

Motor neuropathy with conduction block due to pan-neurofascin antibodies in a patient with chronic lymphocytic leukemia

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Case Report

A 66-year-old male presented with 1 month of progressive limb weakness and altered sensation in his fingertips. His hands were affected initially, proximal arm weakness developed a week later and proximal leg weakness followed. He reported 20kg of weight loss and night sweats over the preceding 2 years.

Nerve conduction studies by surface stimulation showed proximal motor conduction block at Erb's point in median and ulnar nerves with prolonged F-waves and normal distal motor responses. Sensory responses were normal. The proximal conduction block was confirmed on transcranial magnetic stimulation (Table 1). Atypical multifocal motor neuropathy with conduction block was initially diagnosed and he received 3 courses of intravenous immunoglobulin (IVIG) (2g/kg) over 6 weeks. Despite this he deteriorated further becoming bedbound, but with intact bulbar, respiratory and sphincter function. This prompted addition of prednisolone 60mg daily.

2 months after onset, he had moderate weakness of neck flexion but severe weakness of the upper and lower limbs with relative sparing of the ankles. Reflexes were present in the upper limbs but absent in the lower limbs and plantars were downgoing. Sensation was normal. At nadir 3 months into the illness he was effectively quadriplegic.

3 cerebrospinal fluid samples were acellular with mildly elevated protein levels (range 51-67mg/dL). Cytology and flow cytometry were negative for malignancy. There was mild macrocytic anaemia (haemoglobin 11.5g/dL) and IgG lambda paraprotein of 600mg/dL on immunofixation. MRI brachial and lumbar plexus showed T2 hyperintensity but no thickening or enhancement. MRI of the spine was normal. Whole body CT demonstrated right axillary lymphadenopathy.

Ultrasound-guided lymph node biopsy revealed infiltration by small mature lymphocytes and prolymphocytes, positive for CD20, CD79a, CD5 and CD23 with most cells expressing IgD,

consistent with small lymphocytic lymphoma. Bone marrow biopsy confirmed clonal B cells with chronic lymphocytic leukaemia (CLL) phenotype. Repeat neurophysiology at 2 months demonstrated more prolonged distal motor latencies and further slowing of proximal conduction velocities and active denervation distally and proximally in the upper limbs and cervical paraspinal muscles.

Plasma exchange was initiated 3 months after symptom onset, resulting in a small but definite improvement in neck flexion and ankle dorsiflexion strength suggesting an antibody-mediated process (Figure 1). At this point, IgG antibodies cross-reactive with both neurofascin (NF) isoforms (155 and 140/186) were detected, using a transiently-transfected, live, cell-based assay (method previously described¹).

Treatment for CLL was commenced with rituximab, cyclophosphamide and fludarabine, despite absence of a haematological indication, as it was felt to be driving pan-neurofascin antibody production.

After 2 months of chemotherapy and neuro-rehabilitation, the MRC sum score improved from 6 to 25 (Figure 1). By 4 months, he could mobilise independently and was discharged home at 6 months. Currently, 11 months after onset, he has returned to normal neurological function.

Discussion

Neurofascins are a group of cell adhesion molecules. NF140 and 186 isoforms are neuronal proteins at nodes of Ranvier whilst NF155 is a Schwann cell protein at the paranodal junction. Antibodies against these 3 isoforms have been reported in patients initially diagnosed with Guillain-Barre syndrome (GBS) or chronic inflammatory demyelinating neuropathy (CIDP)^{1,2}.

Anti-NF155 antibodies have been found in 7-18% of patients with CIDP^{3,4} and are associated with younger-onset, more aggressive disease with distal motor-predominance, sensory ataxia and tremor^{3,4}. Only 20-30% responded to IVIG^{3,4}, whilst over 60% benefited from oral corticosteroids and plasma exchange in 1 series⁴. Rituximab can be effective in those refractory to corticosteroids⁵.

Anti-NF140/186 antibodies (which almost invariably cross-react with NF155) have been associated with a subset of CIDP patients with subacute-onset, sensory ataxia and cranial nerve involvement without significant tremor. In 1 series, 4 of 5 patients had concomitant autoimmune disorders, with the antibodies proposed to underlie the pathogenesis of both conditions. Most responded well to steroids or IVIG¹. This case shows some similarity to previously reported cases of severe autoimmune neuropathies due to pan-neurofascin antibodies. The pure motor involvement appears to be a unique pattern².

CLL is commonly associated with immune dysregulation, most often autoimmune cytopenias. Immune-mediated peripheral neuropathies have been reported, including GBS and CIDP⁶. In a study of 816 CLL patients with median follow-up of 99 months, 19 (2.2%) developed peripheral neuropathy, of whom 3 fulfilled CIDP criteria. Serum antibodies to gangliosides and sulfatides were absent in all cases. Nodal/paranodal antibodies were not tested⁷.

We describe a patient with CLL and a severe inflammatory motor neuropathy due to IgG antibodies cross-reactive with both nodal (NF140/186) and paranodal (NF155) isoforms, raising the possibility of a paraneoplastic phenomenon similar to other antibody mediated autoimmune diseases in CLL⁸.

References

1. Delmont E, Manso C, Querol L, Cortese A, Berardinelli A, Lozza A, et al. Autoantibodies to nodal isoforms of neurofascin in chronic inflammatory demyelinating polyneuropathy. *Brain*. 2017;**140**(7):1851-1858. doi:10.1093/brain/awx124.
2. Burnor E, Yang L, Zhou H, Patterson KR, Quinn C, Reilly MM, et al. Neurofascin antibodies in autoimmune, genetic, and idiopathic neuropathies. *Neurology*. 2018;**90**(1):e31. doi:10.1212/WNL.0000000000004773.
3. Devaux JJ, Miura Y, Fukami Y, Inoue T, Manso C, Belghazi M, et al. Neurofascin-155 IgG4 in chronic inflammatory demyelinating polyneuropathy. *Neurology*. 2016;**86**(9):800-807. doi:10.1212/WNL.0000000000002418.
4. Ogata H, Yamasaki R, Hiwatashi A, Oka N, Kawamura N, Matsuse D, et al. Characterization of IgG4 anti-neurofascin 155 antibody-positive polyneuropathy. *Ann Clin Transl Neurol*. 2015;**2**(10):960-971. doi:10.1002/acn3.248.
5. Querol L, Rojas-García R, Diaz-Manera J, Barcena J, Pardo J, Ortega-Moreno A, et al. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. *Neurol - Neuroimmunol Neuroinflammation*. 2015;**2**(5):e149. doi:10.1212/NXI.0000000000000149.
6. Lopes da Silva R. Spectrum of Neurologic Complications in Chronic Lymphocytic Leukemia. *Clin Lymphoma Myeloma Leuk*. 2012;**12**(3):164-179. doi:10.1016/j.clml.2011.10.005.
7. Briani C, Visentin A, Salvalaggio A, Imbergamo S, Piazza F, Cacciavillani M, et al. Peripheral neuropathies in chronic lymphocytic leukemia: a single center experience on 816 patients. *Haematologica*. 2017;**102**(4):e140. doi:10.3324/haematol.2016.153064.
8. De Back TR, Kater AP, Tonino SH. Autoimmune cytopenias in chronic lymphocytic leukemia: a concise review and treatment recommendations. *Expert Review of Hematology*. 2018;**11**(8):613-624. doi: 10.1080/17474086.2018.1489720.

Table and figure legends

Table 1: Nerve conduction studies performed one and two months after symptom onset on the right upper and lower limb **(A)** and transcranial magnetic stimulation on the right upper limb **(B)**.

(A)

Motor

	One month		Two months	
<i>Upper limb</i>	<i>Median</i>	<i>Ulnar</i>	<i>Median</i>	<i>Ulnar</i>
CMAP (wrist)	13.0mV	13.0mV	13.0mV	12.0mV
CMAP (elbow)	12.0mV	13.0mV	13.0mV	12.0mV
CMAP (Erb's point)	0.2mV	1.5mV	0.4mV	0.2mV
CV (wrist-elbow)	46m/s	53m/s	43m/s	51m/s
CV (Erb-elbow)	38m/s	39m/s	23m/s	25m/s
DML (APB, ADM)	3.4ms	2.7ms	3.7ms	3.0ms
F response	34ms	35ms	34ms	37ms
<i>Lower limb</i>	<i>Common peroneal</i>		<i>Common peroneal</i>	
CMAP (ankle)	16.0mV		11.0mV	
CMAP (fibular neck)	11.0mV		7.0mV	
CV (fibular neck-ankle)	48m/s		37m/s	
DML (EDB)	4.5ms		3.6ms	
F response	57ms		60ms	

Sensory

	One month	Two months
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<i>Nerve</i>	<i>Median</i>	<i>Ulnar</i>	<i>Sural</i>	<i>Median</i>	<i>Ulnar</i>	<i>Sural</i>
SNAP	13 μ V (digit 3-wrist)	6 μ V (digit 5-wrist)	15 μ V (calf-ankle)	10 μ V (digit 3-wrist)	7 μ V (digit 5-wrist)	12 μ V (calf- ankle)

(B)

Nerve	Amplitude (mV)	Nerve	Amplitude (mV)
Cortex-right ADM	0.8	Cortex-right APB	0.2
Root-right ADM	0.8	Root-right APB	0.1
Elbow-right ADM	10.0	Elbow-right APB	2.5

Abbreviations: CMAP – compound muscle action potential, CV – conduction velocity,

DML – distal motor latency, APB – abductor pollicis brevis, ADM – abductor digiti minimi,

EDB – extensor digitorum brevis, SNAP – sensory nerve action potential, mV – millivolts,

m/s – metres per second, μ V – microvolts.

Figure 1. Change in strength as measured by the MRC sum score and the relationship to different treatment modalities.