Clinical aspects of vestibular and ocular motor physiology: bringing physiology and anatomy to the bedside

Skews

Nystagmus

Tilts

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Outline of the presentation
Physiological principal – Clinical example

• Organization of the semicircular canals: an approach to nystagmus (νυσταγμός, drowsiness, nodding, doze)
  – Peripheral vs. central nystagmus
  – Benign positional vertigo
  – Superior canal dehiscence
• Angular vestibulo-ocular (aVOR) reflex disorders
  – Abnormal amplitude and direction of the aVOR
• Otolith-ocular reflex disorders
  – Skew deviation and the ocular tilt reaction (OTR)
  – Translational vestibuloocular reflex (tVOR)
• Vestibular velocity-storage disorders
  – Periodic alternating nystagmus
  – Head shaking nystagmus
• Adaptive control of the VOR
  – Recovery nystagmus
  – Wearing corrective spectacles
• Effects of magnetic fields on the labyrinth
Basic Physiological Principles

- Two types of acceleration sensors: angular (semicircular canals) and linear (otoliths)
- Two reflexes: vestibulo-ocular reflex (VOR) and vestibulo-spinal reflex (VSR)
  - Canal-mediated (rotational VOR)
  - Otolith-mediated (translational VOR, counterroll)
- Functions:
  - help assure clear vision during head motion (rotation and translation).
  - help maintain upright posture during standing and walking.
  - help the brain create a conscious perception of the position and the movement of the body relative to the environment.
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Ewald’s First Law: Eyes (head) rotates in a plane parallel to that of rotation of the head (detected by the SCC in that plane) and so stabilizes gaze (eye in space) around all three axes of head rotation.
Ophthalmoscope and spontaneous nystagmus
Look for nystagmus

Frenzel Lenses (best used with room lights off) to remove fixation

Strupp, Neurology, 2014
Young man presents with acute onset of sustained vertigo, nausea, vomiting, imbalance, without hearing symptoms.

- Peripheral vestibular nystagmus is increased or brought out by removal of fixation
- Alexander’s Law: Peripheral vestibular nystagmus increases in intensity when looking in the direction of quick phase
Bedside Examination of the SCC – static disturbances

LOCALIZATION OF NYSTAGMUS

– Peripheral lesions
  – Nystagmus is increased or brought out by removal of fixation (Romberg sign of VOR)
  – Mixed horizontal-torsional nystagmus is characteristic for complete loss of function on one side
  – Intensifies when looking in the direction of the quick phase (Alexander’s Law)

– Central lesions
  – Fixation has little effect on nystagmus
  – Pure vertical or pure torsional nystagmus
  – May intensify or diminish when looking in the direction of the quick phase. If diminishes (anti-Alexander’s law) the cause is central
Benign Paroxysmal Positional Vertigo (BPPV)

- Easily diagnosed by history and exam
- Pathophysiology well understood
- Easily treated
- Patients gratified
Benign Paroxysmal Positional Vertigo (BPPV)

- Posterior SCC becomes gravity sensitive due to floating debris (otoconia dislodged from the macula of the utricle)
- Otoconia get trapped in the posterior SCC on the cupula (CUPULOLITHIASIS) or are free-floating in the long arm of the canal (CANALOLITHIASIS).
Otoconia in BPPV (CUPULOLITHIASIS)
Otoconia in BPPV (CANALOLITHIASIS)
BPPV: Debris in posterior SCC
BPPV: Otoconia in posterior SCC

From SCC in BPPV patient at the time of surgery  

From intact otolith

Parnes
Nystagmus in BPPV from right SCC

Epley's Canalith-Repositioning Maneuver for the Treatment of Benign Paroxysmal Positional Vertigo Involving the Right Posterior Semicircular Canal.

Particle repositioning maneuver

Repeat until no nystagmus on positional testing

John Epley
Fistula due to

dehiscence of the roof of the superior SCC

Intact side

Abnormal side
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Physiological principles for the angular (rotational) VOR

1. Normally with the head still, the left and right vestibular nerves and the vestibular nucleus neurons to which they project have equal resting discharge rates (vestibular tone so they can work in “push-pull”; when one side is excited (by rotation to that side) the other is inhibited). This puts the brain in good stead as even with just one labyrinth the brain can still detect rotations in either direction based on the change in activity above and below the tonic firing discharge from just one labyrinth.

2. But because of Ewald’s second law, there will still be an enduring deficit for rotations toward the affected side since excitation is a more effective stimulus than inhibition for high velocity rotations (since tonic firing rate cannot go below zero) and for high acceleration, high frequency rotations, which can never be transduced perfectly using just one labyrinth.

3. The cerebellar flocculus and paraflocculus (tonsils) keep the direction and amplitude of the compensatory slow phase well matched to the direction and amplitude of the rotational stimulus.
Underlying physiological principles for the angular (rotational) VOR

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2. But because of Ewald’s second law, there will still be an *enduring* deficit for rotations toward the affected side since excitation is a more effective stimulus than inhibition for high velocity rotations, since tonic firing rate cannot go below zero, and for high acceleration, high frequency rotations, which are never transduced as well with just one labyrinth.

3. The cerebellar flocculus and paraflocculus (tonsils) keep the direction and amplitude of the compensatory slow phase well matched to the direction and amplitude of the stimulus.
Cerebellar flocculus and paraflocculus (tonsils)
Rhesus Monkey – Flocculus/Paraflocculus

CN VIII

Flocculus

Paraflocculus
Increased VOR GAIN in Cerebellar Disease

Backup Saccades
Abnormal VOR Direction

Yaw head impulses - Patient

X-couple into vertical

Vertical Velocity (deg/sec)
Horizontal Velocity (deg/sec)

-400 -300 -200 -100 0 100 200 300 400

-400 -200 0 200 400

Vertical Velocity (deg/sec)

Horizontal Velocity (deg/sec)

U

Leftward thrust

Rightward thrust

D

R

L

X-couple into vertical

eye

head (inv)
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Ocular Tilt Reaction (OTR) – acute tone imbalance of static utricular righting reflexes

Counterroll

Skew

Head Tilt
Vertical misalignment (skew) in the OTR: Emergence of a phylogenetically-old, ocular righting response to lateral tilt

In the lateral-eyed 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 up (a physiological skew as part of a normal OTR)
Stimulate Left Utricular Nerve

RE

LE

Cat, Suzuki
Mechanism of OTR

In normal, frontal-eyed, foveate animals the normal response to a lateral head tilt is pure ocular counterroll or torsion, without a skew.

In pathology, in frontal-eyed, foveate animals the abnormal response to a perceived shift of the sense of vertical becomes a “compensatory” head tilt, counterroll and a skew that produces vertical diplopia.
Bucket technique for Subjective Visual Vertical (SVV) (ocular counterroll)

After Zwergal, Neurology, 09, and Frisen, Neuro-ophthalmology, 2000
Evaluation of Skew Deviation

Maddox Rod

LE
RE
OTR with medial longitudinal fasciculus (MLF) lesion: Internuclear Ophthalmoplegia
Ocular Tilt Reaction (OTR) PATHWAY
Utricle - Vestibular Nuclei – MLF - III, IV - INC

Wallenberg Laby/VIII N.
EYE LOWER on side of lesion, IPSI TILT

Utricle
Vestibular nuclei

INC- midbrain
INO
EYE HIGHER on side of lesion, CONTRA TILT

Utricle
Vestibular nuclei
Utricular-ocular pathways: Dynamic (side to side translation) and Static (lateral head tilt)

Abnormal “heave” sign: translational VOR

OTR (ocular tilt reaction): ocular counterroll and skew
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Periodic Alternating Nystagmus (PAN)

Null every two minutes
Pathophysiology of PAN: Normal vestibular responses gone awry

Cupula decay

**Velocity Storage Mechanism**

Nystagmus outlasts the displacement of the cupula. ‘Velocity storage’ perseverates peripheral canal signals and so improves the ‘low-frequency’ response of the VOR. Increases VOR duration.

POTENTIAL FOR INSTABILITY
Pathophysiology of PAN:
Normal vestibular responses gone awry

Onset head rotation

Reversal Phase adaptation to sustained nystagmus.

POTENTIAL FOR REVERSING NYSTAGMUS
Pathophysiology of PAN:
Normal vestibular responses gone awry

Onset head rotation: constant velocity

POTENTIAL FOR REVERSING NYSTAGMUS
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 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)

• 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.
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Vestibuloocular reflex (VOR) learning and the cerebellum

Magnification effects associated with habitual wearing of spectacles require a change in the amplitude or direction of the VOR for stabilization of images during head movements.

THREE different VOR gains are required (presbyopia (bifocal), hyperopia (far-sighted) and no-glasses OR contacts).

Change in VOR direction may be required for astigmatism.

Different VOR gains or directions for the two eyes for different corrections for the two eyes (anisometropia).
Rhesus Monkey – Flocculus/Paraflocculus

CN VIII
Flocculus
Paraflocculus
Loss of VOR gain (amplitude) adaptation after floccular/parafloccular lesions

Pre-lesion Increase

Gain

Pre-lesion Decrease

Adapt at 2.0 Hz

Post-lesion No learning

4 hrs of training with increasing or decreasing spectacles

Lisberger, 1984
VOR learning in Purkinje Cells

Ito, NatureNS
Effect of habitually wearing corrective spectacles (not contacts) on VOR testing

![Graph showing the effect of corrective spectacles on VOR gain. The graph plots \( \frac{G_{\text{spec}}}{G_{\text{baseline}}} \) against horizontal disparity (\( \tilde{D}_{\text{horiz}} \)). The graph includes data points for near-sighted and far-sighted conditions.]

Near sighted -- Spectacle magnification -- Far sighted
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THE BACKGROUND

Patients sometimes in a 3T and always in a 7T magnet feel a sense of motion while lying still in the magnet, even before images are taken. They can be dizzy and unsteady when they get up from the table (Glover and colleagues in Nottingham).

Technicians walking near a strong MRI machine may lose balance.

WHY? And what are the scientific and clinical implications?
Why were people getting dizzy in and near these strong magnets?

Key in solving this problem: Eliminate fixation to bring out a peripheral vestibular nystagmus by using Infrared video goggles

(Hallmark clinical rule: peripheral vestibular nystagmus is suppressed by fixation (Romberg sign of the vestibulo-ocular reflex))
MVS Nystagmus in the bore

ADAPTATION followed by REVERAL PHASE just as in caloric, rotational and head-shaking induced nystagmus

24 minutes
The answer is Static MHD
(magneto-hydrodynamics, effects of magnetic fields on fluids in which there is a current flowing)

Current flowing vertically through the liquid experiences a force \( \mathbf{F} = h \mathbf{J} \times \mathbf{B} \) along the tube as shown.
Where is the force in the MRI coming from?

Lorentz forces due to naturally occurring currents flowing through endolymph into hair cells in the utricle which produces a force in the endolymph, which pushes the fluid through the semicircular canal onto and then bending the cupula. This is sufficient to cause a false sense of rotation and an inappropriate nystagmus.

• **Endolymph**: a potassium rich fluid that fills the vestibular labyrinth and serves a dual purpose:
  – It transmits ionic current into hair cells in the utricle and the crista ampullaris to sustain their resting discharge.
  – It transmits force, as pressure onto the cupula (the ear’s rotational sensor) within the semicircular canal.

KEY: SCC is a conduit that channels the Lorenz force in the endolymph onto the cupula. These properties match MHD, in which a conductive fluid carries both a current and a force.
The Lorentz Force model correctly predicts that animals with a smaller vestibular system will experience vestibular stimulation equivalent to a larger head acceleration.

The Lorentz force scales with the first power of the canal size, and head rotation force scales with the second power (square) of the canal size.
Zebra fish are an excellent biological model to study brain development, connectivity, and function using optogenetic imaging and genetic manipulation. Now we have an elegant behavioral assay of the vestibular system using magnetic vestibular stimulation.