Hearing Loss in Infants and Children: Could it be Usher Syndrome?

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Suspecting a diagnosis of Usher Syndrome

- Before universal newborn hearing screening (UNHS) and genetic testing, USH diagnosis usually made by ophthalmologists when vision started to change

- UNHS gives otolaryngologists an opportunity to make an earlier USH diagnosis
  - Need to work with ophthalmology and clinical genetics
  - Need access to genetic testing and ERG
  - Need to know what to do next
Major Causes of Congenital Hearing Loss

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

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

Cx26
First rule out non-Usher diagnoses

- Congenital CMV, toxoplasmosis, syphilis
- Auditory dyssynchrony...probably not USH
- Anatomical abnormalities...probably not USH
- Other genetic causes..Cx26
- Occasionally find more than one cause
Confirmed diagnosis of SNHL in Newborn

- Syndromic
  - Genetics
  - Imaging
  - CMV
- Non-syndromic
  - Positive
    - Infectious Disease
    - Antivirals
    - Imaging
  - Negative
    - Laterality of Hearing Loss
      - Unilateral
        - Imaging
      - Bilateral
        - Genetics or Imaging
Hearing Loss Due to **Prenatal Causes**

- Genetics
- Abnormal inner ear anatomy
- Infections – CMV, toxoplasmosis, syphilis
- Maternal, placental factors
  - Fetal Alcohol exposure
  - Twin-twin transfusion
  - Chorioamnionitis
  - Ototoxic drugs
Epidemiology of CMV

- 1% of all live births
- 10-15% of babies with congenital CMV are symptomatic
  - 75% of these will have CNS symptoms
  - 65% of these will have SNHL
- Of asymptomatic babies 5-10% develop SNHL
- Over 50% have progressive hearing loss
Hearing Loss due to Perinatal Causes

- NICU
  - PPHN
  - Ototoxicity
  - Sepsis
- Hyperbilirubinemia
- ECMO
- Ototoxicity
- Sepsis
- Extreme prematurity
  - Auditory dyssynchrony
Postnatally Acquired: Infections

- Bacterial meningitis
  - Group B strep (perinatal)
  - Marked decrease since HIB, Prevnar®, PCV13
  - N. meningitidis vaccination: MCV4, MPSV4
- Parvovirus B-19 (Fifth’s disease)
  - Associated with autoimmune hearing loss
- Mumps (2007, 800/100,000 US)
- Measles (2005, <1/1,000,000)
- Lyme - Facial nerve dysfunction more common than SNHL
- HIV
- EBV
- HSV
- Ramsay-Hunt (Varicella zoster)
- Otitis media/cholesteatoma
Hearing Loss due to Postnatal Causes

- Head trauma
  - Sports
  - Altercations
  - MVA
  - Child abuse
- Noise
  - Noise in the NICU
  - MP3
  - Recreational other than MP3
  - Musical instruments: violin, rock music
  - Hunting, car repair
- Radiation
- Surgery
- Autoimmune
T-bone abnormalities with Hearing Loss

- Hearing loss
  - may present at birth or later, and is often fluctuating or progressive
  - May present after head trauma
  - Hearing loss is often mixed
- Enlarged vestibular aqueduct
- Superior semicircular canal dehiscence
- Ossification: bacterial meningitis, autoimmune
- Narrow cochlear aperture (cochlear stenosis)
- Narrow internal auditory canal
  - Associated with hypoplastic auditory nerve
- Dysplastic and/or small cochleas
Enlarged Vestibular Aqueduct

- Most common radiographic abnormality with SNHL
- Associated with fluctuating/progressive hearing loss
- HL often mixed
- About 10% of AU EVA associated with full Pendred syndrome
- CT absent eighth nerve AU
- Infant failed UNHS
Seven steps to treatment for an Inherited Disease (Bill Kimberling)

- Find the disease gene
  - Initial discovery of the gene
  - In a particular patient
- 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
Genetics of Hearing Loss

- Loci (genes) for Non-Syndromic HL
  - 71 (39) recessive (DFNB)
  - 54 (25) dominant (DFNA)
  - 5 (3) X-linked (DFNX)
  - 2 modifier (DFNM)
  - Several Mitochondrial (MTN)
  - 1 Y-linked (DFNY)
  - 1 (1) Auditory neuropathy (AUNA1)

- Syndromic hearing loss: hundreds of genes (loci genes)
  - Waardenburg (9/6) (dominant)
  - Branchio-oto-renal (4/3) (dominant)
  - Pendred (3/3) (recessive)
  - Usher (13/10) (recessive)
  - CHARGE (2/2) (dominant)
  - Alport (2/3) (dominant, recessive, x-linked)
  - Jervell and Lange Nielsen (2) recessive
  - Norrie (1/1) recessive
  - Stickler (3/3) dominant
  - Treacher Collins (1/1) dominant

Van Camp G, Smith RJH.
Genetic causes of later onset and progressive HL

- Dominant genes associated with presbycusis
- GJB2 (Connexin 26): 50% progression rate
- SLC26A4 (PDS): Associated with enlarged vestibular aqueduct
- Turner’s syndrome (XO): mid-frequency dip
- Otosclerosis: later onset and progressive
- Usher’s syndrome, types 2 and 3 esp.
- Mitochondrial genes: may cause HL with or without aminoglycosides
GJB2 (Connexin 26)

- Most common genetic cause of hearing loss
- DFNB1: locus name
- GJB2 (gap junction beta 2): name of gene
- Connexin 26: name of protein
- Phenotype
  - Usually congenital SNHL
  - Recessive (10% of mutations dominant)
  - ~50% with severe to profound hearing loss (>75dB HL)
  - Generally no other physical or radiographic findings (except for pts with PPK or KID syndrome)
  - Hearing loss worsens up to 50% of the time
35delG / 35delG
Age 10 years
Sibling has similar audiogram
Connexin 26
35delG / 35delG
Age 15 months

Tympanograms: normal
Pendred Syndrome

- Most common genetic cause after Cx26
- Enlarged vestibular aqueducts
  - 10-20% of pts with AU EVA have PDS
- Goiter resulting from abnormal organification of iodine in the thyroid
  - If have Pendred syndrome, will have abnormal perchlorate washout studies but euthyroid labs
- Mutations in SLC26A4 (PDS) cause both Pendred Syndrome and recessive non-syndromic SNHL (DFNB4)
# Usher Syndrome

<table>
<thead>
<tr>
<th>Type</th>
<th>Hearing Loss</th>
<th>Vestibular System</th>
<th>Retinitis Pigmentosa</th>
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<tbody>
<tr>
<td>Type I</td>
<td>Congenital profound</td>
<td>Congenital balance problems; absent caloric responses</td>
<td>Onset pre-puberty</td>
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<tr>
<td>Type II</td>
<td>Congenital mild-severe sloping; progressive</td>
<td>Normal</td>
<td>Onset in teens-20s</td>
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<tr>
<td>Type III</td>
<td>Progressive later onset</td>
<td>Variable, often progressive balance problems</td>
<td>Variable onset</td>
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<tr>
<td>Locus name</td>
<td>Genome Location</td>
<td>Gene name</td>
<td>Gene Protein Product</td>
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<td>USH1B</td>
<td>11q13.5</td>
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<td>Myosin 7A</td>
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<td>G protein-coupled Receptor 98</td>
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<td>9q32-34</td>
<td>DFNB31 (WHRN)</td>
<td>Cask-interacting protein</td>
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<td>3q21-q25</td>
<td>CLRN1</td>
<td>Clarin-1</td>
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<td>USH3B</td>
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How Common is Usher Syndrome

- Prevalence: 1/16-20,000 US
  - With more genes more common
- Estimated 16,000-25,000 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
- Carrier frequency 1/70 (varies by gene, mutation and population)
How to make the Usher Diagnosis

- Test the hearing
- Test the vision
- Test the balance
- Test the genes
- Test olfaction?
- Look at brain?
Audiologic Features

- **USH 1** - bilateral congenital profound SNHL
- **USH 2** - bilateral moderate SNHL; may progress
- **USH 3** – May be of later onset, may progress
- **All patients initially appear non-syndromic except for the hearing loss**
- **Not all patients with mutations in the same Usher gene have the same presentation**
FREQUENCY IN HERTZ (Hz)

HEARING LEVEL (HL) IN DECIBELS (dB)

USH 1B

Tympanograms: normal

SPEECH AUDIOMETRY

SDT

SRT

SPEECH DISCRIM. (WORD RECOG.) 8% 4%
Adult with USH 2A who presented with “non-syndromic” RP
Usher Gene Phenotype

- Most genes cause congenital/childhood onset SNHL followed by RP
- USH2A also causes non-syndromic RP
- MYO7A, USH1C, CDH23, PCDH15, WHRN may cause hearing loss only
- USH1K reported in association with hyperinsulinism, cognitive impairment and non-autoimmune diabetes
- Change in olfaction (sense of smell)
- Cognition
- Sperm motility
- Cerebral atrophy
- Ataxia
- Registry
Routine Eye Exams in Children with SNHL: Can you diagnose Usher Syndrome?

- 16 children
- All have two pathogenic USH mutations
- “Routine” eye exams did not pick up USH in any patients who were pre-symptomatic (i.e. not night blind)
- 9/16 had diagnosis made by genetic testing; youngest was 8 months
- Age of walking not entirely predictive of USH 1 patients, and was normal in USH 2 and USH 3

Kenna, Fulton, Hansen, Rehm, et al, 2010
Testing for Usher Syndrome

- **Clinical diagnosis**
  - Hearing loss
  - RP
    - Electroretinography
  - Balance
  - ??/olfaction, cognition

- **Genetic diagnosis**
  - Single gene testing
  - Multiple gene testing
Why Pursue Usher Testing: Hearing Loss

- **USH 1** - bilateral congenital profound SNHL
- **USH 2** - bilateral moderate SNHL; may progress
- **USH 3** – May be of later onset, may progress
- All patients initially appear non-syndromic except for the hearing loss
- Eye exams are frequently non-diagnostic or falsely reassuring
- Not all patients with mutations in Usher genes will have the same presentation
  - Hearing loss may be milder than expected
  - **USH 1**: MYO7A, USH1C, CDH23, PCDH15, DFNB31; some with hearing loss only
  - **DFNA11-MYO7A**: Dominant non-syndromic hearing loss
Why pursue genetic testing for Usher Syndrome?

- Recessive syndrome so usually no family history
- Find out what caused the hearing loss
  - Symptoms alone cannot exclude the diagnosis
    - Balance, age at walking
    - Vision, “normal” eye exam
    - Degree of hearing loss
- Find out what did not cause the hearing loss
- Plan for the future
- Plan for other children
- Talk to others with same condition
- If find a definite genetic cause
  - Can apply current therapy
  - May qualify for future therapy/research
Why not pursue genetic testing for Usher Syndrome

- Usher diagnosis seems unlikely
  - Normal balance and vision so must not be Usher
  - No one in the family has it
- We aren't planning to have any more children
- Expensive and maybe insurance won’t cover
- Results will be inconclusive
- No intervention that makes it better or stops progression
- Anxiety
  - Fear of the unknown
  - Fear of the known
  - Parents or patients think they are not smart enough to understand the testing or the results
What if people do not want to get tested?

- If adults, explain why/why not and let them decide.
- If parents, trickier.
  - If no standard intervention then elective.
  - Once interventions are established that improve/stabilize condition then makes it a thornier question.
OtoGenome Test

- 71 genes for nonsyndromic hearing loss as well as a subset of syndromic genes that can mimic NSNHL (e.g. Usher, Pendred, JLNS, BOR)
- Detection of all variant types (substitutions, indels, CNVs)
- Technology: pooled barcoded samples, custom Agilent SureSelect capture, Illumina HiSeq, BWA/GATK alignment, minimum 20X coverage with Sanger fill-in and confirmation of variants
Usher Genes on Otogenome™

- **MYO7A** at 11q13.5
- **USH1C** at 11p15.1
- **CDH23** at 10q21-q22
- **PCDH15** at 10q21-q22
- **USH1G (SANS)** at 17q24-q25
- **USH2A** at 1q41
- **GPR98 (VLGR1)** at 5q14
- **PDZD7** at 10q24.31
- **DFNB31 (WHRN)** at 9q32-34
- **CLRN1 (USH3A)** at 3q21-q25
New Hearing Loss Gene Chips

- **Otogenome™**
  - 71 genes for nonsyndromic hearing loss (NSNHL) and several syndromic genes (Usher, Pendred, JLNS, BOR) that can mimic NSNHL early on
  - [http://pcpgm.partners.org/lmm/tests/hearing-loss/OtoGenome](http://pcpgm.partners.org/lmm/tests/hearing-loss/OtoGenome)

- **OtoSeq™**
  - 23 genes
  - Designed to detect mutations in the most common genes causing early onset Non-syndromic SNHL, Usher and Pendred Syndrome
  - [www.cchmc.org/hearing-loss](http://www.cchmc.org/hearing-loss)

- **OtoScope™**
  - 66 genes for Non-syndromic SNHL, Usher Syndrome and Pendred syndrome
  - [http://www.healthcare.uiowa.edu/labs/morl/](http://www.healthcare.uiowa.edu/labs/morl/)
What do results mean?

- 2 pathogenic mutations in a known USH gene
- 2 mutations of unclear significance in an USH gene (variant of unknown significance=VUS)
- 1 pathogenic mutation and one VUS
- 1 pathogenic mutation in two different USH genes (digenic)
Who Needs Genetic Counseling

- Families/patients being tested for hearing loss genes (pre-testing)
- Families/patients being given genetic results
- There may be a greater need for genetic counseling when test results are negative or inconclusive
  - Patients may not understand that the cause of hearing loss could still be genetic
Summary

- If definitely USH, hearing loss and vision can progress
- If not certain USH, try and confirm a diagnosis
- Rarely, could be more than one diagnosis
- Manage the hearing loss according to degree
- Manage the diagnosis according to what makes sense
- Match USH genetic results to possible clinical trials
THANKS!