Usher Syndrome: When to Suspect it and How to Find It

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Disclosure

I have no actual or potential conflicts of interest in relation to this program/presentation
This presentation is dedicated to our patients and their families, without whom I would have no reason to be here, and to my colleagues, without whom I could not be here.
Why Study Diagnosis

- Many people are here to learn about potential therapies for Usher syndrome.
- Our role as clinicians is to find these patients, so that they can benefit from new therapies.
- And we have gotten much better at finding these patients at younger ages and with a more accurate diagnosis.
Early Usher Diagnosis: Why Now?

• Universal newborn hearing screening, all 50 states and many countries
• Reliable tests to find the hearing loss
• Increasing clinical availability of genetic testing
• Increasing awareness that Usher not as rare as we thought
• Emerging laboratory work which can translate into the clinic means that we need to find the patients sooner
Incidence of SNHL in Children

- Hearing loss most common congenital sensory impairment
- Congenital 1-3/1000 live births with severe to profound SNHL
  - Another 1-2/1000 have milder or unilateral hearing loss
- Later onset/Acquired
  - 19.5% based on NHANES 2005-6 for ages 12-19 years
- May be the hearing loss manifestation of a prenatal occurrence: genetics, CMV, anatomic abnormalities
Incidence of congenital disorders detected by newborn screening in Massachusetts

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital hypothyroidism</td>
<td>1 in 3,800</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>1 in 8,000</td>
</tr>
<tr>
<td>PKU</td>
<td>1 in 12,000</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>1 in 14,000</td>
</tr>
<tr>
<td>Biotinidase deficiency</td>
<td>1 in 32,000</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>1 in 55,000</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>1 in 157,000</td>
</tr>
<tr>
<td>Homocysteinuria</td>
<td>1 in 200,000</td>
</tr>
</tbody>
</table>

**HEARING LOSS**

1-2/1000 bilateral severe to profound
1-2/1000 milder bilateral or unilateral
Why test hearing early?

- Effect of hearing loss on the development of speech and language
  - Academic achievement
  - Social and emotional development
- Age of detection of hearing loss
  - Presence of a “critical period” for auditory development
- Early establishment of language becomes even more critical if vision will change
Seven steps to treatment for an Inherited Disease (Bill Kimberling)

- Find the disease gene
- Correlate genotype with phenotype
- Find or develop animal models
- Elucidate the disease mechanism
- Find or develop an effective treatment in the animal model
- Screen the human population to identify people who might benefit
- Test the treatment in these people
  - Orphan diseases, small numbers
Major Causes of Sensorineural Hearing Loss

- Genetic
  - Nonsyndromic
  - Syndromic
  - Autosomal Recessive
  - Autosomal Dominant
  - X-Linked
  - Mitochondrial

- Traumas/Exposures
- Anatomical
- Infections
- Drugs
- Unknown

Cx26
New Era of Genetic Diagnosis in SNHL

- **1990:** USH2A, Kimberling et al; 1998 Eudy et al
- **1993:** 1555A→G Mitochondrial gene for gentamicin ototoxicity
- **MYO7A:** 1995 Weil et al
- **1997:** Identified Connexin 26 (GJB2) as the first non-syndromic autosomal recessive deafness gene, DFNB1
- **1998:** Presence of large vestibular aqueducts in Pendrin syndrome (SLC26A4 [PDS] gene)
How Common is Usher Syndrome?

- Prevalence: 1/16-20,000 US; 3-6/100,000
- Estimated 16,000-45,000 individuals in the US with USH
- Up to 10% of congenitally deaf children with USH1
- 3-6% of all congenitally hearing impaired children with USH1, 2, 3
- 0.6-28% HOH, deaf population
  - 1:6500 general population have genotype
- Carrier frequency 1/70 (varies by gene, mutation and population)
Why Does USH seem so rare?

- Diagnosis still made late
  - Much later than Connexin 26
- Limited availability of genetic testing
  - Few clinical labs doing testing
  - Insurance does not always pay for testing
  - Physicians not always aware testing is available
- Heterogeneous presentation
- Later onset of visual loss than hearing loss
- Retinal findings difficult to determine on physical exam in young children
- Prevalence of balance abnormalities poorly studied
Genetic Heterogeneity in “Non-Syndromic” Hearing Loss

- Many mutations cause a similar phenotype
- The same mutations may cause a very different phenotype
- Mutations in the same gene can cause both syndromic and non-syndromic HL
  - MYO7A (USH1B)
    - Recessive with RP
    - Dominant no RP
  - CDH23 (USH1D), USH1C, PCDH15 (USH1F) all have a recessive form without RP
## Usher Syndrome

<table>
<thead>
<tr>
<th>Type</th>
<th>Hearing Loss</th>
<th>Vestibular System</th>
<th>Retinitis Pigmentosa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong></td>
<td>Congenital profound</td>
<td>Congenital balance problems; absent caloric responses</td>
<td>Onset pre-puberty</td>
</tr>
<tr>
<td><strong>Type II</strong></td>
<td>Congenital mild-severe sloping; progressive</td>
<td>Normal</td>
<td>Onset in teens-20s</td>
</tr>
<tr>
<td><strong>Type III</strong></td>
<td>Progressive later onset</td>
<td>Variable, often progressive balance problems</td>
<td>Variable onset</td>
</tr>
</tbody>
</table>
USH 1B

Tympanograms: normal

SPEECH AUDIOMETRY
- SDT
- SRT
- SPEECH DISCRIM. (WORD RECOG.)

8% 4%

KEY
- AC (AIR)
- UNMASKED
- MASKED
- BC (BONE)
- UNMASKED
- MASKED
- SOUND FIELD

FREQUENCY IN HERTZ (Hz)

HEARING LEVEL (HL) IN DECIBELS (dB)
35delG / 35delG
Age 10 years
Sibling has similar audiogram
35delG / 35delG
Age 15 months

Tympanograms: normal

Connexin 26

Hearing Level (HL) in Decibels (dB)

Frequency in Hertz (Hz)

KEY
R     L
AC (AIR)
UNMASKED
MASKED
BC (BONE)
UNMASKED
MASKED
SOUND FIELD

SPEECH AUDIOMETRY
R     L
SDT  25  30
SRT
SPEECH DISCRIM.
(WORD RECOG.)
Adult with USH 2A who presented with “non-syndromic” RP
An example of a mild to severe sensorineural hearing loss in both ears.
Why figure out the genetics?

- All of the non-syndromic patients look the same early on
- No distinguishing facial features
- No characteristic audiograms (many audiograms look the same)
- Varying management depending on the gene(s)
- Varying outcomes depending on the gene(s)
## Syndromic Hearing Loss

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Inheritance</th>
<th>Prevalence**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charge</td>
<td>AD</td>
<td>Common</td>
</tr>
<tr>
<td>Treacher-Collins</td>
<td>AD</td>
<td>Common</td>
</tr>
<tr>
<td>Pendred/LVAS</td>
<td>AR</td>
<td>Very common</td>
</tr>
<tr>
<td>Waardenburg</td>
<td>AD</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Usher</strong></td>
<td>AR</td>
<td>Common</td>
</tr>
<tr>
<td>BOR Syndrome</td>
<td>AD</td>
<td>Common</td>
</tr>
<tr>
<td>Norrie Disease</td>
<td>XL, AR</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Alport Syndrome</td>
<td>XL, AD, AR</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Stickler Syndrome</td>
<td>AD</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Jervell &amp; Lange-Nielsen</td>
<td>AR</td>
<td>Rare</td>
</tr>
</tbody>
</table>

**relative to other syndromic forms of hearing loss**
<table>
<thead>
<tr>
<th>Locus name</th>
<th>Genome Location</th>
<th>Gene name</th>
<th>Gene Protein Product</th>
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</thead>
<tbody>
<tr>
<td>USH1B</td>
<td>11q13.5</td>
<td>MYO7A</td>
<td>Myosin 7A</td>
</tr>
<tr>
<td>USH1C</td>
<td>11p15.1-p14</td>
<td>USH1C</td>
<td>Harmonin</td>
</tr>
<tr>
<td>USH1D</td>
<td>10q22-q22</td>
<td>CDH23</td>
<td>Cadherin 23</td>
</tr>
<tr>
<td>USH1E</td>
<td>21q21.1</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>USH1F</td>
<td>10q21.1</td>
<td>PCDH15</td>
<td>Protocadherin 15</td>
</tr>
<tr>
<td>USH1G</td>
<td>17q25.1</td>
<td>USH1G</td>
<td>USH Type 1G protein</td>
</tr>
<tr>
<td>USH1H</td>
<td>15q22-23</td>
<td>USH1H</td>
<td>Unknown</td>
</tr>
<tr>
<td>USH 1 J</td>
<td>15q25.1</td>
<td>CIB2</td>
<td>Ca++ and integrin binding protein 2</td>
</tr>
<tr>
<td>USH 1K</td>
<td>10p11.21-q21.1</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>USH2A</td>
<td>1q41</td>
<td>USH2A</td>
<td>Usherin</td>
</tr>
<tr>
<td>USH2C</td>
<td>5q13</td>
<td>GRP98</td>
<td>G protein-coupled Receptor 98</td>
</tr>
<tr>
<td>USH2D</td>
<td>9q32-34</td>
<td>DFNB31</td>
<td>Cask-interacting protein</td>
</tr>
<tr>
<td>USH3A</td>
<td>3q21-q25</td>
<td>CLRN1</td>
<td>Clarin-1</td>
</tr>
<tr>
<td>USH2A modif</td>
<td>10q24.31</td>
<td>PDZD7</td>
<td>PDZD7</td>
</tr>
<tr>
<td>USH3B</td>
<td>5q31.3</td>
<td>HARS</td>
<td></td>
</tr>
<tr>
<td>USH2J</td>
<td>17p11.2</td>
<td>MYO15A</td>
<td></td>
</tr>
</tbody>
</table>
Vestibular Function in Usher Syndrome

- **USH 1** associated with late walking and poor balance and are “areflexic”
  - Absence of response to cold caloric stimuli
  - Absence of post rotational nystagmus and abnormal VOR
  - Late walkers, average 20 months, but from “late normal” to >24 months
  - Although helps you suspect USH, not entirely reliable indicator
  - There are other causes for late walking, delayed milestones

- **USH 2** – reportedly normal balance

- **USH 3** – variable

- Balance in USH2 and USH3 not well studied
Vestibular Function

- Few labs are able to test children
- Limited norms for young children
- Each test evaluates a different part of the vestibular system
- Tests are sometimes done in the dark, seem scary
- Tests may actually make the child dizzy
- Child may have trouble understanding the tests due to limitations of age, hearing and vision
Genetic Testing for Usher Syndrome

- **Conservative approach**
  - HL with retinal abnormalities (positive ERG test, DAT or pigmentary changes)

- **Less conservative approach**
  - Profound congenital hearing loss with delayed walking

- **Even less conservative approach**
  - Test infants and children with moderate to profound SNHL if Cx26 (and possibly Cx30) negative
  - Test infants and children with any degree of bilateral SNHL

- **No matter which approach, need for genetic counseling**
Interventions for the Hearing Loss

- Hearing aids
- Cochlear Implants
- Early diagnosis of bilateral severe to profound SNHL AND an early diagnosis of USH allows a decision for CI earlier
  - Early USH diagnosis may tip the scales towards CI in families who might have decided on manual communication in other circumstances
Future Directions

- Phenotype-genotype correlation
  - Hearing
  - Balance
  - Why deaf before blind?
  - Other clinical findings; olfaction, brain size and development
  - Response to therapy
  - Vestibular, CI, hearing aids
  - Other interventions: Vit A, Omega 3, light protection
Thank You!!