

Teaching Guide

Module 7: Movement 3 - Ataxia and Cerebellar Disorders

Slide 1: Title.

Slide 2: Learning objectives.

Slide 3: Disclose the chief complaint.

- Ask participants: *What category of neurological disease is this likely to represent?*
 - Most likely ataxia. Could also have unsteady gait with weakness, movement disorder. Sensory and vestibular problems can also cause ataxia (in addition to cerebellar disorders).
- Ask participants for next slide: *How would you define ataxia? What are possible localizations for ataxia?*

Slide 4: Interactive exercise for the chief complaint.

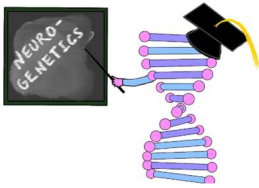
- *What symptom is the patient exhibiting?*
 - Ataxia, most likely.
- *What's the time course?*
 - Chronic, progressive.
- Wide differential and of course it's great if participants name some specific genetic ataxias (but we'll get into that in later slides).

Slide 5: Broad differential of chronic/progressive ataxias. Please make note that there are many causes that are **not** genetic.

Slide 6: Definition of ataxia.

As extra info, if anyone asks (**but ok to skip this**), here's some circuitry/function of cerebellum:

- Does not generate motor commands; it modifies them to make them accurate and adaptive.
- Receives input from the vestibular apparatus, spinal cord, and cerebral cortex (via the pons).
- Localization:
 - Both input and output are ipsilateral.
 - Midline (vermis) controls gait, head and trunk stability, and eye movements.
 - Hemispheres control limb tone and coordination, motor learning, speech and eye movements



Slide 7: How to approach the ataxia differential: *Is this ataxia acute or chronic? Progressive, or episodic?* Here, it is chronic onset with a chronic/progressive and is not episodic. **Ataxias generally can be divided into acute, subacute, and chronic/progressive.**

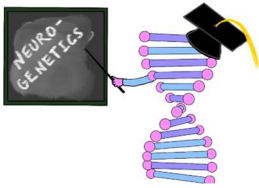
Don't dwell on this, but in case there are questions:

- Acute ataxias in children are generally an emergency, as tumors, intracranial hemorrhage, stroke, and infection can be causes. Common causes are acute cerebellar ataxia, Guillain-Barre-syndrome, toxins, labyrinthitis, migraine syndromes/benign paroxysmal vertigo, and trauma.
- Subacute ataxias can be caused by atypical infections, autoimmune/paraneoplastic, neoplastic, thiamine or Vitamin E deficiency etiologies.
- Hereditary ataxias:
 - Progressive degenerative ataxias
 - Autosomal dominant (spinocerebellar ataxias, often with CAG repeats)
 - Autosomal recessive (multiple autosomal recessive cerebellar ataxias, including Friedreich Ataxia and ataxia-telangiectasia)
 - X-linked (X-linked sideroblastic anemia with ataxia, adrenoleukodystrophy)
 - Mitochondrial (Leigh, ataxia, and myoclonus)
 - Inborn errors of metabolism (usually autosomal recessive)
 - Intermittent ataxias (urea cycle, aminoaciduria, disorders of pyruvate/lactate metabolism)
 - Progressive ataxias (e.g., Niemann-Pick C, Wilson, metachromatic leukodystrophy, neuronal ceroid lipofuscinosis, juvenile or late-onset Tay-Sachs disease)
 - Treatable causes include Refsum, Ataxia with Vitamin E deficiency, and Cerebrotendinous xanthomatosis.
 - Episodic ataxias
 - Type 1, Type 2, and Types 3-7
 - Others, with myoclonus (Unverricht-Lundborg, Sialidosis)

Slide 8: Differential diagnosis of genetic causes of chronic/progressive ataxias. Some genetic diseases have ataxia as a major symptom but is not considered a primary ataxia. It is helpful to divide them into **autosomal dominant versus recessive**, and then each of these in turn to **conventional DNA changes versus repeat expansions**.

Slides 9 and 10: Treatable/reversible causes of ataxia - not to be missed, usually can be diagnosed without genetic testing (and tests listed here).

Slide 11: Diagnostic evaluation for chronic progressive ataxia. Note: that clinical (including imaging) and conventional diagnostic evaluation come BEFORE consideration of genetic testing.

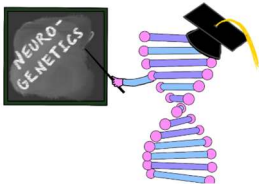


Slide 12: **Typical initial diagnostic laboratory investigations.** *Go through this quickly, without necessarily telling audience what each test is for—this is more for reference or if people ask what these tests are for:*

- CBC (neoplastic causes)
- CMP (electrolyte imbalance, renal function, liver: ataxia-telangiectasia, hypoalbuminemia associated with ataxia with oculomotor apraxia)
- TSH, fT4 (hypothyroidism)
- RPR (neurosyphilis)
- ANA (neuropsychiatric systemic lupus erythematosus)
- ESR (inflammation)
- HbA1c (diabetes, association with anti-GAD antibodies, and Friedreich Ataxia)
- Vitamin deficiencies:
 - Vitamin B12
 - Vitamin B1
 - Vitamin E
 - Folate
 - Homocysteine (high levels can be seen with B12 or folate deficiency)
- MMA (methylmalonic acidemia)
- Lactate (mitochondrial disease)
- Copper (Wilson)
- Ceruloplasmin (Wilson)

Slide 13: **Second tier diagnostic laboratory investigations.** (PAA = plasma amino acids; VLCFA = very long chain fatty acids). *Go through this quickly, without necessarily telling audience what each test is for—this is more for reference or if people ask what these tests are for:*

- Common neuro labs:
 - Lipid panel: cholesterol can be elevated in ataxia with oculomotor apraxia types 1 and 2, decreased in abetalipoproteinemia
 - SPEP + IFE: screen for malignancy, association with neuropathy
 - Lyme:
- Metabolic/biochemical:
 - Ammonia: screen for intermittent ammonia cycle defects
 - CK: screen for mitochondrial myopathy
 - PAA: screen for inborn errors of metabolism
 - Lysosomal enzymes: for metachromatic leukodystrophy, Tay Sachs and the like
 - VLCFA: X-linked adrenoleukodystrophy, peroxisomal biogenesis disorders
 - Acylcarnitine profile: perturbations in fatty acid oxidation can be seen in mitochondrial disorders
- Urine studies:
 - Urine heavy metals: neurological effects from lead, arsenic, mercury, etc.
 - Urine organic acids: screen for metabolic disorders



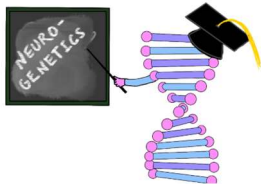
- UPEP + IFE: screen for malignancy, association with neuropathy
- Infectious:
 - HTLV I/II
- Immunological studies:
 - Paraneoplastic panel
 - Celiac antibodies
 - Thyroid autoantibodies
 - Anti-GAD65
 - SSA/SSB
- What might you consider testing from the CSF?
 - Protein, glucose, cell count, cultures, and viral PCRs
 - VDRL (syphilis)
 - Inflammatory
 - IgG index
 - OCBs
 - cerebellar autoantibodies
 - Neoplastic
 - Cytology
 - Flow cytometry
 - Mitochondrial: lactate
 - CJD: 14-3-3, tau, RT-QuIC
 - Neurotransmitter metabolites

Note: that these laboratories should be tailored in adult versus pediatric presentations.

Slide 14: Other assorted laboratory studies to consider. *Go through this quickly*, without necessarily telling audience what each test is for—this is more for reference or if people ask what these tests are for:

- Zinc: note that zinc chelates copper and can cause a secondary copper deficiency.
- AFP: marker for ataxia-telangiectasia and some forms of ataxia with oculomotor apraxia. This cannot be used as a screen for A-T until after the age of one year, given the normal elevation seen in infants.
- Ferritin: elevated with neuroferritinopathy, aceruloplasminemia.
- Coenzyme Q10: we typically measure coenzyme Q10, with the caveat that deficiency can only be reliably diagnosed from a muscle biopsy sample.
- Sterols (specifically cholestanol): to screen for cerebrotendinous xanthomatosis.
- CDG: glycosylated transferrin, see perturbations in congenital disorders of glycosylation.

Slide 15: Additional HPI. Note: that the patient's symptoms are primarily affecting **motor** function not cognitive.



Slide 16: Patient's exam. *What are the major features here?* Some cerebellar involvement given the nystagmus but also concern for a neuropathy.

Note: that there are different scales to measure motor skills, including SARA (below), and FARSn (Friedreich Ataxia Rating Scale neurological examination), **but don't reveal this now** as you'll reveal the diagnosis otherwise:

Scale for the assessment and rating of ataxia (SARA)

- 1) Gait: 5 Severe staggering, permanent support of one stick or light support by one arm required
- 2) Stance: 5 Able to stand >10 s in natural position only with constant support of one arm
- 3) Sitting: 2 Constant sway, but able to sit >10s without support
- 4) Speech disturbance: 1 Suggestion of speech disturbance
- 5) Finger chase:
Right: 2 Dysmetria, under/overshooting target <15 cm
Left: 2 Dysmetria, under/overshooting target <15 cm
- 6) Nose-finger test:
Right: 1 Tremor with an amplitude <2 cm
Left: 1 Tremor with an amplitude <2 cm
- 7) Fast alternating hand movements
Right: 1 Slightly irregular (performs <10 s)
Left: 2 Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs <10 s
- 8) Heel-shin slide:
Right: 1 Slightly abnormal, contact to shin maintained
Left: 1 Slightly abnormal, contact to shin maintained

SARA is typically utilized in the clinic versus the ICARS (International Cooperative Ataxia Rating Scale), which is more cumbersome to administer.

Slide 17: Pedigree – interactive exercise, where 1 person role plays a parent and one role plays clinician. Either the facilitator or another participant should be shown the pedigree before the session, and they should be the pretend parent. Other participants should spend about five minutes constructing a pedigree including questions about recurrent miscarriages, ethnicity, and consanguinity. Consider involving your institutional genetic counselor for this session.

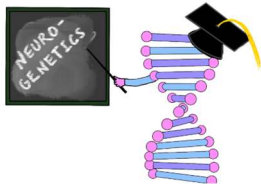
Slide 18: Pedigree – Note: the consanguinity and the large number of unaffected siblings, suggestive of an **autosomal recessive inheritance**. *Discuss that a de novo change would also be possible.*

Slides 19: Differential diagnosis for *autosomal recessive* causes of ataxia with *sensorimotor neuropathy*. This is likely beyond the residents' knowledge base but a good reference.

Slide 20: Patient's MRI: essentially normal. T1 sagittal on L and T2 coronal on R.

- *Is there any evidence cerebellar atrophy?* No
- *With which form of ataxia would this potentially be consistent?* FA, but there can be atrophy late in the course of the disease.

(Note: imaging findings can evolve in the course of the disease.)



Slide 21: NCS report. Ask audience-*what does this show?*

Answer: Absent sensory response in both upper and lower extremities. Mildly slowed peroneal motor conduction velocity in the axonal range (34 m/s, normal range is closer to 48-61 m/s). Severe sensory >>> motor axonal length-dependent polyneuropathy.

Slide 22: *Have a member of audience summarize case* (teenage onset of slowly progressive ataxia, with family history of consanguinity, and with sensory neuropathy and loss of reflexes).

Have audience name most likely diagnosis (Friedreich's Ataxia).

Slides 23: Metabolic investigations. *Which of the following may potentially be affected in some genetic ataxias?*

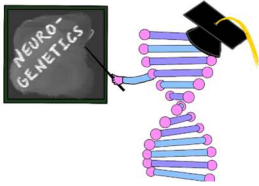
- Vitamin E in Ataxia with Vitamin E Deficiency
- High AFP in Ataxia-Telangiectasia
- Increased CK in Ataxia with oculomotor ataxia (AOA), mitochondrial disorders
- Low albumin level and lipid panel perturbations in AOAs
- CoQ10 low in CoQ10 deficiency
- Lactate elevation and plasma amino acid and urine organic acid perturbations in mitochondrial disorders
- Frataxin level low in Friedreich ataxia

Slide 24: *Interpret the frataxin level.* Frataxin levels are a send-out to Mayo. If you do not have a strong clinical suspicion of FA, it would be fine to send something like a comprehensive ataxia gene panel versus ES. **But a frataxin level is relatively inexpensive**, about \$200, and then if the level is low, the lab can add on repeat expansion testing as a reflex.

Slide 25: *Interpret the FXN repeat expansion testing.* Note: that the testing modality is PCR, and **trinucleotide repeat expansions are not always detected by exome/genome sequencing** using conventional methods (short-read next generation sequencing). But advances in technology are continuously being made to detect repeat expansion disorders, including long-read sequencing.

Slide 26: Discussion points about genetic testing.

- Four groups to answer these sets of questions (breakout rooms or small groups):
 - Team 1:
 - Name of genetic condition: Friedreich ataxia.
 - Autosomal recessive
 - Team 2:
 - If frataxin level is normal, would send ES or complete (AR and AD) ataxia panel
 - Team 3:
 - If de novo or AD, would likely send ES or AD ataxia panel



- Team 4:
 - Commercially available panels that would catch trinucleotide repeats:
Have participants look up panels.
 - Repeat expansion variant for FXN not covered:
 - <https://blueprintgenetics.com/tests/panels/neurology/ataxia-panel/>
 - <https://www.fulgentgenetics.com/Ataxia>
 - <https://providers.genedx.com/tests/detail/ataxia-xpanded-panel-887>
 - Repeat expansion for FXN covered:
 - <https://www.athenadiagnostics.com/view-full-catalog/ataxia-complete-recessive-evaluation1>

So, with suspicion of Friedreich Ataxia, you need to usually send the FXN repeat expansion test separately.

Slide 27: Teaching points about frataxin and typical pathogenic variant in *FXN*.

Slide 28: Many are moving toward ES plus repeat expansion testing.

Slide 29: Teaching points about Friedreich ataxia.

Slide 30:

- Left panel: In healthy cells, oxidative stress causes Nrf2 translocation to the nucleus to increase the expression of antioxidant genes, protecting cells from damage.
- Middle panel: In FA, both mitochondrial function and Nrf2 signaling are impaired. Cells from patients with FA exhibit hypersensitivity to oxidative insults, likely due to impairment in Nrf2 signaling. **Nrf2 fails to activate/translocate to nucleus, and this prevents induction of antioxidant Nrf2 target genes.** This leads to cell death/neurodegeneration.
- Right panel: Omaveloxolone (right panel) activates Nrf2.

Slide 31: Suggested reading.

Slide 32: Acknowledgements.