

Conference Endnote Address

Looking for the Hearing-Impaired Child: Past, Present and Future

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Introduction

Throughout the last century the clinical audiological field has seen a substantial development – nearly a revolution – in technology with the introduction and implementation of equipment for detection of hearing-impaired children, for diagnostic testing of hearing disorders, for restoration of hearing by surgery and for amelioration of hearing impairment (HI) – even profound by hearing instruments including cochlear implants. Numerous hearing-impaired and deaf children have benefited from this development by improving their opportunity for language and speech acquisition, for social adjustment and education through the improvement of their communication skills – and thus also in their quality of life.

This endnote address will concentrate on the early identification of infants/children with congenital/early acquired (i.e., neonatal period) permanent hearing impairment (CHI) and on the etiological evaluation by describing some past and present issues relating to these topics. In this context will not be focused on assessment, nor on amplification, and the reader is referred to Seewald (2000) in addition to other chapters within this volume.

Although the future cannot be predicted, the rapid development during the last decade within molecular genetics will have implications for the detection, diagnosis, and treatment of hearing-impaired children, and these implications will also be hinted at.

Prevalence Estimates

The prevalence of a disabling condition depends on the local and national population demography and its social and cultural characteristics. Thus the prevalence of permanent childhood HI (including congenital and later acquired HI-PHI) varies considerably throughout the world as a result of the varying childhood populations, resulting in differences in prevalences, as a function of country and/or area. However, the prevalence of PHI in children differs considerably, also as a function of birth cohort, definition, degree, and classification of the HI (Parving et al. 1998; Mencher 2000). The prevalence estimates are often based on more or less valid retrospective data collection, related to clinical series of children, comprising specific birth cohorts enrolled into hearing health surveillance programs (Davis and Parving 1994; Fortnum and Davis 1997). This may result in underestimates due to infants with unidentified HI as a result of the delayed identification of congenitally hearing-impaired children. Some variations in the estimated prevalences of CHI in children have been found, however, by using similar criteria for the HI and comparing identical birth cohorts, fairly similar prevalence estimates of CHI have been found in the industrialized countries (see table 1).

The true prevalence of CHI can only be obtained by universal neonatal hearing screening programs with 100% compliance and follow-up of those, who failed, and a screening test with 100% sensitivity/specificity (Davis, Bamford, Wilson, Ramkalawan and Foreshaw 1997). Neither the program, nor the test exists. Table 2 shows some prevalence estimates of bilateral CHI, based on universal neonatal hearing screening by either transient evoked otoacoustic emissions (TEOAE) or automatic ABR (AABR)

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Table 1. Some estimates of congenital hearing impairment from European countries/regions with defined sample characteristics: (95% confidence intervals).

Region	Birth-cohort	BEHL 0.5–4 kHz DB	Prevalence 1/1000	Authors
Waltham	1992–1994	≥40	1.53 (0.89–2.17)	Watkin 1996
Trent	1985–1990	≥ 40	1.12 (1.01–1.23)	Fortnum & Davis 1997
Trent	1985–1990	≥ 90	0.28 (0.28–0.33)	Fortnum & Davis 1997
Copenhagen	1970–1980	≥ 25	1.45 (1.23–1.66)	Parving 1993
Copenhagen	1980–1990	≥ 25	1.53 (1.28–1.78)	Parving 1993
Copenhagen	1977–1981	≥ 20	1.69 (1.24–2.30)	Parving & Christiansen 1996
Copenhagen	1982–1986	≥ 20	2.07 (1.56–2.76)	Parving & Christiansen 1996
“UK & DK”	1982–1988	≥ 40	1.16 (1.02–1.31)	Davis & Parving 1994
Eastern Finland (Kuopio)	1973–1992	≥ 25	1.41 (1.10–1.70)	Vartiainen et al. 1997
Northern Finland	1973–1992	≥ 40	0.98 (0.89–1.11)	Mäki-Torkko et al. 1998
Estonia	1985–1990	≥ 40	1.52 (1.34–1.70)	Uus & Davis 2000
Cyprus	1979–1996	≥ 50	1.19 1.01–1.40	Hadjukahou & Bamford 2000

Table 2. Prevalence of congenital hearing impairment (CHI) based on some universal neonatal hearing screening programs, using TEOAE and/or AABR 95% confidence intervals are indicated in brackets.

	Screened N	Confirmed CHI N	1/1000	Screening test
Mason & Herrmann 1998	10,372	15	1.45 (0.71–2.18)	AABR
Mehl & Thomson 1998	41,796	94 (75)*	2.25/(1.79) (1.79–2.70)/(1.39–2.20)	AABR/TEOAE
Vohr et al. 1998	53,121	111	2.09 (1.70–2.48)	TEOAE
Prieve et al. 2000	43,311	85	1.96 (1.55–2.38)	TEOAE
Messner et al. 2001	7,771	9	1.56 (0.54–2.58)	AABR

* 94 total HI – 75 bilateral SNHI

testing, showing a prevalence compatible with the prevalence of CHI, based on ascertainment studies (see table 1).

Detection of the Hearing-Impaired Child – Past and Present

Throughout the world has been reported a delayed identification of children with CHI with median ages at ascertainment varying from 12 months to 5 years, depending on the degree of hearing level (Harrison and Roush 1996; Mäki-Torkko, Lindholm, Väyrynen, Leisti and Sorri 1998). The importance of an early identification of hearing-impaired children has been emphasized since the late 1960s, and in the 1970s several hearing screening programs, including behavioral auditory screening and high-risk-registration have been implemented in various countries. Table 3 shows some of the past programs and the outcome in relation to sensitivity/specificity (Parving 1985). However, the outcome of a hearing-screening program can also be indicated as age at identification, and several universal neonatal hearing screening programmes have shown that the age at diagnosis has been reduced from around 2–3 years to 3–4 months (Kennedy 1998; Arehart, Yoshinago-

Itano, Thomson, Gabbard and Brown 1998; Dalzell et al. 2000).

Universal behavioral hearing screening has dominantly been performed as a classical distraction test (Ewing and Ewing 1944) or as a modified distraction test (Stensland-Junker, Barr, Maliniemi and Wasz-Hockert 1978; McCormick 1995; Downs 1995). A list of risk indicators has represented a screening method (JCIH 1994), although if 100% effective the indicators would only detect about 40–50% of children with CHI (Parving 1993; Fortnum and Davis 1997; Vohr et al. 2000). The consequences of a delayed identification and treatment of CHI in children have been shown both indirectly (Markides 1986; Ramkalawan and Davis 1992) and directly (Yoshinaga-Itano, Sedey, Coulter and Mehl 1998; Moeller 2000), resulting in the recommendation of universal neonatal hearing screening, implemented as part of the pediatric hearing health services. In addition, it is stated that congenitally hearing-impaired children should be diagnosed before the age of three months and habilitated before the age of six months (NIH 1993; Grandori and Lutman 1999; JCIH 2000). To achieve this goal universal neonatal hearing screening has been implemented predominantly in the United States, and at present more than 30–40 states have formally enacted universal newborn hearing

Table 3. The results of various screening programs including behavioral auditory screening and high-risk registration.

<i>Behavioral screening</i>									
	Hearing Screened n	Confirmed HI (prevalence) n	1/1000	Screening correct n	%	False negative n	%	Fail screening n	%
Mencher (1974)	10,000	9	0.9	7	78	2	22	330	3.3
Feinmesser & Tell (1976)	17,731	25	1.4	6	24	19	76	309	1.7
Barr (1978)	65,000	57	0.9	36	63	21	37		1–1.5
Downs (1978)	10,756	17*	1.6	10	59	6	35		
Bentzen and Jensen (1981)	12,000	4	0.3	2	50	2	50	167	1.4
<i>high-risk registration</i>									
	Infants registered/born		Confirmed HI (prevalence)	Confirmed HI in all registered children		Not registered but hearing-impaired			
	n	%	n	0/1000	n	0/100	n	%	
Feinmesser & Tell (1976)	3,554/17,731	20	25	1.4	18	5	7	28	
Downs (1978)	1,144/10,726	11	17	1.6	17	15	–	–	
Kankkunen (1982)	3,530/57,172	6	179	3.7	30	8	149	83	

* One deaf child not screened.

screening (Hayes 2001). In Europe three countries have implemented universal neonatal hearing screening, and in many regions of Europe universal neonatal hearing screening have been introduced using either OAE-transient or distortion product or AABR (AHEAD II 2001).

Although universal neonatal hearing screening detects 1–2/1000 hearing-impaired children (see table 2) some caution has been raised against implementation of the screening, especially in the developing world, where the diagnostic services are insufficient or lacking (Mencher and DeVoe 2001). No screening should be offered without follow-up and appropriate services! However, the developing world should be supported in the efforts to establish appropriate pediatric hearing health services.

It is important to look for the hearing-impaired child also throughout infancy and childhood. About 15–20% of PHI develops through infancy and childhood, and children with an episode of meningitis should as a routine be referred for audiological evaluation in order to avoid a delay in the diagnosis of a post-meningitic HI. Thus, the focus on universal neonatal hearing screening should not result in delayed identification of children with acquired hearing impairment, and a continuous focus on the hearing sensitivity throughout childhood by means of child health surveillance programs is warranted. In this context, it should be mentioned that the parents or caregivers represent important resources, as they are often the first to suspect a HI in their child (Parving 1984a, 1993) and prefer an early service delivery (Bamford, Davis, Hind, McCracken and Reeve 2000).

In the future can be expected that universal neonatal hearing screening programs with the purpose of secondary prevention will be implemented like other screening programs for phenylketonuria and hypothyroidism for example. Thereby a delay in the detection, identification, and treatment of CHI can be avoided. In addition, an early ascertainment may also lead to an improved etiologic diagnosis, resulting in causal treatment of the hearing impairment.

Etiological Aspects – Past and Present

Although an audiological assessment may offer some information on the factor(s) causing the HI, a systematic evaluation protocol based on an interdisciplinary approach should be offered to the child

Table 4. Protocol for etiological diagnostic evaluation.

Thorough history – including family history
ENT-examination
Assessment of hearing thresholds and speech audiometry
Classification of the hearing impairment
Vestibular examination
Ophthalmological examination
CT/MR-scanning
Urine analysis
Electrocardiography
Blood testing: virus antibodies (e.g., rubella, CMV, HIV)
bacterial antibodies (e.g., lues, toxiplasmosis)
TSH, T ₃ , T ₄
Cytogenetic testing (chromosomal abnormalities)
Mutation analysis: (Connexin 26, Pendrin, KCNQ4, etc.)
Special testing: Perchlorat discharge test

and its family. With such protocols, as shown in table 4, the etiology of a CHI may be evaluated, and thus primary prevention be introduced (Parving 1984b; Newton 1985; France and Stephens 1995; Parker, Fortnum, Young and Davis 1999).

Some Fetal Infections

In the industrialized world primary prevention of CHI caused by fetal rubella infection has been the result of rubella vaccination introduced in the 1960s and 1970s in Australia, USA, and later in the European countries. Previously a proportion of 15–30% CHI could be ascribed to fetal rubella infection, often without any other manifestations than HI and rubella retinopathy, which is found by fundoscopy and occurring in 20–50% of the children. Although the retinal changes are not pathognomonic for fetal rubella, and may occur in other fetal infections, the findings are highly specific and not seen in normal children (Wolff 1973). Any hearing-impaired child should undergo ophthalmological investigation in order to assess the visual acuity, which is of utmost importance for the education and (re)habilitation of the child, but the ophthalmological investigation should also be performed for differential diagnostic purposes, because a large number of syndromes have combined hearing and vision manifestations.

Cytomegalovirus (CMV) is a frequent viral infection in newborns causing HI, which may develop later in childhood and be fluctuating or progressive (Harris, Ahlfors, Ivarsson, Lernmak and Svanberg 1984; Dahle et al. 2000; Hayes and Drieth 2000). Human immunodeficiency virus (HIV) has been reported to cause auditory dysfunction (Birchall, White, French, Cockbanes and Smith 1992), being neurotrophic, and as HIV-infected subjects are susceptible to infectious agents, HI may arise as a complication to these often-bacterial infections.

Genetic Factors

Apart from fetal infections CHI may be ascribed to genetic factors, estimated to account for 50% of CHI, however, as a proportion of approximately 20–45% among CHI is categorized as unknown, genetic factors probably account for a higher proportion than 50% (Parving 1995; Billings and Kenna 1999). The most frequent distribution of the mode of transmission being cited is: 80–85% being autosomal recessive, 10–15% being autosomal dominant, and 1–2% being X-linked with 80–85% being non-syndromic without any additional manifestations of the mutant gene, and 15–20% being syndromic with HI occurring in combination with affection of other organ systems. Thus 427 different forms of human syndromic HI have been reported (Gorlin 1995). Apart from the classical Mendelian mode of transmission of the mutant gene in question mitochondrial inheritance is also found in children in rare cases (e.g., Fischel-Ghodsian 1996).

Before 1994 little or nothing was known about genes responsible for non-syndromic HI, although it had been estimated that more than 100 genes might be responsible for HI – congenital or with later onset (Morton 1991). Thus it has been reported that mutations in the GBJ2-gene or Connexin 26 underlying the DFNB1-form can be found in 10–50% of CHI (Estivill et al. 1998; Lench, Houseman, Newton, Van Camp and Mueller 1998) with the 35 del G mutation accounting for approximately 70% of the mutations (Orzan et al. 1999; Denoyelle et al. 1999; Marlin et al. 2001). In addition, a high-carrier frequency of 2–4% has been reported in the population (Morell et al. 1998; Gasparini et al. 2000). At present, more than 70 genes for non-syndromic HI have been localized, and about 20 of these have been identified (Van Camp and Smith 2001).

The initial sequencing and analysis of the human

genome (Lander et al. 2001; Venter et al. 2001) has resulted in the information that humans have around 30–35,000 protein coding genes – far less than previously suggested. The most important outcome of the human genome mapping is, however, that it represents a unique tool in understanding the complex biological background for human development and characteristics, – and for human diseases – also in the hearing organ. For syndromic HI much can be learned from shared developmental pathways in other organisms such as flies (*Drosophila*), worms (*C. elegans*) and yeast (*S. cervisial*) (Read 2001), and mouse mutants have proved very useful for the understanding of human, both syndromic and non-syndromic HI (Steel 2001). Although many genes responsible for HI have been localized and identified, there is limited knowledge about the function of the various genes, relating to the mechanism of hearing, such as hair-cell transduction, hair-cell synaptic activity, the outer hair-cell motor, the role of the tectorial membrane, the ionic environment of hair-cells, and molecules involved in homeostasis (Steel and Kros 2001).

Future Aspects

The great variation in the clinical expression of genetic HI (phenotype) both within a family and between families showing the same gene mutation (genotype) calls for thorough and detailed description of the phenotypes, resulting in appropriate definitions and in the future even re-definitions of already known non-syndromic/syndromic HI. In combination with detection of mutations by scanning technologies that aim to find unknown mutations in candidate or known disease genes or by screening techniques that aim to find already known mutations, the potential for improvements in diagnosis, predicting prognosis, therapy, and prevention will be offered (Van Ommen, Bakker and den Dunnen 1999).

Most genetic HI is monogenic, and what the audiologist hopes for his/her future etiological diagnostic assessment is to get a rapid tool for mutation testing of already identified and future identified genes responsible for HI. However, all mutations need not cause disease (Temple, McLeod, Gallinger and Wright 2001), and mutation screening for HI is more than another diagnostic test, which also involves interpretation, explanation to families with CHI, and counseling aimed at recurrence risks (Smith 2001). It is, however, unlikely that geneticists will be able to

provide the time requested for counseling covering the needs for families with CHI, and thus it is imperative that physicians working with CHI children are educated about genetics and genetic testing with its pitfalls, and thereby become able to communicate with the parents (Robin, Dietz, Arnold and Smith 2001; Marlin et al. 2001).

By knowing the genotype future prospective studies of CHI detected already within the neonatal period by screening will offer the opportunity for an appropriate prognosis concerning the confirmed HI, which is of utmost importance for the individual child and its family – both concerning syndromic as well as non-syndromic HI.

Although gene therapy, which is the use of nucleic acids as therapeutically useful molecules (Andersson 1998), has been raised as an issue within CHI there are in general major problems concerning low efficacy of gene transfer and gene expression, duration of expression, and safety (i.e., avoid adverse reactions from viral vectors) (Smith 1999). In addition, 5–10% of parents with a deaf child are deaf, belonging to the deaf community, and are, in general, not interested in either genetic counseling, or in future potential gene therapy. The remaining 90–95% of parents with a deaf/hearing-impaired child may be interested, taking all ethical considerations into account before future developments may reveal if and when gene therapy may be feasible in CHI. Apart from gene therapy the molecular biological development may result in pharmaceutical drugs that may prevent progression of a HI, induce regeneration of hair cells as seen in the avian, improve habilitation with cochlear implants combined with growth factors, and in the future even result in cure of CHI (Rubel 2000).

Conclusion

In the 21st century it can be anticipated that universal neonatal hearing screening will be implemented throughout most of the world, representing secondary prevention of CHI, and also that primary prevention, such as vaccination programs and genetic counseling may have been extended to both the developing and developed countries. Thus a reduction in the number of children with CHI may be the result, however, new diseases affecting the hearing sensitivity may arise as well as new knowledge on already existing diseases. This may result in unchanged or even increased prevalence estimates of CHI.

Irrespective of these considerations – looking for the hearing-impaired child remains a challenge!

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