Outline

• Cerebellar anatomy and function
• Clinical features of cerebellar disease
• Diagnoses and treatment of ataxia
  • Genetic ataxias
  • Multiple system atrophy
  • Auto-immune ataxias
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Functions of the cerebellum

• Regulation of balance and posture

• Coordination of voluntary movements
  • Coordinates timing and force of all the different muscle groups required to produce a specific movement

• Motor learning
  • Adapt and fine-tune motor programs through trial and error (think: learning to ride a bike)

• Cognitive function
Functional anatomy

3 phylogenetically defined regions

1. Vestibulocerebellum
   - Oldest section
   - Flocculonodular lobe
   - Input from vestibular nuclei
   - Functions: eye movements and balance

2. Spinocerebellum
   - Anterior and posterior parts of vermis
   - Input from spinal cord
   - Functions: motor coordination, muscle tone

3. Corticocerebellum
   - Newest part
   - Hemispheres and middle vermis
   - Input from cortex via pons/thalamus
   - Functions: fine motor control, speech, cognition, motor learning
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Clinical features of cerebellar dysfunction

Function

• Balance/posture
• Coordination
• Cognition

Dysfunction

• Gait ataxia
• Titubation
• Hypotonia
• Dysmetria
• Eye movement abnormalities
• Dysarthria
• Dysphagia
• Cognitive deficits
Gait ataxia

http://www.youtube.com/watch?v=eBvzFkcvScg
Arm dysmetria and tremor

http://www.youtube.com/watch?v=aVl6PETpAPw&feature=related
Arm dysmetria and tremor

http://www.youtube.com/watch?v=5eBwn22Bnio
Leg dysmetria

http://www.youtube.com/watch?v=fwG6CUD6Puw&feature=related
Eye movement abnormalities

- Square wave jerks
- Nystagmus
- Saccadic smooth pursuits
- Hypo/hypermetric saccades

http://www.youtube.com/watch?v=ALa-YUPV4hM
Outline

• Cerebellar anatomy and function
• Clinical features of cerebellar disease
• Differential diagnoses and treatment of ataxia
  • Genetic ataxias
  • Multiple system atrophy
  • Auto-immune ataxias
What can cause cerebellar disease?

100s of different medical issues can lead to cerebellar disease!

**Vascular** – infarct, hemorrhage, etc

**Infection** – varicella (children), EBV (adult), Lyme, Whipple’s, syphilis, prion

**Toxin/trauma**
- meds (for example, antiepileptics, chemotherapeutic drugs)
- heavy metals
- alcohol

**Autoimmune** – lupus, Sjogen’s, Miller-Fisher variant of Guillain-Barre Syndrome, GAD antibody syndromes, celiac disease, others

**Metabolic** – hypothyroidism, diabetes, vitamin deficiencies (E, B12, B1)

**Neoplastic** – tumors, paraneoplastic syndromes

**Congenital** – Chiari Malformations, hypoplasias, agenesis

**Degenerative** – multiple system atrophy

**Genetic** – spinocerebellar ataxias, Friedreich’s ataxia, many others
General Approach

• History
  • Time course
    • Acute – think stroke, bleed, infection, demyelination
    • Subacute – think paraneoplastic disorder or prion diseases
    • Chronic – still broad range of diagnostic possibilities
  • Age of onset
  • Family History
  • Other neurological sx
  • Past Medical History
  • Medications

• Examination
  • confirm cerebellar findings
  • other neurological signs?

• Imaging and blood tests
  • Lots of potential tests that can be ordered
Case 1

Patient is a 72 yo RH male who presents with **worsening balance**. He first started to notice balance problems in 2008, which was become progressively worse. He started to have **falls** in 2012, and now uses a cane. He has also noticed a **decline in his hand coordination** and fine motor skills. In the last six months, he has noticed **slurred speech** and **difficulty swallowing**. He also notes **trouble with short term memory** and following instructions, and his family notes that he has made **poor decisions** recently. He has several family members on his father’s side that have similar symptoms, including an older brother, father, two paternal aunts, one paternal cousin, paternal grandmother, grandmother's two brothers and their children.
Case 1
Spinocerebellar ataxia 1

- Among most common form of autosomal dominant ataxias
- Marked by ataxia, corticospinal tract signs, neuropathy
- Other potential findings: Parkinsonian features, mild cognitive changes
- Course:
  - Variable based on repeat length
  - On average, disability in 5 years, survival 10-15 years
- Diagnostics:
  - Genetic test confirms diagnosis
  - Due to CAG repeat expansion in ataxin-1 gene
  - Disease caused by repeats 39+
Spinocerebellar ataxias

- SCA 1 is one of many spinocerebellar ataxias
- SCA refers to those inherited ataxias marked by autosomal dominant inheritance
  - 40+ SCAs described so far
- Nearly impossible to make diagnosis based on clinical features without genetic testing
- Different genes are mutated for each SCA
- Exome sequencing studies suggest that >1000 genes can cause genetic ataxias (dominant and recessive forms)
Spinocerebellar ataxias

- Prevalence varies from region to region due to founder effect
- Most common SCAs are SCA 1, 2, 3, 6, 7 (50-65%)
- Most common in US are SCA 2, 3, 6
The patient is a 54 yo RH female who developed gait instability at age 22. She then started to have weakness in her legs with muscle spasms in her feet. She later developed weakness in her arms and hand incoordination. She has numbness and tingling in both feet and tips of fingers for many years. She has been wheelchair bound since her mid 20's. Other complaints include slurred speech and dysphagia. She has blurred vision and jerky of her eyes at times. She also notices tremor in her head. She has had multiple orthopedic procedures. Her sister developed similar symptoms and also diabetes starting at age 15.
Friedreich’s ataxia

- Most common ataxia in Western hemisphere
  - Carrier frequency 1 in 85 in Caucasian populations
  - Accounts for 75% of all ataxias presenting before age 25
- Key symptoms: ataxia, dysarthria, neuropathy, distal muscle weakness, deafness, optic atrophy
- Systemic features: cardiomyopathy, diabetes, scoliosis, pes cavus
- Autosomal recessive inheritance
- Due to GAA repeat expansion in frataxin gene in >90%
  - Result is reduced frataxin protein (mitochondrial protein)
  - Point mutations found in 2-4%
Management of Friedreich’s ataxia

• Neurological: supportive care
  • PT/OT/ST
  • Medications for neuropathic pain
  • Baclofen, benzos, etc for muscle spasms and spasticity
  • Monitor swallowing
  • Treat bladder, bowel, and sexual dysfunction
  • Annual hearing tests
  • Watch for OSA
• Cardiac:
  • Annual EKG and ECHO
  • Cardiology evaluation if symptomatic
• Diabetes:
  • Screen blood glucose at least yearly
  • Treat diabetes
• Ortho:
  • Monitor for scoliosis
  • May need bracing or surgical correction
Case 3

69yo M with progressive gait ataxia for 10+ years. Started noticing **trouble when walking** in mud while hunting. Also noticed progressive **tingling and numbness** in his feet since 2010. Eventually developed **mild dysphagia and dysarthria**.

Neurological exam was notable for scanning speech, moderate dysmetria, and large fiber neuropathy.
Case 3

• I first saw him ~10 years ago
• Extensive work-up was unrevealing for many years
  • Brain MRI with cerebellar atrophy
  • Lab work for sporadic causes negative
    • Vitamins, paraneoplastic panel, rheum, etc
    • CT chest/abd/pelvis negative
      • Eventually diagnosed with colon cancer
• Multiple genetic tests over the years
  • Athena comprehensive panel
  • Invitae HSP panel
  • Gene Dx ataxia panel
• In 2021 we pursued testing for CANVAS
Cerebellar ataxia with neuropathy and vestibular areflexia syndrome
• Newly recognized genetic disorder marked by pentameric repeats in RFC1 gene
  • Gene implicated in DNA replication and repair
• Clinical features include gait imbalance, numbness, tingling, and oscillopsia
• Other features include dysarthria, dysphagia, chronic cough, and autonomic complaints
• Tends to follow slowly progressive course
• Pathology marked by loss of Purkinje cells, especially in the vermis, and loss of sensory neurons in the dorsal roots and CNV, VII, VIII sensory ganglia
• Treatment is supportive
Case 4

The patient is a 63 yo RH male who developed unsteady gait and speech changes starting two years ago. Initially noticed feeling unsteady in shower. Gait progressively got worse with many falls. Speech became slurred with jerky quality to speech. Trouble with writing, shaving, and brusing teeth. More recently has developed urinary incontinence and rare bowel incontinence. He often feels lightheaded and has passed out several times. Family notes that he takes “deep breaths” at times. His PMH is notable for HTN, but he no longer requires blood pressure medications. He also has a history of REM sleep behavior disorder. No family history of ataxia.
Multiple System Atrophy

- Age of onset typically 55
- Clinical features
  - Cerebellar ataxia
  - Parkinsonism
  - Autonomic dysfunction
  - Corticospinal tract signs
  - Others: inspiratory stridor, dystonia, anterocollis, REM sleep behavior disorder
- Two main subtypes
  - MSA-P – more common in Western hemisphere
  - MSA-C – more common in Eastern hemisphere
- MRI findings:
  - cerebellar and brainstem atrophy
  - “hot cross bun” sign
  - T2 hyperintensity in lateral margin of putamen
- Recent study shows 7.3% of MSA patients had SCA gene mutation (Kim et al 2014)
Management of MSA

- Parkinsonism:
  - l-dopa can be helpful at high doses but effect often short-lived
  - Dopamine agonists less effective
- Cerebellar ataxia:
  - No medications are useful
  - PT/OT/ST and assistive devices
- Stridor:
  - Need sleep study and likely CPAP
- Autonomic dysfunction:
  - Orthostatic hypotension:
    - Conservative management: fluids, salt, compression stockings/abdominal binders, elevation of head of bed
    - Fludrocortisone, midodrine, droxidopa
  - Urinary symptoms:
    - Anticholinergics (oxybutynin, tolterodine)
    - Alpha1 blockers (prazosin, tamsulosin)
    - Catherization for retention
  - Sexual dysfunction:
    - sildenafil
Case 5

The patient is a 72 yo RH female who presents with **unsteady gait** over one year. She has had several falls with resulting spine fracture and now uses a walker. She also notes **difficulty with hand coordination** over the last 6 months. Her PMH is notable for diabetes, seizures, and thyroid disease. Her family history is negative for ataxia.
Neurological disease associated with GAD antibody

- Variety of neurological syndromes seen
  - stiff person syndrome
  - cerebellar ataxia
  - seizure disorder
  - limbic encephalitis
- Often associated with other autoimmune disorders
- Testing
  - MRI can be normal or show cerebellar atrophy
  - Blood and CSF: positive for anti-GAD antibodies
- Can be paraneoplastic
  - Need to consider screening for malignancy
  - Likelihood of paraneoplastic syndrome associated with anti-GAD antibodies is low when neurological syndrome is ataxia (Arino et al 2015)
    - Association with cancer is low (estimated ~11%) (Saiz et al 2008)
- Treatment is immunosuppression but variable benefit seen
Other immune-mediated ataxia syndromes

- **Gluten ataxia**
  - Controversial: high rate of anti-gliaden antibodies in the general population but do see Purkinje cell loss in patients with gluten ataxia
  - Transglutaminase 6 (TG6) is likely target antigen in gluten ataxia
- **Anti-TPO associated ataxia**
  - Also controversial diagnosis
  - Clinical criteria includes elevated anti-TPO and responsiveness to steroids
- **Paraneoplastic ataxia**
  - Antibodies produced in the setting of cancer (often undiagnosed)
  - Goal is to find and treat underlying tumor

Mitoma et al 2015; Mitoma et al 2016
Current therapies

- Dependent on diagnosis
- A few genetic ataxias are treatable
  - Vitamin E deficiency associated ataxias
  - Some of the metabolic ataxias
- Immunosuppression for autoimmune ataxias
- Most involve symptomatic treatment
  - Physical therapy, occupational therapy, speech therapy
  - Walking aids
  - Management of other neurological symptoms
    - Treat seizures with antiepileptic drugs; Parkinsonian symptoms with PD meds
    - Management of systemic disease
      - Diabetes management; orthopedic management for skeletal abnormalities; management of cardiomyopathy
- Development of new therapies depends on understanding disease mechanisms
Conclusions

- Key cerebellar functions are regulation of posture and balance, motor coordination, and motor learning.
- Cerebellar disease can cause gait ataxia, limb dysmetria, dysarthria, and eye movement abnormalities.
- There are many causes of cerebellar ataxia.