Vestibulotoxicity

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Learner Outcomes

- After this course, participants will be able to identify and describe the various agents known to cause Vestibulotoxicity,including their mechanism of action and the differential impact on cochlear versus vestibular toxicity.
- After this course, participants will be able to describe a comprehensive assessment of patients presenting with symptoms suggestive of Vestibulotoxicity, utilizing audiometry, vestibular function tests, and assessment strategies outlined in the Alder Hey protocol.
- After this course, participants will be able to list vestibular rehabilitation exercises based on specific vestibular function test results, promoting optimal compensation and recovery in individuals affected by Vestibulotoxic agents.

Introduction

Ototoxicity is defined as the temporary or permanent damage caused by chemical or pharmacological agents leading to temporary or permanent dysfunction of the hearing and vestibular mechanisms when ingested or administered in any form

Avicenna(980-1037) recognised the cochleotoxic effects of therapeutic mercury; heavy metal ototoxicity was recognised in 19th century Europe and antibiotic ototoxicity was discovered in the 20th century


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Ototoxic agents

Antibiotics

Drug	Cochlear toxicity	Vestibular toxicity
Gentamycin – *Reversible/permanent*	++ (5-10%)	+++ (15-50%)
Streptomycin - *Permanent*	+	++++
Tobramycin - *Reversible/permanent*	+	+++
Kanamycin - *Reversible/permanent*	++	+
Amikacin - *Reversible/permanent*	+	+
Neomycin - *Reversible/permanent*	+	+++
Netilimycin - *Reversible/permanent*	++	++
Vancomycin, teichoplanin - *Reversible*	Reported	Reported
Tetracycline – minocycline - *Reversible*	Nil	++
Macrolides – erythromycin/azithromycin - *Reversible*	+	Unknown
Quinolones – ciprofloxacin - *Reversible*	Rare	Unknown

Other anti-infective agents

Drug	Cochlear toxicity	Vestibular toxicity
Antivirals – ribavirin+interferon - *permanent*	++ sudden	Unknown
Antifungals - amphotericin	Rare	Unknown
Chloroquine - *Reversible/permanent*	++	++
Mefloquine - *Reversible*	++	++
Primaquine - *Reversible*	+	++
Proguanil - *Reversible*	Nil	++
Quinine - *Reversible/permanent*	++	++
Metronidazole - *Reversible*	Nil	+
Teichoplanin	Reported	Unknown

Anti cancer agents

Drug	Cochlear toxicity	Vestibular toxicity
Cisplatin - *permanent*	+++ (upto 70%)	++ (upto 20%)
Carboplatin - *permanent*	++	+++
Vinca alkaloids - *permanent*	+	+
Nitrogen mustard - *permanent*	+	+
Cyclophosphamide	Reported	Unknown
Doxorubicin	Reported	Unknown
Bleomycin	Reported	Unknown
Fluorouracil	Reported	Unknown

Other agents

Drug	Cochlear toxicity	Vestibular toxicity
Diuretics – Frusemide, Bumetanide, Ethacrynic acid – *reversible/permanent*	+(0.7% - 7%)	+
NSAID – Aspirin group – *reversible and only on high doses*	++	Unknown
Phenytoin - *reversible*	Nil	+
Immune therapy agents – interferon, anti TNF - *permanent*	+	+
Desferreoxamine	++	Unknown
Heavy metals	++	+
Sodium Valproate	Reported	Unknown
Amiodarone	Unknown	Reported
Industrial agents – Toluene, Styrene, Xylene, Trichloroethylene, Ethyl benzene	Reported	Reported

Intracranial radiation and vestibular damage

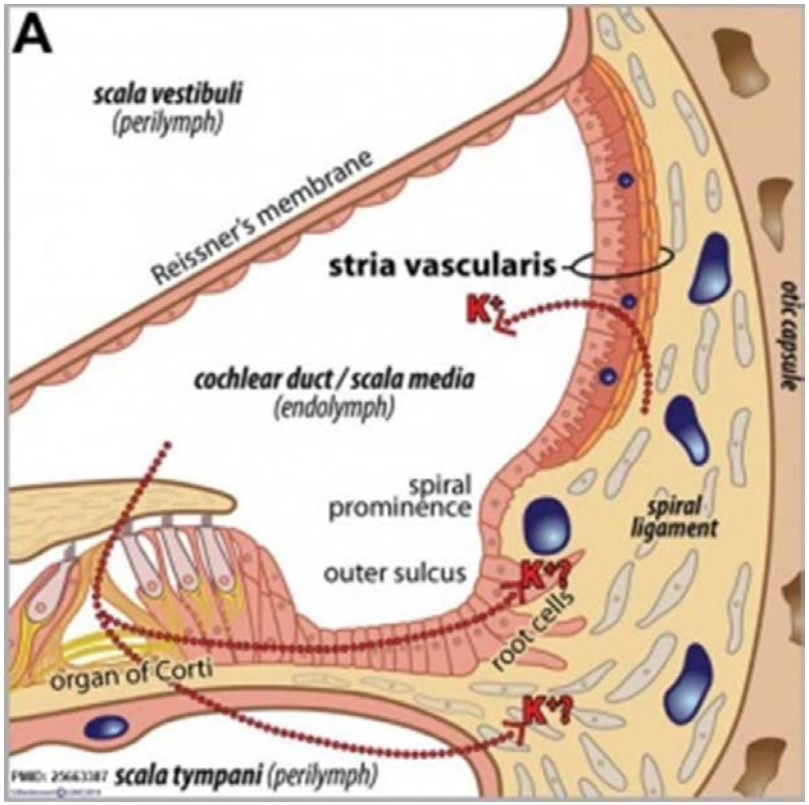
- Traditional photon therapy for intracranial, facial or otologic tumours generate subjective dizziness in 20% and objective vestibular derangement in 44% but the majority are asymptomatic due to compensation
- Proton beam therapy and vestibular damage has not been studied
- Radiation causes radio osteonecrosis of the labyrinth leading to labyrinthitis ossificans or canal dehiscence
- May manifest any time withing 5 years post treatment for activation of damage induced decompensation
- Usually unilateral

Mechanism of action

- All cochleotoxic drugs are potentially vestibulotoxic
- Ionic transport for transduction of kinetic energy to action potential is enzymatically driven in the hair cells of both the cochlea and the vestibule
- These processes follow a biochemical cascade that are interfered with by drug molecules eventually leading to cell apoptosis and loss of function
- The assault if crosses the human asymptote leads to irreversible damage

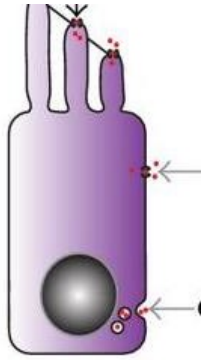
Pharmacokinetics and distribution

- Routes of administration
    - Intravenous
    - Intramuscular
    - Oral
    - Topical
    - Intrathecal
- Routes of entry to the inner ear
    - Crossing blood ear barrier
    - Secreted into perilymph by spiral ligament arteries
    - Secreted into endolymph by stria vascularis
    - Through round window when topical
    - Through CSF when intrathecal


A
scala vestibuli
(perilymph)
Reissner's membrane
stria vascularis
K+
cochlear duct / scala media
(endolymph)
spiral
prominence
outer sulcus
spiral
ligament
otic capsule
root cells
organ of Corti
K+?
K+?
scala tympani (perilymph)

Pathological alterations

- Interfere with ionic transport of the endolymph and change the endolymphatic potential
- Direct vessel changes in the stria vascularis leading to strial atrophy
- Direct entry into the hair cells causing cell death
- Diuretics alter ionic transport more significantly than other agents as the kidneys and the cochlea share enzymatically driven ionic transport
- NSAID inhibit enzymes in lipid cell wall of OHC
- Possible antegrade degeneration of the auditory nerve



- Molecules enter the vestibular hair cell through mechano-tranducer receptors and by endocytosis causing a biomechanical cascade responsible for cell death; supporting cells may also be affected
- Spiral ganglions may be affected
- In the vestibule, the type 1 cells are mainly affected
- Dose and possibly genetic dependence

The main cascade of biochemical reactions

Adenosine receptor stimulation + glutamate activity

↓

Protein kinase system activated by NADPH mobilisation

↓

Reactive oxygen species (ROS) generation

↓

Lipid peroxidation in cellular membranes

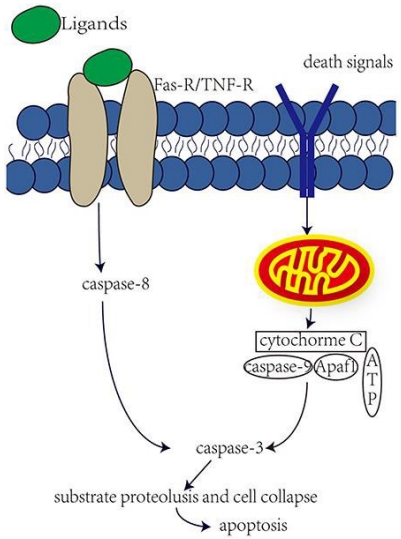
↓

Caspase and calcineurin mediated

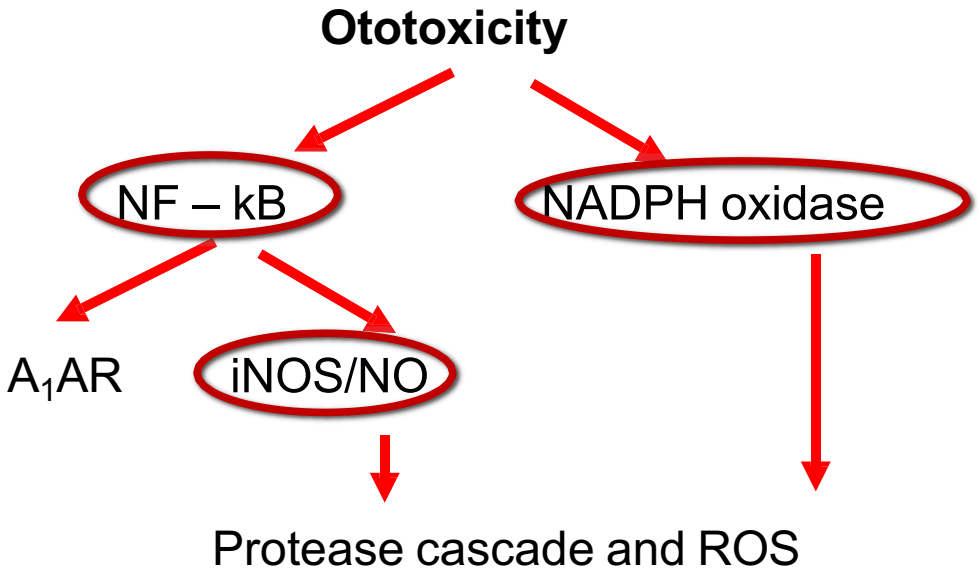
Mitochondrial permeability

↓

Apoptosis and DNA damage



Adenosine receptor activity (Ramkumar et al 2003)



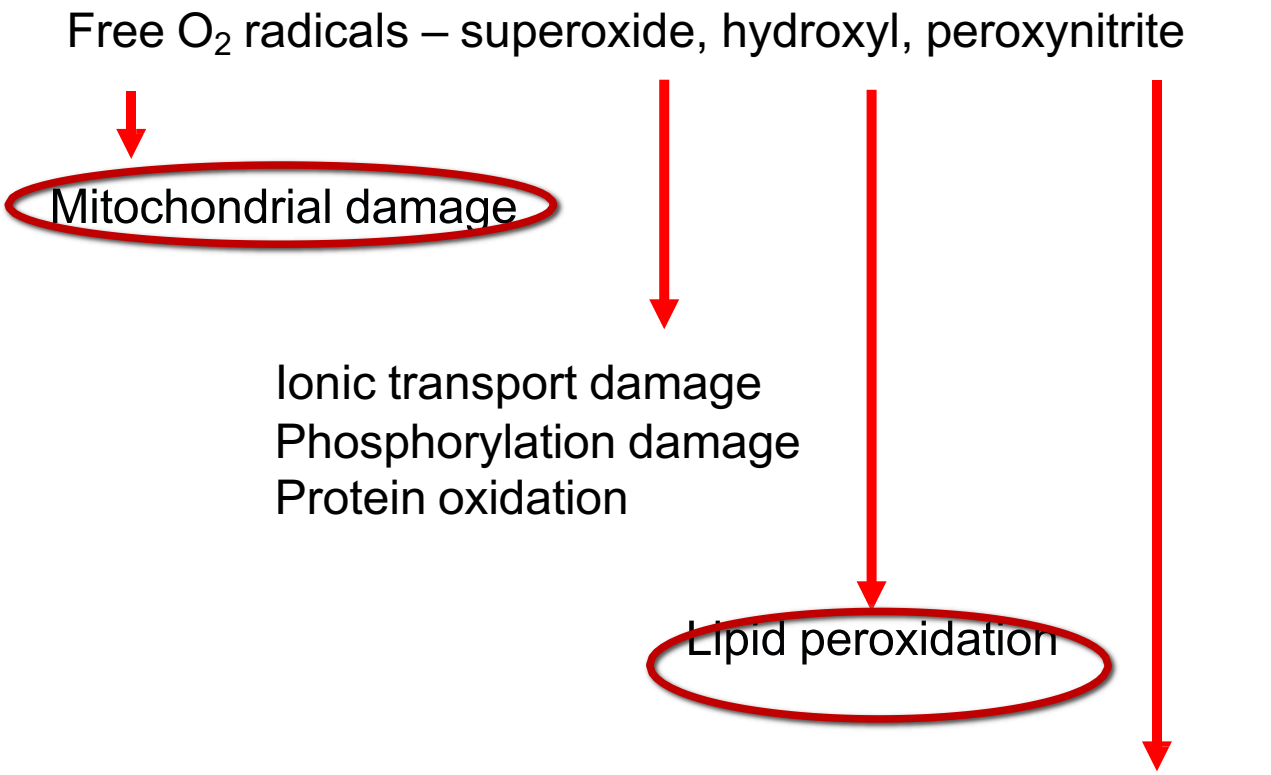
Glutamate excitotoxicity (Puel 1991 et al 1991, Ohinata et al 2002, Jager et al 2000)

Mediated by NMDA and leads to generation of ROS

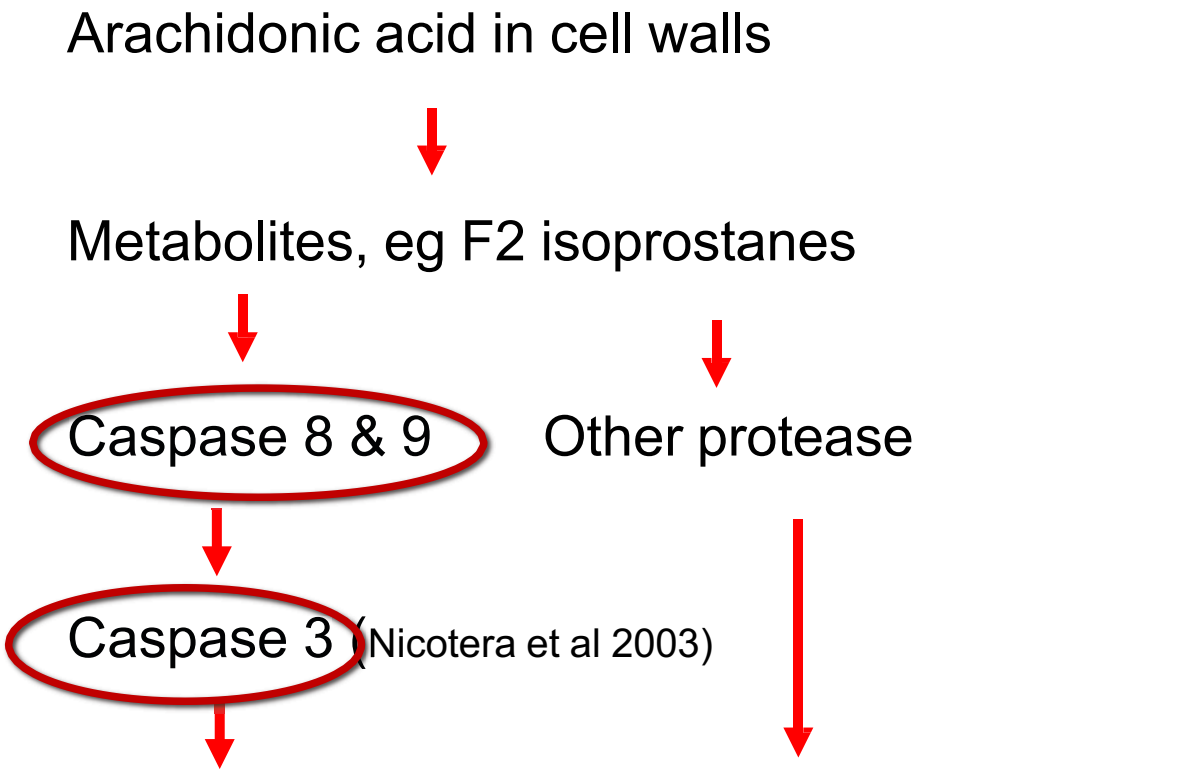
The protein kinase system (Harris et al 2005)

- Src tyrosine kinase signalling cascade
- Integrin; NADPH oxidase and phosphorylation
- c-JunNH_2-terminal kinase (Derijard 1994) initiated apoptosis
- Leads to anoikis and apoptosis via ROS

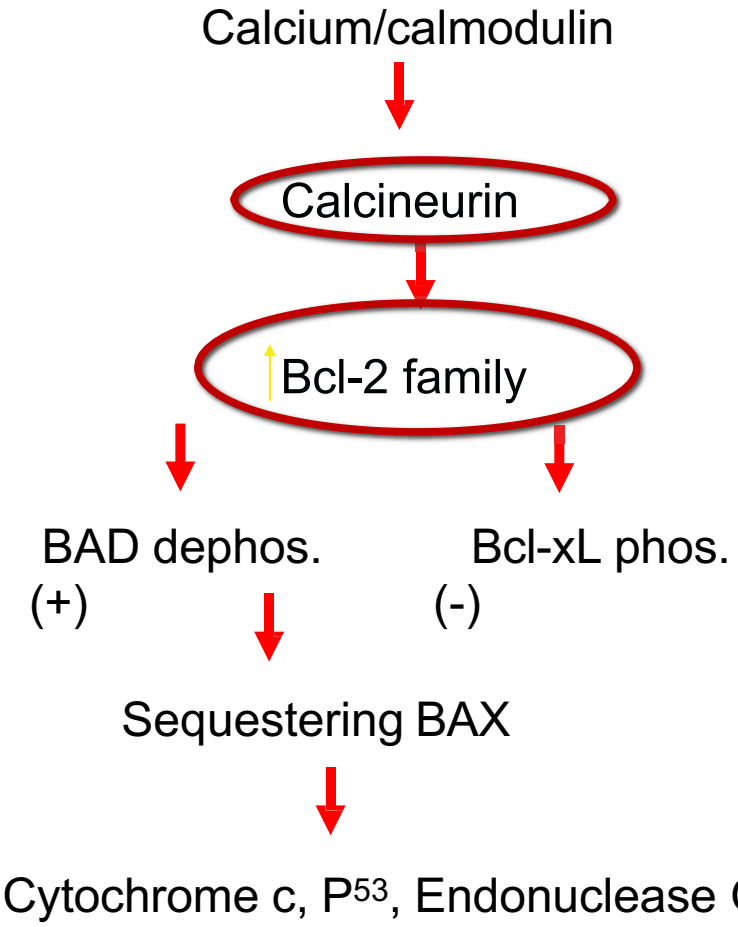
Reactive oxygen species (reviewed by Kopke 1999)



Lipid peroxidation products (Miller 2006)



Mitochondrial changes (Uemaetomari et al 2005, Vicente-Torres and Schacht 2006)



Apoptosis or necrosis? (Hu et al 2000, Yang et al 2004)

- Initial apoptosis

- From day 3, apoptosis and necrosis in equal numbers but missing or lost cells ↑, maximum by day 30

- Unclear data about whether lost cells are due to apoptosis or necrosis

- However statistically proved that apoptosis is the main pathway for missing cells

Risk factors for developing cochleovestibular toxicity

- Genetic susceptibility GST, TPMT and COMT for cisplatin and A 1555 del AG MTRNR1 (17 – 33%); mitochondrial C1494T (0.9 – 1.8%); chromosome 22q13.31 TMRU in aminoglycosides
- Poor nutrition and anaemia
- Renal compromise
- Hypoalbuminemia
- May be dose related
- Extremes of age
- Synergism with other drugs
- Cranial irradiation
- Pre existing hearing losses
- Previous vestibular damage
- Single daily dose regimens

Diagnosis

- Invariably bilateral, therefore disequilibrium, unsteadiness and oscillopsia are main symptoms that are acute, subacute or chronic

- In those with unilateral pre existing vestibular damage for example lateralised vestibular pathology requiring treatment (tumours, Meniere's disease, head injury) present with head movement induced dizziness, vertigo

- Symptoms may occur within a few hours of administration of drug and therefore can be acute or may be late onset in at least 30% due to persistence of vestibulotoxic molecules in the perilymph and the presence of some compensation

- Canal function more affected than otolith function and anterior canals might be spared (greater type 1 cell reserve in otoliths)
- Canal paresis in calorics
- Low VOR gain in rotatory chair
- Low VOR gain in vHIT
- Deranged DVA
- Symmetrical loss of otolith function – VEMP, head heave and ocular counterolling
- Features of asymmetry
- Static and dynamic posturography changes

The acute vestibular event subtype

- Immediate and sudden dependant on dose and genetic suscpetibility
- Acute loss of immobility, imbalance, oscillopsia, vertigo, visual dependence, nausea
- May be ignored as thought to be part of the primary pathology or because of immobility
- Hearing loss is noticed and managed more than a vestibular loss due to a lack of awareness
- Recovers partly within weeks by natural compensation and proceeds to bilateral chronic vestibular dysfunction

Barany criteria for definite bilateral vestibular hypofunction

A. Chronic vestibular syndrome with the following symptoms

1. Unsteadiness when walking or standing1 plus at least one of 2 or 3
2. Movement-induced blurred vision or oscillopsia during walking or quick head/body movements2 and/or
3. Worsening of unsteadiness in darkness and/or on uneven ground

B. No symptoms while sitting or lying down under static conditions

C. Bilaterally reduced or absent angular VOR function documented by vHIT, calorics, chair

D. Not better accounted for by another disease

Diagnostic criteria for probable bilateral vestibulopathy

A. Chronic vestibular syndrome with the following symptoms:
1. Unsteadiness when walking or standing1 plus at least one of 2 or 3
2. Movement-induced blurred vision or oscillopsia during walking or quick head/body movements2 and/or
3. Worsening of unsteadiness in darkness and/or on uneven ground

B. No symptoms while sitting or lying down under static conditions

C. Bilaterally pathological horizontal bedside head impulse test

D. Not better accounted for by another disease

- Audiometry including high frequency when available
- Full set of vestibular function tests and assessment are required in all cases especially the video head impulse test
- Frequency specific vestibular information
- As screening tests, video head impulse test, vestibular evoked myogenic potential test, dynamic visual acuity and clinical test of sensory integration of balance
- Validated psychometric questionnaires – DHI, Berg's Balance Scale including paediatric motor scales

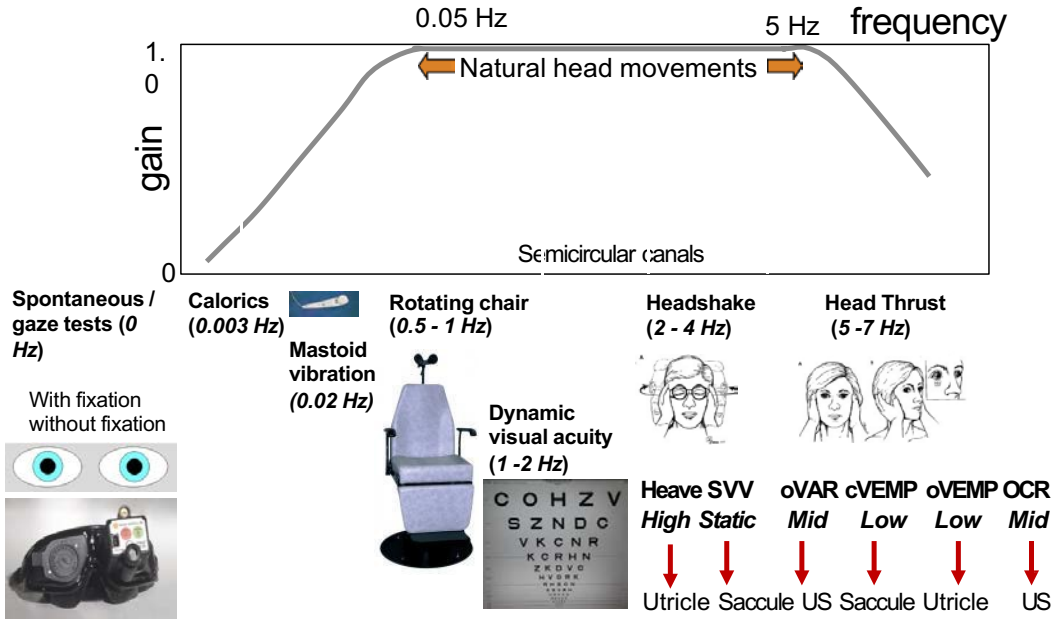
Bedside tests

- The head impulse test
- Dynamic visual acuity test
- Office chair to observe VOR
- Vestibulospinal tests especially Romberg, Unterberger and Fukuda side stepping
- Headshake and subjective visual vertical if asymmterical

Vestibular assessment and vestibular gram

Audiological assessment
- PTA/TYMP/SRT
- OAE/ABR

Ophthalmological assessment
- VA/VF
- Convergence
- Oculomotor
- Ophthalmoscopy

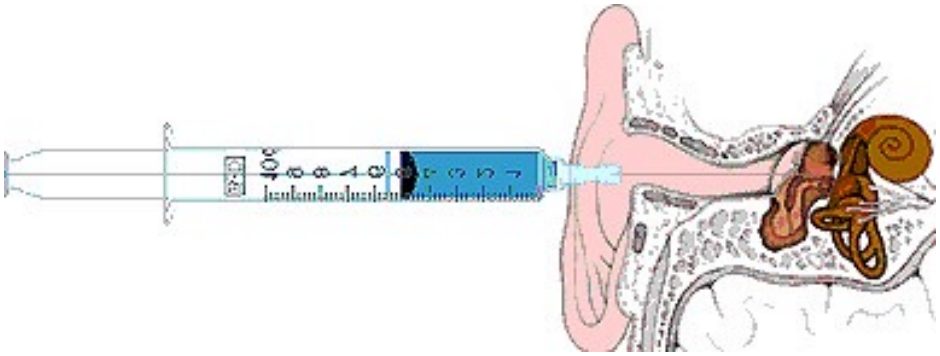


Hyperventilation test
Hennebert's test
fHIT and SHIMP
Static and dynamic posturography

Neurological assessment
- Examination
- Smooth pursuits
- Saccades
- Vertical headshake and perversion
- VOR cancel
- Optokinetic assessment
- Skew deviation
- Caloric disassociation and fixation index
- Oculomotor movements for central signs

Psychometric assessment
- DHI
- Berg

Therapeutic vestibulotoxicity



https://dizziness-and-balance.com/treatment/ttg.html

The vestibulotoxic properties of gentamycin can be used to perform a unilateral medical labyrinthectomy through intratympanic and round window injections of titrated gentamycin in case of Meniere's disease – it is essential that there is reasonable vestibular function on one side

Prevention and management of vestibulotoxicity

Principles of prevention (Fu et al 2021)

- Alternative medication
- Developing ototoxic protective drugs
- Reversing ototoxic induced phenotypes with growth factors
- Genetic screening
- Biomarkers to predict ototoxicity
- Mitigating adverse physical and psychological effects of established ototoxicity

Principles of management

- Diagnosis and explanation
- Prevention
- Monitoring function and titration of drug
- Pharmacological intervention in acute spells with labyrinthine sedatives
- Customised initial vestibular rehabilitation exercises for recalibrating whole system and promote compensation as early as possible for maximal use of cerebral plasticity – usually children compensate well
- Psychological intervention when appropriate
- Correction of visual problems

- Vestibular management is now ***multidisciplinary***
- ***A cognitive approach*** is essential
- ***Pharmacological management*** is recommended to be used ***as a short term measure when absolutely indicated*** for MD, VM and first 3 weeks of an acute vestibular event
- ***Vestibular rehabilitation is now customised*** to frequency specific responses with sensory integration strategies and outcome measured by different tests and psychometric questionnaires – ***it should not be used as a blanket approach***
- ***Balance belt*** is a non invasive device showing good outcome
- ***Vestibular implant*** research is gathering momentum
- ***Virtual reality*** is used to habituate, substitute and adapt to individual needs
- ***Life style changes and situational counselling*** is essential
- ***Music therapy*** has shown promise

Primary prevention

- Often difficult as these medicines are life-saving
- Alternative less toxic agents can be selected and used
- Genetic susceptibility typing
- The use of pharmacological agents to influence the biochemical cascade for upstream and downstream regulation before therapy starts is promising
- Industry regulation of chemicals
- Close multidisciplinary discourse with medical teams responsible for managing the primary pathology

Secondary prevention

- Management of vestibulotoxicity when it occurs soon after administration,
- Can be achieved by adjusting dose and
- Replacing offending agent provided it is a viable decision and drug treatment of symptoms
- Monitoring when therapy starts is a part of primary prevention

Often combined with preventing cochleotoxicity and is a fine clinical decision

Tertiary prevention

- Management of the aftermath of the vestibular damage and directed at type, intensity and disability caused by vestibular damage
- Vestibular rehabilitation
- Device management
- Life style modifications
- Holistic discussion on quality of life and occupation
- Prevention of falls
- Cognitive counselling

Genetic typing for pre therapy intervention

- GST, TPMT and COMT for cisplatin being developed
- A 1555 del AG MTRNR1 (17 – 33%) for aminoglycosides, rapid typing may be available soon
- Mitochondrial C1494T (0.9 – 1.8%) for aminoglycoides
- Chromosome 22q13.31 TMRU in aminoglycosides

Alternative medications

- A clinical decision by the treating clinician that is dependant on patient factors and calculating risk, benefit ratio may be difficult
- When an alternative is not possible, dose regimens, duration and titration of blood levels to assess ototoxicity threshold is mandatory
- Early detection leads to dose adjustments that is achievable and prevents progression of ototoxicity

Biomarker research in the world for predicting ototoxicity

- Renal biomarkers: Total protein (TP), albumin (ALB), B2M, clusterin (CLU), cystatin C (Cys C), KIM-1, and trefoil factor 3 (TFF3), NAG

- Cochlear biomarker: Prestin

Gauvin et al 2019

Monitoring of ototoxicity is important because

- Early diagnosis leads to change in pharmacological intervention
- Clinical decision as to whether to continue with pharmacotherapy can be informed
- Educates and informs colleagues and patients about the possibilities of cochleovestibular involvement
- Early detection is crucial for early rehabilitation from both the cochlea and the vestibular point of view

The Alder Hey protocol for cancer chemotherapy

- Diagnosis
- Chemo schedule
- Duration of treatment
- Radiation
- Surgery

Referral at least 4 weeks in advance before start of cycle

Dedicated clinic once weekly with AVP

Base line – anamnesis; clinical exam; impedance; PTA/FF; EHFPTA; DPOAE & growth; vestibular examination; counselling

Notify AV team of tinnitus, vestibular symptoms

Post cycle assessment within 4 weeks – anamnesis; clinical exam; impedance; PTA/FF; EHFPTA; DPOAE & growth; vestibular examination & vHIT; counselling

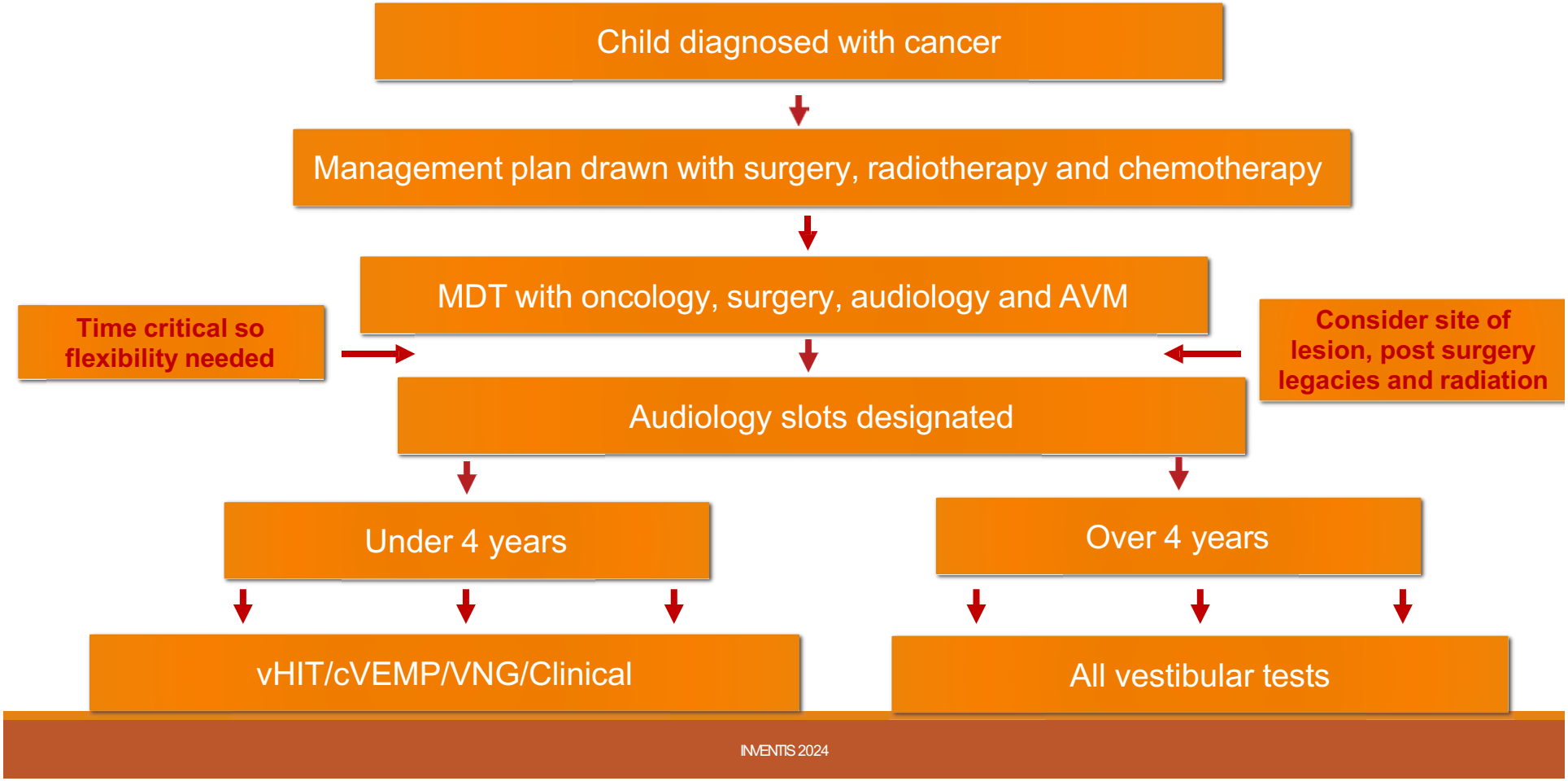
Toxicity detected

No toxicity detected

Usual management pathway

FU 3,6,9,12 months; then every year upto 2 years

The MDT approach to implement the protocol in Alder Hey



Alder Hey aminoglycoside ototoxicity monitoring

Children scheduled for aminoglycoside therapy

↓

Genetic testing for A1555 A-G

↓

Initial screening if symptoms of hearing loss/balance symptoms present, either direct or surrogate

↓

After administration of first dose

↓

First hearing test and balance screening (vHIT/VEMP) regardless of symptoms or not for detecting idiosyncrasy

↓

Subsequent doses

↓

AG levels >2mg/l	15 days of IV G or T therapy per year	Chronic inhaled G or T IV/Neb Amikacin	IV or nebulised Amikacin
↓	↓	↓	↓
Hearing test post exposure	Hearing test annually	Hearing test annually	Hearing test every 6 months
Vestibular assessment	Vestibular assessment	Vestibular assessment	Vestibular assessment

Notes :

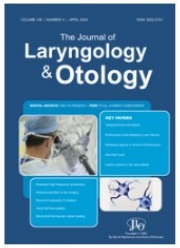
1. After each course of AG, symptoms of hearing loss ascertained and bedside whisper voice test performed where applicable, symptoms of vestibular damage ascertained by vestibulospinal tests – in case of positive symptoms assessment advised– in case of absent symptoms, no immediate hearing test required immediate post exposure of each course but at least one vestibular assessment required
2. The hearing test by choice is behavioural audiometry at least in free field; otherwise DPOAE, when DPOAE not possible TEOAE; EHF audiometry whenever possible
3. Hearing test reported by the SIOP Boston ototoxicity scale wherever possible
4. Information about nephrotoxicity to be enclosed wherever possible
5. After the first dose of any AG, vestibular symptoms must be asked and if present referral to be sent to consultant audiovestibular physician for balance assessment

Other monitoring protocols for ototoxicity in Alder Hey

- Radiation ototoxicity: Often overlooked but important for ototoxicity due to radiation potentiation effects of some chemotherapeutic agents and chemotherapy potentiating effects of radiation – pre and post radiation monitoring and a follow up for up to 5 years
- Bone marrow ablation: Pre and post stem cell transplant monitoring
- Iron chelator monitoring: Monitoring if subjective or behavioural drop of hearing
- Non platinum chemotherapy monitoring: Vinca alkaloids, Cyclophosphamide, Doxorubicin, Bleomycin, Fluorouracil, Etoposide monitoring if 2 agents are given together; vestibular function tests mandated for vinca alkaloids

Quality control and research in Alder Hey

- Regular audits
- Update of protocols with CCLG and Cystic Fibrosis every year
- Part of the International Ototoxicity Monitoring Group
- Multicentre research participation
    - MAGIC study – International
    - TCmegaGWAS study – International
    - PNET study – International
    - Hypatia CTIMP study - National



The Journal of Laryngology & Otology

Article contents

Comments on published article 'An audit of UK audiological practice in specialist paediatric oncology centres regarding hearing assessment of children at risk of ototoxicity due to chemotherapy' by Brown *et al*.

Published online by Cambridge University Press: **17 March 2021**

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Abstract

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Dear Editors


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Our Research
Publications
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International Ototoxicity Management Group (IOMG)
The International Ototoxicity Management Working Group (IOMG) is a global consortium of international stakeholders from universities, task forces, health foundations, professional societies, government agencies and patients created to address healthcare gaps in the clinical management of individuals who experience hearing loss, tinnitus, and/or balance difficulties following medical, occupational or environmental exposures to ototoxicants.
IOMG links:
Overview
OTOTOXIC
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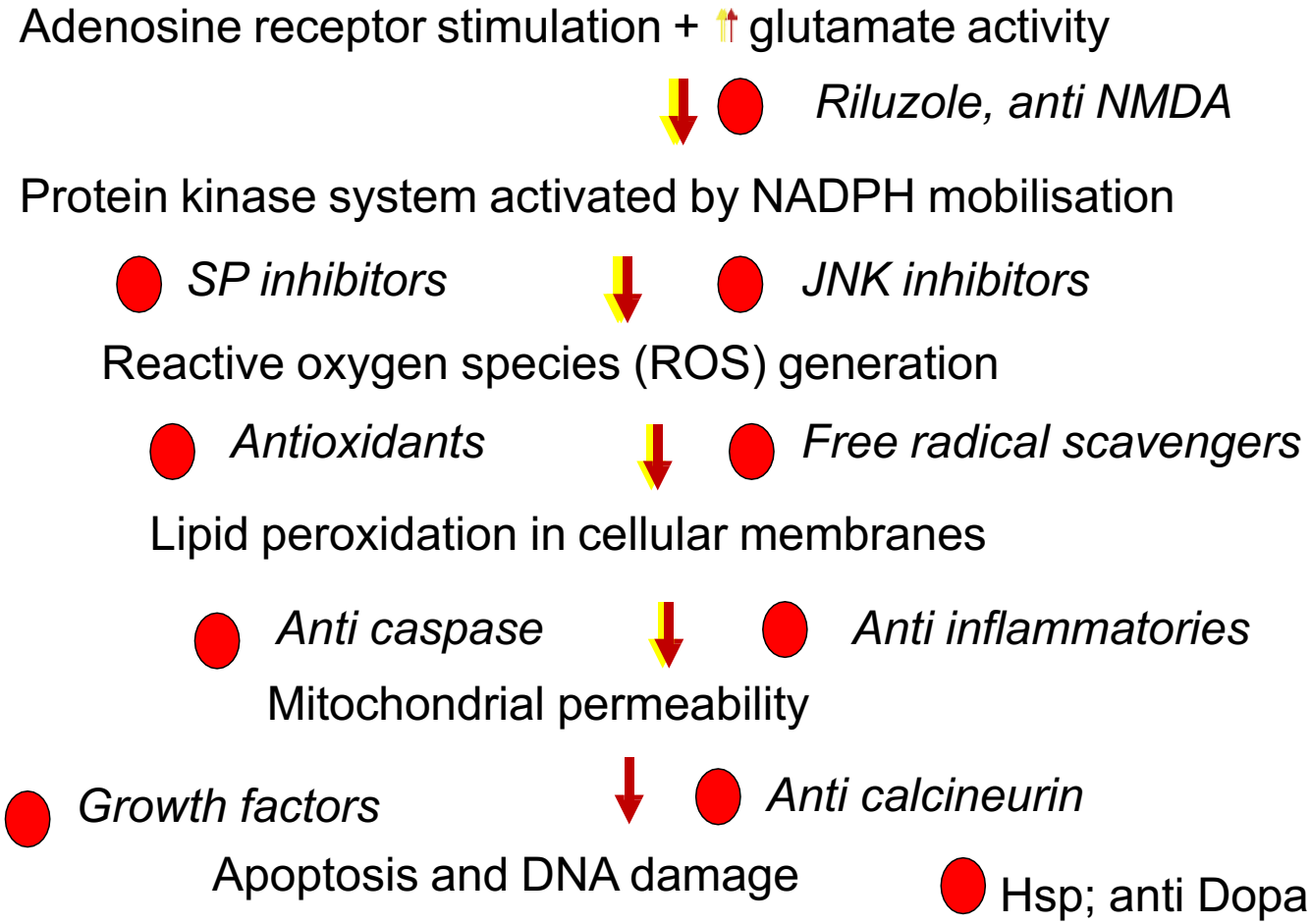
The multidisciplinary approach

- Management of hearing loss → Audiology
- Management of paediatric and surgical comorbidities → Medical/surgical specialities
- Sensory integration strategies → Occupational therapy
- Neuro and musculoskeletal physiotherapy if required → Specialised physiotherapy
- Psychological intervention when appropriate → Psychology
- Correction of visual problems → Ophthalmology and optometry
- Music therapy and hearing therapy → Psychology and audiology
- Engagement significant others → Education, family, social services

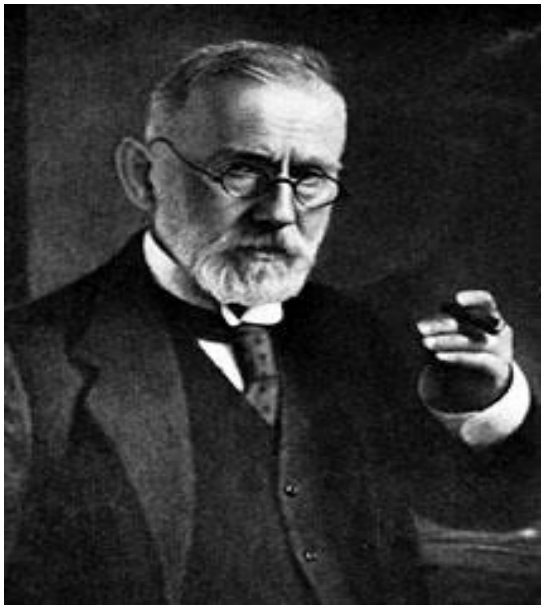
Ototoxicity rescue with pharmacological agents directed at steps of the biochemical enzymatic cascade or by competitively inhibiting platinum compound uptake


Adenosine receptor stimulation + glutamate activity
Riluzole, anti NMDA
Protein kinase system activated by NADPH mobilisation
SP inhibitors
JNK inhibitors
Reactive oxygen species (ROS) generation
Antioxidants
Free radical scavengers
Lipid peroxidation in cellular membranes
Anti caspase
Anti inflammatories
Mitochondrial permeability
Growth factors
Anti calcineurin
Apoptosis and DNA damage
Hsp; anti Dopa

The magic bullet – primary prevention

In folklore, a silver magic bullet kills the invincible werewolf

The magic bullet for ototoxicity



Biochemical modifiers

- NMDA antagonist
- C-jun2-TK antagonist
- ROS scavengers
- Ebselen
- GF/NT promoters
- Caspase inhibitor
- Calcineurin inhibitor

Competitive inhibitors

- NAC
- Thiol compounds
- Pantoprazole

Management of acute vestibular event – secondary and tertiary prevention

- Diagnosis of weakness as soon as stable
- Labyrinthine sedatives – prochloperazine or cinnarizine
- Early ambulation
- The role of steroids is not clear but in case of sudden SNHL, can be administered in a tapering 2 week period
- Vestibular rehabilitation as early as possible for tertiary prevention

Vestibular rehabilitation – secondary and tertiary prevention

- The decision depends on the quality of lives and the proper quantification of a vestibular weakness, evidence of decompensation; if no weakness can be quantified, then it depends on the presence of a vestibular history (central or peripheral) and vestibular behaviour affecting QOL
- When selected correctly, it remains the best option to treat a vestibular syndrome in a child as it promotes natural central compensation
- The outcome that is measured by pre and post rehabilitation validated psychometric questionnaires (paediatric Dizziness Handicap Inventory or Berg Balance Scale) is very favourable and rewarding
- Should be instituted early after diagnosis and needs to be customised according to individual needs

Virtual reality – tertiary prevention

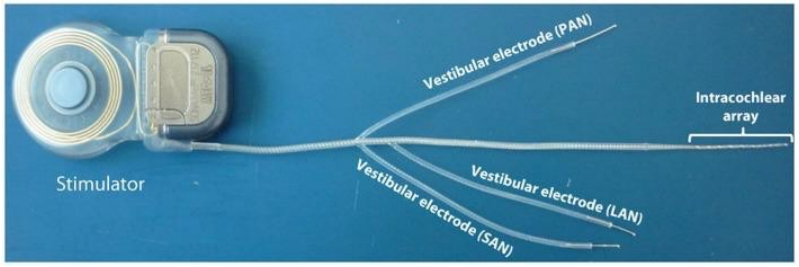
Courtesy – Virtualis and Frank Assaban

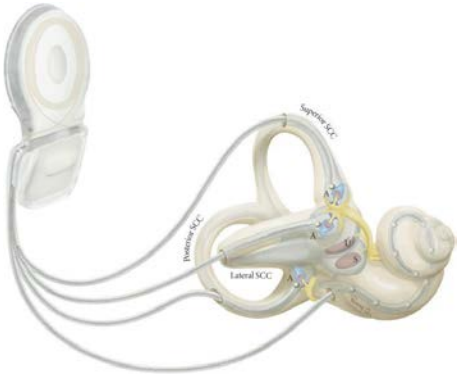
- Part of rehabilitation including visual vertigo
- Good desensitising techniques
- Good outcome reported

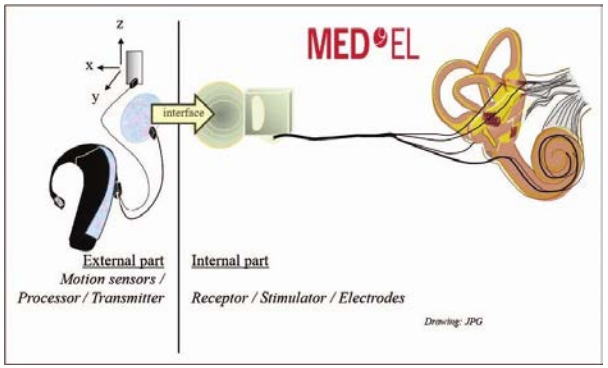
The Balance Belt - tertiary prevention

- Indicated in refractory vestibular/balance disorder with symptoms
- Works by haptic/vibrotactile stimulation delivered at a calibrated rate to improve proprioception
- Efficacy reported so far good but more studies needed

The Vestibular Implant - tertiary prevention







- Engineered with modifications of a cochlear implant
- Electrodes inserted into canals or the otoliths
- Indicated in refractory and resistant cases of bilateral vestibular hypofunction
- Only 4 groups working in the world at the moment and the outcome is varaibale

VNG

- Head heave saccade changes or absence
- Ocular counterolling changes or absence

Video head impulse test

- Improvement in VOR gain
- Changes in saccade morphology – clustering and PR score

Suppression head impulse test

- Improvement in VOR gain
- Changes in saccade morphology – clustering and PR score
- Changes in asymmetry and peak saccadic velocity

Others

- Improvement in chair VOR gain and amplitude in VEMP
- Static and dynamic posturography changes
- Improvement in balance scale scores

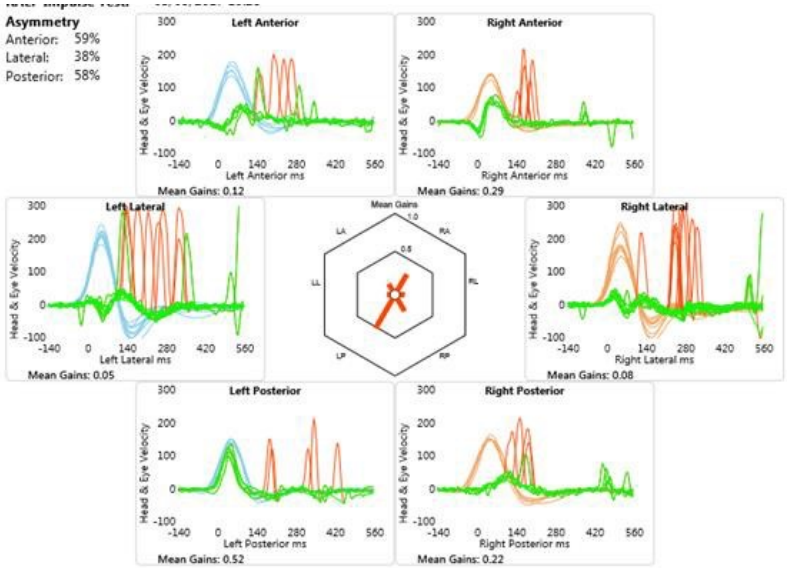
Monitoring dynamic and static vestibular compensation

Anamnesis

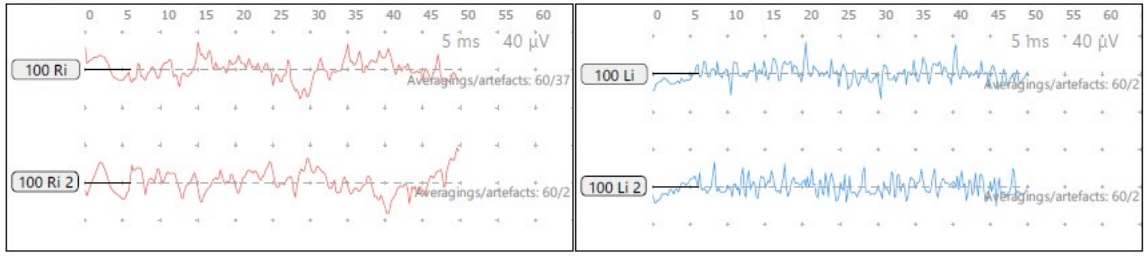
- Improvement in functional performances
- Improvement in cognition
- Improvement in motor skills

Examples

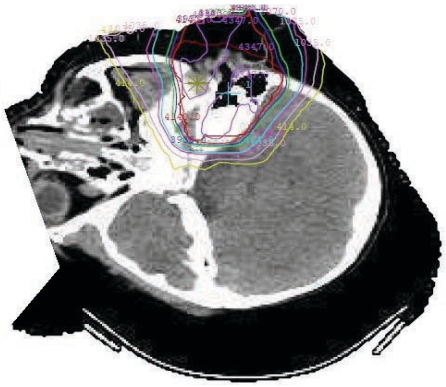
Cisplatin toxicity after brain stem medulloblastoma

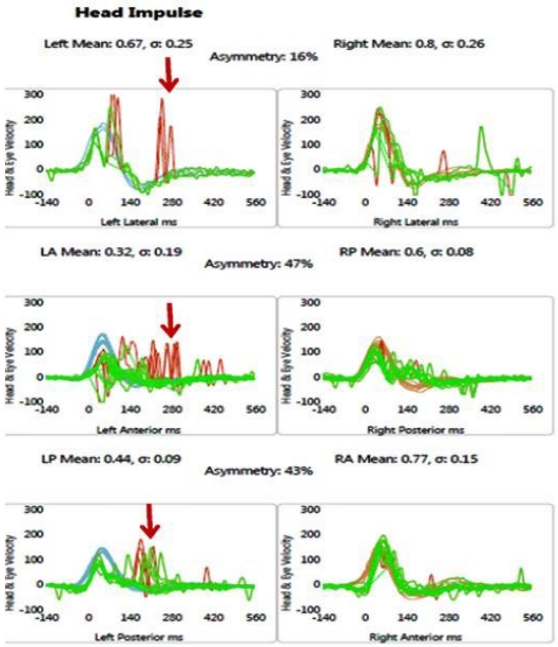


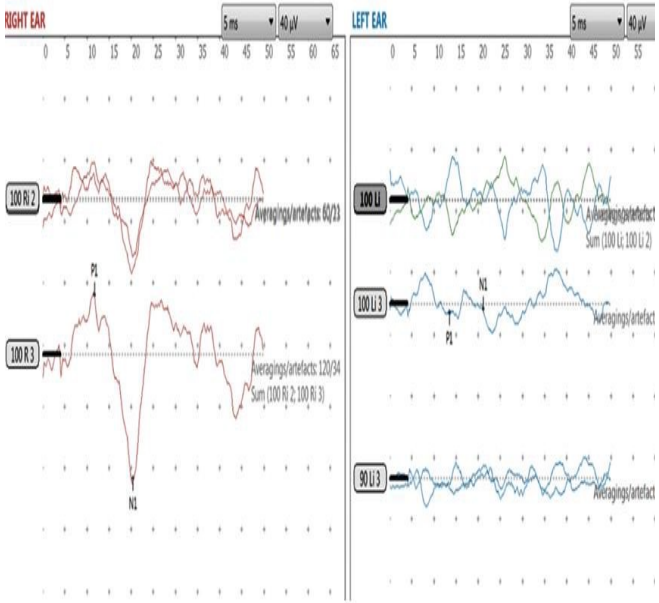
VEMP: cVEMP (cervical)
1: Cz-M1
2: Cz-M2



Proton beam toxicity after EAC rhabdomyosarcoma



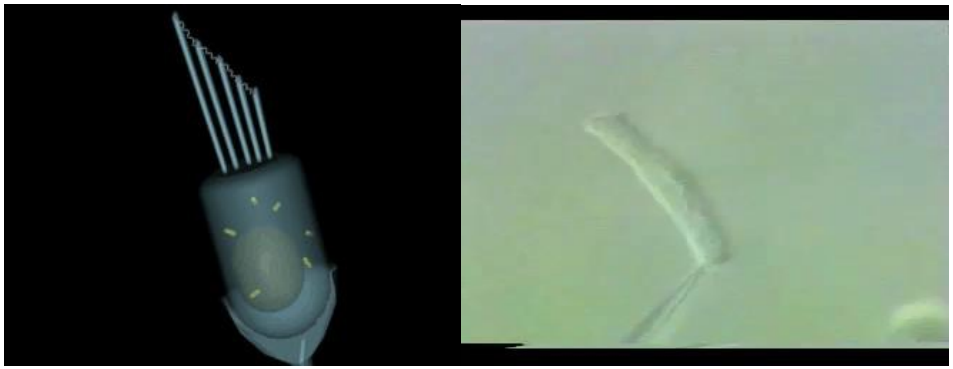




Conclusions

- Ototoxicity involves vestibular toxicity and must be considered

- Early detection and intervention with favourable prognosis by compensation



Thank you

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