has a relapsing or progressive course, and therefore requires both induction and maintenance treatments. Steroids (oral prednisolone, pulsed intravenous methyl prednisolone or pulsed oral dexamethasone), IVIg and PLEX are effective in induction treatment.[4,5,9,14,18,20] All of them are effective as maintenance treatments; however, IVIg is preferred due to the many problems associated with long term use of steroids or PLEX.[5] Subcutaneous immunoglobulin (SCIg) is increasingly gaining acceptance as an alternative to IVIg due to its more user-friendly properties.[4,14] Other immuno-suppressive drugs such as azathioprine, mycophenolate mofetil (MMF), methotrexate and cyclosporine are used as steroid or IVIg sparing agents.[9,15,17,18] Autoimmune nodopathies do not respond well to conventional CIDP treatments such as IVIg, but respond to B cell depleting treatments such as rituximab.[4,10,15,17]

IVIG is considered the first line treatment in MMN, and SCIg is an effective alternative.[5,6,9] Importantly, MMN responds poorly to, and can sometimes worsen with, steroid treatment.[7,9] Both IVIg and steroids are effective treatments in MADSAM neuropathy.[3] Patients with anti MAG neuropathy do not respond well to standard CIDP treatments, and may respond to rituximab.[4,7,10,16]

CONCLUSIONS

Demyelinating peripheral neuropathies are less common than axonal neuropathies. They are length-independent, and exhibit characteristic clinical features such as asymmetric distribution, early upper limb involvement and predominant motor symptoms. These features should enable clinicians to suspect a demyelinating pathology during the initial evaluation of a peripheral neuropathy. Many demyelinating neuropathies have an underlying immunopathological basis. The discovery of autoantibodies associated with some of these neuropathies has led to more accurate classification of these disorders and the development of novel treatment strategies. Consequently, many demyelinating neuropathies can be effectively treated with immune-modulatory treatments. This contrasts with axonal neuropathies, which have numerous underlying aetiologies but lack effective treatments. Clinical suspicion and early diagnosis based on electrophysiological studies would enable the practicing clinician to initiate early and appropriate treatment, which would save lives, minimise long-term disability and lead to greater functional independence in the affected patients.

Key points

1. Demyelinating peripheral neuropathies are not so common.
2. Demyelinating neuropathies have different clinical presentations. They are usually length-independent, and are more likely to feature asymmetric distribution, early upper limb involvement and predominant motor symptoms.
3. Most demyelinating neuropathies are immune-mediated, and associations with autoantibodies are being increasingly recognised.
4. Demyelinating neuropathies have different investigation findings.
5. Demyelinating peripheral neuropathies are treatable, with many of them responding to different immuno-modulatory treatments. Early diagnosis, therefore, is of paramount importance.

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