Meniere’s disease

Pathogenesis and new trends in management

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We have been discussing Meniere’s disease. The possible effects of CSF release. What happens when secretory functions cease. Yet, the patient asks: *help me please!*

Giodo Smoorenburg, 1995
Meniere’s Disease

• Prosper Meniere’s account of the “Maladie de Meniere’s” on January the 8th 1861: (Vertigo, staggering, uncertain gait and a feeling of rotation could be caused by an inner ear disorder)

• The term Meniere’s disease, appeared in Adam Politzer publication in Vienna in 1867 and Barany (Barany’s syndrome in 1911)
Endolymphatic Hydrops

• The condition was discovered in 1938 through histopathological work on the temporal bones of Meniere’s patients by 2 separate groups (Halpike and Carins in London, Yamakawa in Osaka)
• Since then, the terms of Meniere’s disease and endolymphatic hydrops were used to describe the same condition
• But does it?
Clinical features

- A condition of “sudden and recurring episodes of vertigo with nausea and vomiting, accompanied by hearing loss and tinnitus”

- **Three cardinal features:**
  - Hearing loss
  - Vertigo
  - Tinnitus

- **Three stages: (AAOO, 1972):**
  - Early reversible hearing loss
  - Established fluctuant hearing loss
  - Late non-fluctuant hearing loss
The acute attack

- A warning of the attack *Aura* (fullness in the ear, pain, change in tinnitus, vague sense of discomfort,..)
- Vertigo, mild or severe, rotatory or unsteadiness, to-and-fro/up-and-down movement
- Patient maybe thrown to the ground without warning (drop attack, utricular crisis)
The acute attack

- Nausea, vomiting, worsening of hearing
- 20 minutes to 24 hours (*never seconds never days*)
- No loss of consciousness
- No neurological symptoms or sequelae
- Nystagmus always present
The remission phase

• Entirely asymptomatic, hearing return to normal and no tinnitus
• Permanent/fluctuant hearing loss/tinnitus later
• Mild imbalance in remission later
• Migraine attacks?
Some points of interest

- Pathophysiology, theories of causation
- Aetiology; genetic and autoimmune theories
- New trends in treatment:
  - Chemical ablation
  - Pressure generators
Trigger factors

- Salt
- Caffeine
- Alcohol
- Stress
- Allergies
- Menstruation
- Pregnancy
Trigger factors

- Orgasms
- Visual stimuli
- Auditory stimuli
- Barometric pressure
Pathophysiology

• Endolymphatic hydrops was suggested by Meniere in 1861 and confirmed in 1938 during histopathological study of the temporal bone of Meniere’s patients

• **The classical theory:** The distension of the endolymphatic sac and ultimate rupture of Reissner’s membrane as a direct pathogenesis of all the symptoms
The endolymphatic sac

- Parts of the membranous labyrinth with no sensory function
- Located within the petrous pyramid, under the dura matter of the posterior cranial fossa
- Elastic, compliant, surrounded by connective tissue
- Believed to have an important role in hemostasis and endolymph resorption
Pathology and patho-physiology

- **Endolymphatic distension:**
  - Excess endolymph in the scala media with ballooning of Reissner’s membrane into the scala vestibuli
  - The increased pressure is responsible for the feeling of fullness, hearing loss, tinnitus and dysequilibrium
  - Herniation and rupture for the acute attack
Endolymphatic distension

• **The theories of causation:**
  - Insufficient production of perilymph
  - Excess production of endolymph
  - Inadequate absorption in the endolymphatic sac
    • Disruption of formation
    • Mechanical blockage
    • Disturbed absorption
Intra labyrinthine fluid dynamics

• *The longitudinal flow theory of endolymph (Guild 1927):*
  – The most accepted theory so far
  – Endolymph production in the cochlear duct
  – Flows unidirectionally towards the endolymphatic sac where resorption occur
  – Blockage and deficient absorption can explain hydrops
Intra labyrinthine fluid dynamics

• **The radial flow theory:**
  – Endolymph is produced and absorbed throughout the endolymphatic sac
  – Control of endolymph homeostasis is distributed throughout the endolymphatic space (Salt and Ma, 2001)
  – Radial flow would be controlled by local, cellular and molecular factors
Intra labyrinthine fluid dynamics

- **The endolympathic sinus theory:**
  - The endolympathic compartment is regulated by a unidirectional membranous valve (the endolympathic sinus)
  - Anatomical abnormalities or blockage in the sinus as an explanation for the hydrops (Salt et al, 2004)
Histopathological findings in temporal bone studies

• The distension of the endolymphatic sac is mainly confined to the cochlea and saccule, with lesser involvement of the utricle

• The endolymphatic sac becomes narrower in Meniere’s disease, but obstruction is rare!
Histopathological findings in temporal bone studies

- Cochlear degeneration is found in only 44% of ears, with specific apical degeneration in only 26% of cases!
- Spiral ganglion degeneration (73%) and stria vascularis degenerative changes (63%) are by far more common that hair cells degeneration in most of the studies!
Why low frequency SNHL?

- Distension and pressure causing OHCs and IHCs damage at the most dependant part of the basilar membrane (apical turn) is challenged by histopathological findings of minimal hair cells degeneration, not related to the severity of HL.
- Probably the cause lie in synaptic / neuronal damage? Biochemical / ionic pathology?
- Stria vascularis pathology leading to “functional” rather than “physical” injury to HCs?
Hydrops as an *epiphenomenon*

- Temporal bone examination found evidence of hydrops in all patients clinically diagnosed with Meniere’s disease.
- But 9 cases had no clinical symptoms in a series of 35 temporal bones with idiopathic hydrops.
- 42 of 44 cases with secondary hydrops had no clinical symptoms.
- Hydrops *might not be the central cause in symptoms development*.
The Ionic Composition of the Cochlear Fluids

- The Endolymph: High on K (around +80mv), Low on Na (uniquely among extra cellular fluids in the body to resemble intracellular fluids)
- The Perilymph: Mainly an extra cellular fluid with low potential and low K concentration (including the cortilymph)
The Endolymph

- K movement is facilitated by multiple ionic channels, of which water channels of the *aquaporins proteins* family are important
- IHCs has at least 2 distinct K ionic channels, OHCs has three
- Aquaporin 2 was suggested to play an important role in radial flow and some experimental evidences suggest that its increased activity leads to development of hydrops in animals (Takeda et al, 2003)
The Theory

• Hydrops might represent an epiphenomenon rather than an initiating factor in the development of Meniere’s disease (Semaan et al, 2005)

• Vertigo, HL and tinnitus might be the result of ionic imbalance, rather than toxicity by K ions occurring as result of Reissner’s membrane rupture (leakage of K into the perilymphatic compartment with subsequent contamination of the cortilymph resulting in cochlear electrical failure)
Can Meniere’s be a channelopathy? (Gates et al, 2005)

- The strong association between hearing loss and K ion channelopathy
- Meniere’s and Migraine
- The sensitivity of Meniere’s to dietary Sodium, common in channelopathy
- The sensitivity of Meniere’s to acetazolamide
- The episodic nature of Meniere’s
Aetiology

• Aetiology is obscure
• Some theories have been put forward to explain the development of the hydrops and different clinical symptoms
• Probably multi factorial aetiology is in play in most cases
Aetiology

- **Anatomical:**
  - Abnormalities of the temporal bone
  - Hypoplasia of the vestibular duct, abnormal endolymphatic sac

- **Viral:**
  - Antibodies against herpes simples, Epstien-Barr virus, Cytomegalovirus (Calenoff et al, 1995)
Aetiology

• Vascular:
  – The correlation with migraine

• Metabolic:
  – Ionic imbalance in the cochlear fluids

• Psychological:
  – Increased prevalence of obsessional traits
  – Neurosis, psychosomatic personalities
The role of genetics

• A familial predisposition has been recognized for a long time in Meniere’s:
  – 7.7% with positive family history (Morrison, 1995)
  – Familial Meniere’s 2.6-12% (Semaan et al, 2005)
  – 5-13 % (Klar et al, 2006)
The role of genetics

- Most reports suggest a mendelian pattern of *autosomal dominant inheritance*, potential candidate gene on chromosome 14 (COCH gene mutation) or chromosome 6 (HLA antigen)
- Various expressivity and penetrance?
Immunology

- Immunity is the ability of the human body to resist organisms or toxins that tend to damage the tissues and organs.
- Some mechanisms of immunity we are born with (innate), and other type we acquire due to exposure to agents (Acquired).
Immune tolerance

- The ability of the immune system to recognize own cells and not attack them
- Most tolerance is the result of pre processing of the T cells in the thymus gland and the B cells in the bone marrow during embryonic life
- Failure of immune tolerance causes autoimmune diseases
Autoimmune disease

• Break in the immune tolerance leads to autoimmune diseases
• Progressive inflammatory process in the apparent absence of a pathogen
• Most autoimmune diseases are associated with the production of auto antibodies
• Express itself following an insult by unknown environmental agent? Genetically determined?
Mechanisms of autoimmunity

- Lack of auto reactive cells:
  - Due to early failure in embryonic pre processing
- Lack of antigen presentation
  - Cochlear protein not in contact with circulation until damaged/fragmented
- Lack of helper T lymphocytes
- Lack of suppressor T lymphocytes
The immunologically unprivileged inner ear

- The inner ear has long been considered to be “immunologically privileged” site relatively protected from inflammatory immune events by the blood-labyrinthine barrier
- This theory has been challenged by Mogi et al (1982) and Solares et al (2002)
- It is believed now that the inner ear is not “immunologically privileged” and may mount an immune reaction against foreign and auto antigens
Pathogenesis

- Lehnhardt (1958) suggested an autoimmune aetiology to a series of 13 patients with unexplained progressive SNHL.
- He suggested that degeneration of the organ of corti in one ear leads to the generation of auto antibodies (lack of antigen presentation theory).
Pathogenesis

- The auto antibodies then go on and attack the healthy cochlea
- Although no scientific proof is present, this theory is generally acceptable as a likely scenario
- McCabe (1979) work is considered to be the seminal study about AIED
Autoimmunity and Meniere’s disease

- The association with the HLA antigens raises a possible link to autoimmunity.
- Rupture and fragmentation of the Reissner’s membrane leading to the introduction of cochlear antigens to the bloodstream, the immune system can’t recognize it?
- 16% of cases of bilateral Meniere’s or 6% of all cases of Meniere’s might be autoimmune.
- The ES is the site of the immune response of the inner ear.
Autoimmunity and Meniere’s disease

- Evidence of immune complex deposition in the endolymphatic sac (Dornhoffer et al, 1993; Matsuka et al, 2002)
- The rapid improvement in response to corticosteroids treatment in some patients
- The close link of Meniere’s disease and some primary autoimmune conditions:
Secondary autoimmune inner ear disease

- Usually hearing loss is associated with other multi-system affections and might not be the primary presentation
- Diagnosis is usually by finding the auto antibodies of the general disease and treatment is not specific to hearing
Secondary autoimmune inner ear disease

- Cogan’s disease:
  - Although a very rare disease, the involvement of the inner ear is the commonest among secondary autoimmune diseases
  - Non-syphilitic interstitial keratitis associated with fluctuant but aggressive SNHL (around 3 months from start to profound HL in 60% of cases)
  - The HL is bilateral, rapidly progressive and accompanied by tinniuts, vertigo and aural fullness (Meniere’s like)
Secondary autoimmune inner ear disease

- Cogan’s disease:
  - A virus infection prompts antibody response, cross immunity to similar proteins in the eye and ear (Bovo et al, 2009)
  - Primary a disease of young adults
  - Endolymhatic hydrops, Atrophy of the organ of corti, spiral ganglia degeneration
  - Early administration on immune suppressive drugs is indicated, though not curative
Secondary autoimmune inner ear disease

- Vogt-Koyanagi-Harada syndrome:
  - Very similar to Cogan’s disease, with the addition of depigmentation of the hair and skin around the eye lashes
  - Loss of eye lashes and aseptic meningitis can occur
  - Might represent autoimmune reaction to melanin-coating cells
Secondary autoimmune inner ear disease

• Behcet’s disease:
  – Rare chronic relapsing inflammatory disorder
  – Triad of uveitis, oral and genital ulceration
  – Hearing loss typically bilateral, usually appears almost a decade after the initial presentation and slowly progressive
  – Frequently associated with vestibular symptoms
Secondary autoimmune inner ear disease

• Other systemic conditions:
  – Systemic Lupus
  – Polyarteritis nodosa
  – Multiple Sclerosis
  – Susac syndrome
**Primary autoimmune inner ear disease (AIED)**

- **Epidemiology:**
  - Rare disorder, the absence of a definite diagnostic test makes the accurate prediction of the incidence hard
  - It is less common that Sudden SNHL (or is SSNHL sometimes misdiagnosed?)
  - 1% of all cases of hearing impairment and dizziness?
  - 16% of bilateral Meniere’s disease or 6% of all cases of Meniere’s disease?
Management
Trends in treatment and management

• Treatment is empirical
• No treatment has modified the course of the disease prospectively: (Saeed et al, 2006)
  – Aetiology unknown
  – Placebo effect of the drugs
  – Tendency for relapse and remittance
  – Clinical course is towards habituation in 70% of patients
Conservative treatment

- Acute attack
- Salt restriction
- Diuretics
- Vasodilators
- Histamine analogues (Betahistine)
- Chemical ablation
Surgical treatment

- Endolymphatic shunts
- Vestibular nerve section
- Sacculotomy
- **Tympanostomy**
- Cervical sympathectomy
- Destructive procedures
Chemical ablation, Intratympanic injection

• Rapidly becoming one of the most popular methods in treating intractable Meniere’s disease
• The theory is dependant on the toxic effect of aminoglycosides antibiotics group on the vestibular labyrinth
• The toxic effect on the posterior labyrinth is more severe compared to the cochlear toxicity
Chemical ablation

• Cumulative effect of intravenous streptomycin was used before, but the risk of cochlear toxicity, ataxia and oscillopsia is high and limit its use

• The intratympanic injection of vestibulotoxic agents is the favourite method nowadays
Mechanism of action

• Reversible interference with calcium dependant ionic channels
• Irreversible destruction of the cell membrane and interference with protein messenger synthesis
• Damage of the dark cells of the stria vascularis and disturbance of the biological ionic pump
Chemical ablation

- First proposed by Schuknecht in 1957
- Success rate ranging from 75-100% in controlling vertigo
- Cochlear toxicity incidence ranging from 0-75%
- A realistic estimate of success rate around 90% and cochlear toxicity around 15-25%
Protocols of treatment

• Varies between the type of drug, the method of application, the dose and the frequency of the administration

• Odkvist titration protocol is a common method used: (Bertino et al, 2006)
  – One to three administration of 1 ml solution containing 26 grams of gentamicin sulphate
  – Unchanged symptoms for 3 months to perform a second or third injection
Drugs used in intratympanic injection

• Ototoxic drugs
  – Steptomicin
  – Gentamicin

• Dexamethasone (Decadron)
  – Anti inflammatory, autoimmune suspicion

• Labyrinth anathesia
  – Lidocaine
Methods of administration

• *Spinal needle injection*, under microscope, into the postero-inferior portion of the tympanic membrane under local anethesia

• Patient kept supine with head rotated contralaterally 45 degrees for 20 minutes to enhance the passage of the drug to the inner ear via the round window membrane
Methods of administration

• Injection through a hole made by laser into the tympanic membrane
• Using gelfoam (absorbable gelatin sponge), placed close to the round window through a laser made hole in the tympanic membrane, and soaked in the drug
• Silverstein microWick (drug in drops through a Grommet tube)
• Round window Microcatheter
Visualization post injection

- Most protocols work through injection of the drug into the middle ear cavity and “hoping” for the drug to pass though the round window membrane in sufficient concentration.
- Sometimes the permeability is poor, probably due to fibrosis, granulation around the round window membrane.
Visualization post injection

- A technique was developed to use a 3D-MRI to track the a diluted solution of Gadolinium hydrate through the tympanic membrane (Nakashima et al, 2007)
- Observation of the dye was documented in the endolymphatic sac and through the perilymph within a day of injection, and disappeared within a week
The use of pressure alternating devices

• The use of a myringotomy tube (Grommet) to treat Meniere’s disease has been in practice for a long time

• Meniere’s used a long gold needle to apply pressure on the centre of the TM, leading to hearing improvement in a Meniere’s patient (First stapes mobilization?)
The use of pressure alternating devices

- It was theorized that using a pressure alternating device, producing positive pressure pulses of predetermined nature, through a Grommet tube, may lead to increased exchange of inner ears fluids, enhance endolymph resorption and subsequently decrease the endolymphatic fluid volume (Densert et al, 1997)
The use of pressure alternating devices

• The Meniett device and the Enttex P-100 device are two such commercially available devices that use a portable pump to induce positive pressure pulses

• Some studies showed some improvement in clinical symptoms in contrast to a placebo device (Odkvist et al, 2000, Gates et al, 2006)

• A study showed changes in the EchoG SM as a result of pressure (Densert et al, 1995)

• Other studies showed no effect on vestibular functions (Stokroos et al, 2006)
Meniett Device

- So far, no concrete evidence in the literature of the efficacy and sensitivity of the Meniett device in Meniere’s disease. Higher quality independent studies are needed with RCT design are needed to obtain high quality evidences to base clinical intervention (James et al, 2009)
Conclusion

• The field of Meniere’s disease is evolving rapidly, both in basic science and application to management
• The challenge facing audiologist is to equip themselves with as much information as possible, to make the process of management successful
• Fragmentation of management is counterproductive
Thank you