Disclosure and Conflict of Interest

All opinions expressed and implied in this presentation are solely my own. The content of the presentation does not represent or reflect the views of my employer, The Johns Hopkins University. No immediate family member nor domestic partner nor I have a financial arrangement or affiliation with any organization that may have a direct interest in the subject matter of this presentation. My presentation does not reflect nor can be construed as a financial conflict of interest nor will lead to any financial gain (apart from the occasional, usually quite modest, honorarium) to me from any business entity. In fact, almost everything we all do on behalf of Johns Hopkins is out of the goodness of our hearts with disregard for our pocketbooks, and also builds on our lifelong dedication to teaching the best practice of medicine for our patients, to our students, residents, fellows and colleagues and to our fellow practitioners all over the world. Any off label use of medications will be disclosed (*) as such though whenever possible their use will be justified by the best (which unfortunately is rarely that good) empirical data.
LEARNING OBJECTIVES

- Correctly perform bedside maneuvers to elicit different types of cerebellar related ocular motor disorders.
- Localize various patterns of eye movement disorders to particular parts of the cerebellum.
- Know which drugs (off-label) might be used to treat different types of cerebellar ocular motor disorders.
Three basic functional-anatomical cerebellar syndromes

- Syndrome of the nodulus & ventral uvula
- Syndrome of the flocculus and paraflocculus (tonsil)
- Syndrome of the dorsal vermis (OMV) & posterior fastigial nucleus (FOR)
Cerebellar flocculus and paraflocculus (tonsils)
KEY ANATOMY OF LABYRINTH-VESTIBULO-CEREBELLAR CONNECTIONS

The Labyrinth

Semicircular Canals / Otoliths project to

FLOCCULUS, AICA

TONSIL, NODULUS/VENTRAL UVULA, PICA

AICA = anterior inferior cerebellar artery
PICA = posterior inferior cerebellar artery
Flocculus/Paraflocculus syndrome: Downbeat, gaze-evoked and rebound nystagmus in cerebellar atrophy

Cerebellar atrophy: SCA6
Flocculus/Parafloloculus syndrome
Impaired pursuit and vestibuloocular reflex (VOR) cancellation (fixation suppression)

Pursuit and VOR cancellation
Downbeat (DBN), gaze-evoked (GEN) and rebound nystagmus (RBN) in cerebellar atrophy

**PEARL:** As eccentric gaze is maintained:

Gaze-evoked nystagmus (GEN) gets

- Less with cerebellar disease, and RBN occurs
- More with myasthenia gravis, and RBN occurs
- Little change with infantile (congenital) nystagmus, and ??RBN
Middle aged woman with a few months of rapidly progressive ataxia, No alcohol or medications, negative FH, normal MRI
PEARL: Velocity-increasing slow phases imply gaze-holding integrator is unstable.

Downbeat Nystagmus will intensify in UP-gaze (anti-Alexander’s Law)
Downbeat nystagmus in adults

- Paraneoplastic syndrome (anti-yo in women (gyn tumors), anti-hu, anti-gad, anti-ma/ta. Note anti-ri is associated with opsoclonus)
- Lithium, carbamazepine, amiodorone
- Cerebellar degeneration
- Cranio-cervical junction anomalies
- Wernicke's encephalopathy (often converts to upbeat with convergence or vice versa)
- TREATMENT – 4-aminopyridine. Note also some evidence this works in upbeat nystagmus and in EA2 (episodic ataxia type 2). Other choices, though less consistently helpful, include clonazepam and baclofen. (Note upbeat nystagmus is produced by nicotine)
Drug Treatments – Aminopyridines

• 3,4-diaminopyridine
• 4-aminopyridine (more effective and less side effects.
• Improve Purkinje cell function via blocking K channels (Kalla, Brain, 2007; Strupp, Prog Br Res 2008)
• NOTE may also lessen gaze-evoked nystagmus

Videos courtesy of Dr. Michael Strupp
Testing of the VOR: Head impulse sign in a unilateral *peripheral* labyrinthine lesions

Catch-up saccade during brief, high-acceleration, head rotation (left-sided loss)

Head-impulse sign in unilateral labyrinthine loss
Abnormal VOR in cerebellar disease: Abnormal direction
Abnormal VOR in cerebellar disease: Increased gain

Corrective saccades IN THE DIRECTION of head rotation (opposite the slow phase) during fixation of a stationary target indicate a HYPERACTIVE VOR.

Corrective saccades OPPOSITE THE DIRECTION of head rotation (same as slow phase) during attempted fixation of a target indicate a HYPOACTIVE VOR.
Head-shaking induced nystagmus (HSN) in peripheral labyrinthine disease
Head-shaking nystagmus (HSN) in cerebellar disease

PEARL: Think central if HSN is
- Directed DIFFERENTLY than head motion (cross-coupled), e.g., vertical nystagmus with horizontal head-shaking.
- Directed opposite to spontaneous nystagmus
- If there is a reversal of the direction of HSN that is early and strong
Hyperventilation-induced (HVN) downbeat nystagmus

PEARL: HVN

- Cranial-cervical junction anomalies
- Cerebellar degenerations
- Compressive lesions on VIII CN (microvascular compression, tumors)
- Demyelinating diseases (e.g., MS)
- Labyrinthine fistula and SCC dehiscence
Pathology and anatomy of ocular motor abnormalities with cerebellar disease

Cranial-cervical junction: Chiari

Cerebellar atrophy: SCA6

Superior Semicircular Canal dehiscence

PEARL: Remember Valsalva-induced vertigo with cranial-cervical junction anomalies and with labyrinthine fistula and SCC dehiscence
Ocular motor disorders with nodulus lesions:
Periodic Alternating Nystagmus and Central Positional Nystagmus

Nodulus
PAN: Pathogenesis and Treatment

Two key normal mechanisms

• Central velocity storage mechanism located within the vestibular nuclei that improves the ability of the vestibular system to respond to low-frequency (sustained) head motion by perseverating peripheral vestibular signals.

• Adaptation mechanism that acts to null any sustained unidirectional nystagmus (which in natural circumstances is always due to a lesion)
PAN: Pathogenesis and Treatment

- In PAN, instability in velocity storage is produced by **loss of (gaba-mediated) inhibition** from the Purkinje cells of the **nodulus** onto the vestibular nuclei.
- Short-term adaptation (which is working normally) causes **reversals of nystagmus** leading to sustained oscillation.
- **Baclofen (GABA-b)** provides the missing inhibition and stops the nystagmus.
  - Usually need only 10 mg PO TID.
  - Avoid precipitous discontinuation.
  - Does not work as well in congenital PAN.
  - **Memantine** may be of help.
Nodulus lesions and positional nystagmus

- Young woman suddenly developed positional vertigo with nausea and vomiting, without other neurological symptoms or signs. Thought to have BPPV
- Positional nystagmus noted. All eye movement exam and general neurological exam is normal except for findings with positional testing and head shaking.
Downbeat positional nystagmus
Torsional nystagmus after *horizontal* head shaking
Central positional nystagmus and abnormal head shaking nystagmus due to a nodulus lesion (glioneuronal tumor)

IMPERATIVE
• Tell the radiologist where to look
• Look yourself
SOMETHING ‘NEW’ FOR THE ACUTE VERTIGO PATIENT

Tilt suppression (Tilt supp) of post-rotatory nystagmus after a sustained constant-velocity rotation. (Note the head is tilted just when the CHAIR stops moving)

- Normal with peripheral lesions
- Impaired with central (nodulus) lesions

Zuma et al. 2017
Location of lesions in cerebellar patients who have impaired tilt suppression of post-rotatory nystagmus: The **nodulus**

Lee et al., 2017
REMEMBER: 1) The vermis contains Purkinje cells and they INHIBIT their target neurons in the deep nuclei (FOR) 2) Each FOR normally stops ipsilateral saccades
Cerebellar fastigial nucleus lesions produce saccade hypermetria
Hemangiopericytoma
Involving dorsal vermis

Cerebellar dorsal vermis lesions produce saccade hypometria
CLINICAL POINT

• Each Fastigial Oculomotor Region (FOR) sends its axons through the contralateral FOR before projecting to the brainstem alongside the superior cerebellar peduncle (hooked bundle of Russell, uncinate fasciculus). Each FOR acts to STOP ipsilateral saccades.

• A structural UNILATERAL lesion of the FOR is not possible.

• A functional UNILATERAL lesion of the FOR is possible: Wallenberg’s syndrome in which one FOR is inhibited by excessive Purkinje cell activity (from decreased climbing fiber activity and increased mossy fiber activity) causing IPSIpulsion (ipsilateral hypermetria of saccades).

• Functional UNILATERAL overactivity of one FOR is possible when there is a unilateral lesion of the overlying oculomotor vermis. This produces CONTRApulsion (contralateral hypermetria of saccades).
Dysmetria of saccades: *Overshoot* to one side, *undershoot* toward the other, called *lateropulsion* of saccades
Wallenberg’s Syndrome – Posterior Inferior Cerebellar Artery distribution infarct involving the dorsolateral medulla

Restiform body (ICP)

Lateropulsion (IPSIPULSION) of saccades occurs because of an interruption of climbing fiber input thru the ICP which causes INCREASED activity of Purkinje Cells in the dorsal vermis and INCREASED inhibition of the underlying fastigial nucleus.
THE ALIGNMENT CHANGES IN PATIENTS WITH CEREBELLAR DISEASE

- **Esodeviation** (eyes turn in with distance viewing, mimics a divergence paralysis)

- 'Skew' (vertical misalignment (alternating hyperdeviation, usually abducting eye is higher))
Alignment changes in cerebellar disease

Exodeviatıon at near
Alignment changes in cerebellar disease

Alternating hyper (abducting eye is higher)
Alignment changes in cerebellar disease
WHY this pattern? We ALL have a lateral-eyed rabbit inside our ‘human’ brains. In the rabbit, a lateral tilt (one ear up and the other down) leads to the eyes rotating around the *roll axis* with one eye rotating down and the other eye rotating up (a physiological skew).

This is reflected in the Ocular Tilt Reaction (OTR) – in which (the rabbit) emerges when there is imbalance in otolith (utricular) responses.
Alternating Skew in Cerebellar Patients: A misinterpretation of head pitch in a “lateral-eyed” animal?
CEREBELLAR Eye Movement Disorders: Diagnostic & Treatment Pearls for the Daily Clinic

LEARNING OBJECTIVES: Correctly perform key bedside maneuvers to elicit cerebellar related ocular motor disorders.

- Saccades: speed and accuracy
- Pursuit, gaze-holding, rebound
- Head impulse test
- Positional testing
- Head-shaking nystagmus
- Hyperventilation
- Eye alignment
CEREBELLAR Eye Movement Disorders: Diagnostic & Treatment Pearls for the Daily Clinic

LEARNING OBJECTIVES: Localize various patterns of eye movement disorders to particular parts of the cerebellum

- Flocculus/Parafloucculus: Pursuit, gaze-holding, DBN, RebN
- Nodulus/ventral uvula: DBN, Positional nystagmus, PAN, impaired tilt suppression, OTR (contralateral)
- Dorsal vermis: Saccade (ipsilateral) HYPOmetria
- Fastigial Oculomotor Region (FOR): Saccade (ipsilateral) HYPERmetria) BUT structural lesions are inherently bilateral because of immediate crossing of efferent pathways
CEREBELLAR Eye Movement Disorders: Diagnostic & Treatment Pearls for the Daily Clinic

LEARNING OBJECTIVES: Know which drugs (OFF-LABEL) might be used to treat different types of cerebellar ocular motor disorders.

- Baclofen: Periodic alternating nystagmus (PAN)
- 4-aminopyridine: Downbeat nystagmus (DBN)
- Memantine: Excessive saccade intrusions, perhaps saccade dysmetria
- Clonazepan: DBN, pendular nystagmus
- Memantine, Gabapentin: pendular nystagmus
Topical Localization in the Cerebellum

Italics, provisional localization

**NODULUS/UVULA**
- Prolonged rotational VOR
- Periodic alternating nystagmus (PAN)
- Impaired habituation of VOR
- Impaired tilt suppression of post-rotatory nystagmus
- Impaired translational VOR
- Downbeat nystagmus
- Impaired vertical and horizontal pursuit
- Head-shaking nystagmus (beats ipsilesional, strong reversal or misdirected)
- Direction changing, apogeotropic positional nystagmus
- Contraversive OTR, skew (also dentate nucleus)
- Alternating skew deviation

**FLOCCULUS/PARAFLOCCULUS**
- (TONSIL)
- Downbeat, gaze-evoked, rebound, centripetal nystagmus
- Impaired smooth pursuit and cancellation of VOR
- Abnormal amplitude and direction of VOR head impulse response
- Misdirected head-shaking nystagmus
- Contraversive OTR but without skew
- Alternating skew deviation
- Abnormal torsion with vertical pursuit (brachium pontis)

**FASTIGIAL NUCLEUS (FN)**
- Unilateral:
  - Hypermetric ipsiversive saccades
  - Hypometric contraversive saccades
  - Reduced contralateral initial acceleration of pursuit
- Bilateral:
  - Hypermetric saccades
  - Macrosaccadic oscillations
  - Normal pursuit
  - Exophoria
  - Saccade intrusions (square wave jerks)

**OCULAR MOTOR VERMIS (V, VI, VII)**
- Unilateral:
  - Hypermetric contraversive saccades
  - Hypometric ipsiversive saccades
  - Reduced initial acceleration of ipsilateral pursuit
- Bilateral:
  - Hypometric saccades
  - Reduced initial acceleration of pursuit
  - Esophoria (greater at distance, “divergence paralysis”)

(Globose/Emboliform – esophoria, vertical saccade dysmetria)