Hearing Changes in Meniere’s Disease: Categorizing Patterns of Change Over Time

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Michael Hoa, MD
Meniere’s Disease and measurement of hearing loss
- Primary complaint: vertigo
- Traditional phenotype: pure-tone average

Data
- Retrospectively obtained hearing tests
- Hearing affected by both disease and age

Analysis
Why conduct these analyses of hearing data in Meniere’s?

- Hypotheses of pathology affecting function
- Clinical trial endpoints
- Select useful metrics for genetic studies
  - Appropriately identify disease states
    - Medical history of symptom development OR
    - Single hearing measurement OR
    - Time to a specific hearing loss
  - Disease progression
What is Meniere’s Syndrome?

With or without vertigo

Hearing loss in one or both ears

USC Tina and Rick Caruso
Department of Otolaryngology
Head and Neck Surgery
Meniere’s = Miserable

Meniere’s Disease

Vertigo
Tinnitus
Hearing Loss

Results from abnormal fluid and ion homeostasis in the inner ear

May be managed with diuretics and salt restriction

I quit!
Who are the patients?

- Female/Male 2:1
- Average age first vertigo attack: 50-ish
- As few as 3:100,000 to 513:100,000
- Variations:
  - Hearing loss only
  - Both ears affected
  - Sudden onset, both ears
Pathophysiology of Meniere’s
Measurement of Hearing by Ear

![Diagram of hearing levels and frequencies]

- Quiet
- Normal hearing
- Loud

Frequency (Hz):
- Low pitch
- High pitch

Hearing level (dB):
- 125, 250, 500, 1000, 2000, 4000, 8000
Measurement of Hearing by Ear

[Graph showing hearing levels across different frequencies and loudness levels, with a shaded area indicating normal hearing range.]
Measurement of Hearing by Ear

Typical Meniere's

![Diagram showing hearing levels and frequencies.](image)
Conventional hearing measurement

Study endpoint
Low frequency average
Figure 1. Variants in NFKB1 gene and hearing outcome in patients with MD were compared by Kaplan-Meier survival curves and the log-rank test.

Differences in cochlea base to apex

- **High frequency:** Apex: wide and floppy
- **Low frequency:** Base: narrow and stiff
- **Frequency producing maximum amplitude:**
  - 500 Hz
  - 1 kHz
  - 2 kHz
  - 4 kHz
  - 8 kHz
  - 16 kHz
Pathophysiology of Meniere’s
Added complication: Age-related hearing loss
Research questions

• Low frequency affected by disease ONLY
• High frequency affected by age
• Or is high frequency affected by age and disease?
The Data
Data Cleaning

• Collected in 2 waves
• Clinical capture of data
  • Selected evaluations no more than 6 months apart
  • The highest frequency not measured consistently
  • Profound hearing loss (threshold >90 dBHL at any frequency)—coded as missing
  • Unilateral Meniere’s patients only
Time

Frequencies

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Sample characteristics

- n=246 (unilateral)
  - 127 (52%) F, 119 (48%) M
  - Age, first evaluation: 49.6 (SD=12.7 years)
  - Word recognition score: 100%
  - Diagnosed with allergy 98 (40%)
  - 103 had up to 7 evaluations
    - Over 5 years
Raw averages across Evaluation and Frequency
## Association of Age by Frequency

### Unaffected Ear

<table>
<thead>
<tr>
<th></th>
<th>age</th>
<th>f250</th>
<th>f500</th>
<th>f1k</th>
<th>f2k</th>
<th>f3k</th>
<th>f4k</th>
<th>f6k</th>
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<tbody>
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<tr>
<td></td>
<td>.227**</td>
<td>.246**</td>
<td>.283**</td>
<td>.310**</td>
<td>.378**</td>
<td>.416**</td>
<td>.410**</td>
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</table>

### Affected Ear

<table>
<thead>
<tr>
<th></th>
<th>age</th>
<th>f250</th>
<th>f500</th>
<th>f1k</th>
<th>f2k</th>
<th>f3k</th>
<th>f4k</th>
<th>f6k</th>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>.166**</td>
<td>.150**</td>
<td>.185**</td>
<td>.279**</td>
<td>.340**</td>
<td>.379**</td>
<td>.394**</td>
<td></td>
</tr>
</tbody>
</table>
By Frequency

**Unaffected Ear**
- Frequency: 250, 500, 1000, 2000, 3000, 4000, 6000
- Average Threshold (dBHL)

**Affected Ear**
- Frequency: 250, 500, 1000, 2000, 3000, 4000, 6000
- Average Threshold (dBHL)
### Mixed Model

#### Null

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Wald Z</th>
<th>Sig</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeated Measures</td>
<td>AR1 diagonal</td>
<td>204.481122</td>
<td>8.116542</td>
<td>25.193</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>AR1 rho</td>
<td>.652969</td>
<td>.014554</td>
<td>44.866</td>
<td>.000</td>
</tr>
<tr>
<td>freqN [subject = ID * earT]</td>
<td>Variance</td>
<td>485.204016</td>
<td>16.260746</td>
<td>29.839</td>
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</table>

a. Dependent Variable: thrsh.

#### With Fixed

<table>
<thead>
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<th>Estimate</th>
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<th>Sig</th>
<th>95% Confidence Interval</th>
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<tr>
<td>Repeated Measures</td>
<td>AR1 diagonal</td>
<td>141.938039</td>
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</table>

a. Dependent Variable: thrsh.
The Analysis
Analysis

- Descriptive questions
  - Change in level (intercept) or pattern across evaluation (slope)?
  - Groups of similar patterns of change in low and high frequencies over time?
  - Within a group, are low and high frequency changes associated? I.e., the entire cochlea is affected by disease?
  - Demographic characteristic differences by group?
Dimension reduction

- Appears that in the non-diseased ear ~no change
- Modeling only diseased ear
- Created Low and High frequency variables from regressions of frequency on threshold
  - Low = 250, 500, 1000 Hz
  - High = 2000, 3000, 4000, 6000 Hz
  - Unstandardized intercepts (level)
Growth models assembled in stages

- Change in low frequency threshold
- Change in high frequency threshold
- Parallel change low and high frequency threshold
- **Finally**: LCA/mixture
Low frequency growth

Model Fit
$X^2 = .112, \ p=n.s.$
RMSEA = .0001
SRMR = .0004
High frequency growth

Model Fit
$X^2 = 3.2, \ p = \text{n.s}$
$\text{RMSEA} = .018$
$\text{SRMR} = .044$
Parallel Process Model

Model fit
$X^2 = 20.5, \ p=n.s$
RMSEA=.05
SRMR=.07
Mplus Growth Mixture Model

MODEL:

%OVERALL%

il sl | ilo1@0 ilo2@1 ilo3@2 ilo4@3;

ih sh | ihi1@0 ihi2@1 ihi3@2 ihi4@3;

ilo1 with ihi1;

ilo2 with ihi2;  suggestion from Mplus discussion board

ilo3 with ihi3;

ilo4 with ihi4;

il with ih@.5;

il with sh@0;  constrained all classes to have equal loadings

ih with sl@0;

sl with sh;

ih with sh@.5;

il with sl;

sh@1;

[sh@0];

ih@1;
## Selecting number of classes

<table>
<thead>
<tr>
<th>Class</th>
<th>BIC</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 class</td>
<td>10482</td>
<td>.93</td>
<td>.92</td>
<td>.93</td>
<td></td>
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<tr>
<td>4 class</td>
<td>10466</td>
<td>.83</td>
<td>.82</td>
<td>.91</td>
<td>.93</td>
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<tr>
<td>5 class</td>
<td>10468</td>
<td>.88</td>
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<td>.73</td>
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<td>.772</td>
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<tr>
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<td>.745</td>
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<td>k-1 test</td>
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<td>p&lt;.00001</td>
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6 class solution not significantly different from the 5 class
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6 class solution not significantly different from the 5 class
5 Class distributions Eval 1
5 Class distributions Eval 2
5 class distributions Eval 3
5 class distributions Eval 4

Graph showing 5 class distributions for ILO4 and IHI4.
4 Class Low Frequency Factor Scores
4 Class distributions Eval 1

Distribution vs. ILO1

Distribution vs. IHI1
4 Class distributions Eval 2
4 Class distributions Eval 3
4 Class distributions Eval 4
4 class model

Class size
1 17 7%
2 32 13%
3 128 52%
4 68 28%
### 4 Class Demographics

<table>
<thead>
<tr>
<th>Hearing Class</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Allergy (N,Y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Best</td>
<td>49.6</td>
<td>47% M/53% F</td>
<td>53% N/47% Y</td>
</tr>
<tr>
<td>2</td>
<td>48.7</td>
<td>29% M/71% F</td>
<td>47% N/53% Y</td>
</tr>
<tr>
<td>3</td>
<td>54.3</td>
<td>51% M/49% F</td>
<td>66% N/34% Y</td>
</tr>
<tr>
<td>4 Worst</td>
<td>47.6</td>
<td>50% M/50% F</td>
<td>56% N/44% Y</td>
</tr>
</tbody>
</table>
Allergy diagnosis/treatment by Class

- Graph 1: Average Threshold (dBHL) vs. Frequency (Hz)
- Graph 2: Average Threshold (dBHL) vs. Frequency (Hz)
- Graph 3: Average Threshold (dBHL) vs. Frequency (Hz)
- Graph 4: Average Threshold (dBHL) vs. Frequency (Hz)
Wave 2

- Two evaluations
- Need more evaluations to confirm the 4 class solution
Wave 2: 3 Class solution

![Graph showing three class solutions for wave 2. The x-axis represents frequency (Hz), and the y-axis represents average threshold (dBHL). The graph includes three colored lines representing different classes: red, green, and blue. The classes are labeled as Wave 2 Class 1, Wave 2 Class 2, and Wave 2 Class 3.]
Analysis

- Descriptive questions answers
  - Change in level (intercept) or pattern across evaluation (slope)? YES
  - Groups of similar patterns of change in low and high frequencies over time? YES
  - Within a group, are low and high frequency changes associated? I.e., the entire cochlea is affected by disease? YES
  - Demographic characteristic differences by group? YES
Challenges to conventional understanding of Meniere’s

• No one path of disease progression for hearing

• Parallel growth model suggests the entire cochlea is involved
  • Follows the cochlear pathology

• Class with poorest hearing youngest patients
  • More aggressive disease?
Challenge to conventional understanding of Meniere’s

- Allergy diagnosis/treatment actually has a protective affect on hearing for 2 classes of hearing loss
- Supports controversial immunological hypothesis
- LCA revealed salient subtypes of the disease
  - Targeted treatments
In Memoriam

John K. Niparko, MD