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Nodopathies: A Distinct Pathophysiological and Clinical Entity

ABSTRACT

In recent years, antibodies directed against the proteins located at the node of Ranvier have been identified in patients with immune mediated neuropathies. In this article, we review the structure of node of Ranvier and pathology associated with these antibody mediated neuropathies. We summarize the emerging concept of nodopathy/paranodopathy, its clinical relevance and treatment implications.

Key words: Acute motor axonal neuropathy, Anti-ganglioside antibody, Axonal conduction block, Chronic inflammatory demyelinating neuropathy, Node of Ranvier

NODOPATHIES: A DISTINCT PATHOPHYSIOLOGICAL AND CLINICAL ENTITY

The French neurohistologist Louis-Antoine Ranvier (1835–1922), first described the structure of myelin-sheath gap "ëntanglements annulaires" now referred to as 'node of Ranvier' in 1871.[1] In 1949, Huxley and Stampfli demonstrated the role of node of Ranvier in saltatory conduction in myelinated nerve fibers.[2] The node of Ranvier ensures rapid and long distance conduction of nerve impulses in the most energy efficient manner.

Diseases of the peripheral nerves are traditionally classified as axonal or demyelinating based on whether the pathological process primarily affects the axon or myelin. However, in recent years disruption and dysfunction at the nodal and paranodal regions have emerged as key to understanding the pathophysiology of anti-ganglioside antibody-mediated neuropathies. The concept of "nodopathies" focuses on the site of nerve injury and provides a common pathological mechanism ranging from transitory nerve conduction failure to axonal degeneration for different etiologies. It avoids confusion with segmental demyelinating neuropathies such as acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and the fact that axonal appearing neuropathies may have a good prognosis. The concept of nodo-paranodopathy was first applied to axonal Guillain-Barre syndrome (GBS) and later extended to chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) associated with IgG4 antibodies directed against paranodal axo-glial proteins. Nodopathies now involve neuropathies of different etiologies (dysimmune, inflammatory, ischemic, nutritional, and toxic).[3]

STRUCTURAL ORGANISATION OF THE NODE OF RANVIER

The peripheral myelinated nerve fibers have four distinct regions: node, paranode, juxta-paranode and inter-node

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[Figure 1].[3] The nodes of Ranvier refer to the complex consisting of node, paranode, and juxtaparanode regions. Cell adhesion molecules, cytoskeletal elements, and extracellular matrix proteins contribute to the formation of these distinct regions. At the node, there is short gap in the myelin sheath where axolemma is in direct contact with extracellular fluid. At the paranode, uncompacted myelin loops tightly adhere to axolemma whereas the internodal axolemma is surrounded by compact myelin. Each of these regions has various site specific molecules and different distribution of Na^+ and K^+ channels. The node has high concentration of voltage gated Na^+ channels and slow K^+ channels. The juxta-paranode has high density of voltage-gated fast K^+ channels. The internode region is characterized by highest absolute number of Na^+ and fast/slow K^+ channels with relatively low density. Concentration of voltage gated sodium channels in the axon initial segment and node is a critical step in the evolution, providing a faster means of conducting electrical impulses along large myelinated fibers. The main function of paranode is to prevent passage of nodal currents into the internode, crucial for saltatory propagation.

The nodal Na^+ channels are attached to the spectrin of axonal cytoskeleton through ankyrinG and to gliomedin of the Schwann cell microvilli via neurofascin-186 [Figure 2].[3-6] Three cell adhesion molecules: Contactin-1 (CNTN1) and

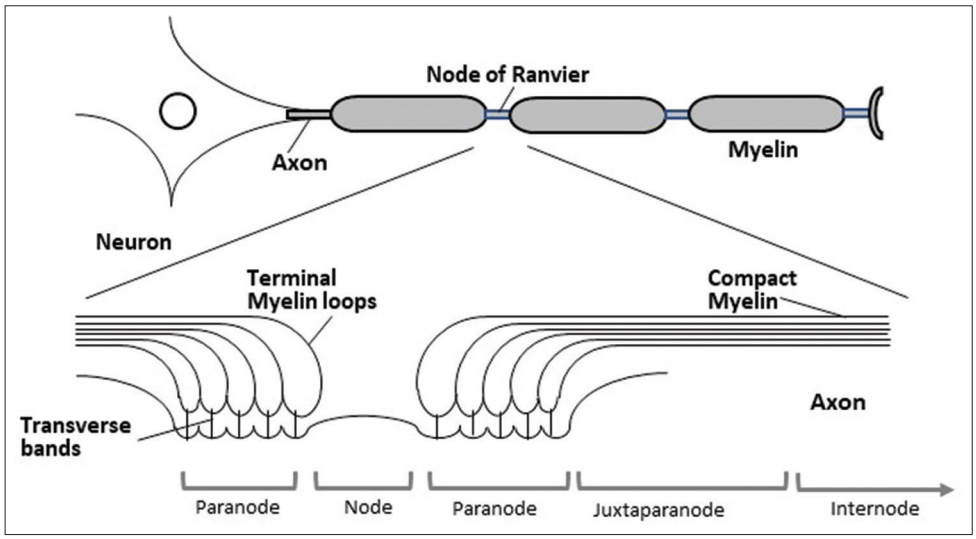

Figure 1: Schematic illustration of various regions of axon and the node of Ranvier. Modified from Uncini *et al.*[3]

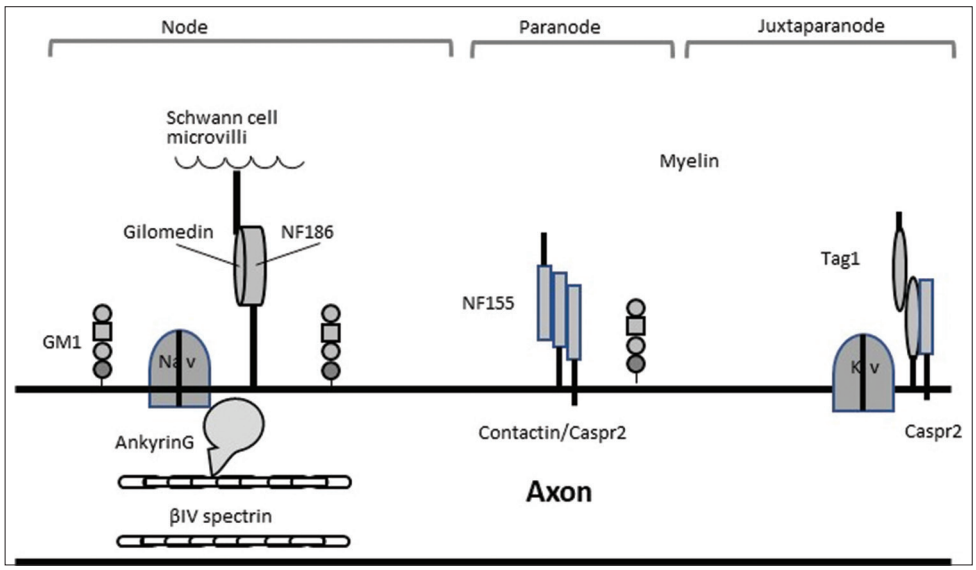

Figure 2: Schematic representation of nodal and paranodal components targeted by auto-antibodies in various nodopathies. Modified from Uncini *et al.*[3]

contactin associated protein-1 (CASPR1) in the axolemma, and neurofascin-155 (NF155) in the myelin account for formation of junctional complexes referred to as transverse bands at paranodal region. The juxta-paranodal K^+ channels are connected by Caspr-2 and transient axonal glycoprotein between axolemma and Schwann cell. Gangliosides are glycolipids composed of ceramide embedded in lipid bilayer with one or more sugars in extracellular region to which 0, 1 or more sialic acid residues are attached. Gangliosides interact with the nodal proteins to provide stability to axon-glia complex. GM1, GD1a, GD1b, GT1a, and GQ1b are different gangliosides present in peripheral nerves. They differ in the number and position of their sialic acids. M, D, T, and Q denote mono-, di-, tri- and quadri-sialosyl groups and "b" refers to gangliosides with disialosyl group attached to internal galactose. Gangliosides GM1 are found at nodal and paranodal axolemma, abaxonal Schwann cell membrane and Schwann cell microvilli and GD1a on nodal axolemma and abaxonal Schwann cell membrane. The presence of antibodies to different ganglioside is associated with specific clinical phenotype[4] IgG anti-GM1 or -GD1a antibodies are associated with AMAN or acute motor and sensory axonal neuropathy (AMSAN). IgG anti-GQ1b antibodies are associated with Fisher syndrome, acute ophthalmoparesis (without ataxia), ataxic GBS, Bickerstaff brainstem encephalitis or pharyngeal-cervical-brachial weakness; together referred to as "anti-GQ1b

antibody syndrome." IgG anti-GQ1b or -GD1b antibodies are described in acute sensory ataxic neuropathy.

NODOPATHIES OF THE PERIPHERAL NERVE

Acute motor axonal neuropathy (AMAN)

AMAN was initially characterized as axonal sub-type of GBS with motor neuronopathy pattern on electrophysiological studies: reduced motor compound muscle action potential (CMAP) amplitudes and absent F-waves with normal sensory responses. However, patients with anti-GM1 antibodies with conduction block (CB) which rapidly resolved without development of temporal dispersion were described. Due to rapid recovery and lack of temporal dispersion, this CB was thought to be secondary to impaired conduction at nodes of Ranvier and was termed reversible conduction failure (RCF) by Kuwabara *et al*.[7,8] to differentiate it from classical demyelinating CB. AMAN is associated with high frequency (67%) of preceding Campylobacter jejuni infection and IgG anti-GM1 antibodies in 64%, GM1b in 66%, GD1a in 45%, and GalNac-GD1a in 33% of patients.[3,9] Post-infectious molecular mimicry is considered predominant pathophysiological mechanism in AMAN. Binding of antibody to target antigen at the node results in complement activation, formation of membrane attack complex, Na^+ channel disruption, paranodal myelin detachment resulting in node lengthening, and altered ion and water homeostasis. This process may reverse rapidly or progress to axonal degeneration from calcium influx and protease activation explaining why some patients with AMAN recover rapidly whereas others have prolonged course with poor outcome.

Axonal CB has also been reported in motor and sensory fibers in AMSAN associated with IgG anti-GM1 antibodies.[3] Axonal CB restricted to sensory fibers is seen in acute sensory ataxic neuropathy associated with IgG anti-GD1b or anti-GQ1b antibodies. RCF has been described in Miller-Fisher syndrome with antibodies anti-GQ1b, -GT1a, -GD1a, and -GD1b and pharyngeal-cervical-brachial variants of GBS with antibodies IgG anti-GT1a, -GM1, or -GD1a.

Besides gangliosides other axonal or glial proteins at the nodes may be a target of dysimmune neuropathies. Recently IgG antibodies to NF186 or gliomedin have been found in small number of patients (<5%) with GBS; anti-NF186 antibodies being more prevalent in AMAN and anti-gliomedin in AIDP.[4] IgG antibodies to moesin located in microvilli of Schwann cells at the node have been reported in sera of patients with GBS following cytomegalovirus infection.[10]

Multifocal motor neuropathy (MMN)

MMN with CB is a distinct clinical entity with immune-mediated attack on motor fibers of at least two peripheral nerves. Clinically, it is characterized by asymmetric motor weakness affecting distal upper extremity with cramps and fasciculations in affected nerve territory. Cold paresis is a clinical hallmark. T2 hyperintensity and contrast enhancement of brachial plexus are commonly seen on MRI. About 40–60% of patients have IgM antibodies directed anti-GM1 ganglioside.[11] Recently, antibodies to neurofascin NF186 and/or gliomedin have been found in 62% of patients with MMN. 10% of MMN patients negative to IgM anti-GM1 had antibodies to NF186 and gliomedin.[3] MMN is now characterized as a chronic nodo-paranodopathy. Injection of human sera containing anti-GM1 antibodies to rat myelinated axons induced CB, immunoglobulin deposition at nodes of Ranvier, nodal widening and some paranodal demyelination.[12] Excitability studies have shown stable, steady hyperpolarization of axons in MMN explaining persistence of CB.[13]

Anti-GM1 antibodies are found in patients with AMAN and MMN but they have very varied clinical course. A recent study looking at the clonality of anti-GM1 IgM antibody showed that more than 90% of MMN patients have anti-GM1 IgM antibodies of a single light chain of either kappa or lambda as opposed to polyclonal IgM antibodies in GBS patients.[14]

CIDP

CIDP is considered a chronic counterpart of AIDP as it has similar macrophage mediated demyelination. Recent studies have shown that approximately 10% of patients with CIDP have antibodies directed against nodal or paranodal antigens.[6,15] The targets for these autoantibodies are three cell adhesion molecules: CNTN1 and CASPR1 located in axolemma and NF155 located on myelin in the paranodal region. Antigenic targets at the node of Ranvier are neurofascin isoforms 140 and 186 (NF140 and NF186). Antibodies against NF155, NF186, and Caspr are very rarely seen in patients with GBS. Instead their presence may signal development of acute-onset CIDP. Clinically this sub-group of CIDP patients has sub-acute onset of symptoms, predominant tremor, sensory ataxia or distal dominant symptoms with early evidence of axonal degeneration in contrast to typical CIDP patients with proximal and distal weakness and less prominent axonal degeneration. Pathologically there is the absence of macrophage-mediated demyelination and inflammatory cell infiltration with more pronounced axonal pathology. The aberrant nerve conduction in these patients is caused by deposition of autoantibodies to paranodal region resulting in detachment of myelin terminal loops from axolemma.

Anti-CNTN1 antibodies

In 2013, Querol *et al*. showed the presence of antibodies to CNTN1 in four out of 53 patients with CIDP.[5,16] These patients had a distinctive clinical syndrome with more advanced age of onset, initial rapid progression with GBS like-subacute onset, severe motor, moderate sensory symptoms with early axonal involvement, and a relapsing and remitting course not seen with typical CIDP.[17] In a study by Miura *et al*., 2.4% of their CIDP cases (n = 13) had antibodies to CNTN1. About 23% of these patients had sub-acute onset with poor response to IVIg.

Their patients presented with sensory ataxia and 73% showed good response to corticosteroids.[18]

Koike *et al*.[19] reported detachment of paranodal terminal myelin loops from the axolemma, reduction of myelinated fiber density and lack of macrophage mediated segmental demyelination. In an animal model, Manso *et al*.[20] showed that intraneural injections of anti-CNTN1 IgG4 antibodies in sciatic nerve preparations caused progressive and selective disruption of axo-glial junction at paranode supporting the immunopathogenicity of these antibodies.

Anti-NF155antibodies

Antibodies to NF155 isoform are found in small group of patients <3% with CIDP[21] and are strongly associated with HLA-DRB1*15.[6] Querol *et al*. described the distinct phenotype: Young patients around 20–30 years, sub-acute and severe onset with predominant distal weakness, sensory and cerebellar ataxia and often disabling low-frequency tremor.[17,22] Nerve conduction studies showed distal acquired demyelinating symmetric neuropathy phenotype with marked prolongation of distal and F-wave latencies. Autoantibodies were predominantly of IgG4 subtype and these patients had poor response to IVIg like patients with CNTN1 positive CIDP. MRI findings in seven patients showed marked symmetric hypertrophy of cervical and lumbosacral roots/plexuses more marked than anti-NF155 negative CIDP.[5,23,24] Proximal cranial nerves such as oculomotor and trigeminal nerves also showed hypertrophy. Some patients also develop demyelinating lesions in the CNS. In an animal model, Manso *et al*. provided supportive evidence for pathogenic role of anti-NF155 IgG4 antibodies by chronic intrathecal administration of anti-NF155 IgG4 from CIDP patients' plasma in Lewis rats.[5,25] Animals developed clinical deterioration, decreased compound action potentials amplitude and selective loss of CASPR1/CNTN1/NF155 complex at paranodes.

Anti-CASPR1 antibodies

CASPR1 antibodies have been described in two patients, one with CIDP and other with GBS. Both patients had intense neuropathic pain. Skin biopsy revealed disruption of paranode in myelinated fibers. Sera from this patient not only bound to paranode but also to some posterior ganglion cells which convey pain sensation suggesting their role in painful neuropathy.[5,17,26]

Anti-NF186/140 antibodies

In 2017, Delmont *et al*. described the association of anti-Nfasc (neurofascin) 140/186 IgG3 in a sub-set of patients with CIDP.[27] Their clinical features were distinct from those with anti-NF155 IgG4 antibodies. Four patients had sub-acute sensory ataxia. None of them had tremor. Predominant finding on nerve conduction was CB s with reduced distal motor amplitudes. Three patients recovered with IVIg and steroid, one patient needed rituximab.

Treatment

The first-line treatment for immune-mediated neuropathies is plasmapheresis, corticosteroids, and IVIg. They help improve the strength and restore functional activity. In additional they ease the pain, provide improvement in sensory loss, gait, and autonomic instability.

Plasmapharesis

Good response to Plex has been reported in patients with nodo-paranodopathies except one patient with anti-NF186/140 antibodies.[5] However, Plex may not be ideal for long term maintenance treatment.

IVIg

As compared to classic CIDP, only 40% of patients with nodal/paranodal antibodies respond to IVIg with an exception of anti-NF186/140 antibody positive patients.[5] IgG4 subtype of autoantibodies do not activate complement or bind to Ig Fc domain receptors, accounting for lack of response to IVIg.

Corticosteroids

About 40–60% of CIDP patients with antibodies to nodal/paranodal antigens respond to corticosteroids.

Rituximab

CIDP patients with IgG4 antibodies who do not respond to first line therapies have shown long-lasting, very good response to rituximab.[5,26,27] In some of these patients where antibody levels were measured, antibody titers decline in parallel to clinical and electrophysiological improvement.

Critical illness polyneuropathy

About 50–70% of critically ill patients develop neuropathy. Altered polarization of axolemma at the node of Ranvier, triggered by soluble factors released during sepsis may account for neuropathy in critically ill patients. This process may be reversible to a certain extent; however persistent depolarization may trigger axonal degeneration in other patients.[3]

Ischemic neuropathy

Ischemic neuropathies are often encountered in patients with vasculitis or after acute occlusion of major artery in extremities. Pseudo-CB which resolves if nerve conduction studies are repeated after 2 weeks has been described in vasculitic neuropathies. It is thought to be related to advancing Wallerian degeneration. Nodal region has high density of mitochondria and high metabolic demand to sustain nerve activity. Ischemia causes impairment of energy dependent processes including functioning of ATP-dependent Na+/K+ pump which results in accumulation of Na+ inside and K+ outside the axons, depolarization of nodal membrane, and development of depolarizing CB.[3]

Beriberi neuropathy

Thiamine deficiency is associated with Wernicke-Korsakoff encephalopathy and axonal polyneuropathy with severely reduced motor and sensory amplitudes. Thiamine infusion in these patients normalizes the motor and sensory amplitudes in 2–4 weeks with improvement in clinical symptoms as well. Thiamine deficiency decreases pyruvate dehydrogenase activity and ATP leading to nodopathy due to energy depletion.[3]

Tetrodotoxin (TTX) poisoning

TTX poisoning related to puffer fish consumption is clinically characterized by perioral and limb paresthesias, numbness, bulbar weakness, and flaccid quadriparesis which may progress to respiratory failure with cardiovascular involvement. Nerve conduction studies reveal reduced motor and sensory amplitudes with slowing of conduction velocities, prolonged distal motor latencies and F-wave latencies. TTX blocks the outer pore of Na+ channel impairing the action potential at node of Ranvier in terminal axons. Tick-paralysis and saxitoxin are other examples of purely functional toxic nodopathy.[3]

DIAGNOSIS OF NODOPATHIES

Motor and sensory nerve conduction studies are routinely performed to study the peripheral nerves. Based on characteristic features on nerve conduction studies neuropathies are classified as demyelinating or axonal. Slowing of conduction velocity, temporal dispersion and CB are considered as features of demyelinating neuropathies. However, this can be misleading in interpretation of electrophysiological findings associated with nodopathies. Conditions affecting the axolemma at nodal region can also produce CB referred to as axonal CB or nodal CB. Temporal dispersion (increased duration and dispersion of CMAP) helps to differentiate classical demyelinating CB from axonal CB. However; differentiation between demyelinating and axonal CB or between axonal degeneration and distal CB can only be reliably made on serial nerve conduction studies. In acute inflammatory demyelinating neuropathy, serial nerve conduction studies show progressive reduction in amplitudes, dispersed CMAPs, prolonged distal latencies and slowed conduction velocities. Whereas, AMAN with CB will reveal drop in motor amplitudes between two stimulation sites without the development of excessive temporal dispersion. Conduction velocity may be slow but it also improves in parallel with resolution of CB on subsequent examination. In AMAN with axonal degeneration, motor amplitudes are reduced on initial study which may further drop on successive study and remain low. In contrast, AMAN with distal CB also reveals reduced distal and proximal motor amplitudes on initial study which improve on successive studies without development of temporal dispersion.[3,4,8] Thus a patient needs at least two studies, between 1 and 3 weeks apart - first study confirms the presence of acute neuropathy and the second study helps with classification of neuropathy into specific sub-type.

Chronic nodopathy is characterized by presence of persistent CB with signs of axonal degeneration (reduced distal CMAP amplitude, spontaneous activity, and neurogenic pattern on needle electromyography). In addition, positive titers of antibodies to gangliosides or other axo-glial proteins strongly support the diagnosis of acute or chronic nodo-paranodopathies.

CONCLUSION

Nodopathies defined as neuropathies with immune mediated attack confined to nodal region are characterized by:

1. Different etiologies with a common pathophysiological process of dysfunction/disruption of axonal membrane at nodal region
2. The pathophysiologic spectrum extends from RCF early on to axonal degeneration
3. CB can be rapidly reversible without development of temporal dispersion
4. Axonal degeneration eventually follows CB
5. In clinical practice, diagnosis can be established by doing serial nerve conduction studies.

Concept of nodopathy allows better classification of GBS sub-types and provides explanation for persistence of CB in MMN expanding their spectrum from acute to chronic neuropathies. Large multicenter studies are needed to understand the prevalence of nodopathies, their correlation with different auto-antibodies and response to various immunotherapies. Novel immunotherapies based on these new antigenic targets are needed as some patients do not response to current therapeutics. Emerging therapeutic trends include complement and neonatal Fc receptor (FcRn) inhibitors and hypersialylated IVIg.[28] Eculizumab, a humanized antibody against complement C5 has shown promising results as add on therapy to IVIg in a small Phase II trial.[29] Significantly more patients treated with Eculizumab were able to run at 6 months as compared to placebo group. Another complement inhibitor, humanized antibody against C1q is also under investigation. FcRn protects IgG from catabolism and its antagonism shortens the half-life of circulating pathogenic anti-neuronal autoantibodies thus reducing the antibody mediated nerve damage. It is currently under development for CIDP. Hypersialylated IgG is a glyco-modified product derived from commercially available IVIg and has 10 times more anti-inflammatory activity compared to currently available IVIg. Ongoing research promises to identify more potent immunotherapies and neuroregenerative therapies to help patients with predominant axonal pathology and residual deficits.

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