Progressive Neuropathy with Cerebellar Ataxia

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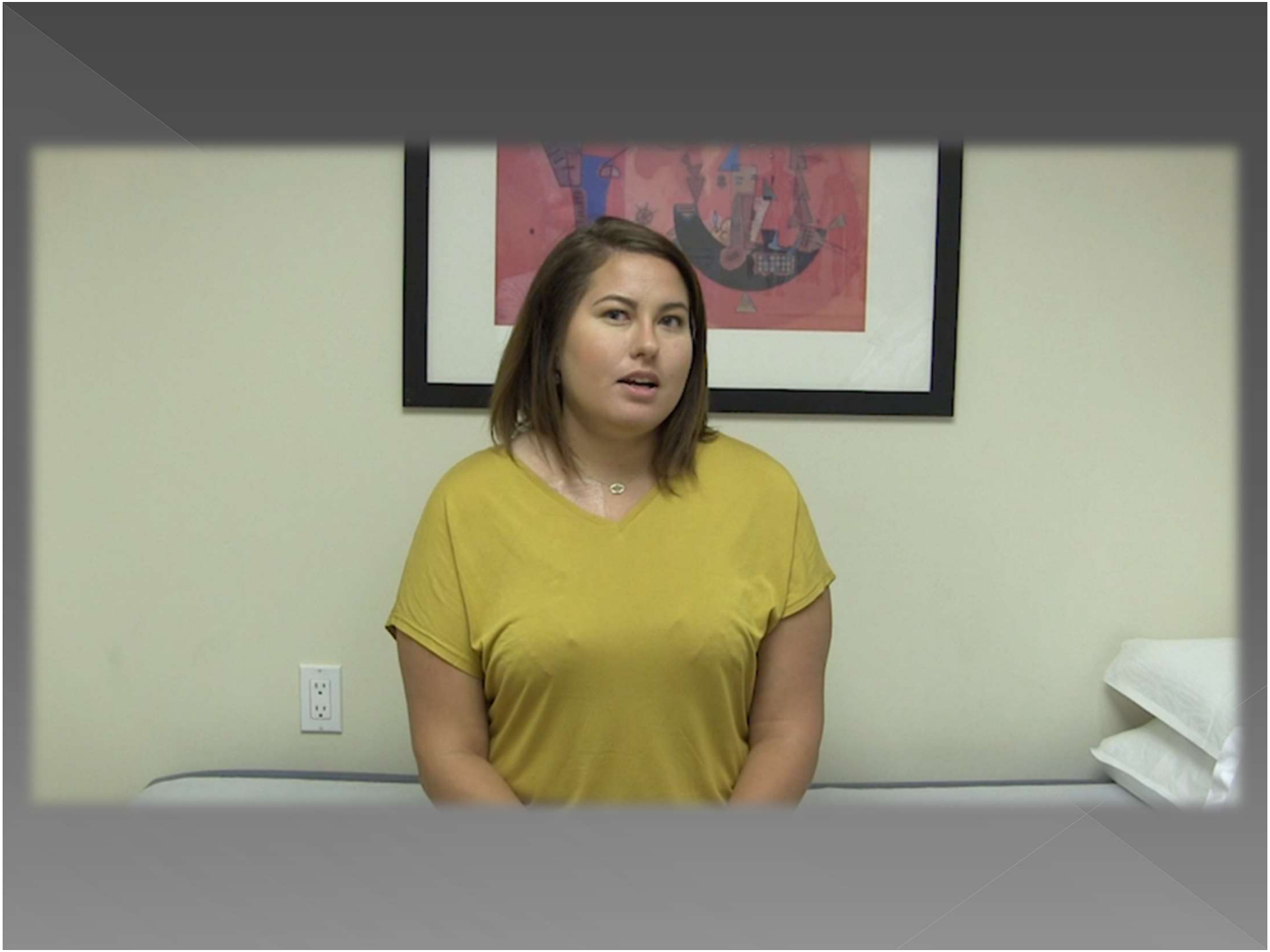


- A 28YOF with inability to get up from a chair and frequent falls, that evolved over days.
- Those preceded a month earlier by acute feet numbness.
- Muscle pain, cramping, hoarseness, slurred speech, double vision, poor coordination, and fatigue.
- PMhx: Controlled Diabetes Mellitus, Gastric sleeve surgery a week before this presentation

- CSF: protein level of 479 mg/L with no pleocytosis.
- NCS: 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.
- Diagnosed with CIDP (INCAT criteria)

Treatment

- Unfortunately, she responded only slightly and transiently to an IVIG and developed severe hemolytic anemia .
- Later, she mildly and transiently responded to a 5-day course of an intravenous methylprednisolone, followed by a monthly booster for 3 months.

Laboratory testing

- Normal IFPE and VGEF level
- MAG antibodies: negative

Any suggestions for more testing?

- Neurofascin-155 IgG4 (NF155) antibody titer was elevated, confirming the diagnosis of NF-155 antibody associated CIDP.
- She has made slow but steady progress on monthly plasma exchanges and azathioprine.

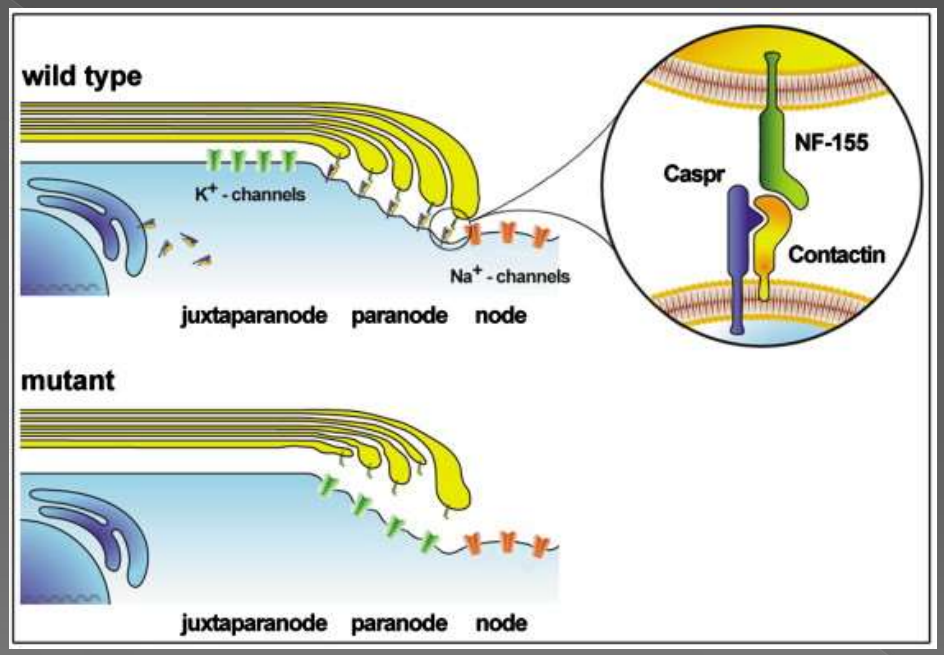
Refractory CIDP

- 25% of patients with CIDP does not respond to the traditional treatment.
- Refractory CIDP variants can be associated with:
  - NF-155 antibodies.
  - MAG antibodies.
  - POEMS.
  - Multiple myeloma.
- It is important to check for these conditions.

CIDP with NF-155 antibodies

- Earlier age of onset.
- Cerebellar signs.
- Severe peripheral demyelination.
- Very high CSF protein.
- CNS demyelination.
- Responds less frequently to IVIG.

- NF-155 :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).



- 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.

NF-155 antibodies and HLA

- 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.

- Other causes of refractory CIPD such as multiple myeloma, POEMS syndrome, MAG antibody syndrome, and Castleman disease are not associated with cerebellar abnormalities

NF-155 Ab syndrome pathology

- 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

Take home message

- Check antibodies to NF-155 in refractory CIDP especially with cerebellar tremor
- Best approach is not known but there are case reports of good response to Rituximab or PLEX.

References

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- Others...