Monitoring Ototoxic Changes in Auditory and Vestibular Systems

Jaynee A. Handelsman, Ph.D.

Dawn Konrad-Martin, Ph.D.

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Special Interest Division 6

Ototoxicity

- Damage to the inner ear from toxic agents
- Negative consequence of the availability and use of medications that prolong life through treatment of serious infections and cancer
  - Chemotherapy agents
  - Antibiotics
- Result is damage to cochlear and/or the vestibular end organs
- Evidence suggests that there are no “safe” levels

Short Course Objectives

- Provide overview of pathophysiology involved in damage related to aminoglycoside, platinum-based drug, and noise exposure
- Discuss clinical features of auditory and vestibular system damage
- Discuss the challenges involved in monitoring for auditory and vestibular system changes

Short Course Agenda

- Presentation of issues related to auditory system monitoring
- Presentation of issues related to vestibular system monitoring
- Interaction with course participants including questions and discussion of possible solutions

Monitoring for Ototoxicity-Induced Hearing Loss

VA RR&D
National Center for Rehabilitative Auditory Research

Portland VA Medical Center
Portland, Oregon

Dawn Konrad-Martin
Jane S. Gordon
James A. Henry
Kelly M. Reavis
Kristi Gilmer Knight
Stephen A. Fausti

Pathophysiology: Platinum-based Drugs

- Oxidative Damage (Evans & Halliwell, 1999; Gratton & Smith, 2004; Rybak & Kelly, 2003)
  - Hair cell damage/death
  - Damage to stria vascularis and sprial ganglion cells (Tsukassaki et al., 2000)
- Hair cell damage begins at base, progresses toward apex, first row of OHCs followed by second and third rows, and then the IHCs (Gratton & Smyth, 2004)

Pathophysiology: Noise-Induced Hearing Loss

- Noise exposure during and after treatment can act synergystically with ototoxic drugs
- Causes additional oxidative stress and production of free radicals

Clinical Features

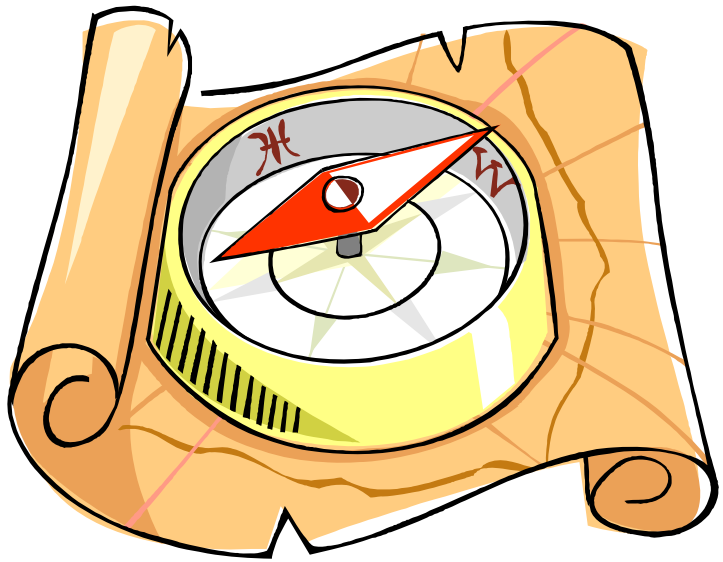
- Tinnitus
- Hearing loss
  - Difficulty understanding speech in noise
  - Sensorineural, usually bilateral, symmetric
  - Progresses from high to low frequencies
- Symptoms can be delayed days, months
- Usually permanent, sometimes recovers
  - Hearing changes from ototoxicity in young children increased from 11% during early post-treatment evaluations to 44% after 2 years (Bertolini et al., 2004)

Challenges

- Complaints of ototoxic damage are uncommon until communication problem becomes significant
  - how much change at how many frequencies is “significant”
- Difficult to predict ototoxic damage
  - Relationship to drug dosage, peak serum levels, and other toxicities is variable

Things to Consider

- Define Purpose
- Target Patients
- Create Referral Base
- Choose Tests
  - Test schedule
  - Change criteria
- Communicate Results
- Education, Counseling & Rehabilitation



Purpose of Monitoring

- Early Identification, prevention

  Should we care about early changes enough to take the time to measure them?

Consequences for Communication

- Audibility of consonants critical for understanding speech (De Paoli et al., 1996)
  - Most energy from 2 to 4 kHz
  - 50% of English consonants are fricatives (/v,f,z,s/, etc.) & contain energy through at least 8 kHz
  - /s/ spoken by women & children indistinguishable from /f/, /th/ when energy cut off at 4 kHz (Stelmachowicz et al., 2001)
- Consonants are low in level compared to vowels
  - Unvoiced (/s,p,t,k,th,f,sh/) often below normal thresholds in rapid speech (Northern & Downs, 2002)

Rationale for Monitoring

- Loss within 2 to 9 kHz range clinically significant for children
- Some impact of high frequency loss on speech understanding, even in adults
- And… hearing aid amplification typically cuts off at 5 kHz
- Moreover, continued damage may affect more of the critical speech frequencies

Benefits of Monitoring

- Early detection may prevent hearing damage that requires amplification/rehabilitation
- If change observed, treatment modification can prevent further hearing loss
- If no change observed, continued treatment warranted
- Provides opportunity for counseling and rehabilitation during and post treatment

Informed medical decisions

Target Patient Population

- Receiving highly ototoxic drugs
- Very old & very young people
- Poor medical condition
- Poor renal function
- Poor hydration status
- Familial tendency for susceptibility (aminoglycoside antibiotics)
- Receiving more than one ototoxic drug
- Receiving large or multiple doses

Incidence

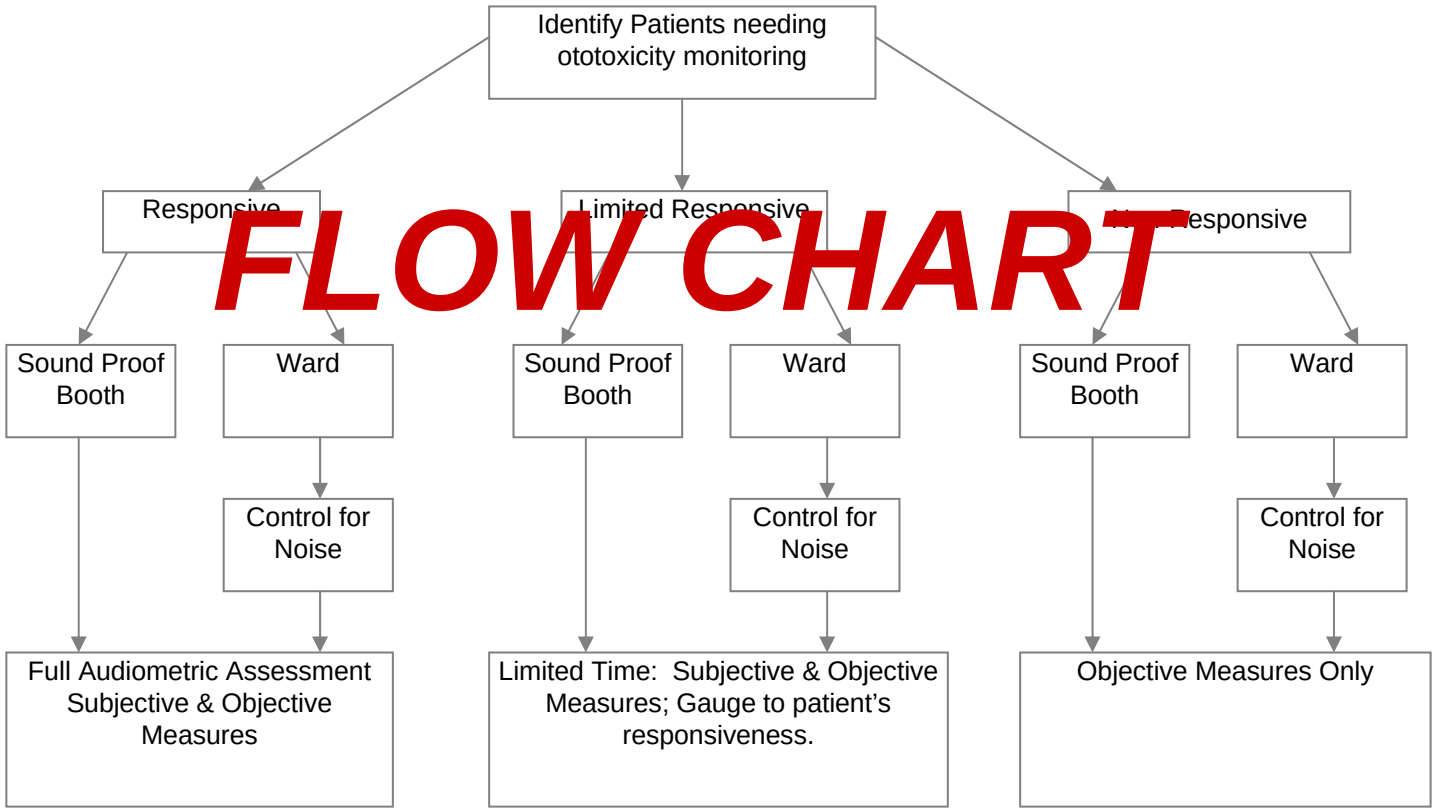
- Patient population differences
  - Different risk factors
- Methodological differences
  - Established baseline
  - Criteria
  - Frequency range tested for hearing change
- No standard monitoring techniques

Evaluation Tools

- Pure-tone thresholds
  - near upper frequency hearing limit (e.g., ultra-high frequency audiometry)
- Otoacoustic Emissions
- HF Auditory Brainstem Responses

Tests sensitive to damage at high-frequencies provide earliest detection (Fausti et al., 1999; Ress et al., 1999)

Testing Protocol



Baseline Evaluation

(1) Case history, family history of ototoxicity, noise exposure and tinnitus history
(2) Otoscopy
(3) Tympanometry
(4) Pure-tone AC thresholds 0.5 to upper frequency limit
(5) Identification of uppermost frequency with a threshold of ≤ 100dB SPL followed by the adjacent six lower frequencies in 1/6th octave steps (SRO re: Fausti et al., 1999)
(6) DPOAEs
(7) Vestibular testing, visual acuity

Baseline Re-Check

- Repeated pure-tone thresholds within 24 hours or as soon as possible, to determine intersession reliability
- If test-retest differences exceeded 5 dB, signals importance of cross-check.

Monitor Evaluations

- CDDP and Carbo subjects tested w/in 24 hours of each dose
- AMG and Control subjects monitored every 2 to 3 days throughout treatment course.

Post-Treatment Evaluations

- ASAP following treatment cessation, and at one, three, and six months following treatments
- Same procedures used as for baseline evaluations

Criteria for Hearing Change

- Always referenced to baseline measures
- Criteria from ASHA 1994 guidelines:
  - (1) $\geq$ 20 dB change at any one test frequency
  - (2) $\geq$ 10 dB change at any two consecutive test frequencies
  - (3) loss of response at three consecutive test frequencies where responses were previously obtained.
  - Hearing change by any of these criteria was confirmed by retest

ASHA Change Criteria

- Normal variability in pure-tone thresholds occurs at random frequencies
- Threshold shifts at adjacent test frequencies indicate more systematic change (Atherly, 1963; Dobie, 1983)
- Threshold shifts on repeated tests are also a stronger indication of a true threshold change (Royster & Royster, 1982)

EHF Sensitivity

- High- to low- frequency progression
- High-frequency testing is reliable (Fausti et al., 1998; Frank, 1990; Frank & Driesbach, 1991; Gordon et al., under review)
- Studies have shown the efficacy of high-frequency monitoring (Dreschler et al., 1989; Fausti et al. 1984; Jacobson et al., 1969; Ress et al., 1999; Tange et al., 1985; Van der Hulst et al., 1988; Fausti et al., 1993; Fausti et al., 1994)
- Studies have shown testing in 1/6-octave intervals provides earlier detection (Fausti et al., 2003; Vaughan et al., 2003)
- Individualized protocols targeting the *highest frequencies* a person can hear

Problems: EHF Testing

- There are no normative high-frequency sensitivity (i.e. threshold) standards due to lack of standardization in
  - calibration,
  - instrumentation,
  - and methodological procedures

Fausti SA, Frey RH, Rappaport BZ, Schechter MA. High-frequency audiometry with an earphone transducer. Sem Hear 1985;6:347-357

Problems: EHF Testing

- There is a high degree of inter-subject threshold variability in high frequency sensitivity
  - Threshold variability increases with age (in elderly) and with higher test frequencies

Schechter MA, Fausti SA, Rappaport BZ, Frey RH. Age categorization of high-frequency auditory threshold data. J Acoust Soc Am 1986;79:767-771.

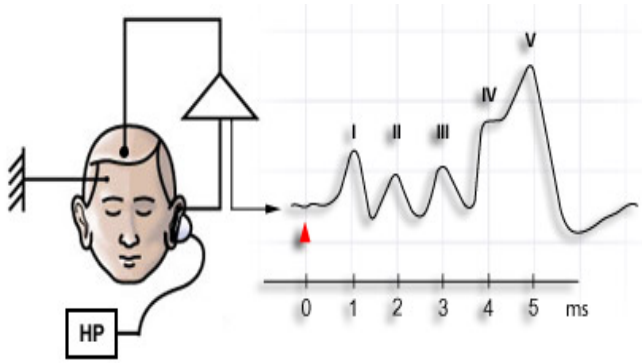
Matthews LJ, Lee FS, Mills JH, Dubno JR. Extended high-frequency thresholds in older adults. J Speech Lang Hear Res 1997;40:208-214.

Does it Matter for Monitoring?

- The key to serial monitoring is intrasubject (test-retest) **reliability**
- High-frequency test-retest threshold variability is within a clinically acceptable range ($\pm$ 10 dB)
- As a result, monitoring near individual's high-frequency hearing limit is effective

ABR Sensitivity

- Elongation of latency and/or disappearance of click-evoked wave V following administratior of ototoxic drugs



- Ultra-high frequency tone bursts (8-14 kHz) more sensitive than clicks
  - Sensitivity was 84% in Fausti et al., 1992
  - Latency changes found
  - However, 60% of all initial changes were from scorable at baseline to non-scorable

Problem: Frequency Specificity

- Two problems at high stimulus levels
  - Increased spectral splatter (stimulus energy spreads)
  - Response could be due to tails of off-frequency neurons
- Pertains to all measures of auditory function with all kinds of stimuli
  - e.g., evoked potentials, behavioral measures
  - Clicks, tone bursts, pure tones

Problem:
Change Criteria

- No broadly accepted ABR latency change criteria
- In veterans receiving cisplatin, shift of 0.3 ms for wave I or wave V or change of a previously scoreable response to non-scoreable was used

  (Fausti et al., 1992)

ABR Advantages

- Good test-retest reliability
- Can be performed at bedside
- Can estimate thresholds (magnitude of ototoxicity-induced hearing loss)
- Can obtain in patients with substantial pre-existing hearing loss (up to severe to profound)

ABR Disadvantages

- Time consuming
- Limited frequency specificity (depending on how performed)
- Limited high-frequency output
- Response interpretation at high frequencies
- Subject noise, hearing loss may preclude measurement
- Infants & children may require sedation

OAE Sensitivity

- Link between ototoxic DPOAE changes and OHC changes (for review see Whitehead et al., 1996)
- Conventional audiometric changes occurred later relative to OAE, or not at all (AMG: Katbamna et al., 1999; Stravroulaki et al., 2002; Mulheran & Degg, 1997; CDDP: Ress et al., 1999)
- Compared to behavioral testing within the high frequency (> 8000 Hz) range, DPOAEs showed effects of ototoxicity in similar proportion of ears (Ress et al., 1999)

Problems: Change Criteria

- ≥ 6 dB change
  - Based on test-retest variability in normal subjects
  - 6 dB change was more than variability in about 95% of subjects tested--so likely to be real change
  - Confirm by re-test to decrease false positive rates
  - Change at two adjacent frequencies would decrease false positive rates
  - Verify YOUR own test-retest reliability

DPOAE Advantages

- Earliest ototoxicity detection
- Frequency specific and can measure over a wide frequency range
- Good test-retest reliability
- Rapid
- Can be performed at bedside

DPOAE Disadvantages

- Limited high-frequency (> 6 kHz) measurements
- DPOAE amplitudes linked to hearing sensitivity only for losses < 50-60 dB
- Pre-existing hearing loss may preclude measurable responses at baseline
- Depends on normal middle ear function

Monitoring for Vestibular System Ototoxicity

Jaynee A. Handelsman, Ph.D.
Vestibular Testing Center
University of Michigan Health System

Early Observations of Bilateral Vestibular System Disorders

- James first reported “sense of dizziness” in deaf-mutes in 1882
- failure to experience vertigo following rotation
- loss of orientation under water
- failure to experience “seasickness” when exposed to rough weather at sea
- approximately 50% of deaf-mute patients had deficient equilibrium function

Early Observations of Bilateral Vestibular System Disorders

- Barany (1907) reported reduced caloric and rotational-induced nystagmus in deaf-mutes
- At first it appeared as if there were no clinical (functional) differences between subjects with and without vestibular responses
- later studies (1920s and 1930s) revealed permanent absence of past positioning reactions and oscillopsia with bilateral loss

Classic Self Report of J.C.
1952

- 76-day course of streptomycin for treatment of knee sepsis
- Symptoms progressed over a 2-3 day period
- Head movement caused by pulse sufficient to disturb vision without head stabilization
- Instability when trying to ambulate
- Gradually learned to minimize head movements when reading and to use visual and somatosensory information to compensate

Case Report by Minor
1998

- Gradually noticed unsteadiness and disturbed vision over a two month period following a two-week course of gentamicin
- Final gentamicin course occurred after 30 days of induction chemotherapy and pre-chemo treatment with vancomycin, ciprofloxin, and a 3-week course of gentamicin
- This case represents a more delayed and gradual onset of symptoms than was the case with J.C.

Two Most Common Causes of Acquired Bilateral Vestibulopathy

- Vestibular Ototoxicity
- Idiopathic vestibulopathy

Factors Determining Individual Vestibulotoxicity

- Individual tolerance
- Impaired renal function
- Hyperthermia
- Prior or concomitant exposure to other ototoxic agents
- Dosing strategy perhaps, although recent evidence suggests this might not be the case
- Aging

Aminoglycosides

- Selective cochlear and/or vestibular toxic agents
- Readily absorbed from intramuscular and subcutaneous sites; poorly absorbed from intestinal tract
- From blood, about 50% is excreted unchanged in 24 hours
- With renal insufficiency, blood levels may remain high for many days
- Distributed to all extra-cellular fluids (e.g. endolymph and perilymph)

Most Vestibulotoxic Aminoglycosides in Humans

- gentamicin
- steptomycin
- tobramycin

Mechanisms of Ototoxicity

- It appears that ototoxicity is not caused by accumulation of the substance in the ear
- Rather, it appears to be caused by the drug's penetration into compartments from which the half-life of distribution is extremely long
- Likely results from rapid uptake, early saturation, and long exposure of the inner-ear tissues to the drug

Gentamicin Ototoxicity

- Caused by a metabolized or “activated” form of the drug
- Activation may result from formation of an iron-gentamicin complex that produces toxic free radicals

Future Outlook: Protective Drugs May Limit Aminoglycoside and Cisplatin-induced Ototoxicity

- antibiotic fosfomycin may compete with aminoglycosides for reactive sites on the hair cell membrane, thereby reducing intracellular aminoglycoside accumulation
- other drugs studied in animals include glucarolactam, sodium thiosulfate, cepharanthine, and poly-l-aspartic acid
- antioxidants shown to be protective in animals

Terms Used to Discuss Vestibular Dysfunction

- Vertigo – the sensation of movement of self or environment without movement
  - Objective – environment
  - Subjective - self
- Oscillopsia
- Disequilibrium
- Unsteadiness, ataxic gait
- Dizziness

Signs of Acute Bilateral Vestibular Loss

- ataxia of gait
- ataxia of stance
- saccadic eye movements with rapid head turning
- changes in visual acuity with head shaking or nodding

Symptoms of Bilateral Loss

- Oscillopsia – an illusory movement of viewed stationary objects or surrounds occurring with head movement

- Gait ataxia – uncoordinated wide-based gait that is commonly associated with a variety of disorders including cerebellar disease and bilateral peripheral vestibular loss

Vestibular System is Responsible for Sensing and Controlling Motion

- Receptors located within the labyrinth of each inner ear transduce information about angular and linear acceleration as well as gravity
- Information combined with visual and somatosensory signals on neurons in vestibular nuclei
- Integration of sensory signals produces information required to control vestibulo-ocular reflex (VOR) and the vestibulo-spinal reflex (VSR)

Responsibilities of VOR and VSR

- VOR facilitates maintenance of binocular fixation, thereby stabilizing gaze during rapid, short-duration head movements
- Reflexes move the eyes in the correct direction and by the precise angle required to offset the effects of head movements
- VSR enables person to maintain desired head and body positions with respect to gravity, even following imposed movement of the head or trunk

Explanation of Symptoms

- Oscillopsia is a direct result of the loss of the VOR, which is responsible for maintaining foveal vision when the head is moving, especially at relatively high speeds
- Quick movements of the head are associated with saccadic gaze readjustments rather than smooth compensatory eye movements
- Ataxic gait is due to loss of vestibular input and the need to rely on visual and proprioceptive information for maintenance of postural control

Onset May be Acute or Insidious

- dramatic onset of severe imbalance and loss of orientation in space
- vertigo
- illusion of tilting

- slowly increasing unsteadiness of gait and imbalance
- oscillopsia
- frequent use of contact cues in darkness or when walking on uneven ground

Disequilibrium Associated with Bilateral Loss

- The sensation of being off balance, perhaps even when lying down

- When the loss occurs during the course of a long illness, patients may be unaware of balance problems until they get out of bed, and then it may be attributed to weakness

Oscillopsia Associated with Bilateral Vestibular Loss

- It is a bi-directional to-and-fro and up-and down illusory movement along the same axis as head movement but in opposite direction
- typically occurs during rapid, not slow, head movement because visual pursuit provides retinal stabilization for slow movements
- Reading while walking or riding in a car is impossible
- Walking downstairs, jumping, running, head shaking or nodding produce severe reactions

Factors Determining Oscillopsia in Bilateral Vestibular Loss

- age at onset
- severity of semicircular canal dysfunction
- extent of otolithic dysfunction
- individual compensatory faculties

Reasons to Monitor Cochlear and Vestibular Function

- Cochlear function is affected by almost all aminoglycosides
- Even slight ototoxic cochlear dysfunction is noticeable, particularly via high frequency audiometry and otoacoustic emissions
- Slowly progressive vestibular dysfunction may go undetected for some time
- Vestibular ototoxicity is variable in terms of onset and progression
  - Typically bilateral involvement
  - Unilateral involvement possible

Laboratory Tests for Monitoring Vestibular Ototoxicity

- Dynamic visual acuity testing
- Caloric testing
- Rotational testing
- Dynamic posturography

Bedside Tests of Vestibular Function

- Head thrust
- Testing of dynamic visual acuity
- Romberg, tandem walking, stepping tests
- Rapid full-body turns
- Response to external perturbations

Laboratory Diagnosis of Bilateral Vestibular Loss

- Absence or reduction of caloric responses, providing physical and technical problems ruled out
- Abnormal gain and time constant for impulsive rotary testing for post-rotary nystagmus
- Breakdown of nystagmus gain and phase for sinusoidal rotational testing

Response Pattern for Partial Vestibular Loss

- Symmetrically decreased VOR gain and increased phase leads at low frequencies (≤.16 Hz)
- Normal phase and gain at high frequencies (≥.32 Hz)
- May or may not have gait imbalance
- Good high frequency gain is important to maintenance of gaze stability

Rotational Testing Has Value

- Caloric testing evaluates only very low frequency function ($\leq$.003 Hz)
- Rotational testing tests mid- to high frequency function (.01-.32 Hz)
- Testing the VOR at lowest rotational frequencies may provide early signs of vestibular dysfunction (e.g. due to aminoglycoside toxicity)

Unilateral Involvement

- Significant unilateral weakness in caloric testing
- Increased phase leads in rotational testing
- During the acute phase, might have spontaneous nystagmus and asymmetries in rotational testing
- Patient more likely to describe vertigo and unsteadiness, although oscillopsia is possible

Dynamic Posturography

- Useful for quantifying ataxia
- Useful for evaluating patient's ability to use visual and proprioceptive information to maintain postural stability following bilateral loss of vestibular function
- Is not an electrophysiological measure of vestibular function

Given Limited Time of Patient Cooperation

- Otoacoustic emissions (can be done bedside without any patient input, provided patient has normal middle ear function)
- Rotational testing (patient must be transportable, alert, and without IV)
- Dynamic visual acuity testing

Vestibular Rehabilitation is Effective in Aiding Patients with Bilateral Vestibular Loss

- Therapy aimed at fostering the substitution of visual and somatosensory cues for lost vestibular function
- Gaze stabilization exercises
- Balance retraining exercises

Adaptive and Compensatory Mechanisms Involved in Stabilization of Eye Movements

- Adaptation of saccadic eye and head movement
- Use of neck and other somatosensory afferents
- Enhanced eye tracking
- Centrally preprogrammed eye movements
- Central suppression of undesired image movement across the retina

Functional Adaptations Build within One Year

- Gaze stabilization most improved through centrally preprogrammed slow eye movements during active (predictable) head movement
- During unpredictable head movements, cervico-ocular reflexes and increased fixation may yield best stabilization
- Strongest suppression of oscillopsia achieved by central adaptive rearrangements

Compensatory Mechanisms Effective in Suppressing Oscillopsia

- Only one third of adult patients with acquired bilateral vestibular loss of function suffer from permanent oscillopsia
- This underlines the paramount biological importance of maintaining clear vision during locomotion

Roles of Vision and Propriception

- Patients are able to use vision and somatosensory input to maintain postural control in the absence of vestibular function
- When circumstance prevent their use (e.g. in darkness or when walking on uneven or compressible surfaces), gait ataxia persists for almost every patient

Bilateral Vestibular Loss - Practical Implications

- Oscillopsia, which results in visual blurring or “bobbling” - may prevent patients from driving, or even walking unassisted
- Because patients rely on vision and proprioception to maintain postural control while ambulating, darkness combined with compressible or uneven support surfaces result in increase risk of falling

At- Risk Populations

- Diabetic patients may be more profoundly affected by bilateral vestibular loss due to concurrent loss of vision and proprioception
- Renal patients are more susceptible to aminoglycoside ototoxicity because drugs are metabolized by the kidneys
- Dialysis patients are frequently at increased risk of infection, and may be more likely to have repeated exposure to aminoglycosides

Vestibular Rehabilitation - The Good News

- Research supports the fact that responses of a partially functioning vestibular system can be modified
- For patients with some residual function, VR is focused on optimizing the use of the remaining VOR, as well as increasing the effectiveness of the COR
- For all patients with bilateral vestibular loss, increasing the use of vision and proprioception is a goal

Variables Affecting Therapy Outcome

- Extent of the vestibular loss
- The presence of coexisting disease that may impact sensory system function
- Overall patient heath and fitness
- Patient motivation and compliance with program

Summary

- Ototoxicity not only relates to hearing, but to vestibular system function
- Bilateral vestibular loss can be devastating, causing ataxia and oscillopsia
- Unilateral loss is possible as well
- There is a need to monitor closely patients at risk for vestibular loss
- Vestibular rehabilitation is a useful too, and should be considered in all cases of uncompensated vestibular system involvement

Questions…