Pediatric Syndromal Hearing Loss

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OUTLINE

• Introduction
• Basic Mendelian Genetics
• Approach to the syndromic child
• Specific syndromes
1/1,000 Born Deaf

50% Hereditary-genetic

1/3 syndromic
  - Dominant
    - Waardenburg
    - BOR
    - Stickler’s
    - NF2
    - Treacher Collins
  - Recessive
    - Usher
    - Pendred
    - Jervell/Lange-Nielsen
  - X-linked
    - Alport

2/3 nonsyndromic
  - 23% dominant
  - 75% recessive
  - 2% X-linked
  - 1% mitochondrial

50% acquired prenatally
  ½ idiopathic
  Intrauterine infection (TORCHS)
  Low birth weight
  Hypoxia
  Hyperbilirubinemia
  Non-genetic syndromes
    - Goldenhar’s
    - FAS

X-linked
  - 23% dominant
  - 75% recessive
  - 2% X-linked
  - 1% mitochondrial
Approach to the Syndromal Patient

• Family History
  – Is there a FHx reported?
  – Associated clinical features in the family?
  – Do not assume parents hear normally
    • Eval parents’ hearing
  – Inquire about hearing of other family members
  – Consanguinity?

• Birth/developmental Hx
  – Rubella status of mother
  – Motor delay
  – Global developmental delay
Approach to the Syndromal Patient

Physical exam

- External ears (size, shape)
- Eyes (color, spacing, etc)
- Neck (cyst, fistulas, length)
- Pigmentation
- Hands/feet/fingers/toes
- How does child look at first glance?
  - Dysmorphic or is this a family trait?
- Facial asymmetry

Investigations

- Audiogram of 1st-degree relatives
- Ophthalmology exam
- Serologies (TORCH)
- Urinalysis
- EKG
- Chromosome analysis
- CT temporal bone
Dominant Inheritance

Deaf x Hearing

Deaf  Deaf  Hearing  Hearing
Recessive Inheritance

Hearing × Hearing

Deaf  Hearing  Hearing  Hearing
X-linked Inheritance

Hearing  X-linked Inheritance  Hearing

Human offspring from a crossing:
- Hearing
- Hearing
- Hearing
- Deaf

Chromosomal representation:
- X chromosome
- Y chromosome
- X chromosome
Autosomal Dominant Syndromes
Waardenburg Syndrome

• Epidemiology
  – 1 in 20,000 to 1 in 40,000
  – 3% of congenitally deaf children

• Etiology
  – PAX3 mutation (type 1 and 3)
  – MITF mutation (type 2)
  – EDNRB mutation (type 4)
Waardenburg Syndrome

- General clinical characteristics
  - Dystopia canthorum
  - Pinched nose
  - Heterochromia iridis
  - Abnormal pigmentation of skin and hair
  - Broad nasal bridge and hypoplastic alae nasi
  - High arched or cleft palate

http://dermatology.cdlib.org/123/case_presentations/waardenburg/1.jpg
Waardenburg Syndrome

**Otologic characteristics**
- Hypoplastic ear cartilage
- Abnormal vestibular function (type 2)
- SNHL
  - Bilateral most common
  - Low-mid frequency loss
  - CI can be expected to yield improved speech perception and speech intelligibility capabilities

**4 subtypes**
- Type 1: every patient exhibits dystopia canthorum
- Type 2: void of dystopia canthorum, but vestibular abnormalities present
- Type 3: Type 1 + upper extremity abnormalities + unilateral upper lid ptosis
- Type 4: Type 2 + pigmentation abnormalities + Hirschsprung disease
Branchio-Oto-Renal Syndrome

• Epidemiology
  – 2% of profoundly deaf children

• Etiology
  – EYA1 gene mutation
  – High penetrance, variable expressivity

• Diagnosis
  – At least 3 major criteria
  – Two major criteria and at least two minor criteria
  – One major criteria with one first-degree relative meeting BOR criteria
<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
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<tbody>
<tr>
<td>Branchial anomalies</td>
<td>External ear anomalies</td>
</tr>
<tr>
<td>Deafness</td>
<td>Middle ear anomalies</td>
</tr>
<tr>
<td>Preauricular pits</td>
<td>Inner ear anomalies</td>
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<tr>
<td>Renal anomalies</td>
<td>Preauricular tags</td>
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<tr>
<td></td>
<td>Other: facial asymmetry, palate abnormalities</td>
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Branchio-Oto-Renal Syndrome

- Hearing impairment
  - estimated to be present in 70-93%
  - Variable age of onset
  - Mild to profound severity
  - SNHL, CHL, or mixed
  - Mondini’s dysplasia and stapes fixation can also be present

- Other characteristics
  - cup-shaped pinnae,
  - preauricular pits/tags
  - Lacrimal duct stenosis
  - branchial cleft fistulae
  - bilateral renal anomalies.
  - deep overbite and a long, narrow face
Branchio-Oto-Renal Syndrome

Kochhar, et al. 2007
Stickler Syndrome

General characteristics

- Progressive SNHL
- Cleft palate,
- abnormal development of the epiphysis,
- vertebral abnormalities/osteoaarthritus.
- Genetics
  - COL2A1, COL11A1, and COL11A2 mutations

Subtypes

- Type 1
  - progressive myopathy,
  - retinal detachment
  - Vitreoretinal degeneration
- Type 2:
  - no retinal detachment
- Type 3
  - eye and ear findings present in type 1 but has facial abnormalities
Treacher Collins Syndrome (TC)

- Fraceschetti-Zwahlen-Klein Syndrome or Mandibulo-Facial Dysostosis
- Etiology
  - TCOF gene mutation on 5q32-q33.1
- Typical features
  - microtia and malformed ears
  - midface hypoplasia
  - micrognathia
  - downslanting palpebral fissures
  - coloboma of outer 1/3 of lower eyelids.
Treacher Collins Syndrome (TC)

• Airway
  – Upper airway narrowing a major issue
  – Nasopharynx 50% smaller than normal
  – More prone to OSA and SIDS

• Ears/Hearing
  – Usually CHL
    • Absent/stenotic EAC
    • Middle ear anomalies
      – as monopodal stapes
      – ankylosed foot plate
      – malformed incus
      – cochlea and vestibule abnormalities
  – SNHL
    • Affects high frequencies
Treacher Collins Syndrome (TC)
Neurofibromatosis Type 2 (NF2)

• Epidemiology
  – Prevalence of 1 in 210,000 people

• Etiology
  – NF 2 tumor suppressor gene mutation on chromosome 22

• Diagnosis
  – Manchester criteria
  – Audiometry
  – MRI with gadolinium
Table 1
Manchester criteria for the diagnosis of NF2 (Baser et al [10])

| A. Bilateral vestibular schwannomas |
| B. First-degree relative with NF2 AND unilateral vestibular schwannoma OR any two of the following: meningioma, schwannoma, glioma, neurofibroma, juvenile posterior subcapsular lens opacity |
| C. Unilateral vestibular schwannoma AND any two of the following: Meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities |
| D. Multiple meningiomas (two or more) AND unilateral vestibular schwannoma OR any two of the following: schwannoma, glioma neurofibroma, cataract |
NF 2 Clinical Features

- Meningiomas
- Ependymomas
- Gliomas
- Lens opacities
- Café-au-lait spots (few)
- Cranial nerve, spinal and peripheral nerve schwannomas

Otologic
- Bilateral vestibular schwannomas
- Tinnitus, disequilibrium, cranial nerve symptoms
- Usually present in 2nd and 4th decade
- Many present with unilateral SNHL instead of bilateral SNHL
- Children < 15 yo often present w/o HL or schwannoma development
- Rehab
  - Hearing aids for moderate HL
  - Success with CI s/p tumor removal
  - Neff and Welling, Oto Clin N Amer, 2005
Osteogenesis Imperfecta (OI)

- **Triad**
  - Bone fragility
  - Blue sclera
  - Hearing impairment

- **Incidence**
  - 1 in 20,000 - 1 in 30,000

- **Etiology**
  - Mutation in *COL1A1* or *COL1A2*
  - Type I collagen defect

www.gfmer.ch/.../gendis_detail_list.php?cat3=742
OI Clinical Characteristics

- Hypermobile joints
- Short stature
- Triangular face
- Cardiovascular abnormalities
- Skin disorders

- Hearing Impairment
  - Usually presents in 2nd or 3rd decade
  - Mixed (prevalence 26-78%)
    - CHL due to thickened, fixed stapes footplate
    - SNHL
      - cochlear hair cell atrophy
      - Atrophy of stria vascularis
      - Bony formation around cochlea
  - Stapedotomy may facilitate hearing aid rehab
    - Swinnen et al., 2009 Laryngoscope
Osteogenesis Imperfecta

Otospongiosisis
Autosomal Recessive Syndromes
Usher Syndrome

• Epidemiology
  – Most common autosomal recessive cause of HL
  – incidence ~ 3-5 per 100,000 in the general population
  – 1-10% among profoundly deaf children
  – Approximately 50% of blind and deaf in US

• Etiology
  – USH1 and USH2 gene mutations
Usher Syndrome

• 3 Main subtypes
• Type 1
  – severe hearing loss and vestibular dysfunction.
  – onset of retinitis pigmentosa in childhood
• Type 2
  – Retinitis pigmentosa begins after childhood.
  – Mild to moderate hearing loss
  – Normal vestibular function.
• Type 3,
  – Progressive hearing loss & vestibular dysfunction.
  – Retinitis pigmentosa can occur anytime in life.
Pendred Syndrome

• Characterized by hearing impairment & abnormal iodine metabolism.

• Etiology/Pathogenesis
  – SLC26A4 (PDS) gene mutation
  – Encodes protein which helps regulate iodine and chloride ion transport

• Characteristics
  – Euthyroid goiter
    • Diagnose with thyroid function tests
Pendred Syndrome

• Hearing
  – Severe SNHL
    • present at birth or progressive
  – Inner ear abnormalities
    • Mondini’s
    • EVA

Journal of Clinical Endocrinology & Metabolism
Jervell and Lange-Nielsen Syndrome

• Incidence:
  – 1.6-6 cases per million in certain parts of Europe
  – 6 per 1,000 in congenitally deaf children

• Characterized by severe-profound hearing loss and prolongation of the QT interval on EKG
  – syncopal episodes due to cardiac conduction defect

• Can manifest as early as the 2nd or 3rd year of life
• Should suspect in a child with hearing loss and seizures of unknown origin and/or a family history of sudden death
Jervell and Lange-Nielsen Syndrome

• Etiology
  – Cardiac conduction defects attributed to mutations in potassium channel genes
    • loci on the KVLQT1 and KCNE1 genes located on chromosomes 11p15.5 and 21q22 respectively.

• Hearing rehabilitation with cochlear implant
  – Comparable auditory and speech outcomes compared to nonsyndromic patients with SNHL
    • Yanmei et al. *In J Pediatr Otorhinolaryngol* 2008
Biotinidase Deficiency

- **Features**
  - Rashes
  - Seizures
  - Hair loss
  - Hypotonia
  - Emesis & acidosis
  - Hearing loss
    - 75% occurrence if left untreated

- **Etiology**
  - lacks of enzyme responsible for proper biotin metabolism

[Link to Van Waveren Marken's website](http://www.vanwaverenmarken.com/bioti.htm)
X-linked Syndromes
Alport Syndrome

Features
• Eye
  – Congenital cataracts
• Renal
  – Glomerulonephritis
  – Hematuria
  – Renal failure
• Ear
  – Bilateral progressive SNHL
  – Onset in 2nd decade

Etiology
• mutation in type IV collagen gene COL4A5
Infectious Syndromes
Cytomegalovirus (CMV)

• Epidemiology
  – Incidence of 0.2-2.3% of live births
  – One of the most frequently occurring viruses
  – Leading cause of congenital malformation and mental retardation
  – Most prevalent TORCH infection
CMV Common Clinical Characteristics

- Microcephaly
- IUGR*
- Petechiae*
- Hepatosplenomegaly
- Encephalitis

*2-3 times more likely to have SNHL

Deafness
- 1/3 of SNHL in young children
- May be delayed
- Can be fluctuating and progressive
- Temporal bone studies
  - CMV inclusion bodies in stria vascularis, saccule utricle, SCC, Reissner’s membrane.
  - Endolymphatic hydrops in cochlear ducts
- Stabilization or improvement of hearing with antiviral tx of symptomatic neonates.
  - Dahle et al, J Am Acad Audiol 2000

*SNHL = Sensorineural Hearing Loss

* IUGR = Intrauterine Growth Restriction
CMV
Congenital Rubella

• Classic triad
  – Deafness
  – Congenital cataracts
  – Heart defects

• Etiology
  – RNA togavirus

• Transmission
  – Congenital and postnatal transmission possible
    • Congenital- transplacental
    • Postnatal- saliva, sputum, direct contact
Congenital Rubella

• Diagnosis
  – Positive viral culture
  – Rubella specific IgM antibody
  – Significant rise in IgG antibody in acute and convalescent phase
Congenital Rubella: Clinical

- Microcephaly
- Thrombocytopenia
- Hepatosplenomegally
- Motor/neural retardation
- Encephalitis
- Interstitial pneumonitis

- Hearing loss
  - Asymmetric, SNHL
    - Variable severity
    - May be progressive
    - Usually 500-2000Hz
    - Usually evident by 5 yo
      - May be isolated finding
  - Bento et al., 2005
    - ~30% of infants born to rubella infected mothers had SNHL
      - 80% were profound
Rubella congenital cataracts

www.vaccineinformation.org/photos/rubeiac003a.jpg
Non-Genetic Syndromes
Goldenhar’s Syndrome

• Aka hemifacial microsomia (HFM), facioauriculo-vertebral dysplasia (FAVD)

• Incidence: 1 in 5600 live births
  – Most significant asymmetric craniofacial disorder
Goldenhar’s Syndrome

Facial anomalies (unilateral)
- Hypoplasia of mandible
  - Ramus and condyle
- Hypoplasia of maxilla, malar and temporal bones
- Macrostomia and pseudomacrostomia
- Cleft lip/palate
- Delayed dental development

Otologic abnormalities
- microtia/anotia
- preauricular tags
- ossicular abnormalities
- abnormal facial nerve course
- hearing loss (conductive > sensorineural).
  - HL secondary to abnormal development of 1<sup>st</sup> and 2<sup>nd</sup> arch structures

www.earreconstruction.co.uk/fig-microtia/Pair
Goldenhar’s: Non-Head & Neck Manifestations

- **Cardiac**
  - COA
  - VSD
  - TOF
  - PDA

- **Renal**
  - Hydronephrosis
  - Renal ectopia

- **Musculoskeletal**
  - Limb deformities

- **Ocular**
  - blepharoptosis
  - Microphthalmia
  - epibulbar tumors
  - retinal abnormalities leading to reduced visual acuity.
Fetal Alcohol Syndrome (FAS)

- Epidemiology
  - Occurs in 30-40% of children born to alcoholic mothers

- Etiology/Pathogenesis
  - Exact amount of alcohol required unknown
  - Teratogenic restriction of cell growth during critical periods
FAS Characteristics

- Neural tube defects
- Seizure disorder
- Microophthalmia
- Optic nerve hypoplasia
- Tortuous retinal vessels
- Colobomas
- Malignant neoplasms of embryonal origin
- Deafness
  - SNHL or CHL
- Pre/Postnatal growth deficiency
- Behavioral
  - Mental retardation; IQ=63
  - Irritability & hyperactivity
- Cardiac, renal, musculoskeletal abnormalities
Facial Dysmorphisms
Narrow forehead
Short palpebral fissures
Ptotic eyelids
Midface hypoplasia
Short nose
Smooth philtrum
Thin upper lip
Hypoplastic mandible
Cleft palate/lip
Down’s Syndrome

• Epidemiology:
  – Most common syndrome caused by chromosome abnormality

• Etiology
  – Trisomy of chromosome 21
Down’s: Clinical Features

- **Cardiovascular**
  - VSD, TOF, PDA,

- **Genitourinary**
  - Small penis, low testosterone, infertility

- **Musculoskeletal**
  - Atlantoaxial instability, short digits

- **Ocular**
  - Brushfield spots

- **Behavioral/Psych**
  - IQ=30-50
Down’s: Clinical Otolaryngologic

• Ears
  – Small ears, stenotic EAC, ETD
  – Increased incidence of OM
    • ETD
    • Increased propensity for URI
    • Reduced B and T cell function (immune system immaturity)
  – Hearing loss (CHL, SNHL, or mixed)
    • OM
    • Middle ear abnormalities (stapes)
    • May suffer presbycusis
Down’s: Clinical Otolaryngologic

• Airway
  – Upper airway obstruction and OSA
    • Midface hypoplasia
    • Relative macroglossia
    • Relatively enlarged tonsils and adenoids

• Speech
  – Articulation defects/ dysarthria
• The method of treatment should be selected to meet the individual needs of the patient to achieve the most benefit.
• The main purpose of arriving at a syndromic diagnosis is to identify those that will have hearing loss so that early and aggressive hearing rehabilitation can be initialized.
Real life scenario

• www.usherssyndromefoundation.org
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