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Short Communication

Tongue tremor in neurofascin-155 IgG4 seropositive chronic inflammatory polyradiculoneuropathy

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ABSTRACT

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with anti-neurofascin-155 antibodies is a subgroup of CIDP with tremor and poor response to intravenous immunoglobulins.

A 23-year-old male presented with a 6-month history ataxic-stepping gait, stocking tactile hypoesthesia, areflexia, tremor at limbs and tongue. Neurophysiology and cerebrospinal fluid analysis supported the diagnosis of CIDP. Tongue EMG was negative. Serum was positive for neurofascin-155 IgG4. His symptoms improved with intravenous methylprednisolone and then immunoglobulins, but not the tremor. Neurofascin-155 antibodies binding to cerebellar neurons suggests its central origin. This is the first neurofascin-155 antibody-seropositive patient with also tongue tremor, who is candidate to rituximab.

1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with anti-neurofascin (NF)-155 antibodies of IgG4 isotype has recently been described as a subgroup of CIDP patients with young age at onset, tremor and poor response to intravenous immunoglobulins (Querol et al., 2014; Devaux et al., 2016) though response to rituximab has been described (Querol et al., 2015). NF-155 is the myelin ligand of the contactin-1/contactin-associated protein 1 (CNTN1/CASPR1) complexes at the paranode and their localization around the node of Ranvier is essential for saltatory conduction. Anti-NF-155 antibodies, disturbing the glial-axon interaction and the functional organization of the node of Ranvier, induce paranodal dissection likely responsible for the neurophysiological findings of slow velocities and conductions blocks (Vallat et al., 2017; Koike et al., 2017). We report on a young patient affected with NF-155 IgG4 seropositive CIDP who, along with the typical symptoms of the disease, presented with therapy unresponsive tongue tremor.

2. Case report

A previously healthy 23-year-old man came to our attention for a 6 months history of gait difficulties secondary to sensory-motor deficit at lower limbs, and upper limbs tremor. The patient (height 160 cm, weight 44 kg, body max index 17.19) had discontinued sport activity (soccer) for incapability of using the feet, reported little autonomy in the gait and was severely limited in fine motor tasks because of the upper limbs tremor. At neurological evaluation he had ataxic-stepping gait (left > right), bilateral distal weakness (left tibialis anterior 3/5 MRC, right tibialis anterior 4/5 MRC, extensor hallucis longus 2/5 MRC bilaterally, gastrocnemius 4/5 bilaterally, left peroneus longus 4/5 MRC, iliacus 4/5 MRC bilaterally, hand intrinsic muscles 4/5 bilaterally), tactile hypoesthesia and loss of vibration sense up to the knees, areflexia. High amplitude and low frequency tremor was present at both arms (more on the left side) and tongue, The tremor was marked in the upper extremities and minimal in the legs (Supplementary Video 1). No tongue or limb fasciculations were present nor myoclonus. Besides the tremor, no cerebellar signs were present. Namely the heel-to-shin and finger to nose tests were normal. Inflammatory Neuropathy Cause and Treatment (INCAT) leg disability score was 1, and INCAT arm disability score was 3. Neurophysiology showed signs of diffuse demyelinating neuropathy, with significant slowing of conduction velocities, increased distal latencies and F wave latencies, temporal dispersion and bilateral conduction blocks at the median and ulnar nerves in the Erb-axilla tract

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Table 1
Nerve conduction studies.

Nerve	Stimulation site	Recording site	DL (ms)	CV (m/s)	Amplitude (cMAP = mV SAP = μV)	F (ms)
L Median (m)	Wrist	ABP	5.38		8.8	67
	Elbow	ABP		25	6.9	
	Axilla	ABP		28	5.8	
	Erb	ABP		19	0.5	
R Median (m)	Wrist	ABP	6.28		5.4	74
	Elbow	ABP		26	3.6	
	Axilla	ABP		25	3.5	
	Erb	ABP		20	0.2	
L Ulnar (m)	Wrist	ADM	4.27		5.1	67
	BE	ADM		25	5.0	
	AE	ADM		27	4.1	
	Axilla	ADM		32	3.8	
	Erb	ADM		19	0.7	
R Ulnar (m)	Wrist	ADM	4.66		7.5	71
	BE	ADM		25	5.9	
	AE	ADM		30	5.1	
	Axilla	ADM		25	5.1	
	Erb	ADM		18	0.5	
L Peroneal (m)	Ankle	EDB	12.9		0.6	
	BFH	EDB		16	0.4	
	LPF	EDB		22	0.3	
R Peroneal (m)	Ankle	EDB	11.9		0.9	
	LPF	EDB		20	0.9	
L Tibial (m)	Ankle	AH	13.7		0.1	
	PF	AH		20	0.1	
R Tibial (m)	Ankle	AH	13.8		0.3	
	PF	AH		28	0.2	
L Median (s)	1th finger	Wrist	4.98	21	3.2	
	3rd finger	Wrist	5.86	21	3.8	
R Median (s)	1th finger	Wrist	5.13	21	3.0	
	3rd finger	Wrist	5.83	21	2.8	
L Ulnar (s)	5th finger	Wrist	5.59	20	2.1	
R Ulnar (s)	5th finger	Wrist	5.20	21	1.7	
L Radial (s)	1th finger	Wrist	3.96	23	3.7	
R Radial (s)	1th finger	Wrist	3.77	23	5.0	
L Sural (s)	Mild calf	Ankle	4.31	33	6.6	
R Sural (s)	Mild calf	Ankle	5.05	28	6.5	

DL: distal latency; CV: conduction velocity; cMAP: compound motor action potential; SAP: sensory action potential; BE: below elbow; AE: above elbow; BFH: below fibular head; LPF: lateral popliteal fossa; PF: popliteal fossa; APB: abductor pollicis brevis; ADM: abductor digiti minimi; EDB: extensor digitorum brevis; AH, abductor hallucis; R: right; L: left; m: motor; s: sensory.
Normal values: median nerve DL ≤3,5 ms; sensory CV ≥48 m/s; SAP ≥15 μV; MCV ≥50 m/s; cMAP ≥6 mV; ulnar nerve DL ≤3,1 ms; sensory CV ≥48 m/s; SAP ≥10 μV; motor CV ≥50 m/s; cMAP ≥4 mV; radial nerve sensory CV ≥40 m/s; SAP ≥10 μV; peroneal nerve DL ≤5,5 ms; motor CV ≥40 m/s; cMAP ≥3 mV; tibial nerve DL ≤6 ms; motor CV ≥ 40 m/s; cMAP ≥4 mV; sural nerve sensory CV ≥50 m/s; SAP ≥5 μV; F-wave median/ulnar < 32 ms.

consistent with inflammatory demyelinating polyradiculoneuropathy, according to European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria (Van den Bergh et al., 2010) (Table 1). Fibrillation potentials (positive waves and brief spike) were observed at distal muscles at lower limbs (tibialis anterior, extensor digitorum longus and medial gastrocnemius) and rare fasciculation potentials were observed at biceps femoris. No complex repetitive discharges or myokymic discharges were detected. Tongue EMG was negative.

Nerve ultrasound (Esaote MyLab Seven, Genova, Italy) showed increased cross sectional area (CSA) of the brachial plexus (156 mm^2 on the right side, 129 mm^2 on the left side, normal values ≤80 mm^2), left median (24 mm^2 at elbow, normal values ≤13 mm^2), right median (19 mm^2 at axilla, normal values ≤13 mm^2), left radial (10 mm^2 at omeral sulcus, normal values ≤6 mm^2), posterior interosseous (7 mm^2, normal values ≤3 mm^2), distal radial sensory (9 mm^2, normal values ≤2 mm^2), left sciatic (53 mm^2 at proximal thigh, normal values ≤50 mm^2) nerves. Cerebrospinal fluid analysis showed increased total protein level (175 mg/dL) and blood-spinal nerve root-barrier damage, with normal leukocyte count. Laboratory testing were unremarkable, except for serum positivity at high titer (OD 2.9, cutoff 0.2–0.3) for IgG4 antibody to neurofascin-155.[1-2] Brain and spine MRI with Gadolinium was negative. 3D MR Neurography revealed bilateral hypertrophy of brachial and lumbosacral plexi (Fig. 1). The patient was diagnosed with neurofascin-155 IgG4 seropositive CIDP and treated with intravenous methylprednisolone (1 g/day for 5 days, followed by 1 g/day for 2 days in the next 2 months) with improvement of motor and sensory deficit, but tremor persisted. Subsequently he underwent intravenous immunoglobulins without improvement of the limbs and tongue tremor. The patient is now candidate to rituximab therapy.

3. Discussion

Among CIDP, the recently described patients with IgG4 anti-NF-155 antibodies represent a peculiar and distinct subgroup in terms of phenotype, pathophysiology, response to therapy and possible central nervous system involvement. Latest reports, as the present, are still enriching the definition of this subgroup of CIDP patients with younger age, severe weakness, predominantly distal sensory disturbances, intention tremor, sensory ataxia, subacute onset and poor response to intravenous immunoglobulins (Querol et al., 2014; Devaux et al., 2016). NF-155 is a paranodal molecule crucial for glia-axonal interaction, and the discovery of antibodies to NF-155 has opened new avenues in the understanding of the disease. NF-155 antibodies have been shown also to stain rat cerebellum, predominantly the molecular and granular layer (Querol et al., 2014), suggesting a possible central origin of the therapy unresponsive tremor, and in some patients central nervous system demyelinating alterations have also been detected at the

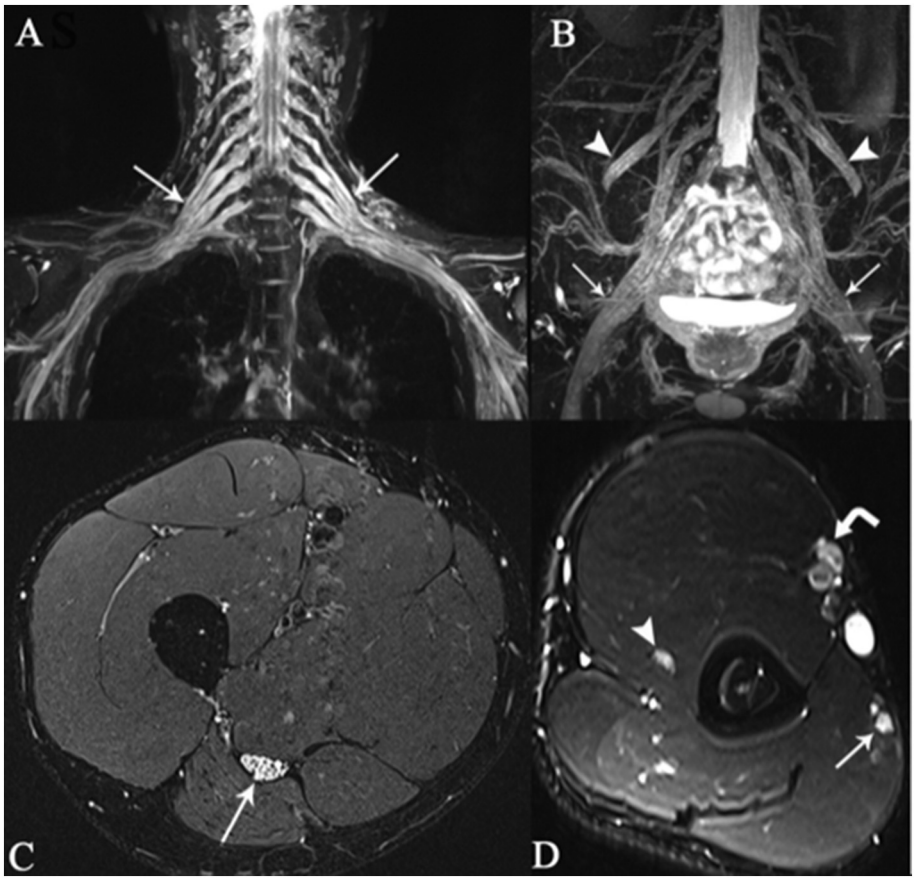

Fig. 1. 3D MR Neurography of the brachial (A) and lumbosacral plexus (B), coronal views; 2D MR neurography of the right sciatic nerve at mid-thigh (C) and of the right arm at mid-humerus (D). A) Bilateral, symmetric hypertrophy of the brachial plexus, which is predominant in the nerve roots, with gradual normalization toward the proximal limbs (arrows). B) Bilateral symmetric hypertrophy of the lumbosacral plexus, involving the terminal branches, intrapelvic femoral nerves (arrowheads) and sciatic nerves at the sciatic notch (arrows). C) Increased signal intensity and size (CSA = 89 mm^2) of the right sciatic nerve, with diffuse fascicular hypertrophy (arrow). D) Increased signal intensity and size of the right median (CSA = 16 mm^2, curved arrow), ulnar (CSA = 10 mm^2, arrow) and radial (CSA = 7.6 mm^2, arrowhead) nerves.

brain MRI (Devaux et al., 2016). Moreover, NF-155 positive CIDP may also have cranial nerve hypertrophy (Franques et al., 2017). Besides one patient with immunotherapy-responsive head and voice tremor (Painous et al., 2018), this is to our knowledge the first NF-155 antibody seropositive patient with arms and tongue tremor, who is now candidate to rituximab treatment. Our findings show that the nerve ultrasound and 3D MR Neurography abnormalities are similar to those observed in both seronegative CIDP patients (Padua et al., 2014) and in NF-155 antibody positive CIDP patients (Ogata et al., 2015, Garg et al., 2018).

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Declarations of interest

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