Otology Seminar

The medical treatment of otosclerosis

R3 許軍偉
Introduction

- Fibrous osteodystrophy of human **otic capsule**
- Conductive hearing loss >> SNHL and mixed HL
- Abnormal resorption and deposition of bone
  - disease process
- Autosomal dominant, Female/male = 2/1

- In 1873, Schwartze described
  - a reddish hue behind an intact tympanic membrane
  - increased vascularity of the cochlear promontory in active otosclerosis lesions (the phase known as **otospongiosis**).
  - **Schwartze sign**
  - in 10% of patients with OS
In 1881, von Troltsch
- abnormalities of the middle ear mucosa in this disease
- first to use the term “otosclerosis (OS)”.

In 1912, Siebenmann: the possibility of OS causing SNHL.
- Numerous etiologies of OS
  - hereditary, endocrine, biochemical, metabolic,
  - infectious (measles), traumatic, vascular,
  - Autoimmune factors.

Lopez-Gonzalez and Delgado (2000)
- Oral vaccination with type II collagen
- Decrease the autoimmune reaction ➔ otosclerosis

Embryology

- Otic capsule: mesenchyme surrounding the otic vesicle at 4 weeks
- Cartilaginous framework: at 8 weeks
- Endochondral bony replacement of the cartilaginous framework: at 16 weeks
- In some people, complete bony replacement does not occur and leaves cartilage in certain locations.
- **Fissula ante fenestram**: anterior to the oval window
  - last area of endochondral bone formation in the labyrinth
Fissula ante fenestram $\rightarrow$ most common site
80% to 90% of patients with OS

Otosclerosis

Otosclerosis is a genetically mediated metabolic bone disease of unknown etiology.
It is sometimes called otospongiosis because the disease begins with an otospongiotic phase, which is followed by an otosclerotic phase when osteoclasts are replaced by osteoblasts and dense sclerotic bone is deposited in areas of previous bone resorption.

When this process involves the oval window in the region of the footplate, the footplate becomes fixed, resulting in conductive hearing loss.

Conductive hearing loss develops early in the third decade and is considered to be the hallmark of the disease. However, involvement of other portions of the otic capsule can result in mixed sensorineural hearing loss.

The process starts in the region of the oval window, classically at the fissula ante fenestram, i.e. in front of the oval window (fenestral otosclerosis).

It can also occur around the cochlea (retrofenestral otosclerosis).

On the left a transverse CT-image of a 23-year old female with conductive hearing loss.
There is a subtle otosclerotic focus in the characteristic site: the fissula ante fenestram (arrows).
A mature otosclerotic focus (*) involving the promontory and anterior stapes footplate (sf).

st, scala tympani; v, vestibule; fn, facial nerve.
• Three forms of otosclerotic lesions:
  ◦ otospongiosis (early phase), → transitional phase
  ◦ → otosclerosis (late phase).

□ 60% family history, hearing loss 15~45 y/o (33 y/o)
□ 75% tinnitus, **Carhart notch** (2k bone conduction decay), Speech discrimination excellent
□ Dizziness occurs in up to 30% of patients with OS.
□ In all races, 80% bilaterally
□ 90 % no symptoms and signs > 20 y/o appear
Diagnosis of otosclerosis

**History**
- Progressive hearing loss
- Family history of otosclerosis
- Tinnitus
- Possible vestibular symptoms (rule out Meniere or SSCD)
- Otitis media/otorrhea (absent)
- Head trauma (absent)

**Physical examination**
- Tympanic membrane (normal)
- Schwartze sign
- Rinne test (negative at 256 and 512 Hz)
- Weber test (lateralizes to side $\Rightarrow$ greater CHL)

**Ancillary studies**
- Audiogram (assess for CHL, mixed HL, SNHL, Carhart notch)
- Tympanometry (type A or As; absent or on-off stapedius reflex)
- Imaging (CT scan showing radiolucent areas around bony labyrinth)
  - SSCD, superior semicircular canal dehiscence.s
Introduction

- **Treatment**
  - Observation
  - Amplification (Hearing aid, BAHA)
  - *Medical managements*
    - (Calcium fluoride, NaF, Biphosphonates, Etidronate)
      - ↓ Rate of bone resorption
      - ↓ Rate of new bone formation → ↓ Osteospongiosis
  - **Surgery (stapedotomy, stapedectomy)**
    - Indications of stapedectomy:
      - Conductive hearing loss (due to fixation of stapes). Air bone gap of at least 30 dB.
      - Presence of Carhart’s notch with conductive hearing loss (relative)
      - Good cochlear reserve with good speech discrimination.
Introduction of medical treatment of otosclerosis

- 1916 \(\rightarrow\) first indication that sodium fluoride have a potential role of resorptive bone diseases

- School children with a high content of fluoride in drinking water
  - Decrease in the incidence of dental decay

- Women living in areas with low fluoride content in water compared with those having drinking water with high fluoride content
  - Osteoporosis was detected twice

Sodium fluoride (NaF) to inactivate and help in the maturity of an active focus of otosclerosis

Shambaugh GE Jr, Sodium Fluoride for Arrest of Otosclerosis; Theoretical Considerations.

Arch Otolaryngol 1964; 80: 263–70.

Medical therapy for otospongiosis: slow down and eventually stop the phase of bone resorption

Petrovic AG, Shambaugh GE Jr. Experimental studies on pathology and therapy of otospongiosis.

Efficacy of medical treatment for otosclerosis

- Histological studies
- Enzymatic studies
- Molecular studies
- Epidemiological studies
- Clinical studies
- Medical effect on tinnitus associated with otosclerosis
- NaF effect on vertigo associated with otosclerosis
- NaF effect on early stages and role in prophylaxis
- NaF side effects and contraindications
- Criteria, follow up, treatment schedule of NaF
- Biphosphonates effects on otosclerosis
Histological studies

- Petrovic et al. (1985)
  - NaF to inhibit bone resorption by mononuclear cells
  - New bone formation effect: minor importance.

- Parahy and Linthicum (1984)
  - NaF slows the progression of otosclerotic hearing loss
  - Neutrolising and inactivating the hydrolytic and proteolytic enzymes (Toxic to hair cells)
Enzymatic studies

- Wolff and Bellucci (1960) → enzymatic theory of progression of SNHL in otospongiosis

- Causse et al. (1972) cytotoxic enzymes found in the perilymph proteolytic and hydrolytic enzymes (trypsin, α-1 antitrypsin, α-2 microglobulin, collagenase, α-chymotrypsin, phosphatic acid, ribonuclease, lactate dehydrogenase) → SNHL

- Chevance et al. (1976)
  → High α-1 anti-trypsin activity in 97.3% patients
  → non-progressive hearing loss for 2 years prior to surgery
Enzymatic studies

- Causse et al. (1982) → trypsin responsible for the damage to the hair cells leading to SNHL in 75% patients
  - Effect on collagen fibrils → bone destruction
  - NaF inhibits trypsin directly
  - NaF lower the overall level of enzymes in the perilymph → arrest cochlear deterioration in otospongiotic disease

- Causse et al. (1985)
  - Average concentration of trypsin was 7.01 µg/ml before NaF therapy, and 5.93 µg/ml after NaF therapy for 1 year
  - Fluoride in bone: fluorapatite crystals
  - Resistant to osteoclastic enzymatic bone resorption in the active phase of otosclerosis
  - Reducing further bone remodelling and promoting recalcification
Arresting active phase of otosclerosis (1)

- **Linthicum et al. (1973):**
  - 鋇 Strontium$^{85}$: the deposition of calcium in the footplates
  - **25 mg NaF** for 6 months
  - decrease or cessation of activity at the otosclerotic focus
  - neutralising and inactivating the hydrolytic and proteolytic enzymes

- **Linthicum et al. (1974):**
  - proteolytic and hydrolytic enzymes on the **organ of Corti**
  - Stapedial fixation halted: destruction of collagen fibres secondary to the inhibition of enzymes
Arresting active phase of otosclerosis (2)

- Bretlau et al. (1981):
  - 20 stapes from patients:
    - minimum of 12 months of NaF treatment
  - 16 stapes from patients:
    - no treatment
  - NaF group: sclerotic type
  - Non-treated group: mixed type

- Calcium fluoride ratio statistically higher ($p < 0.001$),
- (mean 2.59, of NaF group: mean 2.05 of Non-treated group)
Arresting active phase of otosclerosis (3)

- Shambaugh (1981):
  - Rate of osteogenesis $\rightarrow$ rate of uptake of radioactive calcium from living otospongiotic bone
  - Rate of resorption $\rightarrow$ production of acid phenylphosphatase
  - Increased level of acid phenylphosphatase compared with otosclerotic bone

- NaF short-term therapy $\rightarrow$ level of the enzyme starts to decline
- NaF for one year $\rightarrow$ enzyme declines to the level of mature otosclerotic bone
Molecular studies

- **Bodo et al. (1995, 1997)**
  - Otosclerosis pathogenesis:
    - Abnormal increase of sulphation of bone matrix glycosaminoglycan
  - *Diastrophic dysplasia sulphate transporter (DTDST):* correlate with SNHL of otosclerosis
    - Increased in bone cells derived from the stapes and the EAC on otosclerotic patient
  - NaF: block intracellular calcium-signal pathway in stapes

- **DTDST:**
  - Sulfation of bone matrix glycosaminoglycans (S-GAG)
  - Increased bone turn over
Increased Activity of the DTDST in Otosclerosis and Its Inhibition by NaF

- BOZORG GRAYELI (2003)
  - NaF inhibits DTDST activity in otosclerosis
    - in the stapes: via the intracellular calcium pathway
    - in the EAC: via both cAMP and intracellular calcium

Verapamil (type-L calcium channel inhibitor)
  - suppresses the action of NaF on DTDST

- *Otology & Neurotology, Vol. 24, No. 6, 2003*
Glucocorticoids Inhibit DTDST Activity in Otosclerosis

- **Imauchi (2006):**
  - Dexamethasone inhibits the DTDST activity
  - Reduction of IL-6 secretion only in otosclerotic cells
  - Decreasing the autocrine/paracrine interleukin production
  - Reduction of bone turnover

*Laryngoscope 116: September 2006*
Human osteoblast-like cell cultures obtained from otosclerotic stapes

[Diagram showing biological pathways involving substances like Dex, Interleukines, Cl-, NaF, DTDST, SO4^2-, S-GAG, Extracellular matrix S-GAG, Turnover and cell proliferation.]
Epidermiological studies

- **Vartiainen et al. (1997)**
  - Fluoridation of water study in 294 patients
    - (94 fluorinated water (1mg/l) and 200 fluoride poor water) average of 21 years
    - long-term bone and air conduction thresholds after large fenestra stapedectomy
    - no different change either in the short term (6–12 months) or in the long term (9 years).

- **Daniel et al. (1973)**
  - Fourfold increase in the incidence of stapedial otospongiosis in a low-F area compared to high-F area (1.9 mg/l)
  - whole of their life
Clinical studies

- Shambaugh and Petrovic (1967)
  - CT scan of NaF 3-6 months: no significant change (71%)

- Shambaugh et al. (1977): 465 ears
  - NaF treatment for 1~6 years hearing remain unchanged in 80% ones and 3% improved

- Causse et al. (1985) → 10441 retrospective review
  - NaF slow the stapedial fixation in some cases but does not release the fixation

- Derks et al. (2001)
  - NaF more effective > 2 years when initial SNHL < 50 dB
  - slow down the progression of SNHL in low and high frequencies
Effects on tinnitus associated with OS

- Otosclerosis tinnitus $\rightarrow$ 64.9~84.5% (1955,2003)

- Sziklai et al. (1992)
  - 7-isopropoxy-isoflavone (bioflavinoid)
  - 9 used, 7 placebo
  - all improved after 6 months drugs used
    (3 months prior to stapedectomy and a further 3 months after surgery)
  - only up 50% in control group

- Poor methodological quality and has insufficient power
NaF effects on vertigo

- Otosclerosis vertigo
  - mild imbalance, or true vertigo with severe imbalance
  - recurrent attacks of severe vertigo

- Cole, Funkhouser (1972), and Cody (1978)
  - NaF control vestibular symptoms of otosclerosis

- Bretlau et al. (1985, 1989) → NaF for dizziness
  - short term: anti-enzymatic effect
  - long term effect: decrease bone remodelling

- Causse et al. (1993) → 224 patients nystagmography
  - 70% operated and 60% unoperated ones improved of 6+ months NaF
Early stage of otosclerosis

- Forquer et al. (1986) → retrospective review of 192 patients with 25 mg NaF for 2 years → 104/192 (54%) slowed or stopped the progression of hearing loss

- Bretlau et al. (1989) → 95 patients → 12-24 months 40 mg/day NaF → 7% of 43 used ones and 25% of 52 controls hearing worse (P<0.025)

- Colletti and Fiorino (1991) → 93 ears (63 patients) use NaF + Ca + Vit. D for 2 years, 100 ears (65 patients) nil
  - Stapedial reflex stable in 90.5% treated ones and 76.7% controlled ones at 2 years → 3 years F/U 80.2% and 57.7%

- Conductive hearing loss occurs later, preceded involvement of footplate a few years
NaF side effects and contraindications

- Riggs et al. (1980) → 42% of patients (NaF 50 mg/day)
  - arthralgias, GI upsets
  - myelopathy, exostosis, ligament calcifications, bone pain
- (1984) 35000 patients used NaF worldwide
  → minor side effects, most *gastric distress*

- Contraindications:
  - Renal impairment
  - Breast-fed fetus and infants (pregnant and nursing women decrease the dose of NaF)
  - < 12 y/o decrease dose due to bone growth delay
NaF criteria for treatment

☐ Shambaugh GE Jr. (1977)
  ☐ Hearing loss of 2 dB/year in the speech frequencies
  ☐ Hearing loss of > 5 dB/year in any frequency
  ☐ Unexplained, progressive SNHL disproportionate to the age, particularly with otosclerosis family history
  ☐ Radiological evidence of an active lesion in the otic capsule
  ☐ Vertigo or severe tinnitus in a patient with otosclerosis
  ☐ A positive Schwartz’s sign found
Follow up of NaF used

- Serum Ca, P, alk-P, stool blood, skeletal imaging, side effects
- Hearing check after 6 months NaF used, then 1 to 2 years interval
- No progress of H-L, continuously for 2 years
- Progress H-L, dosage doubled
NaF treatment schedule

- Causse et al. (1993)
  - > 20 mg for inhibit enzymatic activity
    - 20 mg/day, 5 days/week for advanced otospongiosis, continued for 6~8 months
  - 3-10 mg/day for the enzymatically less active stapedial fixation
  - 2 mg/day for children due to skeletal development
  - Pregnant women → 2 mg/day and 5 days/week
Biphosphonates effects on OS

- Stimulate trabecular bone formation
- Reduce bone resorption and turnover
- Causse et al. (1993)
  - Alternative for NaF intolent ones
  - Good efficacy to active otospongiosis and Schwartz’s sign (+), young people
  - Side effects: Etidronate (one of biphosphonates)
    - impaired mineralisation of bone (similar to Vit. D deficiency and osteomalacia)
- 20~30 % nausea and diarrhea
- dyspepsia, GI ulcers, Acute renal failure, Hypocalcemia
NaF on the difficulty of working with the footplate

- **Fe'lix-Trtijill et al (2009)**
  - 20 mg of NaF every 12 hours for a 6-month period
  - Not increase the difficulty of working with the footplate during stapedectomy
  - Not increase the difficulty of fenestration and extraction on the footplate, presence and number of lyses, the number of calcified foci, or footplate thickness
  - Greater hearing gain for frequencies 125, 500, 8,000 Hz
  - Greater bone conduction hearing gain at 500, 1,000, and 2,000 Hz

Conclusion

- NaF → neutralising and inactivating the hydrolytic and proteolytic enzymes → inhibit trypsin activity
- Fluorapatite crystals to resist osteoclastic enzymatic bone resorption, reduce bone remodelling
- NaF inhibit → diastrophic dysplasia sulphate transporter (DTDST) to SNHL in
- Drinking water with fluorinated water 1.9 mg/L prevent progress
- NaF can improve otosclerosis vertigo and also suggested for early otosclerosis used
Reference


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Thank You For Attention~