NCRAR Workshop

Ototoxicity
Early Identification & Monitoring

VA Rehabilitation Research & Development
National Center for Rehabilitative Auditory Research
Outline

I. Learner Outcomes
II. Overview: Basic Principles
III. Tinnitus Monitoring
IV. Ototoxicity Monitoring in Adults
V. Objective Monitoring
VI. Ototoxicity Monitoring in Children
VII. Establishing Program
VI. Ototoxicity Monitoring in Children

Kristy Gilmer Knight MS CCC-A
Doernbecher Children’s Hospital
Background

- Incidence of ototoxicity in children treated with platinum chemotherapy: 26% to over 90%
  - Differences in dose of drug, time between courses, time of administration, cumulative dose
  - Differences in age
  - Definition of ototoxicity
  - Individual variability
Characteristics of platinum ototoxicity

- Hearing loss in the high frequencies initially.
- Hearing loss increases in severity and spreads to lower frequencies with continued treatment.
- Platinum causes damage to stria vascularis, outer hair cells, and eventually inner hair cells.
  - Blakely et al., Otolaryngology Head & Neck Surgery, 1993
Factors that increase a child’s risk for platinum ototoxicity

- Young age
- Cranial radiation before platinum chemotherapy.
- Cumulative cisplatin dose >400 mg/m2.
- Treatment with cisplatin and carboplatin.
- Use of aminoglycoside antibiotics (common), and/or loop diuretics during chemotherapy.
- Kidney disease/dysfunction.

Li et al., Pediatric Blood and Cancer, 2004
Why monitor for ototoxicity?

- Oncologist may be able to decrease platinum dose or delete platinum from treatment.
- Recommend habilitation for hearing loss if needed.
- Provide information to parents/teachers – children may not report difficulty hearing.
Consequences of High Frequency Hearing Loss

- Difficulty hearing/discriminating high frequency speech sounds (s, f, th, k, p, h, sh, ch).
- Difficulty hearing speech over distance and in noise.
- Difficulty hearing morphological markers of speech (plurals, tense).
- Delay in speech and language development in young children.
- Increased risk for difficulty in school.
Need for Long-term Monitoring:

- 120 children treated with platinum chemotherapy were followed for a median 7 years after treatment.
- 37% treated with cisplatin and 43% treated with cisplatin and carboplatin had further deterioration of hearing (>20 dB).
- Progression seen in lower frequencies on follow-up.
- Hearing loss seen in children who did not show ototoxicity during treatment.

Ototoxicity Monitoring at DCH

- Baseline before the first platinum treatment:
  - Pure tone thresholds 500-8000 Hz.
  - Tympanometry.
  - Measurement of DPOAE’s.
    - $f_2$: 1500-10,000 Hz, $L_1/L_2=65/55$ dB SPL, $f_2/f_1=1.22$
  - Extended high frequency audiometry.
Monitoring Evaluations

- Before each platinum cycle:
  - Repeat pure tone thresholds 500-8000 Hz.
  - Tympanometry.
  - DPOAE’s.
  - Extended high frequency audiometry.
  - Bone conduction thresholds if significant threshold shift.
Long-term Monitoring

- Children without hearing loss at the end of treatment: 6 months and then annually for 3 years.
- Children with hearing loss: 3 months and then every 6 months.
Methods of Behavioral Evaluation

6 to 30 months: Visual reinforcement audiometry (with insert earphones whenever possible).

24 months – 6 years: Conditioned play audiometry.

Over 6 years: Standard pure tone audiometry (6-20 years).
Methods of Behavioral Evaluation

- Tone evoked ABR
  - Used to estimate thresholds of hearing in children too young or too ill to provide reliable pure tone thresholds.
  - Pediatric sedation.
  - Thresholds measured for 500, 1000, 2000, 4000 Hz stimuli.
  - Measured down to threshold within 5 dB nHL.
  - ABR repeated if DPOAE’s or behavioral responses indicate change in hearing.
Retrospective Study of Children Seen at DCH

- N=67
- 8 months – 20 years treated with cisplatin/carboplatin or both.
- Dose of cisplatin/carboplatin and treatment schedule varied depending on diagnosis.
- Monitored with conventional audiometry.
- Ototoxicity defined by ASHA criteria.

- Gilmer Knight et al., Journal of Clinical Oncology, in press.
Results:

- 41/67 (61%) bilateral ototoxicity.
- Most children met ASHA criteria by 2\textsuperscript{nd} or 3\textsuperscript{rd} treatment.
- 17/41 children with ototoxicity referred for hearing aids.
- Children who had higher cumulative doses of cisplatin acquired more severe hearing loss.
- As a group, children treated for neuroblastoma had the most severe hearing losses (moderate-severe 3000-8000 Hz).
DPOAE’s & Conventional Audiometry

- N=30 children (7 months to 20 years).
- 20/30 (67%) bilateral ototoxicity (ASHA criteria) in the conventional frequencies.
- Additional 4 with unilateral ototoxicity (left ear).
- 25/30 (83%) bilateral changes in OAE’s.
- Additional 2 with unilateral decreases in OAE’s (left ear).
- DPOAE’s changed before pure tone thresholds.
- DPOAE’s were decreased in every child who had ototoxicity in the conventional frequencies.
15 children (5-20 years) had monitoring with pure tone audiometry 500-16,000 Hz and DPOAE’s.

14/15 (93%) had bilateral ototoxicity by ASHA criteria in the EHF (and one in the right ear only).

10/15 (67%) bilateral changes in OAE’s, (and 2 left only).

8/15 (53%) bilateral ototoxicity conventional frequencies, (and 2 left only).
Challenges:

- Cooperation, attention, poor response reliability when child is ill.
- Difficulty measuring EHF audiometry in children younger than 5 years.
- Middle ear pathology.
- Need for sedation to measure threshold ABR’s.
- Need for quiet child when measuring OAE’s.
Suggestions:

- Use a trained test-assistant.
- Schedule enough time to complete the evaluation.
- Measure high frequencies first (start at 8000 Hz).
- Have many interesting, quiet toys.
- Measure OAE’s in the child’s room during sleep, or following sedated procedure.
Case Study

- 8 year old female diagnosed with hepatoblastoma September 2004.

- Medical history: congenital grade 3 hydronephrosis and duplication anomalies of the left kidney. Corrective surgery at 9 months.
Chemotherapy Treatment:

- Vincristine, 5-Fluorouracil, Cisplatin
- Cisplatin dose
  - 100 mg/m2 over four hours every 3 weeks, 6 courses.
  - Target cumulative dose 600 mg/m2.
Baseline Evaluation

- Normal hearing sensitivity 250-8000 Hz.
- Normal DPOAE’s 1500-5000 Hz. OAE’s were reduced at 5900-10,000 Hz.
- EHF thresholds 30 dB SPL or lower 9000-16,000 Hz.
Right: 09-Sep-04: 1.5-10 kHz Ototoxic Test: 04l09D03.OAE
Ear: Left

Left: 09-Sep-04: -: 1.5-10 kHz Ototoxic Test: 04I09D02.OAE
Ototoxicity EHF after first cisplatin treatment.

OAE’s significantly reduced in the high frequencies after 2\textsuperscript{nd} cisplatin treatment.

Ototoxicity in speech frequencies after 2\textsuperscript{nd} treatment.

Cisplatin dose reduced 50% following 3\textsuperscript{rd} cycle due to ototoxicity.
# Audiometric Measurement Test

**Date:** 9/27/04

**Audiometer:** 1A AC-40

**Audiologist:** Natasha Carmichael, MS CCC-A

**Referral Source:** Stacy Nicholson, MD

**Test Reliability:** Good ✗ Fair Fair Poor

## Frequency in Hertz

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>125</th>
<th>250</th>
<th>500</th>
<th>750</th>
<th>1000</th>
<th>1500</th>
<th>2000</th>
<th>3000</th>
<th>4000</th>
<th>6000</th>
<th>8000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level (dB HL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Audiogram Key

- **Unmasked**: EAR AC BC, Masked EAR AC BC, Sound Field Unaided Aided
- **No Response - NR**: EAR AC BC

<table>
<thead>
<tr>
<th>Right PTA</th>
<th>SAL</th>
<th>SRT</th>
<th>dB</th>
</tr>
</thead>
<tbody>
<tr>
<td>WRS 100</td>
<td>25dB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WRS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Left PTA</th>
<th>SAL</th>
<th>SRT</th>
<th>dB</th>
</tr>
</thead>
<tbody>
<tr>
<td>WRS 98%</td>
<td>25dB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WRS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SF PTA</th>
<th>SAL</th>
<th>SRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaided WRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WRS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SF PTA</th>
<th>SAL</th>
<th>SRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aided WRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WRS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ear: Right

Right: 27-Sep-04: -: 1.5-10 kHz Ototoxic Test: 04I27D01.OAE
Patient:
Birthdate:
ID:
Comment:

Ear: Left

Left: 27-Sep-04: -1.5-10 kHz Ototoxic Test: 04I27D02.OAE
At Completion of Treatment:

- Mild to moderate bilateral high frequency hearing loss at 4000-8000 Hz.
- OAE’s normal through 3000 Hz, absent in the high frequencies.
- Significant hearing loss in the EHF thresholds at all frequencies.
BIO-LOGIC OTOACOUSTIC EMISSIONS (OAE) REPORT - Page 1 of 1

Patient: J
Birthdate: 
ID: 
Comment: 

Ear: Right

Right: 23-Feb-05: - : 1.5-10 kHz Ototoxic Test: 05B23D03.OAE
Left: 23-Feb-05: -: 1.5-10 kHz Ototoxic Test: 05B23D04.OAE
Extended high frequency thresholds

![Bar chart showing extended high frequency thresholds for baseline, after 1st tx, 4th tx, and end of tx at different frequency levels (9000, 11200, 14000).]
Follow-up

- Completed treatment in April 2005
- Attending 4th grade this fall.
- Preferential classroom seating and FM system recommended.
- Post-therapy audiologic evaluation in October 2005 to monitor for progression of hearing loss.