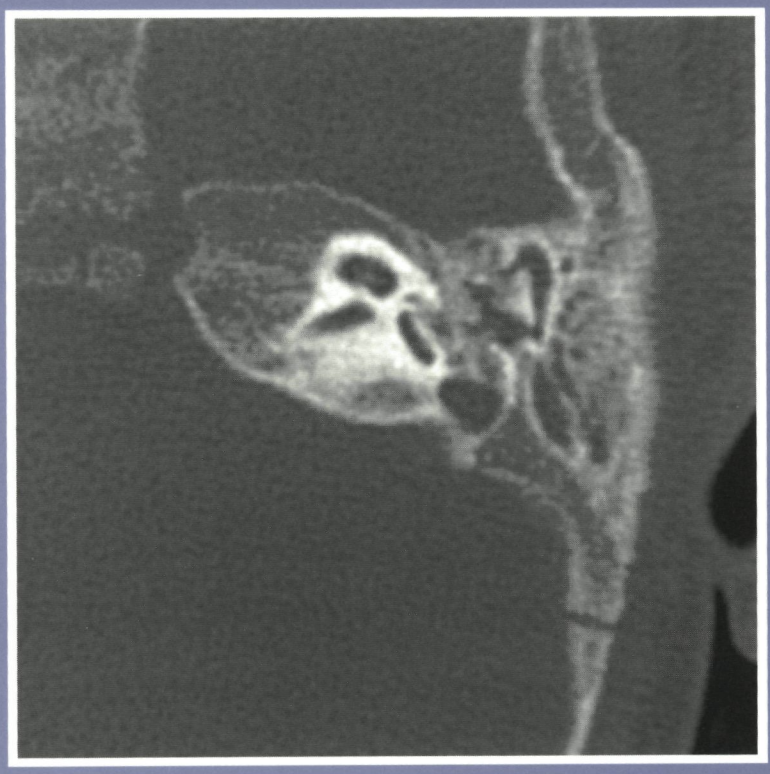
Hearing Impairment and Associated Handicaps

An aetiological study



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ISBN: 90-9013836-6
Printed: Benda BV, Nijmegen

Hearing Impairment and Associated Handicaps

An aetiological study

Een wetenschappelijke proeve
op het gebied van
de Medische Wetenschappen

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Katholieke Universiteit Nijmegen,
volgens besluit van het College van Decanen
in het openbaar te verdedigen
op dinsdag 27 juni 2000
des namiddags om 1.30 uur precies

door

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Geboren 21-09-1955
te Schiedam

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Chapter 1

Introduction

1.1 History of education of the deaf

Although there are numerous examples of education of deaf persons in ancient history, the Benedictine monk Pedro Ponce de León (1520-1584) was said to be the first to educate deaf persons on a regular basis. He founded a school in Valladolid and tutored deaf children of the Spanish nobility. His first student had been denied the right of primogeniture because of his deafness. This student learned to speak and write and thus attained his lawful inheritance. As the written account of his work was either lost or destroyed, very little is known about the techniques employed by Ponce de León, but it has been suggested that he began with reading and writing and then moved on to speech and used a manual alphabet for instruction [1,2]. Education of the deaf children of Spanish nobility was continued in the early 1600s by Juan Martin Pablo Bonet (1579-1633) who introduced a one-handed manual alphabet for fingerspelling words in combination with speech and writing.

Several decades later the Swiss doctor Johann Conrad Amman (1669-1724) wrote his famous book "Surdus loquens" (The speaking deaf) in which he strongly advocated spoken language as the most important means of communication for the deaf. His ideas concerning the primacy of speech and speechreading were followed in Germany by Samuel Heinicke (1723-1790). He was opposed to the use of methodical signs, but not to natural signs and the manual alphabet. There was a continuing and vehement controversy over these issues between Heinicke and Abbé de l'Epée (1712-1789), who founded a school for the education of the deaf in Paris in 1760 based on sign language and the manual alphabet. His main aim was to teach the deaf to read and write, so that they could read the Bible and become good christians. Spoken language was only a secondary objective, although his sign language followed the French language word for word. The controversy between the oral method and the manual method continued for more than a century and was also seen in the United States, where Thomas Hopkins Gallaudet (1787-1851) founded the American school for the Deaf in Hartford, Connecticut, in 1817 based on the methodical method of De l'Epée, while at the Clarke School for the Deaf in Northampton, Massachusetts, the oral methods originally developed by Heinicke were used since 1867 and strongly advocated by Alexander Graham Bell (1847-1922) [3].

The climax of the controvery regarding oral versus manual in the schools for the deaf came in 1880 at the International Congress on the Education of the Deaf in Milan. It was stated that the method of oral teaching was by far superior to that of using signs and that it should be implemented at all schools for the deaf. Since then the education of the deaf became based on speech and speechreading; sign language was no longer officially taught at schools for the deaf [4].

Since 1960, when William Stokoe [5] proved that American Sign Language met all the criteria of a formal language, sign language has slowly been reintroduced at schools for the deaf. More attention was paid to communication than to the mode of communication and Total Communication was introduced (sign language in combination with finger spelling, speech, reading and writing) [6]. As a result, sign language became the most important mode of communication at the expense of speech and speechreading. In the mid 1990s the bilingual method was introduced, in which the deaf child learns sign language and as soon as possible, or even simultaneously, speech and speechreading.

1.2 Education of the deaf in the Netherlands

In the Netherlands the first school for the deaf was founded by vicar Daniel Henri Guyot in Groningen in 1790, based on the method of De l'Epée. In 1930 the Institute for the Deaf was officially recognised. In 1840, it was located in Gemert, then it was moved to Herlaer and since 1910 it has been established in Sint Michielsgestel. Three other Dutch schools for the deaf were founded in Rotterdam (1853), The Hague (1889) and Amsterdam (1911) [7].

The founder of the Institute for the Deaf in Sint Michielsgestel, Martinus van Beek, created a Dutch version of De l'Epée's sign language: Dutch in signs. This method was used at the Institute for the Deaf until 1906, when the Institute changed to the oral method. The other Dutch schools for the deaf had already been using the oral method since about 1864 onwards. This situation changed following William Stokoe's publication "Sign language structure" in 1960 [5]. Since then Total Communication has been used in the Netherlands, except at Sint Michielsgestel, where the Maternal Reflective Method, a strictly oral method, designed by father Van Uden [8-10], was used until the beginning of the 1990s. Sign language and fingerspelling were only used in the education of deaf pupils with additional

physical and mental handicaps. Special departments were founded for deaf children with cognitive handicaps and for deafblind children in 1967. The Van Dijk method of education of the deafblind [11,12] has become widely acknowledged, especially his research on the education of children with the congenital rubella syndrome. In the mid 1990s the bilingual method was introduced at the Institute for the Deaf in Sint Michielsgestel.

After the development of hearing aids and their introduction at the schools for the deaf in the Netherlands in the late 1940s, several schools for the hard of hearing were founded. Children with hearing loss of < 90 dB were educated at these schools, while children with hearing loss of > 90 dB went to schools for the deaf.

In view of the strictly oral method being used at the Institute for the Deaf in Sint Michielsgestel for deaf pupils without any additional handicaps, there was great interest in audiological and medical research. The Institute for the Deaf has its own audiological and medical department, where all admitted pupils are being examined by an otolaryngologist and an ophthalmologist, and if necessary by a paediatrician. For the past few years, there has also been a genetics consultant. The present author has been the ENT consultant for many years. There has been a longstanding collaboration with the Nijmegen University and especially the ENT Department of the Nijmegen University Hospital, where the author is a staffmember. Much of this thesis reflects this close collaboration.

2.1 History of genetic hearing impairment

The medical profession first took interest in the aetiology of deafness at the beginning of the 19th century. Wilde, an Irish otologist, conducted the first systematic study on the causes of congenital deafness in 1853 [13]. Several years later, the first reports appeared on syndromic deafness. The German ophthalmologist Von Graefe described a syndrome of retinitis pigmentosa and congenital deafness in 1858 [14]. In 1861, Liebreich [15] elaborated on this syndrome that was later to become known as the Usher syndrome after the Bowman lectures given by Charles Usher in 1935. His first report on this syndrome was published in 1914 [16]. The Branchio-Oto-Renal syndrome was described by Paget in 1878 [17]. In 1896, Pendred reported on a syndrome with deaf mutism and goitre [18]. In 1900, Edward Treacher Collins [19] described the syndrome named after him, although it had probably

been recognised earlier by Thomson in 1847 [20] and certainly by Berry in 1889 [21]. In 1907, Hammerschlag [22] mentioned a syndrome with congenital deafness, blue eyes, a white forelock and "rotatory" nystagmus. This syndrome was later designated as the Waardenburg syndrome following a report by this Dutch ophthalmologist in 1948 [23]. Much attention has been paid to syndromic forms of deafness, although it has been estimated that 70% of hereditary deafness is non-syndromic [24].

Inherited hearing impairment in childhood is estimated to be autosomal recessive in 70-80% and autosomal dominant in 20-30%, whereas X-linked or mitochondrial inheritance is seen in only a few percent. It has been suggested that a relationship exists between the severity of hearing impairment and the mode of inheritance [25]. Severe to profound hearing loss at a young age is more likely to have an autosomal recessive pattern of inheritance, while moderate but frequently progressive hearing impairment is more likely to be autosomal dominant [26]. Progression in hearing loss has been reported in 4-30% of children with congenital hearing impairment [27-32], especially in hereditary types and in hearing impairment caused by viral agents, including rubella and cytomegalovirus [33].

2.2 Major causes of acquired hearing impairment

Deafness can have syndromic and non-syndromic hereditary causes, but it can also arise as a result of prenatal, perinatal or postnatal factors. For example, as early as in 1866, Vaele [34] reported on German measles, later called rubella. In 1941, Sir Norman Gregg drew attention to the relationship between maternal rubella during pregnancy and congenital defects, with special emphasis on ophthalmic defects in 1941 [35]. Further reports on the association between congenital deafness and maternal rubella were published by Swann et al. in 1943 [36] and in a further paper by Gregg in 1944 [37]. The risk of fetal infection varies with the onset of maternal infection [38], but the wide range of defects caused by rubella result almost exclusively from infection in the first 16 weeks of gestation. Infection in the fifth month or later does not usually cause disability, although cases of hearing impairment have been reported to result of infection as late as at 28 weeks [39]. The main rubella-related defects are hearing impairment, ocular defects, cardiovascular defects and CNS damage that

leads to mental retardation. Sensorineural deafness is the most common rubella-related defect; it is seen in up to 70% of congenital rubella syndrome (CRS) cases. Vaccination programmes have led to a dramatic drop in the prevalence of CRS. However, vaccination does not completely eliminate the problem of CRS, as a low percentage of those vaccinated show no or a very poor immune response and the duration of protection can be highly variable [40,41].

Since the drop in the prevalence of CRS, congenital cytomegalovirus (CMV) is the leading infectious cause of mental retardation and congenital sensorineural deafness in the United States [42]. The prevalence is 0.5-1 per 1000 births [43-45]. The majority of congenital CMV cases have no signs or symptoms at birth, but about 10% have clinical manifestations. Asymptomatic congenital CMV may follow either primary or secondary maternal infection, while most, but not all, infected babies born with clinical manifestations have been infected after primary maternal infection [46]. About 15% of asymptomatic congenital CMV cases will develop long-term neurological sequelae, the most common of which is sensorineural, often progressive, hearing loss [47-50]. Severe neurodevelopmental sequelae occur in up to 90% of the cases with symptomatic congenital CMV infection. Abnormal cerebral CT scans were noted in 70% of such cases: intracerebral calcification was the most frequent finding; it was highly correlated with the presence of sequelae, especially mental retardation [51] and hearing impairment [49]. Perinatally acquired CMV infection is not associated with significant sensorineural hearing impairment [52]. As congenital CMV infection can only be diagnosed in the first 2 or 3 weeks after birth, it is possible that the hearing impairment in many children with 'deafness of unknown aetiology', but without any additional defects was caused by asymptomatic congenital CMV infection.

The major cause of postnatally acquired deafness is bacterial meningitis. In the first few weeks after birth, infection can be caused by a variety of agents, but later on the most important causative agents are *Haemophilus influenzae*, *Neisseria meningitides* and *Streptococcus pneumoniae* [53]. Major sequelae are neurological damage and deafness [54-56]. The rate of postmeningitic hearing impairment ranges from 31-51% for *Streptococcus pneumoniae* infections to 10% for *Neisseria meningitides* and to 3-16% for *Haemophilus influenzae* infections [57]. Fluctuating and progressive hearing impairment have been reported [55,58-60]. Improvements in treatment for meningitis have led to lower mortality and

less morbidity. Especially dexamethasone adjuvant to antibiotics for *Haemophilus influenzae* meningitis has led to a significant decrease in sequelae [61-64], although the value of dexamethasone in the treatment of pneumococcal meningitis is less clear, or perhaps even controversial [59,65]. Pneumococcal meningitis shows a mortality rate of 8-19%, high rates of neurological sequelae (25%) and deafness (24-32%) [56,66].

3. Aetiological studies on hearing impairment in the 2nd half of the 20th century

In the second half of the 20th century much research was done on the aetiology of childhood deafness. In 1976, two standard books were published: "The Causes of Profound Childhood Deafness" by Fraser [67] and "Genetic and Metabolic Deafness" by Konigsmark and Gorlin [68]. In the latter, more than 150 (non-)syndromic hereditary types of deafness are described. More recently in 1990, Gorlin et al. [69] published "Syndromes of the Head and Neck". In 1995 Gorlin et al. published "Hereditary Hearing Loss and Its Syndromes" [70], a revised edition of "Genetic and Metabolic Deafness. These books describe over 450 syndromes with hearing impairment as one of the main features.

Epidemiological studies on aetiological factors in childhood hearing impairment have led to increased understanding of genetic and acquired causes of deafness. Prelingual hearing impairment affects 1 to 2 infants per 1,000 [71]. To detect congenital deafness as early as possible, neonatal screening programmes have been implemented in many western countries. An early aetiological diagnosis helps to prevent or lessen the disabling consequences of prelingual hearing impairment and to anticipate the course and degree of hearing impairment. Early diagnosis is also of crucial importance for genetic counselling of the parents and children [72]. Thorough examination programmes have been proposed to reduce the number of cases with deafness of unknown cause. Following such a programme, Holten and Parving [73] showed that this is indeed possible. Nevertheless most of the aetiological studies in this field have continued to encounter a high proportion (about 1/3) of cases with unknown causes. Hereditary causes and acquired causes also account for 1/3 each (Table 1).

Table 1:
Previous studies on the causes of childhood hearing impairment

First Author	n	Hearing threshold (dB)	Hereditary (%)	Acquired (%)	Unknown (%)
Fraser 1964 [75]	2355	>30 dB	32	32	36
Ruben 1971 [76]	348	>30 dB	21	39	40
Taylor 1975 [77]	86	>30 dB?	24	48	28
Cremers 1976 [81]	60	deaf	37	38	25
Kankkunen 1982 [78]	179	>25 dB	55	29	16
Janzen 1984 [82]	176	>50 dB	21	43	36
Parving 1984 [83]	117	>35 dB	48	42	10
Newton 1985 [79]	111	>25 dB	30	32	38
Holten 1985 [73]	94	>65 dB	33	41	26
Van Rijn 1989 [25]	162	>35 dB	40	27	33
Dereymaeker 1991 [84]	155	>50 dB	28	45	27
Das 1996 [80]	339	>30 dB	34	27	39
Total	4182		32	34	34

Considerable differences in populations, methodologies and diagnostic criteria exist between previous studies on the aetiology of hearing impairment [74]. In the majority, hearing impairment was defined as a threshold of > 25 - 30 dB HL [75-80]; some others used a threshold of > 65 dB for hearing impairment [73] or a threshold of > 90 dB for deafness [81] (Table 1). All the studies were performed on deaf persons with normal intelligence.

4. Impact of recent developments in general health programmes and clinical medicine

4.1 Immunization programmes

New developments in medicine have influenced the prevalence of the causes of childhood hearing impairment. Immunization programmes against rhesus antagonism, mumps, measles and rubella have been introduced. The prevalences of the congenital rubella syndrome and kernicterus as major prenatal causes of deafness have decreased strongly in the developed countries. Billings and Kenna [85] reported a decrease of TORCH infections (toxoplasmosis, rubella, cytomegalovirus, herpes) associated with sensorineural hearing impairment from 16.2% - 19.7% down to 1.4%. Since the introduction of the morbilli, parotitis, rubella vaccination programme in Sweden, there have been no more cases of rubella or mumps-induced hearing impairment [86]. In Finland, a decrease in rubella-related deafness was reported from 7.8% to 0.9% [87,88]. Parving [89,90] also mentioned a significant decrease in the prevalence of rubella cases in Denmark and a significant increase in the proportion of inherited deafness.

The reduction in the prevalence of *Haemophilus influenza* type b meningitis as a result of immunization [91,92] has decreased the prevalence of postnatally acquired forms of deafness, but increased the impact of pneumococcal meningitis, which is notorious for its severe sequelae [56,65].

4.2 (Very) Low birth weight infants and hearing impairment

Improvements in resuscitation techniques for very small preterm babies at neonatal

intensive care units have resulted in higher survival rates. However, a possible drawback is an apparent increase in the number of young children with deafness and additional handicaps [93]. Most of these low birth weight children do not show any long-term complications, but some of them suffer from serious complications such as deafness, mental handicap or visual impairment. Darlow et al. [94] performed a prospective study on very low birth weight infants (<1500 g) and reported that 5% had severe disability, 4.7% had moderate disability and 15.4% had mild disability. Blindness occurred in 2.7%, deafness in 1.3%, cerebral palsy in 5.7% and 20.8% had an IQ score of >1 SD below the mean. Similar figures were reported by Tudehope et al. [95] and Waugh et al. [96]. In very low birth weight babies (< 1000 g) Lefebre mentioned deafness in 7% [97].

Davis and Wood [98] found a 10.2 to 1 odds ratio for hearing impairment in babies at neonatal intensive care units (NICU) compared to the "normal" baby population. Veen et al. [99] stated that at the age of 5 years the prevalence of sensorineural hearing impairment among the children that had been preterm and required NICU was 15 times higher than that in 5-7-year-old children in the general Dutch population.

4.3 Chromosomal abnormalities and hearing impairment

A growing category of causes of childhood deafness seems to be chromosomal anomalies. Longitudinal studies showed an increase from 3.7% in 1988 to 5.3% in 1996 [80,100]. This increase is the result of improvements in chromosomal examination methods that enable the detection of even very small chromosomal deletions or other abnormalities, and the higher survival rates of preterm babies . However, these children often have additional disabilities.

5. Hearing impairment and associated disabilities in childhood

In recent years, a tendency has been noted that an increasing proportion of hearing impaired children have additional disabilities. In 1982, Martin [102] reported additional deficits in 29% of the children, while more recent studies have reported percentages of up to 67%, depending on the inclusion criteria for additional disabilities and the selection criteria for the causes of hearing impairment (Table 2). Das [100] found additional disabilities in 34% of all

children with hearing impairment in 1988, while 67% of the children with perinatal causes were also suffering from additional major disabilities. In 1996, Baille et al. [101] found additional handicaps in only 14%, although marked learning disabilities were observed in 64%. In 1997, Davis et al. [71] reported that permanent childhood hearing impairment was associated with additional disabilities in 39%: 36% of these cases had cognitive deficits, 10% had ocular problems and 13% had systemic disorders. The major risk factor for additional disabilities was a history of requiring neonatal intensive care. Darin [86] reported associated disabilities in 62% of the children with hearing impairment: speech retardation in 33%, visual abnormalities in 30%, mental retardation (IQ < 70) in 12% and neuropsychiatric disorders in 9% of the cases.

Table 2:
Hearing impairment and additional disabilities

Author	year	additional disabilities	additional disabilities subdivided			
		total	cognitive deficits	visual problems	systemic disorders	speech retardation
Martin [102]	1982	29%				
Das [100] (all causes)	1988	34%				
Das [100] (perinatal causes)	1988	67%				
Baille [101]	1996	14% (64%)				
Davis [71]	1997	39%	36%	10%	13%	
Darin [86]	1998	62%	12%	30%		33%

5.1 Hearing impairment with visual problems

As mentioned above, ocular abnormalities are often associated with sensorineural hearing impairment. The frequency of ocular deficiencies in deaf children can be as high as 45% [103,104]. Although much attention has been paid to oculo-auditory syndromes [105] (the most well-known are the Usher syndromes type 1 and 2 and the Stickler syndrome), not all these syndromes lead to deaf-blindness. In a study correlating the various causes of deafness with ocular abnormalities, congenital rubella had the highest prevalence, while inherited (non-syndromic) deafness had the lowest prevalence [106]. The importance of good vision to deaf persons cannot be overemphasized. Associated blindness in deaf children carries a severe risk of subnormal development [11,12]. Although it is known that children with certain causes of deafness are at risk for visual impairment, a high prevalence of visual impairment is also found in children without any risk factors [104], which makes ophthalmological screening obligatory in all deaf children.

6. Imaging of the temporal bones and vestibular examination for congenital inner ear anomalies

New medical techniques or refinement of existing techniques have increasingly led to the identification of new syndromes. For example, refinements to CT and MR imaging have led to better understanding of congenital inner ear abnormalities, such as the enlarged vestibular aqueduct (EVA) syndrome. Inner ear abnormalities were found in 13-25% [85,107-110] of patients with congenital hearing impairment. The most common findings were a short and wide lateral semicircular canal, a wide vestibule, large vestibular aqueduct and Mondini's dysplasia [107,111]. Often the findings were nonspecific, but recently fairly characteristic CT abnormalities have been detected in several syndromes, for example, in the X-linked stapes gusher syndrome [112,113], the branchio-oto-renal (BOR) syndrome [114] and the CHARGE association (this thesis). A wide vestibular aqueduct is an (almost) obligatory feature of the Pendred syndrome (this thesis); this syndrome shares mutations in the *PDS* gene with the EVA syndrome [115]. CT scanning of the inner ear should always be conducted during the clinical investigation of the aetiology of deafness (European Work

Group on Genetics of Hearing Impairment) [116].

The European Work Group has also made strong recommendations to perform vestibular examination in deaf children. The prevalence of vestibular abnormalities is very high in deaf persons [117-121] and it has heavy impact on motor skill development [118,122,123]. Vestibular deficits have been found in association with hereditary conditions, e.g. the Usher syndrome [124-126] and with acquired causes of deafness, e.g. meningitis [66,120].

7. Gene linkage analysis and mutation analysis for syndromic and non-syndromic genetic hearing impairment

New developments in the field of human genetics have led to linkage and cloning of genes in various syndromes and non-syndromic types of hereditary deafness. At present, 31 different loci are known to be responsible for autosomal dominant non-syndromic hearing impairment (DFNA 1-31), while 28 loci have been identified for autosomal recessive non-syndromic hearing impairment (DFNB 1-28). Several loci have been found for X-linked forms of non-syndromic hearing impairment (DFN) and two non-syndromic forms of mitochondrial hereditary hearing impairment [24,127,128] (Table 3a-c). Connexin 26 mutations (DFNB1) are considered to account for up to 50% of the cases of prelingual autosomal recessive non-syndromic hearing impairment. Genes have been identified for several hereditary deafness syndromes: the Alport, Branchio-Oto-Renal, Jervell and Lange-Nielsen, Norrie, Pendred, Stickler, Treacher Collins, Usher and Waardenburg syndromes [72] (Table 4).

It is now possible to make individual diagnoses of various syndromic and non-syndromic forms of genetic hearing impairment on the basis of mutation analysis. At the present rate of progress in genetics, this will soon be possible for an even broader range of genetic disorders.

Extensive data are available on the Hereditary Hearing Loss Homepage:
Van Camp G, Smith RJH: http://dnalab-www.uia.ac.be/dnalab/hhh.

In the light of recent developments, it can be expected that the prevalence of acquired deafness will diminish and that of hereditary hearing impairment with an identified cause

will increase. However, children with acquired deafness are tending to show more additional disabilities. Consequently, the population of children at schools for the deaf are altering as a result of changing indications and selections. Children with isolated hearing impairment are mainly treated as outpatients, while those with associated severe pathology attend special schools. In the children with isolated hearing loss, the type of care required depends on the degree of deafness: children with bilateral severe hearing impairment are more likely to be treated as outpatients than those with bilateral profound hearing impairment [101]. This trend also seems to be occuring at the schools for the deaf and hard-of-hearing in the Netherlands.

8. Design and aims of this study

The thesis focused on various aspects of acquired and genetic childhood hearing impairment.

Chapter 1 gives an overview of the causes of acquired and genetic childhood deafness, to provide a background for the aetiological studies on childhood deafness presented in this thesis.

Chapter 2 presents two school studies on childhood deafness. These studies are the first to have been performed on pupils with multiple handicaps at schools for the hearing impaired. By performing these studies on a longitudinal basis, we could evaluate the changes in the prevalence of the different causes of childhood deafness over the years.

Chapters 3 and 4 address to the diagnostic value of imaging (CT and MRI) and vestibular testing in the delineation of specific causes of deafness. Chapter 3 presents two studies on the CHARGE association, while Chapter 4 describes the audiovestibular sequelae of congenital CMV infection. Further delineation of the Pendred syndrome with special emphasis on audiological aspects and imaging is presented in Chapter 5. In Chapter 6, audiological findings in the non-ocular Stickler syndrome type II are presented and discussed in the context of a more detailed phenotypic description of this syndrome. Chapter 7 presents a discussion of the findings in Chapters 2-6 and the conclusions.

Table 3a:
Thirty-one loci related to autosomal dominant non-syndromic sensorineural hearing impairment

Locus	Chromosomal Location	Year	Gene Cloned	Year
DFNA1	5q31	1992	DIAPH1	1997
DFNA2	1p34	1994	GBJ3 (Cx31)	1998
			KCNQ4	1999
DFNA3	13q12	1994	GJB2 (Cx26)	1997
			GBJ6 (Cx30)	1999
DFNA4	19q13	1995	-	-
DFNA5	7p15	1995	DFNA5	1998
DFNA6	4p16.3	1995	-	-
DFNA7	1q21-q23	1996	-	-
DFNA8/DFNA12	11q22-24	1996	TECTA	1998
DFNA9	14q12-q13	1996	COCH	1998
DFNA10	6q22-q23	1996	-	-
DFNA11	11q12.3-q21	1996	MYO7A	1997
DFNA13	6p21	1997	COL11A2	1999
DFNA14	4p16.3	1997	-	-
DFNA15	5q31	1998	POU4F3	1998
DFNA16	2q24	1999	-	-
DFNA17	22q	1999	-	-
DFNA18	3q22	1998	-	-
DFNA19	10	1998	-	-
DFNA20	17q25	1999	-	-
DFNA21	reserved	-	-	-
DFNA22	reserved	-	-	-
DFNA23	14q	1999	-	-
DFNA24	4q	1999	-	-
DFNA25	12q21-24	1999	-	-
DFNA26	17q25	-	-	-
DFNA27	4q12	1999	-	-
DFNA28	8q22	1999	-	-
DFNA29	reserved	-	-	-
DFNA30	15q26	1999	-	-
DFNA31	reserved	-	-	-

For reference: Van Camp G, Smith RJH. Hereditary Hearing Loss Homepage. World Wide Web URL: http://dnalab-www.uia.ac.be/dnalab/hhh.

Table 3b: Twenty-eight loci related to autosomal recessive non-syndromic sensorineural hearing impairment

Locus	Chromosomal Location	Year	Gene Cloned	Year
DFNB1	13q12	1994	GJB2 (Cx26)	1997
DFNB2	11q13.5	1994	MYO7A	1997
DFNB3	17p11.2	1995	MYO15	1998
DFNB4	7q31	1995	PDS	1998
DFNB5	14q12	1995	-	-
DFNB6	3p14-p21	1995	-	-
DFNB7	9q13-q21	1995	-	-
DFNB8	21q22	1996	-	-
DFNB9	2p22-p23	1996	OTOF	1999
DFNB10	21q22.3	1996	-	-
DFNB11	9q13-q21	1996	-	-
DFNB12	10q21-q22	1996	-	-
DFNB13	7q34-36	1998	-	-
DFNB14	7q31	1998	-	-
DFNB15	3q21-q25 19p13	1997	-	-
DFNB16	15q21-q22	1997	-	-
DFNB17	7q31	1998	-	-
DFNB18	11p14-15.1	1998	-	-
DFNB19	18p11	1998	-	-
DFNB20	11q25-qter	1999	-	-
DFNB21	11q	1999	TECTA	1999
DFNB22	reserved	-	-	-
DFNB23	10p11.2-q21	-	-	-
DFNB24	11q23	-	-	-
DFNB25	4p15.3-q12	-	-	-
DFNB26	reserved	-	-	-
DFNB27	reserved	-	-	-
DFNB28	22q13	1999	-	-

For reference: Van Camp G, Smith RJH. Hereditary Hearing Loss Homepage. World Wide Web URL: http://dnalab-www.uia.ac.be/dnalab/hhh.

Table 3c:
Eight loci related to X-linked non-syndromic sensorineural hearing impairment

Locus	Chromosomal Location	Year	Gene Cloned	Year
DFN1	Xq22	1995	DDP	1996
DFN2	Xq22	1996	-	-
DFN3	Xq21.1	1995	POU3F4	1995
DFN4	Xp21.2	1994	-	-
DFN5	withdrawn	-	-	-
DFN6	Xp22	1996	-	-
DFN7	withdrawn	-	-	-
DFN8	reserved	-	-	-

For reference: Van Camp G, Smith RJH. Hereditary Hearing Loss Homepage. World Wide Web URL: http://dnalab-www.uia.ac.be/dnalab/hhh.

Table 4:
Loci related to syndromic hearing impairment

Locus	Chromosomal location	Gene Cloned	Year
Alport syndrome			
X-linked	Xq22	COL4A5	1990
autos.recess.	2q36-q37	COL4A3	1994
		COL4A4	1994
Branchio-Oto-Renal	8q13.3	EYA1	1997
Jervell and Lange-Nielsen syndrome			
JLNS1	11p15.5	KVLQT1	1997
JLNS2	21q22.1-q22.2	KCNE1	1997
Norrie disease	Xp11.3	Norrin	1992
Pendred syndrome	7q21-34	PDS	1997
Stickler syndrome			
STL1	12q13.11-q13.2	COL2A1	1996
STL2	6p21.3	COL11A2	1995
STL3	1p21	COL11A1	1996
Treacher Collins syndrome			
TCOF1	5q32-q33.1	TCOF1	1996
Usher syndrome			
USH1A	14q32	-	1992
USH1B	11q13.5	MYO7A	1995
USH1C	11p15.1	-	1992
USH1D	10q	-	1996
USH1E	21q	-	1997
USH1F	10	-	1997
USH2A	1q41	USH2A	1998
USH2B	3p23-24.2	-	1999
USH2C	5q14.3-q21.3	-	1998
USH3	3q21-q25	-	1995
Waardenburg			
WS type I	2q35	PAX3	1992
WS type II	3p14.1-p12.3	MITF	1994
WS type III	2q35	PAX3	1993
WS type IV	13q22	EDNRB	1995
WS type IV	20q13.2-q13.3	EDN3	1996
WS type IV	22q13	SOX10	1998

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Chapter 2

Causes of hearing impairment with associated handicaps

Chapter 2.1

Causes of hearing impairment in deaf pupils with a mental handicap

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International Journal of Pediatric Otorhinolaryngology
1999; 51: 101-108

Abstract

An aetiological study was performed on 122 deaf pupils (57 aged < 20 y, 65 aged > 20 y) at the Institute for the Deaf in Sint-Michielsgestel, the Netherlands. Besides hearing impairment with thresholds of > 60 dB HL, all the participants had a mental handicap with a non-verbal IQ of 40-80. Sixteen per cent of them were of non-Dutch origin. The cause of hearing impairment was acquired in 48%, inherited in 17%, chromosomal in 4% and unknown in 30%. In comparison with other studies on the aetiology of childhood deafness, acquired causes predominated over inherited causes, which may be typical of deafness combined with a mental handicap. We found a significant predominance of non-Dutch pupils among the rubella aetiology cases and male predominance among the hearing impaired pupils in general.

1. Introduction

Epidemiological studies on aetiological factors in childhood hearing impairment have led to increased understanding of genetic and acquired causes of deafness. Prelingual hearing impairment affects 1 to 2 infants per 1000. To detect congenital deafness as early as possible, neonatal screening programmes have been implemented in some western countries. An early aetiological diagnosis helps to prevent or lessen the disabling consequences of prelingual hearing impairment and to anticipate the probable course and degree of hearing impairment. It is also of crucial importance for genetic counselling of the parents and children [1]. Thorough examination programmes have been proposed to reduce the number of cases whose cause of deafness remains unknown. Following such a programme, Holten and Parving [2] showed that this is indeed possible. Nevertheless, most of the aetiological studies in this field have continued to encounter a high proportion (about one-third) of unknown causes. Hereditary causes and acquired causes also account for one-third each (Table 1).

Considerable differences in populations, methodologies and diagnostic criteria can be noted between previous studies. In the majority, hearing impairment was defined as thresholds of > 25 - 30 dB HL [3-5,7,10,13], while some used a threshold of > 65 dB for hearing impairment [2] or a threshold of > 90 dB for deafness [6] (Table 1).

Table 1:
Previous studies on the causes of childhood hearing impairment

First Author	n	Hearing threshold (dB)	Hereditary (%)	Acquired (%)	Unknown (%)
Fraser 1964 [3]	2355	>30 dB	32	32	36
Ruben 1971 [4]	348	>30 dB	21	39	40
Taylor 1975 [5]	86	>30 dB?	24	48	28
Cremers 1976 [6]	60	deaf	37	38	25
Kankkunen 1982 [7]	179	>25 dB	55	29	16
Janzen 1984 [8]	176	>50 dB	21	43	36
Parving 1984 [9]	117	>35 dB	48	42	10
Newton 1985 [10]	111	>25 dB	30	32	38
Holten 1985 [2]	94	>65 dB	33	41	26
Van Rijn 1989 [11]	162	>35 dB	40	27	33
Dereymaeker 1991 [12]	155	>50 dB	28	45	27
Das 1996 [13]	339	>30 dB	34	27	39
Total	4182		32	34	34

All the studies were performed on deaf persons with normal intelligence.

In this study we analysed the aetiological diagnoses of deaf pupils with a mental handicap who were residents at an Institute for the Deaf. We compared the results to those obtained previously in studies on the aetiology of hearing impairment and deafness in general populations.

2. School types, pupils and methods

In 1997, about 500 children and adolescents were residing as pupils at the Institute for the Deaf in Sint-Michielsgestel, the Netherlands. There are four different school types within this Institute: a school for deaf pupils with normal intelligence comprising a primary and a secondary school; a school for deaf pupils with learning disabilities but normal intelligence; a school for the deaf-blind; and a school for deaf pupils with a mental handicap. Pupils at the latter school have an IQ of 40-80 as measured with non-verbal tests, such as the WISC (non-verbal part), the Hiskey-Nebraska test and the CID preschool performance test. Many of these pupils have social and/or behavioural problems and problems with communication. The communication mode at this school is total communication, which includes sign language.

The present study was performed on 122 of the deaf and mentally handicapped pupils. They were all the pupils except 9 with normal or nearly normal hearing, who besides mental retardation showed a very severe speech/language retardation requiring signing for communication.

Fifty-seven of them were younger than 20 years-of-age and were being educated on a day-school basis or on a residential basis, while 65 pupils were older than 20 years-of-age and were living in sheltered homes and pursuing day-time activities. Their hearing thresholds were > 60 dB HL in the best ear at the frequencies 0.25-4 kHz as measured with pure-tone audiometry, behavioural audiometry or brainstem evoked response audiometry. Almost all cases had sensorineural hearing impairment (SNHI), although some pupils had additional conductive loss related to congenital ossicular anomalies. Twenty out of the 122 pupils were of non-Dutch origin and came from countries such as the Dutch Antilles, Turkey or Morocco (see Tables 2 and 3 for the age distribution by ethnic origin).

Table 2:
Subdivision by age group and ethnic origin of 57 pupils aged < 20 years

Origin	Age (y) 4-5	6-10	11-15	16-20	Total
Dutch	3	7	20	12	42
Non-Dutch	1	4	6	4	15
Total	4	11	26	16	57

Table 3:
Subdivision by age group and ethnic origin of 65 pupils aged > 20 years

Origin	Age (y) 21-25	26-30	31-35	36-40	41-45	Total
Dutch	7	16	18	14	5	60
Non-Dutch	1	1	1	2	-	5
Total	8	17	19	16	5	65

We performed a retrospective investigation on the medical records of the pupils, which included anamnestic re-evaluation with special emphasis on family history, occurrence of (inherited) hearing impairment in relatives, consanguinity, the pre-, peri- and postnatal periods, occurrence of ear infections, head injury, meningitis and/or encephalitis and the use of ototoxic drugs. Examinations were performed by an otolaryngologist, a paediatrician and an ophthalmologist. Special attention was paid to the presence of dysmorphic stigmata. When indicated, a clinical geneticist was consulted. Audiological evaluation was always performed.

The diagnosis of an autosomal dominant inherited type of hearing impairment was made

on the basis of one of the following conditions:

- hearing impairment in childhood, by history in at least three successive generations, without any other apparent cause;
- audiometrically verified hearing impairment without any other cause in at least two successive generations and documented male-to-male transmission;
- established autosomal dominant syndrome or type of nonsyndromic hearing impairment.

An autosomal recessive inherited type of hearing impairment was diagnosed if one of the following conditions was fulfilled:

- at least two hearing impaired children per sibship without any other apparent cause of hearing impairment;
- one hearing impaired child without any other apparent cause, in a family with proven consanguinity within five generations;
- established autosomal recessive syndrome [11].

3. Results

The aetiologies of deafness in the 57 pupils aged < 20 years are summarized in Table 4. Using the above-mentioned criteria, a hereditary cause of deafness was found in 11 pupils (19%), five Dutch and six non-Dutch (three of them had consanguineous parents); while ten cases (18%) had an autosomal recessive disorder, one (2%) had an autosomal dominant disorder. Using a 2 x 2 contingency table, Fisher's exact probability test indicated a significant predominance ($P = 0.027$) of hereditary causes among the young non-Dutch pupils, which was mainly due to the significant predominance ($P = 0.036$) of non-syndromic autosomal recessive causes. A total of six pupils had a non-syndromic autosomal recessive type of inheritance, while four pupils had an autosomal recessive syndrome. One Dutch pupil presented with the Fountain syndrome and one with the Beckwith-Wiedemann syndrome. In one non-Dutch pupil the Usher syndrome type I was found and one had the Shah-Waardenburg syndrome. One Dutch pupil had the autosomal dominant Noonan syndrome.

An acquired cause of deafness was found in 22 of the 57 pupils (39%), 16 Dutch and six non-Dutch. Pre-, peri- and postnatal causes were found in 21%, 10% and 7%, respectively.

Table 4:
Aetiology by ethnic origin in 57 pupils aged < 20 years

Aetiology	Origin Dutch	Non-Dutch	Total	%
Hereditary	**5**	**6**	**11**	**19**
Autosomal recessive	4	6	10	18
Non-syndromic	2	4	6	
Syndromic	2	2	4	
Autosomal dominant	1	-	1	2
Non-syndromic	-	-	-	
Syndromic	1	-	1	
Acquired	**16**	**6**	**22**	**39**
Prenatal	7	5	12	21
Rubella	5	5	10	
CMV	2	-	2	
Perinatal	5	1	6	10
Pre/dysmaturity	5	-	5	
Kernicterus	-	1	1	
Postnatal	4	-	4	7
Meningitis	3	-	3	
Mumps	1	-	1	
Chromosomal	**3**	**1**	**4**	**7**
Trisomy 21	2	-	2	
2q(del)	1	-	1	
7q-18q translocation	-	1	1	
Unknown	**18**	**2**	**20**	**35**
Total	**42**	**15**	**57**	**100**

In the prenatal group, congenital rubella was by far the most common cause of deafness. The youngest Dutch case with congenital rubella was 13 years old in 1997; a new immunisation programme for mumps, measles and rubella was started in 1987 in the Netherlands. There were only two pupils with congenital CMV infection.

In the perinatal group, all the Dutch cases had been severely premature or dysmature with a birth weight of < 1200 g and/or a gestational period of < 33 weeks. All these cases had received several weeks of treatment at a neonatal intensive care unit.

The postnatal group contained only Dutch pupils, whose main cause of deafness was meningitis.

Pupils with a chromosomal anomaly (four cases, 7%) constituted a special group, which included two cases of Down's syndrome, one case with a chromosomal deletion syndrome and one case with a translocation syndrome.

We were unable to determine the cause of hearing impairment in 20 out of the 57 pupils (35%). In some of them not the slightest indication was found, while in others there were several possible competing causes. One case had the Goldenhar syndrome and one case had the CHARGE association.

In Table 5 the degree of hearing impairment is related to the cause of deafness. Most of the pupils had hearing impairment with tresholds of > 80 dB, or were profoundly deaf. In the prenatal category, most of the rubella cases showed severe deafness, while the two CMV cases were profoundly deaf. Four out of the five premature or dysmature cases were also profoundly deaf. The cases with a chromosomal anomaly had relatively good residual hearing.

Table 5:
Degree of hearing impairment in 57 pupils aged < 20 years by aetiology

Aetiology	Threshold (dB HL) 60-69	70-79	80-89	90-99	100-109	110-119	>120	Total
Hereditary	-	-	**2**	**1**	**2**	**2**	**4**	**11**
Acquired	**2**	-	**1**	**2**	**4**	**4**	**9**	**22**
Prenatal	-	-	1	1	3	4	3	12
Perinatal	1	-	-	1	-	-	4	6
Postnatal	1	-	-	-	1	-	2	4
Chromosomal	-	**1**	**1**	**2**	-	-	-	**4**
Unknown	**3**	**1**	**4**	**1**	**2**	**2**	**7**	**20**
Total	**5**	**2**	**8**	**6**	**8**	**8**	**20**	**57**

The aetiologies of deafness in the 65 pupils aged > 20 years are summarized in Table 6. In contrast with the group aged < 20 years, only five out of the 65 pupils in this group were of non-Dutch origin. A hereditary cause was found in ten Dutch cases (15%): nine (14%) with autosomal recessive inheritance and one (2%) with autosomal dominant inheritance. Seven of these pupils showed nonsyndromic autosomal recessive inheritance and two cases had autosomal recessive syndromes: one Usher syndrome type I and one Pendred's syndrome. One case presented with the autosomal dominant Noonan syndrome.

Table 6:
Aetiology by ethnic origin in 65 pupils aged > 20 years

Aetiology	Dutch	Non-Dutch	Total	%
Hereditary	**10**	**-**	**10**	**15**
Autosomal recessive	9	-	9	14
Non-syndromic	7	-	7	
Syndromic	2	-	2	
Autosomal dominant	1	-	1	2
Non-syndromic	-	-	-	
Syndromic	1	-	1	
Acquired	**33**	**4**	**37**	**57**
Prenatal	11	3	14	22
Rubella	7	3	10	
Viral	2	-	2	
Toxoplasmosis	1	-	1	
Ototoxic medication	1	-	1	
Perinatal	11	1	12	18
Severe asphyxia	2	-	2	
Kernicterus	8	1	9	
Pre/dysmaturity	1	-	1	
Postnatal	11	-	11	17
Meningitis	10	-	10	
Encephalitis	1	-	1	
Chromosomal	**1**	**-**	**1**	**2**
Trisomy 21	1	-	1	
Unknown	**16**	**1**	**17**	**26**
Total	**60**	**5**	**65**	**100**

An acquired cause of deafness was found in 37 out of the 65 cases aged > 20 years (57%). The percentages of prenatal, perinatal and postnatal causes were 22%, 18% and 17%, respectively. Congenital rubella was the most common cause in the prenatal group, especially in the group of non-Dutch pupils. The predominance of rubella cases was significant in the non-Dutch pupils aged > 20 years (Table 6, $P = 0.023$), and in pupils of any age ($P = 0.0048$) i.e. when the rubella entries of Tables 4 and 6 were combined. In the perinatal group, kernicterus as a complication of rhesus antagonism was the main cause of deafness. Severe asphyxia without any prematurity or dysmaturity, which required prolonged artificial ventilation, was seen in two cases. Only one case had been severely premature or dysmature. The major postnatal cause of deafness was meningitis: there were five cases of pneumococcal meningitis, two cases of *Haemophilus influenzae* meningitis and three cases in whom the causative organism could not be identified.

There was only one case with Down's syndrome in this group of older pupils. The cause of hearing impairment could not be determined reliably in 17 pupils (26%). In some of them insufficient data could be retrieved or the available data were inconclusive. There was one case with the CHARGE association.

In Table 7 the degree of hearing impairment is related to aetiology in the 65 pupils aged > 20 years. Most of the cases, especially those with hereditary causes, showed hearing impairment with thresholds of > 90 dB. In the perinatal causes group, the cases with kernicterus had hearing thresholds of 80-109 dB, while the pupils in the other categories were profoundly deaf (Table 6).

Table 8 shows the results for the total group of 122 pupils. The (suspected) causes of hearing impairment in this selected group of hearing impaired pupils were classified as follows: hereditary (17%), acquired (48%), chromosomal anomaly (4%) and unknown (30%).

The above-mentioned predominance of young, non-Dutch (especially autosomal recessive) hereditary cases, was not associated with an overall predominance of non-Dutch hereditary cases (Table 8), or a predominance of non-Dutch, autosomal recessive causes, when the two age groups (Tables 4 and 6) were combined.

The significant predominance of prenatal causes in the group of non-Dutch pupils ($P = 0.03$) was entirely due to assigning eight non-Dutch pupils with rubella (n = 5 in Table 4 and n = 3 in Table 6) to the "prenatal causes" group.

Table 7:
Degree of hearing impairment in 65 pupils aged > 20 years by aetiology

Aetiology	Threshold (dB HL) 60-69	70-79	80-89	90-99	100-109	110-119	>120	Total
Hereditary	-	-	-	**2**	**5**	**2**	**1**	**10**
Acquired	**1**	**2**	**5**	**9**	**6**	**4**	**10**	**37**
Prenatal	-	2	3	1	4	2	2	14
Perinatal	-	-	2	5	2	-	3	12
Postnatal	1	-	-	3	-	2	5	11
Chromosomal	-	-	-	-	-	-	**1**	**1**
Unknown	-	-	**2**	**1**	**5**	**5**	**4**	**17**
Total	**1**	**2**	**7**	**12**	**16**	**11**	**16**	**65**

Table 8:
Aetiology by ethnic origin in 122 pupils

	Dutch	Non-Dutch	Total	%
Hereditary	**15**	**6**	**21**	**17**
Acquired	**49**	**10**	**59**	**48**
Prenatal	18	8	26	21
Perinatal	16	2	18	15
Postnatal	15	-	15	12
Chromosomal	**4**	**1**	**5**	**4**
Unknown	**34**	**3**	**37**	**30**
Total	**102**	**20**	**122**	**100**

4. Discussion

The results of previous studies are summarized in Table 1. There were considerable differences in the degree of hearing impairment. None of the studies was based on (selected) cases with hearing impairment and a mental handicap. This may explain the differences in the prevalence of hereditary and acquired causes between those studies and the present one. In our study, the proportion of cases with hereditary causes was about half that reported in previous studies and there was a relatively higher proportion of syndromes (eight out of 21; see, for example, ref. [14]). Although there are numerous hereditary syndromes that include a combination of deafness and a mental handicap, their combined prevalence is fairly low. In this study we found several cases with a syndrome that is not usually associated with a mental handicap, such as the Usher and the Pendred syndromes. The combination of such a syndrome and a mental handicap may have been caused by chance alone. Remarkably, similar combinations were found in relatively large numbers of the relatives of pupils with an autosomal recessive pattern of inheritance (i.e. of deafness) without any additional syndromic features. Such relatively high familial prevalence may also be explained by chance alone, although it should be realised that certain combinations may be more common in families with consanguinity. In addition, it cannot be excluded that (not yet determined) syndromes comprising the features of deafness and a mental handicap are responsible, if adequate information and direct examination results of affected relatives are lacking.

Acquired causes were much more prevalent in our selected population than in previous studies (48% vs 34%). The most important causes in this group were congenital infections, such as rubella and CMV, severe prematurity or dysmaturity, kernicterus and meningitis. The general prevalence of congenital rubella infection in the Netherlands has diminished substantially since the start of a new immunisation programme in 1987. Given the fact that most of our pupils were born before 1988, they did not benefit from this programme.

Owing to immunisation against rhesus antagonism in the past few decades, kernicterus has almost vanished from western countries. The prevalences in the two age groups confirm this general finding: in the older group, kernicterus was the main cause of deafness in the perinatal period, while in the younger group only one non-Dutch pupil had kernicterus.

Severe prematurity or dysmaturity was rare in the group of older pupils, while in the group of younger pupils it was the main cause of deafness in the subgroup of perinatally acquired causes. Due to fairly recent improvements in resuscitation techniques for very small preterm infants, more severely dysmature or premature newborns survive. Most of these children do not show any long-term complications, but some of them suffer from serious complications, such as deafness, mental handicap and visual impairment [15-18]. Children in the latter category are not often enrolled in hearing screening programmes, because of strict follow-up by paediatricians and because of the difficulties encountered in testing the hearing of mentally handicapped children. It should be noted that a lack of auditory response is more often attributed to the mental handicap than to possible hearing impairment. Therefore concomitant deafness tends to be underdiagnosed, or is diagnosed with considerable delay.

Immunisation against *H. influenzae* type b started several years ago in most western countries and has led to a decreased incidence of the associated type of meningitis. The prevalence of pneumococcal meningitis, however, which is notorious for its severe complications [19], has not diminished.

Chromosomal disorders, which were more prevalent in the younger group than in the older group, form a clearly outlined new group of causes of prelingual deafness. Nowadays the survival rate of children with such disorders is higher than it was in the past, which favours the possibility of a combination of deafness and additional handicaps.

The group with unknown aetiologies was large: 30%. This percentage is not substantially different from those reported in previous studies.

Previous studies reported a male predominance among deaf pupils and this was also observed in the present study (Table 9). Cremers et al. [20] mentioned an average of 54% men and 46% women, while we found a sex ratio of 1.65 (63% males and 37% females). Das [21] found a male:female ratio of 1.54 in 155 hearing impaired children; the difference was significant in children with adverse perinatal factors, as well as in the meningitis group. These groups correspond with our acquired causes group. Also, Newton [10] observed a significant male predominance (54%) in the perinatal group and in the group with chromosomal abnormalities. We have found no explanation for the male predominance among cases with hearing impairment in general, nor in cases with acquired hearing impairment.

Table 9:
Sex ratio by age group in 122 pupils

	n	Male	Female	Sex ratio
Age < 20 years	57	32	25	1.28
Age > 20 years	65	44	21	2.10
Total	122	76	46	1.65

This epidemiological study on a selected group of hearing impaired or deaf pupils with a mental handicap revealed various features that were different from those found in more general populations of children with hearing impairment or deafness. Although the prevalences of some causes of deafness, such as congenital rubella and kernicterus, are steadily diminishing, the prevalences of other causes, such as severe prematurity or dysmaturity and chromosomal anomalies, are apparently increasing. With all the efforts made to diagnose childhood deafness as early as possible, special attention should therefore be paid to such types of aetiology by health professionals involved in the care of mentally handicapped and/or hearing impaired children.

Acknowledgements

We wish to thank the pupils and their parents for participating in this study. Numerous colleagues, paramedical and education workers employed at our hospital and the Institute for the Deaf contributed to the evaluation of our cases. We also wish to thank Mrs H Brink, GJA Janssens Capriles, GJMEN Timmerman, AHF van Olphen, B Hamel, JPM Brokx, M Broesterhuizen, JPM van Dijk and Mrs A Dona for performing the ophthalmological, paediatric, clinical genetic and audiological examinations, neuropsychological assessments and physiotherapeutic evaluations.

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Chapter 2.2

Longitudinal study on changes in the aetiology of hearing impairment in deaf-blind pupils and deaf infant pupils at an institute for the deaf

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International Journal of Pediatric Otorhinolaryngology
1999, Submitted

Abstract

An aetiological study was performed on 57 pupils at the deaf-blind department of the Institute for the Deaf at Sint-Michielsgestel, the Netherlands, in the school year 1998-1999 and on 49 deaf-blind pupils at the same department in the school year 1986-1987. The pupils were 5-20 years of age. In addition, the aetiologies were studied in 55 deaf infant pupils in 1998 and compared to those in 68 deaf infant pupils in 1988. Their age was 1-5 years. All the pupils showed hearing impairment with thresholds of > 60 dB HL. Among the deaf-blind pupils and deaf infant pupils, there were several cases with rare hereditary syndromes. The prevalence of acquired causes of deafness, especially congenital rubella, had decreased over the years, whereas perinatal causes of deafness had increased. Chromosomal anomalies were found in 15% of the infant pupils in 1998. Over the study period, the percentage of pupils with multiple handicaps increased from 25 to 38%.

1. Introduction

Numerous studies have been performed on the aetiology of sensorineural hearing impairment (SNHI) in childhood. This has led to increased understanding of genetic and acquired causes of deafness. Substantial differences in methods and classifications mean that it is very difficult to make comparisons between studies [1]. The use of thorough examination programmes has reduced the number of cases with an unknown cause of deafness [2]. The current assumption is that hereditary, acquired and unknown causes account for one third each. There seems to be some change in these proportions because of new immunization programmes for rhesus antagonism, mumps, measles and rubella and, fairly recently, for *Haemophilus influenzae* type b. Improvements in resuscitation techniques for very small preterm babies in neonatal intensive care units have resulted in higher survival rates, but a possible drawback is an apparent increase in the number of young children with deafness and additional handicaps [3].

Hearing impaired children in the Netherlands receive education at schools for the hard of hearing and schools for the deaf. Children without additional handicaps tend to go to schools for the hard of hearing, whereas children with additional handicaps tend to go to schools for the

deaf. In this study we analysed the aetiological diagnoses of 5-to-20-year-old deaf-blind pupils and 1-to-5-year-old infants at the Institute for the Deaf at Sint-Michielsgestel. These aetiologies were compared to those recorded in these age categories at the same institute several years ago.

2. School types, pupils and methods

At the Institute for the Deaf in Sint-Michielsgestel about 500 severely to profoundly deaf children and adolescents (mean threshold 100-110 dB HL) are educated at several different types of school: infant, primary, secondary, a school for deaf children with mild to moderate mental handicap [4] and a school for the deaf-blind.

The present study was performed on 57 pupils who attended the school for the deaf-blind in 1998-1999. Their aetiologies were compared to those of 49 pupils from the school year 1986-1987. The age of these pupils was 5-20 years. Four pupils from the year 1998-1999 and 3 pupils from 1986-1987 were excluded because of their central type of deafness. We also analysed the aetiological diagnoses of the infants in 1998 (N=55) and compared them to those of 68 infants in 1988. Their age was 1-5 years.

The hearing thresholds were >60 dB HL in the best ear at the frequencies 0.25-4 kHz as measured with behavioural audiometry, brainstem evoked response audiometry or pure-tone audiometry. Although some pupils had (additional) conductive hearing loss related to congenital ossicular chain anomalies, almost all cases had sensorineural hearing impairment (SNHI). We performed a retrospective investigation, using the medical records of the pupils and infants, which included anamnestic re-evaluation with special emphasis on family history, occurrence of (inherited) hearing impairment in relatives, consanguinity, the pre-, peri- and postnatal periods, occurrence of ear infections, head injuries, meningitis and/or encephalitis and the use of ototoxic drugs. The pupils and infants were examined by an otolaryngologist, a paediatrician and an ophthalmologist. Special attention was paid to the presence of dysmorphic stigmata. When indicated, a clinical geneticist was consulted, although most of the younger children had already been examined extensively elsewhere. Prevalences in (sub)groups of pupils and infants were compared using Fisher's exact probability tests applied on 2x2 contingency tables. The level of significance was P=0.05.

Table 1:
Aetiology by ethnic origin in 49 deaf-blind pupils in the school year 1986-1987

Aetiology	Origin Dutch	non-Dutch	Total	%
Hereditary	**8**	**-**	**8**	**16**
autosomal recessive syndromic	6	-	6	12
autosomal dominant syndromic	2	-	2	4
Acquired	**18**	**20**	**38**	**78**
prenatal	17	20	37	76
rubella	17	19	36	73
CMV	-	1	1	2
perinatal	1	-	1	2
postnatal	-	-	-	-
Unknown*	**2**	**1**	**3**	**6**
Total	**28**	**21**	**49**	**100**

*, or undetermined

3. Results

The aetiologies of deafness in the 49 deaf-blind pupils in the school year 1986-1987 are summarised in Table 1. A hereditary cause was found in 8 - all Dutch - cases (16%): 6 had the autosomal recessive Usher syndrome type 1, 1 had the autosomal dominant Marshall syndrome and 1 had the autosomal dominant Stickler syndrome. All the Usher cases showed substantial peripheral visual field loss and profound deafness. The case with the Marshall syndrome underwent bilateral cataract surgery at the age of 3 years, had high myopia and bilateral retinal ablation (in his right eye at 11 years and in his left eye at 17 years). His hearing loss was 85 dB.

The case with the Stickler syndrome showed severe myopia of -20/-18D and reduced visual

acuity (VODS 0.2), a cleft palate and mixed hearing loss of about 60 dB.

An acquired cause of deafness was found in 38 pupils (78%), 18 Dutch and 20 non-Dutch (9 from Belgium, 6 from the Dutch Antilles, 2 from Surinam, 1 from Portugal, 1 from Morocco and 1 from Hong Kong). Almost all the acquired cases showed the congenital rubella syndrome.

There was 1 congenital CMV case and 1 case who had been severely premature and dysmature (gestation of 32 weeks and a birth weight of 570 g), necessitating prolonged treatment at a neonatal intensive care unit. There were no postnatal causes of deafness. There were 3 cases with unknown or undetermined aetiology; the 2 Dutch pupils showed the CHARGE association.

The distribution of the numbers of cases by ethnic origin over the categories of hereditary syndromes (8 Dutch, none non-Dutch) and the congenital rubella syndrome (17 Dutch, 19 non-Dutch) differed significantly (P=0.0061).

In Table 2 the degree of hearing impairment is related to aetiology. Hearing loss in the hereditary group is specified above. Almost half of the acquired cases showed hearing impairment of 110 dB or more.

Table 2:
Degree of hearing impairment in 49 deaf-blind pupils in the school year 1986-1987 by aetiology

Aetiology	Threshold (dB HL)							
	60-69	70-79	80-89	90-99	100-109	110-119	>120	Total
Hereditary	**1**	**-**	**1**	**-**	**-**	**-**	**6**	**8**
Acquired	**1**	**4**	**5**	**2**	**8**	**12**	**6**	**38**
prenatal	1	4	4	2	8	12	6	37
perinatal	-	-	1	-	-	-	-	1
Unknown	**-**	**-**	**-**	**1**	**-**	**1**	**1**	**3**
Total	**2**	**4**	**6**	**3**	**8**	**13**	**13**	**49**

Table 3:
Aetiology by ethnic origin in 57 deaf-blind pupils in the school year 1998-1999

Aetiology	Origin Dutch	Non-Dutch	Total	%
Hereditary	**14**	**1**	**15**	**26**
autosomal recessive syndromic	14	1	15	26
Acquired	**14**	**16**	**30**	**53**
prenatal	8	15	23	40
rubella	8	14	22	39
CMV	-	1	1	2
perinatal	5	1	6	11
postnatal	1	-	1	2
Chromosomal	**3**	**-**	**3**	**5**
Unknown*	**9**	**-**	**9**	**16**
Total	**40**	**17**	**57**	**100**

*, or undetermined

The aetiologies of deafness of the 57 deaf-blind pupils in the school year 1998-1999 are summarised in Table 3. The 17 non-Dutch cases originated from the Dutch Antilles (7), Morocco (2), Australia (1), Bosnia (1), Surinam (2), Hong Kong (1), Belgium (2) and Haïti (1). A hereditary cause was found in 15 cases (26%); 14 of them were Dutch. All the pupils in this category showed an autosomal recessive syndrome: 4 cases had the Usher syndrome type 1, 1 case had the Usher syndrome type 2, 1 case had the Alström syndrome, 1 case had the Wolfram syndrome and 8 cases had peroxisomal disorders (formerly known as the Zellweger and the infantile Refsum syndromes). The pupils with the Usher syndrome type 1 were profoundly deaf. The pupil with the Alström syndrome has shown highly progressive pigmentary retinopathy from his sixth year onwards and is now legally blind. He also has progressive hearing

impairment with recent thresholds of 60 dB. The pupil with the Wolfram syndrome has also become blind and has progressive hearing loss of about 60 dB, diabetes mellitus since the age of 8 and diabetes insipidus since the age of 17 years. The 1 case with the Usher syndrome type 2 demonstrated flat hearing loss of about 100 dB, substantial peripheral visual field loss and intact vestibular function. The 8 pupils with peroxisomal disorders showed progressive pigmentary retinopathy, neurological features and progressive hearing loss of 70-100 dB.

An acquired cause of deafness was found in 30 pupils (53%). The percentages of prenatal, perinatal and postnatal causes were 40, 11 and 2, respectively. Congenital rubella was the most common cause in the prenatal group, especially in the non-Dutch group. A new immunization programme against rubella was started in the Netherlands in 1987; the youngest Dutch congenital rubella case in this series was born in 1991. His mother had been immunized in 1972. The next-youngest Dutch pupil with congenital rubella was born in 1987. Comparison of Tables 1 and 3 shows that the prevalence of rubella cases decreased significantly in the group of Dutch pupils from 1988/1987 to 1998/1999 (P=0.00073), but not in the group of non-Dutch pupils (P=0.40). In the perinatal group, 5 cases had been severely pre- or dysmature and 1 had suffered from severe asphyxia. In the postnatal group, there was 1 pupil with meningococcal meningitis. There were 3 cases with chromosomal abnormalities: 1 case with the Turner (XO) syndrome and 2 with the Wolf-Hirschhorn (4p) syndrome. In the group of unknown or undetermined causes, 4 had the CHARGE association, 3 had unknown aetiology and 3 had a severe form of the Goldenhar syndrome. These latter pupils showed severe hemifacial microsomia, cleft lip/palate, unilateral colobomas of the eyelid and/or retina, meatal atresia, epibulbar dermoids and severe fusion of the cervical vertebrae.

The distribution of the numbers of cases by ethnic origin over the categories of autosomal recessive syndromes (14 Dutch, 1 non-Dutch) and congenital rubella syndrome (8 Dutch, 14 non-Dutch) differed significantly (P=0.0018).

The degree of hearing impairment related to the aetiology is shown in Table 4. In the prenatal group, 14 out of the 23 rubella cases showed hearing loss of > 110 dB. In the perinatal group, the thresholds were 70-95 dB. The chromosomal group showed relatively good residual hearing (thresholds of < 80 dB).

There were more hereditary causes of deafness in the younger group, although the difference (i.e. 15 out of 57 cases compared to 8 out 49 cases) was not significant (P=0.16) (Table 5).

Table 4:
Degree of hearing impairment in 57 deaf-blind pupils in the school year 1998-1999 by aetiology

Aetiology	Threshold (dB HL)							
	60-69	70-79	80-89	90-99	100-109	110-119	>120	Total
Hereditary	**2**	**3**	**2**	**-**	**4**	**-**	**4**	**15**
Acquired	**2**	**4**	**6**	**3**	**1**	**7**	**7**	**30**
prenatal	2	2	3	1	1	7	7	23
perinatal	-	1	3	2	-	-	-	6
postnatal	-	1	-	-	-	-	-	1
Chromosomal	**2**	**1**	**-**	**-**	**-**	**-**	**-**	**3**
Unknown	**2**	**-**	**1**	**3**	**1**	**1**	**1**	**9**
Total	**8**	**8**	**9**	**6**	**6**	**8**	**12**	**57**

Table 5:
Aetiology in 106 deaf-blind pupils by school year

	School year 1986-1987 n (%)	1998-1999 n (%)
Hereditary	**8 (16)**	**15 (26)**
Acquired	**38 (78)**	**30 (53)**
prenatal	37 (76)	23 (40)
perinatal	1 (2)	6 (11)
postnatal	-	1 (2)
Chromosomal	**-**	**3 (5)**
Unknown	**3 (6)**	**9 (16)**
Total	**49 (100)**	**57 (100)**

Owing to the selected population of deaf-blind cases, it was not surprising that there were only syndromic conditions among the hereditary causes in the two groups. However, it was remarkable that some of the syndromes identified in the younger group are fairly rare. The prevalence of the acquired causes had diminished significantly (P « 0.05) over the years, which was especially due to the decreased prevalence of Dutch congenital rubella cases. Furthermore, there were more cases of severe prematurity or dysmaturity in the younger group (not significant, P=0.084); chromosomal conditions were only found in this group (P=0.17). Perinatal/-postnatal causes and chromosomal anomalies (combined figures) showed a significant increase in prevalence (P=0.0083). The number of cases with unknown or undetermined aetiology was low in the two groups in comparison with the literature.

Table 6:
Aetiology by ethnic origin of the infants in 1988 (N=68)

Aetiology	Origin			
	Dutch	non-Dutch	Total	%
Hereditary	**18**	**5**	**23**	**34**
autosomal recessive	17	5	22	32
non-syndromic	13	4	17	25
syndromic	4	1	5	7
autosomal dominant	1	-	1	1
non-syndromic	-	-	-	
syndromic	1	-	1	1
Acquired	**19**	**8**	**27**	**40**
prenatal	6	5	11	16
rubella	5	5	10	15
CMV	1	-	1	1
perinatal	4	-	4	6
postnatal	9	3	12	18
Chromosomal	**1**	**-**	**1**	**1**
Unknown*	**16**	**1**	**17**	**25**
Total	**54**	**14**	**68**	**100**

*, or undetermined

Table 6 summarizes the aetiologies of deafness of the 68 infants in 1988. Fourteen infants were of non-Dutch origin (Morocco 3, Dutch Antilles 3, Turkey 3, Surinam 1, Poland 1, Hong Kong 1, Vietnam 1, China 1). A hereditary cause was found in 23 infants (34%): 18 Dutch and 5 non-Dutch (3 of them had consanguineous parents). Seventeen infants had a non-syndromic autosomal recessive type of inheritance, while 5 infants had an autosomal recessive syndrome. Two Dutch cases had the Usher syndrome type 1, one had the Ziprkowski-Adam syndrome and one had a peroxisomal disorder. In one non-Dutch infant, the Bartter syndrome was found. One Dutch infant had the autosomal dominant Noonan syndrome.

Acquired causes of deafness were found in 27 infants (40%): 19 Dutch and 8 non-Dutch. Pre-, peri- and postnatal causes were found in 16, 6 and 18%, respectively. In the prenatal group, congenital rubella was the main cause of deafness, which was significantly more prominent in the group of non-Dutch infants than in the Dutch infants (P=0.025). In the perinatal group, 3 cases had been severely pre- or dysmature and one had suffered from severe asphyxia. In the postnatal group the most common cause of deafness was meningitis, mainly pneumococcal infection. One case had become deaf after histiocytosis. One pupil with immunodeficiency showed sudden deafness after simultaneous measles and varicella infections.

Table 7:
Degree of hearing impairment in the infants (numbers of pupils indicated as: with no additional handicaps / with additional handicaps) in 1988 (N=68) by aetiology

Aetiology	Threshold (dB HL)							
	60-69	70-79	80-89	90-99	100-109	110-119	>120	Total
Hereditary	**1/0**	**-**	**0/1**	**1/0**	**12/0**	**3/1**	**2/2**	**19/4**
Acquired	**-**	**-**	**0/1**	**4/2**	**2/1**	**4/2**	**7/4**	**15/10**
prenatal	-	-	-	1/1	0/1	3/2	0/3	4/7
perinatal	-	-	0/1	0/1	-	-	1/1	1/3
postnatal	-	-	-	3/0	2/0	1/0	6/0	12/0
Chromosomal	**-**	**-**	**-**	**0/1**	**-**	**-**	**-**	**0/1**
Unknown	**-**	**-**	**1/1**	**3/0**	**6/0**	**2/1**	**3/0**	**15/2**
Total	**1/0**	**-**	**1/3**	**8/3**	**20/1**	**9/4**	**12/6**	**51/17**

There was one case with an 18p chromosomal anomaly.

In 17 pupils the cause of deafness was unknown or undetermined; one of them had the CHARGE association.

In Table 7 the degree of hearing impairment in the 1988 infants is related to the cause of deafness. Most of the infants showed hearing loss of > 90 dB. The table also shows which infants had additional handicaps, such as psychomotor retardation, problems with vision, cardiac involvement and neurological complications. Seventeen out of the 68 infants had additional handicaps (25%). The prevalence of handicaps did not correlate significantly with the degree of hearing impairment.

The aetiologies of hearing impairment in the infants in 1998 (N=55) are shown in Table 8.

Table 8:
Aetiology by ethnic origin in the infants in 1998 (N= 55)

Aetiology	Origin		Total	%
	Dutch	nonDutch		
Hereditary	**15**	**3**	**18**	**33**
autosomal recessive	12	3	15	27
non-syndromic	7	1	8	15
syndromic	5	2	7	13
autosomal dominant	3	-	3	5
non-syndromic	2	-	2	4
syndromic	1	-	1	2
Acquired	**10**	**2**	**12**	**22**
prenatal	1	1	2	4
perinatal	3	1	4	7
postnatal	6	-	6	11
Chromosomal	**7**	**1**	**8**	**15**
Unknown*	**13**	**4**	**17**	**31**
Total	**45**	**10**	**55**	**100**

*, or undetermined, or possibly multiple

There were 45 Dutch and 10 non-Dutch infants (Turkey 6, Morocco 1, Surinam 1, Poland 1, Italy 1). Hereditary causes were found in 18 infants (33%): 15 Dutch and 3 non-Dutch (2 of them from consanguineous parents). Autosomal recessive non-syndromic heredity was found in 8 infants, while 7 had an autosomal recessive syndrome: 1 Cornelia de Lange syndrome, 1 Marden-Walker sydrome, 1 Usher syndrome type 1, 1 Kniest syndrome and 3 peroxisomal disorders. Autosomal dominant inheritance was found in 3 infants; 2 of them had nonsyndromic hearing impairment and 1 had a severe form of the Treacher Collins syndrome with unilateral microphthalmia with colobomas of the iris and retina, cleft lip/palate, bilateral zygoma aplasia, bilateral microtia and meatal aplasia, as well as severe mandibular hypoplasia, necessitating tracheostomy for respiration.

Acquired causes were found in 12 infants (22%). Prenatal, perinatal and postnatal causes were found in 4, 7 and 11%, respectively. The prenatal causes comprised 1 Dutch CMV case and 1 non-Dutch rubella case. Perinatal causes were found in 1 non-Dutch infant with kernicterus, 2 infants with severe asphyxia at birth and 1 infant with severe pre- or dysmaturity. All the post-natal causes were seen in Dutch infants: 5 had meningitis, mainly pneumococcal meningitis and 1 had sudden deafness of unknown aetiology.

There were 8 (7 Dutch) cases with rare chromosomal anomalies (15%):
mosaic 45X/46XX der(12), balanced translocation 2-18-19, trisomy 21 (2 cases), trisomy 22 mosaic, 13q-, 4p- and 7q36.1del.

Among the cases with an unknown or undetermined cause, or possibly multiple causes (31%), there was 1 case with both congenital rubella and meningococcal meningitis, 2 cases with the CHARGE association and 14 cases without any reliable indication about the aetiology.

Table 9 shows the degree of hearing impairment in the 1998 infants and the cases with additional handicaps. In the inherited group, the nonsyndromic cases and the Usher type 1 case had hearing loss of 100 dB or more, while the other syndromic cases had less severe hearing loss. In the Dutch CMV case, hearing impairment had progressed to profound deafness. The infants with chromosomal anomalies had relatively good residual hearing; their hearing loss was between 60 and 80 dB. There were more infants with moderate to severe hearing impairment in 1998 than in 1988 (Table 7). Statistical analysis demonstrated that two groups can be distinguished in Table 9: a group of infants with severe to profound hearing impairment (110 dB or more, N=19) none of whom had additional handicaps and a group with less severe hearing

impairment (thresholds of < 110 dB, N=36) many of whom (N=21) had additional handicaps ($P=6.6x10^{-6}$). Additional handicaps where found in 21 out of the 55 infants (38%), which is a higher percentage than in the 1988 group (17 out of 68, 25%), although not statistically significant (P = 0.084).

Table 9:
Degree of hearing impairment in the infants (numbers of pupils indicated as: with no additional handicaps / with additional handicaps) in 1998 (N=55) by aetiology

Aetiology	Threshold (dB HL) 60-69	70-79	80-89	90-99	100-109	110-119	>120	Total
Hereditary	**0/4**	**0/1**	**1/1**	**2/1**	**3/0**	**-**	**5/0**	**11/7**
Acquired	**0/1**	**0/1**	**-**	**1/0**	**1/2**	**3/0**	**3/0**	**8/4**
prenatal	-	-	-	-	0/1	-	1/0	1/1
perinatal	0/1	0/1	-	-	0/1	1/0	-	1/3
postnatal	-	-	-	1/0	1/0	2/0	2/0	6/0
Chromosomal	**0/7**	**0/1**	**-**	**-**	**-**	**-**	**-**	**0/8**
Unknown	**1/0**	**-**	**-**	**1/0**	**5/2**	**3/0**	**5/0**	**15/2**
Total	**1/12**	**0/3**	**1/1**	**4/1**	**9/4**	**6/0**	**13/0**	**34/21**

Table 10 compares the aetiologies of hearing impairment in the 1988 and 1998 infant pupils. In the hereditary group, the figures are very similar (although in the 1998 group - see Table 8 - relatively more syndromic conditions were found than in the 1988 group - see Table 6: 8 out of 18 vs 6 out of 23; the difference is not statistically significant, P=0.18). The prevalence of acquired conditions had diminished strongly, especially in the prenatal group (12 out of 55 cases vs 27 out of 68 cases, P=0.026). In contrast, the prevalence of chromosomal conditions had increased significantly (P=0.0068) over the years and thus formed a new important category in the aetiology of deafness. The proportions of unknown or undetermined aetiology were fairly similar and did not differ substantially from the rates reported in the literature.

Table 10:
Comparison of aetiologies between the 1988 infants and the 1998 infants

	Year 1988 n (%)	1998 n (%)
Hereditary	**23 (34)**	**18 (33)**
Acquired	**27 (40)**	**12 (22)**
prenatal	11 (16)	2 (4)
perinatal	4 (6)	4 (7)
postnatal	12 (18)	6 (11)
Chromosomal	**1 (1)**	**8 (15)**
Unknown	**17 (25)**	**17 (31)**
Total	**68 (100)**	**55 (100)**

4. Discussion

The results of earlier studies on the aetiology of SNHI in children have generally shown that hereditary, acquired and unknown causes account for one third each. Recent investigations have led to the assumption that a shift has occurred in the prevalence of these causes due to medical developments, such as new immunization programmes, better survival rates with neonatal intensive care treatment and better genetic examination methods. Although survival rates in very low birth weight infants have improved greatly, there seems to be a risk of severe handicaps, such as blindness (an estimated 2.7-3%) and deafness (1.3-2%) [5,6]. Das [7] found more deaf children in the perinatal group (13%), while the percentage of congenital rubella aetiology had decreased to 5. Chromosomal conditions accounted for 5%. Additional disabilities were seen in all the cases with chromosomal anomalies, in 44% of those with congenital rubella, in 80% of the CMV cases and in 60% of the cases in the perinatal group. Davis et al. [3] mentioned 40% genetic causes and 41% unknown causes. Perinatal adverse

factors were found in 7%. In their study, 39% of the cases showed permanent childhood hearing impairment associated with an additional disability; 36% had cognitive deficits, 10% had visual problems and 13% had systemic disorders. The major risk factor for additional disabilities was a history of requiring neonatal intensive care, as they have also demonstrated in an earlier study [8]. In contrast, Baille et al. [9] found additional handicaps in only 14%, although marked learning difficulties were observed in 36%. Singh Pabla et al. [10] reported a shift in aetiology from prenatal to postnatal causes. In a previous study [4], we found a decrease in the prevalence of kernicterus cases and an increase in the prevalence of perinatal and chromosomal conditions in deaf pupils with a mental handicap. Very few of the older studies mention chromosomal abnormalities. In a review of the more recent studies on the aetiology of childhood SNHI, Wendell Todd [11] only found a description of chromosomal anomalies in the above-mentioned study by Das [7].

Billings and Kenna [12] studied 301 children with SNHI and compared their findings to those from earlier studies. They found 19% perinatal factors, in comparison with 13% in earlier studies. The percentage of TORCH infections (Toxoplasmosis, Rubella, CMV, Herpes) decreased from 16-20 to about 1. Similar findings were reported by Parving and Hauch [13], who found a decrease of 6% in prenatal infections between 1983 and 1993 at a school for the deaf.

The above-described findings were corroborated by our study. We found a decrease in congenital rubella cases in the deaf-blind groups, as well as in the infants. As congenital rubella was the main cause of deaf-blindness in childhood in the Netherlands for many years, this change was reflected in our deaf-blind group in particular. The second largest group of causes of auditory-visual impairments were hereditary syndromic conditions. Oculo-auditory syndromes have been reviewed by Regenbogen and Coscas [14], although not all the syndromes summarised by these authors cause deaf-blindness. Regenbogen and Godel [15] found ocular anomalies that were interfering with vision in 45% of the cases. Armitage et al. [16] found normal ophthalmic characteristics in 54%, visual impairment in 35% and ophthalmic abnormalities without visual impairment in 11% of a group of 83 deaf children. In a study correlating the various causes of deafness with visual abnormalities [17], congenital rubella had the highest prevalence, whereas inherited (nonsyndromic) deafness had the lowest prevalence. In our deaf-blind groups, all the cases showed syndromic inheritance.

An increase in the prevalence of perinatal causes was found in the present study, especially in the deaf-blind groups. This was to be expected, because perinatal factors often produce additional handicaps. The increase in the infants was less clear. Another finding in this study was an increase in the prevalence of chromosomal anomalies. As the children with these anomalies all showed additional handicaps, chromosomal conditions were a major factor in the increase in prevalence of additional handicaps, from 25 to 38% in the infant groups. However, the children with additional handicaps had only moderate hearing impairment, whereas those with no additional handicaps tended to have more severe hearing impairment.

It can be concluded that over the years the prevalence of cases with rare hereditary syndromes has increased, while that of acquired causes of deafness, especially prenatal infections, has decreased, although there has been a relative increase in the prevalence of perinatal causes. Recently, more cases have been identified with chromosomal anomalies, which were the major cause for the increased prevalence of multiply handicapped children. Combining the present findings with those obtained in a previous study on the causes of hearing impairment in deaf pupils with a mental handicap [4] showed that various characteristics in the populations of children attending schools for the deaf and schools for the hard of hearing have changed in the Netherlands. More pupils with additional handicaps or very severe hearing impairment are being enrolled at schools for the deaf, whereas more pupils without additional handicaps, or with less severe hearing impairment, are being enrolled at schools for the hard of hearing.

Acknowledgements

We wish to thank the children and their parents for participating in this study. Numerous colleagues, paramedical and education workers employed at our hospital, other hospitals and the Institute for the Deaf contributed to the evaluation of our cases. We wish to thank D de Bekker, H Brink, M Broesterhuizen, J Brokx, A Dona, J van Dijk, B Hamel, G Janssens Capriles, A van Olphen, G Timmerman and J Toorman for performing the ophthalmological, paediatric, clinical genetic and audiological examinations, neuropsychological assessments and physiotherapeutic evaluations. Furthermore, we wish to express our thanks to H Tibosch, director of the Infants'

Department and to A Visser, director of the Deaf-blind Department of the Institute for the Deaf in Sint-Michielsgestel for their co-operation.

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Chapter 3

The CHARGE association

Chapter 3.1

Vestibular areflexia as a cause of delayed motor skill development in children with the CHARGE association

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International Journal of Pediatric Otorhinolaryngology
1997; 39: 205-222

Abstract

Six cases of the CHARGE association are described that were encountered consecutively at an institute for the deaf. Five of them showed external ear anomalies and according to expectations all of them showed some degree of hearing impairment: two had moderate mixed hearing loss, three had severe to profound sensorineural hearing loss and one was completely deaf. In addition, they all had vestibular areflexia and the five cases examined with computer tomography of the petrosal bones showed aplasia of the semicircular canals. One case with poor visual acuity also showed subnormal optokinetic responses and horizontal pendular nystagmus during visual fixation. All these children were initially diagnosed as having severe psychomotor retardation, because of their failure to acquire speech and their delayed motor skill development. Given the fact that (mild) mental retardation was found in only one case, the delayed development could at least in part have been caused by vestibular areflexia. The vestibular findings support previously reported temporal bone findings that indicate dysplasia or aplasia of the superior part of the labyrinth. Early detection of the full extent of (multiple) sensory deficits is necessary in children with the CHARGE association who have similar abnormalities, because aggressive intervention and special educational support are likely to be of great benefit to sensorimotor development.

1. Introduction

Hall [15] and others [16] have recognized the nonrandom association of coloboma of the eye (C), atresia choanae (A) and other congenital anomalies. Pagon et al. [31] used the acronym CHARGE to indicate the association of the above features with heart anomaly (H), retardation of growth and/or development (R), genital hypoplasia (G, most obvious in males) and external ear anomaly and/or hearing loss or deafness (E). It has been proposed that the diagnosis of the CHARGE association should be based on the presence of one or two of the features indicated by C and A and, in addition, some of the other anomalies designated by the acronym, to a total of at least four features (i.e. counting retarded growth as a separate feature from retarded development) [30,31]. The cardinal features (covered

by the acronym) were observed in 29-100% of the reported cases (Table 1); external ear anomalies [7] and/or low-set ears were found in almost all cases and hearing impairment in (on average) about two thirds of the cases. Other features are also included in Table 1; (congenital) facial palsy has been emphasized as an important additional diagnostic feature [8,16,28], because it is rarely seen in other syndromes. Dysfunction of other cranial nerves [4] and/or other central nervous system abnormalities [2,16,24], which may be visible with computer tomography (CT) or magnetic resonance imaging (MRI) of the brain, may also be important. Especially relevant to the present report is the finding of aplasia of the superior part of the labyrinth (Section 5).

Table 1:
Findings (weighted mean percentage and range) in reported cases based on 17-245 observations

Cardinal features		Associated features	
Coloboma	81% (77-91%)	Micrognathia	79%
Heart anomaly	81% (56-89%)	Cleft palate/lip	21% (16-35%)
Atresia choanae	60% (29-89%)	Facial palsy	43% (22-89%)
Retardation	89% (76-100%)	DiGeorge sequence	8%
Genital hypoplasia	74% (51-100%)	Tracheo-oesophageal fistula	8% (7-10%)
External ear anomaly	97% (78-100%)	brain CT: abnormal findings	48%
and/or hearing loss	65% (60-89%)	Absent semi-circular canals	50%
		Nystagmus	28%
		Strabismus	32%
		Skeletal abnormalities	42% (40-47%)

Three major review series [4,6,24] were averaged (weighted means) before calculation took place. Other series were: Davenport et al. [8, sporadic cases only]; this is (almost) the same series as that reported on by Blake and colleagues [1,2,16,28,35,44].

There is overlap between the CHARGE association and the velocardiofacial syndrome [42], the VATER (vertebral defects, anal atresia, tracheo-(o)esophageal fistula with (o)esophageal atresia and radial dysplasia) association [8] and the DiGeorge sequence [23].

Although the majority of cases reported in the literature were sporadic, somewhat similar familial cases have also been reported ([7,8,27,31] or [44] and references, see also the references in [2]).

Balanced whole arm translocation involving chromosomes 6 and 8 was reported in a sporadic case with CHARGE [17]. North et al. [29] reported on a case with *de novo* inverted duplication (14)(q22→24.3). Numerous chromosomal abnormalities have been found in association with CHARGE-like features in patients with the cat-eye syndrome, trisomy 22, triploidy, long arm deletions of chromosomes 9, 11 and 13, partial duplications of chromosomes 4 and 14 [13], or translocations involving other chromosomes [6].

Although, by definition [9,45], there is no indication of an underlying cause in an association, it is probable that the CHARGE association represents a defect in neural crest development that occurs between 35 and 45 days after conception [14,24,31,39,48]. Pagon et al. [31] proposed the possibility of a teratogenic effect, as CHARGE can be part of the abnormal features in thalidomide fetopathy [40]. Thalidomide has been found to cause - apart from phocomelia and other limb deformities - complete aplasia of the labyrinth (Michel's type) or aplasia of the superior part of the labyrinth [43]; the features of the CHARGE association might be consistent with a less severe teratogenic effect (i.e. without limb deformities).

An intriguing cardinal feature of the CHARGE association is developmental retardation (R). Although some authors reported mental retardation with or without formal testing, given many of the case descriptions, the question can be raised as to whether delayed development of motor skills is (also) involved (Section 5). Our general experience is that the possibility of vestibular areflexia has seldom been considered. It will be clear from the reported findings (see above and Section 5) that vestibular function may be impaired in many cases. Vestibular impairment is an established cause of gross motor developmental delay [3,21,34]. We therefore decided to perform vestibular examination on a small group

of patients, all of whom had been previously diagnosed and institutionalised at the Institute for the Deaf (IvD) in St. Michielsgestel. It should be realised that our CHARGE association cases therefore comprised a selected group with severe hearing impairment and, presumably, were at increased risk of having (possibly) associated anomalies or dysfunctions. On the grounds that gaze stabilisation and ocular motor function may also be relevant within the context of the development of motor skills and it is well-known that the CHARGE association often involves visual problems and may present with ocular motor abnormalities such as nystagmus (Table 1) or pareses, we also performed ocular motor examination.

Our working hypothesis was that the delayed development of motor skills in CHARGE - especially in cases with severe hearing loss or complete deafness - is at least partly due to vestibular areflexia, particularly if this feature is combined with ocular motor instability (nystagmus), gaze paresis, or reduced visual acuity.

2. Case histories (also see Tables 2 and 3)

2.1. Case 1

This 5-year-old girl was a pupil at the Institute for the Deaf (IvD) at St. Michielsgestel. She was the product of an uncomplicated pregnancy and a normal delivery. Shortly before delivery, the amniotic fluid appeared to be stained with meconium. She had a birth weight of 3500 g and her Apgar scores were 7 and 9 after 1 and 5 minutes, respectively. The auricles were normal. A cleft lip and palate on the left side were present and coloboma of the iris of the left eye; ophthalmological examination showed bilateral choroideal colobomata. Examinations elsewhere at the age of 3 months revealed normal visual evoked responses; brain stem auditory evoked potentials (BAEPs) showed responses to 80 dB from both ears. Grommets were inserted because she had bilateral otitis media with effusion. Surgery was performed on the soft palate at the age of 3 months and on the hard palate and cleft lip at 11 months and 2.6 years. Cardiological examination at the age of 1.6 years proved to be normal.

Table 2:
Clinical findings in six cases with the CHARGE association

Case no.	Coloboma R/L VA_R/VA_L	Heart anomaly	Atresia choanae	Retardation -growth -age (y) at walking -intelligence	Genital hypoplasia	Ear anomalies -external ear -hearing loss	Comment (mother/pregnancy/delivery)
1	+ / + 0.25/0.25	-	-	< 3rd percentile 2.5 NVIQ 70-75	?	- +	(meconium-stained amniotic fluid) L cleft lip and palate feeding problems
2	- / - n / n	+	R/L	< 10th percentile 3 NVIQ 70-75	+	+ +	(hypertension, polyhydramnios) oesophageal atresia, tracheo-oesophageal fistula, aqueductal stenosis, hydrocephalus, epilepsy, necrotising enterocolitis
3	+ / + sn / sn	+	-	< 3rd percentile 3.7 NVIQ 70	?	+ +	R facial paresis, feeding problems, obstructive sleep apnoea syndrome
4	- / + sn / sn	+	-	< 10th percentile 3 NVIQ 75-80	+	+ +	(chloroquine medication) R facial palsy, minor midline clefting of the nose
5	- / + 0.8/0.4	+	R	< 3rd percentile ? NVIQ 85	+	+ +	(haematuria) recurrent urinary tract infections, transient epilepsy, feeding problems, submucous cleft palate
6	+ / + 0.6/(1/40)	+	-	< 3rd percentile 2.1 NVIQ 65-70	+	+ +	facial asymmetry, L cleft lip and palate

L, left; n, normal; NVIQ, non-verbal IQ; R, right; sn, subnormal; VA, visual acuity; +, present; -, absent; ?, unknown.

Table 3:
Audiological and oculovestibular findings in six cases with the CHARGE association

Case no.	Pure tone threshold (dB HL) at frequency (kHz):					Type of hearing loss		Oculo-vestibular findings	Comment
	0.25	0.5	1	2	4	8			
1	R 20/ 75[a] L 70[b]	R 20/ 75 L 75	R 20/ 80 L 90	R 40/ 80 L 95	R 55/110 L 115	R ↓ L ↓	mixed	pendular nystagmus vestibular areflexia OKN sn	BAEPs (3 mo) R/L 80 dB BAEPs (2 y) R 60 dB, L 90 dB recurrent otitis media
2	R 100 L 100	R ↓ L 90	R ↓ L 85	R ↓ L ↓	R ↓ L ↓	R ↓ L ↓	SNHL	vestibular areflexia OKN n?	BAEP (7 y) no responses
3		R 60 L 55	R 20/ 55 L 20/ 55	R 25/ 60 L 25/ 55	L 20/ ?		mixed	vestibular areflexia OKN sn	BAEP (1 y) not retrocochlear recurrent otitis media
4	R 90 L 90	R 110 L 110	R ↓ L ↓	R ↓ L ↓	R ↓ L 125	R ↓ L ↓	SNHL	vestibular areflexia OKN ↑?, COR ↑?	Ewing test (11 mo) ?
5	R 110 L 110	R ↓ L 125	R ↓ L 125	R 125 L 130	R 115 L ↓	R ↓ L ↓	SNHL	vestibular areflexia OKN n	electrocochleography (2 y): R n, L no response
6	R 95 L 110	R 110 L 115	R 120 L 115	R 115 L 110	R 95 L 120	R ↓ L ↓	SNHL	vestibular areflexia OKN n?, COR ↑	recurrent otitis media

[a], bone conduction / air conduction; [b], air conduction; BAEP, brain stem auditory evoked potential; COR, cervico-ocular reflex; L, left; n, normal; OKN, optokinetic nystagmus; R, right; sn, subnormal; ?, unknown; ↓, out of scale; ↑, increased response

After a repeat insertion of grommets, body-worn hearing equipment was fitted, but she hardly showed any response. Repeat BAEPs performed elsewhere at the age of 2 years showed responses to 60 dB stimulation of the right ear and to 90 dB stimulation of the left ear. She was fitted with bilateral behind-the-ear hearing aids. Her motor development was retarded; she did not start walking until the age of 2.5 years. Her growth curve was below the third percentile of normal. At her last examination, at the age of 5 years, she still had eating/swallowing problems, which prevented her from coping with solid food. Recent ophthalmological examination showed coloboma of the left iris, irregular bilateral nystagmus, a kidney-shaped choroid coloboma of the right eye which spared the macula, and a larger choroid coloboma of the left eye which involved the macula. Visual acuity (VA) was estimated at 0.25. Her non-verbal IQ was 70-75, as measured by the CID (Central Institute for the Deaf) preschool performance test.

2.2. Case 2

The second case was a 13-year-old girl, who was a pupil at the IvD. She was born after a complicated pregnancy: hypertension from the fifth month onwards as well as polyhydramnios. Toxicosis occurred at 7 months of pregnancy with aggravation of the polyhydramnios, for which amniocentesis was performed twice. Echoscopic examination showed oesophageal atresia. Delivery took place by means of vacuum extraction. The infant was asphyxic because of umbilical strangulation. The Apgar score was 2 after 1 minute and 6 after 5 minutes. The left auricle showed posterior rotation and the right auricle showed a flattened helix superior; there were triangular conchae, bilaterally. Examination showed oesophageal atresia, a tracheo-oesophageal fistula and bilateral choanal atresia. Gastrostomia was performed, later followed by surgical closure of the tracheo-oesophageal fistula and cardio-oesophageal anastomosis. A patent ductus arteriosus was corrected at the age of 2 months. Necrotising enterocolitis developed 2 months later. She had aqueductal stenosis with hydrocephalus. She had several epileptic seizures, for which medication was necessary for 1 year. She showed severe motor retardation. Her balance was very poor and, with daily physiotherapy, she finally started walking at the age of 3 years. Her growth

curve was below the tenth percentile of normal. Because of these complications, audiological examinations were not performed before the age of 3.8 years (Section 4). A body-worn hearing aid was fitted, but she showed poor auditory responses. Ophthalmological examination was normal. VA was normal. Bilateral choanal atresia was corrected surgically at the age of 13 years. At the same age, echoscopic examination showed hypoplasia of the uterus and ovaries. Non-verbal IQ was 70-75 assessed with subtests of the Hiskey-Nebraska test, the Wechsler Intelligence Scale for Children Revised (WISC-R) and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI).

2.3. Case 3

This case was a 3-year-old girl, who was a pupil at the IvD. She was born after an uneventful pregnancy and normal delivery with a birth weight of 2800 g. Right facial paresis was noted. The left auricle was cup shaped with a triangular concha. The right ear also showed a triangular concha with hypoplasia of the lobule. There was also mild hyperbilirubinaemia, but she did not require any phototherapy. She had persistent swallowing difficulties. Ophthalmological examination disclosed coloboma of the left iris and bilateral choroid colobomata that involved the optic disc and the macula in the left eye. MRI of the cerebrum did not reveal any abnormalities. When she was several weeks old, cardiological examination showed an atrial septal defect and a patent ductus arteriosus; the latter was closed at the age of 8 months. She had recurrent infections of the upper respiratory tract. When we first examined her at the age of 2 years, she could walk along holding on to objects, but could not walk unaided. Recent follow-up data indicated that she started walking alone at 3.7 years of age. Growth retardation was obvious and her growth curve was below the third percentile of normal. She showed right facial paresis, coloboma of the iris and microphthalmia of the left eye. VA was estimated to be 0.2 in the right eye. Both external auditory meati were funnel-shaped. There was no choanal atresia. The soft palate was elongated and hypotonic. A few months later, polysomnographic examination demonstrated the obstructive sleep apnoea syndrome, which could be cured with adenotonsillectomy, but her swallowing difficulties persisted. The most recent

developmental examination had been performed at the age of 2.8 years, which showed a non-verbal IQ of 70, assessed by the CID preschool performance scale, motor retardation of 1.7 years and a language developmental age of 8 months. VA had improved to 0.6. She has a female maternal cousin with Goldenhar's syndrome.

2.4. Case 4

This was a 32-year-old woman, who had been a pupil at the IvD. She was born after an uncomplicated pregnancy. Her mother had taken chloroquine medication for a short period. As the pregnancy had occurred at the beginning of the sixties, we specifically asked her mother whether she had used any thalidomide, which she had not. Delivery had been difficult and the infant cyanotic. She showed multiple deformities: right facial palsy, bilateral auricular abnormalities consisting of a triangular concha of the right ear, an overfolded antihelix of the left ear and bilaterally hypoplastic lobules. There was a pre-auricular fistula on the left side and minor midline clefting of the nose. A patent ductus arteriosus was corrected surgically a few months later. Ophthalmological examination revealed mild microphthalmia and retinal coloboma of the left eye that extended to just below the optic disc. At the age of 11 months, she had an apparently positive Ewing test elsewhere. She showed severe motor retardation. WAIS (Wechsler Adult Intelligence Scale) and Raven tests indicated an IQ of 75-80. She did not start walking until the age of 3 years. Her growth curve was below the tenth percentile of normal. Physiotherapy was applied at the age of 10-15 years because she showed spastic movements of the right leg during gait. From the age of 19 years onwards, she was treated for hypogonadotropic hypogonadism. Her most recent ophthalmological examination showed bilateral subnormal VA.

2.5. Case 5

This was a 26-year-old woman, who had been a pupil at the IvD. She was born by forceps delivery, after a pregnancy which had been complicated by haematuria. She

showed multiple dysmorphic features: a patent ductus arteriosus, an intraventricular septal defect, pulmonary stenosis and choanal atresia on the right side. There was a low-set small ear on the left and a cup ear on the right. Both ears had a triangular concha. There was microcephaly and microphthalmia on the left. She had recurrent urinary tract infections. The choanal atresia was operated on in her first year. Ophthalmological examination disclosed microphthalmia of the left eye with microcornea and coloboma of the inferior part of the choroid that involved the optic disc. Pneumencephalography showed dilated ventricles. She showed motor skill retardation. Electrocochleography performed elsewhere at the age of 2 years failed to show any responses from her left ear; responses from her right ear were normal. At the age of 6 years, she developed epilepsy for which she was treated with anticonvulsant medication. Repeated EEGs showed diffuse β and δ activity with specific paracentral focal epileptic activity, which gradually normalized after the age of 12 years. Cerebral CT scans at the age of 11 years showed no abnormalities. Her cardiac anomalies were operated on at 10 years of age, after which her development improved considerably. Renograms and cystography were normal, although she continued to have frequent urinary tract infections. From the second decade onwards, she has been receiving suppletion therapy for her hypogonadotropic hypogenitalism. Recent examination revealed a minor submucous cleft palate. Her growth curve remained below the third percentile of normal. Her right eye had 0.8 VA and her left eye 0.4. Her nonverbal intelligence quotient, assessed by subtests of the WISC-R was 85.

2.6. Case 6

This 10-year-old boy was a pupil at the IvD. He was born after an uncomplicated pregnancy with a birth weight of 2800 g. He showed facial asymmetry, left cleft lip and palate (which was operated on later at the age of 0.3 , 0.10 and 2.0 years), coloboma of the left iris, cryptorchidism and phimosis. Both auricles showed posterior rotation and triangular conchae. The left ear had an overfolded antihelix. He underwent surgery for a patent ductus arteriosus at the age of 4 months. The boy showed developmental retardation, and profound hearing impairment was diagnosed elsewhere at the age of 15 months.

Grommets were placed but there was no improvement in hearing and behind-the-ear hearing aids were fitted. These were later replaced by body-worn hearing equipment because of insufficient responses. Poor vision was suspected from the age of 10 months onwards. Ophthalmological examination was performed under general anaesthesia at the age of 2 years. The right eye showed coloboma of the optic disc and -15 diopters myopia. The left eye showed colobomas of the optic disc as well as the macula which reduced his vision to light perception only. Glasses were fitted 1 month later with -11 diopter lenses. From then on, after a considerable delay in the development of general motor skills, the boy began to explore his everyday environment and started walking (unaided) already one week later (2.1 years). His growth curve was still below the third percentile. His right eye had 0.6 VA and his left eye 1/40 VA. Visual field examination was close to normal in the right eye. Non-verbal intelligence was assessed using the Hiskey-Nebraska test, the Kaufmann non-verbal test and other Dutch non-verbal intelligence tests, which produced an IQ of 65-70.

3. Methods

Audiograms, behavioural audiometry and BAEPs were obtained in a sound treated room with the usual methods. Eye movements were recorded with d.c. electronystagmography. Calibration saccades were obtained by having the patient look in alternation at light dots at 10° lateral from the primary position. Calibration saccades were used to measure saccade peak velocity [18,46]. Gaze positions were examined with targets at 30-40° lateral positions. Smooth pursuit eye movements were elicited with a light dot moving sinusoidally at 20°/s maximum (horizontal) velocity. Optokinetic nystagmus was elicited by a shadow-projected pattern of stripes (7.5° width and separation, hemicylindrical screen covering a visual field of 90 x 50°) moving at 40°/s and 60°/s constant velocity. Age-dependent normal values were derived from 78 ENT patients without any relevant ocular motor dysfunction. Spontaneous nystagmus, i.e. slow phase velocity of > 6°/s, was monitored in the dark with the eyes open. In the same condition, vestibular responses were evaluated, which were elicited with a rotatory chair (Toennies, Freiburg im Breisgau,

Germany) using velocity step tests of 90°/s (after 0.8°/s^2 acceleration and 200°/s^2 deceleration) or sinusoidal rotation (50°/s peak velocity, frequency 0.05 Hz). Nystagmus elicited by sinusoidal rotation (i.e. in the light, see below) was evaluated by calculating the gain from the peak eye velocity. Cervico-ocular responses were only obtained from case 4 (our oldest patient) and case 6 (our most recent patient). The head was fixed (by hand) in space, while the body moved sinusoidally at 0.1 Hz with 60° peak-to-peak amplitude. These responses were evaluated by measuring the eye velocity gain or the eye position gain (cumulated eye position angle per hemicycle divided by 60°) and comparing the values obtained to previously established normal values [20].

4. Results

4.1. Audiological evaluation

All six cases were institutionalised because of their severe hearing impairment. The results obtained from examinations elsewhere (Case histories, Section 2) confirmed moderate to severe mixed hearing loss in cases 1 and 3. After bilateral insertion of grommets, our case 1 showed improved hearing/BAEP responses from her right ear (but not from her left), which suggested mixed hearing loss in at least one ear. In case 2, no responses were observed with either behavioural audiometry or BAEPs until the age of 7 years (Table 3), when she showed some low-frequency residual hearing (about 100-85 dB at 0.25-1 kHz) in her left ear; her right ear showed profound sensorineural hearing loss (SNHL). Case 3 showed mixed hearing loss of about 55-60 dB in both ears. Bone conduction thresholds were at about 20-25 dB. Insertion of grommets did not improve her hearing. BAEPs did not indicate any retrocochlear cause for her hearing impairment. In case 4, Ewing examination at the age of 11 months was believed to be normal and she seemed to be showing the beginning of speech development. However, at the age of 1.6 years her hearing deteriorated and speech development was arrested. Behavioural audiometry at the age of 6 years showed profound bilateral SNHL, which has not changed since: at the age of 31 years her hearing thresholds were between 90 and 110 dB at 0.25-

0.5 kHz. In case 5, audiometry at the age of 4 years demonstrated profound deafness. At the age of 21 years, she had bilateral residual hearing with thresholds in the range of about 110-125 dB at 0.25-2 kHz. Case 6 did not show any reaction to stimulation of the left ear at the age of 20 months. The most recent audiograms showed bilateral thresholds at 95-120 dB.

4.2. Oculovestibular examination

There was no spontaneous or gaze-evoked nystagmus, except in case 1 who showed a horizontal pendular nystagmus (Table 3) during visual fixation only; this patient had poor VA (corrected 0.25). Saccades were normal in the other cases, although we could not calibrate the eye movement in case 3. In the latter case, we did not evaluate smooth pursuit responses; the same also applied to case 1 because of her pendular nystagmus. This case showed a subnormal optokinetic nystagmus (OKN) gain (0.28-0.48 at 40°/s constant velocity stripe rotation, 0.34-0.70 during sinusoidal rotation in the light, in the absence of canal reflexes). Case 2 showed a subnormal (0.5) to marginally low (0.75) OKN gain at 60°/s stripe rotation, whereas the gain during optovestibular sinusoidal rotation (in the absence of canal function) was 1.0. In case 3 (without calibration) OKN responses to stripe rotation were lacking, but the child could not be pursuaded to look at the stripes sufficiently. The gain of the optovestibular response could not be quantified, but nystagmus was present (which disappeared in the dark); the nystagmus response level seemed to be subnormal on visual inspection. Case 4 had an OKN gain of 1.0 at 60°/s stimulation. Case 5 showed normal OKN responses. Case 6, whose responses could not be evaluated exactly, presumably had a normal OKN response.

All the patients showed vestibular areflexia (Table 3). Case 4 had a cervico-ocular reflex (COR) gain of about 0.30 when calculated from eye displacement and 0.42 when calculated from maximum slow phase velocity. Given the statistics for gain (at 0.1 Hz, all conditions similar) in normal subjects and patients with vestibular areflexia [20], this implies that the COR gain in case 4 was between the 72th and 88th percentiles of normal subjects and in the range of between the 12th and eigth percentiles of labyrinthine-

defective subjects. Case 6 showed an impressively high COR gain of close to one.

5. Discussion

5.1. External ear anomalies and pure tone audiograms

External ear anomalies and/or hearing loss or deafness are prominent features of the CHARGE association. Thelin et al. [44] described 15 patients, of whom all but one had external ear malformations. The prevalence of hearing loss was approximately 85%, ranging from mild to profound impairment. Hearing loss was mixed; the conductive component was caused by ossicular chain anomalies and/or middle ear effusions, which had affected either the low frequencies or all frequencies. SNHL was usually most prominent at the high frequencies. Hearing loss, conductive, sensorineural or both, may have been progressive. These authors suggested that a 'wedge-shaped' audiogram may be unique to the CHARGE association. Their findings on mixed hearing loss were in contrast with those of Pagon et al. [31], who reported predominant SNHL in 84% of their patients. Mitchell et al. [27] also described predominant mixed hearing loss with a wedge-shaped audiogram in a family with probable dominant CHARGE association. We did not find any wedge-shaped audiograms in our cases.

Edwards et al. [11] reported normal hearing in 24%, conductive hearing loss in 33%, SNHL in 24% and mixed hearing loss in 19%. All the children with SNHL had severe to profound hearing impairment. Mixed hearing loss also tended to be severe to profound. They did not find any progressive hearing impairment. External ear anomalies were present in 86%.

Five of our six cases showed external ear anomalies. Two had moderate mixed hearing loss, three had severe to profound SNHL and one was completely deaf. The high prevalence of major hearing impairment in the present group of patients was due to selection bias, because they were/are pupils at an institute for the deaf.

Our case 1 had mixed hearing loss in at least one ear. Case 3 had moderate mixed hearing loss that did not improve after the insertion of grommets, which suggests the existence of a

congenital middle ear malformation. All our cases with SNHL (2, 4, 5 and 6) were profoundly hearing impaired with some residual hearing only at the low frequencies. In two of them (cases 4 and 5), hearing impairment might be progressive, but we do not know whether we can fully depend on the first assessment which took place at a young age.

Recurrent middle ear effusion was present in three out of the six cases, although in cases 1 and 6 this could have been associated with the cleft lip and palate.

Edwards et al. [11] suggested that persistent facial weakness can serve as a reliable predictor of SNHL; of our two cases with facial paresis, case 3 showed moderate mixed hearing loss, while case 4 showed profound SNHL.

5.2. Oculovestibular examination

Horizontal pendular nystagmus was also reported by Chestler and France [5] in two out of five cases with colobomata, both of whom showed macular and optic nerve involvement. `Nystagmus' without any further details was reported by Blake et al. [2]. However, their series was apparently almost identical to that reported on by Russell-Eggitt et al. [35], who specified nystagmus in 28% (n = 50) of the cases. Nystagmus was associated with reduced VA and all of the children with nystagmus had optic disc colobomata, with only one exception. Nystagmus was horizontal in 11 cases, torsional in two and consisted of bursts in a vertical direction in one. Monocular upgaze paresis was observed in four cases with facial palsy, on the contralateral side to that palsy; it was particularly clear in adduction. There was one case of saccade palsy or oculomotor apraxia. The visual behaviour improved in all seven children who were initially thought to be blind, with no apparent visual fixation or following movements, and `chaotic' eye movements; nystagmus developed in three of them. Three other reports only mentioned `nystagmus' in one case each. One of these had CHARGE with the Möbius syndrome [4], another had Joubert's syndrome [26] and the third had `horizontal nystagmus' with athyreosis [25]. The case with CHARGE and Joubert's syndrome also showed defective smooth pursuit. Similar findings were reported by Lambert et al. [22], who described

pendular torsional nystagmus or see-saw nystagmus in Joubert's syndrome alone - which includes hypoplasia or aplasia of the cerebellar vermis and may include retinal dystrophy [22,37]. In such cases, but also in CHARGE cases such as those described above (e.g. vertical nystagmus in bursts, upward gaze palsy), it is possible that the nystagmus is central in origin. In the cases who also had colobomata, as mentioned above, nystagmus may have been secondary to macular or optic nerve involvement, as was suggested by Russell-Eggitt et al. [35].

Our case 1, who had horizontal pendular nystagmus during fixation only, also showed subnormal optokinetic responses. Case 3 may have also had subnormal optokinetic responses. Although these two cases had macular coloboma in one eye, only case 3 had optic disc involvement in one (the same) eye. It should be noted, however, that cases 4, 5 and 6, who (presumably) had normal optokinetic responses, also had some degree of unilateral optic disc (and macular - case 6) involvement. The only reported case with defective smooth pursuit eye movements that we are aware of is the above-mentioned case with Joubert's syndrome, but it seems likely that more cases, when formally tested, would demonstrate impaired smooth pursuit and/or impaired optokinetic nystagmus.

The major finding in our patients was vestibular areflexia. This feature was present in all of our patients and it was combined with bilateral hearing impairment, either moderate mixed hearing loss or severe SNHL, or even complete deafness; they also showed marked retardation in motor skill development. In addition, (only) case 6 had tangible mental retardation. There is no doubt that our CHARGE association cases were selected on the basis of their hearing impairment. Therefore, there was an increased risk of (additional) inner ear anomalies (as was demonstrated by CT scans performed in cases 2-6, which revealed aplasia of the semicircular canals) with (associated) impaired function such as vestibular areflexia.

5.3. Vestibular areflexia and delayed motor skill development

Given that our cases comprised a sample of selected cases, it should be emphasized that their selection did not involve assessments of motor skill development, but only hearing

impairment. Owing to the severe SNHL or even complete deafness caused by the inner ear anomaly, the finding of vestibular areflexia did not come as a complete surprise in four of our cases. It was surprising, however, to find areflexia in the two cases with moderate hearing impairment. At least part of the delay in motor skill development in all of our cases can be attributed to vestibular areflexia, but this does not exclude other (or additional) causes for the delay in other (or the present) cases (see below).

We could find only one reported case who underwent vestibular examination: Goldson et al. [12] did not observe any caloric responses in a girl with severe mixed hearing loss, who did not start walking until 3 years of age. That case was somewhat similar to ours. As only one of our patients showed some degree of (mild) mental retardation, there must have been other causes for the delayed motor skill development, such as, for example, vestibular areflexia. Somewhat similar cases with a combination of severe hearing loss, delayed motor skill development and apparently normal (or close to normal) intelligence have been reported previously [7,9,11,16,44,45,48]. The relevant case descriptions suggest a close relationship between profound hearing loss and delayed motor skill development. Blake and Brown [1] also reported marked delays in motor development and, in addition, demonstrated that a significantly higher proportion of children who needed a hearing aid showed balance problems than those who did not. In some of the reported cases, the authors emphasized that the developmental delay was initially considered to be caused by mental retardation, but that the children continued to improve and finally did better than had initially been anticipated; the results of formal testing supported this. Remarkable examples of the developmental potential of some of these children were Davenport et al.'s [8] and Thelin's et al.'s [44] patient JM, Goldson et al.'s [12] patient 2 and Harvey et al.'s [16] patient 7. Blake et al. [1,2] stated that the diagnosis `mental retardation' should be applied with caution to children with the CHARGE association. They suggested that it should not be used as one of the cardinal features of the CHARGE association, but that instead, the term `developmental delay' may be more appropriate. Blake et al. [1,2], as well as other authors, admit that in their experience, the mental capabilities of these patients have been underestimated, because the possible effects of sensory deprivation have not been considered. We would like to re-emphasize our previous recommendation [19] and

that of others [3,21,34] that, preferably, vestibular areflexia should be detected at an early age. The potential risks associated with activities such as swimming or cycling will then become apparent and, if necessary, the child can receive therapy to improve his/her motor development [33]. Our patients showed that visual impairment did not appreciably influence optokinetic responses, except in case 1, with the lowest VA, who had a somewhat reduced optokinetic response gain; nevertheless, she started to walk at an earlier age than the other cases.

5.4. Previously reported temporal bone and associated findings

The characteristic abnormality of the labyrinth in the CHARGE association is Mondini's dysplasia of the pars inferior and aplasia of the pars superior, which includes the utricle, semicircular canals and the neural supply to the pars superior [14,28,48]. Spiral and vestibular ganglion cells are absent or strongly reduced in number [14,48 (case 4)] but the cochlear and vestibular nuclei in the brain stem are normal, which indicates a defect in neural crest development [14]. In the case described by Guyot et al. [14], a girl who died at the age of 7½ months, the saccule, macula and nerve supply were intact bilaterally. In that girl, BAEPs had revealed profound bilateral hearing loss. Wright et al. [48] described a boy, case 4, with similar temporal bone findings, who died after 10 days. The saccular maculae were reduced to two thirds of their normal size, while the utricular maculae were rudimentary and showed only sparse innervation.

In a review study by Guyot et al. [14], somewhat similar temporal bone anomalies were present in cases that in retrospect may be diagnosed with the CHARGE association ([32] case 1, [38]). Similar observations were made by Sekhar and Sachs [38] in a girl who died after 12 days: absent utricles and semicircular canals, with a deformed, sparsely innervated saccular macula. Paparella and ElFiky [32] identified an underdeveloped saccule with an abnormal macula and very few saccular nerve fibres in their case 1. Interestingly, that case concerned a boy who died at 5½ years of age; he had severe hearing loss and did not start walking until he was 2 years of age. It will be clear from the above-described findings that semicircular canal reflexes must have been lacking, while the latter case exemplifies the

link between anatomical defects on the one hand and impaired hearing and vestibular function on the other. The vestibular deficit in the latter case can be held responsible for (at least part of) the delay in motor skill development. It is an intriguing finding that the saccule can be the only vestibular end organ that is spared, completely or at least to some extent, and may therefore be functioning. It is possible that intact saccular function may be important for detecting the vertical accelerations that occur in stance and gait. For example, despite the apparant vestibular areflexia, the patient may not experience any vertical oscillopsia when walking straight forward, i.e. without any turning movements.

5.5. Educational support for motor development

There is no doubt that adequate assessment and correct diagnosis are of vital importance to the development of multi-handicapped children. Others (e.g. Blake and Brown [1]) have already emphasized that it is a well-documented fact that children with severe visual and/or multisensory impairment are likely to show delayed motor skill development (e.g. [10,41]). Davenport et al. [8] remarked that `All older retarded individuals, ..., had a peculiar shuffling gait which consisted of scuffing the toe down first rather than the usual smooth heel-toe pattern, and a decreased arm swing.' In their follow-up study, Blake and Brown [1, p. 405] concluded that many of the CHARGE children might have benefited from physiotherapy at an early stage of their development: this `may have helped some of the balance problems that were common in this group. Reassurance from a physiotherapist that the child's movement patterns are primitive rather than abnormal can have an enormous impact on the parents' ability to take a positive view of the future.' We are not convinced that the motor skill development in such children is `primitive'. Their development might better be referred to as `alternative' rather than abnormal. The adaptive capacities of the systems involved and the plasticity of the central nervous system that adequately enhances compensatory reflexes can be quite impressive in such cases.

We feel that more special attention should be paid to possible vestibular impairment, especially in cases with severe SNHL and/or roentgenographic evidence of labyrinthine anomalies. After a correct diagnosis of vestibular areflexia has been made, preferably at a

young age, the (probable or possible) consequences and remedies can be explained to (and discussed with) the parents and the physiotherapist. It is of crucial importance that any central nervous system abnormalities are also detected as soon as possible, in order to accurately estimate the child's developmental scope. For example, cerebellar hypoplasia, which has been detected (by CT and MRI of the brain) in some children with the CHARGE association [16,24,26] is notorious for causing hypotonicity and the very severe delay in motor skill development: one example is the disequilibrium syndrome (DES) [36,47]. Presumably, the vestibular system is intact in the DES and other syndromes which include cerebellar hypoplasia; developmental disability may be even greater if cerebellar hypoplasia is combined with absent peripheral vestibular function (and even greater still with the additional disability of poor vision).

In general, when a child shows delayed (or lack of) acquisition of both motor skills and speech, one is tempted to diagnose psychomotor retardation, as initially happened also in the case of our CHARGE patients. It should be realised, however, that (combined) cochleovestibular impairment may produce a fairly similar developmental deficit, even if a child has normal (or close to normal) intelligence.

6. Acknowledgements

Numerous colleagues, paramedical and education workers employed at our hospital, the IvD and elsewhere, contributed to the evaluation of our cases. We wish to thank Mrs M Broesterhuizen, JPM Brokx, GJA Janssens Capriles, GJMEN Timmerman, AHF van Olphen, JPM van Dijk, MGM Nicolasen and H Meys for performing paediatric, ophthalmological, audiological and oculo-vestibular examinations, neuropsychological assessment and physiotherapeutic evaluation.

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Chapter 3.2

Temporal bone CT findings in the CHARGE association

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International Journal of Pediatric Otorhinolaryngology
1998; 45: 151-162

Abstract

Ten out of 20 cases with the CHARGE association and two CHARGE-like cases underwent temporal bone CT scanning and/or MRI: they all showed bilateral aplasia of the semicircular canals and obliteration of the oval windows. Vestibular examination was performed in nine CHARGE cases and the two CHARGE-like cases, which disclosed vestibular areflexia in all of them. Of the 16 evaluable CHARGE cases, eight had bilateral mixed hearing impairment, while eight had sensorineural hearing impairment which was bilateral in six and unilateral in two cases. Temporal bone CT scanning is therefore indicated in suspected CHARGE cases, even if they show normal hearing or a relatively good bone conduction threshold in one or both ears.

1. Introduction

Although Hall [1] was the first to describe the nonrandom association of coloboma of the eye and other anomalies, Pagon et al. [2] introduced the acronym CHARGE to indicate the association of coloboma (C), heart defects (H), atresia choanae (A), retardation of growth and/or development (R), genital hypoplasia (G) and ear anomaly (E) and/or hearing impairment or deafness. These authors proposed that the diagnosis of the CHARGE association should preferably be based on the presence of at least four of the six cardinal features, provided that these include coloboma and/or choanal atresia. Since then, many additional features have been reported in the CHARGE association, such as cleft lip/palate, facial palsy, tracheo-oesophageal fistula, cranial nerve abnormalities and skeletal abnormalities, see ref [3] for a review.

The recent finding of vestibular areflexia in the CHARGE association [3,4] agrees with previously reported temporal bone findings that indicate dysplasia or aplasia of the superior part of the labyrinth.

Over the past few years, we have seen 20 patients with the CHARGE association; they all underwent a general examination (Tables 1 and 2). Remarkably similar vestibular and temporal bone findings were obtained in two additional CHARGE-like cases (nos 21 and 22, included here for this reason), who showed all but two of the cardinal features of the CHARGE association. We were able to perform vestibular testing on the latter cases and on

nine of the CHARGE cases; the results of cases 1-6 have been reported previously [3]. CT or MR scanning of the temporal bones was possible in 12 cases, the results of which are the main subject of this report.

2. Case histories (also see Tables 1 and 2)

For the histories of cases 1-6, we refer to our previous report [3]. Below we present the histories of two additional typical cases.

2.1. Case 8

This eight-year-old girl was born after an uneventful pregnancy and normal delivery with a birth weigth of 2980 g. After a few weeks, she developed chronic obstructive pulmonary disease, for which she had to use medication for several years. Examination at 8 months of age showed severe deafness and her latest audiograms showed severe hearing impairment with thresholds at 105-115 dB. The right pinna was low-set and cup-shaped, but the left one was normal. She showed motor skill retardation: aided walking at 17 months and walking alone at 2 years. She had a normal karyotype. There were no cardiac abnormalities. Cerebral MRI showed extensive frontal and frontotemporal atrophy and hypomyelination. She underwent occlusion therapy for amblyopia in her right eye but, only recently, choroid colobomata were discovered. The right eye showed a large coloboma around the optic disc and the left eye a smaller coloboma inferior to the optic disc. Her visual acuity was 0.4 in the right eye and normal in the left eye. Her growth curve was below the 3rd percentile of normal.

2.2. Case 9

This nine-year-old girl was born after a pregnancy which had been complicated by intrauterine growth retardation, with a birth weigth of 2500 g. She had feeding difficulties. After 4 weeks she was operated on for hernia diaphragmatica.

Table 1:
Clinical findings in 20 cases with the CHARGE association and two CHARGE-like cases (marked as *)

Case no.	Coloboma Right/ Left	Heart anom-aly	Atresia choa-nae Right/ Left	Retar-dation	Genital hypo-plasia	Ear anomalies (hearing loss in all cases)
1	+ / +	-	- / -	of	?	-
2	- / -	+	+ / +	growth	+	external
3	+ / +	+	- / -	and	?	ear
4	- / +	+	- / -	motor	+	anomalies
5	- / +	+	+ / -	skill	+	present
6	+ / +	+	- / -	present	+	in
7	- / +	+	- / +	in	+	cases
8	+ / +	-	- / -	all	?	2-22
9	+ / +	-	- / -	case	+	
10	+ / +	-	- / -		?	
11	+ / +	+	+ / +		?	
12	- / -	+	+ / -		+	
13	+ / -	+	?		+	
14	+ / +	+	- / -		?	
15	+ / +	+	+ / -		?	
16	- / +	+	- / -		?	
17	- / -	+	+ / +		?	
18	+ / +	-	+ / +		-	
19	+ / +	+	- / -		+	
20	+ / +	+	- / +		+	
21*	- / -	-	- / -		+	
22*	- / -	+	- / -		+	

+, present; -, absent; ?, unknown

She had a blind microphthalmic left eye with a large choroid coloboma. Her right eye showed a smaller coloboma and a visual acuity of 0.4. She had small auricles with flattened posterior helices and triangular conchae bilaterally.

Table 2:
Audiological and oculovestibular findings in 20 cases with the CHARGE association and two CHARGE-like cases (*)

Case no. and sex	Hearing threshold (dB)		Type of hearing impairment	Oculo-vestibular indings
	Right ear	Left ear		
1 F	30/ 80[a]	90[b]	mixed	pendular nystagmus vestibular areflexia OKN sn
2 F	totally deaf	90 below 2 kHz	SNHI	vestibular areflexia OKN n?
3 F	25/ 60	25/55	mixed	vestibular areflexia OKN sn
4 F	110 below 1 kHz	110 below 2 kHz	SNHI	vestibular areflexia OKN ↑?, COR ↑?
5 F	115	125	SNHI	vestibular areflexia OKN n
6 M	115	115	SNHI	vestibular areflexia OKN n?, COR ↑
7 M	30/90	30/90	mixed	ne
8 F	105	115	SNHI	vestibular areflexia OKN n
9 F	10	totally deaf	SNHI?	vestibular areflexia OKN impaired left gaze paresis gaze-evoked nystagmus
10 M	70	80	SNHI	ne
11 M	30/60	40	mixed	ne
12 M	40/75	40/75	mixed	ne
13 M	40/65	80	mixed	ne
14 M	40	40	mixed	ne
15 F	50	totally deaf	SNHI	ne
16 F	50	90	mixed	ne
17 F	90	45	?	vestibular areflexia OKN n
18 M	90	90	?	ne
19 M	100	100	?	ne
20 F	totally deaf	totally deaf	?	ne
21 M*	totally deaf	25	SNHI	vestibular areflexia OKN n
22 M*	60	60	conductive	vestibular areflexia OKN n

[a], bone conduction / air conduction; [b], air conduction; COR, cervico-ocular reflex; n, normal;
ne, no examination; nr, no response; OKN, optokinetic nystagmus; SNHI, sensorineural hearing impairment;
sn, subnormal; ?, unknown; ↑, increased response

Brain stem auditory evoked potentials (BAEPs) showed normal responses from the right ear and absent responses on the left. Audiometry was performed at a more advanced age, which confirmed normal hearing in the right ear and total deafness in the left. Owing to transient problems with middle ear effusion, grommets were inserted three times. Extensive examinations did not show any abnormalities of her karyotype, serum amino acids levels, cardiac and renal functions and cerebral MRI. Her growth curve was below the third percentile of normal. Her motor skill development was retarded with crawling at 11 months and walking alone at 3.6 years. She started running and riding a bicycle at about 8 years of age. In addition to the above-described developmental problems and impairments, she showed retardation of speech development, for which she was sent to a school for the speech-retarded. She made good progress at this special school and could therefore be transferred to a regular school later on. Recent ultrasound examination disclosed a hypoplastic uterus and absent ovaries.

3. Patients and methods

All 22 patients had undergone general paediatric, otorhinolaryngological and ophthalmological examinations at the ENT Department of the Nijmegen University Hospital, the Institute for the Deaf in St. Michielsgestel and/or elsewhere. Chromosomal abnormalities were excluded and nearly all cases were examined by a clinical geneticist. We were able and allowed to perform vestibular examination, temporal bone CT and/or MR scanning on 12 of these cases, including the two CHARGE-like cases. This group comprised eight females and four males, aged between 2 and 47 years. Their extensive medical history was recorded, audiometry was performed and BAEPs were obtained where possible. Vestibulo-ocular testing was also performed in ten cases as previously described [3]. In 11 patients (22 ears) high resolution CT scanning of the temporal bone was conducted with 1 mm contiguous slices in the transverse plane. Direct coronal sections were not always possible because some patients required anesthesia during temporal bone CT scanning. In incidental cases, additional reformatted coronal views were made from the transverse scans. In one patient, only an MRI study was available; T1 and T2 weighted studies were made with 3 mm slices.

4. Results

4.1. General, auditory and vestibulo-ocular findings (Tables 1 and 2)

Coloboma was present in 17 cases. Heart defects were noted in 16 cases. Only nine cases showed choanal atresia. Growth retardation as well as delay in motor skill development were always present. Genital hypoplasia was absent in one case, present in 12 cases and undetermined in nine cases. Given the fact that our cases comprised a selected sample (all had been referred to the Institute for the Deaf or to the paediatric audiological unit of an ENT department), it was to be expected that they all showed hearing impairment. Recurrent otitis media was noted in 13 cases.

The additional features of the CHARGE association comprised swallowing/feeding difficulties in 13 cases, cleft lip/palate in ten and facial nerve paresis in seven, combined in one of them (case 7) with ipsilateral abducens paresis. There were three cases with oesophageal atresia, one of whom also had a tracheo-oesophageal fistula. Polydactyly was found in one case.

Central abnormalities were present in at least nine cases. Hydrocephalus was found in case 2, who had aqueductal stenosis, as well as in case 8. Case 9 showed abnormal ocular motor responses: gaze paresis (i.e. slowing of conjugate saccades) to the left, hypometria of leftward saccades and gaze-evoked nystagmus, which was more pronounced to the left (with an exponential slow phase) than to the right and impaired OKN/SP responses. These findings were compatible with (vestibulo)cerebellar and pontine dysfunction and were most prominent on the left side. However, MR images were normal. It may have been relevant that unilateral deafness also occurred on the left. There was no facial nerve palsy. Case 10 had microcephaly. Cerebral atrophy was seen on the MRI in case 12 and in case 8, who also showed evidence of dysmyelination but had normal ocular motor responses. In the CHARGE-like case no. 21, MRI revealed cavum septum pellucidi et Vergae and periventricular cysts; this case had neonatal hyperbilirubinaemia and showed palsy of the cranial nerves VI, VII and XII on the right and VI on the left. Apart from the VIth cranial nerve palsy that had previously led to the diagnosis of Möbius' syndrome, ocular motor responses were normal.

Table 3.
Temporal bone CT / MRI findings in ten cases with the CHARGE association and two CHARGE-like cases (*)

Case no	Mastoid	Ossicles	Oval window	Cochlea	Vestibule	SCCs	Vest aqueduct
1	normal	normal	obliterated bilaterally	Normal	small on both sides	absent bilaterally	not visible right, short left
2	bilaterally decreased pneumatization	bilateral small incus body	obliterated bilaterally	normal turns, large basal turn	small on both sides	absent bilaterally	short
3	bilaterally decreased pneumatization	fixed malleus head bilaterally	obliterated bilaterally	Dysplasia both sides, 1 5 turns	small on both sides	absent bilaterally	short
4	normal	bilateral small incus body	obliterated bilaterally	Dysplasia both sides, 1 5 turns	small on both sides	absent bilaterally	not visible
5	bilaterally decreased pneumatization	deformed incus body on both sides	obliterated bilaterally	Dysplasia both sides, 1 5 turns	small on both sides	absent bilaterally	not visible
6 (MRI)	-	-	-	Hypoplastic	normal	absent bilaterally	-
7	normal	deformed ossicular chain, fixation	obliterated bilaterally	Dysplasia both sides, 1 5 turns	small on both sides	absent bilaterally	not visible
8	normal	abnormal incus body, ring-like ossification	obliterated bilaterally	Dysplasia both sides, 1 5 turns	small on both sides	absent bilaterally	short
9	bilaterally decreased pneumatization	normal	obliteration right, fistula left	Normal	normal	absent bilaterally	not visible
20	bilaterally decreased pneumatization	normal	normal left, obliterated right	Dysplasia both sides	small on both sides	absent bilaterally	normal
21*	normal	normal	obliterated bilaterally	normal left side, dysplasia right, 1 5 turns	small on both sides	absent bilaterally	not visible
22*	normal	normal	obliterated bilaterally	normal right side, dysplasia left, 1 5 turns	normal	absent bilaterally	normal

Case 17 showed central and cortical atrophy as well as hyperostosis and an asymmetrical neurocranium. The CHARGE-like case 22 showed ventriculomegaly and suffered from epilepsia for several months; ocular motor responses were normal. The CHARGE case 5 also had transient epilepsia.

4.2. Temporal bone CT findings in relation to other findings (Tables 2 and 3, Figs 1-4)

Bilateral absence of the semicircular canals (SCCs) was noted in all the cases in whom vestibular areflexia was assessed and in two cases without vestibular evaluation (Tables 2 and 3). The vestibule was diminished in size in most cases (Figs 1-3). The internal auditory canal was bilaterally normal (Fig. 2) in 11 cases, but narrow in one (Fig.1). The cochlea was hypoplastic (Fig. 3) in many cases. Although there were only 1.5 turns present (Fig. 3) in 7 cases, the typical combination with a wide basal turn that constitutes Mondini's deformity was only found in cases 3 and 21 (a CHARGE-like case). Surprisingly, case 3 had cochlear dysplasia combined with close to normal bone conduction thresholds on both sides. The CHARGE-like case 22 had symmetrical conductive loss, but the cochlea was normal only on one side. In case 9, the cochlea was normal bilaterally, but hearing was normal only on the right side. As noted above, there may have been a retrocochlear cause for the hearing impairment on the other side in this case.

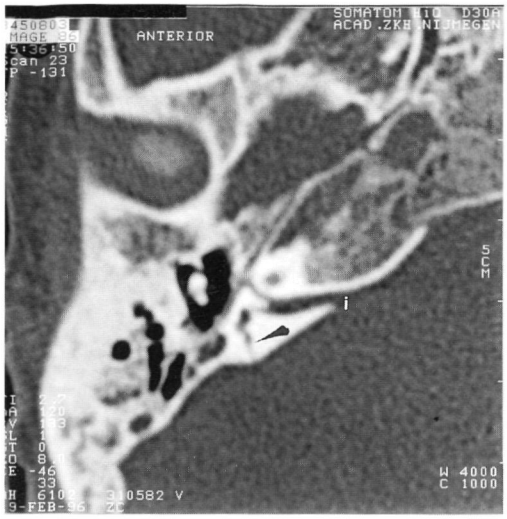
The external meatus was bilaterally normal in eight, but too wide in two of the evaluated cases (Figs 1 and 3).

The Eustachian tubes had a normal shape in eight cases, but were wide in one of the ten evaluated cases.

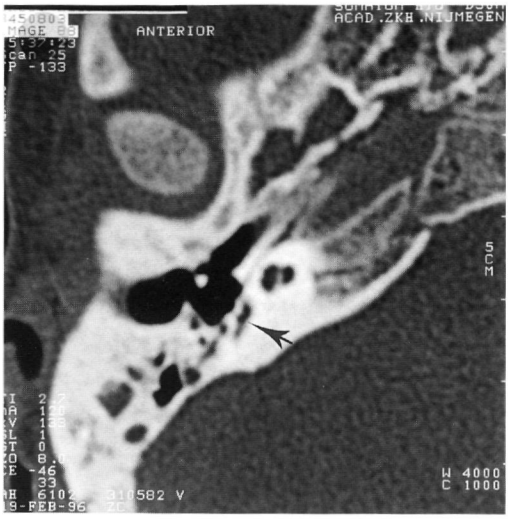
The facial nerve canal showed a normal course and size (Fig. 2) bilaterally in the six cases evaluated.

Pneumatization arrest (Figs 2 and 4) was present in several cases, which presumably correlates with the high prevalence of recurrent otitis media with effusion. Aberrant veins were noted in the left mastoid of case 3.

Ossicular chain malformation (Figs 1,3,4) was observed in six out of the 11 evaluable cases, as well as bilateral obliteration of the oval window (Figs 1,3,4) in all the evaluable cases.



(A)



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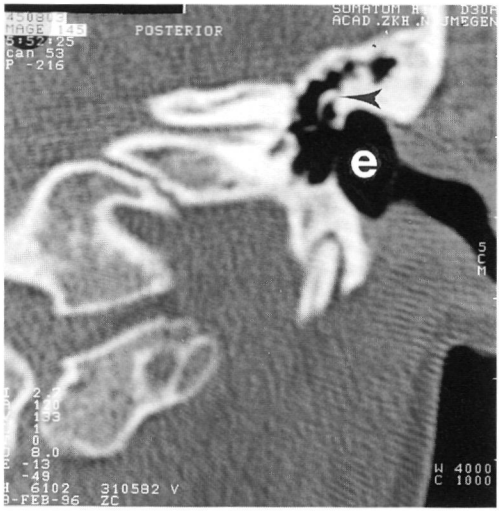


(C)

Figure 1. (Case 2)
Axial (A and B) and coronal (C) sections of the left (A and B) and right (C) ear. Section A at the level of the internal meatus and facial nerve canal, B a little lower at the level of the oval window. (A) The vestibular aqueduct is visible and short but not enlarged (arrow head). Narrow internal meatus (i). The incus body is small, the vestibule is small, the SCCs are absent. (B) The very small vestibule has an obliterated oval window (arrow). (C) Extremely wide external meatus (e) and hypoplastic body of the incus (arrow head).

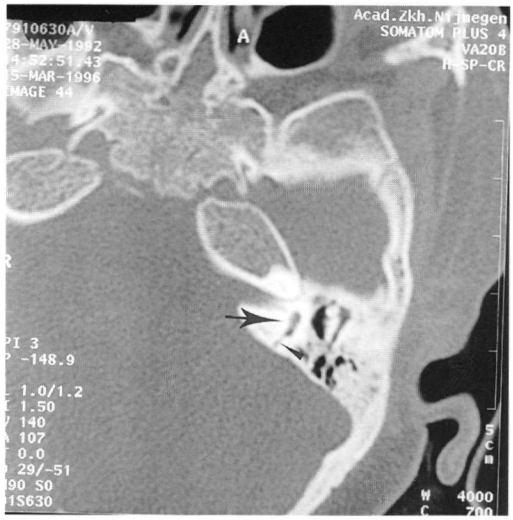


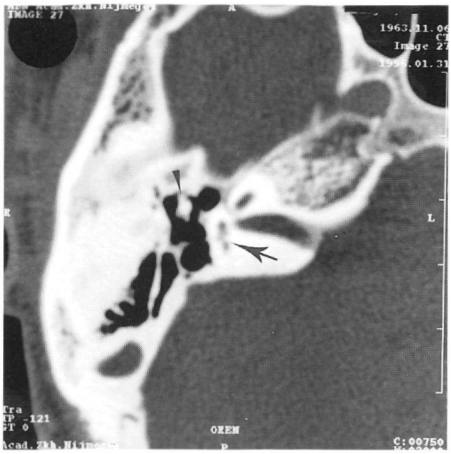
Figure 2. (Case 3)
Axial 1 mm section of the left ear at the level of the internal meatus and facial nerve canal which are both normal. The vestibule is small (long arrow) and there are no SCCs visible. At this level no abnormalities of the ossicular chain can be noted. The vestibular aqueduct is visible and short but not enlarged (arrow head). There is decreased pneumatization of the mastoid.

The round window was described as bilaterally normal in nine evaluable cases. It seems that most, if not all, of these cases whose hearing capacity could be evaluated, had a mixed (or conductive) type of hearing impairment. It was remarkable that despite the obliteration of the oval window, there was only limited conduction impairment in case 3 (30-35 dB), no apparent air-bone gap at all (?) in the right ear in case 9 or in the left ear in case 21 (CHARGE-like).

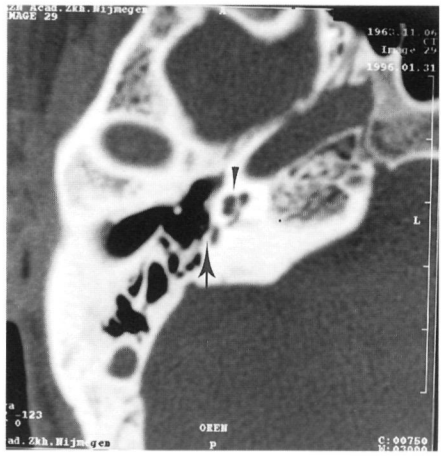
5. Discussion

5.1. General, temporal bone and vestibular findings

Delayed motor skill development and vestibular abnormalities are not uncommon in congenitally deaf children [5-10]. If a child has complete vestibular areflexia, caused by absence of the SCCs, as was documented in our cases with the CHARGE association, motor skill retardation can certainly be expected to occur [3,4].



(A)



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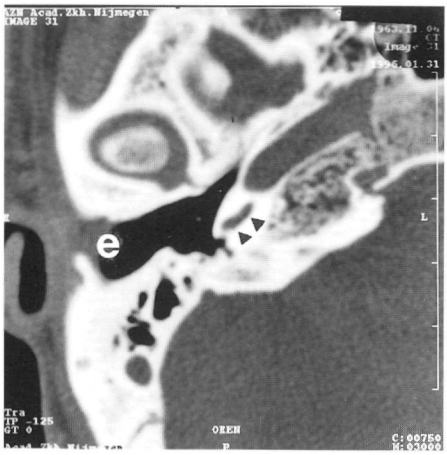

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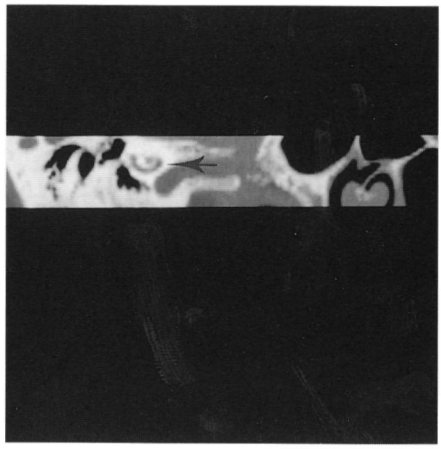

(D)

Figure 3. (Case 4)
Axial sections from cranial to caudal (A,B and C) and parasagittal reformatted image (D) of the right ear.
(A) Level as in figure 1A. Small incus body (arrow head), almost absent vestibule (arrow) and absent SCCs.
(B) Section at the level of the oval window, which is obliterated (arrow) and the cochlea at the level of the modiolus (arrow head). In a normal cochlea, three turns of the same size can be seen at this level, but in this dysplastic cochlea only two turns are visible, one of which is too large, while the other is of normal size.
(C) The basal turn of the cochlea is normal (small arrows), the external meatus too wide (e).
(D) Reformatted parasagittal section - only 1.5 turns of the cochlea are present (arrow).

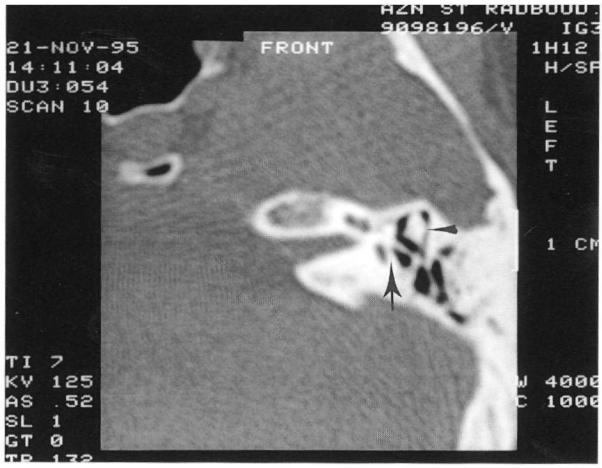

Figure 4. (Case 5)
Axial section of the left ear. Bony obliteration of the oval window (arrow), deformed body of the incus (arrow head) and decreased pneumatization of the mastoid (m).

This is a strong indication for educational support, as elaborated on previously [3]. The presence of central abnormalities as noted above and elsewhere [11,12] may be an additional indication for such support.

As already reviewed in our previous report [3], prior histopathological studies have assessed the absence of SCCs in patients with the CHARGE association [13,14]. Paparella and ElFiky's [15] first case, who was suggested to show Mondini's dysplasia, in fact represents a case of absent SCCs combined with the relevant features of the CHARGE association.

In patients with congenital sensorineural hearing impairment (SNHI) in general, radiological abnormalities of the inner ear have been reported in a range from 13-20% [16-18], to about 80%, or less when more tolerant normal values were used [19]. The most common findings were a short and wide lateral SCC, a wide vestibule, a short and wide vestibular aqueduct and Mondini's dysplasia [16,19]. Absence of the lateral SCC was observed in only 7% of the cases reported on by Jackler et al. [16], while Pappas et al. [19] mentioned this finding without any further specification. In a series of patients with external ear malformations, some of which could be attributed to branchial arch syndromes and/or maternal use of thalidomide during pregnancy, a short wide lateral SCC was also the most frequent abnormality [20]. Parnes and Chernoff [21] described 2 cases with bilateral SCC aplasia with (almost) no cochlear involvement; they claimed to be the first to report such a combination

of findings. Both patients had bilateral conductive hearing impairment due to congenital middle ear malformations, while one of them had a slit-like external auditory canal on one side; one patient showed mental retardation. Our cases 21 and 22 also showed bilateral SCC aplasia. As these cases lacked the cardinal features of coloboma and choanal atresia, they did not fulfil the criteria for the CHARGE association, but nevertheless showed considerable similarity. These findings may raise the question of whether the clinical findings or the radiological findings are more important in establishing the diagnosis, especially in CHARGE-like cases.

Murofushi et al. [4] recently described temporal bone CT findings in five cases with the CHARGE association, which consisted of complete aplasia of the SCCs in all cases. Tellier et al. [22] found aplasia of the SCCs in all 12 cases with CT scans, with total aplasia in six and partial aplasia also in six cases. Our findings in ten cases confirm these findings. Remarkably, as in Murofushi et al.'s [4] case 1, two of our patients had (almost) normal hearing on one side, while the CT scans showed complete bilateral aplasia of the SCCs. In contrast with Murofushi et al. [4], we found no widened vestibules; on the contrary, the vestibules were small in most of our cases. We found only one case (no. 3) with (possible) enlargement of the vestibular aqueduct; if it was visible in our cases, it was shortened.

Some previously reported studies showed a lack of radiological details or failed to diagnose the CHARGE association. Shusterman et al. [18] (page 502) included a CHARGE case in their table with the CT finding of "Bilateral congenital anomaly of the semicircular canals". Tsuzuku and Kaga's [10] case 1 had bilaterally absent SCCs; the presence of the features of growth/developmental retardation, bilateral profound hearing impairment, choanal atresia and a cardiac defect were already sufficient for the diagnosis of the CHARGE association. Morgan et al. [23] described deformed or absent SCCs in 90% (23 out of 26) of their CHARGE cases without specifying the type of deformities or the number of cases in the relevant categories. They mentioned the occasional finding of `a small stump of dilated semicircular canal' (page 50).

Obliteration of the oval windows was a prominent finding in the present study, but we found this feature mentioned in only two previous reports [22,23]. Morgan et al. [23] reported it in about half the proportion of cases with abnormal SCC findings and Tellier et al. [22] in two out of 11 cases. An absent oval window was also reported in previous histopathological studies [13,14,24].

Cochlear dysplasia was found in the majority of our cases, although only two cases clearly had Mondini's deformity. The latter abnormality was found in one of the cases described by Murofushi et al. [4], who also described finding small but complete cochleas, hypoplasia without widening as well as widening without hypoplasia in proportions fairly similar to ours. Tellier et al. [22] found Mondini's deformity in four out of the 12 cases with CT scans and Morgan et al. [23] in half the proportion of patients with abnormal SCC findings. Histopathology reports described Mondini's deformity [13,14] (case 4) or cochlear hypoplasia [24].

Malformed ossicles were noted in the majority of our cases. In the study by Morgan et al. [23], a hypoplastic incus was as prominent as their abnormal SCC findings, which may be fairly similar to the present study, although the latter indicates a broader range of ossicular abnormalities. Murofushi et al. [4] mentioned abnormal (bilaterally hypoplastic) ossicles in only one case, while Tellier et al. [22] reported finding a hypoplastic incus in one out 11 cases. Ossicular chain anomalies were also described in some temporal bone reports [14,24].

The frequent ossicular chain anomalies encountered in our study and the apparently ubiquitous obliteration of the oval windows form sufficient reason to expect a mixed type of hearing impairment in patients who can be evaluated, i.e. those who do not have severe deafness. In patients with severe SNHI, bone conduction thresholds cannot be established in a reliable way. Furthermore, audiometry in these patients is often difficult to perform. Severe mixed hearing impairment therefore cannot be always ruled out. Mixed hearing impairment was indeed a frequent finding in the present study and in previous studies on the CHARGE association (see Ref. [3] for review). In the light of the oval window abnormalities and the frequent finding of ossicular chain anomalies, it is difficult to explain why in some cases the apparent air-bone gap was only small (case 3, bilaterally), or even lacking (cases 9 and 21, unilaterally). These observations seem to contradict our knowledge and understanding of

sound conduction mechanisms relating to the middle ear.

5.3. Speculating about the syndromology of the CHARGE association

There seems to be some overlap between the hereditary Kallmann syndrome and the CHARGE association. Cortez et al. [25], Levy and Knudtzon [26] and Klein et al. [27] described cases with Kallmann syndrome, who also showed clinical findings of CHARGE association. Recently, Hill et al. [28] described two isolated patients with Kallmann syndrome and radiological evidence of aplasia of the SCCs. On the other hand, Pagon et al. [2] and Lin et al. [12] reported olfactory tract abnormalities in CHARGE patients. So there seem to be considerable similarities between the Kallmann syndrome and the CHARGE association. Both disorders are probably caused by defective neural crest cell migration [25,27,29,30]. The Kallmann syndrome and the CHARGE association may represent different subtypes of one single developmental disorder, or they may constitute two different entities. Perhaps aplasia of the SCCs together with obliteration of the oval windows, as seen in CHARGE association, are distinguishing features. If so, this can be important in genetic counseling. This also applies to CHARGE-like cases who show a close phenotypical resemblance, but do not meet the current criteria for establishing the diagnosis. We therefore recommend performing temporal bone CT scanning on all suspected CHARGE or CHARGE- like cases, as well as vestibular testing, if possible, regardless of the patient's hearing ability. This may be important, not only to outline the contours of any possibly related disorders (or perhaps the diagnostic overlap between them) but also for the purpose of educational/developmental counseling.

6. Acknowledgements

Numerous colleagues, paramedical and education workers employed at our hospital, other hospitals and the Institute for the Deaf contributed to the evaluation of our cases. We wish to thank Mrs H Brink, M Broesterhuizen, JPM Brokx, GJA Janssens Capriles, GJMEN Timmerman, AHF van Olphen, JPM van Dijk, MGM Nicolasen, H Meys, AFM Snik, B Hamel and Mrs CC Hoekstra and A Dona for performing the paediatric, ophthalmological, audiological and oculo-vestibular examinations, neuropsychological assessment and

physiotherapeutic evaluations. We also wish to thank the patients and their parents for their cooperation in this study.

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Chapter 4

Audiovestibular sequelae and cytomegalovirus infection

Chapter 4.1

Audiovestibular sequelae of congenital cytomegalovirus infection in 3 children presumably representing 3 symptomatically different types of delayed endolymphatic hydrops

P.L.M. Huygen and R.J.C. Admiraal

International Journal of Pediatric Otorhinolaryngology
1996; 35: 143-154

Abstract

Three cases of congenital cytomegalovirus (CMV) infection with long-term audiovestibular sequelae are presented. Case 1 had no hearing in one ear and severe progressive hearing loss in the other ear; he showed vestibular symptoms at the age of 4.5 years. Case 2 had severe but stationary hearing loss in one ear and showed hearing impairment symptoms in the other ear at 9-13 years of age. Case 3 did not have hearing impairment symptoms, or vestibular symptoms, but was found to have severe progressive hearing loss from the age of 15 months onwards, which led to profound deafness at the age of 2 years and vestibular areflexia at or before the age of 4 years. These cases may represent 3 symptomatically different types of delayed endolabyrinthine hydrops. Type 1 (ipsilateral hydrops) incorporates vestibular symptoms only because of a lack of hearing in the offending labyrinth. Type 2 (contralateral hydrops) incorporates hearing impairment symptoms only because of a lack of vestibular function on both sides and type 3 does not incorporate hearing impairment symptoms or vestibular symptoms (other than those relating to a complete lack of function). Given the present findings, those described by Weiss and Ronis (Trans Pa Acad Ophthalmol Otolaryngol 1977; 30: 52-54) in one case and other reported findings relating to histopathological or imaging methods in somewhat similar cases, it seems appropriate to include congenital CMV infection in the differential diagnosis of delayed endolymphatic hydrops.

1. Introduction

During the last number of years evidence has accumulated which indicates that cytomegalovirus (CMV) infection is an important cause of viral induced congenital sensorineural hearing loss (SNHL) [14,16,33,37] and it has been suggested [33] that it has become increasingly important following the introduction of immunisation against rubella. Congenital CMV infection has been reported to account for at least one third of SNHL in young children [16]; in Sweden, it has been found to be the most common identifiable cause of SNHL, accounting for 40% of infant cases [14]. CMV is a DNA virus of the herpes virus group which can produce characteristic changes in infected cells that finally lead to cytolysis. Light microscopy shows that infected cells become exceptionally large and have intranuclear

and cytoplasmatic inclusions. Electron microscopy demonstrates that the inclusion bodies within the nucleus consist of viral particles in a chromatin matrix. The congenital form of CMV infection, which is symptomatic at birth, is called cytomegalic inclusion disease (CID). CID may cause a low birth weight and prematurity, microcephaly, chorioretinitis and psychomotor retardation. Additional findings may include jaundice, petechiae, purpura and hepatosplenomegaly [1,4,8,11,42,45-47,51]. Prospective studies have shown that a number of sequelae develop in a proportion of the children with CID, of which SNHL appears to be the most frequent [12,33,41,45]. SNHL has been detected in 20% to 65% of children with CID (see [35,46,47] for references). It has been detected more often in children with symptomatic infection (33-48%) than in children with asymptomatic infection (7-25%) [35,36,42]. Primary maternal infection during pregnancy was associated with more severe (hearing) sequelae [12,24]. Saigal et al. [36] did not detect progressive SNHL but Stagno et al. [42] indicated that in about 25% of the children followed, hearing impairment had either developed or become more severe after the first year of life. Strauss [46] also detected progressive SNHL in 3 children in a prospective study on 6 children with CID. Dahle et al. [6], Newton and Rowson [31] and Hickson and Alcock [17] reported significant deterioration in the hearing of children with congenital CMV within the first 4 years of life. Williamson et al. [49] demonstrated that children with asymptomatic congenital CMV infection may also show progressive SNHL. Connolly et al. [5] recently reported abnormal dichotic speech perception test results in children with asymptomatic congenital CMV and normal pure-tone audiograms, which might have been caused by severe periventricular encephalitis, which is known to lead to microcephaly in survivors [7]. Kumar et al. [24] and Johnson et al. [21] did not find any hearing abnormalities in postnatally infected children.

As far as we know, the studies by Pappas [32] and Strauss [46] were the only ones on children with CMV that included vestibular examination. Pappas [32] evaluated caloric responses in 6 children with subclinical CID that caused SNHL and found bilateral normal function in 3, unilateral hypofunction in 1 and bilateral hypofunction in 2 children. He found more caloric abnormalities in a group of 5 children with symptomatic CID but normal hearing; only 1 had bilateral normal function, 2 had unilateral hypofunction and 1 showed bilateral areflexia. He did not mention any vestibular symptoms. Strauss [46] performed a longitudinal study on 6 children with symptomatic CID, 3 of whom showed SNHL. In one

child, brain stem auditory-evoked potentials (BAEPs) revealed elevated thresholds at 1 month of age; the hearing threshold increased over the first year of life (to beyond 90 dB SPL); caloric tests showed minimal responses bilaterally at 1 year and 2 years of age. The two other children showed mild SNHL on one side and moderate to severe SNHL on the other side, which progressed to deafness between the ages of 4 years and 7 years, whereas at the same time, they developed caloric areflexia on the same side. Clinical vestibular symptoms did not correlate with these findings in any of the children.

A recent high-resolution CT study of the temporal bone demonstrated Mondini-type dysplasia in a child with symptomatic CMV infection and severe SNHL. Other malformations or abnormal dimensions of labyrinthine structures were detected in some of the other children with congenital CMV and SNHL [3].

Temporal bone studies revealed endolabyrinthitis with inclusion bodies in non-neuroepithelial cells in both the cochlear and the vestibular parts of the labyrinth, with some differences in severity between these separate parts ([46,47] and references). Labyrinthine hydrops was noted in 2 temporal bone reports [29,34] with extensive damage to the neuroepithelia in the most recent report.

Weiss and Ronis [48] presented a report on a patient previously diagnosed as having CID and severe bilateral SNHL. As a young adult, at the ages of 19 and 21 years, he had developed vestibular symptoms which were attributed to postinflammatory (delayed) hydrops. Strauss [46] commented that `it is unlikely that hydrops, which is felt to require many years to evolve, would produce symptoms in congenitally infected CMV infants and children'. However, an analysis of previous reports on delayed endolymphatic hydrops (see Discussion) shows that a shorter lapse of time may suffice.

The first case in this report is a 4-year-old boy with congenital CMV infection and profound (although asymmetrical) bilateral SNHL, who developed severe attacks of vertigo. Our second case concerns a boy with congenital (or perinatal?) CMV infection and unilateral profound SNHL, who developed progressive SNHL in the other ear from the age of about 7 years to 13 years in the absence of any vestibular function. Our third case is a 4-year-old girl whose hearing loss was detected at about 1 year of age and thereafter was found to be rapidly progressive. She did not start walking until the age of 28 months and was found to have vestibular areflexia at the age of 4 years. Delayed endolymphatic hydrops, presumably of 3

symptomatically different types, offers a plausible explanation for the findings in our cases.

2. Case histories

2.1. Case 1

This boy was the product of an uncomplicated pregnancy and a normal delivery. Shortly after birth he showed petechiae all over his body and laboratory examinations revealed thrombocytopenia and an increased serum CMV IgM antibody titre (1:128). He soon recovered from the thrombocytopenia and 6 months later, the serum CMV antibody titre was normal, which suggests that he had sustained an intra-uterine infection with CMV and probably had CID. The child showed delayed psychomotor development: he was floppy on examination at the age of 1 year and behaved clumsily at 2 years of age. He first started walking at the age of 18 months. CT scans revealed a porencephalous cyst in the left frontal lobe which seemed to increase somewhat in diameter on follow-up. SNHL had already been suspected 1 month previously, but after his third birthday, he suffered sudden deafness bilaterally. He was referred for observation to our out-patient department for hearing-impaired children: his left ear was almost completely deaf and his right ear showed moderate to severe hearing loss which gradually increased. He attended a school for the hearing impaired (first in Arnhem, later in Eindhoven) from the age of 4 years onwards; shortly after his 4th birthday, he began having episodic vertigo and from the age of 4.5 years onwards he suffered several attacks of severe vertigo per week, unsteadiness ('ataxia') with nausea and vomiting, after which he slept for several hours. EEG examination was not contributory. He underwent his first vestibular examination (see below). A few hours after the examination, he was observed while having an attack. Episodic vertigo gradually abated over the next few months and was absent at the age of 5.5 years.

2.2. Case 2

After a pregnancy with recurrent episodes of pyelitis, this boy was born via a normal delivery. Postnatal examination showed a dystrophic infant with hepatosplenomegaly and

hydrocele on the right, for which surgery was performed at the age of 2.5 months. Preoperative examination revealed anaemia (Hb 5.5 mmol/l), abnormal serum liver function values and CMV viruria. The diagnosis was congenital (or perinatally acquired?) CMV infection. Liver function tests had normalized at the age of 2 years but became abnormal again after hepatitis A infection at the age of 7 years. He showed left hemiplegia, a general delay in motor development from the age of 1 year onwards and delayed speech development. CT scans revealed hydrocephalus with cavum Vergae. He had severe but stationary hearing loss in the right ear and suffered sudden deafness in the left ear at the ages of 9 years and 13 years.

2.3. Case 3

This girl was born via a normal delivery after a pregnancy of 38 weeks, during which the mother sustained a CMV infection. After birth she had been hospitalized elsewhere for 4 weeks and found to be dystrophic with hepatosplenomegaly, abnormal liver function, normal pressure hydrocephalus, microcephaly and petechiae. The newborn infant had become icteric within 24 h and during the first few days of her life, she developed thrombocytopenia and was found to show CMV viruria. Serological tests did not show any clear increase in the CMV IgM antibody titre, but total CMV antibodies were positive. There were no ocular or cardiac abnormalities and EEG findings were normal. At the age of about 1.5 years, she was again hospitalized because of a risk of dehydration and a viral infection of the mouth and upper airways. By that time, she was already suspected of having hearing impairment. Grommets were placed because of bilateral otitis media. She showed a general developmental delay and had not started walking until the age of 28 months. At the age of 18-24 months, she was followed at our out-patient department for hearing-impaired children and, because of our findings and advice, was placed at the Institute for the Deaf at St.-Michielsgestel at the age of 3 years 3 months. She never showed any symptoms of dizziness.

3. Methods

Audiograms were obtained using a clinical audiometer in a sound treated room and BAEP

examination was performed as described previously [19]. Eye movements were recorded with d.c. electronystagmography (ENG). Calibration saccades were obtained by having the patient look in alternation at light dots at 10° lateral from the primary position. Gaze positions were examined with targets at 30-40° lateral positions. Smooth pursuit (SP) eye movements were elicited with a light dot moving sinusoidally at 20°/s maximum (horizontal) velocity. Optokinetic nystagmus (OKN) was elicited by a shadow-projected pattern of stripes (7.5° width and separation, hemicylindrical screen covering a visual field of 90 x 50°) moving at 40°/s and 60°/s constant velocity. Spontaneous nystagmus, i.e. slow phase velocity (SPV) > 6°/s, was monitored in the dark with the eyes open. In the same condition, vestibular responses were evaluated, which were elicited with a rotatory chair (Toennies, Freiburg im Breisgau, Germany) using velocity step (VS) tests of 90°/s (after 0.8°/s^2 acceleration and 200°/s^2 deceleration). Postrotatory nystagmus was analyzed with a computer as previously described ([20]; response parameters and age-dependent normal limits below). Caloric tests (details below) were performed in one case. Cervico-ocular reflex (COR) responses were obtained (only in one case with vestibular areflexia) with the head fixed, the body moving sinusoidally at 0.1 Hz with 60° peak-to-peak amplitude. The responses were evaluated by measuring the eye velocity gain or the eye position gain (cumulated eye position angle per hemicycle divided by 60°) and comparing the values obtained to previously established normal values [18].

4. Results

4.1. Case 1

4.1.1. Hearing (age 3-6 years).

Thirteen audiograms were obtained. The left ear showed a threshold (at 0.5-4 kHz) of about 100 dB hearing level (HL) and higher at the age of 3 years, which progressed to about 120 dB HL 1 year later and could no longer be measured 1 month later and thereafter. The right ear showed a threshold of about 55 to 75 dB at 0.5 to 4 kHz (with normal BAEP findings) during the third year of life, which had increased to about 85-115 dB by the age of 4 years and remained stationary during a 2-year follow-up period.

4.1.2. Oculomotor and vestibular examination (age 4.5 years).

Saccades, SP and OKN responses were normal. There was no gaze-evoked nystagmus. Spontaneous nystagmus to the right (SPV 9°/s) was noticed. The VS responses with right-beating postrotatory nystagmus showed a low initial velocity and a short response superposed on persistent nystagmus to the right. After correction for spontaneous nystagmus, we found a significantly low initial velocity (V20°/s, P5 normal limit V > 50°/s according to ref. [18]), a presumably normal time constant (T 6 s, normal T < 8 s) and a significantly low *Gesamtamplitude* (cumulative eye displacement, G 120°, normal G > 1000°). The left-beating response showed only 2 nystagmus beats (maximum SPV 45°/s) and a rapid decline in the response (T 1 or 2 s) with nystagmus reversal as early as 5 s. These findings were consistent with severe vestibular hyporeflexia, close to areflexia. Some hours after this examination, the boy returned to our Department because he was having an attack of vertigo with nausea and vomiting. We observed (in full light) vigorous spontaneous nystagmus beating to the left with major torsional (cycloversional) components. The boy looked very pale and ill; he vomited and was photophobic. Six weeks later, a repeat examination was performed with ENG. Spontaneous nystagmus to the right (SPV about 15°/s) was found. No response could be obtained on either side after caloric irrigation with tap water (24°C) for 20 s (150 cm^3).

4.2. Case 2

4.2.1. Hearing (age 7-13 years).

Twenty audiograms were obtained. The hearing threshold for the right ear was about 75 to 110 dB at 0.5-4 kHz throughout the observation period. The left ear showed a flat threshold at about 20 dB between age 7 years and 9 years. After sudden deafness (with tinnitus), the threshold was somewhere between 40 and 60 dB until the age of 12.5 years, when his hearing further deteriorated and threshold values of between 100 and 120 dB (or even worse) were measured, which improved in a few months time with prednisone treatment to a level of some 80-90 dB.

4.2.2. Oculomotor and vestibular examination (age 13 years).

Saccades, SP and OKN responses were normal. There was no spontaneous or gaze-evoked nystagmus. The VS test showed vestibular areflexia. The COR showed similar enhancement to that generally found in patients with vestibular areflexia [18].

4.3. Case 3

4.3.1 Hearing (age 1-2 years).

A Ewing test showed responses at about 70-90 dB HL at the age of 17 months. At the age of 18 months, BAEPs were found at 70-75 dB HL stimulation of the right ear, but could not be obtained from the left ear because of movement artefacts. ECoG/BAEP examination under general anaesthesia at 27 months of age failed to show any responses to stimuli of up to 100 dB HL.

4.3.2 Oculomotor and vestibular examination (4 years).

Saccades, SP and OKN responses were normal. There was no spontaneous or gaze-evoked nystagmus. The VS test demonstrated vestibular areflexia.

5. Discussion

5.1. Case 1

Case 1 showed vestibular symptoms not previously reported in cases with congenital CMV infection or CID, i.e. without any (further) hearing impairment symptoms (such as those described by Weiss and Ronis [48]). The vertigo attacks were reminiscent of the attacks experienced by patients with active Ménière's disease that can be attributed to labyrinthine hydrops. In classical Ménière's disease, it has been said that there can be ipsilateral, 'irritative' nystagmus. Jung and Kornhuber ([22], p.456) wrote: '...during Ménière attacks we have in some cases seen ipsilateral spontaneous nystagmus at the onset of attacks of vertigo, apparently as an irritative phenomenon.' McClure et al. [28] have questioned such

observations on account of their ENG monitoring findings, but recent recordings at the very beginning of an acute vertiginous attack demonstrated shortlived `irritative' nystagmus that was beating towards the compromised labyrinth and was soon followed by contraversive 'paralytic' nystagmus [2]. The (less intense) ipsiversive nystagmus which is usually found at later intervals, is interpreted as `recovery' nystagmus [28] *(Erholungsnystagmus* according to Stenger [43]*)*. The left-beating nystagmus observed in our case during the attack, which was followed by right-beating nystagmus, may be interpreted as: (1) paralytic nystagmus (thus indicating a deficit on the right) followed by recovery nystagmus, or (2) irritative nystagmus (indicating irritation of the left labyrinth) followed by paralytic nystagmus (deficit on the left). Because hearing impairment symptoms were lacking during the attacks of vertigo, it seems likely that the left labyrinth, in which no hearing impairment symptoms could be elicited, was involved. This favours the second of the above interpretations. According to Strauss [46], most infant temporal bone studies showed only mild infection of the vestibular labyrinth. However, some studies revealed extensive vestibular endolabyrinthitis or hydrops [9,29,34]. Strauss [46] wrote that children with CMV infection.. 'may have CMV viruria for several months to years.' (also see [34,35,44]); children with progressive SNHL may have 'active infection with cell lysis and other forms of cell damage may continue to occur in the labyrinth at the same time.' Another possibility, which may apply especially if there are no signs of active infection, is the development of postinflammatory hydrops as proposed by Weiss and Ronis [48] to explain the findings in their patient. Their patient suffered attacks of vertigo and tinnitus with further hearing loss and was found to have 'calorics - depressed bilaterally (absent on right)' and spontaneous left-beating nystagmus. Reference can be made to delayed endolymphatic hydrops which Schuknecht [38] explained as being the result of the (much earlier) infection. Relevant histopathological findings have been reported recently in 2 cases with presumed viral labyrinthitis and delayed endolymphatic hydrops in the contralateral ear [40] (contralateral type, see below). As commented on by Strauss [46], too little time may have elapsed for such delayed development in the present case of a 4-year-old child. However, the study by Nadol et al. [30] included 2 cases with an estimated delay of only 1-2 years. These authors also presented a case with a delay of 6 years, whereas Wolfson and Leiberman [50] reported on 5 cases with a delay of 6-9 years (see the surveys [25, 26]).

5.2. Case 2

There are some indications that case 2 may have had congenital CMV rather than a perinatally acquired CMV infection, although, unfortunately, virus excretion was not found before 2.5 months. Arguments in favour of this are firstly that healthy term babies who acquire CMV infection rarely show acute symptoms or develop long-term sequelae [24]. Secondly, premature and ill term infants, who commonly show acute signs and symptoms of perinatally acquired CMV infection, do not show a significant increase in long-term hearing impairment sequelae ([21] and references). In case 2, delayed hydrops of the left labyrinth, i.e., the labyrinth contralateral to the (almost completely) deaf right ear, is also a plausible explanation for our findings. Schuknecht [38] specified the contralateral type of delayed endolymphatic hydrops as: (1) profound hearing loss and (2) the subsequent development of 'fluctuating hearing loss, also sometimes with episodic vertigo, in the opposite ear.' The apparent difference between our case 1 and the case reported by Weiss and Ronis [48], i.e. the lack of vestibular symptoms in our case 2, can be readily explained by the complete lack of peripheral vestibular function combined with (initially) functional hearing in the offending labyrinth. The boy might have had 'Ménière-like' attacks, however, without being able to feel any dizziness. Schuknecht [38] reported on similar cases. Given the obervation of well-developed COR enhancement in this boy [18] found at the age of 13 years (3 months after complete loss of hearing in the left ear, see above) and the observation made by Dichgans et al. [10] that similar enhancement took about 3 months to develop after bilateral labyrinth-ectomy in the monkey, we cannot conclude whether the vestibular areflexia in case 2 was already present before complete hearing loss or whether it developed simultaneously. However, the lack of any vestibular symptoms associated with complete (unilateral!) deterioration in hearing, suggests that vestibular areflexia was pre-existent.

5.3. Case 3

SNHL proved to be rapidly progressive in the first 2 years of life. There were no symptoms that could be attributed to fluctuations in inner ear function. This does not exclude the

possibility that such fluctuations had occurred, but the symptoms may have been obscured because of the existing severe impairment. Vestibular areflexia had presumably already occurred before she started walking at 28 months and it may have been completed by that time. Fluctuating hearing loss might have occurred in the age range of 17 - 27 months, in which the hearing threshold increased from some 70-90 dB to more than 100 dB, but it could have escaped our attention. This case was fairly similar to the child who was followed for the first 2 years of life by Strauss [46] (see Introduction). Our presumption that endolabyrinthine hydrops was the underlying cause for the (progressive) inner ear impairment in the present case is based purely on the histopathological findings reported previously in somewhat similar cases [9,29,34,46]. Definite proof may come from applying powerful new imaging methods, such as CT scanning, which produce sufficient detail to detect endolabyrinthine abnormalities.

5.4. Delayed endolymphatic hydrops?

We feel that endolymphatic hydrops is the most plausible explanation for the findings in our patients; it was presumably delayed in case 1 (ispilateral hydrops) and in case 2 (contralateral hydrops) and perhaps also in case 3. Schuknecht [38] wrote that (ipsilateral) delayed endolymphatic hydrops typically occurs in patients who have sustained profound hearing loss in one ear, usually from infection or trauma; then after a prolonged period of time, episodic vertigo develops in the same ear. The ipsilateral type of this disorder has been described previously in almost simultaneous publications by Nadol et al. [30] and Wolfson and Leiberman [50], followed by others [13,15,23,25,27,40]. In all of the ipsilateral cases, the emphasis was placed fully on vestibular symptoms in patients with pre-existing profound hearing loss. It seems reasonable to add our case 1 to the cases with delayed (ipsilateral) endolymphatic hydrops with vestibular symptoms only, which puts congenital CMV infection on the list of disorders which are relevant to the differential diagnosis of delayed endolymphatic hydrops. The case reported by Weiss and Ronis [48] might also be added, although the patient also had some (further) hearing impairment symptoms. It is remarkable that many cases have been described with histories somewhat similar to the present ones, whose hearing impairment of unknown cause was discovered in childhood

[13,15,23,27,38,40,50] and whose complaints of vertigo started at an age of between 5 and 33 years. Many of the contralateral cases had bilateral vestibular impairment or areflexia. The history of patient DB in Schuknecht's [38] report is particularly suspicious of CMV. DB had had 'idiopathic' thrombocytopenic purpura in infancy, 'was noted to be a clumsy child with poor motor coordination.' [38] and at the age of 17 years 'noticed the onset of intermittent tinnitus and hearing loss in his right ear.' There was no vertigo; vestibular areflexia was demonstrated at the age of 18.5 years.

Combining the terminology employed by Schuknecht [38] and Schuknecht and Gulya [39], it can be suggested that our first 2 cases illustrate 2 different monosymptomatic forms of delayed endolymphatic hydrops: one confined to vestibular symptoms originating from the ipsilateral labyrinth and the other confined to hearing impairment symptoms originating from the contralateral labyrinth. Features similar to the latter one may be identified in more cases of long-term sequelae of congenital CMV infection than have been previously recognized, provided that vestibular areflexia can be demonstrated by vestibular examination. Peckham et al. [33] suggested that vestibular impairment was a possible cause of `problems of motor coordination' encountered in some children with hearing loss due to congenital CMV infection. Our case 3 could be an asymptomatic form of (delayed?) endolymphatic hydrops. Symptoms were presumably lacking because of severe (bilateral) impairment. This is the type designated 'asymptomatic endolabyrinthine hydrops' by Schuknecht and Gulya [39], who presented a number of cases. The existence of such a type remains speculative, unless it becomes possible to demonstrate endolabyrinthine hydrops with (non-invasive) imaging methods (e.g. [3]) or (postmortem) histopathological methods.

6. Acknowledgements

Numerous colleagues and paramedical or educational workers employed at our hospital or elsewhere have been involved in the evaluation of our 3 cases. We wish to thank G. Albers, A.A.M.L.P. Baaijens, M. Bierens de Haan, P.H.H.M. Blok, R.J. de Boer, G.H.J. Boers, C.M.I. Bogaart, P. van den Broek, J.P.L. Brokx, W.F.M. Coppens-Schellekens, Th.A.M. Crul, P. Folman-Efferink, M.A.G. Frösch-Verhoeven, J. Goossens, P.J. Govaerts, A.A.M. Haagen, K. Hagedoorn, Ch.P.J. Hanrath, C.C. ten Hoopen-Hoekstra, F. Hoevenaars,

R.J.A.M. van der Hulst, P.H. Jongerius, H.H. Koch, E. Meijer, L.H.M. Mens, J. Merx, L.A.H. Monnens, M.G.M. Nicolasen, M. Pijpers-Karmaat, R. Polée, P.M. van Rijn, W.J. van Rijssen, G.M.A.C. de Saar, A.G.M. Schilder, Chr.F. Sepmeijer, G.A.M. Slaghekke, A.F.M. Snik, J.A.A.M. van der Stappen, I. van Steen, F.E.L.M. Sutorius, N.C.W.M. Vlaar, H.W.C.M. Vos and A.C.M. Woudenberg.

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Chapter 5

Pendred syndrome

Chapter 5.1

Progressive sensorineural hearing loss and a widened vestibular aqueduct in Pendred syndrome

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Archives of Otolaryngology – Head and Neck Surgery
1998; 124: 501-505

Abstract

Pendred syndrome is an autosomal recessive inherited disorder. Obligatory features are profound deafness in childhood and defective organic binding of iodine in the thyroid gland. Therefore, goiter is a common symptom. Hypoplasia of the cochlea is another feature. Recently, the gene for Pendred syndrome was identified.

We describe a boy whose sensorineural hearing loss in both ears progressed rapidly from about 50 to 60 dB at the age of 3 years and 3 months to more than 100 dB at the age of 4 years and 4 months. This loss was preceded by a medical history of a progressive hearing loss. The progressive nature of the hearing loss motivated a search for the cause. Dysplasia of the cochlea and a widened vestibular aqueduct were found. The results of thyroid function tests were normal, but he had an elevated level of thyroglobulin. The diagnosis of Pendred syndrome was confirmed by the positive results of a potassium perchlorate test, indicating defective organic binding of iodine in the thyroid gland. It is possible that the widened vestibular aqueduct was responsible for the increase in the hearing impairment. Aside from the branchio-oto-renal syndrome, Pendred syndrome is the only other known genetic disorder with a widened vestibular aqueduct. If a child has progressive sensorineural deafness and a widened vestibular aqueduct, it is important to consider a diagnosis of Pendred syndrome. A widened vestibular aqueduct may help to elucidate the pathophysiologic characteristics of hearing loss in these genetic types of deafness in childhood.

Introduction

Pendred [1], an English general physician, described in 1896 an Irish family with 10 children, 5 sons and 5 daughters. Two of the girls were congenitally deaf and developed large goiters at the age of 13 years. Almost 3 decades later, Brain [2] described 4 additional multiaffected families. In 1958, Morgans and Trotter [3] demonstrated that the thyroid enlargement was caused by an impairment of thyroxine synthesis due to a defect in the incorporation of inorganic iodide into the thyroglobulin molecule where it is bound to tyrosine radicals, the so-called organification of iodine. The degree of intrathyroidal organification of iodine can be measured easily in vivo during iodine I^{131} uptake studies. Administration of certain inorganic anions, such as potassium perchlorate or thiocyanate,

results in discharge of the anorganic (nonorganificated) iodine pool, which can be measured as a decrease in I^{131} uptake over the thyroid gland. In a normal thyroid gland, this washout effect accounts for less than 10% of the total thyroidal iodine pool because organification of iodine is rapid and little inorganic iodine is present. Intermediate levels of iodine discharge following potassium perchlorate exposure are now also considered to be an essential diagnostic criterion of Pendred syndrome [4].

Brain [2] and Deraemaeker [5] showed the autosomal recessive pattern of inheritance. Fraser et al. [6-8] confirmed this pattern in an extensive study of 207 families comprising 334 cases of Pendred syndrome. Atypical families have been described with pseudodominance, especially regarding enlargement of the thyroid gland [9]. Mondini dysplasia, normal hearing thresholds, and positive results of a potassium perchlorate test were reported in 3 of 4 mothers of children with Pendred syndrome [10].

The hearing loss is thought to be congenital and is certainly prelingual in most cases [7]. Fraser [8] stated that it is not known whether the deafness is truly congenital or rapidly progressive after birth; however, it is certain that by the age that reliable audiometry is possible, progression of the hearing loss is no longer detectable. In many cases, profound deafness in childhood is reported. There are occasional reports [8,11-16] of a milder hearing impairment. Until now, only 3 case reports have described some fluctuation or progression of the hearing loss [14,17,18].

Hypoplasia of the cochlea in Pendred syndrome was proved by the results of histological studies of the inner ear [19,20], conventional polytomographic studies, and early generation computed tomographic (CT) scanning of the temporal bones in patients with this syndrome [15,20,21]. Dysplasia of the cochlea (Mondini dysplasia) is a frequent but nonobligatory feature in Pendred syndrome [22].

Successful gene linkage studies [23-26] have recently been followed by the identification of the gene [27] and mutation analysis.

We report a case of Pendred syndrome showing progressive sensorineural deafness in childhood during the third year of life and dysplasia of the cochlea in combination with a widened vestibular aqueduct. There may be a causal relation between the widened vestibular aqueduct and the progressive hearing loss. Moreover, strong changes in cerebrospinal fluid pressure along the widened vestibular aqueduct may make the cochlea vulnerable to damage.

Report of a case

A 4-year-old boy was referred to the pediatric audiological unit of the Otorhinolaryngology Department, Nijmegen University Hospital, Nijmegen, the Netherlands, because there was some doubt about his hearing. He was the third child of the family. There was no known consanguinity. The parents and the older brother and sister did not have any complaints of hearing impairment, and there was no history of early childhood deafness in their family. The pregnancy and delivery were uneventful. He was born at term with a birth weight of 3900 g and length of 57 cm. His motor development was normal. At the age of 9 months, the Ewing sign was normal. His mother said that there was more response in the Ewing sign the first time in comparison with the hearing tests administered in our setting at the age of 2½ years. He babbled during the first year of life and responded well to his mother's singing until his first birthday. In his second year, his baby talk gradually decreased. He had gained an understanding of some words. According to the parents, communication with this child was more difficult than it was with the 2 older children. At the age of 2½ years, hearing impairment was diagnosed and confirmed by the results of brainstem audiometry 3 months later. A hearing loss of 50 to 60 dB was found (Table). The middle ears were well aerated. Six months later, the results of audiometric testing confirmed the parents' suspicions that there was an additional increase in the hearing impairment after a relatively mild head trauma.

Table 1:
Audiometric tests showing progressive and fluctuating hearing levels*.

			Air conduction levels, dB									
	Otoscopy		Right ear					Left ear				
Age,y,mo	right ear	left ear	500	1000	2000	4000	8000	500	1000	2000	4000	8000
3,3	Air	Air	BERA60					BERA50				
3,3	Air	Air	Music 60-70					Music 60-70				
3,4	NA	NA	BERA 70					BERA no response				
3,6	Air	Air	80	80	85	85	110	100	110	115	105	100
3,7	OME	OME	80	100	95	120	NA	100	115	>120	>120	NA
3,11	Air	Air	75	75	80	110	NA	95	105	100	>120	NA
4,3	NA	NA	80	100	100	120	NA	85	105	115	>120	NA
4,4	NA	NA	75	80	85	95	NA	90	105	100	100	>120

* BERA indicates brainstem evoked response audiometry, OME, otitis media with effusion, and NA. data not available

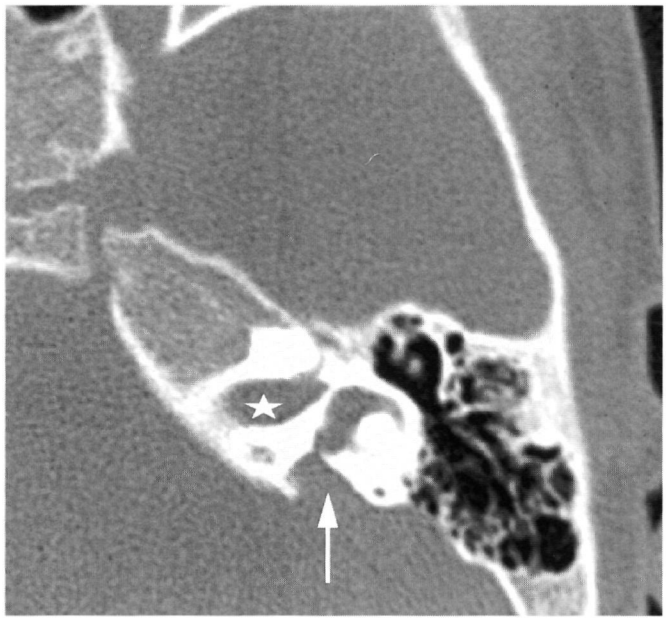

Figure 1:
Computed tomographic scan of the left ear. The star indicates the normal size of the internal acoustic canal; the arrow, a widened vestibular aqueduct.

This hearing loss was again confirmed by the results of brainstem audiometry at the age of 3 years and 4 months, which showed a 70 dB loss in the right ear and no response in the left ear.

The results of CT scanning of the petrous bones revealed bilateral dysplasia of the cochlea and a widened vestibular aqueduct (Figure 1, Figure 2, and Figure 3). The parents would not grant permission for vestibular testing. Recently, pure-tone audiometry at the age of 4 years and 3 months demonstrated a 100 dB hearing impairment in both ears. Hearing in the right ear has shown the most improvement recently. The results of testing at the age of 3 years showed normal intelligence and also some autistic behavior.

Owing to the rapid progression of the hearing impairment, the patient was examined thoroughly in search of the cause. The thyroglobulin concentration was elevated on 2 occasions with levels of 128 and 60 μg/L (normal value < 50 μg/L) (194 and 91 pmol/L [normal value <75 pmol/L]). There were no dysmorphic features. The thyroid gland could not be palpated. At the age of 4 years, his height was 107.5 cm (90th percentile) and his weight was 17.1 kg. He was eurothyroid.

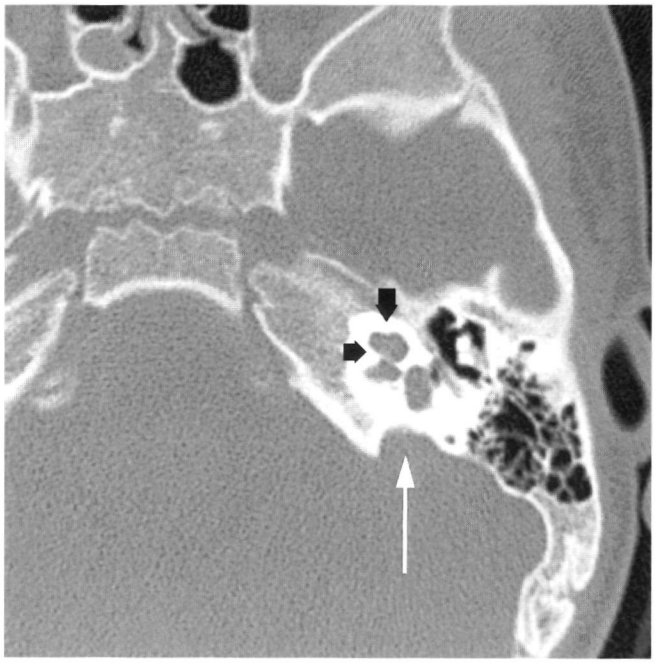

Figure 2:
Computed tomographic scan of the left ear. The black arrows indicate hypoplasia of the cochlea; the white arrow, a widened vestibular aqueduct.

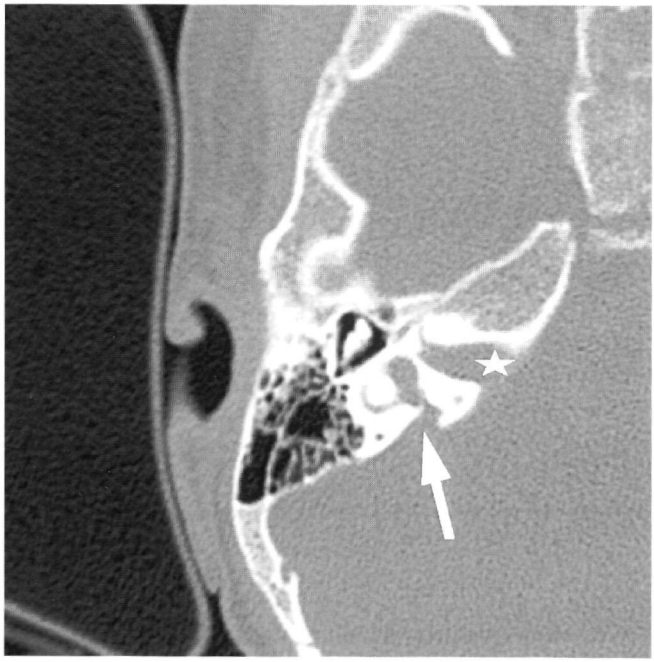

Figure 3:
Computed tomographic scan of the right ear. The star indicates the normal size of the internal acoustic canal; the white arrow, a widened vestibular aqueduct.

The results of laboratory tests showed the following values, which were all within the normal range: total thyroxine, 116 nmol/L (9.0 μg/dL); free thyroxine, 13.6 pmol/L (1.0 ng/dL); free thyroxine percentage, 0.0117%; total triiodothyronine, 2.8 nmol/L (181 ng/dL); and thyrotropin, 2.72 mIU/L. The results of thyroid scanning showed that the gland had a normal size and configuration. A discharge rate of 24% was found in the results of the potassium perchlorate test, confirming the clinical diagnosis of Pendred syndrome. We performed mutation analysis of the Pendred syndrome putative sulphate transporter (*PDS*) gene by exon-specific polymerase chain reaction amplification and DNA sequencing, as described before [27]. This analysis enabled us to screen the entire *PDS* region of the proband for mutations.

We found 2 missense mutations: 1558T to G (1558T→G) and 1375A to G (1375 A→G). The 1558T→G mutation changes a leucine at position 445 into a tryptophan (L445W). Interestingly, this mutation has also been found in another Dutch family with Pendred syndrome (P.H., written communication, February 1997). The 1375A→G mutation changes a glutamic acid residue at position 384 into a glycine (E384G) and has not been described before. However, since this mutation changes the second base of exon 10, it is also possible that the 1375A→G mutation causes aberrant splicing of the *PDS* messenger RNA. The effect of the mutation on the *PDS* messenger RNA has not been investigated. Everett et al. [27] identified several conserved amino acid positions by aligning the pendrin protein with 5 other sulphate transporter proteins. Both mutations found in the proband alter a conserved amino acid.

Comment

In this patient with rapidly progressive sensorineural hearing impairment, an early diagnosis of Pendred syndrome was established although he was completely euthyroid and did not have a goiter. The hearing loss proved to be very progressive, as documented by the results of objective audiometric tests. Molecular analysis of the coding region of the *PDS* gene of the proband revealed 2 disease-causing mutations, confirming the clinical diagnosis of Pendred syndrome.

In the 1960s and 1970s, Pendred syndrome was considered to be a relatively frequent cause of profound childhood deafness. In 1958, the potassium perchlorate test proved to be a reliable diagnostic test for Pendred syndrome in individuals with congenital

sensorineural deafness [3]. Goiter was a common feature. In 1964, more than 200 cases had been reported in the literature. The earliest report on more moderate hearing impairment dates from 1964 [11]. Nevertheless, sensorineural hearing impairment of less than 80 dB is reported rarely. No long-term follow-up data on the hearing impairment are available in these cases. Progression or fluctuation of the hearing impairment has only been described in 3 case reports [14,17,18] of Pendred syndrome. One report [14] mentioned 20 dB progression of hearing loss in a patient. Another report [17] described 10 to 20 dB progression combined with episodic vertigo, tinnitus, and occasional vomiting. More recently, a case report [18] described fluctuating and recovering hearing impairment in the best ear combined with episodic vertigo.

Dysplasia of the cochlea is a frequent but nonobligatory feature of Pendred syndrome [19,20,22,28]. Magnetic resonance imaging in female siblings with Pendred syndrome showed bilateral enlargement of the vestibular aqueduct and Mondini dysplasia [29]. Recently, axial CT scanning of the temporal bones in 3 of 6 patients with Pendred syndrome showed a widened vestibular aqueduct and dysplasia of the cochlea [28]. These 3 adult patients with Pendred syndrome and a widened vestibular aqueduct were described as having profound congenital sensorineural hearing impairment. In addition, it was stated that 80% of confirmed cases of Pendred syndrome will have inner ear anomalies, such as a widened vestibular aqueduct [22,28]. Dysplasia of the cochlea and a widened vestibular aqueduct can also be part of the branchio-oto-renal syndrome. Recently, this was reported to be present in 11 of 24 ears of patients with this branchio-oto-renal syndrome [30].

The widened vestibular aqueduct may be responsible for the progression in hearing impairment. This phenomenon has only recently been found in 2 different genetic syndromes with hearing impairment, the branchio-oto-renal syndrome and even more recently in Pendred syndrome. Other than these 2 distinct genetic syndromes, there are only a few descriptions of sisters and brothers with profound deafness in childhood and a widened vestibular aqueduct without a diagnosis of a genetic syndrome [31,32]. Nevertheless, it is still difficult to prove the assumption that the widened vestibular aqueduct is fully responsible for the progressive hearing loss. In the X-recessive progressive mixed stapes gusher syndrome (DFN3), it has been shown that the gush of perilymph after opening the footplate is conducted through the internal acoustic canal [33]. Lateral widening of the internal acoustic canal and vestibule has been demonstrated with CT scanning, and various authors [33-38] consider this to be pathognomonic in many

cases. Long-term follow-up of affected individuals in a large Dutch pedigree [39] has shown stability of the conductive component and an increase in the sensorineural component. The increase in the sensorineural component may be the result of fluctuations in cerebrospinal fluid pressure that are conducted into the cochlea, owing to the too-wide communication along the internal acoustic canal. Long-term family studies on the branchio-oto-renal syndrome and Pendred syndrome with long-term audiological follow-up and corresponding axial CT scanning or magnetic resonance imaging of the petrous bones may be able to show whether there is an increase in the sensorineural component of the hearing loss and whether this is correlated with the presence of a widened vestibular aqueduct.

The genes for the branchio-oto-renal syndrome and Pendred syndrome have recently been identified [27]. The clinical genetic diagnosis of Pendred syndrome can now be confirmed by mutation analysis of the *PDS* gene involved (P.H., written communication, February 1998) [27]. Therefore, the clinical phenotype can be redefined based on the genotype. This could help to elucidate the significance of the widened vestibular aqueduct in the progression of hearing impairment in the patient described herein. This case report shows that an euthyroid situation without an enlarged thyroid gland, hypoplasia of the cochlea, and a widened vestibular aqueduct my be the phenotype of Pendred syndrome.
Two further questions arise: How frequently can this phenotype be based on the results of genotype studies in Pendred syndrome? How frequently is a widened vestibular aqueduct the result of Pendred syndrome?

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Chapter 5.2

Progressive hearing loss, hypoplasia of the cochlea and widened vestibular aqueducts are very common features in Pendred's syndrome

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International Journal of Pediatric Otorhinolaryngology
1998; 45: 113-123

Abstract

Long-term hearing threshold-on-age follow-up data, including non-linear regression analysis, are given for 12 consecutive Pendred patients. The clinical diagnosis of Pendred's syndrome was confirmed by a mutation analysis of the *PDS* gene in 11 out of the 11 cases tested. Recent imaging of the temporal bones in seven out of these 12 patients showed widened vestibular aqueducts in each case.. The diagnostic perchlorate test was negative in one patient, but this test was positive in her affected sister. Mutation analysis of the *PDS* gene in these patients confirmed that Pendred's syndrome is a monogenetic disorder. Progressive sensorineural hearing loss and widened vestibular aqueducts are characteristic features of Pendred's syndrome, which provides the opportunity to diagnose Pendred's syndrome clinically in the first few years of life, as has recently been suggested in a case report (Cremers et al., Progressive sensorineural hearing loss and a widened vestibular aqueduct in Pendred syndrome, Arch. Otolaryngol. 1998; 124: 501-505). Mutation analysis of the involved gene can be used to confirm the clinical diagnosis.

1. Introduction

The features of Pendred's syndrome are congenital, mostly profound sensorineural hearing loss and a positive perchlorate test. It is difficult to diagnose Pendred's syndrome at an early age, because suspicion for this diagnosis is only raised by a goitre or hypothyroidism. The goitre seldom appears during the first year of life, but starts to develop during puberty or in early adulthood. The sensorineural hearing loss is more pronounced in the higher frequencies. It is thought to be congenital and certainly prelingual in most cases [2,3]. Occasionally there is asymmetrical hearing loss, with moderate sensorineural hearing impairment in the best ear.

Recently we reported on a boy with Pendred's syndrome with progressive and fluctuating hearing loss and periods of dizziness. Bilateral widened vestibular aqueducts were found. The diagnosis of Pendred's syndrome was confirmed by mutation analysis of the *PDS* gene [1].

Over the past 25 years we have diagnosed Pendred's syndrome in 14 cases from 11 families. We restudied the medical files of 13 out of these 14 cases from 10 families and collected their audiometric data for a long-term follow-up study of their hearing impairment. MRI or CT scanning of the temporal bones was performed whenever possible. The diagnosis of Pendred's syndrome was recently confirmed by mutation analysis of the *PDS* gene. We especially addressed the questions whether a widened vestibular aqueduct and progressive hearing loss are frequent features in Pendred's syndrome.

2. Patients and methods

Over the past 25 years, Pendred's syndrome has been diagnosed in 14 patients from 11 families. Thirteen out of these 14 could be traced and included in this follow-up study. The results of our youngest patient have been published recently [1]. Below the hearing threshold-on-age follow-up of the remaining Pendred cases are reported. The first group of patients was traced early in the seventies as part of a school study on the causes of profound childhood deafness at the Institute for the deaf in St. Michielsgestel [4-6]. Later on at the outpatient clinic of the Nijmegen ORL Department, an additional group of patients was diagnosed as having Pendred's syndrome. Some of them were referred for genetic counselling. The most recent cases were traced at the paediatric audiology unit of the Nijmegen ORL Department in cooperation with the Department of Paediatric Endocrinology, as part of an aetiological search because of the progressive nature of their sensorineural hearing loss. All had therefore undergone the diagnostic perchlorate test. Pairs of sibs are patients 1 and 2, patients 3 and 4 and patients 9 and 10. More recently we invited all the patients who had not been investigated previously to have MRI studies of their temporal bones, to see whether there was hypoplasia of the cochlea or a widened vestibular aqueduct. Vestibular tests were performed with electronystagmography, rotary chair and caloric testing. From 1994 onwards we have been collecting blood samples from patients, parents and sibs for gene linkage studies and more recently, mutation analysis.

Table 1:
General and laboratory data on 12 patients with Pendred's syndrome

No Patient	Born in	Sex	Hearing loss supposed	Hearing loss diagnosed	Hearing loss progressive	Enlarged Thyroid	0-4 perchlorate test (%) positive	Imaging temporal bones		Mutation PDS-gene	Case history or mutation published previously
1	1947	M	23 months	Unknown	Yes	18 months	31	Not available	Not available	+	Family no. 3+4 [4]
2	1961	M	6 months	Unknown	Yes	4 years	60	CT scan hypoplasia, cochlea, widened vestibular aqueduct	CT scan hypoplasia cochlea, widened vestibular aqueduct	+	Family no 4 Coucke et al. [15] 1997, family no. 5 [7]
3	1956	F	6 months	3 years	Yes	2 months	52	Not available	Not available	+,L236P,L445W	Family no 1+2 [4]
4	1959	F	6 months	2 years	Yes	12 years	66	Not available	Not available	Not tested. sister of no 3	
5	1957	M	3 years	3 years	Yes	14 months 18 years	55	Not available	Not available	+	Family no 5 [4], Family no 3 [7]
6	1961	F	18 months	4 years	Yes	18 months	52	MRI,hypoplasia cochlea, widened vestibular aqueduct	MRI,hypoplasia cochlea, widened vestibular aqueduct	+	Family no 8 [7]
7	1963	F	6 years	6 years	Yes	14 years	36	MRI,hypoplasia cochlea, widened vestibular aqueduct	MRI,hypoplasia cochlea,widened vestibular aqueduct	+	Family no. 3 Coucke et al. [15] 1997, Family no 2 [7]
8	1968	M	1 year	1 year	Yes	13 years	24	Not available	Not available	+	Family no 13 [7]
9	1973	F	5 years	5,5 years	Yes	15 years	63	MRI,normal cochlea, widened vestibular aqueduct right side larger	MRI,normal cochlea, widened vestibular aqueduct	+	Family no 6 [7]
10	1980	F	3 years	3 years	Yes	No	<10	MRI,normal cochlea, widened vestibular aqueduct right side larger	MRI,normal cochlea, widened vestibular aqueduct	+	Family no. 6 [7]
11	1985	F	2 years	2.5 years	Yes	No		MRI,hypo-plasia cochlea, widened vestibular aqueduct	MRI,hypo-plasia cochlea, widened vestibular aqueduct	+	Family no. 12 [7]
12	1986	F	1 year 4 months	1 year 6 months	Yes	3 years	35	MRI,normal cochlea, widened vestibular aqueduct	MRI,normal cochlea, widened vestibular aqueduct	+	Family no. 7 [7]

2.1. Statistical analyses

A commercial programme (Prism, version 2.0, GraphPad, San Diego, USA) was used to perform nonlinear regression analysis on the longitudinal threshold-on-age data, as well as additional statistical calculations and tests. The binaural mean threshold was used for the regression analysis. For each ear separately, we obtained the difference in threshold between two adjacent frequencies as a measure of audiogram slope. The frequency distribution of this variable in each case at each frequency was tested for normalcy by using the Kolmogorov-Smirnov test, which was followed by tests (one-way analysis of variance) on inter-age and inter-frequency differences. Their audiograms were collected to perform a statistical analysis.

3. Results

Table 1 shows the clinical data for the 12 Pendred patients. All of them met the criteria for the diagnosis of Pendred's syndrome. Hearing loss was generally detected at a relatively advanced age (Table 1). Mutation analysis had confirmed the diagnosis in 11 out of these 12 cases [7]. The test results of case 3 have not been published elsewhere and are presented in Table 1. Her sister, case 4, refused to give blood samples. Results of temporal bone imaging are presented for seven out of these 12 patients in Table 1. Four out of these seven showed bilateral hypoplasia of the cochlea. In two sisters, cases 9 and 10, a normal cochlea was seen bilaterally. All seven patients had bilateral widened vestibular aqueducts (fig. 1). The sensorineural hearing loss proved to be progressive in all of them.

3.1. Analysis of longitudinal threshold data

The serial audiograms of all cases are shown in Fig. 2. High thresholds were present at a young age. The high frequencies were most severely affected and many cases showed substantial progression, some from a young age. Case 4 was exceptional, because of relatively good thresholds, but he also showed progression.

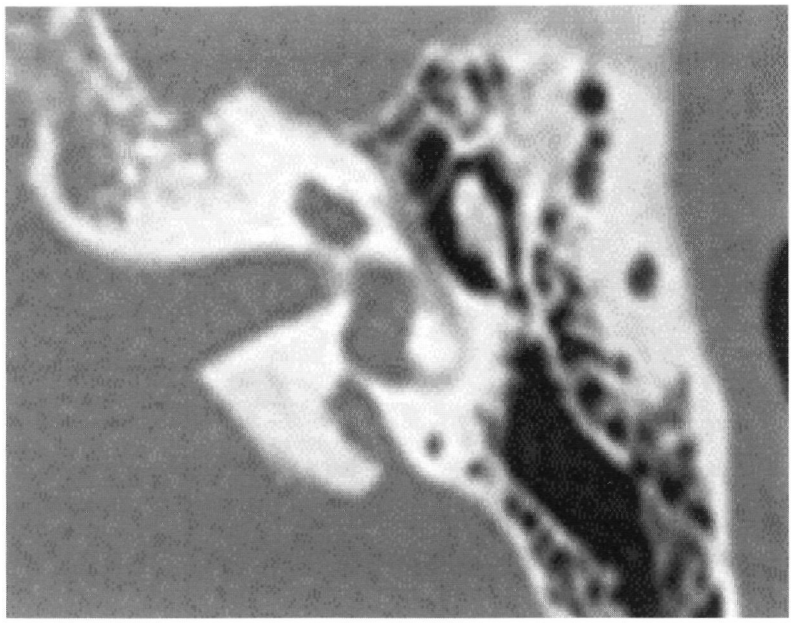

Figure 1:
Hypoplasia of the cochlea and enlarged vestibular aqueduct of the left ear (case no. 2).

The threshold increase per octave, evaluated in each ear at each frequency, generally showed approximately normal and fairly uniform distributions that did not differ significantly between the frequencies or the subjects at any age. The overall mean increase was 7 dB/octave. This implies that the audiograms generally had similar shapes, with a mean slope fairly close to -7 dB/octave.

Fig. 3 shows the individual plots of the threshold-on-age data for all frequencies in each case. A close look at the individual plots at each frequency showed that progression was initially (i.e. at a young age) relatively rapid in most cases - also note that in cases 1 and 5 it was more rapid than suggested by the fitted curves - and then slowed down to an asymptotic saturation level as the patient grew older. Thus, progression was clearly nonlinear, even when the episodes of hearing improvement were ignored. Inspection of plots of the residues relating to attempted linear curve fits (not shown) disclosed systematic departure from linearity; the occurrence of some relatively large residues, especially at a younger age, were related to relatively large residual SDS. We therefore decided to employ nonlinear regression analysis in an attempt to fit the data.

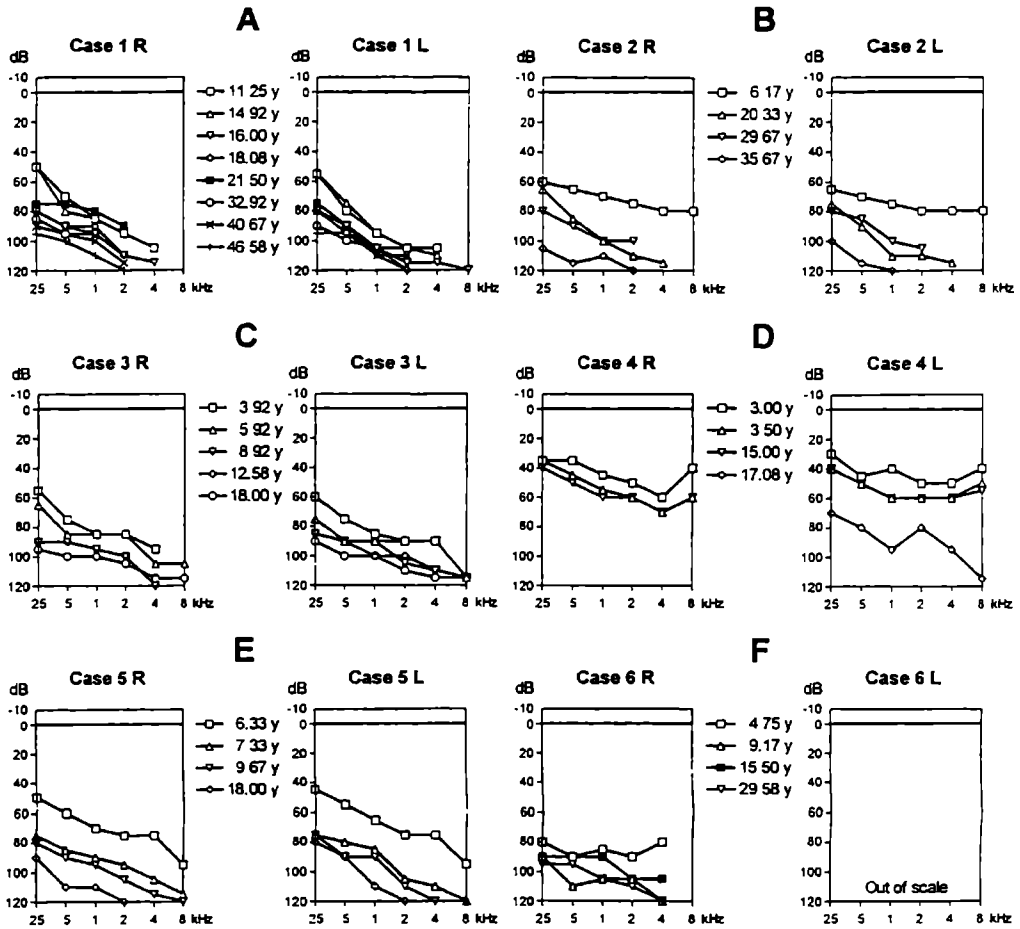

Figure 2. (A) Serial audiograms, for the two ears for cases 1-6 (A-F). The audiograms are generally downsloping with an average slope of fairly close to -7 dB/octave. Filled symbols mark the beginning of a transient episode of hearing improvement (case 1,6).

Table 2 presents the essentials of the fitted curves and the results obtained. The maximum threshold (T_{max}) fitted for each frequency probably reflects the general slope of -7 dB/octave.

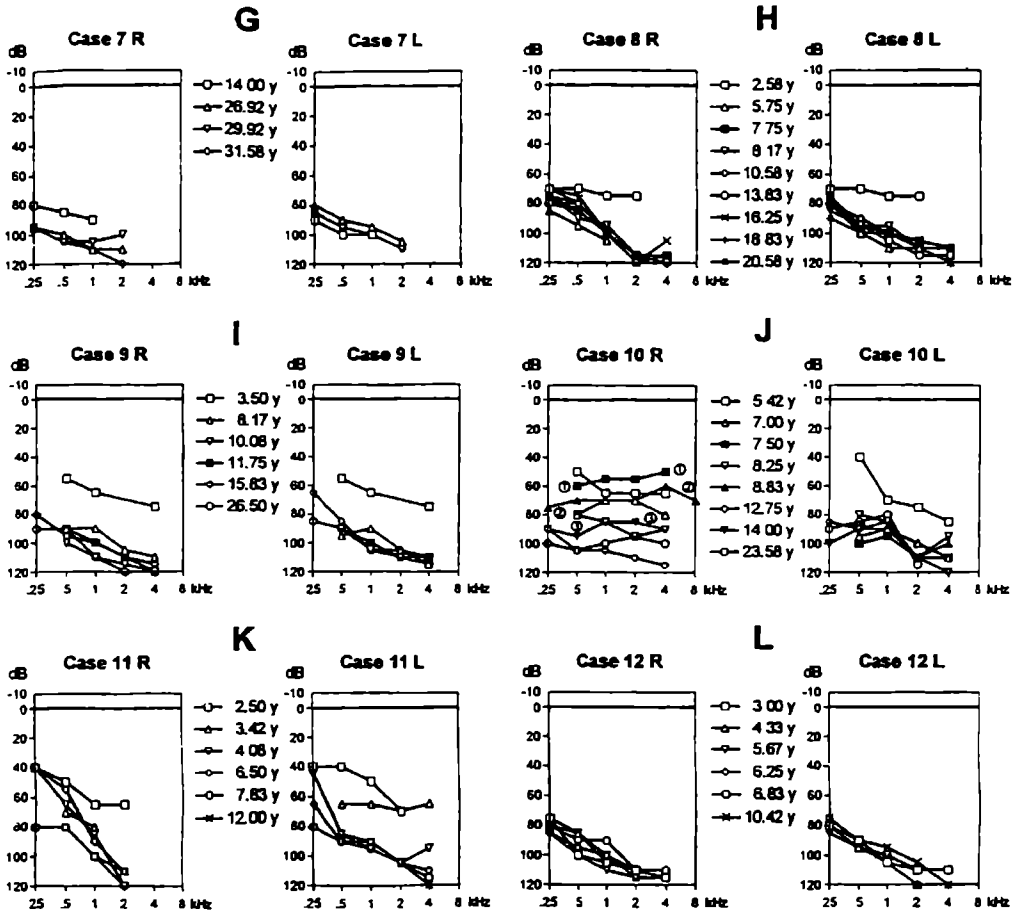

Figure 2. (B) Serial audiograms, for the two ears for cases 7-12 (G-L). The audiograms are generally downsloping with an average slope of fairly close to -7 dB/octave. Filled symbols mark the beginning of a transient episode of hearing improvement (case 8,9,10).

3.2. Vestibular tests

Vestibular tests were performed with electronystagmography, rotatory chair and/or caloric testing in five cases (nos 2, 5-7 and 9). All showed abnormal responses, except for case 7. Case 2 was examined in 1997 as part of the evaluation for a cochlear implant procedure, 4 years after severe head trauma with sudden progressive hearing loss. He showed complete vestibular areflexia.

Table 2:
Hyperbolic equation employed in the nonlinear regression analysis of the longitudinal data shown in Fig. 3 with a synopsis of the fitted parameter values and the goodness of fit

Equation

$T=T_{max}.t\ (t_{0,5}+t)$

T is the threshold (dB) at age t (y), T_{max} is the maximum threshold (asymptomic saturation) level, $t_{0,5}$ is the 'half-value' age, i.e. the age at which $T=0.5\ T_{max}$

Parameter Values

$t_{0,5}$ mean[a] 3 y (SD[a] 2 y) at any frequency

T_{max} at the frequency (kHz)	0.25	0.5	1	2	4	8
Mean[a] (SD[ab] 8 dB)	108	109	116	127	132	(116)[c]

Goodness of fit

Mean[a] residual SD 8 dB (SD[a] 3 dB) in any case, at any frequency

[a] Inter-subject

[b] At each frequency

[c] Based on a relatively small no. of observations

Case 5 showed bilateral caloric weakness on examination in 1976. Vestibular impairment may have progressed in this case: he experienced episodes of dizziness in 1983 and 1987 and later developed specific symptoms related to head movements (he was not retested). Case 6 had experienced episodes of vertigo at the age of 9, 25 and 29 years and was tested at the age of 26 and 30 years. She showed caloric areflexia on the left side. Case 7 had had several episodes of vertigo during puberty. Vestibular examination at the age of 31 years did not reveal any abnormalities. Case 9 underwent her first rotatory test at the age of 9 years (see below). At the age of 14 years, she had a repeat examination, because she had experienced several episodes of vertigo with fluctuant hearing loss: she showed a decreased gain in the vestibulo-ocular reflex compared to her previous examination, while a caloric test disclosed bilateral weakness.

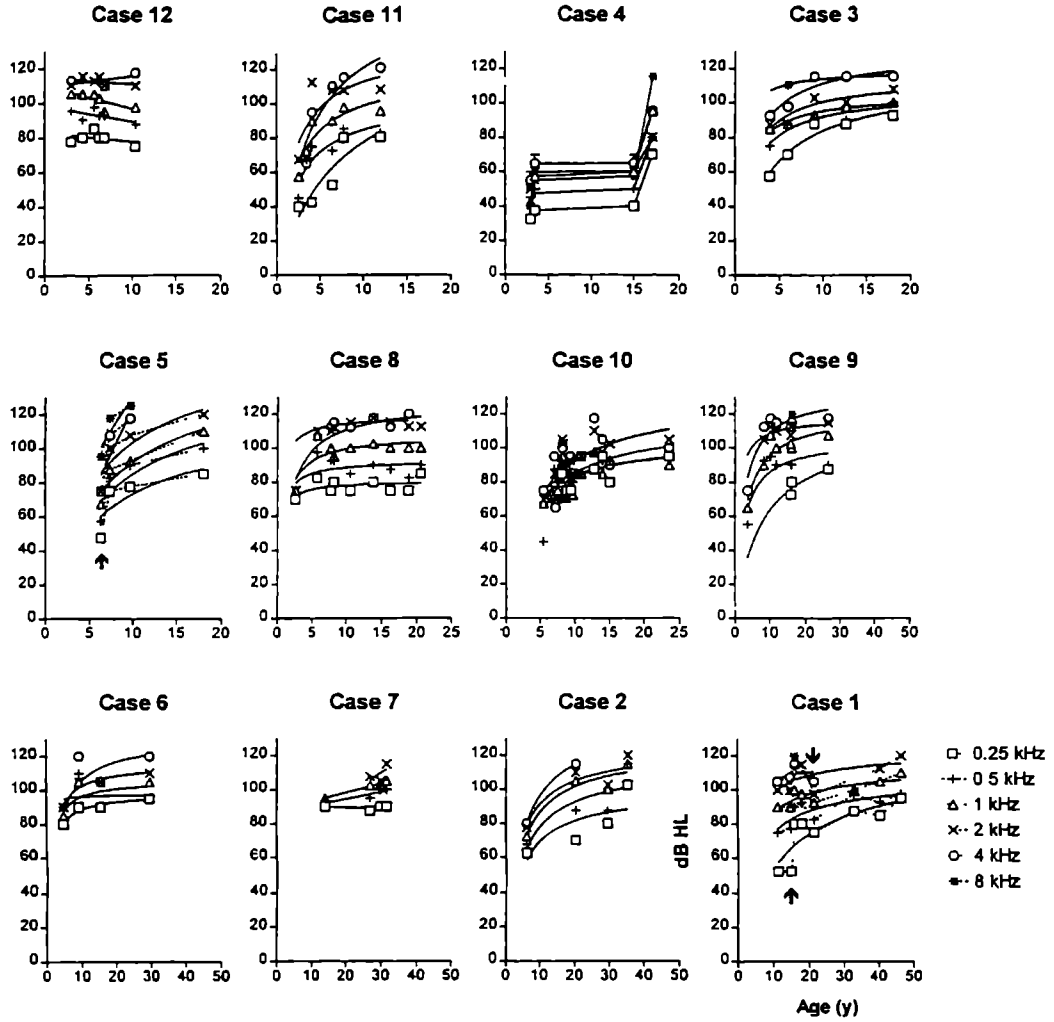

Figure 3.
Longitudinal (binaural mean) threshold data presented for each case, ordered by the age at which the most recent audiogram was obtained, with the fitted regression curves (or straight regression lines in cases 7 and 12 and simple connecting lines in case 4). Note the different age scales. Details about the nonlinear regression analysis are presented in Table 2. The dashed lines (cases 1 and 5) are connecting lines, which are included to emphasize that initial progression (upward arrows) was more rapid than is suggested by the regression curves and to demonstrate the presence of an episode of hearing improvement (case 1, downward arrow).

4. Discussion

The classical phenotype of Pendred's syndrome has to be rewritten. Pendred's syndrome has been diagnosed in the past in deaf subjects mostly relatively late during adolescence or in early adulthood. The diagnosis was guided by an enlarged thyroid and sometimes hypothyroidism and confirmed later by the perchlorate discharge test. The *PDS* gene is the gene involved in Pendred syndrome [8]. Recent mutation analysis of this gene in Pendred's syndrome confirms that it is probably a monogenetic disorder [1,7]. The same gene is affected in the nonsyndromic autosomal recessive type of childhood deafness (DFNB4). The description of DFNB4 is only based on a large consanguineous family from South West India: ten individuals (between 5 and 38 years old) are affected with congenital, profound, non-syndromic autosomal recessive deafness [14]. Stigmata of syndromic deafness, like a palpable thyroid, were excluded. Thyroid-stimulating hormone (TSH) serum T3 and T4 levels were normal in three affected individuals. The perchlorate discharge test was not available in the area where the family resides. CT scanning of the temporal bones was performed in the same 3 affected family members who all showed a normal bilateral configuration of the cochlea and enlarged vestibular aqueducts. Normal TSH serum T3 and T4 levels are not unusual in Pendred's syndrome. Based on our personal experience, a euthyroid status is usual. Enlarged vestibular aqueducts seem to be almost an obligatory feature of Pendred's syndrome [1,4]. This feature was present in 8 out of our 8 patients [1] tested and in 20 out of 20 Pendred patients as part of a larger series reported by Phelps et al. [9]. It is therefore only natural to assume that the Indian family reported to have DFNB4 with widened vestibular aqueducts and a mutation in the *PDS* gene, without having had the perchlorate test, may in fact have Pendred's syndrome. It would be therefore of interest to let have all the affected members of this family perchlorate test to come to a sound conclusion.

Owing to previous experience of progressive sensorineural hearing loss, widened vestibular aqueducts, a positive perchlorate test and a mutation in the *PDS* gene in a 3-4 year-old boy [1], we started to re-evaluate the onset and the progressivity of the sensorineural hearing loss in our previous Pendred patients. Some of them have also experienced Ménière-like attacks of vertigo and substantial fluctuation in their hearing

loss. We found some indications that vestibular impairment may also be progressive. Only a few similar case reports have been published [10-12].

This report substantiates the progressivity of the hearing loss genetically proven in Pendred's syndrome to be related to an almost obligatory finding of widened vestibular aqueducts.

Therefore we feel justified to rewrite the phenotype of Pendred's syndrome. Progressive sensorineural hearing loss in childhood should guide the diagnostic process into the direction of Pendred's syndrome with imaging of the temporal bones, a perchlorate discharge test and mutation analysis of the *PDS* gene. Thyroid hormone substitution should be considered early on to prevent an enlarged thyroid and possible hypothyroidism. The natural course of a progressive sensorineural hearing loss could influence decisions regarding education and possibly cochlear implantation of the child.

This report raises the question of how frequent Pendred's syndrome is among patients with the enlarged vestibular aqueduct syndrome. The only other genetic condition we are aware of with an enlarged vestibular aqueduct is the Branchio-Oto-Renal syndrome [13]. Mutation analysis and perchlorate tests could settle this issue. The progressivity of the hearing loss in Pendred's syndrome may be secondary to widened vestibular aqueducts. Although at present there is no surgical technique to adequately narrow an enlarged vestibular aqueduct, there is still hope that that one will be developed in the future.

Acknowledgement

The authors thank Ambereen Quraishi for her technical assistance in mutation screening.

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Chapter 6

Non-ocular Stickler syndrome

Chapter 6.1

Hearing loss in the nonocular Stickler syndrome caused by a *COL11A2* mutation

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Laryngoscope
2000; 110: 457-461

Abstract

Objective: Evaluation of hearing impairment as a feature of the nonocular Stickler syndrome (type II) linked to *COL11A2*. *Study Design:* Family study. *Methods:* General, orthopaedic, ophthalmologic, and otorhinolaryngologic examinations were performed on 15 affected persons in a Dutch family. Audiograms were obtained and/or retrieved from elsewhere. Cross-sectional and longitudinal analyses were conducted on the hearing threshold (sensorineural component) in relation to the patient's age to evaluate whether hearing impairment was progressive. *Results:* Mixed hearing loss, i.e. including a substantial air-bone gap of up to 20-60 dB, was present in six cases, concomitantly with a submucous or overt cleft palate in five of them. The audiograms in 14 evaluable cases showed the following types of threshold: U-shaped (n = 3), flat (n = 2), flat or gently (downward) sloping (n = 3), gently sloping (n = 3), or steeply sloping (n = 3). Cross-sectional analysis did not reveal any significant effect of age on sensorineural hearing impairment. *Conclusion:* In contrast to the classic Stickler syndrome (type I) with high myopia, this nonocular type shows a high prevalence of sensorineural hearing impairment. The mean sensorineural hearing threshold in our patients was about 40 dB HL (95% confidence interval 15-65 dB) and was liable to increase (presumably by presbycusis) by several tens of decibels at the highest frequencies. Given the tendency for otitis media to develop in many of these patients, appropriate otologic care is of major importance.

Introduction

The Stickler syndrome is an autosomal dominant connective tissue disorder that includes ocular, auditory, orofacial, skeletal, cardiac and other features. Stickler et al. [1] described a family with progressive myopia beginning in the first decade of life that resulted in retinal detachment and blindness. As the affected persons also exhibited premature degenerative changes in various joints with abnormal epiphyseal development and slight hypermobility, the disorder was tentatively termed "hereditary progressive arthro-ophthalmopathy". Stickler and Pugh [2] added radiographic abnormalities and mild sensorineural hearing impairment (SNHI) to the features typical of this syndrome. Hall [3] pointed out that the Pierre Robin

sequence also forms part of the syndrome, together with typical orofacial features. Hearing impairment was attributed to chronic otitis media, although SNHI was also described. The latter author concluded that within a given family, marked variability in gene expression occurred, both with regard to the severity of involvement and to the organ systems involved. Liberfarb and Goldblatt [4] found that 50% of the affected women and 43% of the affected men had mitral valve prolapse. The Stickler syndrome is nowadays recognised as the most common form of autosomal dominant connective tissue dysplasia.

Zlotogora et al. [5], who described three families with the Stickler syndrome, concluded that the phenotype showed higher interfamilial than intrafamilial variability. Linkage between the ocular Stickler syndrome (type I) and the type II procollagen gene on chromosome 12 *(COL2A1)* was found by Francomano et al. [6] and Knowlton et al. [7] and later supported by the findings of Ahmad et al. [8]. It is assumed that in approximately one third to one half of the families the Stickler syndrome is not linked to *COL2A1* [9]. Brunner et al. [10] demonstrated close linkage with polymorphic markers at 6p22-p21.3 in the present Dutch family with the nonocular Stickler syndrome (type II), while Vikkula et al. [11] found a *COL11A2* mutation in this family: a G to A transition at a splice donor site causing in-frame skipping of a 54-bp exon, encoding 18 amino acid residues within the triple-helical and C-propeptide domains of the α_2(XI) collagen molecule. The fact that the α_2(XI) chain collagen is not found in the vitreous may explain the lack of ocular involvement. Delineation of a second family with a *COL11A2* mutation causing the Stickler type II syndrome (without eye involvement) confirmed the role of *COL11A2* in the etiopathogenesis of this disorder [12]. It was recently found that the Stickler type I syndrome can also be linked to the *COL11A1* gene [13], while other findings suggest the existence of at least a fourth locus for the Stickler syndrome [14]. (See Snead and Yates [15] and Spranger [16] for recent reviews.)

Despite the fact that in the past three decades hearing impairment has been repeatedly described as one of the main features of the Stickler syndrome, relatively few studies have outlined the features of this hearing impairment (see Nowak [17] for a review). Sensorineural, mixed and conductive hearing impairments have been reported, the latter often as a secondary effect of craniofacial anomalies, i.e., cleft palate. The degree of hearing impairment can show considerable variability [18]. We performed otorhinolaryngologic and audiologic examinations on a previously described Dutch family with the Stickler type II

syndrome, i.e. without ophthalmic involvement [10,11].

Material and methods

Patients

All 15 affected members of the present family (Fig. 1) who participated in this study showed linkage to *COL11A2* [10] and had the same *COL11A2* mutation [11]. One deceased family member (III-2 in pedigree, Fig. 1) was affected according to history.

Procedures

After informed consent had been obtained, history was taken and general physical and otorhinolaryngologic examinations were performed. After obtaining each patient's written permission, orthopaedic, ophthalmologic, and other relevant medical information was obtained from elsewhere and previous audiograms were retrieved. Pure-tone audiograms were obtained in a sound-treated room according to the usual clinical standards and included assessment of air conduction and bone conduction levels and speech discrimination scores. Evaluation of hearing impairment was based on air conduction level only if there was no substantial air-bone gap. Otherwise, bone conduction level was taken to represent sensorineural hearing level. Statistical analyses were performed using a commercial programme (Prism, version 3.0, GraphPad, San Diego, CA) and comprised cross-sectional analyses (Student *t* test, if necessary with Welch's correction, and one-way ANOVA) and longitudinal analyses (linear regression analysis) of threshold-on-age data. The cross-sectional analysis of threshold-on-age data (last-visit audiograms) was performed on all the evaluable affected persons. Longitudinal analyses were conducted on cases with a sufficient number of serial audiograms covering a substantial age range, to test whether the progression in hearing impairment was significant, i.e., the regression coefficient differed significantly from zero. Within relevant subgroups, the mean thresholds were compared per frequency. The mean threshold at each frequency was also compared between relevant subgroups.

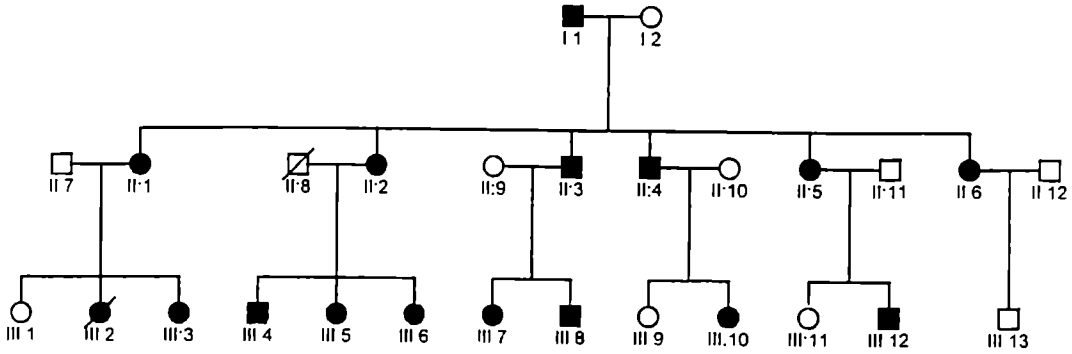


Figure 1.
Pedigree. Squares indicate men, circles indicate women. Filled symbols indicate affected persons, slashed symbols indicate deceased persons.

Results

General, orthopaedic, ophthalmologic and otorhinolaryngologic features

In generations I to III, 16 of the 20 persons were affected: all 6 members in generation II and 9 of the 13 persons in generation III. One patient (III-2) died neonatally from severe asphyxia and aspiration; she had micrognathia and a cleft palate.

Facial features included a flat midface and short upturned nose with depressed nasal bridge and protruding eyes. These features were most prominent in childhood and became less obvious with age.

Eleven of the 15 affected persons complained of painful joints. Degenerative changes in spinal and knee joints were documented radiographically in three subjects.

All the patients underwent ophthalmic and optometric examinations. Patient II-5 had -3.75 and -4 diopters myopia, patient II-6 had -4.25 and -0.25, and patient III-11 had -4.5 in both eyes. Such moderate myopia cannot reasonably be attributed to the Stickler syndrome. None of the other affected persons showed ophthalmologic symptoms.

Three patients had a cleft palate (III-4, III-7, III-10), two cases had a submucous cleft (II-6 and III-8) and one patient (II-5) had a high-arched palate (Fig. 2).

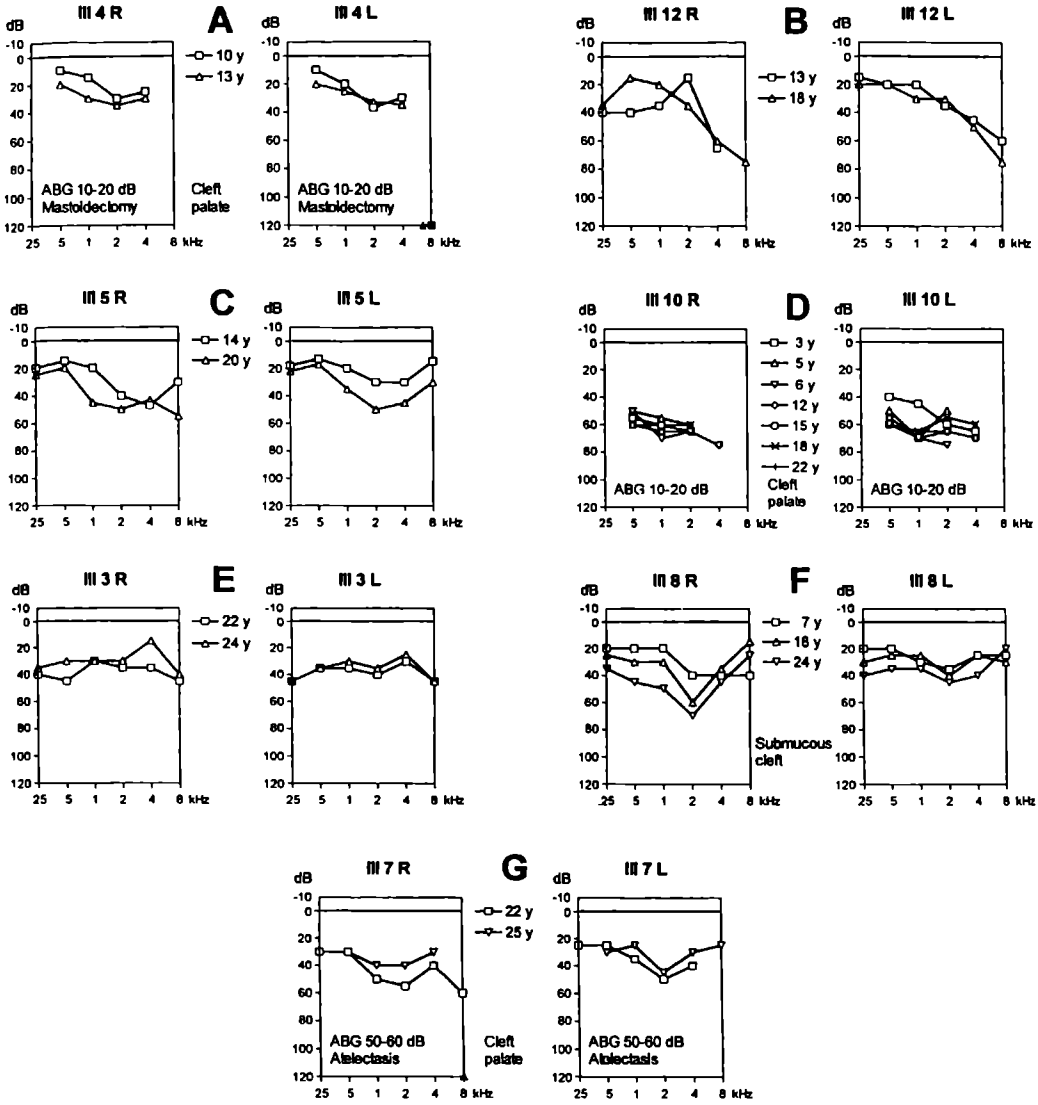
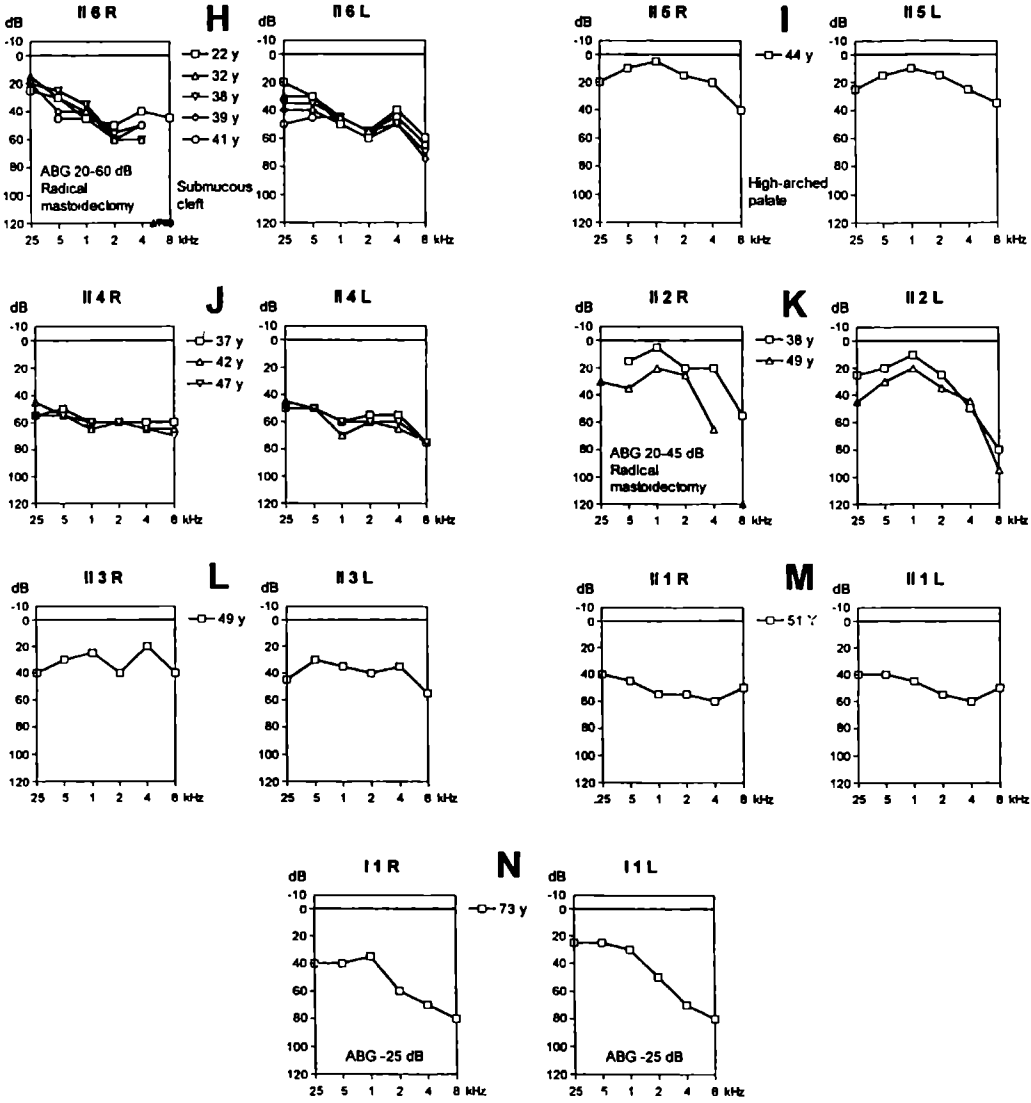


Figure 2:
Audiograms of all participants with reliable evaluation of the sensorineural hearing component (n = 14; R = right ear; L = left ear). Threshold level in dB HL. ABG = air-bone gap. Air conduction level is shown, unless an ABG is specified, in which case bone conduction level is plotted. Various open symbols relate to serial audiograms, the corresponding age (in years) is given in the key to each panel. Filled symbols indicate out-of-scale measurements (all these cases concern bone conduction). Panels (A-N) are ordered by the age at which the most recent audiogram was obtained.


II 6 R
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dB
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mastoidectomy
Submucous
cleft
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I
II 5 L
44 y
High-arched
palate
II 4 R
J
II 4 L
37 y
42 y
47 y
II 2 R
K
II 2 L
38 y
49 y
ABG 20-45 dB
Radical
mastoidectomy
II 3 R
L
II 3 L
49 y
II 1 R
M
II 1 L
51 y
I 1 R
N
I 1 L
73 y
ABG -25 dB
ABG -25 dB

Audiograms

All 15 affected participants were known to have hearing impairment. Figure 2 shows the audiograms for the two ears separately in the 14 cases who could be analysed. Person III-6 is not included in Figure 2 because of a lack of details; she had been examined previously by an otorhinolaryngologist elsewhere, who only reported that she showed bilateral conductive hearing loss of about 20 dB without any otologic symptoms. Mixed hearing loss, in one or both ears, was present in six cases; in four of them it was due to chronic ear disease, for which ear surgery - radical mastoidectomy - had been performed in three cases. Only one patient (II-2) showed a steeply sloping type of threshold as is sometimes seen after mastoid surgery.

All but one of the five affected participants with a submucous or overt cleft palate showed an air-bone gap, while only two of the nine affected persons without clefts had an air-bone gap (not significant according to Fisher's exact probability test, $P = .063$).

After exclusion of the 73-year-old patient in generation I, one-way ANOVA did not reveal any significant difference in threshold between the frequencies. It was obvious that the 8 kHz frequency showed greater variability in threshold than any of the other frequencies: the threshold SD was about 22 dB, which was significantly greater according to Bartlett's test than the SDs of about 10 and 13 dB for the thresholds at 0.25 and 0.5 kHz, respectively. We calculated a grand mean threshold for the affected cases in generations II and III of about 40 dB and a 95% confidence interval of about 15 to 65 dB. It should be noted that there was a distinct tendency for the threshold to increase by several tens of decibels at the highest frequencies, which was not unlike what could have been expected from presbycusis (Fig. 2).

According to the criteria of the European Work Group on Genetics of Hearing Impairment [19], the 14 evaluable cases showed the following types of threshold: U-shaped (n = 3), flat (n = 2), flat or gently sloping (downward) (n = 3), gently sloping (n = 3), or steeply sloping (n = 3). Two cases with a sloping type (one gently, one steeply sloping) showed dome-shaped thresholds.

There was no uniformity in audiogram shape. Speech audiometry revealed speech perception thresholds in accordance with the pure-tone threshold data; a 100% discrimi-

nation score was obtained in all the cases and there was no sign of "roll-over" (i.e., decrease in discrimination score with increasing stimulus intensity), which might be suggestive of retrocochlear hearing impairment.

Cross-sectional analysis of sensorineural hearing threshold in relation to age

The mean threshold at each frequency was compared between generation II (n = 6; mean age 46.8 y; range, 41-51 y) and generation III (n = 7; mean age 20.9 y; range, 13-25 y). Student *t* test did not reveal any significant difference in mean hearing threshold between these generations.

Longitudinal analysis of sensorineural hearing threshold in relation to age

Sufficient serial audiograms were available for longitudinal analysis in four cases (II-4, II-6, III-8 and III-10). In the right ear only, 2 of the 20 regression lines that could be calculated showed significant progression (case II-4, slope 0.5 dB/y [small but significant] at 8kHz; case III-8, slope 1.8 dB/y at 2 kHz) (Fig. 2J and F, respectively). In the left ear this was the case in only 1 of the 22 regression lines (case II-6, slope 1.4 dB/y at 0.25 kHz) (Fig. 2H). These relative frequencies were not beyond chance level: given a probability of $P = .025$ that significant progression (i.e., positive slope) will occur by chance alone, the tail probability for one or two such occurrences is $P > .05$ in a binomial distribution with N = 20 or 22. Apart from these findings, case III-5 showed remarkable progression between the age of 14 and 20 years: about 4 dB/y in the right ear at 1 and 8 kHz and about 3 to 4 dB/y in the left ear at 1 to 8 kHz (Fig. 2C). In summary, tangible progression was only found in a few incidental cases at a particular frequency or frequencies and was certainly not a characteristic feature of the trait.

Discussion

All the affected participants had hearing impairment, which contrasts with the previously reported findings on the Stickler syndrome, i.e., unspecified or type I. Popkin and Polomeno [20] found SNHI in approximately 9% of their cases. Vanniasegaram and Bellman [21] reported that 5 of their 11 cases had hearing impairment, and 2 of them (18%) had SNHI. Liberfarb et al. [22] confirmed hearing impairment in 30 of the 35 cases tested from a total of 70 cases: 22 of them had high-frequency SNHI, 4 had presbycusis, 2 had congenital hearing impairment and 2 may have had early high-frequency SNHI. In the study by Lucarini et al. [23], 6 of the 14 cases showed hearing impairment: 3 cases had mixed hearing impairment and 3 cases had high-frequency SNHI. All these cases had close to normal hearing at 0.25 to 2 kHz, while elevated thresholds were found almost exclusively at 8 kHz, which is substantially better than in our cases. Gorlin et al. [24] stated that progressive high-frequency hearing impairment is present in 80% of Stickler cases. We did not find any substantial progression in SNHI in the present family.

Although at least some hearing loss has been indicated as a feature of all Stickler-related osteochondrodysplasias linked to *COL2A1, COL11A1,* and *COL11A2* [25], it is difficult to compare the present findings in a family with a *COL11A2* mutation to those obtained in previously reported, unlinked, families. Annunen et al. [26] reported on seven *COL2A1*-linked patients and mentioned normal hearing or only slight hearing impairment. Wilkin et al. [14] reported on six *COL2A1*-linked families. Remarkably, only one (family C) showed SNHI in the majority of cases (there were no details about SNHI). Linkage to *COL2A1* was excluded in families G and H and linkage to *COL11A1* and *COL11A2* was also excluded. Interestingly, five of the eight affected individuals in Family G showed SNHI (unspecified) and only one had (mild) myopia; thus the SNHI was apparently present in a type of nonocular Stickler-like syndrome.

There is considerable phenotypic variability among patients with the Stickler syndrome, which is also reflected in the degree and type of hearing impairment. In the present trait with a *COL11A2* mutation, SNHI was a typical feature, showing 100% penetrance. The degree of SNHI, although variable, was mild to moderate, i.e., in the range of 30 to 60 dB in the majority of cases. In addition, close to half of the participants showed a substantial

air-bone gap, associated in the majority with an overt or submucous cleft palate. The sensorineural hearing threshold led to various types of audiogram, downsloping in most cases. Allowing for presbycusis, there was no tangible progression in SNHI. Sirko-Osadsa et al. [12] described a family with a different mutation in *COL11A2*. They observed approximately 30 to 50 dB SNHI in the seven individuals tested, which seems fairly similar to our findings. Although they mentioned that four individuals had a cleft palate, they did not specify any conductive hearing loss.

Remarkably similar phenotypes to the one characteristic of our family have been described recently in families with otospondylomegaepiphyseal dysplasia (OSMED), which is caused by different mutations in the *COL11A2* gene. Pihlajamaa et al. [25] found mutations in the heterozygous state, while Vikkula et al. [11] and van Steensel et al. [27] reported homozygosity for a mutation in this gene in three siblings born to consanguineous parents. The latter authors compared the features of the affected persons to those of the present family and concluded that OSMED can be considered as a clinically more severe autosomal recessive variant of the present autosomal dominant Stickler type II syndrome. SNHI in their cases was documented from the age of 5 to 9 years onward; it showed downsloping hearing thresholds from about 50 dB at 0.25 kHz to 80 dB at 8 kHz (i.e., worse than in Fig. 2). One case also had conductive hearing loss of approximately 20 dB; there was no progression in SNHI in any of these cases.

Some authors [15,16] have recently suggested to replace the term "nonocular Stickler syndrome" with "autosomal dominant OSMED syndrome". However, recent findings [26,28,29] suggest that heterozygous OSMED is unlikely to cover most or all of the clinical problems associated with heterozygous *COL11A2* mutations.

The audiograms in our affected cases clearly showed that most of them have borderline social hearing (i.e., mean threshold of about 35 dB HL for the speech frequencies), if unaided and as judged from the sensorineural hearing component (Fig. 2). In view of the fact that many of these patients had an overt or submucous cleft palate and a tendency toward developing otitis media, it is worth emphasizing that appropriate otologic care, which includes fitting suitable hearing aids at a sufficiently young age, may be of major benefit to young patients with this type of nonocular Stickler syndrome.

Acknowledgements

We wish to thank the participants in this study, our colleagues who provided us with additional relevant medical information, and Mr. J. Noten for technical assistance.

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Summary and conclusions

Summary and conclusions

Hearing loss is the most common form of sensory impairment in humans [1]. With advancing age, a growing proportion of the population will encounter the problems related to diminishing auditory acuity. When hearing impairment is present from birth or is acquired in early childhood, it can be devastating for normal development. Spoken language development, a natural process in children with normal hearing, becomes a major problem. Early childhood deafness also has implications for cognitive, emotional and social development. Telling the parents of a young child that their child is deaf, is one of the most emotional and difficult tasks for the paediatric otolaryngologist. At that moment, the happy and optimistic ideas of the parents about their child's future are destroyed. Even with recent improvements in audiology, such as modern hearing aids, bone anchored hearing aids, implantable hearing aids and cochlear implants, the child's development will not be as natural as that of children with normal hearing. In the majority of cases of early childhood hearing impairment, deafness is an isolated disorder. With the help of the parents, teachers of the deaf and many others, but most importantly with compensation of cognitive, visual and other skills by the child itself, (near) normal development is within reach. However, in a substantial part of cases, early childhood hearing impairment is not isolated, but forms part of a genetic syndrome with associated handicaps, or is acquired through pre-, peri- or postnatal causes possibly with associated deficits. In these cases, development is hampered, while normal development may even be impossible. This means that more demands are made on the child's family, the teachers and medical professionals to help these children cope with their needs and demands. One can only admire the dedication of the parents and the professionals in the field of education of the deaf in raising and educating children with hearing impairment and associated handicaps. However, one must also admire the children in coping with their handicaps.

Chapter 1 presents an overview of the history of education of the deaf in general and in the Netherlands in particular. The discussion of oral versus manual language pervades this historic overview.

Medical interest in the aetiology of deafness started at the beginning of the 19th century, with special emphasis on syndromic forms, although it is estimated that 70% of hereditary deafness is non-syndromic. In the second half of the 20th century, much research was conducted into the aetiology of childhood deafness. Studies continued to encounter a high proportion (about 1/3) of unknown causes, while hereditary and acquired causes accounted for 1/3 each. New medical technologies have influenced the prevalence of causes of childhood hearing impairment. Immunization programmes against rhesusantagonism, mumps, measles and rubella have strongly reduced the prevalence of kernicterus and the congenital rubella syndrome (CRS). Since this drop in the prevalence of CRS, congenital cytomegalovirus is the leading infectious cause of mental retardation and congenital sensori-neural deafness in the United States. The reduction of *Haemophilus influenza* type b meningitis as a result of immunization has decreased the prevalence of postnatally acquired forms of deafness, but increased the impact of pneumococcal meningitis, which is notorious for its severe sequelae. Improvements in resuscitation techniques for very small preterm babies at neonatal intensive care units have resulted in higher survival rates, but a possible drawback is an apparent increase in the number of young children with deafness and additional handicaps. Improvements in chromosomal examination methods, as well as higher survival rates in children with chromosomal abnormalities, have led to an increase in the prevalence of such conditions as causes of deafness with additional disabilities.

New or refined imaging (CT and MRI) techniques have led to the identification of many new syndromes. More often inner ear abnormalities are found in patients with congenital hearing impairment, and by now, fairly characteristic CT abnormalities have been described in various types of deafness. Also vestibular deficits are reported in hereditary and acquired forms of deafness.

Developments in the field of human genetics have led to linkage and cloning of genes in various syndromic and non-syndromic forms of hereditary deafness. At the present rate of progress, it may soon become possible to make individual diagnoses on the basis of mutation analysis in many persons with a genetic cause of deafness.

Chapter 2 presents two aetiological school studies on hearing impaired pupils with multiple handicaps, performed at the Institute for the Deaf in Sint-Michielsgestel in the

Netherlands. We performed a retrospective investigation on the medical records of the pupils, which included anamnestic re-evaluation with special emphasis on possible causes of deafness. In addition, examinations were performed by an otolaryngologist, a paediatrician and an ophthalmologist. Special attention was paid to the presence of dysmorphic stigmata. When indicated, a clinical geneticist was consulted. Audiological examination was always performed. All the pupils showed hearing impairment with threshold of > 60 dB HL.

In the first study (**Chapter 2.1**), all participants (N=122) had a mental handicap with a non-verbal IQ of 40-80. 57 pupils were < 20 years of age and 65 > 20 years. In the younger group, hereditary causes were found in 19%, acquired causes in 39%, chromosomal causes in 7% and unknown causes in 35%. In the older group, these rates were 15%, 57%, 2% and 26% respectively. Owing to the fact that most pupils were born after the introduction of rubella immunization, no differences were found between the younger group and the older group in this respect. Among the perinatal causes, kernicterus was the main cause of deafness in the perinatal period in the older group, while severe prematurity or dysmaturity was the main cause in the younger group. Chromosomal disorders were more prevalent in the younger group, while postnatal causes were more prevalent in the older group.
Hereditary, acquired, chromosomal and unknown causes were found in 17%, 48%, 4% and 30%, respectively. In comparison with other studies on the aetiology of childhood deafness (in children with normal intelligence), acquired causes predominated over inherited causes, which may be typical of deafness combined with mental handicap.

Chapter 2.2 presents the results of a longitudinal aetiological study on 57 pupils at the deaf-blind department in the school year 1998-1999 and on 49 deaf-blind pupils at the same department in the school year 1986-1987. Hereditary causes were found in the younger group and in the older group in 26% and in 16%, respectively. There were only syndromic conditions among the hereditary causes in the two groups. The prevalence of acquired causes had diminished significantly over the years (78% vs 53%), which was chiefly due to the decreased prevalence of congenital rubella cases. There were more cases of severe prematurity or dysmaturity in the younger group and chromosomal conditions were only found in this group.

Another longitudinal study was performed on pupils at the infants' department in 1998 (N=55) and in 1988 (N=68). The proportion of hereditary causes remained stable (34 vs

33%), while that of the acquired causes diminished strongly (40% vs 22%), especially in the prenatal causes group (16% vs 4%), due to a significant drop in the prevalence of rubella cases. In contrast, the proportion of chromosomal conditions had increased significantly (1% vs 15%). Over the study period, the percentage of infants with multiple handicaps increased from 25 to 38%.

Chapter 3 describes two studies on the CHARGE association. The acronym CHARGE indicates the association of coloboma (C), heart defects (H), atresia choanae (A), retardation of growth and/or development (R), genital hypoplasia (G) and ear anomaly (E) and/or hearing impairment or deafness. Many additional features have been reported. According to the literature, the diagnosis should preferably be based on the presence of at least four of the six cardinal features (covered by the acronym), provided that these include coloboma and/or choanal atresia. Our studies addressed the audiological findings in 22 cases. Vestibular areflexia was a constant finding in nine CHARGE cases and two CHARGE-like cases (who did not meet all the criteria for diagnosis as mentioned above), who underwent vestibular testing. Although the literature emphasized that developmental delay was considered to be caused by psychomotor retardation, the diagnosis "mental retardation" should be used with caution in multisensory-impaired children. Moreover, vestibular areflexia could have been mistaken for motor retardation, particularly if combined with visual problems.

Ten out of the 20 cases with the CHARGE association and two CHARGE-like cases underwent temporal bone CT scanning and/or MRI: bilateral aplasia of the semicircular canals and obliteration of the oval windows were characteristic findings. The vestibule was hypoplastic in most cases, while the cochlea was hypoplastic in many cases, even in the few cases with close to normal bone conduction thresholds. Ossicular chain malformation was observed in about half of the cases. These findings indicate that not only clinical findings but also radiological findings are important to diagnose the CHARGE association and CHARGE-like cases.

In **Chapter 4** three symptomatically different types of delayed endolymphatic hydrops are described in children with congenital cytomegalovirus infection. In the first case, ipsilateral delayed endolymphatic hydrops was postulated in a boy with ipsilateral deafness and

contralateral progressive hearing impairment, who developed severe attacks of vertigo. The second case concerned a child with unilateral deafness and recurrent periods of sudden deafness in the contralateral ear in the absence of vestibular function. Delayed hydrops of the labyrinth contralateral to the (almost completely) deaf ear was a plausible explanation for these findings. The third case was found to have severe progressive hearing loss, which led to profound deafness at the age of 2 years and vestibular areflexia before the age of 4 years. Endolymphatic hydrops was probably the underlying cause for the (progressive) inner ear impairment. It can be suggested that the first two cases illustrate two different monosymptomatic forms of delayed endolymphatic hydrops: one confined to vestibular symptoms originating from the ipsilateral labyrinth and the other confined to hearing impairment symptoms originating from the contralateral labyrinth, while the third case could be an asymptomatic form of delayed endolymphatic hydrops.

In **Chapter 5.1** a case study is presented of a boy with rapidly progressive sensorineural hearing impairment. CT scanning showed bilateral dysplasia of the cochlea and a wide vestibular aqueduct. Although thyroid function tests were normal, thyroglobulin levels were elevated and the diagnosis of the Pendred syndrome was confirmed by the positive results of a potassium perchlorate test. In a follow-up study (**Chapter 5.2**) we were able to trace 12 patients known to have the Pendred syndrome. We made a thorough review of their clinical presentation. Vestibular and radiological examinations were performed. Additionally, we reviewed their long-term audiological data. In most cases, progression in hearing impairment was relatively rapid initially (i.e. at a young age) and then slowed down as the patients grew older. Vestibular testing in five patients showed abnormal responses in four of them. Imaging of the temporal bones in seven out of these 12 patients showed bilateral wide vestibular aqueducts in each case. Mutation analysis of the *PDS* gene confirmed the diagnosis in all cases tested, although the potassium perchlorate test was negative in one patient. In the literature, the Pendred syndrome is described as congenital, mostly profound, sensorineural hearing loss with hypothyroidism and a positive perchlorate test. This classical phenotype has to be rewritten. Our study substantiated the early-onset and progressivity of the hearing impairment in relation to an almost obligatory finding of wide vestibular aqueducts.

These findings provide the opportunity to diagnose the Pendred syndrome clinically in infancy or early childhood.

The Stickler syndrome (**Chapter 6**) is an autosomal dominant connective tissue disorder that includes ocular, auditory, orofacial, skeletal, cardiac and other features. The Stickler syndrome is generally linked to *COL2A1*, *COL11A1* or *COL11A2*. We performed otorhinolaryngological and audiological examinations on a previously described Dutch family with the non-ocular Stickler type II syndrome, linked to *COL11A2*. All 15 affected participants had hearing impairment. Mixed hearing loss was present in six cases; in four of them it was due to chronic ear disease, for which surgery had been performed in three cases. Three patients had a cleft palate, two cases had a submucous cleft and one patient had a high-arched palate. All but one of the five cases with a submucous or overt cleft palate showed an air-bone gap, while only two out of the nine affected persons without clefts had an air-bone gap. The mean sensorineural hearing threshold was about 40 dB HL and was liable to increase (presumably by presbyacusis) at the highest frequencies. Progression was not a characteristic feature. The audiograms showed various types of threshold: U-shaped (n=3), flat (n=2), flat or gently (downward) sloping (n=3), gently sloping (n=3), or steeply sloping (n=3).

There is considerable phenotypic variability among patients with the Stickler syndrome, which is also reflected in the degree and type of hearing impairment. In our family with a *COL11A2* mutation, sensorineural hearing impairment was a typical feature, showing 100% penetrance, which contrasts with the classical Stickler syndrome (type 1) with high myopia.

Conclusions

This thesis aimed to make a contribution to the ongoing research in the field of deafness or hearing impairment. Recent developments in general health programmes and clinical medicine have had and are having a great impact on the prevalence of causes of childhood hearing impairment.

The significant reductions in congenital rubella, kernicterus and *Haemophilus influenza*

meningitis cases have caused a decrease in the prevalence of acquired causes of deafness. On the other hand, new causes of acquired hearing impairment, such as congenital cytomegalovirus infection, severe prematurity or dysmaturity and chromosomal disorders, have led to increasing numbers of children with hearing impairment and associated handicaps. Nowadays children with an isolated hearing deficit tend to be treated as outpatients, whereas those with severe pathology go to schools for the deaf. Consequently, these schools have changed into institutes for multiply handicapped hearing impaired children.

Developments in human genetic research have increasingly led to the identification of genes underlying various syndromic and non-syndromic forms of hereditary deafness. As a result, further phenotypic-genotypic delineation of various hereditary forms of deafness has become possible. Genetic studies have shown, that some genes are responsible for both syndromic and non-syndromic deafness, and that both autosomal recessive and autosomal dominant forms of deafness can be associated with the same gene [2]. Therefore it is imperative to make a detailed clinical description of various types of deafness. Our study on the Stickler syndrome is a further example of such an approach. This non-ocular type of the Stickler syndrome was associated with mutations in *COL11A2*, while mutations in this gene also cause the autosomal recessive OSMED syndrome [3] and autosomal dominant non-syndromic hearing impairment DFNA13 [4-6]. Identification of the *PDS* gene responsible for the Pendred syndrome (but also for the non-syndromic enlarged vestibular aqueduct syndrome) [7] has enabled an earlier diagnosis of this syndrome, as well as our findings of early-onset rapidly progressive sensorineural hearing impairment and an enlarged vestibular aqueduct as obligatory features. Presently, the clinical diagnosis can be confirmed on a molecular basis, which improves the quality of clinical assessment.

The finding of characteristic radiological abnormalities in the CHARGE association could be made by a further clinical description (i.e. vestibular areflexia) and refinements of existing imaging techniques. These findings have been corroborated by others [8,9] and have led to special research into saccular function in the CHARGE association [10,11]. These new findings have helped to delineate this association more clearly, but the aetiology is still unknown. Perhaps the characteristic radiological findings will help to elucidate the cause of this association. They already provide the opportunity to make the clinical diagnosis at a younger age.

We expect that further developments in medicine will continue to extend our knowledge about deafness and we hope that this will be beneficial, especially for multiply handicapped deaf children to cope with their needs and demands.

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Samenvatting en conclusies

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Gehoorverlies is bij de mens de meest voorkomende vorm van zintuiglijke beperking [1]. Met toenemende leeftijd ondervindt een steeds groter deel van onze samenleving problemen van een verminderde gehoorscherpte. Wanneer het gehoorverlies reeds vanaf de geboorte aanwezig is, of in de eerste levensjaren ontstaat, kan het een zeer grote invloed hebben op de normale ontwikkeling. De ontwikkeling van gesproken taal, een natuurlijk proces bij normaal horende kinderen, wordt een groot probleem. Vroegkinderlijke doofheid heeft daarnaast ook gevolgen voor de cognitieve, emotionele en sociale ontwikkeling. De ouders van een klein kind te moeten mededelen dat hun kind doof is, is een van de moeilijkste en meest emotionele taken van een KNO-arts die zich bezighoudt met kinderaudiologie. Op dat moment worden de optimistische verwachtingen van de ouders over de toekomst van hun kind de grond in geboord. Zelfs met de nieuwe ontwikkelingen op het gebied van de audiologie, zoals moderne hoortoestellen, in het bot verankerde hoortoestellen, implanteerbare hoortoestellen en cochleair implants, zal de ontwikkeling van het kind niet meer zo natuurlijk verlopen als wanneer het normaal gehoord zou hebben. Gehoorverlies komt bij het overgrote deel van vroegkinderlijke doofheid als geïsoleerd symptoom voor. Met de hulp van de ouders, leerkrachten in het dovenonderwijs en vele anderen, maar vooral door compensatie door middel van de eigen cognitieve, visuele en andere mogelijkheden van het kind, is een normale ontwikkeling mogelijk haalbaar. In een aanzienlijk deel van de gevallen komt vroegkinderlijke doofheid echter niet geïsoleerd voor, maar is de doofheid onderdeel van een erfelijk syndroom waarbij andere handicaps kunnen voorkomen, of is de doofheid verworven in de pré-, peri- of postnatale periode en zijn ook andere beperkingen aanwezig. In dergelijke situaties kan de normale ontwikkeling van het kind nog meer belemmerd worden of zelfs bijna onmogelijk zijn. Dan zal een nog groter beroep gedaan worden op de ouders, dovenonderwijzers en medici om deze kinderen te helpen in hun ontwikkeling. Men kan slechts bewondering hebben voor het doorzettingsvermogen van ouders en leerkrachten om meervoudig gehandicapte dove kinderen op te voeden en te onderwijzen. Vooral kan men deze kinderen zelf bewonderen voor het omgaan met hun handicaps.

In **Hoofdstuk 1** wordt een historisch overzicht gegeven van het dovenonderwijs in het algemeen en in Nederland in het bijzonder. In dit overzicht staat de discussie tussen oraal dovenonderwijs en gebarentaal centraal.

Medische belangstelling voor de oorzaken van doofheid ving aan in het begin van de negentiende eeuw, waarbij men bijzondere aandacht had voor syndromale vormen van doofheid, alhoewel momenteel geschat wordt dat 70% van de erfelijke vormen van doofheid van niet-syndromale origine is. Vooral in de tweede helft van de twintigste eeuw werd veel onderzoek verricht naar mogelijke oorzaken van vroegkinderlijke doofheid. In de meeste studies worden erfelijke oorzaken en verworven oorzaken beide in 1/3 deel van de gevallen gevonden, terwijl eveneens in 1/3 deel, ondanks uitgebreid onderzoek, geen oorzaak voor de doofheid vastgesteld kan worden. Nieuwe ontwikkelingen binnen de geneeskunde zijn van invloed op de verscheidene oorzaken van vroegkinderlijke doofheid. Vaccinatieprogramma's tegen rhesusantagonisme, bof, mazelen en rode hond hebben het voorkomen van kernicterus en het aangeboren rode hond syndroom (congenitaal rubella syndroom, CRS) sterk gereduceerd. Sinds deze sterke vermindering in het voorkomen van CRS, is de aangeboren cytomegalovirus infectie de belangrijkste infectieuze oorzaak van aangeboren mentale retardatie en doofheid in de Verenigde Staten. Het aantal kinderen met postnataal verworven oorzaken van doofheid nam af als gevolg van de vaccinatie tegen *Haemophilus influenzae* type b meningitis, maar momenteel wordt de *Pneumococcen* meningitis, die berucht is vanwege de ernstige restverschijnselen, meer gezien. Verbeteringen in levensreddende technieken op de neonatale intensive care hebben geleid tot grotere overlevingskansen voor te vroeg geboren babies (prematuren) en babies met een ernstig ondergewicht (dysmaturen). Een mogelijk gevolg hiervan is echter een duidelijke toename van jonge dove kinderen met bijkomende handicaps. Ten gevolge van verbeterde chromosomale onderzoekstechnieken en betere overlevingskansen voor kinderen met chromosomale afwijkingen worden tegenwoordig vaker chromosomale defecten gezien als oorzaak van doofheid met nevenhandicaps.

Nieuwe en/of verbeterde beeldvormende technieken (CT- en MRI-scan) hebben ook in toenemende mate bijgedragen aan de identificatie van nieuwe syndromen. Steeds vaker worden binnenoorafwijkingen gevonden bij patiënten met een aangeboren doofheid en tegenwoordig worden in verscheidene vormen van doofheid specifieke CT-scan afwijkingen

beschreven. Ook evenwichtsafwijkingen worden beschreven bij zowel erfelijke als verworven oorzaken van doofheid.

Ontwikkelingen op het gebied van de menselijke genetica hebben geleid tot genkoppeling en genbepaling in verscheidene vormen van syndromale en niet-syndromale erfelijke doofheid. Wanneer men in ogenschouw neemt hoe snel de ontwikkelingen binnen de genetica verlopen, is het niet ondenkbaar dat binnen afzienbare tijd een individuele diagnose gesteld kan worden op basis van genetische analyse bij personen met een erfelijke vorm van doofheid.

In **Hoofdstuk 2** worden twee schoolstudies naar oorzaken van doofheid gepresenteerd. Dit zijn de eerste studies die verricht zijn op scholen voor meervoudig gehandicapte dove kinderen. Beide studies vonden plaats op het Instituut voor Doven in Sint Michielsgestel. We verrichtten een retrospectief onderzoek aan de hand van de medische dossiers van de pupillen en een anamnestische reëvaluatie met speciale aandacht voor mogelijke doofheidsoorzaken. De kinderen werden onderzocht door een KNO-arts, een kinderarts en een oogarts. Er werd speciaal gelet op uitwendig zichtbare dysmorfieën. Zonodig werd een klinisch geneticus geconsulteerd. Gehooronderzoek werd bij alle kinderen verricht. Alle pupillen hadden een gehoorverlies van meer dan 60 decibel.

In de eerste studie (**Hoofdstuk 2.1**) hadden alle deelnemers (N=122) een mentale handicap met een nonverbaal IQ van 40-80. 57 pupillen waren jonger dan 20 jaar en 65 ouder dan 20 jaar. In de jongste groep werden erfelijke oorzaken gevonden bij 19%, verworven oorzaken bij 39%, chromosomale oorzaken bij 7% en een onbekende oorzaak bij 35%. In de oudste groep betrof dit respectievelijk 15%, 57%, 2% en 26%. Aangezien de meeste pupillen geboren waren na de invoering van de rode hond vaccinatie, werd in dit opzicht geen verschil gevonden tussen beide groepen. Met betrekking tot perinatale oorzaken bleek dat kernicterus de voornaamste doofheidsoorzaak was in de oudste groep en ernstige pré- en/of dysmaturiteit de voornaamste doofheidsoorzaak was in de jongste groep. Chromosomale afwijkingen werden meer gezien in de jongste groep en postnatale oorzaken meer in de oudste groep.
Met betrekking tot de beide groepen tesamen werden erfelijke, verworven, chromosomale en onbekende oorzaken in respectievelijk 17%, 48%, 4% en 30% van de pupillen gevonden. Wanneer men dit vergelijkt met andere studies naar vroegkinderlijke doofheidsoorzaken (bij

kinderen met een normale intelligentie), valt op dat verworven oorzaken belangrijker waren dan erfelijke oorzaken, hetgeen wellicht typisch is voor doofheid in combinatie met een mentale handicap.

In **Hoofdstuk 2.2** wordt een longitudinale studie naar doofheidsoorzaken beschreven, die verricht werd bij 57 pupillen van de doofblinden afdeling in het schooljaar 1998-1999 en bij 49 pupillen van dezelfde afdeling in het schooljaar 1986-1987. Erfelijke oorzaken werden in de jongste groep gevonden bij 26% en in de oudste groep bij 16%. In beide groepen was alleen sprake van erfelijke syndromen. In de loop van de tijd waren verworven oorzaken duidelijk afgenomen (78% vs 53%), hetgeen met name het gevolg was van een vermindering van het aantal gevallen met aangeboren rubella syndroom. Er werden meer gevallen van ernstige pré- en/of dysmaturiteit in de jongste groep gevonden terwijl chromosomale afwijkingen alleen in deze groep gezien werden.

Voorts werd een longitudinale studie verricht bij de kinderen van de vroegbegeleidingsafdeling (minder dan 5 jaar oud) in 1998 (N=55) en in 1988 (N=68). Het aandeel van de erfelijke oorzaken bleef stabiel (34% vs 33%), terwijl dat van de verworven oorzaken duidelijk afnam (40% vs 22%), met name in de prenatale groep (16% vs 4%), ten gevolge van een significante afname van het aantal gevallen met aangeboren rubella syndroom. Daarentegen was er een duidelijke toename van het aantal gevallen met chromosomale afwijkingen (1% vs 15%). Het percentage meervoudig gehandicapte dove kinderen was toegenomen van 25 tot 38%.

Hoofdstuk 3 beschrijft twee studies over de CHARGE associatie. Het acroniem CHARGE geeft de associatie aan van bepaalde oogafwijkingen (Colobomen), Hartafwijkingen, een aangeboren afsluiting van de neusgangen (Atresia choanae), Retardatie in groei en/of ontwikkeling, onderontwikkelde geslachtsorganen (Genitale hypoplasie) en oorschelp afwijkingen (Ear anomalies) en/of slechthorendheid cq. doofheid. Nog vele andere bijkomende aandoeningen zijn beschreven. Volgens de literatuur zou de diagnose pas gesteld kunnen worden indien tenminste vier van de zes bovengenoemde hoofdkenmerken aanwezig zijn, waarbij ten minste Colobomen en/of Atresia choanae. In onze studies werden de audiologische bevindingen bij 22 gevallen beschreven. Het niet werken van de evenwichtsorganen (vestibulaire areflexie) was een constante bevinding in de negen personen

met CHARGE associatie en de twee met een CHARGE-achtige aandoening (die wel veel kenmerken vertoonden van de CHARGE associatie, maar die niet voldeden aan alle criteria nodig voor het stellen van de diagnose), bij wie evenwichtsonderzoek was verricht. Hoewel in de literatuur benadrukt wordt, dat de vertraagde ontwikkeling waarschijnlijk het gevolg is van een psychomotore retardatie, moet men in de praktijk zeer terughoudend zijn met de diagnose mentale retardatie bij kinderen met een meervoudig zintuiglijke handicap. Bovendien kan vestibulaire areflexie ook een oorzaak zijn voor motore retardatie, met name bij kinderen met een visuele handicap.

Bij tien van de twintig personen met CHARGE associatie en de twee met een daarop lijkende aandoening zijn CT- en/of MRI-scan opnames vervaardigd van het gehoororgaan: beiderzijds afwezige halfcirkelvormige kanalen (het evenwichtsorgaan) en niet goed tot ontwikkeling gekomen ovale vensters waren typische bevindingen. Eveneens was in de meeste gevallen het vestibulum niet goed ontwikkeld, evenals het slakkenhuis, zelfs bij die enkele gevallen die een bijna normaal gehoor hadden. Afwijkingen aan de gehoorbeenketen werden in ongeveer de helft van de gevallen waargenomen. Deze resultaten geven aanleiding tot de gedachte dat niet alleen de klinische, maar ook de röntgenologische bevindingen van belang zijn bij het stellen van de diagnose CHARGE associatie.

In **Hoofdstuk 4** worden drie verschillende types van vertraagde endolymfatische hydrops beschreven bij drie kinderen met een congenitale cytomegalovirus infectie. Bij het eerste kind werd een vertraagde endolymfatische hydrops aannemelijk gemaakt bij een ipsilaterale doofheid en een progressief gehoorverlies in het andere (contralaterale) oor, hetgeen gepaard ging met ernstige duizeligheidsaanvallen. Het tweede kind vertoonde doofheid in het ene oor en herhaaldelijk terugkerende periodes van plotseling optredende gehoorsvermindering in het andere oor bij een volledig ontbrekende evenwichtsfunctie. Vertraagde hydrops van het labyrint contralateraal aan het bijna volledig dove oor is een plausibele verklaring voor deze bevindingen. Het derde kind had een ernstig progressief gehoorverlies, dat aanleiding gaf tot ernstige doofheid op de leeftijd van twee jaar en volledige vestibulaire onprikkelbaarheid voor het vierde levensjaar. Het progressieve gehoorverlies werd waarschijnlijk veroorzaakt door endolymfatische hydrops. Het lijkt aannemelijk dat de eerste twee kinderen twee verschillende monosymptomatische vormen van vertraagde endolymfatische hydrops hadden,

waarbij in het eerste geval vestibulaire symptomen afkomstig waren van het ipsilaterale dove labyrint, terwijl in het andere geval symptomen van gehoorsvermindering afkomstig waren van het contralaterale labyrint. Het derde kind zou een asymptomatische vorm van vertraagde endolymfatische hydrops kunnen hebben.

In **Hoofdstuk 5.1** wordt een klinische beschrijving gepresenteerd van een jongen met een sterk progressieve binnenoor-slechthorendheid. CT-scans toonden een onderontwikkeld slakkenhuis aan en een verwijd vestibulair aquaduct. Alhoewel bloedonderzoek betreffende de schildklier normale uitslagen liet zien, bleek het thyreoglobuline gehalte te hoog te zijn en werd de diagnose Pendred syndroom bevestigd door de positieve uitslag van de kaliumperchloraat test. In een vervolgstudie (**Hoofdstuk 5.2**) konden 12 patiënten, die reeds bekend waren met het Pendred syndroom, getraceerd worden. Het klinisch beeld werd opnieuw beoordeeld en uitgebreid met behulp van evenwichts- en röntgenologisch onderzoek. Bovendien werden de lange termijn audiologische bevindingen opnieuw beoordeeld. Aanvankelijk was het gehoorverlies op jonge leeftijd sterk progressief en verminderde deze progressiviteit naarmate de patiënten ouder werden. Evenwichtsonderzoek bij vijf patiënten liet abnormale bevindingen zien bij vier van hen. Bij zeven van de twaalf patiënten werden röntgenopnames van het gehoororgaan vervaardigd en telkenmale werd een beiderzijds verwijd vestibulair aquaduct gevonden. Genetisch onderzoek naar het *PDS* gen bevestigde de diagnose bij alle patienten, alhoewel de kaliumperchloraat test bij één van hen negatief was. In de literatuur wordt het syndroom van Pendred beschreven als een congenitaal, meestal zeer ernstig, perceptief (binnenoor) gehoorverlies in combinatie met een vertraagde werking van de schildklier en een positieve perchloraat test. Deze gebruikelijke omschrijving moet gewijzigd worden. Onze studie maakte duidelijk dat er sprake is van een vroegtijdig en sterk progressief gehoorverlies in combinatie met een bijna obligate bevinding van verwijde vestibulaire aquaducten. Deze bevindingen maken het mogelijk de diagnose Pendred syndroom reeds op jonge leeftijd op klinische gronden te stellen.

Het Stickler syndroom (**Hoofdstuk 6**) is een autosomaal dominante bindweefselaandoening, waarbij oog-, gehoor-, aangezicht-, skelet en hartafwijkingen worden gevonden. Het Stickler syndroom is genetisch gezien gekoppeld aan *COL2A1*, *COL11A1* of *COL11A2*. We hebben

een reeds eerder beschreven Nederlandse familie met het non-oculaire Stickler type II syndroom (een vorm van Stickler syndroom zonder oogafwijkingen) gekoppeld aan *COL11A2* KNO-heelkundig en audiologisch onderzocht. Alle vijftien aangedane familieleden die werden onderzocht vertoonden een perceptief gehoorverlies. Een gemengd gehoorverlies (zowel van het middenoor als van het slakkenhuis) werd bij zes personen gevonden: bij vier van hen was dit het gevolg van chronische ooraandoeningen, waarvoor drie personen waren geopereerd. Drie patiënten hadden een gehemeltespleet, één patiënt had een submuceuze gehemeltespleet en één patiënt had een hooggewelfd gehemelte. Vier van de vijf patiënten met een (submuceuze) gehemeltespleet hadden een middenoor (geleidings)-gehoorverlies, terwijl dit gezien werd bij slechts twee van de negen patiënten zonder een gehemeltespleet. De gemiddelde perceptieve gehoordrempel bedroeg 40 decibel en was ernstiger in de hogere frequenties (mogelijk ten gevolge van ouderdomsslechthorendheid). Progressiviteit van gehoorverlies werd zelden gezien. Er werden verschillende types gehoordrempels gevonden.

Er bestaat een aanzienlijke variatie in uitingsvormen bij patiënten met het syndroom van Stickler, die ook de ernst en het type gehoorverlies betreft. In de bestudeerde familie met een *COL11A2* mutatie werd een perceptief gehoorverlies bij alle patiënten gezien, hetgeen afwijkt van de bevindingen bij het klassieke Stickler syndroom met oogafwijkingen.

Conclusies

In dit proefschrift is getracht een bijdrage te leveren aan het onderzoek op het gebied van slechthorendheid en doofheid. Recente ontwikkelingen op het gebied van de gezondheidszorg en de specialistische geneeskunde zijn van grote invloed (geweest) op het vóórkomen van de verscheidene oorzaken van vroegkinderlijke doofheid.

Door de duidelijke afname van het aantal nieuwe gevallen van congenitale rubella, kernicterus en *Haemophilus influenzae* meningitis komen verworven doofheidsoorzaken minder vaak voor. Daar staat tegenover dat nieuwe oorzaken van verworven gehoorverlies, zoals congenitale cytomegalovirus infecties, ernstige pré- en dysmaturiteit en chromosomale afwijkingen, aanleiding geven tot een toenemend aantal dove kinderen met nevenhandicaps.

Omdat tegenwoordig steeds meer kinderen met een geïsoleerd gehoorverlies, vaker dan kinderen met ernstige afwijkingen, geïntegreerd worden in het regulier onderwijs, lijken dovenscholen zich te ontwikkelen tot scholen voor meervoudig gehandicapte dove kinderen.

Ontwikkelingen op het gebied van de menselijke genetica hebben in toenemende mate geleid tot de ontdekking van genen, die verantwoordelijk zijn voor verscheidene syndromale en niet-syndromale vormen van erfelijke doofheid. Ten gevolge hiervan kan de relatie tussen de klinische verschijningsvorm en het genetisch substraat beter beschreven worden. Inmiddels is duidelijk geworden, dat sommige genen zowel voor syndromale als voor niet-syndromale vormen van erfelijke doofheid verantwoordelijk zijn en dat zowel autosomaal dominante als autosomaal recessieve vormen van doofheid met hetzelfde gen geassocieerd kunnen zijn [2]. Ook om die reden is een nauwkeurige beschrijving van de verscheidene vormen van doofheid noodzakelijk. Onze studie betreffende het Stickler syndroom is hier een goed voorbeeld van. Dit non-oculaire Stickler syndroom is geassocieerd met mutaties in *COL11A2*, terwijl mutaties in dit gen eveneens verantwoordelijk zijn voor het autosomaal recessieve OSMED syndroom [3] en autosomaal dominant niet-syndromaal gehoorverlies DFNA 13 [4,5,6]. De identificatie van het *PDS* gen, verantwoordelijk voor het syndroom van Pendred, maar ook voor het niet-syndromale verwijd vestibulair aquaduct syndroom, maakt een vroegere diagnose van dit syndroom mogelijk, evenals onze bevindingen van een vroegtijdig sterk progressief perceptief gehoorverlies en een verwijd vestibulair aquaduct als typische kenmerken van dit syndroom. Tegenwoordig kan de klinische diagnose op moleculaire gronden bevestigd worden, hetgeen weer de kwaliteit van de klinische diagnostiek bevordert.

De ontdekking van typische röntgenologische afwijkingen bij de CHARGE associatie vond plaats in het kader van een nadere klinische beschrijving (vestibulaire areflexie) en verfijning van reeds bestaande beeldvormende technieken. Onze bevindingen werden bevestigd door anderen [8,9] en hebben reeds geleid tot nader onderzoek naar de sacculaire (otolieten)-functie bij de CHARGE associatie [10,11]. Derhalve hebben ook deze bevindingen geleid tot een nadere beschrijving van deze associatie. De oorzaak is echter nog steeds onbekend, maar wellicht kunnen de typische röntgenologische bevindingen een bijdrage leveren om de oorzaak van de CHARGE associatie te vinden. Ze verschaffen ons in ieder geval de mogelijkheid om de diagnose op een jongere leeftijd te stellen.

We verwachten dat nieuwe ontwikkelingen binnen de geneeskunde onze kennis omtrent doofheid verder zullen vergroten en we hopen dat dit met name de meervoudig gehandicapte dove kinderen meer ontwikkelingskansen zal verschaffen.

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Dankwoord

Allereerst gaat mijn dank uit naar alle pupillen en ex-pupillen van het Instituut voor Doven en hun families, die meegewerkt hebben aan de onderzoeken, die tot dit proefschrift geleid hebben. Ook aan alle andere families en mensen met bepaalde syndromen wil ik mijn dank uitspreken voor hun medewerking. Tevens wil ik de kinderen met de CHARGE associatie en hun ouders bedanken voor hun deelname aan dit onderzoek. Jullie vriendelijkheid tijdens onze contacten en jullie bereidwilligheid deel te nemen aan meerdere onderzoeken werd zeer op prijs gesteld. Ik heb wellicht meer van jullie geleerd dan jullie van mij.

Dit proefschrift is het resultaat van een goede multidisciplinaire samenwerking met talrijke collega's. In het bijzonder wil ik vermelden (zonder anderen tekort te willen doen):
Prof.dr. C.W.R.J.Cremers; Cor, bedankt dat je me de vrijheid gegund hebt mij in mijn eigen tempo aan dit proefschrift te laten werken. Jouw interesse en energie was echter wel steeds voelbaar.
Dr. P.L.M.Huygen; Patrick, je bent van onschatbare betekenis geweest voor de realisatie van dit proefschrift. Jouw enorme kennis en het steeds opnieuw herlezen van "onze" manuscripten heeft me zeer geholpen.
Prof.dr. P.van den Broek dank ik als opleider, collega en hoofd van de KNO-afdeling, waarbinnen dit onderzoek kon plaatsvinden.
De collega's op het Instituut voor Doven, met name Dr. H.Brink, Dr. M.Broesterhuizen, Dr.ir. J.P.L.Brokx, Prof.dr. J.P.M.van Dijk, A.Dona, Dr. G.J.A.Janssens Capriles, Drs. A.H.F.van Olphen, Drs. G.J.M.E.N.Timmerman, Drs. J.Toorman hebben ieder op hun eigen wijze hun bijdrage geleverd aan dit onderzoek. Ook de medewerkers van de Medische Afdeling wil ik bedanken voor hun steun.
Prof.dr. H.G.Brunner en Dr. B.C.J.Hamel hebben mij talrijke malen laten delen in hun klinisch genetische kennis en ervaring.
Dr. F.B.M.Joosten ben ik dankbaar voor zijn bijdragen op röntgenologisch gebied. Steeds was hij bereid om weer nieuwe CT-scans te beoordelen.
Mijn collegae binnen de staf KNO wil ik bedanken voor de plezierige werksfeer en de vrijheid die ze me bieden.
De medewerkers van het Kinder Audiologisch Centrum en de afdeling Stem- en Spraak-

stoornissen zeg ik dank voor het tolereren van mijn nukken en grillen, wanneer ik weer eens (gelukkig zelden) gestresst was.
Dr.ir A.F.M.Snik; beste Ad, jouw inzet, kennis en collegialiteit worden zeer op prijs gesteld. De werkdruk en de problemen met het thuisfront zijn uiterst herkenbaar.
Diny Helsper-Peters wil ik bedanken voor de vele hulp bij de lay-out van het proefschrift.
Mevr. J.Abma-Hill heeft de correcties van het Engels verzorgd.

Mijn ouders hebben mij de kans gegeven om te gaan studeren en later te specialiseren. Ze zijn mij tot voorbeeld geweest en hebben mij het doorzettingsvermogen meegegeven om te bereiken wat nu gerealiseerd is.
Peter wil ik bedanken voor de vele gezamenlijke tochten naar ver afgelegen tennishallen, zodat ik weer eens een goede reden had om even niet aan dit proefschrift te hoeven werken en ik kon genieten van vader-zoon gesprekken.
Lilian heeft me geleerd dat het ook leuk kan zijn een opgroeiende dochter te hebben, alhoewel het mij intussen wel duidelijk gemaakt is, dat mijn opvattingen niet meer in deze eeuw passen en waarschijnlijk ook niet in de vorige eeuw.
Jongens, jullie hebben me te veel gemist en ik hoop dat dit nog ingehaald kan worden. Dit geldt ook in het bijzonder voor Doreen, die mij voortdurend (on)voorwaardelijk gesteund heeft.

Curriculum vitae

De auteur van dit proefschrift werd op 21 september 1955 geboren in Schiedam. Na het behalen van het Gymnasium ß diploma aan het St.Norbertus Lyceum te Roosendaal in 1973 werd in hetzelfde jaar aangevangen met de studie Psychologie aan de Rijks Universiteit Utrecht. In 1980 werd het doctoraalexamen in de studierichting Psychologische Functieleer cum laude behaald met als doctoraalscriptie "Begrijpend lezen bij het dove kind". Na inmiddels driemaal uitgeloot te zijn werd aan dezelfde universiteit de studie geneeskunde aangevangen in 1976 en werd het artsexamen behaald in 1983. Vervolgens was de auteur gedurende een half jaar werkzaam als arts-assistent aan de afdeling Interne Geneeskunde (hoofd Dr.J.Lockefeer) van het St.Elisabeth Ziekenhuis te Tilburg. Eind 1983 begon hij de opleiding Keel-, Neus- en Oorheelkunde in het Academisch Ziekenhuis Nijmegen St.Radboud (hoofd Prof. Dr.P.van den Broek). Tijdens de opleiding werd reeds een bijzondere belangstelling aan de dag gelegd voor de pediatrische audiologie. In 1987 werd de opleiding tot Keel-, Neus- en Oorarts voltooid. Sindsdien is hij als staflid verbonden aan de afdeling Keel-, Neus- en Oorheelkunde, met name het Kinder Audiologisch Centrum en de afdeling Stem- en Spraakstoornissen, van het Academisch Ziekenhuis Nijmegen St.Radboud (inmiddels Universitair Medisch Centrum St.Radboud). Tevens is hij sedert 1986 als consulent verbonden aan het Instituut voor Doven te St.Michielsgestel.

This study was supported by grants from:
Stichting Atze Spoor Fonds
Nederlandse Vereniging voor Slechthorenden

This thesis was financially supported by:
Beter Horen, Electro Medical Isntruments BV, Entermed Audiologie BV, Faazen-Schoonenberg BV, Glaxo Wellcome BV, GN ReSound BV, Harting V.O.F. Optiek en Hoortoestellen, Kooij Optiek / Hoortoestellen, Oticon Nederland BV, Philips-Beltone Nederland, Phonak Hearing Systems BV, Veenhuis Medical Audio BV

Stellingen
behorend bij het proefschrift

Hearing Impairment and Associated Handicaps
An aetiological study

Nijmegen, 27 juni 2000

R.J.C. Admiraal

1. De verdeling tussen de verscheidene oorzaken van vroegkinderlijke doofheid is afhankelijk van de onderzochte populatie en van ontwikkelingen binnen de geneeskunde. *(dit proefschrift)*

2. Vestibulaire areflexie op basis van aplasie van de semicirculaire kanalen dient toegevoegd te worden als een van de hoofdkenmerken van de CHARGE associatie. *(dit proefschrift)*

3. Congenitale CMV infectie hoort in de differentiaal diagnose van een vertraagde endolymfatisch hydrops. *(dit proefschrift)*

4. Het Pendred syndroom wordt gekenmerkt door een vroegtijdig en sterk progressief gehoorverlies in combinatie met een bijna obligate bevinding van verwijde vestibulaire aquaducten. *(dit proefschrift)*

5. Bij patiënten met het non-oculaire Stickler syndroom gekoppeld aan *COL11A2* lijkt gehoorverlies een constante bevinding, hetgeen afwijkt van de bevindingen bij het klassieke Stickler syndroom met oogafwijkingen. *(dit proefschrift)*

6. Ieder kind dat een bacteriële meningitis heeft doorgemaakt, dient gehooronderzoek te ondergaan *(proefschrift B. van den Borne, 1999)*

7. Het verdient aanbeveling om bij meervoudig gehandicapte kinderen tijdig gehooronderzoek te verrichten om onvermoede slechthorendheid op te kunnen sporen.

8. De kans op verlies van vestibulaire functie hoort meegenomen te worden in de afwegingen bij cochleaire implantatie. *(Huygen et al., Arch Otolaryngol 1995; Suppl 520: 270-272)*

9. Het wekt verwondering dat vergoeding voor doventolken wel in het Ziekenfondspakket wordt opgnomen, en dat de kosten voor cochleaire implantatie daarvoor niet in aanmerking komen.

10. Met behulp van nieuwe onderzoeksmethoden zoals otoacoustische emissies en geautomatiseerd hersenstamonderzoek lijkt neonatale gehoorscreening een haalbare optie.

11. Voor het voltooien van een proefschrift dient men tegenwoordig over uitgebreide computerkennis te beschikken. Indien dit niet het geval is, is het handig om jonge kinderen te hebben, die het je kunnen (en willen) uitleggen.

ISBN: 90-9013836-6