ORIGINAL ARTICLE

Clinical Presentations of Different Types of Nodopathies

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Abstract

Background and objectives: Nodoparanodopathies are subtypes of inflammatory polyneuropathies that differ in clinical presentation, duration, and response to intravenous immunoglobulins. Antineurofascin antibodies are detected by cell-based assays from serum or cerebrospinal fluid. The aim of our study was to describe the clinical presentation, electrophysiology, antibody assay, and response to treatment in different types of nodopathies.

Methods: During the last 1 year, we came across three patients with neurofascin 140/186 positivity and one patient with neurofascin 155 antibody positivity. The clinical features, electrophysiology, treatment response, and outcome were studied after obtaining informed consent from the patients.

Results: Both groups improved with treatment; however, patients with neurofascin 140/186 positivity were older, with proximal weakness and a good response to intravenous immunoglobulins, while the patient with neurofascin 155 positivity was younger, with cranial and respiratory involvement, gait ataxia, high cerebrospinal fluid protein, a prolonged clinical course, and an inadequate response to intravenous immunoglobulins. The interesting observation made was that both groups of patients had varying conduction blocks without temporal dispersion on nerve conduction studies, which reversed rapidly with treatment.

Conclusion: The spectrum of illness, electrophysiology, and treatment varied widely in affected patients. Ultimately, the outcome depended on one's clinical acumen, antibody levels, and prompt treatment, as illustrated in the patients mentioned. This patient series was small, but the results were illustrative of the complexities of the disorder and the necessity for testing for nodopathies in patients with atypical clinical presentations, a prolonged clinical course, or conduction blocks in nerve conduction studies.

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Introduction

Nodopathies are a fascinating group of disorders involving the nodes of Ranvier. The nodes of Ranvier play a crucial role in the rapid conduction of electrical impulses in myelinated nerves. In 3% of cases of chronic inflammatory demyelinating polyradiculoneuropathy, antibodies expressed against nodal or paranodal axoglial proteins, such as neurofascin 155 immunoglobulin G4 (IgG4), neurofascin 140/186 immunoglobulin G3 (IgG3), contactin 1, or contactin-associated protein 1, lead to axolemmal dysfunction and impaired saltatory conduction with a reversible conduction block. Thus, nodopathies are variants of chronic inflammatory polyneuropathy but differ in their clinical course, electrophysiology, and response to treatment. The spectrum of nodopathies depends on the type and levels of antibodies, as illustrated in the case reports mentioned below.

Case Description

Patient 1

A 52-year-old right-handed man, a nonsmoker, presented with a history of weakness of both hands of 6 months' duration. He had trouble with fine motor movements, such as buttoning clothes and opening bottle caps. Two months later, there was weakness of both feet with bilateral foot drop. There were no muscle cramps, fasciculations, or stiffness. There was no history of exposure to heavy metals or toxins. On examination, there were no neurocutaneous markers or visible fasciculations. Higher mental functions and cranial nerve examination were normal. There was hypotonia of all four limbs with bilateral foot drop and wasting of the intrinsic muscles of the hands and feet. By the MRC grading, power in the wrist and finger dorsiflexors was 3/5, elbow flexors and extensors were 4/5, dorsiflexors and plantar flexors of the feet were 2/5, and knee flexors and extensors were 4/5. Superficial reflexes were present, and deep tendon reflexes were absent. There was no sensory loss, cerebellar signs, or thickened peripheral nerves. Routine investigations were normal, viral markers were negative, cerebrospinal fluid examination was normal, and vasculitic markers, collagen markers, antiganglioside antibodies, and the myeloma panel were negative. Neurofascin 140 and 186 antibodies were elevated at 320 ng/mL (normal: 0–233 ng/mL) and 388 ng/mL (normal: 0–366 ng/mL), respectively. Nerve conduction studies revealed motor demyelinating polyneuropathy with conduction block in the left radial nerve at the spiral groove, and sensory nerve conductions were normal in the upper and lower limbs. Electromyography revealed active denervation with neurogenic changes, more prominent in the distal and proximal muscles of all four limbs. Magnetic resonance imaging (MRI) of the cervical spine was normal. Sural nerve biopsy revealed a reduction in myelinated fibers with axonal loss. He was treated with intravenous immunoglobulin at 0.4 gm/kg/day for 5 days with ongoing physiotherapy. 10 days later, motor power was 4/5 in all four limbs with normal deep tendon reflexes. In 1 month, he recovered from his illness and returned to work with no motor weakness. Repeat nerve conduction studies revealed normal motor and sensory conductions.

Patient 2

A 44-year-old right-handed woman complained of pain and paresthesias with walking difficulty of 1 year's duration. She experienced a burning sensation in the hands with weakness of hand grip 6 months later. There was slowly progressive walking difficulty, loss of balance, and bilateral foot drop. Higher mental functions and cranial nerve examination were normal. Power was 4/5 in the upper limbs and 3/5 in the lower limbs by MRC grading, with hypotonia, areflexia, and bilateral flexor plantar reflexes. There was no sensory loss, cerebellar signs, thickened and palpable nerves, or neurocutaneous markers. Routine investigations were normal, viral markers were negative, cerebrospinal fluid examination was normal, and vasculitic and collagen markers were negative. Autoimmune antibody profiling revealed

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elevated levels of neurofascin 140 and 186 antibodies at 280 ng/mL (normal: 0–233 ng/mL) and 366 ng/mL (normal: 0–366 ng/mL), respectively. An immunoglobulin A (IgA) lambda band was seen in the beta region on serum protein electrophoresis, with restriction in the gamma region corresponding to IgA without excess kappa or lambda light chains on immunofixation electrophoresis. Bone marrow biopsy was cellular with trilineage hematopoiesis, 7% plasma cells, and dysmegakaryopoiesis. Nerve conduction studies revealed demyelinating motor polyradiculoneuropathy affecting the bilateral lower limbs, with conduction block in the tibial nerves at the popliteal fossa and prolonged F-wave latencies in both lower limbs. MRI of the whole spine showed contrast enhancement in the cauda equina. There was a fluorodeoxyglucose (FDG)-avid osteosclerotic lesion in the D5 vertebra on whole-body positron emission tomography-computed tomography (PET-CT) scan. Treatment was started with intravenous immunoglobulin at 0.4 gm/kg/day for 5 days, followed by intravenous steroids at 250 gm/day for the next 5 days. She received simultaneous treatment for POEMS syndrome with lenalidomide 20 mg daily, followed by daratumumab injection. Six months later, serum protein electrophoresis revealed no monoclonal band. However, pain, paresthesias, and weakness continued with recurrent foot drop. On examination, there was areflexia, MRC grade 3/5 power in the upper limbs, 2/5 power in the right lower limb, and 1/5 power in the left lower limb. Repeat nerve conduction studies revealed a demyelinating motor polyradiculoneuropathy involving both upper and lower limbs without conduction block. Treatment was resumed with intravenous immunoglobulin at 0.4 gm/kg/day for 5 days, followed by intravenous methylprednisolone 1 gm daily for 5 days. The patient received low-dose radiation to the D5 vertebral body and cauda equina. However, despite medication, there was no relief of symptoms; hence, intravenous rituximab was administered, following which motor power improved in all four limbs.

Patient 3

A 42-year-old right-handed woman presented with numbness and weakness of the left hand with a fine tremor of 1 year's duration. Six months later, there was numbness and paresthesias of the right hand with weakness. Later, there was weakness of both lower limbs with tripping of the feet while walking. Higher mental functions and cranial nerves were normal. There were no fasciculations or muscle wasting. Power was MRC grade 4/5 in the proximal muscles and 3/5 in the distal muscles of the upper and lower limbs, with impairment of touch and pain sensation in a glove-and-stocking distribution. Deep tendon reflexes were diminished, with bilateral flexor plantar responses. There were no cutaneous markers or thickened peripheral nerves. Routine investigations were normal, viral markers were negative, cerebrospinal fluid examination was normal, and vasculitic markers, collagen markers, antiganglioside antibodies, and serum immunofixation electrophoresis were negative. Neurofascin 140 levels were 279 ng/mL (normal: 0–233 ng/mL), and neurofascin 186 levels were 489 ng/mL (normal: 0–366 ng/mL). Nerve conduction studies revealed a distal sensorimotor polyneuropathy involving all four limbs. Sural nerve biopsy revealed loss of myelinated fibers with axonopathy. MRI of the brachial plexus showed increased signal along the brachial plexus and dorsal root ganglia. She responded to treatment with intravenous immunoglobulin at 0.4 gm/kg/day, intravenous methylprednisolone 1 gm daily for 5 days, and physiotherapy.

Patient 4

A 15-year-old right-handed boy, who had recovered from acute inflammatory polyneuropathy 1 year earlier, developed recurrent flaccid quadriparesis. Nerve conduction studies done previously revealed prolonged distal latencies, normal compound muscle action potential (CMAP) amplitudes, reduced conduction velocities with conduction block of the bilateral tibial and left peroneal nerves, persistence of F waves in the lower limbs, and normal conductions in the bilateral upper limbs. He recovered motor power after 2 months following treatment with intravenous immunoglobulin at 0.4 gm/kg/day for 5 days and physiotherapy. During the present admission, there was MRC grade 3/5 power in all four limbs, neck and trunk weakness, and reduced respiratory excursions requiring ventilation. However, his illness progressed rapidly to bilateral total ophthalmoplegia, bulbar weakness, hypotonia, and areflexia. Routine investigations were normal, viral markers were negative, cerebrospinal fluid examination was normal except for elevated protein levels, and vasculitic markers, collagen markers, antiganglioside antibodies including GM1 ganglioside and GQ1b, and the myeloma panel were negative. Neurofascin 155 antibodies were 129 ng/mL (normal: 0–232 ng/mL), and repeat nerve conduction studies revealed sensorimotor axonal polyneuropathy. As he had a low Glasgow Coma Scale (GCS) score of E1M1VET, autonomic dysfunction, total ophthalmoplegia, absent brainstem reflexes, and flaccid areflexic quadriparesis, plasmapheresis and supportive treatment were started immediately, followed by intravenous immunoglobulin at 0.4 gm/kg/day for 5 days and intravenous methylprednisolone 1 gm daily for 5 days. Repeat autoimmune antibody profiling revealed decreasing levels of neurofascin 155 antibodies at 25 ng/mL (normal: 0–232 ng/mL). By 1 month, there was recovery of eye movements. With ongoing physiotherapy and occupational therapy, he made a slow recovery and was discharged from the hospital with mild gait ataxia 3 months later.

Discussion

Nodo-paranodopathies are the clinical continuum of acute or chronic immune-mediated polyneuropathies with varied presentations and positive neurofascin antibodies, as described above. Nerve conduction reports vary between reversible conduction failure and secondary axonal degeneration.[1]

This paper focuses on four patients with neurofascin antibody-induced polyneuropathies, of whom the first three patients were neurofascin 140/186 positive and the last patient was neurofascin 155 antibody positive. Patients with neurofascin 140/186 antibodies presented with progressive limb weakness causing limitation of daily activities. The first two patients had demyelinating motor neuropathy of all four limbs with reversible conduction block and no temporal dispersion, while the third patient had sensorimotor axonal polyneuropathy. Neurofascin 140/186 antibodies caused detachment of paranodal myelin, lengthening of nodes, disequilibrium of sodium ions, and depolarization.[2] This resulted in an immune-mediated attack on the nodes of Ranvier with disruption of sodium channels, causing conduction failure that reversed with therapy (Fig. 1).[3] Uncini coined the term nodo-paranodopathies in 2013 for diseases of the nodes of Ranvier presenting as demyelinating or axonal polyneuropathies.[3] Notturno et al. reported that 62% of patients with multifocal motor neuropathy harbored anti-NF186 antibodies, while in 10%, anti-GM1 ganglioside antibodies were negative, as was observed in the first patient.[4] Vallat et al. described a case similar to the second patient, presenting with motor weakness, areflexia, a

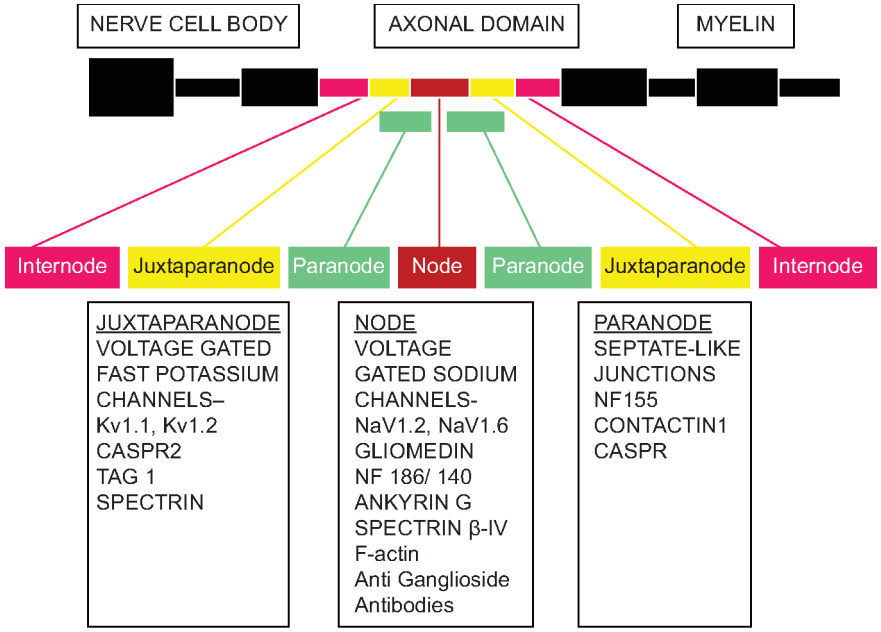

Fig. 1: Schematic illustration showing the structure of a myelinated neuron and the different subdivisions of the axonal domain: the node of Ranvier, the paranode, the juxtaparanode, and the internode. Receptors and antibodies at the node, paranode, juxtaparanode, and internode

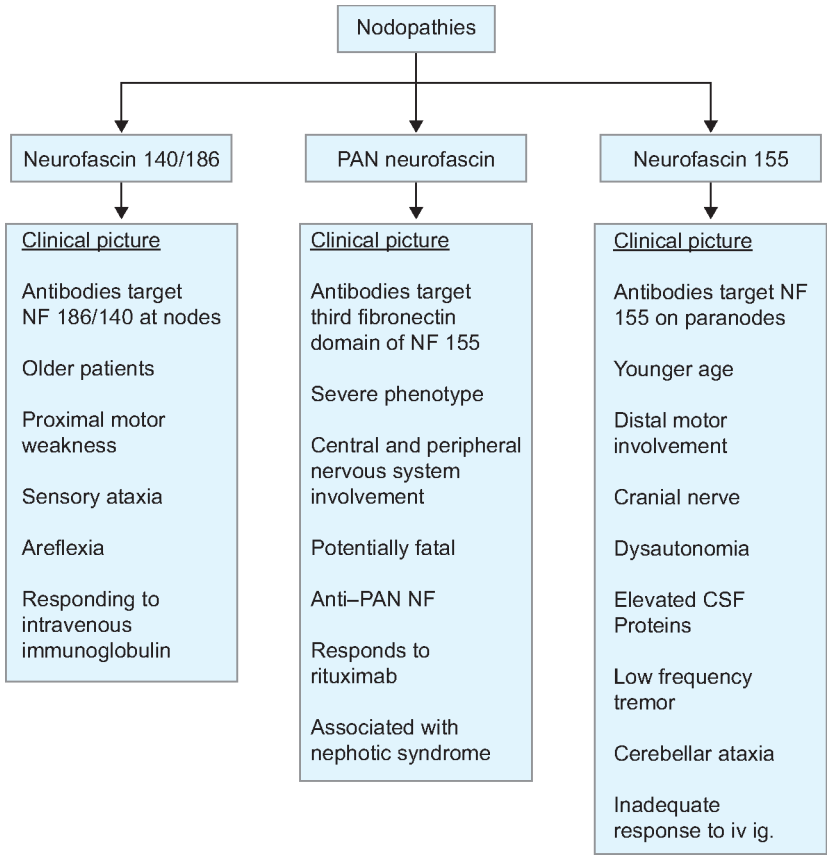

Fig. 2: Schematic illustration of the three different types of nodopathies

low-grade IgA-lambda myeloma, neurofascin 140/186 positivity, and conduction block without temporal dispersion.[5] Secondary axonal degeneration was consequent to complement-mediated damage at the nodes of Ranvier, proteolytic cleavage of neurofilaments, mitochondrial damage, and Wallerian degeneration.[5]

On the other hand, anti-NF155 autoimmune nodopathies differed in the clinical spectrum, as illustrated in the last case. In a case series of 40 patients with neurofascin 155 antibodies described by Aguilar et al., patients presented with distal weakness, tremor, and ataxia at a young age.[6] There was associated cranial nerve and respiratory involvement, elevated protein in cerebrospinal fluid, and an inadequate response to intravenous immunoglobulins.[7,8] Quinot et al. highlighted the occurrence of cranial nerve palsies, autonomic dysfunction, brainstem and respiratory impairment in neurofascin 155 autoimmune nodopathy, similar to the patient described.[9]

The juxtaparanode harbors voltage-gated fast potassium channels that prevent propagation of nodal currents to the internode (Fig. 1).[10,11] Caspr2 and transient axonal glycoprotein at the juxtaparanode link neurofascin 155 isoforms to septate-like junctions on the axolemma (Fig. 1).[12,13] Potassium channels enable repolarization of the neuronal membrane and generation of action potentials.[14] IgG4 antibodies react with paranodal glial neurofascin 155, resulting in malfunctioning of sodium-potassium pumps and reversible conduction failure with conduction blocks in the absence of temporal dispersion, which respond to treatment.[15] The clinical continuum of the different nodopathies is well illustrated through the four cases mentioned above (Fig. 2).

Conclusion

Our understanding of immune neuropathies has expanded beyond the realm of peripheral nerves to involve conduction at nodes and paranodes. The clinical manifestations caused by these antibodies are diverse and require a high index of suspicion for diagnosis. Thus, the above-mentioned cases stand apart from peripheral neuropathies because of their prolonged clinical course, reversible conduction blocks, central and peripheral nervous system involvement, and inadequate response to conventional therapy.

The lessons learned were that autoimmune nodopathies comprised 3% of inflammatory polyneuropathy cases. Neurofascin 140/186 nodopathies occurred in older patients with proximal motor weakness and areflexia, responding to intravenous immunoglobulins, steroids, and plasma exchange. In contrast, neurofascin 155 nodopathies occurred in young people with distal weakness, cranial nerve palsies, elevated cerebrospinal fluid protein levels, tremors, and ataxia, which responded to intravenous rituximab treatment. Pan-neurofascin nodopathies presented

with central and peripheral nervous system involvement, a higher mortality rate, and a good response to rituximab treatment. This article aims to enhance clinician awareness about the diverse presentations of these rare disorders.

Limitations of the Study

The number of cases was small, and further studies need to be conducted to validate our results. Nerve biopsies were performed in only two of four patients.

Patient Consent

Informed consent was obtained from the patients for publication of their case reports.

Author Contributions

All authors contributed equally to the clinical cases, writing, drafting, and preparation of the manuscript.

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