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

Vivien Li MD FRACP[1], Frederick Schon MD[2], Janev Fehmi MD[3], Hamid Modarres MD[2], Simon Rinaldi PhD MRCP[2], Alexander M Rossor PhD FRCP[4]

1. University College London Hospitals NHS Foundation Trust, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK WC1N 3BG

2. Croydon Health Services NHS Trust, 530 London Rd, Thornton Heath, Croydon, London, UK CR7 7YE

3. University of Oxford Nuffield Department of Clinical Neurosciences, West Wing, John Radcliffe Hospital, Oxford, Oxfordshire, UK OX3 9DU

4. MRC Centre for Neuromuscular Diseases, Queen Square, London, UK WC1N 3BG

Corresponding author:

Dr Alexander Rossor

Address: National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, United Kingdom

Email: a.rossor@ucl.ac.uk

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/mus.26851

Running title: Pan-neurofascin neuropathy

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.

None of the authors has any conflict of interest to disclose.

Key words: Peripheral neuropathy, neurofascin, paraneoplastic, chronic lymphocytic leukemia, chemotherapy

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 normal distal median and ulnar motor responses, mildly prolonged F-waves and normal sensory studies. EMG showed fibrillations and positive sharp waves in proximal upper limb muscles, leading to stimulation at Erb's point which demonstrated proximal motor conduction block. This finding 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 (Table 1), he had moderate weakness of neck flexion but severe weakness of upper and lower limbs with relative sparing of ankle dorsiflexion. 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 (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 of brachial and lumbar plexus showed T2 hyperintensity but no

thickening or enhancement. MRI cervical 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 with 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 1a). At this point, IgG antibodies cross-reactive with both neurofascin (NF) isoforms (155 and 140/186) were detected[1] (Figure 1b).

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 1a). By 4 months, he could mobilise independently and was discharged home at 6 months. Currently, 11 months after onset, neurological function is normal.

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 isoforms have been reported in patients initially diagnosed with Guillain-Barre syndrome (GBS) or chronic inflammatory demyelinating polyneuropathy (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 series[4]. Rituximab can be effective in those refractory to corticosteroids[5].

Anti-NF140/186 antibodies (which usually 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 IVIG[1]. This case shows some similarity to previously reported cases of severe Guillain-Barre type presentations due to pan-neurofascin antibodies. The pure motor involvement appears to be a unique pattern[2].

CLL is commonly associated with immune dysregulation, most often autoimmune cytopaenias. Immune-mediated peripheral neuropathies have been reported, including GBS and CIDP[6]. 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 tested[7].

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 CLL[8].

Pan-neurofascin neuropathy

Abbreviations

Intravenous immunoglobulin (IVIG)

Chronic lymphocytic leukaemia (CLL)

Neurofascin (NF)

Guillain-Barre syndrome (GBS)

Chronic inflammatory demyelinating neuropathy (CIDP)

References

1. Delmont E, Manso C, Querol L, Cortese A, Berardinelli A, Lozza A, Belghazi M, Malissart P, Labauge P, Taieb G, Yuki N, Illa I, Attarian S, Devaux JJ. 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, Rossor AM, Scherer SS, Lancaster E. 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, Sekiguchi K, Kokubun N, Ichikawa H, Wong AHY, Yuki N. 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, Kuwahara M, Suzuki H, Kusunoki S, Fujimoto Y, Ikezoe K, Kishida H, Tanaka F, Matsushita T, Murai H, Kira J. 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, Sedano MJ, Seró-Ballesteros L, Carvajal A, Ortiz N, Gallardo E, Illa I. 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, Campagnolo M, Frezzato F, Semenzato G, Trentin L. 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 Rev Hematol*. 2018;11(8):613-624. doi:10.1080/17474086.2018.1489720.

Table and figure legends

Table 1: Nerve conduction studies one and two months after symptom onset.

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

Sensory						
Nerve	***Median***	***Ulnar***	***Sural***	***Median***	***Ulnar***	***Sural***
SNAP (μV)	13 (digit 3-wrist)	6 (digit 5-wrist)	15 (calf-ankle)	10 (digit 3-wrist)	7 (digit 5-wrist)	12 (calf-ankle)
TMS	**Amplitude (mV)**			**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, μV – microvolts, TMS – transcranial magnetic stimulation.

Figure 1. Change in strength as measured by the MRC sum score and the relationship to different treatment modalities **(A)**. A transiently-transfected, live, cell-based assay **(B)** showing IgG from patient sera binding to **(i)** Neurofascin (NF) 155 and **(ii)** NF186-transfected human embryonic kidney (HEK) cells. NF expression is confirmed by a commercial pan-NF antibody (red), which co-localises with patient IgG (green). No binding of human IgG is seen in untransfected HEK cells **(iii)**. There is IgG1 subclass specificity with no binding seen with IgG2, IgG3 or IgG4 subclasses **(iv)**. Abbreviations: IVIG – intravenous immunoglobulin, pred – prednisolone, PLEX – plasma exchange, ritux – rituximab, cyc –

cyclophosphamide, FCR – fludarabine/cyclophosphamide/ rituximab, NF – Neurofascin, IgG – immunoglobulin, DAPI – 4',6-diamidino-2-phenylindolenuclear stain.

Figure 1A

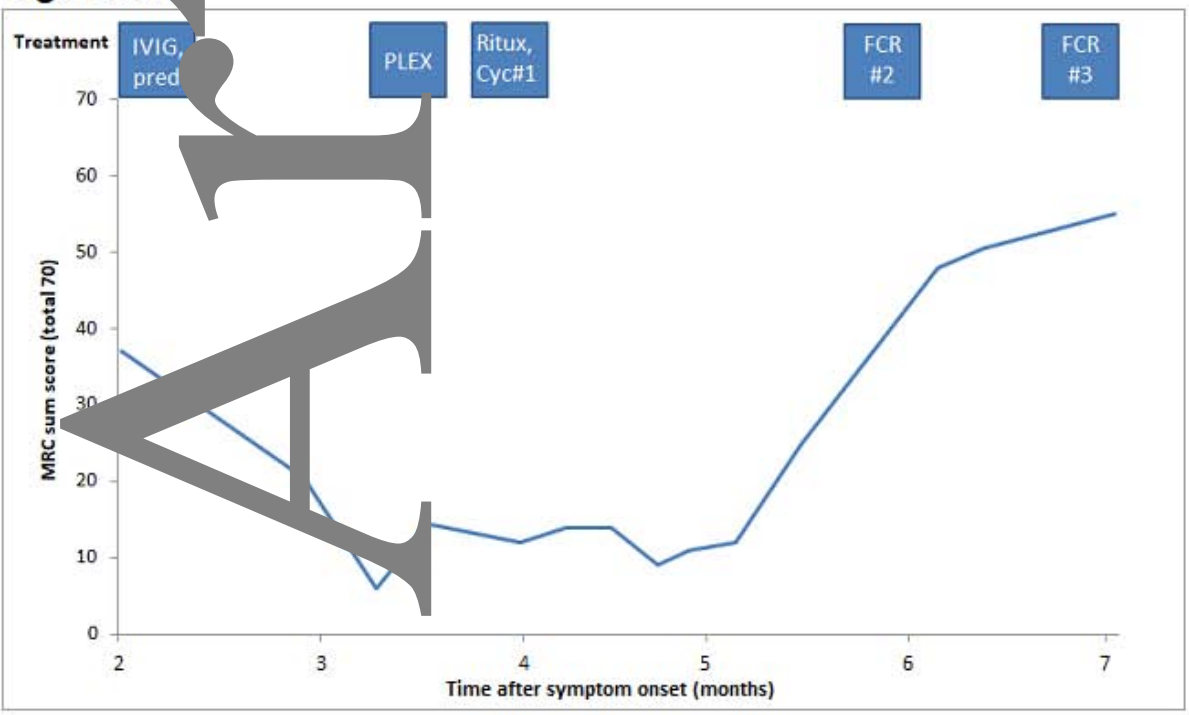
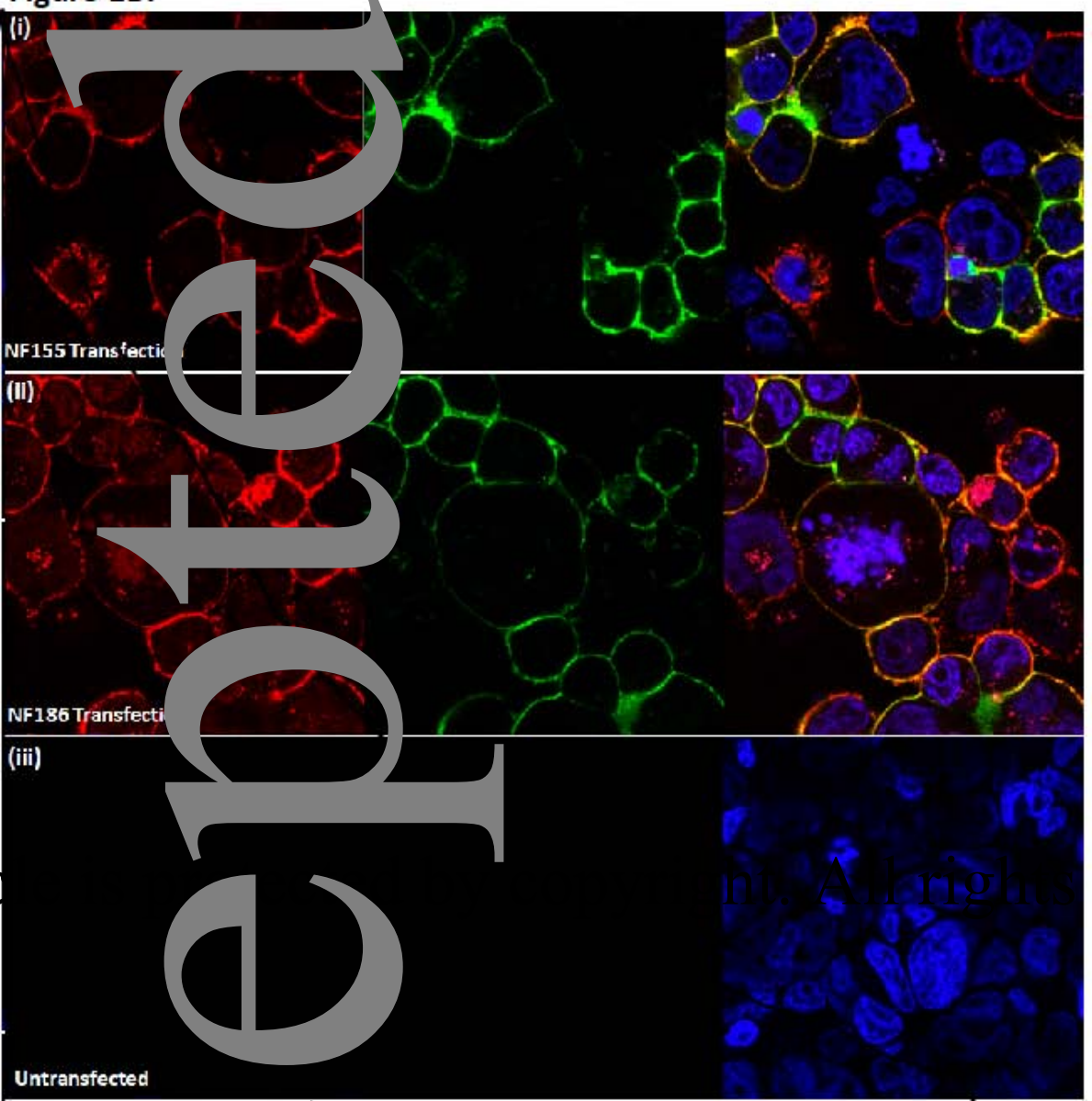


Figure 1B.



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

Sensory						
Nerve	***Median***	***Ulnar***	***Sural***	***Median***	***Ulnar***	***Sural***
SNAP (μV)	13 (digit 3-wrist)	6 (digit 5-wrist)	15 (calf-ankle)	10 (digit 3-wrist)	7 (digit 5-wrist)	12 (calf-ankle)

TMS	**Amplitude (mV)**		**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, µV – microvolts, TMS – transcranial magnetic stimulation.