Two Brothers With Lower Extremity Weakness

Chaitanya Konda, DO, PGY3
Yessar Hussain, MD

Austin Neuromuscular Center

The University of Texas at Austin Dell Medical School

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.

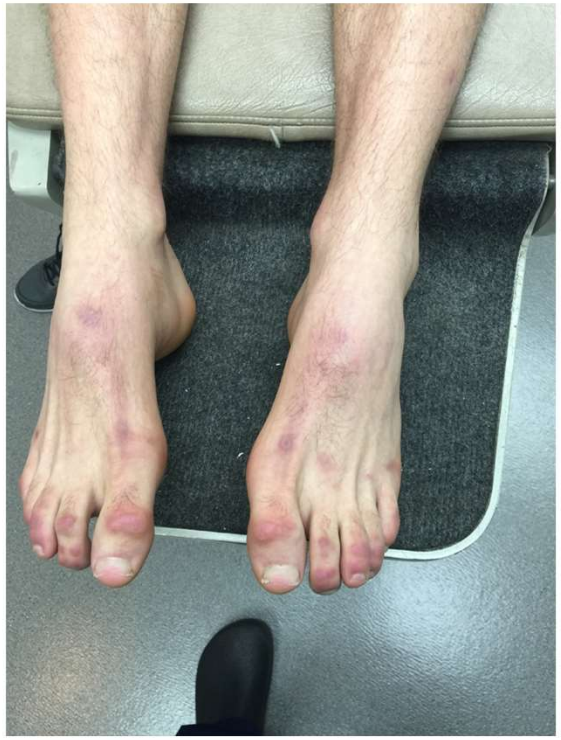
Coordination: No dysmetria, FNF test intact. Mild action tremor

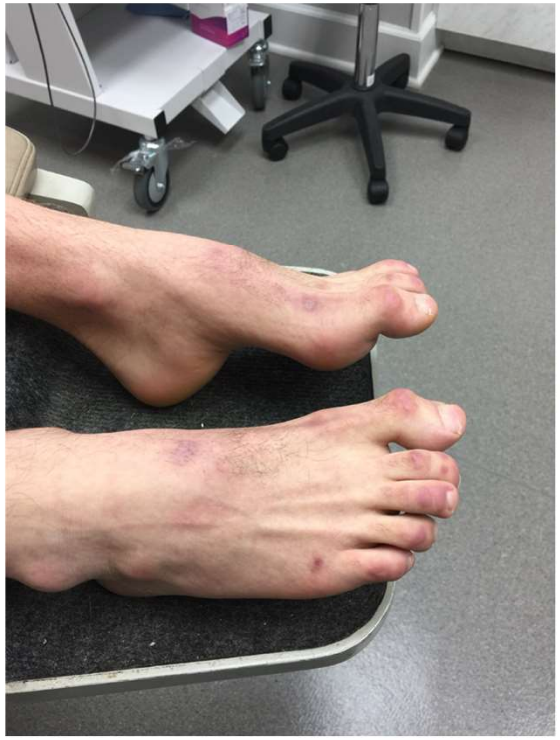
Gait: Spastic gait

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

Nerve / Sites	Rec. Site	Onset Lat ms	Peak Lat ms	Amp µV	Segments	Distance mm	Velocity m/s
L Median - Digit II (Antidromic)							
Wrist	Dig II	3.13	4.01	26.2	Wrist - Dig II	140	45
L Ulnar - Digit V (Antidromic)							
Wrist	Dig V	2.86	3.75	33.2	Wrist - Dig V	140	49
L Radial - Anatomical snuff box (Forearm)							
Forearm	Wrist	1.98	2.45	19.7	Forearm - Wrist	100	51
L Sural - Ankle (Calf)							
Calf	Ankle	3.18	4.06	13.6	Calf - Ankle	140	44
R Sural - Ankle (Calf)							
Calf	Ankle	2.97	3.85	18.5	Calf - Ankle	140	47

MNC

Nerve / Sites	Muscle	Latency ms	Amplitude mV	Duration ms	Rel Amp %	Segments	Distance mm	Lat Diff ms	Velocity m/s
L Median - APB									
Wrist	APB	4.27	4.6	6.82	100	Wrist - APB	70		
Elbow	APB	8.91	3.9	6.93	85.3	Elbow - Wrist		4.64	
L Ulnar - ADM									
Wrist	ADM	3.54	10.2	7.03	100	Wrist - ADM	70		
B.Elbow	ADM	7.03	10.3	7.40	101	B.Elbow - Wrist	190	3.49	54
A.Elbow	ADM	9.17	10.5	7.29	102	A.Elbow - B.Elbow	100	2.14	47
						A.Elbow - Wrist		5.63	
L Peroneal - EDB									
Ankle	EDB	5.78	5.0	5.89	100	Ankle - EDB	100		
Fib head	EDB	11.35	4.4	6.09	88	Fib head - Ankle	280	5.57	50
						Pop fossa - Ankle			
R Peroneal - EDB									
Ankle	EDB	6.82	1.5	5.89	100	Ankle - EDB	100		
						Pop fossa - Ankle			
L Tibial - AH									
Ankle	AH	5.94	3.8	7.97	100	Ankle - AH	100		
Pop fossa	AH	12.55	3.2	8.65	84.1	Pop fossa - Ankle	320	6.61	48
R Tibial - AH									
Ankle	AH	5.42	5.8	7.24	100	Ankle - AH	100		

Electrodiagnostics

EMG

EMG Summary Table												
			Spontaneous					MUAP			Recruitment	
Muscle	**Nerve**	**Roots**	**IA**	**Fib**	**PSW**	**Fasc**	**Other**	**Dur.**	**Amp**	**Polys**	**Pattern**	**Activation**
R. Tibialis anterior	Deep peroneal (Fibular)	L4-L5	Normal	None	None	None	.	Normal	Gr Incr	None	Mod Red	Normal
R. Peroneus tertius	Deep	L5-S1	Normal	1+	1+	None	.	Normal	Gr	None	Mod	Normal

EMG Summary Table												
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	peroneal (Fibular)								Incr		Red	
R. Gastrocnemius (Medial head)	Tibial	S1-S2	Normal	1+	1+	None	.	Normal	Gr Incr	None	Mod Red	Normal
L. Tibialis anterior	Deep peroneal (Fibular)	L4-L5	Normal	None	None	None	.	Normal	Gr Incr	None	Mod Red	Normal
L. Peroneus tertius	Deep peroneal (Fibular)	L5-S1	Normal	1+	1+	None	.	Normal	Gr Incr	None	Mod Red	Normal
L. Gastrocnemius (Medial head)	Tibial	S1-S2	Normal	None	None	None	.	Normal	Gr Incr	None	Mod Red	Normal
L. First dorsal interosseous	Ulnar	C8-T1	Normal	1+	1+	None	.	Normal	Gr Incr	None	Mod Red	Normal

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

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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

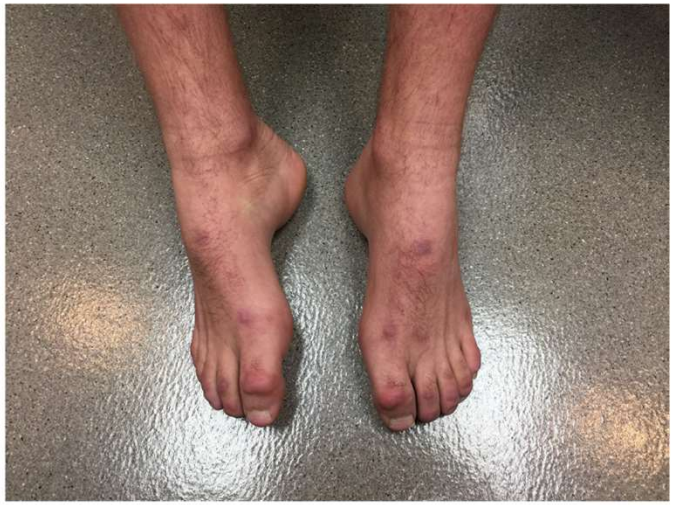
Sensory: Intact to pain and temperature

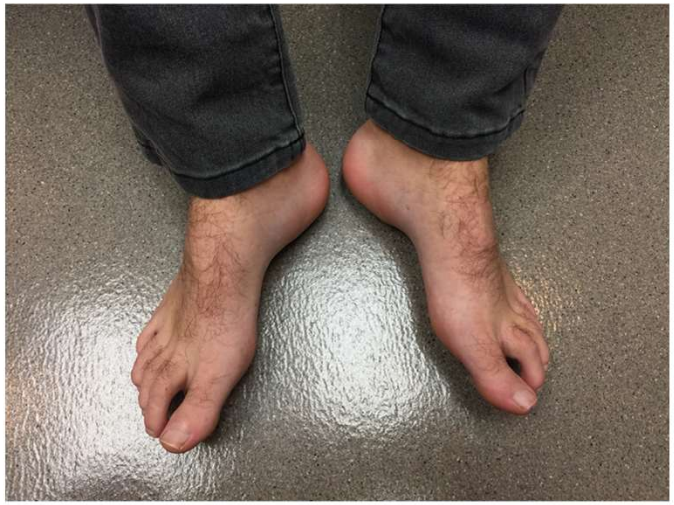
Coordination: No dysmetria, FNF test intact.

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 Amytrophic 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

Amytrophic 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

Chen, et al. DNA/RNA helicase gene mutations in a form of juvenile amyotrophic lateral sclerosis (ALS4). Am. J. Hum. Genet. 74: 1128-1135, 2004.

Moreira, et al. Senataxin, the ortholog of a yeast RNA helicase, is mutant in ataxia-ocular apraxia 2. Nature Genet. 36: 225-227, 2004.

Chance, et al. Linkage of the gene for an autosomal dominant form of juvenile amyotrophic lateral sclerosis to chromosome 9q34. Am. J. Hum. Genet. 62: 633-640, 1998.

Rabin, et al. Autosomal dominant juvenile amyotrophic lateral sclerosis. Brain 122: 1539-1550, 1999.

Blair, et al. A gene for autosomal dominant juvenile amyotrophic lateral sclerosis (ALS4) localizes to a 500-kb interval on chromosome 9q34. Neurogenetics 3: 1-6, 2000.

De Jonghe, et al. Autosomal dominant juvenile amyotrophic lateral sclerosis and distal hereditary motor neuronopathy with pyramidal tract signs: synonyms for the same disorder? Brain 125: 1320-1325, 2002.

Myrianthopoulos, et al. Nerve conduction and other studies in families with Charcot-Marie-Tooth disease. Brain 87: 589-610, 1964.

Suraweera, et al. Functional role for senataxin, defective in ataxia oculomotor apraxia type 2, in transcriptional regulation. Hum. Molec. Genet. 18: 3384-3396, 2009.

Questions?