Progressive Neuropathy With Cerebellar Ataxia

Investigation of antibody titers is essential for patients who have neuropathy with cerebellar ataxia who do not respond to IVIG treatment.

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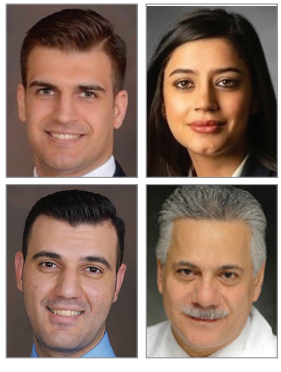


Case

Clinical Presentation

A woman, age 28, presented with inability to stand from a chair and frequent falls that were preceded a month earlier by acute numbness in her feet. She had muscle pain, cramping, hoarseness, slurred speech, double vision, poor coordination, and fatigue. On physical examination, she had hand tremor, sensory ataxia, moderate proximal and distal limb weakness, and diffuse areflexia (Video). Impaired tandem gait was also observed.

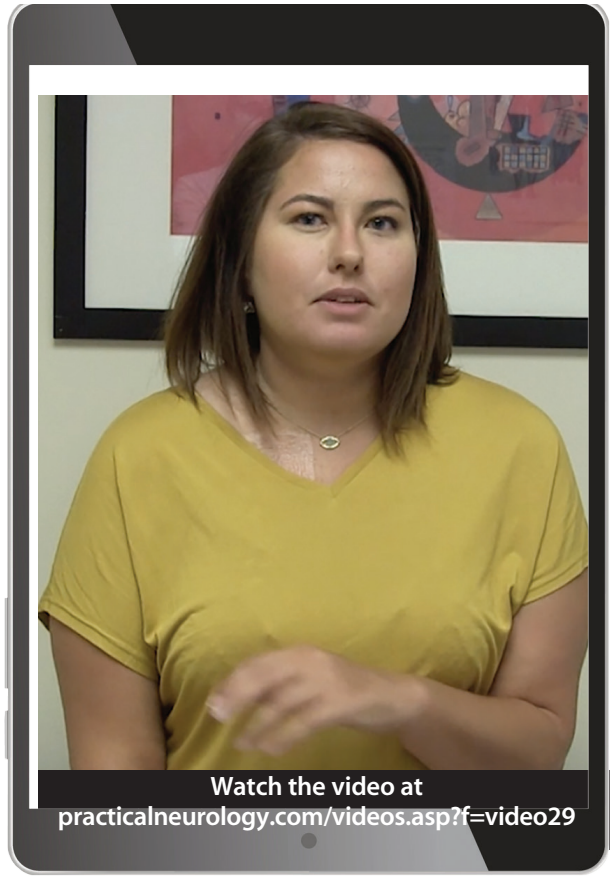
Diagnostic Studies

Cerebrospinal fluid (CSF) analysis showed a protein level of 479 mg/L with no pleocytosis. Nerve conduction studies revealed severe prolongation of distal motor latencies, severe motor slowing, temporal dispersion and prolonged F responses in multiple nerves, and absent sensory responses in the limbs. Brain MRI findings were normal.

Treatment and Definitive Diagnosis

The findings met diagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP), as defined by the Inflammatory Neuropathy Cause and Treatment (INCAT).[1] Our patient was treated with intravenous IgG immunoglobulin (IVIG). Unfortunately, she responded only slightly and transiently and developed severe hemolytic anemia as a reaction to IVIG. She then received a 5-day course of intravenous methylprednisolone, followed by a monthly booster for 3 months. Her response to these treatments was mild and transient.

A blood test was ordered and showed normal immunofixation protein electrophoresis (IFPE) results and normal vascular endothelium growth factor (VEGF) level. Antibodies against myelin-associated glycoprotein (MAG) were negative. Neurofascin-155 IgG4 (NF155) antibody titer was elevated, making the diagnosis of NF-155 CIDP definitively.



She has made slow but steady progress on monthly plasma exchanges and azathioprine.

Discussion

CIDP is a chronic heterogeneous disease with a classic presentation of symmetric motor weakness of proximal and distal

muscles with diffuse areflexia and distal sensory neurologic impairment. Onset typically occurs at age 40 to 60, and slightly more men than women are affected.[2] Rarely, CIDP presents atypically with unilateral, multifocal, or distal involvement.[3] Back pain is common.[4] Cranial nerves can also be involved causing facial nerve palsy and ophthalmoplegia.[5,6]

Diagnosis is made with clinical and EMG criteria.[1] Approximately 25% of patients with CIDP do not respond to traditional treatment.[7,8] Refractory CIDP variants can be associated NF-155 antibodies, MAG antibodies, increased blood level of VEGF (a marker for polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes [POEMS]), and pathologic monoclonal antibodies (eg, multiple myeloma and Waldenstrom macroglobulinemia). It is important to check antibody titers for NF155 and MAG, blood levels of VEGF, and IFPE in patients with refractory CIDP. In the case discussed, the patient had an NF-155 antibody-associated CIDP that characteristically has earlier onset, cerebellar signs, severe peripheral demyelination, high CSF protein, and CNS demyelination. This variant responds less frequently to IVIG.[1]

A member of the L1 family of adhesion molecules, NF155 is expressed at the paranodes by the terminal loops of myelin. It is associated with the axonal cell adhesion molecules CNTN1 and contactin-associated protein-1 (Caspr1).[9-11] Antibodies to NF155 block neurofascin and inhibit interaction with CNTN1/Caspr1. Specifically, IgG4 binding to NF155 cause paranode dismantling and conduction defects, surprisingly without inflammatory cell infiltration.[1,12,13]

Studies showed that some patients who have CIDP are positive for NF155 IgG, whereas none with multifocal motor neuropathy or antiMAG neuropathy or healthy controls had these antibodies. The predominant subclass of NF155 IgG in anti-NF155 positive patients was IgG4 with minimal detection of IgG1 at a serum dilution of 1:500.[14] Antibodies to NF155 are strongly related to HLA-DRB1*,[15] which is reported in 10 of 13 patients with CIDP who were positive for anti-NF155 compared to 5 of 35 patients with CIDP who were negative for anti-NF155.

Genetic studies show that NF155 glycoprotein is encoded by *NFASC*. Inactivation of *NFASC* in adult mouse cerebellar Purkinje cells causes rapid loss of NFASC glycoproteins, which might explain the predominant cerebellar signs and symptoms associated with anti-NF155-associated CIDP variant.[14]

Patients with neurofascin antibody-mediated CIDP have distinct pathological features compared to patients with typical CIDP, including lack of macrophage infiltrates and a selective loss of the transverse bands at the paranodal loops.[13]

Other causes of refractory CIPD such as multiple myeloma, POEMS syndrome, MAG antibody syndrome, and Castleman disease are not associated with cerebellar abnormalities. Plasma exchange removes the pathological antibodies and azathioprine supresses the antibody-producing cells. This combination showed promising results in our patient.

Conclusion

NF-155 antibody titers should be measured in patients with refractory CIDP with cerebellar tremor. Early diagnosis mandates more aggressive treatment that may improve outcomes. This variant responds better to plasmapheresis than IVIG and IV steroids. Further studies are needed to determine the best therapeutic approach. ■

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