Evaluation of Pediatric Hearing Loss in the Age of Genetic Testing

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Objectives

- Identify genetic tests for pediatric hearing loss
- Consider sequential testing for pediatric hearing loss
- Eliminate unnecessary testing
- Highlight ongoing/debated aspects of testing
Epidemiology

- Neonatal hearing loss
  - 1.4 to 3 per 1000 live births
  - > 50% genetic
    - 75-80% autosomal recessive
    - 15-20% autosomal dominant
    - 1-2% X-linked; few mitochondrial
  - 25% acquired
  - 25% unknown
- Ongoing changes in epidemiology
  - e.g. immunization, neonatal care
- UNHS may not identify progressive loss
  - 15-20% of preschool children with SNHL

Identifying Etiology

- No consensus
  - Tests to perform
  - Order of testing
- Rapid evolution
  - New data on identified etiologies
  - New etiologies
History

- Prenatal
  - Maternal factors
    - TORCHS
      - CMV #1 in developed world
    - Medications
    - Drug, alcohol, tobacco use
    - Diabetes

- Perinatal
  - Prematurity
  - Low birth weight
  - Hypoxemia
    - NICU admission, ventilation, low APGARs
  - Hyperbilirubinemia
  - Sepsis
  - Ototoxic medications
History

- Postnatal
  - Infectious
    - Bacterial meningitis
      - S. pneumo & N. meningitidis >> H. flu
    - Viral: mumps, measles
    - Check vaccination record
  - Delayed motor milestones
  - Syncope, arrhythmias

History

- Family History
  - HL < 30 years old
  - Consanguinity
  - Ethnic subgroups
  - Sudden death in childhood
  - Consider unrecognized HL in siblings
Physical Exam

Physical Exam
Physical Exam

Syndromic features
- White forelock
- Facial shape
- External ear anomalies
- Maxillary and mandibular hypoplasia
- Preauricular pits/tags
- Branchial cleft anomalies
- Digits
- Skin
- Neurologic
Physical Exam

- Acquired etiologies
  - Microcephaly
  - Chorioretinitis
  - Cataracts

Audiologic Evaluation

- ABR
  - Infants and young children
  - Children unable to undergo audiometry
- Audiometry
- Family member testing
What tests do you get next?

Possible Diagnostic Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Diagnosis</th>
<th>Cost, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count with differential</td>
<td>Anemia, sickle cell disease, polycythemia, macrothrombocytopenia</td>
<td>19.25</td>
</tr>
<tr>
<td>Thyroid function tests (thyroxine, triiodothyronine)</td>
<td>Hypothyroidism (cretinoid or Pendred syndrome)</td>
<td>76.94</td>
</tr>
<tr>
<td>Sedimentation rate</td>
<td>Autoimmune disease</td>
<td>20.46</td>
</tr>
<tr>
<td>Renal function/electrolytes</td>
<td>Renal failure, Alport syndrome</td>
<td>15.77</td>
</tr>
<tr>
<td>Glucose</td>
<td>Diabetes</td>
<td>17.87</td>
</tr>
<tr>
<td>Cholesterol/lipid profile</td>
<td>Hyperlipidemia</td>
<td>17.87</td>
</tr>
<tr>
<td>Fluorescent treponemal antibody</td>
<td>Syphilis</td>
<td>47.36</td>
</tr>
<tr>
<td>E/D/LI filters</td>
<td>Congenital infection (toxoplasmosis, rubella, cytomegalovirus, herpes simplex)</td>
<td>211.00</td>
</tr>
<tr>
<td>Consultations (genetics and ophthalmology)</td>
<td>Syndromes and retinal pigmentosa</td>
<td></td>
</tr>
<tr>
<td>Electric/audiogram</td>
<td>Pendred, Stensen, Woolsey, and London-De Mee syndrome</td>
<td>386</td>
</tr>
<tr>
<td>Computed tomography of the temporal bones</td>
<td>Enlarged vestibular aqueduct, incomplete partition</td>
<td>1019.70</td>
</tr>
</tbody>
</table>

*Charges at Children's Hospital, Cincinnati, Ohio.

Greinwald, et al., 2002
Ophthalmologic Evaluation

- Recommendations vary:
  - All severe-to-profound SNHL
    - 50% have ocular abnormalities
  - All bilateral congenital SNHL of unknown etiology
  - Delayed motor milestones

Genetic Testing

- > 70 loci for non-syndromic AR deafness
- Mutations in GJB2 (Connexin 26)
  - 50% of non-syndromic AR SNHL
  - Compound heterozygosity with GJB6 (connexin 30)
  - Few AD SNHL
- As high as 30% of all pediatric SNHL
- U.S. carrier rate 3%
GJB2 Testing

- >60 allele variants
  - 70% are 35delG mutations
    - Europe, N. America, Mediterranean
  - 167delT in Ashkenazi
  - 235delC in Japanese
  - V37I in Taiwanese
  - R143W in Ghana (>80% mutations)
  - No mutations in Indonesian deaf patients

GJB2 Phenotype

- GJB2 phenotype
  - Significant heterogeneity
  - Severe to profound bilateral SNHL
    - Truncating mutations: 35delG
  - Milder impairment
    - Missense mutations: L90P, V37I
  - Progressive SNHL
  - Unilateral SNHL
  - Recurrent sudden SNHL
**GJB2 Mutations by SNHL Category**

![Bar chart showing GJB2 mutations by SNHL category](image)

**GJB2 Testing**

- **Recommendations for GJB2 testing**
  - First step for bilateral severe to profound SNHL. [Preciado, 2005]
  - First step in all bilateral > 40 dB. [Greinwald, 2002]
  - First step in all, with genetic counseling and regular follow-up. [Robin, 2005]
Can Diagnostics Be Streamlined?

- Sequential Diagnostic Algorithm Study Preciado, 2005
  - 150 patients underwent full diagnostic evaluation
  - Outcome measures
    - diagnostic yield and cost analysis
  - Results:
    - 12% biallelic GJB2 mutations: cost $500
    - 30% temporal bone abnormalities: cost $1100
    - Lab tests: no contribution: cost $360

- Logistic regression significantly predicted negative results on further testing
Proposed Algorithm

Can we stop with a positive GJB2 test?

- Kenna, et al., 2001
  - 18 biallelic mutations
    - 2 temporal bone abnormalities
- Preciado, et al., 2005
  - 18 biallelic mutations
    - 1 EVA
- Normal CT in all GJB2 patients
  - Cohn, et al., 1999; Denoyelle, et al., 1999; Green et al., 2003
- Propst, et al., 2006
  - 53 pediatric CI users with biallelic GJB2 mutations
    - 55% temporal bone anomalies in GJB2
    - 29% in controls
Should we limit CT scans?

- In utero radiation
  - ~ 50% greater risk of cancer than baseline
  - 1.6 to 2.1-fold mortality excess

Linet, et al., 2009

Radiation Exposure Risk

- CT in U.S.
  - 3 million total CT annually in 1980
  - >70 million total CT annually in 2009
  - Up to 7 million children annually in 2009
  - 15% of imaging
  - 70% of radiation dose
  - Head is most common region for pediatric CT

The use of CT scans has more than tripled since the early 1990s.

Linet, et al., 2009
Projected Number of Future Cancers That Could Be Related to CT Scans Performed in the United States in 2007, According to CT Scan Type

Table 2. Projected Number of Future Cancers That Could Be Related to CT Scans Performed in the United States in 2007, According to CT Scan Type

<table>
<thead>
<tr>
<th>Type of CT Scan</th>
<th>No. of Scans</th>
<th>No. of Cancers</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
<th>Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>18.7 (32)</td>
<td>1900 (1300-2600)</td>
<td>11</td>
<td>2100 (1600-2600)</td>
<td>19</td>
</tr>
<tr>
<td>Chest</td>
<td>71.1 (12)</td>
<td>7030 (3900-11000)</td>
<td>17</td>
<td>1000 (500-2000)</td>
<td>9</td>
</tr>
<tr>
<td>Cervical spine</td>
<td>1.9 (5)</td>
<td>700 (250-1100)</td>
<td>4</td>
<td>300 (150-600)</td>
<td>3</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>0.5 (&lt;1)</td>
<td>300 (65-500)</td>
<td>1</td>
<td>50 (25-100)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Abdomen/abdominoplasty</td>
<td>10.9 (2)</td>
<td>900 (600-1500)</td>
<td>6</td>
<td>500 (250-1000)</td>
<td>4</td>
</tr>
<tr>
<td>CTA head</td>
<td>2.3 (4)</td>
<td>200 (100-400)</td>
<td>12</td>
<td>500 (200-900)</td>
<td>5</td>
</tr>
<tr>
<td>CTA other</td>
<td>1.6 (5)</td>
<td>400 (200-900)</td>
<td>2</td>
<td>500 (250-1100)</td>
<td>5</td>
</tr>
<tr>
<td>Whole body</td>
<td>0.3 (&lt;1)</td>
<td>300 (65-500)</td>
<td>3</td>
<td>150 (75-225)</td>
<td>1</td>
</tr>
<tr>
<td>Coronography</td>
<td>0.2 (&lt;1)</td>
<td>70 (35-100)</td>
<td>&lt;1</td>
<td>50 (25-100)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Carotid imaging</td>
<td>0.6 (1)</td>
<td>150 (75-300)</td>
<td>1</td>
<td>50 (25-100)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Other</td>
<td>3.5 (6)</td>
<td>10 (3-20)</td>
<td>&lt;1</td>
<td>20 (10-35)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Total</td>
<td>56.9 (100)</td>
<td>10 000 (8000-12000)</td>
<td>100</td>
<td>11 000 (6000-16000)</td>
<td>100</td>
</tr>
</tbody>
</table>


Radiation Exposure Risk

- Pediatric diagnostic radiation exposure
  - Younger patients receive higher radiation dose/unit tissue
  - Children are more sensitive to radiation
    - 10 fold neoplastic potential
  - More years at risk for cancer occurrence

Based on projections from the more than 10,000 adults imaged, patients run the risk of developing cancer from radiation received during CT scans. Risks from a heart scan:

- One cancer for every 270 scans
- One cancer for every 600 scans

Radiation Exposure Risk

- Risk for cancer with early life diagnostic radiation
  - 1958 and 1988 studies show no increased risk of pediatric cancer
  - 2001 and 2003 studies show small but significant increase in lifetime risk of fatal cancer
    - 1/1000 children with a single CT scan
    - 0.35% increase > baseline
  - Large, long-term studies are needed in children


CT-limiting Algorithm?

Preciado, et al., 2005
Abnormal CT – What now?

- Enlarged vestibular aqueduct (EVA) most common
  - Alone
  - Incomplete partition of cochlea
- Hearing loss
  - Pre- or perilingual
  - SNHL or MHL
  - Fluctuating or progressive
  - Unilateral or bilateral
- Two entities
  - Enlarged vestibular aqueduct
  - Pendred syndrome
    - EVA and goiter

EVA Evaluation

- Thyroid function tests
  - Often euthyroid, lack specificity without goiter
- Perchlorate discharge test
  - Low specificity, variation in criteria, host factor confounders
- SLC26A4 mutations
  - 2nd most common cause of non-syndromic HL
  - Autosomal recessive
    - Monallelic mutation unclear diagnostic information
      - More common in isolated EVA than Pendred
  - No clear common mutation
    - Requires full gene sequencing

Pryor, et al., 2009
Genetic Mutations

- Other genes
  - ARNSHL
    - MYO15A
    - OTOF: consider testing in auditory neuropathy patients
    - CDH23
    - TMC1
  - ADNSHL
    - Not frequent etiology do HL
    - WFS1
    - KCNQ4
    - COCH: consider in progressive, late-onset with vestibular abnormalities
    - GJB2: HL with skin disorders
  - X-linked
    - POU3F4: bony labyrinth defects
  - Mitochondrial
    - MT-RNR1
    - MKT-TS1

Genetic Mutations

- Syndromic HL
  - Waardenburg Syndrome: PAX2, MITF, EDNB, EDNRB, and SOX10
  - Velocardiocular syndrome: 22q11 deletion
  - Stickler syndrome: COLIIA1, COLIIA2
  - CHARGE: CHD7
  - Branchio-oto-renal Syndrome: EYA1
  - Treacher-Collins: TCOF1
  - Ostogenesis Imperfecta: COLIA1, COLIA2
  - Usher’s Syndrome: MY07A, USH1C, CDH23, PCDH15, SANS, USH2A, VLGR1, WHRN, USH3A
  - Jervell and Lange-Nielson: KCNE1, KCNQ1
  - Alport’s: COL4A5, COL4A3, COL4A4
Genetic Counseling

- Pre- and post-diagnosis counseling
- Establishing genetic diagnosis
  - Pros
    - Dispel incorrect notions of etiology
    - Accurate recurrence rate
    - Prognostic information
    - Limit other diagnostic tests
  - Cons
    - Understanding/interpretation
    - Uncertain results
    - Non-genetic counselors uncomfortable

Summary Recommendations

- **GJB2** first in all bilateral SNHL
  - Temporal bone CT in negative **GJB2**
  - Repeated audiologic evaluation in + patients
- Temporal bone CT in all unilateral, fluctuating, or progressive SNHL, MHL, goiter
  - **GJB2** testing in negative CT
- Continue to evaluate data on **GJB2** mutations and temporal bone CT
- **SLC26A4** testing in EVA
Recommendations

- Selective additional testing based on history/clinical findings
- Ophthalmologic and ECG in all severe-to profound negative on GJB2 and CT imaging
- Genetic counseling for all patients undergoing genetic testing

Future Testing

- DNA sequencing microarray
  - Possible results
    - All children who do not pass UNHS tested
    - More accurate incidence/prevalence
    - Genotype/phenotype correlations
    - Enhanced clinical care
Further Research

- Further radiation exposure data
- Further clarification of \textit{GJB2} phenotypes
- Additional gene identification

Thank You!