

Combined Central and Peripheral Demyelination With IgM Anti–Neurofascin 155 Antibodies

Case Report

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Immunoglobulin (Ig) G anti–neurofascin 155 antibodies (anti-NF155 Abs) have been described in rare forms of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and in combined central and peripheral demyelination (CCPD).¹ We report herein a case of a patient presenting CCPD and IgM anti-NF155 Ab.

Case Report

A 43-year-old woman with no medical history was referred to our department for a 3-year history of progressive hand and feet paresthesia, with mild postural and head tremor. She had quadridistal hypesthesia, with ataxic gait, and diffuse diminished tendon reflexes. The Overall Neuropathy Limitations Score (ONLS) was 1/12. Electroneuromyography (ENMG) revealed a diffuse homogeneous demyelinating neuropathy. Nerve ultrasonography and MRI of the cervical plexus (Figure 1, D and E) found a diffuse enlargement of peripheral structures. CSF analysis showed elevated protein level (0.7 g/L, normal <0.4) and 14 white blood cells/mm³ (normal <2) with oligoclonal IgG bands. Cerebral MRI revealed multiple hyperintensities in the periventricular and juxtacortical white matter (diagnosis of radiologically isolated syndrome). All the 97 genes of a panel of genes involved in hereditary neuropathies, especially demyelinating Charcot-Marie-Tooth (CMT), were negative. Peripheral involvement fulfilled the CIDP diagnosis,² and the patient received 3 monthly IVIg doses (2 g/kg) leading to a subjective improvement of the paresthesia.

Eighteen months later, she reported an acute onset (within 3 weeks) of abnormal stiff gait with increased paresthesia in the 4 limbs and tremor. Clinical examination revealed mild spastic paraparesis, with quadridistal weakness (Medical Research Council score between 3 and 4/5 and ONLS score at 4/12). Complementary examinations (Figure 1, A–C and F) revealed increased demyelinating parameters on ENMG, associated with 3 cervical myelitis lesions and new cerebral lesions responding to the multiple sclerosis criteria. A simultaneous peripheral and central relapse of CCPD was diagnosed. The patient presented positive antinuclear antibodies (1/1,280), positive IgM anti-GM3 and GM4 Abs without anti-MAG Abs, and an IgM (lambda) monoclonal gammopathy of undetermined significance (MGUS).

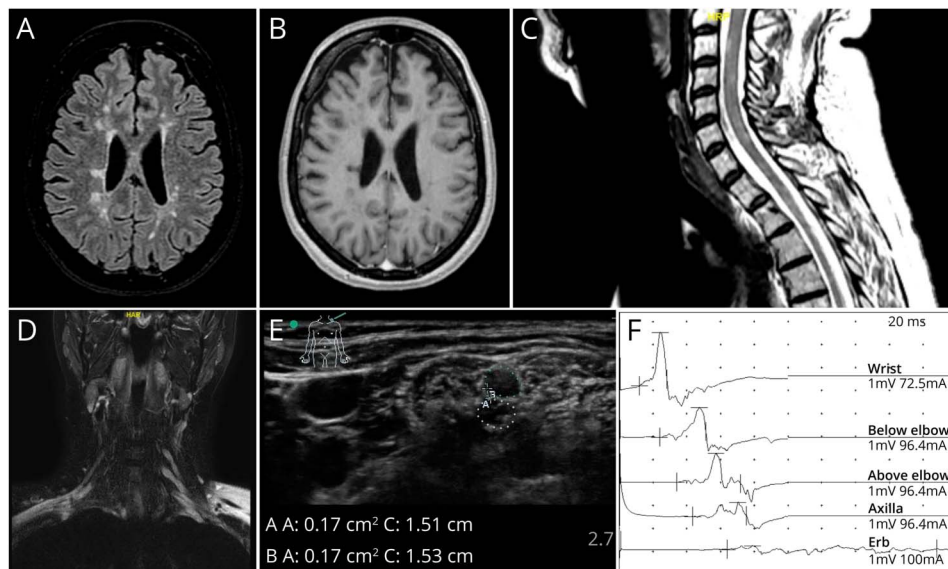
Using flow cytometry (human embryonic kidney cells),³ IgG4 anti-NF155, anti-contactin 1, anti-NF186, and anti-CASPR1 Ab were negative, but IgM anti-NF155 Abs were positive (Figure 2). The patient was treated with 3 monthly IV corticosteroid pulses, with concomitant rituximab treatment (2 infusions of 1 g within 2 weeks and then 1 every 6 months), and experienced a great clinical improvement, as only a mild postural tremor (ONLS at 1/12) remained, without any clinical or radiologic relapse after 2 years of follow-up.

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(A) Cerebral MRI fluid-attenuated inversion recovery (FLAIR) images (axial): periventricular and juxtacortical lesions on hypersignal. (B) Cerebral MRI T1 images (axial): black hole lesions on hyposignal. (C) Spine MRI FLAIR images (sagittal): medullar hypersignal in C3, C4, and C5-C6. (D) MRI T2 fat saturation (coronal): bilateral diffuse hyperintensity and diffuse severe hypertrophy of the bilateral brachial plexus. (E) Nerve ultrasonography of the brachial plexus (interscalene): upper, middle trunk enlargement (cross-sectional area [CSA] at 17 mm²; nerve enlargement if CSA >9 mm²).² (F) Electroneuromyography of the left ulnar nerve: reduced distal compound muscle action potential (CMAP) amplitude at 2.3 mV (normal >4 mV), associated with severe demyelinating abnormalities with prolonged distal motor latency at 11.9 milliseconds (normal <3.6 milliseconds), slow motor conduction velocities at 17 m/s (normal >45 m/s), motor conduction blocks until 62% amplitude reduction at axilla and temporal dispersion, and prolonged distal CMAP duration at 16.4 milliseconds (demyelination if >8.6 milliseconds).²

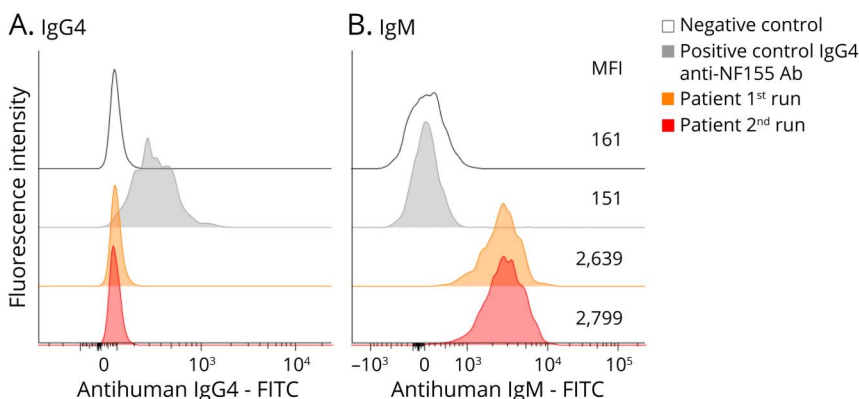
Discussion

We reported herein an instructive case with (1) a peripheral clinical picture of CIDP with ataxia and tremor associated with simultaneous acute relapse of cervical myelitis leading to CCPD diagnosis, (2) a positivity of IgM anti-NF155 Ab without IgG4, and (3) an effectiveness of corticosteroid and rituximab treatment. CIDP associated with IgG4 anti-NF155 Ab is rare (5%–10% of CIDP cases) and presents specific clinical characteristics: young age at onset, distal motor lower limb weakness, sensory ataxia, tremor, poor response to IVIg, and good response to corticosteroids and rituximab.¹ NF155 protein is expressed in both the central and peripheral nervous systems explaining the CCPD due to anti-NF155 Ab (up to half the cases of CCPD reported in a Japanese study).¹

IgM anti-NF155 Abs have also been rarely described, and their pathogenicity remains unknown. Most IgM anti-NF155 Abs have been associated with IgG4 in patients with neuropathies,³⁻⁵ but some were found isolated.^{4,7} Isolated IgM anti-NF155 Abs have been reported in only 20 patients: 10 with CIDP (3 with tremor), 2 with Guillain-Barré syndrome, 4 with axonal neuropathies, 2 with CMT, 1 with upper trunk brachial plexopathy, and 1 with facial numbness with normal ENMG, none in CCPD.^{4,7}

We are unable to demonstrate a pathophysiologic link between this case of CCPD and IgM anti-NF155 Ab; however, few elements can be discussed. First, the clinical presentation resembles the previously reported cases of CIDP with IgG4 anti-NF155 Ab, notably regarding ataxia, tremor, and associated demyelinating lesion in the CNS,¹ although other cases

Figure 2 Detection and Monitoring of Anti-NF155 Antibodies in the Blood by Flow Cytometry, Using Human Embryonic Kidney Cells



Antihuman immunoglobulin (Ig) G4 (A) or IgM (B) using fluorescein isothiocyanate (FITC) was used. The mean fluorescence intensity (MFI) is reported in the figure (number per row). In white, a negative control (without IgG4 or IgM antibodies) is shown. In gray, a patient with IgG4 anti-NF155 CIDP (without associated IgM) is shown. In orange, the first sample of a patient positive for IgM anti-NF155 antibody at 2639 MFI (without associated IgG4), and in red, a second sample from the same patient (18 months later), still positive for IgM anti-NF155 antibody at 2799 MFI.

of neuropathies with IgM anti-NF155 Ab have been described with various heterogeneous characteristics.⁴⁻⁷ Second, the patient presented an IgM-MGUS, an immune disease, and an antibody with IgM isotype, as in anti-MAG neuropathies, and chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies, in which this pathophysiologic link is already known. Finally, an enhancement and prolongation of experimental autoimmune neuritis has been reported in rats after injection of anti-neurofascin IgM, suggesting a pathogenicity of these IgM anti-NF155 Ab.³

In published studies, several techniques have been used to detect IgM anti-NF155 Ab (e.g., cell-based assay [CBA], flow cytometry, ELISA, and Western blot), sometimes with unspecific rat-NF155, which can explain the clinical heterogeneity of patients, especially considering the possible false-positive results.⁴⁻⁸ Some authors recommend another confirming technique (e.g., ELISA and immunohistochemistry) associated with CBA (the gold standard technique) because this technique yields a 5.6% false-positive rate in a cohort of 108 patients with inherited neuropathies; in addition, the authors advise against the use of rat-NF155 (leading to false-positive results) and recommend the use of human-NF155.⁸ Anti-CD20 is a classical treatment of multiple sclerosis and is sometimes effectively used in CIDP, especially with IgG4 anti-NF155, and has been found effective in CCPD.¹

Our study presents some limitations. Only 1 method of detection was used without confirming technique. Also, the search for IgM anti-NF155 Ab in the CSF was not performed, neither was nerve biopsy to investigate the presence of disruption of myelin paranodal loops. Moreover, the titers of IgM anti-NF155 Ab remained unchanged after treatment, despite clinical improvement.

In conclusion, this patient presented a CCPD with concomitant peripheral relapse and cervical myelitis leading to find isolated IgM anti-NF155 Ab and responded well to corticosteroids and rituximab. Prospective studies are necessary to demonstrate a pathophysiologic link between IgM anti-NF155 Ab and CCPD and assess the prevalence of this Ab in CCPD.

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Francoise Bouhour, MD	Service ENMG et Pathologies Neuromusculaires, Hôpital Neurologique Pierre Wertheimer, Hospices civils de Lyon, Bron, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data

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