Early Diagnosis and Management of Hearing Loss in Medically Fragile Children

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  • Ed Neuwelt, MD and Peppy Brock, MD
  • Working Group on Ototoxicity Grading Systems
Universal Newborn Hearing Screening
Diagnostic Follow-Up, Goals

What are the goals of our work?

Identify who has hearing loss and who doesn’t

• You can’t tell by looking…
• They are too young to show you (consistently)
• High-risk infants account for only ½ of babies with hearing loss (and vast majority of high-risk, in fact, have normal hearing)
• Our screening measures (by design) over-refer
• Need to monitor for delayed-onset hearing loss (screening is NOT a vaccination!)
Shifting Populations, Goals

Who are our patients?
- They are younger
- Many more are sick

Implications for
- Standards for diagnosis and surveillance
- Interventions (timeliness and effectiveness)
- Family preparedness
- Counseling
- Clinicians’ skill set
Shifting Populations, Goals

What are the goals of our work?

Effect interventions so that our patients have…

1. Expressive language on-par with normal-hearing peers?
2. Well established social-emotional connections with family and friends?
3. Maximized potential to become literate tax-payers?
4. School placement staying within district, limiting special education spending?
Who has hearing loss?

Children

• 3-4/1000 live births in developed countries, with prevalence increasing throughout childhood (19/1000* end of high school)

• 1-2/100 of NICU graduates

Infants

• 33 born each day with hearing loss in the U.S.

*Billings & Kenna (1999)
Shifting Populations, Shifting Goals

**JCIH (2007) Quality Indicators:**

- > 95% screen by age 1 month (AABR if NICU>5 days)
- 90% with hearing loss diagnosed by 3 months
- 90% with hearing loss receive intervention by 6 months
- Surveillance through childhood for those at risk for delayed onset hearing loss
  (>95% on intervention plan 45 days of Dx)
Congenital/Prelingual causes of SNHL

• Hereditary: syndromic and non-syndromic
• In utero infection: e.g., CMV, toxoplasmosis, rubella, syphilis, herpes simplex virus
• Premature birth (and associated low-birth weight and respiratory distress/hypoxia)
• Ototoxic medications (e.g., aminoglycosides)
• Birth complications (anoxic events, such as MAS, PPHN)
• Maternal exposures to toxins
• Bacterial meningitis
• Head or ear trauma
What about surveillance?

JCIH (2007) Benchmarks:
Surveillance through childhood for those at risk for delayed onset hearing loss

Examples: CMV infection, aminoglycosides, chemotherapeutics, ECMO
Noise and Drug-induced SNHL?

Shared pathophysiology: apoptotic death of OHC from metabolic dysfunction
- Dose-effect relationship
- Cumulative through lifetime
- Genetic predisposition
- Similar insidious impact on speech intelligibility
- Concomitant tinnitus (and hyperacusis?)
Mechanisms of Ototoxicity: The known pathophysiology of SNHL from medical interventions

- Oxidative stress, metabolic activity
- Genetic predisposition (e.g., A1555G, TMPT/COMT)
- Systematically lesions cochlea base to apex
- Cochleotoxic vs. vestibulotoxic
Mechanisms of Ototoxicity

Oxidative stress:

- Reactive Oxygen Species (ROS): 98% of oxygen used in the ear is to convert ADP into ATP, 2% into super oxide (highly reactive molecule, unpaired electron)
- Pathologic process, 7-fold increase in ROS production
- Cascade of events leading to “programmed” cell death of OHC

= apoptosis
Cascade of Apoptosis

Cascade of Apoptosis

“Once you start down the dark path [of apoptosis], forever will it dominate your destiny, consume [your hair cells] it will!”
Need for Surveillance: ECMO

- **What is it?** Cardio-respiratory bypass for acute, reversible profound cardiopulmonary failure (e.g., severe Meconium Aspiration Syndrome, Congenital Diaphragmatic Hernia)

- **How often used?** 50-80 cases per year at CHB; ~1000 nationally in U.S.

- **Why?** Reduce mortality from 80% to 20%

- **Who cares?** Checklist off the JCIH High Risk register
ECMO Circuit
Subject #5
Late Onset and
Progressive
First Audio Normal

A = ABR at 6 mos

KEY
Subject #5
Late Onset and Progressive

A = ABR at 6 mos
B = Audio at 12 mos
Subject #5
Late Onset and Progressive

A = ABR at 6 mos
B = Audio at 12 mos
C = Audio at 18 mos
Subject #5
Late Onset and Progressive

KEY
A = ABR at 6 mos
B = Audio at 12 mos
C = Audio at 18 mos
D = Audio at 24 mos
E = Audio at 29 mos
Subject #5
Late Onset and Progressive

A = ABR at 6 mos
B = Audio at 12 mos
C = Audio at 18 mos
D = Audio at 24 mos
E = Audio at 29 mos
F = Audio at 34 mos
ECMO: Delayed onset SNHL

- Kaplan-Meier Curve for CDH vs. No CDH

Fligor, et al, 2005
ECMO: Delayed onset SNHL

- Kaplan-Meier Curve for Number of Hours of ECMO

**Diagram:**
- **Top 3rd** (160-575 hrs)
- **Middle 3rd** (112-158 hrs)
- **Lowest 3rd** (21-109 hrs)

Fligor, et al, 2005
ECMO: Delayed onset SNHL

- Kaplan-Meier Curve for Aminoglycosides (AG)

Fligor, et al, 2005
The Tale of an Unlikely Friendship between an Audiologist and an Oncologist
In 2007, I was asked to take over a clinical trial for pediatric germ cell tumors that was examining whether giving the chemotherapy—cisplatin, bleomycin and etoposide—was as efficacious when given over 3 days as compared to 5.

One of the concerns was that giving a higher daily dose of cisplatin (33 mg/day vs. 20 mg/day) would lead to more hearing loss.

I had serial audiograms on 130 patients that needed to be evaluated.

- A. Lindsay Frazier, MD, ScM
Questions most oncologists can’t answer

- How do you read an audiogram?
- Is high frequency hearing loss important?
- Why does high frequency hearing loss appear first?
- What else can contribute to chemotherapy-induced ototoxicity?
- Will changing from a more ototoxic drug to less ototoxic drug really help?
- How do you interpret auditory evoked potentials vis a vis an audiogram?
- How long do I have to monitor a patient with ototoxicity after treatment

- A. Lindsay Frazier, MD, ScM
Most children with cancer now survive.

A focus on quality of life—such as hearing—is now the appropriate benchmark.
Section 5.7 Dose Modifications: Ototoxicity during Induction

“For inner ear/hearing toxicity ≥ Grade 3, decrease cisplatin dose by 50% for subsequent cycles. If loss extends below 2000 Hz, delete further cisplatin/etoposide cycles and replace this cycle of CE with a cycle of CDV so that patient receives a total of 5 cycles of chemotherapy. Note replacement therapy on data form.”
The oncologist’s dilemma

• Cure the patient or preserve hearing?

• Should you eliminate or replace a drug that causes hearing loss and risk not curing the patient?
Cisplatin ototoxicity in children

- 1/3 of children with cancer receive cisplatin therapy

- Ototoxic hearing loss
  - Reported incidence in pediatric patients: 21 to 90%
  - Variation due to differences in treatment, age, ototoxicity criteria
Pediatric cancers treated with platinum-based chemotherapy

- Osteosarcoma
- Germ cell tumors
- Neuroblastoma
- Hepatoblastoma
- Retinoblastoma
- Brain and CNS tumors
Chemotherapy ototoxicity

- Typically bilateral, symmetrical, sensorineural, permanent
  - Can be asymmetrical

- Appears first in the high frequencies
  - Can progress to low frequencies with continued treatment, higher cumulative dose

- Time course
  - Gradual onset, progressive and cumulative, or sudden
  - Evidence that hearing loss can progress years after cisplatin is discharged: Bertolini et al (2004)
Cisplatin ototoxicity risk factors

1. Younger age
   Children < 5 years at treatment: 21x the risk for hearing loss re: adolescents

Li et al., 2004
Cisplatin ototoxicity risk factors

2. Cisplatin dose:
   - **Individual** (120mg/m² x 1 day vs 60 mg/m² x 2 days: OR=12x)
   - **Cumulative dose** (480mg/m²: OR=12.7x; 360mg/m²: OR=5x re: 120mg/m²)

Lewis et al., 2009
Cisplatin ototoxicity risk factors

3. Cranial radiation

- Cranial irradiation alone
  - As the dose of radiation increases, risk for hearing loss increases
  - Hearing loss may not appear until 18 months or more after completion of treatment (Hua et al, 2008)

- Combination of cisplatin and radiation therapy
  - Statistically significant increase in the degree of hearing loss as the average cochlear dose of radiation increased (Paulino et al. 2010)
  - Radiation therapy potentiates the ototoxic effect of cisplatin (Hitchcock et al 2009)

Brock et al, 2012
Cisplatin ototoxicity risk factors

4. Use of other ototoxins during treatment
   aminoglycosides, combined cisplatin and carboplatin therapy

Chang and Chinosornvatatna, 2010
Cisplatin ototoxicity risk factors

5. Genetic predisposition

Genetic differences in drug metabolism genes cause a significant portion of serious ADRs

Adapted from Ross et al, 2009
Case Studies

Case 1
- 14 y/o
- Osteosarcoma of right proximal tibia
- Dx: Nov 2000
- Chemotherapy
  - Cisplatin
  - Doxorubicin
  - Methotrexate
- Alive and well

Case 2
- 12 y/o
- Osteosarcoma of right proximal tibia
- Dx: Oct 1998
- Chemotherapy
  - Cisplatin
  - Doxorubicin
  - Methotrexate
- Alive and well

Adapted from Carlton, B. 2010
Case 1
Baseline audiograms

Case 2
Baseline audiograms

Adapted from Carlton, B. 2010
Case 1

Case 2

After 2 cycles of cisplatin

Adapted from Carlton, B. 2010
Case 1

Most recent audiograms

Case 2

+ for genetic polymorphism

Most recent audiograms

Adapted from Carlton, B. 2010
Patient JB, Dx neuroblastoma
Rx carboplatin
5/1999: Baseline (11 months old)
Patient JB, Dx neuroblastoma
Rx carboplatin
7/1999: 13 months old
Patient JB, Dx neuroblastoma
Rx carboplatin
10/1999: 16 months old
Patient JB, Dx neuroblastoma
Rx carboplatin
8/2000: 2 yrs 3 months old
Patient JB, Dx neuroblastoma s/p bone marrow transplant 11/2000: 2 yrs 6 months old
Patient JB, Dx neuroblastoma s/p bone marrow transplant 8/2001: 3 yrs 3 months old
Patient JB, Dx neuroblastoma
1/2007: Nearly 9 years old
Fitting with FM system for school
Patient GS, Dx medulloblastoma, Osteosarcoma behind left ear
Tx: cisplatin and radiation, Surgery
LONG-TERM EFFECTS OF POST-CHEMOTHERAPY RADIATION FOR MEDULLOBLASTOMA

SPEECH RECOGNITION
IN SF AT 60 dB SPL

<table>
<thead>
<tr>
<th></th>
<th>HINT (QUIET)</th>
<th>WRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE-OP WITH BOTH AIDS</td>
<td>55%</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PBK</td>
</tr>
<tr>
<td>POST-OP, WITH RIGHT CI ONLY</td>
<td>84%</td>
<td>82% W-22</td>
</tr>
</tbody>
</table>

BLUE: BASELINE
RED: POST 3 ROUNDS OF CISPLATIN FOLLOWED BY RADIATION
BLACK: 9 YEARS POST RADIATION
GREEN: WITH RIGHT COCHLEAR IMPLANT

MW Neault
Treatment Dilemma

- Ototoxicity is (thought to be) a dose-limiting toxicity
- Reducing the cisplatin dose stabilizes the hearing loss
- Dose reductions may affect efficacy of chemotherapy
- Need for strategies that can reduce/prevent hearing loss without interfering with chemotherapy
Treatment Dilemma

- Ototoxicity is (thought to be) a dose-limiting toxicity
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- Need for strategies that can reduce/prevent hearing loss without interfering with chemotherapy
  - A scale sensitive to small changes
  - A metric for describing severity of hearing loss that is understandable to families and NON-AUDIOLOGIST clinicians
Why Monitor During Treatment?

Communicate information to managing physician
  • May be possible to change treatment to avoid further hearing loss

Inform caregivers about changes in hearing
  • Communication strategies to maintain communication
  • Early intervention/management of hearing loss
Potential Otoprotective Agents

- Sodium Thiosulfate
- D-Methionine
- N-Acetylcysteine
- Amifostine

Evaluation of efficacy of otoprotectants in children will require
- multi-center cooperative clinical trials with careful audiologic measurement
- standard ototoxicity criteria
Challenges with pediatric ototoxicity monitoring

- Multi-center study of cisplatin-induced hearing loss in 120 children treated for hepatoblastoma (does amifostine protect?)
- Degree of ototoxicity could not be determined in 32% of patients (38/120) due to inadequate or incomplete audiologic data

*Katzenstein et al 2009*
Clinical challenges

- No standard pediatric monitoring protocols
- Baseline tests are often not conducted
- Children are often sick, they may be fearful in the clinical setting, and their attention and cooperation may be limited. Complete evaluation is not always possible.
- Bedside evaluation may be required, impacting the quality and extent of the testing
Clinical challenges

*Most variation in evaluations of children 3 years and younger*

- 3000, 6000, and 8000 Hz often not tested
- Other missing frequencies when complete evaluation is not possible
- Screening level/stopping level if responses not measured down to threshold
- Tympanometry and/or bone conduction measurement when hearing loss is detected
Many ototoxicity criteria and grading scales

- In the past two years of published clinical ototoxicity research, *at least 7 different ototoxicity grading scales* were used to analyze and report results
  - Difficult to compare ototoxicity in different studies and patients
  - Need international standard for evaluation of end-of-treatment audiologic results
- International Society of Pediatric Oncology (SIOP) convened working groups Oct 2010, Boston, MA
SIOP Boston Ototoxicity Grades

**Grade 0:** ≤ 20 dB HL at all frequencies

**Grade 1:** > 20 dB HL (i.e. 25 dB HL or greater) SNHL above 4000 Hz (i.e. 6 or 8 kHz)

**Grade 2:** > 20 dB HL SNHL at 4000 Hz and above

**Grade 3:** > 20 dB HL SNHL at 2000 Hz or 3000 Hz and above

**Grade 4:** > 40 dB HL (i.e. 45 dB HL or more) SNHL at 2000 Hz

Based on sensorineural hearing thresholds in dB HL (bone conduction or air conduction with a normal tympanogram)

SIOP Minimal Test Battery

- Sequence for testing: used only when complete evaluation is not possible
  - Purpose: direct testing to critical components for grading hearing loss
  - Improve consistency of data in multi-center studies
  - Allow grading when only 2-3 frequencies can be measured
  - Children tested with minimal battery will require complete evaluation as soon as child is able
Minimal test battery sequence

1. 4000 Hz
   - 4000 Hz >20 dB
   - 4000 Hz <20 dB

2. 2000 Hz
   - 2000 Hz <20
   - 2000 Hz >20

3. 3000 Hz
3. 1000 Hz
3. 6000 Hz

4. 8000 Hz <20
4. 8000 Hz >20
Minimal test battery

After 1\textsuperscript{st} cisplatin cycle, previous evaluation normal.

After 2\textsuperscript{nd} cisplatin cycle. Known hearing loss at 4000 Hz.
I can see there’s a difference in the tic-tac-toe signs but what does it mean?

A proposed metric...

Baseline

End of treatment (6 months later)
Impact of Ototoxicity in Children: Accelerated Ear-Age?

ANSI S3.44 (1996): Expected hearing thresholds as a function of age (years)

\[ H_{Q} = a \cdot (Y-18)^2 \]

*Where:*

- \( H_{Q} \) = hearing as a function of age, re: an 18-year-old of same gender
- \( a \) = a constant based on the frequency (Hz) and gender (table in ANSI S3.44, 1996)
- \( Y \) = age (years)

*Johnson (1988)* suggested solving for \( Y \) to describe *age-equivalent hearing shift* in years:

\[ Y = \text{Square Root} \left( \frac{H_{Q}}{a} \right) \]

(“18” dropped, all subjects \(<=18 \text{ yrs}\)
Ear Age (Y) = Avg Ear Age assigned to 4k, 6k, and 8k Hz post-treatment
Patient 1: 4 yo (EA=44yrs); Patient 6: 18 yo (EA=51yrs); Patient 7: 10 yo (EA=65yrs)

SUMMARY

- Find the 4/20 refers who have permanent hearing loss by 3 months of age!
- Identify the additional 15/1000 with adventitious onset of hearing loss
- Monitor those most at-risk for onset of hearing loss
- Provide intervention by 6 months of age (including appropriately fitted, objectively verified hearing aids)
- Team up with physicians involved in the care of children with complex medical needs
- Team up with PCP and Early Intervention