Overview

• Childhood hearing loss
  – Review of auditory system
  – How we measure hearing
  – Medical evaluation

• Usher Syndrome and hearing loss
  – Classification
  – Genetic causes
  – Treatment
How the ear functions – microscopically
How the ear functions – microscopically
How the ear functions – microscopically
How the ear functions – microscopically
How the ear functions – hair cells
Milestones in diagnosis of childhood hearing loss

• **1960’s** Auditory brainstem response testing
• **1980s** Automated auditory testing
  – ABR and EOAE
• **1999** Walsh Bill
• **2000’s** Early Hearing loss Detection and Intervention (EHDI)
  – Screening by 1 month
  – Diagnosis by 3 months
  – Intervention by 6 months
## How we measure hearing

<table>
<thead>
<tr>
<th>Type of test</th>
<th>Requirements</th>
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<th>Disadvantages</th>
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| ABR, BSER, BAER     | Sleep or quiet| - Ear specific responses  
- Does not require patient cooperation  
- Correlates well with behavioral responses | - Requires sedation over 6 months of age  
- Physiologic response |
| EOAE                |              |                                                                             |                                                                              |
| Behavioral          |              |                                                                             |                                                                              |
| VRA-visual reinforced| >6 months old Cooperative | Gold standard for assessment of hearing | Patient must be developmentally ready |
| CPA-conditioned play|              |                                                                             |                                                                              |
| CA-conventional     |              |                                                                             |                                                                              |
Audiograms 101

NORMAL
MILD
MODERATE
SEVERE
PROFOUND
Medical evaluation of childhood hearing loss

• History
• Physical examination
• Characterization of hearing loss
• Imaging studies
  – CT and/or MRI scans
• Tests for causes of hearing loss
  – CMV testing
  – Genetic tests
Medical evaluation of childhood hearing loss

- Tests to look for associated problems
  - Balance testing
  - Ophthalmologic evaluation
  - Electrocardiogram
  - Renal ultrasound
  - Thyroid function studies
  - Electroretinogram
  - Others
CT scans

- Normal
- Mondini
- Normal
- Large vestibular aqueduct
Evaluation of children with hearing loss

- CMV testing
  - Infants
  - Need to get specimen from first 3 wks of life

- Genetic testing
  - Single mutation analysis
  - Next Gen Sequencing
Management of children with hearing loss

Exposure to language

Early intervention

Amplification
  Hearing aids
  Cochlear implants
  FM systems

School accommodations
Childhood Hearing Loss

Prelingual Deaf Children 1/1000

- Idiopathic 25%
- Non-genetic 25%
- Genetic 50%

Non-syndromic 70%

- Autosomal recessive 75% - 85%
  - DFNB1 50%
  - Other DFNB 50%
- Autosomal dominant 15% - 24%
- X-linked 1% - 2%

Syndromic 30%

From www.genetests.org
Hearing loss and Usher syndrome

• CHILDHOOD HEARING LOSS IN USA
  – 1-3/1000 newborns have severe to profound HL
  – 2-5/1000 newborns have milder degrees of HL
  – Over 95% of children with hearing loss have parents with normal hearing.
Hearing loss and Usher syndrome

- **USHER SYNDROME ACCOUNTS FOR**
  - About 1:25,000 in USA
  - 3-6% of children with hearing loss in USA*
  - 50% of people with deaf-blindness in USA
  - Most common recessively inherited form of syndromic hearing loss
Diagnosis of Usher syndrome

- Family history
- Congenital bilateral profound hearing loss and bilateral vestibular areflexia (US 1)
- Retinitis pigmentosa
- Clinical presentation
Diagnosis of Usher Syndrome

• Genetic testing (11 loci on 9 different genes)
  – Otochip
  – Otoscope

• Other tests: vestibular testing and ERG
## Hearing loss and Usher Syndrome

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<th>Balance</th>
<th>Vision</th>
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<td><strong>Congenital</strong> Bilateral Profound</td>
<td><strong>Congenital</strong> Bilateral Areflexia</td>
<td>RP Progressive loss</td>
<td>MYO7A, CDH23, PCDH15, USH1C, USH1G</td>
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<td>Normal</td>
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* All these genes have also been described with nonsyndromic HL
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<th>Disorder</th>
<th>Mode of Inheritance</th>
<th>Gene(s)</th>
<th>Cost</th>
<th>Estimated Turnaround</th>
<th>Methodology</th>
<th>CPT Codes</th>
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<td>Usher Syndrome</td>
<td>Autosomal Recessive</td>
<td>CDH23, CLRN1, MYO7A, PCDH15, USH1C, USH1G &amp; USH2A</td>
<td>First Tier Testing $575</td>
<td>8-10 weeks</td>
<td>Allele-Specific Testing Followed by Conventional Sequencing</td>
<td>81400, 81407, 81408, 81479</td>
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<td>ABHD12, CDH23, CIB2, CLRN1, DFNB31, GPR98, HARS, MYO7A, PCDH15, USH1C, USH1G &amp; USH2A</td>
<td>Second Allele Testing $575-$1,626</td>
<td>10-12 weeks</td>
<td>Conventional Sequencing</td>
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<td>Exome Testing $2200</td>
<td>14-16 weeks</td>
<td>Allele-Specific Testing Followed by Conventional Sequencing and Next Generation Sequencing</td>
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Treatment for Usher syndrome

• EXPOSURE TO LANGUAGE
• Early intervention
• Support for vision impairment
• Psychosocial support
• Exposure to spoken language
  – Amplification
  – Cochlear implantation
Cochlear implantation

- Indications/guidelines
  - No significant speech benefit from appropriately fit hearing aids
  - 12 months of age
  - Absence of medical contraindications
Cochlear implantation

- Emerging trends in CI
  - Earlier age
  - Lesser degrees of HL
  - Hearing preservation surgery
Hearing loss and US1

PROFOUND
Aided hearing and US1

SEVERE

PROFOUND
CI responses and US 1

- NORMAL
- MILD
- MODERATE
- SEVERE
- PROFOUND
Usher syndrome and hearing loss

• Genetic therapies for US hearing loss are not yet available for humans.

• Understanding the molecular mechanisms of hearing loss will pave the way for biologic interventions.
On the horizon…

- Usher Type 3
  - Mutation affects production of clarin-1
  - Abnormal protein does not reach cell membrane
  - Abnormal protein degraded
  - Research group aimed to stabilize clarin-1
  - Compound BF844

Summary

• Identification of Usher Syndrome in children with hearing loss:
  – Diagnosis is based upon clinical findings.
  – Genetic testing has an important role.
  – Work with hearing health care team.
  – Early diagnosis will be important.

• Treatment options will improve with our understanding of molecular mechanisms of hearing loss.
Questions?

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