Split hand with tremors in a mid-Missouri family

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Disclosures

I have no financial relationships or contracts to disclose.

Dr. Govindarajan has no financial relationships or contracts to disclose.

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History of present illness

- 63-year-old woman referred to neurology clinic
- Slowly-progressing weakness and foot drop
- Bilateral foot weakness in teenage years with foot deformities
  - Correctional surgery for hammer toes
  - Pes cavus
- Leading up to time of referral to our institution, experiencing worsening foot drop and gait difficulties, stumbling, tripping

Past medical and surgical history

- Breast cancer diagnosed nine years prior – treated with lumpectomy, chemotherapy (5-FU, cyclophosphamide, methotrexate) and radiation therapy
- Essential tremor controlled with propranolol
- Hypertension
- Hyperlipidemia
- Cataracts
- Prediabetes
- Depression
- Corrective surgery for hammer toe deformities
- No history of alcohol abuse or illicit drug use

Family history

- Grandfather used a cane
- Mother - stroke
- Three siblings
  - One brother with tremor
  - No history of polyneuropathy, myopathy, or other neurological disease
- Three sons
  - One son afflicted with similar symptoms to the patient with earlier onset and increased severity as well as speed of progression
  - The two other children without medical problems

Neurological exam

- Mental status normal and fluid speech
- Motor:
  - Marked atrophy of small hand muscles with more prominent wasting of thenar more than hypothenar groups
  - Atrophy of intrinsic muscles of the feet
  - Pes cavus
- CN II-XII intact
  - No tongue fasciculations noted
- Muscle strength
  - Toe extension 0/5
  - Foot dorsiflexion 2/5
  - FDI, APB 3/5
- Sensory
  - Light touch, pinprick impaired in hands and feet
  - Proprioception decreased in the toes

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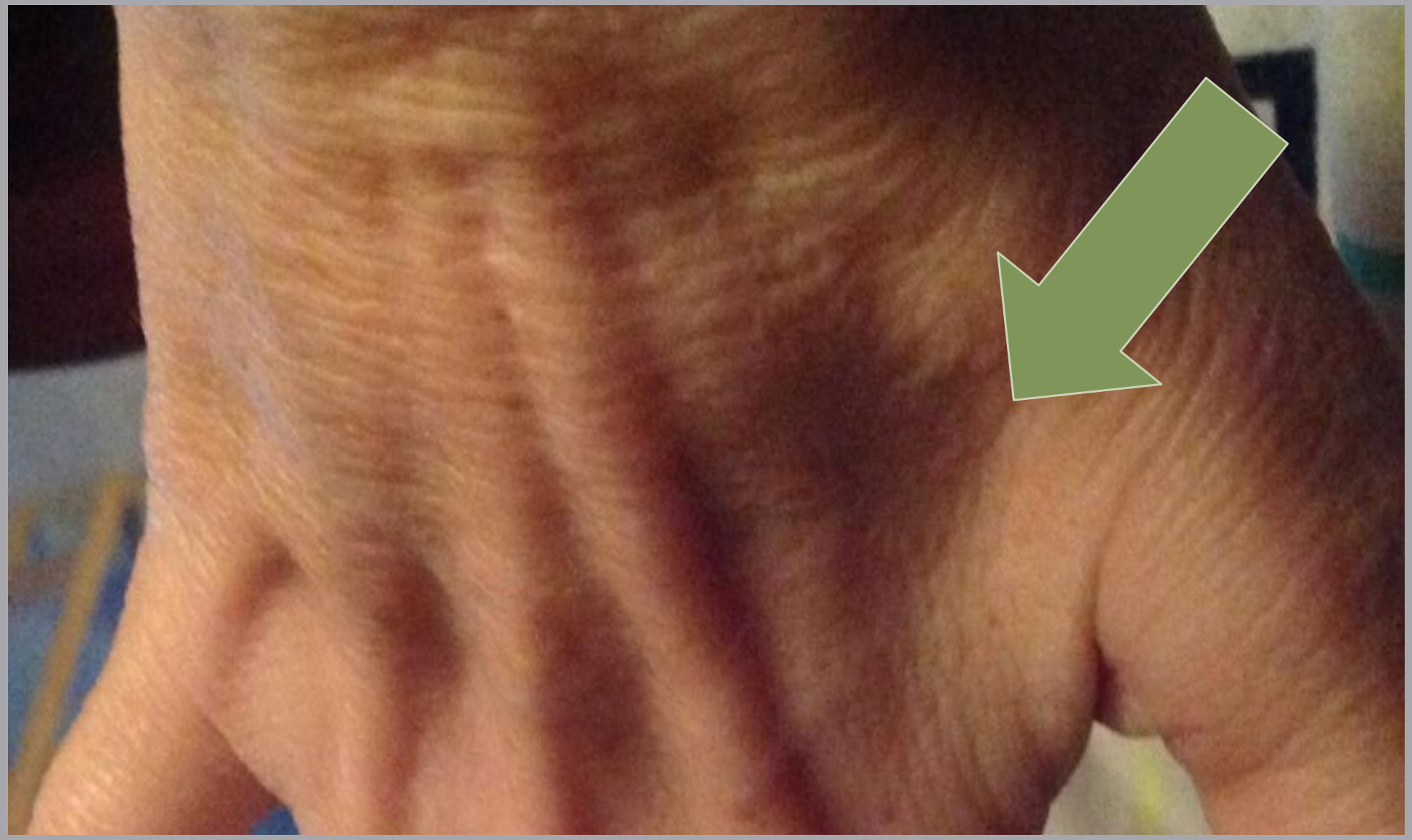
Neurological exam

- Reflexes
  - Absent at ankle and biceps
  - Diminished in triceps
  - Normal patellar
- Coordination and gait
  - Bilateral foot drop and inability to walk on toes and heels
- Involuntary movements
  - Postural and action tremors of the hands



Summary – key points

- Childhood-onset, slowly-progressing, symmetric, distal-worse-than proximal weakness
- No earlier-generation family history of neuromuscular disease; son with similar constellation of signs and symptoms, although increased severity and earlier onset
- Foot deformities with prominent wasting in the small muscles of the foot, split hand sign with thenar wasting
- Prominent weakness in lower extremities distally, lesser degree of weakness in the distal upper extremities
- Sensory impairment to light touch, pinprick, proprioception in distal extremities
- Decreased to absent distal deep tendon reflexes
- No autonomic symptoms

Pattern most suggestive of chronic sensorimotor polyneuropathy

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Diagnostic testing

- Needle EMG and nerve conduction studies (NCS) – determine axonal versus demyelinating primary underlying pathophysiology
- Motor NCS
  - Reduction in amplitude of median and tibial nerves with significant velocity attenuation in distal extremities
  - Unremarkable latencies
  - Conduction block
  - Marked temporal dispersion
- Sensory NCS
  - Prominent decrease in amplitude
  - Borderline normal/decreased velocities
- EMG
  - Gastrocnemius and tibialis anterior
  - Mild active denervation with prominent chronic reinnervation without insertion, spontaneous, or voluntary activity from the right extensor digitorum brevis muscle

NCS and EMG findings consistent with axonal sensorimotor polyneuropathy.

Diagnostic testing

- Genetic testing performed through GeneDx revealed a **novel heterozygous T to A transversion (c.605 T>A) in exon two of GJβ1 gene, resulting in a p.Ile202Asn amino acid substitution.**
- Predicted to be pathogenic
- Son was hemizygous for the same mutation.

Based on these studies, the patient's clinical presentation and diagnostic testing are supportive of a CMT1X diagnosis.

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Charcot-Marie-Tooth Disease

- CMT1X results from mutations in the gap junction beta 1 gene (GJβ1) on chromosome Xq13.1 and is of X-linked inheritance.
- GJβ1 encodes Connexin 32, a protein of unknown exact function. It is present in high concentrations in Schwann cells and oligodendrocytes, amongst other cell types.[2]
- One hypothesis maintains that through the gap junctions it forms, couples adjacent myelin layers through permissive diffusion of potassium ions and signaling molecules.[3]

2. Wang Y, Yin F. A Review of X-linked Charcot-Marie-Tooth Disease. J Child Neurol. 2016;31(6):761-772. doi:10.1177/0883073815604227.

Charcot-Marie-Tooth Disease

- There are six subtypes of CMTX: CMT1X-CMT6X, with CMT1X and 6X having X-linked dominant inheritance, and the remainder of subtypes X linked recessive.[2]
- In X-linked dominant CMTX, onset of symptoms is typically second decade in life and results in a more severe clinical course in males.[2]
- Two-thirds of females have mild symptoms, and one-third have severe symptoms of CMT. [1,2]

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Charcot-Marie-Tooth Disease

- Clinical presentation involves slowly progressive distal weakness and atrophy with more significant involvement of the lower extremities.[2]
  - Decreased or absent deep tendon reflexes
  - Sensory disturbances
  - Foot deformities
- Some CMTX patients may have transient, reversible white matter lesions and central nervous system manifestations, including sensorineural deafness, dysarthria, dysphagia, and paralysis.[2]
- Mild postural hand tremor has been reported in some patients with CMT6X, interestingly.[4]

2. Wang Y, Yin F. A Review of X-linked Charcot-Marie-Tooth Disease. J Child Neurol. 2016;31(6):761-772. doi:10.1177/0883073815604227.
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Acknowledgements

- First and foremost, we thank our patient and her family.
- We extend great thanks to the clinicians and providers who assessed and took care of the patient in this vignette.
- A special thank-you to Raghav Govindarajan, MD for his constant support and mentorship.

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Questions?

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