Hearing loss in osteogenesis imperfecta: an overview

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• PART I: Introduction: the EAR
• PART II: Hearing loss in OI
  – Audiologic, otologic and radiologic phenotype
  – Correlation with genotype
  – Correlation with bone mineral density
• PART III: Summary
The Ear
Anatomy & physiology
Hearing loss classification

- Conductive
- Sensorineural
- Mixed

Outer | Middle | Inner | Auditory nerve
Audiometry

- Air conduction
- Bone conduction
- Air-bone gap
- Sensorineural component
- Conductive component
PART I: Introduction: the EAR

PART II: Hearing loss in OI
  – Audiologic, otologic and radiologic phenotype
  – Correlation with genotype
  – Correlation with bone mineral density

PART III: Conclusion
2.1. Cross-sectional study

Subjects:
- **Origin:**
  - Belgium: 84
  - Netherlands: 67
  - Italy: 31
  - **TOTAL:** 182

- **OI types:**
  - Mild OI type I: 4
  - Severe OI type III: 26
  - Moderate OI type IV: 152

- **F/M ratio:** 94/88
- **Mean age:** 30.2 y (SD:16.9; 3-89 years)
- **Confirmed mutation in** COL1A1 or COL1A2

2.1. **Otological findings**

- **Micro-otoscopy revealed**
  - Normal eardrums in 52.2%
  - Translucent eardrums in 42.3%
  - Tympanosclerosis and scarring in 5.5%

- **21.2% used hearing amplification**
  - Hearing aids 18% (39 patients)
  - Cochlear implants 2% (4 patients)
  - Bone-anchored hearing aid 0.5% (1 patient)
2.1. **Audiologic characterization**

<table>
<thead>
<tr>
<th>Age category</th>
<th>Deafness</th>
<th>Sensorineural</th>
<th>Mixed</th>
<th>Conductive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 y.</td>
<td>6.3%</td>
<td>34.1%</td>
<td>5%</td>
<td>3%</td>
<td>45</td>
</tr>
<tr>
<td>10-19 y.</td>
<td>38.5%</td>
<td>38.5%</td>
<td>9%</td>
<td>6%</td>
<td>92</td>
</tr>
<tr>
<td>20-29 y.</td>
<td>76.0%</td>
<td>48%</td>
<td>14%</td>
<td>3%</td>
<td>141</td>
</tr>
<tr>
<td>30-39 y.</td>
<td>54.5%</td>
<td>44%</td>
<td>16%</td>
<td>4%</td>
<td>118</td>
</tr>
<tr>
<td>40-49 y.</td>
<td>78.1%</td>
<td>26%</td>
<td>16%</td>
<td>7%</td>
<td>123</td>
</tr>
<tr>
<td>50-59 y.</td>
<td>77.3%</td>
<td>22%</td>
<td>15%</td>
<td>6%</td>
<td>116</td>
</tr>
<tr>
<td>60 y. ≤</td>
<td>92%</td>
<td>6%</td>
<td>14%</td>
<td>4%</td>
<td>105</td>
</tr>
</tbody>
</table>

N=364 ears
2.1. Audiologic characterization

- Quisling et al. (1979) (N=68)
  - Deafness: 47%
- Riedner et al. (1980) (N=70)
  - Sensorineural: 41%
- Cox & Simmons (1982) (N=30)
  - Conductive: 37%
- Shapiro et al. (1982) (N=55)
  - Sensorineural: 64%
- Pedersen (1984) (N=173)
  - Sensorineural: 56%
- Stewart & O'Reilly (1989) (N=56)
  - Conductive: 58%
- Garretsen et al. (1997) (N=142)
  - Deafness: 78%
- Kuurila et al. (2002) (N=133)
  - Mixed: 45%
- Swinnen et al. (2012) (N=182)
  - Mixed: 52%

- Deafness: 1.4%
- Sensorineural: 11.6%
- Mixed: 26.4%
- Conductive: 8.5%
## 2.1. Audiologic characterization

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Conductive/mixed loss (36.3%)</th>
<th>Pure sensorineural loss (11.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>2\textsuperscript{nd} to 4\textsuperscript{th} decade (mean 21.3 y.)</td>
<td>Any age (mean 30.2 y.)</td>
</tr>
<tr>
<td>Gender</td>
<td>No gender dependency</td>
<td>No gender dependency</td>
</tr>
<tr>
<td>Severity</td>
<td>• Age &lt; 40 y.: mild (15-40 dB HL) to moderate (40-70 dB HL)</td>
<td>Mild (95.2%) or moderate (4.8%)</td>
</tr>
<tr>
<td></td>
<td>• Age ≥40 y.: mild to profound (≥ 95 dB HL)</td>
<td></td>
</tr>
<tr>
<td>Audiometric configuration</td>
<td>• Flat (70.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sloping (27.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rising (2.3%)</td>
<td></td>
</tr>
<tr>
<td>Symmetry</td>
<td>Predominantly symmetric</td>
<td>Predominantly symmetric</td>
</tr>
<tr>
<td>ARTAs</td>
<td>• ABG frequency-specific but age-independent</td>
<td>• ATD: 0.2 dB/y. (0.5-1.0-2.0 kHz) to 1.2 dB/y. (0.8 kHz)</td>
</tr>
<tr>
<td></td>
<td>• Annual threshold deterioration (ATD) 0.6 dB/y. (≤ 2 kHz) to 0.8 dB/y. (8 kHz)</td>
<td></td>
</tr>
</tbody>
</table>
Age-related typical audiograms (ARTAs)

Conductive / mixed hearing loss

Sensorineural hearing loss
2.1. Audiologic characterization

**Conductive component**
- Stapes footplate fixation: otosclerosis-like lesion
  - discontinuity due to atrophic/fractured ossicles

**Sensorineural component**
- Otosclerosis-like lesions affecting the otic capsule
- Microfractures of the cochlea
- Atrophy hair cells or stria vascularis

- Isolated disease of temporal bone
- Prevalence 0.3-0.4
- Hereditary factors
- F/M ratio 3:1

Prevalence 0.3-0.4
Hereditary factors
F/M ratio 3:1

Hereditary factors
F/M ratio 3:1
2.2. Radiologic characterization

• Subjects
  o 17 hearing-impaired OI patients
  o Age: 9-67 y.
  o COL1A1 or COL1A2 mutation

• Retrospective study
  o Audiograms
  o CT images temporal bone (17 patients, 33 ears)
  o MR images (4 patients, 8 ears)

2.3. Radiologic characterization

- Fenestral hypodensities in 26/33 ears (79%)

Correlation with air-bone gap
($r=0.464; p<0.05$)
2.2. Radiologic characterization

- Retrofenestral hypodensities in 20/33 ears (61%)

Correlation with average bone conduction threshold
($r=0.471; p <0.05$)
2.2. Audiologic phenotype-genotype correlation

• Subjects:
  114 OI subjects
  o Hearing-impaired (conductive/mixed/sensorineural)
  o Normal hearing and age ≥ 40 y.

• Genetic analysis:
  Mutation screening/analysis of COL1A1/COL1A2

• Correlation analysis:
  o Between-subjects comparisons (N=114)
  o Intrafamilial comparisons (26 families)

2.3. **Audiologic phenotype-genotype correlation**

**Mutated gene**

- COL1A1
- COL1A2

<table>
<thead>
<tr>
<th>Normal</th>
<th>Conductive/Mixed</th>
<th>Sensorineural</th>
</tr>
</thead>
</table>

**Type I collagen defect**

- Quantitative
- Qualitative

Audiologic phenotype independent of mutated gene or type I collagen defect
2.3. Audiologic phenotype-genotype correlation

Intrafamilial variability:

- **Affected** COL1A1 c.1354-12G>A
- **Unaffected**

<table>
<thead>
<tr>
<th>Generation</th>
<th>Age</th>
<th>Genetics</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>67 y</td>
<td>SNHL/SNHL</td>
<td>SNHL/SNHL</td>
</tr>
<tr>
<td>II</td>
<td>42 y</td>
<td>M/M</td>
<td>SNHL</td>
</tr>
<tr>
<td>III</td>
<td>14 y</td>
<td>C/C</td>
<td>sensorineural</td>
</tr>
<tr>
<td>III</td>
<td>12 y</td>
<td>NL/C</td>
<td>mixed</td>
</tr>
<tr>
<td>III</td>
<td>6 y</td>
<td>NL/NL</td>
<td>conductive</td>
</tr>
<tr>
<td>III</td>
<td>4 y</td>
<td>NL/NL</td>
<td>normal hearing</td>
</tr>
</tbody>
</table>

Intrafamilial variability in audiologic phenotype
2.3. Audiologic phenotype-clinical OI type correlation

Audiologic phenotype independent of clinical OI type
2.4. Genetic modifiers for hearing loss in OI

Introduction

- No correlation between audiologic phenotype and mutation in *COL1A1* or *COL1A2*
- Genetic modifier?

- Clinical similarities with *otosclerosis*

Associated with SNP T263I in *TGFB1* (protective)*

<table>
<thead>
<tr>
<th>Audiologic phenotype</th>
<th>C allele n (%)</th>
<th>T allele n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal hearing</td>
<td>18 (17.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>86 (82.7)</td>
<td>5 (100.0)</td>
</tr>
<tr>
<td>o Conductive/mixed hearing loss</td>
<td>70 (67.3)</td>
<td>3 (60.0)</td>
</tr>
<tr>
<td>o Pure sensorineural hearing loss</td>
<td>16 (15.4)</td>
<td>2 (40.0)</td>
</tr>
</tbody>
</table>

*Audiologic phenotype in OI is NOT associated with SNP T263I in *TGFB1*

2.5. Association between audiologic phenotype and BMD

Introduction

• Principal characteristic of OI: bone fragility

• Hearing loss in OI ~ bony changes temporal bone

Hearing loss in OI ~ bone quality?

2.5. Association between audiologic phenotype and BMD

Methods

Subjects:
  • 56 adult OI patients

Measurements:
  • Audiometry
  • Bone densitometry: bone mineral density (BMD)
    o Dual X-ray absorptiometry
    o Peripheral quantitative computed tomography
2.5. *Association between audiologic phenotype and BMD*  

**Methods**

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Body level</th>
<th>Bone</th>
<th>Parameter</th>
<th>Illustrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXA</td>
<td>Lumbar spine (L1-L4)</td>
<td>Trabecular bone</td>
<td>Areal BMD (aBMD)</td>
<td><img src="image1" alt="DXA Illustration" /></td>
</tr>
<tr>
<td></td>
<td>Whole body</td>
<td>Cortical bone</td>
<td>aBMD</td>
<td><img src="image2" alt="DXA Illustration" /></td>
</tr>
<tr>
<td>pQCT</td>
<td>Radial metaphysis (4%)</td>
<td>Trabecular bone</td>
<td>Volumetric BMD (vBMD)</td>
<td><img src="image3" alt="pQCT Illustration" /></td>
</tr>
<tr>
<td></td>
<td>Radial diaphysis (66%)</td>
<td>Cortical bone</td>
<td>vBMD</td>
<td><img src="image4" alt="pQCT Illustration" /></td>
</tr>
</tbody>
</table>

4% and 66% indicate the percentage of bone density at different locations.
2.5. **Association between audiologic phenotype and BMD**

**Results**

- ANCOVA (age, weight, type I collagen defect): lower BMD in OI patients with **conductive/mixed hearing loss** ($p<0.05$)
2.5. **Association between audiologic phenotype and BMD**

- **Observation:**
  Conductive/mixed hearing loss in OI associated with low BMD

- **Hypothetical explanation:**

  ![Diagram of bone remodeling process](image)

  - Low BMD
  - Accumulation of microfractures
  - Destruction of bone remodeling inhibition pathways
  - Abnormal bone remodeling in temporal bone

  ! Temporal bone: cortical bone
• PART I: Introduction: the EAR
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  – Correlation with genotype
  – Correlation with bone mineral density
• SUMMARY
### Summary

**Hearing loss in OI: clinical characteristics**

**Hearing loss prevalence:**
- Overall: 52% (≈ literature) but might be overestimated

**Hearing loss type:**

<table>
<thead>
<tr>
<th>Type</th>
<th>%</th>
<th>Onset</th>
<th>Etiopathology</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conductive</td>
<td>8.5%</td>
<td>2\textsuperscript{nd} - 4\textsuperscript{th} decade</td>
<td>Abnormal bone remodeling fenestral structures</td>
<td>Mild to moderate (progressive)</td>
</tr>
<tr>
<td>Mixed</td>
<td>27.8%</td>
<td>From 2\textsuperscript{nd} decade onwards</td>
<td>Abnormal bone remodeling proliferating to retrofenestral structures</td>
<td>Mild to profound (progressive)</td>
</tr>
</tbody>
</table>
Summary
Audiologic phenotype – genotype correlation

• Present study: 114 OI subjects no association between
  - Hearing loss occurrence
  - Type of hearing loss
  - Mutated gene (COL1A1 or COL1A2)
  - Type I collagen defect (quantitative or qualitative)
  - Location of mutation in proα chain

• Hartikka et al (2004): 49 OI subjects no association between
  - Hearing loss occurrence
  - Type of hearing loss
  - Severity of hearing loss
  - Mutated gene (COL1A1 or COL1A2)
  - Mutation type
Summary

Audiologic phenotype – genotype correlation

- **TGFB1**: SNP T263I
  - No influence on audiologic phenotype in OI

- Hearing loss in OI is variable and unpredictable.

Future perspectives:
- Effect of pharmacological agents for remediation of bone on the hearing in OI
- Identification of modifier genes
  - Candidate-genes associated with otosclerosis (BMP2, BMP4, ACE, AGT, RELN, ...)
  - Genetic linkage in large OI families with normal-hearing and hearing-impaired relatives
- SNP arrays in a large OI population
THANK YOU!