

Bilateral Vestibular Loss

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Learning Objectives

- Learn how to recognize bilateral vestibular loss
- Learn treatment of bilateral vestibular loss

Bilateral Vestibular Loss

A stewardess developed a toe-nail infection. She underwent course of gentamicin and vancomycin. 12 days after starting therapy she developed imbalance. 21 days after starting, she was "staggering like a drunk person". Meclizine was prescribed. Gentamicin was stopped on day 29. One year later, the patient had persistent imbalance, visual symptoms, and had not returned to work. Hearing is normal. She unsuccessfully sued her doctor for malpractice.

Diagnosis of vestibulotoxicity is usually easy

- History of recent course of IV antibiotic
- Eyes closed tandem Romberg is failed
- Dynamic illegible 'E' test (DIE) failed
- Ophthalmoscope test failed
- ENG and Rotatory chair confirm diagnosis (you will need this when you give your deposition).

SYMPTOMS OF BILATERAL VESTIBULAR LOSS

- OSCILLOPSIA
- ATAXIA



Eyes closed tandem Romberg test is failed. →

Romberg Testing: a gradient of difficulty.

- Eyes Closed Tandem Romberg (6 seconds)
- Eyes Open Tandem Romberg
- Eyes Closed Regular Romberg
- Eyes Open Regular Romberg

Bilateral loss patients will all fail ECTR.

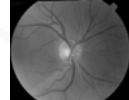
Dynamic Illegible 'E' test (DIE test) is failed

- Distance vision with head still
- Distance vision with head moving
- Normal: 0-2 lines change.
- Abnormal: 4-7 lines change



OPHTHALMOSCOPE TEST

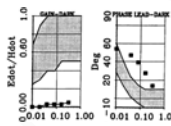
- Gently oscillate head side to side at greater than 1 hz while viewing the optic disk
- Optic disk may appear stable (normal) or move (abnormal)
- Acutely, all patients with bilateral vestibular loss will fail this test
- Chronically, some patients will pass (because high-frequency VOR recovers)



Patient should wear habitual spectacles

DIAGNOSIS Continued

- ENG and Rotatory chair to confirm diagnosis (you will need this when you give your deposition).



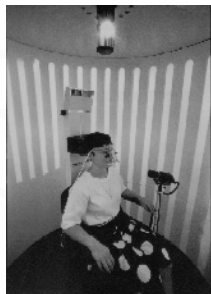
ENG testing should show

- Reduced total response to water (< 20), often 0
- No response to ice water
- Tests only low-frequency VOR

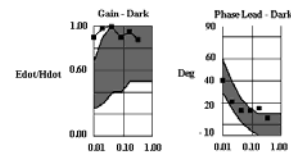
(of course, ENG does not test vertical canals or otoliths)

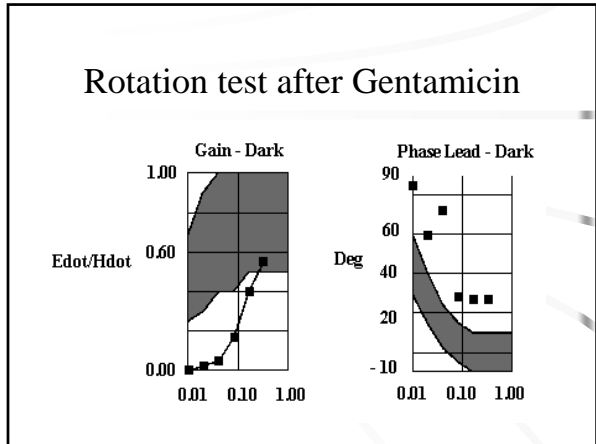
Rotation testing is the gold standard for vestibulotoxicity

- Tests both ears
- Tests high and low frequencies
- Probably more sensitive than calorics
- Does not test vertical canals or otoliths



Normal Rotation Test





Bilateral Vestibular Loss Causes:

- Ototoxicity !
- Bilateral forms of unilateral disorders (e.g. bilateral vestib neuritis)
- Congenital (e.g. Mondini malformation)
- idiopathic

N=43, NMH 1990-1998

Aminoglycosides

- General Structure – amino sugar bound by glycosidic linkage to a central hexose nucleus

$C_1: C_{21}H_{43}N_5O_7$

Things you need to know

About 3% of hospital admissions involve aminoglycoside antibiotics.

- The aminoglycosides are all ototoxic and nephrotoxic
- They build up in the ear over long periods of time.
- Some people are genetically predisposed to get aminoglycoside toxicity.
- Aminoglycoside ototoxicity is potentiated by several other commonly used medications

Aminoglycoside Toxicity: Specific agents

High Vestibulotoxicity ↑

- Streptomycin
- Gentamicin
- Tobramycin
- Neomycin
- Kanamycin
- Amikacin

↓ High Cochleotoxicity

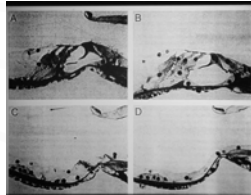
Aminoglycoside ototoxicity

Cochleotoxicity
Related to number of free amino (-NH2) groups
Neomycin, kanamycin

Vestibulotoxicity
Related to number of free methylamine groups (-NHCH3)
Streptomycin, gentamicin

Aminoglycoside pathology

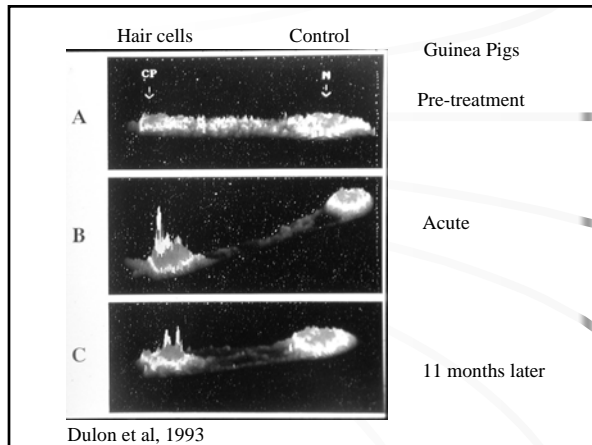
- Vestibular damage occurs first in the crista of the semicircular canals and then extends to the saccule and utricle.
- Pathologically there is hair cell loss.



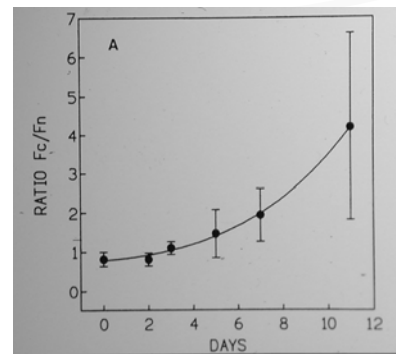
Aminoglycosides: Pharmacokinetics are different in the ear than blood

- All aminoglycosides have roughly a 2 hour serum half-life in persons with normal renal function¹
- IV gentamicin in humans rapidly transfers from serum to inner ear (5 minutes)²
- Inner ear levels build up over days and persist for months²

- Edson et al, 1991
- Becvarovski et al, 2002
- Dulon et al, 1993

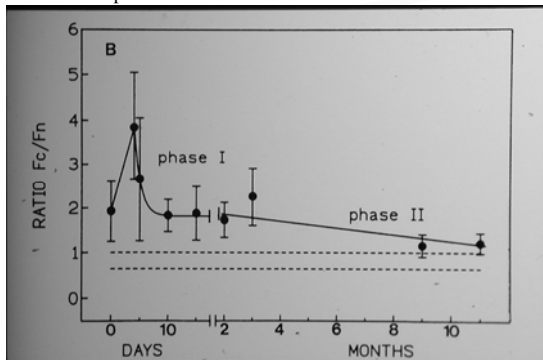


Gentamicin builds up in the inner ear (Guinea pigs)



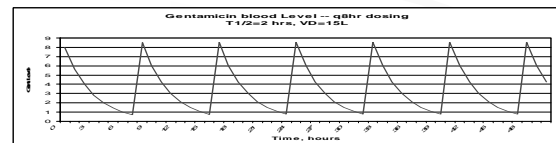
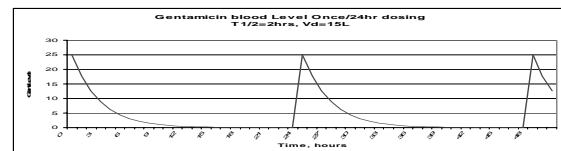
Dulon et al, 1993

Gentamicin persists in the inner ear for months



Dulon et al, 1993

Different peaks, same toxicity



Aminoglycoside pharmacokinetics Implications

- High serum "peak" levels are not necessarily correlated with ototoxicity because drug bound to the inner ear gradually builds up over weeks and is eliminated very slowly. Contemporary regimens use single doses every day or other day (with very high peak levels).
- Ototoxicity can occur with normal levels (prolonged doses)

▪ Yee GC, Evans WE. 1981, Nicolau et al. 1995, Barza M, Lauermann M. 1978

Genetic Susceptibility

- Mutation of 12S rRNA makes the region homologous to that which is involved in aminoglycoside binding in bacterial rRNA
- Three Chinese and two Japanese pedigrees with aminoglycoside otosensitivity had A to G mutations.
- 17% of persons with hearing loss after systemic aminoglycoside exposure had this mutation.

Fischel-Ghodsian et al, 1997

MEDICATIONS WHICH POTENTIATE AMINOGLYCOSIDE OTOTOXICITY

- VANCOMYCIN
- LOOP DIURETICS
- CIS-PLATINUM
- METRONIDAZOLE

Other ototoxins

- Loop diuretics (hearing only)
- Anti-neoplastic agents (hearing mainly)
- Organic solvents (very rare)

Prognosis of vestibulotoxicity

- Hair cells don't regrow (in humans)
- Vestibular damage may progress for months after drug is stopped (because drug is bound to inner ear for months)
- Rule of thumb – 6 months damage is complete
- High-frequency VOR nearly always eventually recover (which reduces oscillopsia)

Aminoglycoside Vestibulotoxicity

- Streptomycin
- Gentamicin
- Tobramycin
- Kanamycin
- Amikacin
- Neomycin



Begg EJ, Barclay ML. Aminoglycosides—50 years on. Br. J. Clin Pharm 39, 597-603, 1995

Streptomycin vestibulotoxicity

- Streptomycin is mainly vestibulotoxic
- 15% of patients treated with 1g of Streptomycin daily for tuberculosis developed vestibulotoxicity (Bignall et al, 1951).
- Hearing disturbance is an uncommon complication of systemic streptomycin

Gentamicin vestibulotoxicity

- Gentamicin is a mainly a vestibulotoxin.
 - About 2-10% of IV courses of Gentamicin result in ototoxicity (usually mild cochleotoxicity). Nobody knows the exact incidence of vestibulotoxicity (probably higher)
 - Gentamicin solution is used to purposefully ablate vestibular function in Meniere's disease.

Neomycin vestibulotoxicity (Cortisporin, Coly-mycin S) Amikacin

- Vestibulotoxicity of Neomycin is thought to be minor, as is Amikacin
- Cochleotoxicity is substantial (more discussion later)

Tobramycin vestibulotoxicity

- Tobramycin is only mildly ototoxic systemically. It is significantly less vestibulotoxic than gentamicin (Prazma et al, 1981; Israel et al, 1976)

Treatment of Bilateral Vestibular Loss

- Avoidance of ototoxins
- Physical Therapy



Prevention

- Use non-ototoxic antibiotics
- Avoid potentiating agents (e.g. loop diuretics, Vancomycin)
- Consider pharmacokinetics of inner ear buildup carefully

Bedside Monitoring (?)

- High frequency audiometry (Fausti, 1992).
- OAE –Reduction in TEOAE found in amikacin treated patients(Holtz, 1994) and gentamicin(Stavroulaki 1999).
- Tinnitus
- DIE test ?

Ameliorating agents

- In theory, antioxidants/Iron chelators
- Intratympanic steroids prior to administration may be protective (in animals)

Wu, Sha and Schacht, 2002

Himeno et al, 2002

Question #2

- A man says he can't see when his head is moving. Hearing is normal. He has had two severe spells of vertigo in his life.
- The most likely diagnosis is:
 1. Bilateral vestibular neuritis
 2. Gentamicin ototoxicity
 3. BPPV

Answer #2

- The most likely diagnosis is Bilateral vestibular neuritis

Bilateral sequential vestibular neuritis presents with two bouts of vertigo, separated in time. A clue is that while horizontal canal function is absent, the inferior division (posterior canal, saccule) generally continues to function – patient can have BPPV.

Summary

- The signs of bilateral vestibular loss are ataxia and oscillopsia.
- Aminoglycoside antibiotics cause most bilateral loss
- Prevention is the best treatment -- avoid ototoxins when possible, use for short times.
- Vestibular rehabilitation is indicated in all patients with bilateral loss