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BRIEF COMMUNICATION

# Head and voice tremor improving with immunotherapy in an anti-NF155 positive CIDP patient

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## Abstract

Chronic inflammatory demyelinating polyradiculoneuropathy with NF155 antibodies (anti-NF155+) constitutes a specific chronic inflammatory demyelinating polyradiculoneuropathy subset with a high incidence of limb's tremor and poor response to conventional therapies. We report a patient with chronic inflammatory demyelinating polyradiculoneuropathy anti-NF155+ with a severe tremor involving limbs, head and voice that responded very well to rituximab. This response correlated with a sharp decrease in the anti-NF155 titers. This case is the first report associating head and voice tremor to chronic inflammatory demyelinating polyradiculoneuropathy, reinforces the hypothesis of the cerebellar origin of this tremor and provides indirect evidence that the antibodies may be the cause of the tremor in these patients.

## Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune neuropathy displaying a heterogeneous clinical spectrum.[1] Recent description of pathogenic antibodies against neural cell-adhesion molecules, such as contactin-1[2,3] and neurofascin,[4,5] has allowed the description of specific clinical phenotypes within the CIDP spectrum.[6] CIDP associated with NF155 antibodies (anti-NF155+) constitutes a specific CIDP subset with predominantly distal weakness, high incidence of low-frequency and high-amplitude postural and intentional limb tremor, poor response to intravenous immunoglobulin (IVIg),[4] good response to B-cell depleting therapies[7] and association to the human leukocyte antigen (HLA) class II allele DRB1*15.[8] Although tremor is a frequent finding in inflammatory neuropathies,[9] head and voice tremor have never been described in CIDP patients. We report a patient with an anti-NF155+ CIDP that presented head, voice and limb tremor that improved with immunotherapy.

A 64-year-old man with unremarkable medical history, presented at the age of 61 with progressive distal paresthesia and gait ataxia which notably worsened during the first month. Action tremor involving voice, head and limbs appeared 2 months after first symptoms developed. Cephalic tremor was changing in direction (yes-yes and no-no tremor) and limb's tremor, more severe in the upper limbs, showed low-frequency (4 Hz) and high-amplitude and determined significant disability in his daily activities. Intentional tremor and dysmetria were prominent, despite normal proprioception in the upper limbs, and did not worsen in the finger to nose test with eyes closed. Proprioceptive sensation in lower extremities

was severely impaired. Muscle strength was almost normal in upper limbs (5/5 proximal, 4+/5 distal) and moderately weak in legs (4/5 proximal, 3/5 distal). The neurological examination also showed areflexia in legs, hyporeflexia in upper limbs, and a severe truncal and gait ataxia. The EMG showed features of acquired demyelination (Tables 1 and 2) fulfilling CIDP diagnostic criteria[10] and his cerebrospinal fluid demonstrated albumin-cytologic dissociation (1 cell/mm$^3$–135 mg/dL proteins titer). HLA class II testing revealed the DRB1*15:01/DRB1*01:02 alleles. Brain magnetic resonance imaging was normal. A first course of IVIg was ineffective. The weakness, ataxia and tremor worsened significantly, and the patient eventually become wheelchair bound. He received six plasmapheresis cycles that were also ineffective and oral corticosteroids (1 mg/Kg) were started with mild improvement. During corticosteroid tapering the patient developed a severe relapse and was referred to our center.

Five plasma exchange cycles followed by rituximab (375 mg/m$^2$, 6 doses) were added to the corticosteroids.

**Table 1.** Electrophysiological study, 9 months after the onset of CIDP.

| Motor conduction study | | | | | | |
|---|---|---|---|---|---|---|
| | Distal Motor Latency, ms | | Amplitude, mV | | Conduction velocity, m/sec | |
| Nerve | Values | Normal values | Values | Normal values | Values | Normal values |
| Median, right/left | 6.4/7.1 | <3.9 | 7.8/7 | >6 | 27.4/27.2 | >50 |
| Ulnar right/left | 5.3/5.9 | <3.3 | 7.5/6 | >5 | 21.7/24 | >48 |
| Peroneal, right/left | 16.4/18.8 | <5 | 1.2/0.1 | >2 | 15/14 | >42 |

Motor conduction study.

**Table 2.** Electrophysiological study, 9 months after the onset of CIDP.

| Sensory conduction study | | | | |
|---|---|---|---|---|
| | Amplitude, $\mu$V | Normal values | Conduction velocity, m/sec | Normal values |
| Nerve | | | | |
| Median, right/left | NR/NR | >16 | NA/NA | >44 |
| Ulnar, right/left | NR/NR | >15 | NA/NA | >42 |
| Radial, right/left | NR/NR | >14 | NA/NA | >51 |
| Superficial peroneal, right | NR/NR | >6 | NA/NA | >39 |

Sensory conduction study. NR, No response; NA not applicable.

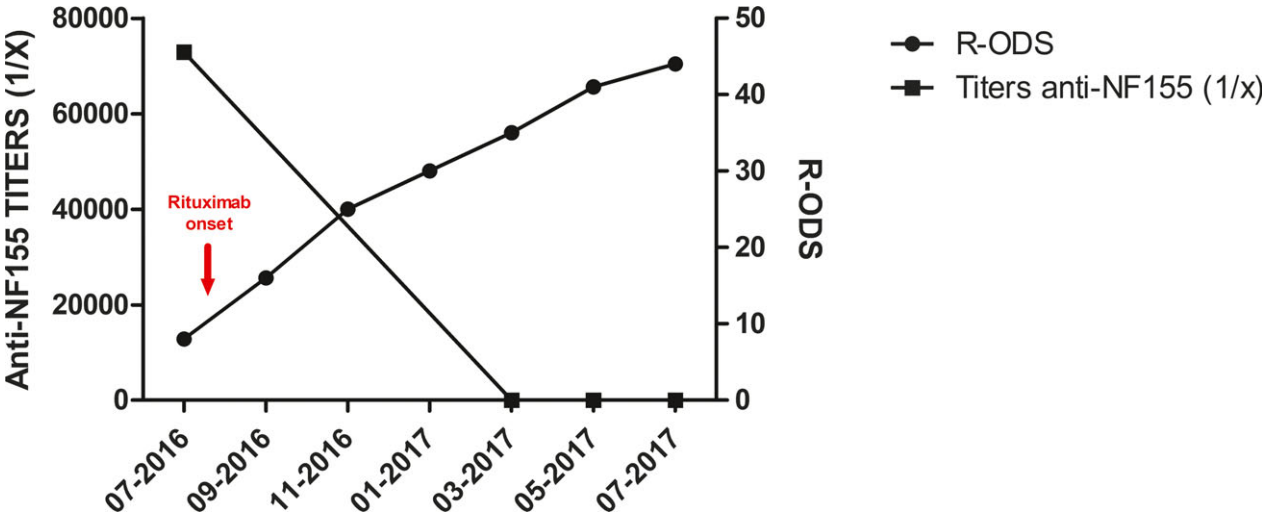


**Figure 1.** The patient improved dramatically after rituximab treatment in Rasch-built Overall Disability Scale and anti-NF155 antibody titers fell from 1/72,900 to become undetectable.

 

3 months later the weakness, ataxia and tremor, including the head and voice tremor, started to improve greatly. Six months later the patient was able to walk unaided. Voice tremor improved substantially, and limb and cephalic tremor resolved (Video S1). The anti-NF155 antibody titers fell from 1/72,900 pre-rituximab to become undetectable (Fig. 1).

Neuropathic tremor (NT) involving limbs is a well-known accompanying feature of peripheral neuropathies[9] but, to the best of our knowledge, this is the first report of a CIDP patient presenting with treatment-responsive head and voice tremor.

Tremor in patients with inflammatory neuropathies was traditionally considered of peripheral origin. However, the disproportion of the tremor and the ataxia to the degree of joint position sensation involvement and the presence of head and voice tremor in our patient, as it happens in essential tremor, suggest cerebellar involvement in these patients. The involvement of cerebellum in neuropathic tremor was proposed in a study in which patients with inflammatory neuropathy with and without tremor differed in their performance on diverse cerebellar tests.[11] This study also showed a lack of correlation between the development of tremor and the severity of the neuropathy. To further support this hypothesis, selective knockout of the 155 isoform of neurofascin in mice causes degenerative changes in Purkinje neurons, leading to prominent tremor and ataxia.[12] Finally, we showed in the original description of the association of NF155 antibodies to tremor in CIDP that sera of four anti-NF155+ CIDP patients react intensely with the neuropil of rat brain, with a pattern of immunostaining of hippocampus and cerebellum that was identical in all cases,[4] suggesting that NF155 in the central nervous system may also be targetted in these patients.

In conclusion, this first description of an anti-NF155+ CIDP patient with treatment-responsive head, voice and limb postural and action tremor provides additional evidence on the likely involvement of cerebellum in anti-NF155+ CIDP pathogenesis.

## Conflicts of Interest

LQ has provided expert testimony for Grifols and CSL Behring and received research funds from Novartis Spain and Grifols (Spin Award). II provided expert testimony and received speaking fees and travel grants from Pfizer. All other authors do not have any conflicts to declare.

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## Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

**Video S1.** The video summarizes main findings in the neurological exam of the patient before and after rituximab treatment.

 