R.C.P.U. NEWSLETTER

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R.C. Philips Research and Education Unit
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Hearing Loss

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Introduction

It is estimated that 70 million people world-wide, or 1% of the world's population have some form of hearing loss that affects language communication. Profound congenital hearing loss is estimated to affect 1 in 1000 births (Tekin et al. 2001). If significant hearing loss is not detected early in life, it can have negative impacts on speech, language and cognitive development.

Newborn Screening

The history of newborn screening dates back to the 1960's when newborns were first screened for phenylketonuria (PKU). Since then, numerous screening tests have been added, including newborn hearing screening. Newborn screening (NBS) is now recognized as an essential public health initiative aimed at providing the best health outcome for a state's newborn population. For a condition to be included as a primary target for NBS the following minimum criteria should be met:

1. It can be identified at a phase (24-48 hours after birth) at which it would not ordinarily be clinically detected.
2. A test with appropriate sensitivity and specificity is available.
3. There are demonstrated benefits of early detection, timely intervention and efficacious treatment of the condition being tested.

In 1999 the American Academy of Pediatrics published a policy statement in support of universal newborn hearing screening. As of July 2001, two thirds of all states have begun early hearing detection and intervention (EDHI) programs and legislation was pending in the remaining states. The early hearing detection and intervention (EDHI) programs have three phases for the detection of hearing loss: screening, audiologic intervention and intervention.

Phase 1: Screening

All newborns are screened for hearing loss shortly after birth using either evoked otoacoustic emissions (EOAE) or auditory brainstem response testing (ABR) to look for permanent bilateral, unilateral, sensory or conductive hearing loss averaging 30-40 dB or more.
ABR testing uses a series of clicks to evoke responses, originating in the eighth cranial nerve and auditory brainstem and recorded by electrodes placed on the head. EOAE testing uses a probe inserted into the ear to measure sounds originating within the cochlea. EOAEs reflect the activity of the outer hair cells of the cochlea across a broad frequency range and are present in ears with hearing sensitivity better than 40-50 dB HL (www.geneclinics.com)

Phase 2: Audiologic Confirmation

Infants who do not pass their initial screen should be evaluated by diagnostic audiologic tests by 3 months of age.

Phase 3: Intervention

Early Intervention services should be implemented before 6 months of age for all confirmed cases of hearing loss.

Classification of Hearing Loss

There are many different classifications used to identify hearing loss. They can be broken down into three main categories: type of hearing loss, onset of hearing loss and severity of hearing loss.

Types of Hearing Loss

Sensorineural hearing loss: impairment in the inner ear structures (i.e., cochlea)
Conductive hearing loss: impairment in the sound conducting mechanism of the ear; ear canal, tympanic membrane or ossicles.

Central auditory dysfunction: damage or dysfunction at the eighth cranial nerve, auditory brainstem or cerebral cortex
Mixed hearing loss: components of sensorineural and conductive hearing loss

Onset of Hearing Loss
Congenital: present at birth. All congenital hearing loss is prelingual, but all prelingual hearing loss is not congenital.
Prelingual: present before language acquisition (about age 3 years)
Postlingual: after language acquisition

Severity of Hearing Loss
Hearing is measured in decibels (dB). The threshold or 0 dB mark for each frequency refers to the level at which normal young adults perceive a tone burst 50% of the time (www.geneclinics.com).

Mild hearing loss: 26-40 dB
Moderate hearing loss: 41-55 dB
Moderately severe hearing loss: 56-70 dB
Severe hearing loss: 71-90 dB
Profound hearing loss: >90 dB

Genetics of Hearing Loss
Approximately 60% of cases of congenital hearing loss have a genetic causation. Deafness is different than many other complex genetic diseases, in that most cases of genetic hearing loss result from mutations in single genes or gene pairs. There are currently over 400 genetic syndromes that include hearing loss and over 70 genes for nonsyndromic hearing loss have been identified (Tekin et al 2001). The genetic causation for hearing loss can be syndromic or non-syndromic, and inherited by autosomal recessive, autosomal dominant, X-linked or mitochondrial inheritance. Syndromic hearing loss is hearing loss that is also associated with additional medical complications in other body systems and non-syndromic hearing loss is isolated and is not associated with additional medical complications.

Nonsyndromic Hearing Loss
Nonsyndromic hearing loss accounts for 70% of all congenital cases of hereditary hearing loss. The majority of cases of congenital nonsyndromic hearing impairment are sensorineural with impairments in the inner ear structures such as the cochlea (Nadol & Merchant 2001).

Congenital nonsyndromic hearing loss is inherited in the following manner:
Table 1.
Inheritance of Congenital Nonsyndromic Hearing Loss

Inheritance Pattern	% congenital nonsyndromic deafness	Gene loci
Autosomal recessive	77%	DFNB
Autosomal dominant	22%	DFNA
X linked	1%	DFN

Mutations in the gene GJB2 account for 50% of all cases of autosomal recessive non-syndromic hearing loss in some populations (Zelante et al 1997). The gene GJB2 codes for connexin 26, a gap junction protein that is involved in cell to cell diffusion and the recycling of small molecules such has K^+. Genotype-phenotype correlation is the association between the presence of a certain mutation or mutations (genotype) and the resulting pattern of abnormalities (phenotype) (www.geneclincs.com) . Mutation studies on GJB2 have shown that there is a correlation between the GJB2 genotype and the associated hearing loss (Snoeckx et al 2005).

Syndromic Hearing Loss
The remaining 30% of cases of congenital hereditary hearing loss can be attributed to one of greater than 400 genetic syndromes that include deafness (Steel & Kros 2001). In Table 2, we review the most common syndromic causes of hearing loss.

Genetic Testing
If a genetic causation for hearing loss is suspected, it is recommended that the child be referred to a genetic program for evaluation. With over 400 genetic syndromes known to cause hearing loss, a comprehensive evaluation should be performed before genetic testing is pursued. Genetic testing for hereditary hearing loss can include molecular DNA testing for genetic syndromes as well as molecular testing for mutations in GJB2, and other genes as appropriate.

Genetic Counseling
The importance of appropriate genetic counseling regarding the results of genetic testing for hearing loss cannot be underscored. Genetic counseling is imperative to ensure accurate interpretation of the significance of the genetic testing results and recurrence risks.

The genetic counseling provided to patients with hearing loss is highly dependent on family history and the molecular causation of hearing loss. Greater than 90% of children with congenital, profound, non- syndromic hearing loss are born to parents with normal hearing and 10% are born to parents who are deaf. In patients with a GJB2 mutation causing hearing loss, the recurrence risk for subsequent siblings of an affected individual is 25%. Genetic counseling for individuals with GBJ2 hearing loss is unique because it is estimated that 1 in 33 individuals are carriers for GBJ2 mutations causing hearing loss.

Table 2 – Syndromic Hearing Loss

Syndrome	Inheritance	Frequency	Features	Gene
Pendred Syndrome (includes DFNB4)	Autosomal recessive	~ 4-8% of all hearing loss patients	-hearing loss -(+) perchloride discharge test -enlarged vestibular aqueduct, Mondini deformity -goiter beginning in 2nd decade -hypothyroidism	SLC26A4
Usher Syndrome-Types I,II, and III	Autosomal recessive	~ 3-6 % of all hearing loss patients	- Congenital deafness - Retinitis Pigmentosa	MYO7A USH1C CDH23 USH2A SANS PCDH15
Branchio-Oto-Renal Syndrome (BOR)	Autosomal dominant	~2% of all hearing loss patients	-hearing loss, pre-auricular pits, pinna deformities, external auditory canal stenosis -branchial fistulae -renal anomalies	EYA1 SIX5
Waardenburg Syndrome	Autosomal dominant	~1-4% of all hearing loss patients	-sensouri-neural hearing loss-often variable or mild. -midline, white forelock, widows peak -heterochromia, telecanthus	PAX3 MITF SOX10 EDN3 EDNRB
Alport Syndrome	Autosomal recessive and dominant; X linked recessive	~1% of all hearing loss patients	- sensori-neural deafness - nephritis, chronic renal failure in teens and adults -hematuria	COL4A3 COL4A4 COL4A5
Treacher Collins Syndrome	Autosomal dominant with variable expression	~1%	-bilateral conductive hearing loss -external ear malformations -hypoplastic zygomas -downslanted palpberal fissures	TCOF1
Stapes Fixation/ Perilymph Gusher (DFN3)	X-linked recessive	~0.5%	-mixed, progressive hearing loss starts early in infancy -perilymphatic duct abnormalities	POU3F4 Xq21
Jervell and Lange-Nielsen	Autosomal recessive	~0.25%	-hearing loss -prolonged QT interval -syncope, seizures, sudden death	KVLQT1 KCNE1

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About the RCPU

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20 of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is run through the Division of Pediatric Genetics, University of Florida, and is funded through a contract with the Department of Children and Families.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects.

Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

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