Patient Centered Research: The Audiology Experience

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Patient Centered Research?

- Who are we?
- What do we do?

- A.I. duPont Hospital for Children
- The Clinic for Special Children: Collaborating to improve children’s lives
Nemours – a children’s health system

- 1936 - Alfred I. duPont
  American industrialist

- 1940 - Opened as 60-bed hospital for children with orthopedic conditions
Nemours/Alfred I. duPont Hospital for Children

- 1985 –200-beds
  - full range of pediatric specialties
- Caring for 250,000 children annually in:
  - Delaware Valley
  - Florida
- 2012 - Nemours Children’s Hospital to open in Orlando
Nemours/Alfred I. duPont Hospital for Children

- Expansion of facilities
  - to open 2014
  - 250 single-bed rooms
  - New, larger ED
  - New PICU
  - 188-space underground parking garage
  - Rooftop helipad
  - Five-story atrium entrance and welcome center
Department of Otolaryngology

Dr. Robert O’Reilly

Audiology Clinic

Dr. Yell Inverso

Auditory Physiology and Psychoacoustics Research Laboratory

Dr. Thierry Morlet
Division of Pediatric Otolaryngology

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Patrick Barth, MD        Douglas Johnston, MD        Heather Nardone, MD        Katie Bacik, PA-C        Colin Drake, PA-C        Erin Field, PA-C

Nemours. Alfred I. duPont Hospital for Children
Audiology Clinic

Yell Inverso, PhD

Liesl Looney, Aud

Thomas Jefferson University Dept. of Otolaryngology

Mindy Rabinowitz, MD PGY-4
Clinical Audiology
Full-Spectrum Pediatric Audiology Services

- 12 Audiologists, 2 Audiology Assistants, 1 Audiology Doctoral Extern & 3 support staff
- Comprehensive Behavioral Hearing Evaluations
  - Visual Reinforcement Audiometry
  - Conditioned Play Audiometry
  - Standard Behavioral Audiometry
- Distortion Product and Transient Evoked Otoacoustic Emission Testing
- Sedated and un-sedated Auditory Brainstem Response Testing (Diagnostic and Newborn Screening)
- Comprehensive Middle Ear Diagnostic Evaluations
Audiologic Specialty Care

- Cochlear Implant Program
- Central Auditory Processing Disorders (CAPD) Program
- Pediatric Amplification and Assistive Listening Devices Program
- Auditory Neuropathy Spectrum Disorders Program
- Pediatric Vestibular Program
Pediatric Vestibular Program

Vestibular Evoked Myogenic Potential (VEMP)
- 500 Hz tone burst (75-95 dB HL air or 66 dB pip bone)
- Tonic SCM contraction = EMG 50-250 microvolts
- 80-100 samples averaged

Rotary Chair Testing (RC)
- 0.01, 0.04, 0.16, 0.64 Hz at max velocity 50 deg/s
- Gain, Phase, Assymetry

Video Nystagmography Test Battery (VNG)
- IR system to record corneal movement
- Saccades, Pursuit, OPK
- Spontaneous, positional, positioning nystagmus
- Air induced binaural, bithermal, calorics
Pediatric Vestibular Program

- **Computerized Dynamic Posturography (CDP)**
  - Limits of stability using 8 standard trials
  - Reaction time, movement velocity, endpoint excursion, max excursion, directional control

- **Gross Motor Development**
  - Peabody Developmental Scale (<4 yrs)
  - Bruininks-Ostresky Test Motor Proficiency

- **Full Gait Analysis**
  - Dynamic balance kinetics and kinematics
  - Position / movement CM walking straight line (60 Hz data collection)
    - Self selected speed for 9 meters
Auditory Physiology and Psychoacoustics Research Laboratory
Thematic

- Development of Efferent Auditory Pathways: Cortical control of the auditory periphery
- Speech processing at the cortical level (Quiet and noise)
- Auditory and Vestibular impairment
  - Otoacoustic Emissions
  - Suppression of Otoacoustic Emissions
  - Evoked Potentials:
    - Auditory Brainstem Responses
    - Middle Latencies
    - Cortical Potentials (Speech/noise)
Specific Studies

- Auditory Processing Disorders and Specific Language Impairment:
  - Efferent function and Hemispheric specialization
- Friedreich Ataxia
  - Auditory, Speech and Vestibular functions
- Rett Syndrome
  - Auditory function
- Late Onset Hearing Loss
- Vestibular Compensation
- Inner Ear Malformation
- Noise Induced Hearing Loss
- Auditory Neuropathy Spectrum Disorder
- ....
Defining Community Needs
Collaborate to Improve Patient Care

A.I. DuPont Hospital for Children

Nemours. Alfred I. duPont Hospital for Children
“Start With a Healthy Child”

Create a Medical Home
Link Services to Research

Translate Research into Practice
Translate Research into Practice: Otosclerosis
Fixation disturbs transmission of sound waves through middle ear ossicles, resulting in a CHL
Epidemiology

Prevalence

- Caucasians: 0.3-0.4%
- Tunisians: 0.4-0.8%
- Asians/Blacks/Native Americans: ~0%

Age of Onset

- 3rd decade (late teens – 6th decade)

Gender

- Female:Male = 2:1 (Clinical Otosclerosis)

Laterality

- 70–80 % bilateral

References:

Ealy, Smith. 2009
Thys, Van Camp. 2009
Markous, Goudakos. 2009
Csomor, Sziklai, Karosi. 2012
Moumoulidis, Axon, Baguley, 2007
Modes of Inheritance

Otosclerosis

- AR
- AD
- Sex-linked
- Sporadic

Monogenic
Polygenic

Markous, Goudakos. 2009
Saeed, Briggs, Lobo, et.al. 2007
Modes of Inheritance

Otosclerosis

Monogenic

Believed to occur rarely in otosclerosis

Polygenic

Likely a genetically heterogenous disease
Challenges to Genetic Analysis

1. Diagnosis is presumptive
2. Pedigree construction difficult
   - AD family:
     Ideal for linkage
     analysis = 10 meioses
     \( \rightarrow \) diff to find
3. Incomplete penetrance & variable expression

Schrauwen, Van Camp. 2010
Saeed, Briggs, Lobo, et al. 2007
Otosclerosis

- 3 Generations of affected family
- Audiometrics, Op-notes, Genetic analysis
Translate Research into Practice:
SLITRK6
SLITRK6 Family of Proteins control:

- Neurite outgrowth
- Synaptic development

SLITRK6 play role in survival and innervation:

- Auditory System
- Vestib apparatus
- Retina
Mouse model: SLITRK6

Organ of Corti normal

\[\downarrow\text{Cochlear innervation density}\]

- Development:
  - Sensory neurons
  - Spiral & vestibular ganglia die

Affected mice

- \[\downarrow\text{Wave I ABR}\]
- \[\downarrow\text{Auditory startle}\]
- \[\downarrow\text{Vertical VOR gain}\]
- \[\downarrow\text{Locomotor activity}\]
- Mid-Frequency hearing loss
**Methods**

**Patients**
- 9 subjects
- Endogamous Amish Community
- Age 0.3-36.8 years (mean: $15.3 \pm 13.9$)

**Genetic Testing**
- SNP genotype & mapping
  - GeneChip Mapping 10K Assay Kit
- All Pts homozygous for novel nonsense variant of SLITRK6

**Auditory/Vestibular**
- Tympanometry
- MEMR
- DPOAE
- ABR
- PTA, SDS, SRT
- VEMP
## Results

- VEMPS present in 3 of 4 ears tested

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<tr>
<th>Subject ID</th>
<th>Age (years)</th>
<th>MEMR</th>
<th>DPOAE</th>
<th>CM (duration in ms)</th>
<th>Waves</th>
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<td>100 dB/4 kHz 100 dB/4 kHz</td>
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*No latency/intensity shift. Abbreviations: CM, cochlear microphonic; DPOAE, distortion product otoacoustic emission; MEMR, ipsilateral middle ear muscle reflex; nt, not tested; "-", absent response.
Results

Audiologic Testing (Audiogram)

- Hearing level vs. frequency for different age groups (Age 1-6 years, Age 11-14 years, Age 29-37 years)
- Speech reception threshold vs. hearing level

$r_s = 0.81, p=0.0002$
Conclusions

Speech & Language Development

• Speech perception impaired out of proportion to pure tone threshold
• OHC dysfunction & auditory dys-synchrony
  • Youth: Develop speech/language
  • Adult: Good lip reading
• 2 oldest subjects
  • Hearing aid users
  • Limited benefit
• No cochlear implants used
  • Possible benefit?
A homozygous nonsense mutation of SLITRK5 is associated with an autosomal recessive auditory neuropathy

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<th>The Laryngoscope</th>
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<tr>
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<td>Scope-13-0434-R1</td>
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**Keywords - Combos:**
- Molecular Biology, Central auditory processing < Audiology, Molecular biology
- Audiology, Hearing loss < Pediatric audiology < Pediatrics
Translate Research into Practice:
GM3 Synthase Deficiency
What is the Defect in GM3 Disease?
Where are Gangliosides Found in the Brain?
Where are Gangliosides Found in the Brain?
Seizures
Hearing
Vision
Diet

$GM_x$

$GM_x$

Brain
Monitoring

- Otoacoustic Emissions (cochlear amplifier)
- Auditory Brainstem Responses
- Cortical Responses

- We will also check the status of the external ear and middle ear.
- All tests are non invasive!
Translate Research into Practice:
Bowling-Haught Family Waardenberg’s Type SNHL
Translate Research into Practice:
The Difference for One Child
Translate Research into Practice: The Difference for One Child