Two Brothers With Lower Extremity Weakness

Chaitanya Konda, DO, PGY3
Yessar Hussain, MD
Conflicts of Interest

• Nothing to disclose.
• 23 year old male, competitive swimmer of French descent who presented with weakness in both feet.

• Age 17 - weakness in right foot with dorsiflexion

• Age 18 - developed similar left foot weakness.

• Progressive stiffness in his legs leading to more frequent falls

• Muscle cramps/spasms

• Was mostly utilizing a wheelchair and walker for mobility
• Denied any sensory complaints

• Denied bulbar and ocular symptoms

• No upper extremities symptoms at the time of presentation.

• No significant past medical history

• No significant family history at time of presentation
Physical Exam

AAOx4
CN II – XII intact
Motor: 5/5 in all manual muscle testing groups in the bilateral UE and LE except for FDI and APB 4+/5 and Tibialis Anterior at 3/5
Reflexes: 3+ in biceps, triceps, brachioradialis, patellar bilaterally, diminished Achilles reflex bilaterally
Sensory: Intact to pain and temperature and normal QVT.
Coordination: No dysmetria, FNF test intact. Mild action tremor
Gait: Spastic gait
Modified Ashworth Scale: Quadriceps 2, Hamstrings 1+
Noted Atrophy of bilateral first dorsal interossei, Abductor pollicis brevis, and bilateral feet dorsal interossei
Bilateral severe Pes Cavus, Hammer Toes
**Workup**

- MRI of brain, cervical spine, and thoracic spine – normal
- B12, copper, zinc, TSH, celiac panel, ANA panel – negative
## Electrodiagnostics

### SNC

<table>
<thead>
<tr>
<th>Nerve / Sites</th>
<th>Rec. Site</th>
<th>Onset Lat ms</th>
<th>Peak Lat ms</th>
<th>Amp μV</th>
<th>Segments</th>
<th>Distance mm</th>
<th>Velocity m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>L Median - Digit II (Antidromic)</td>
<td>Wrist</td>
<td>3.13</td>
<td>4.01</td>
<td>26.2</td>
<td>Wrist - Dig II</td>
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<tr>
<td>L Ulnar - Digit V (Antidromic)</td>
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<td>Wrist - Dig V</td>
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<tr>
<td>L Radial - Anatomical snuff box (Forearm)</td>
<td>Forearm</td>
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<td>2.45</td>
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<td>L Sural - Ankle (Calf)</td>
<td>Calf</td>
<td>3.18</td>
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<td>13.6</td>
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### MNC

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<thead>
<tr>
<th>Nerve / Sites</th>
<th>Muscle</th>
<th>Latency ms</th>
<th>Amplitude mV</th>
<th>Duration ms</th>
<th>Rel Amp %</th>
<th>Segments</th>
<th>Distance mm</th>
<th>Lat Diff ms</th>
<th>Velocity m/s</th>
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<tbody>
<tr>
<td>L Median - APB</td>
<td>APB</td>
<td>4.27</td>
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<td>Elbow</td>
<td>APB</td>
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<td>L Ulnar - ADM</td>
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<td>B.Elbow</td>
<td>ADM</td>
<td>7.03</td>
<td>10.3</td>
<td>7.40</td>
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<td>B.Elbow - Wrist</td>
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<td>Fib head</td>
<td>EDB</td>
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<td>100</td>
<td>Ankle - EDB</td>
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<td>L Tibial - AH</td>
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<td>Ankle - AH</td>
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<td>Pop fossa</td>
<td>AH</td>
<td>12.55</td>
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<td>5.8</td>
<td>7.24</td>
<td>100</td>
<td>Ankle - AH</td>
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## Electrodiagnostics

### EMG

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<thead>
<tr>
<th>Muscle</th>
<th>Nerve</th>
<th>Roots</th>
<th>IA</th>
<th>Fib</th>
<th>PSW</th>
<th>Fasc</th>
<th>Other</th>
<th>Dur.</th>
<th>Amp</th>
<th>Polys</th>
<th>Pattern</th>
<th>Activation</th>
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<tbody>
<tr>
<td>R. Tibialis anterior</td>
<td>Deep peroneal (Fibular)</td>
<td>L4-L5</td>
<td>Normal</td>
<td>None</td>
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<td>Normal</td>
<td>Gr Incr</td>
<td>None</td>
<td>Mod Red</td>
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<td>R. Peroneus tertius</td>
<td>Deep</td>
<td>L5-S1</td>
<td>Normal</td>
<td>1+</td>
<td>1+</td>
<td>None</td>
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<td>Normal</td>
<td>Gr</td>
<td>None</td>
<td>Mod</td>
<td>Normal</td>
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<th>Amp</th>
<th>Polys</th>
<th>Pattern</th>
<th>Activation</th>
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<tbody>
<tr>
<td>R. Gastrocnemius (Medial head)</td>
<td>Tibial</td>
<td>S1-S2</td>
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<td>Mod Red</td>
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<td>1+</td>
<td>1+</td>
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<td>None</td>
<td>None</td>
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<td>Normal</td>
<td>Gr Incr</td>
<td>None</td>
<td>Mod Red</td>
<td>Normal</td>
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<tr>
<td>L. First dorsal interosseous</td>
<td>Ulnar</td>
<td>C8-T1</td>
<td>Normal</td>
<td>1+</td>
<td>1+</td>
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<td>Normal</td>
<td>Gr Incr</td>
<td>None</td>
<td>Mod Red</td>
<td>Normal</td>
</tr>
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</table>
Electrodiagnostics

Summary:
- Bilateral peroneal motor NCSs recorded from EDB were normal from the left side and small CMAP amplitudes from the right side with normal distal latency and conduction velocity.

- Bilateral tibial motor NCSs recorded from AH were normal with no significant side to side difference.

- Bilateral sural sensory NCSs were normal, with normal sural to radial ratio with no significant side to side difference.

- Left upper extremity motor NCS for the median and ulnar nerve, recorded from the APB and ADM/FDI respectively were normal. Left upper extremity sensory NCS for the median, ulnar, and radial nerves were normal.

- Needle EMG of bilateral peroneus tertius, TA, gastrocnemius and left FDI showed large MUPs and reduced recruitment and fibs/PSWs from the gastrocnemius and peroneus tertius.

- Conclusion: This study showed evidence of distal axonal motor neuropathy, with mild asymmetry and active denervation and sensory sparing.
Genetic panel

• Genetic results were suggestive, but not particularly conclusive of the diagnosis
Differential Diagnosis?
• 2 years later, his 19 year old brother presented with similar signs and symptoms

• Age 16 – stiffness in both hips and R knee

• Gait difficulties with minimal extension/flexion of right knee and minimal hip flexion

• Muscle cramp/spasms

• No foot drop

• Patient was not utilizing a wheelchair
Physical Exam

AAOx4
CN II – XII intact
Motor: 5/5 in all manual muscle testing groups in the bilateral UE and LE except for Tibialis Anterior at 4/5
Reflexes: 3+ in biceps, triceps, brachioradialis, patellar bilaterally, diminished Achilles reflex bilaterally
Sensory: Intact to pain and temperature
Coordination: No dysmetria, FNF test intact.
Gait: Spastic gait
Modified Ashworth Scale: bilateral Iliopsoas 2, right Quadriceps 2, Foot extensors 1+
Bilateral Pes Cavus
Workup

No electrodiagnostics, MRI, or laboratory workup was performed due to our suspicion.

Patient was sent for genetic testing.
Additional information

• No significant family history was stated. Mother had been at every visit, and was evaluated.
• Her physical exam was mainly significant for bilateral pes cavus.
• Grandmother also had bilateral pes cavus
Additional information

• Father is presumably asymptomatic, without any issues. He has not been evaluated by us.

• Per patient’s mother, researching other family members, there is nobody in the family that has these signs and symptoms
Genetic Panel Results

• Results were the same for both patients

• Two variants of Senataxin (SETX) gene
  – c.2411T>C (p.Leu804Ser), heterozygous
  – c.2755G>C (p.Val919Leu), heterozygous
Differential Diagnosis

- Distal denervation on patient’s EMG with sensory sparing
- Spastic lower extremities
- Hyperreflexia
- A lack of bulbar or oculomotor symptoms
- Noted atrophy and weakness of distal muscles
- SETX gene variant unspecified
Why not?
Senataxin Gene

- Produces protein that belongs in the class of helicases
- Involved in DNA repair and RNA production
- Mutations in the gene typically disrupt DNA repair – accumulated DNA damage in cells
- Neuronal degeneration through dysfunction of helicase activity or other steps in RNA processing.
Senataxin Gene

- Senataxin gene mutations have been associated with:
  - Distal hereditary motor neuropathy with upper motor neuron signs
  - Ataxia with oculomotor apraxia 2 (AOA2)
  - Spastic Paraplegia 19 (SPG19)
  - Juvenile Amyotrophic Lateral Sclerosis 4 (ALS4)
Distal hereditary motor neuropathy with Upper motor neuron signs

- Epidemiology: Belgian, Austrian & English families
- Genetics: Allelic with:
  - Juvenile ALS: EMG show sensory sparing with distal denervation, bulbar involvement, slowly progressive.
  - SPG19: Similar presentation, older age group, sensory and motor neuropathy.
- Clinical: Weakness at distal hands and legs/feet.
  - Sensory: Usually normal
  - Tendon reflexes: Normal or Increased
  - Babinski sign: Positive in 50%
  - Pes cavus (50%)
- Laboratory
  - Electrophysiology
    - Nerve conduction velocity: Normal or Mildly reduced
    - CMAPs: Reduced amplitude
    - Sensory: Normal SNAP amplitude; Conduction velocity borderline or mildly slow
    - EMG: Distal denervation
  - MRI: White matter changes
Ataxia with Oculomotor Apraxia 2

- Also called Spinocerebellar ataxia, recessive, non-Friedreich type 1
- Epidemiology: Common in French Canadians
- Genetics:
  - Mutations: premature termination in 2/3, missense in some families, often homozygous
  - Missense mutations in
    - Juvenile ALS: EMG show sensory sparing with distal denervation, bulbar involvement, slowly progressive, dominant heritance
    - Distal hereditary motor neuropathy with upper motor neuron signs
- Clinical: onset 2-22 years; mean 15 years
  - Severe ataxic gait, mild ataxia of trunk and limbs
  - Extrapyramidal: choreoathetosis, dystonic posturing with walking, masked faces when disease severe
  - Ophthalmological: oculomotor apraxia, disordered smooth pursuit, absent optokinetic nystagmus, saccade palsy
  - Tendon reflexes: absent in legs, plantar reflex – extensor
  - Sensory: Peripheral neuropathy; sensory loss including vibratory, proprioception, and light touch
  - Motor: distal weakness and wasting in 3rd decade
  - Babinski sign: Positive in 50%
  - Pes cavus (50%)
- Laboratory
  - Electrophysiology
    - Nerve conduction velocity: Axonal loss, absent sensory potentials;
    - CMAPs: Mildly Reduced amplitude
    - Sensory: Absent or reduced amplitudes
    - EMG: Distal denervation
Spastic Paraplegia 19

- Epidemiology: Italian family
- Genetics: Similar locus with:
  - Juvenile ALS: EMG show sensory sparing with distal denervation, bulbar involvement, slowly progressive.
  - Hereditary Motor Neuropathy with upper motor neuron signs
- Onset: mean age 47 years, range from 36 to 55 years
- Clinical:
  - Spastic paraparesis: spasticity in legs, hyperreflexia in legs>arms, extensor plantar responses
  - **Bladder dysfunction**
  - **Sensory:** Reduced vibration in 40%
  - Functional deficit: mild in most; wheelchair in 10%
  - Skeletal: Scoliosis
  - No systemic disorders
- Laboratory
  - Motor Evoked potentials: Slowed central motor conduction velocity in legs
Amyotrophic Lateral Sclerosis 4

- **Epidemiology:** England, Southern Maryland
- **Genetics:** Mutations: Missense, Locations: L389S; R2136H; T3I; Similar locus to Spastic Paraplegia 19; Allelic with Ataxia with Oculomotor Apraxia 2 (recessive) and Distal hereditary motor neuropathy with upper motor neuron signs
- **Clinical:** onset 2nd decade; Mean age range from < 6 years to 21 years
  - Early signs: spastic gait disorder
  - Weakness: distal in hands and feet; progresses to proximal; distal wasting
  - Bulbar disorders: infrequent
  - Upper motor neuron signs: hyperreflexia; upgoing toes less frequent
  - Sensory: normal; minor changes in a few older patients
  - Severity is variable
- **Course**
  - Slowly progressive over decades; 5th and 6th decades: Wheelchair, loss of hand function
  - Milder phenotype: Mild gait disorder
- **Electrophysiology**
  - Nerve conduction velocity: Reduced CMAP amplitude; Normal NCV; Normal Sensory
  - EMG: Denervation – Distal > Proximal
- **Pathology**
  - Reduced number of anterior horn cells, especially lumbar; spinal cord atrophy
  - Sensory pathways: Posterior column fiber loss; Loss of DRG neurons
  - Axonal swelling of roots, spinal gray matter, Dentate nucleus, Cranial nerves 3&4
  - Spinal Cord atrophy
References


Questions?