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Congenital Sensorineural Hearing Loss
a contribution to its detection, diagnosis and treatment

[Congenitaal Neurosensorieel Gehoorverlies
een bijdrage tot de detectie, diagnose en therapie**]**

Proefschrift voorgelegd tot het behalen van de graad van
doctor in de Medische Wetenschappen aan de
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Promotor: Prof FE Offeciers **Antwerpen, 2002**

*Opdracht **

Het is met een gevoelen van groot respect dat ik dit werk opdraag aan Mevrouw Paula D'Hondt-Van Opdenbosch, Minister van Staat en voormalig Voorzitter van Kind en Gezin. In die laatste functie heeft zij ervoor gezorgd dat het project "universele neonatale gehoorscreening in Vlaanderen" op een kritisch moment een juiste wending kreeg en daardoor ontsnapte, tenminste tijdelijk, aan een bestemming als instrument van politiek en macht. Zij heeft daardoor in dit concrete dossier de aura van "la grande dame" bevestigd, een epitheton dat zij in andere en maatschappelijk zwaardere dossiers reeds ruimschoots verdiend had. Het is te harer ere dat ik deze thesis bij momenten voorzie van citaten van die andere "grande dame", Marguerite Yourcenar, schrijfster, Brusselse van origine, Vlaamse van hart, en als eerste vrouwelijke auteur opgenomen in de onsterfelijke Académie française. Beiden hebben geweigerd de macht te dienen, beiden waren wars van het evidente, beiden hebben tegen de stroom in geroeid. Omdat de macht behoudsgezind is, vooruitgang zelden evident en de stroom enkel vloeit over de weg van de minste weerstand.

"L'or vierge du respect serait trop mou sans un certain alliage de crainte."

* Dedication to Mrs Paula D'Hondt-Van Opdenbosch, Minister of State and former President of the Flemish Well Baby Organization, and introduction of the Belgian writer M Yourcenar, citations of whom are given at the beginning of each chapter.

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PREFACE

When the last Muslim was expelled from the European continent in the 15-16thth Century by Carlo Quinto, native from the Belgian City of Ghent, the Arabs had left a tremendous cultural and intellectual patrimony throughout Europe.


Charles V (Carlo Quinto)

The 11th Century Avicenna (Abu Ali al-Husain ibn Abdallah ibn Sina, Isfahan, modern Irak) was the Master of the state-of-the-art Medicine in those days. The Muslim intruders had managed to impregnate the European mind and to sow the seed of intellectual opposition against the pillars of European medical knowledge, which was still based on the writings dating back to the Ancient Greek Aristotle and the Roman Galenus. Midieval Europe was easily seduced by the aristocratic flavour of centres of knowledge and excellence, the architectural embodiment of which was to be found in "universities" all over the continent (Bologna, Salerno, Paris, Toledo, Narbonne, Montpellier, Naples, etc.) The homo universalis was born, well trained, rather snobbish, and above all master of the universe. Whatever there was to know, they knew it. The Renaissance Man was a rhetorician, for whom ratio prevailed over spirit or mysticism. The 17th Century Descartes was convinced of the power of the mind. The mind did have limits, but they were not different from the limits of the universe. The universities, centres of excellence and of growing power, felt that all this knowledge could never be passed from one generation to the next in just a single cycle of teaching. One cycle could cope with the theoretical aspects of knowledge, but a second was needed to apply the theoretical acquisitions and turn them into practical skills. Therefore the theoretical competence was worth a first degree, the degree of

Magister with a licence to teach, a licentia docendi, but only the practical application of this knowledge would allow joining the guild of the homines universales, and this was to be honoured with a second degree, the Doctoral title. All knowledge in those days was science and science was philosophy. No mathematics without philosophy, no philosophy without chemistry etc. This was the Universal Man. So obviously the doctoral degree was a degree in philosophy, a Ph.D. A philosopher was trained in the theory of science and logic before receiving his Master's degree. With this, he had to prove his competence by applying the theoretical knowledge in practical experiments, mathematical formulas, etc. and this would be worth a Ph.D. title. This was the case for science. Medicine, though different and more mystical, could not but accept the same rules. But the proof of one's ability to apply the theoretical knowledge in medical practice could not be given by laboratory experiments. The proof was rather given by being a good doctor, dealing compassionately with the patient, compromising between rigid theory and never-fitting reality, and always believing that somewhere a remedy is available even for the most unfortunate of circumstances. This proof was also judged and rewarded with a doctoral degree and the receiver was called a Doctor in Medicine, or M.D. So M.D. and Ph.D. were equivalent, both based on theoretical knowledge and practical application and both requiring several years of academic study.

Hence, the Cartesian spirit also started to influence Medicine. Since two or three centuries, Medicine is slowly being demystified, slowly gaining scientific momentum. Although the single case experiment still rules the majority of the medical doctor's decisions, it is no longer our sole piece of evidence. Statistics have entered our profession, as well as randomised controlled trials, blind studies etc. And as if by coincidence, the M.D. degree is loosing its authority and right of existence. Already now it has stopped to exist in several university systems. At the same time, medical doctors or their non-doctoral contemporary equivalents, have to prove their skills by depositing a Ph.D. thesis. In addition to the theoretical education, the practical ("doctoral") training, the specialty training, society and the Alma Mater now


ibn Sina

require a thesis in Philosophy, in Science. Congratulations to those who can combine everything, but too high ambitions can easily turn into illusions, of the kind that made Icaros tumble down from the sky. Medical Doctors who are able and competent to combine real science with their daily clinical duties are rare and even less common are those who do both well. Perhaps one day medicine will have grown into a mature scientific discipline, where every pathology will be understood and every therapy based on scientific evidence. But if ever this is to be achieved, we should understand and accept that the road towards that end-point is taken by steps of adventure rather than of evidence. Until then and for every new development, someone has to make the first move, well considered, careful and ever-alert, but above all driven by conviction and believe rather than by evidence. Evidence will surely follow, it has to and it is absolutely compulsory, not to guide the present step, but to justify it, and to allow the following step to be taken based on the confidence that has been obtained thanks to the knowledge that the former step, adventurous as it was, has been proven to be the right one.

The ambition of this dissertation is not to plead for evidence-based medicine, but to defend the case of ten years of adventure, always vigilant and well-considered, never frivolous, and with the failing human conscience as ultimate guide.

Introduction

“Rome m’avait préparé un triomphe, que cette fois j’acceptai. Je ne luttais plus contre ces coutumes à la fois vénérables et vaines ; tout ce qui met en lumière l’effort de l’homme, ne fût-ce que pour la durée d’un jour, me semblait salutaire en présence d’un monde si prompt à l’oubli.”

Congenital bilateral sensorineural hearing loss (>30 dB HL) occurs in approximately 1.2 to 3.2 per 1000 live births (Watkins 1991, White 1993, Mauk 1993, Parving 1993, Davis 1994, Northern 1994, Fortnum 1997, Stein 1999). This hearing loss is permanent and results in significant delays in speech and language development and consequently in important integration problems in the mainstream educational system (Brannon 1966, Davis 1974, Davis 1986, Andrews 1991, Geers 1989). Deaf-mutism is the most extreme consequence and this has been part of all cultures in human history. Until recently, no other therapy than hearing aids existed. Because of factors that will be discussed later, even hearing aids were unable to restore hearing sufficiently to prevent these severe consequences of congenital deafness.

This situation has dramatically changed in the last decade. The reason for this is the development of cochlear implants in the late seventies. These are implantable electronic devices that aim at replacing the cochlear function. Initially these implants were used to restore hearing in elderly patients with acquired deafness. With time, and encouraged by improving results and technology, the field of indications broadened towards younger patients and lower degrees of hearing loss. Initially congenital (or "prelingual") deafness was considered a relative contraindication for cochlear implantation, because it was observed that these persons with severe speech and language retardation hardly improved after the intervention. However it was felt by many professionals in the field that cochlear implants could have significant impact on the speech and language development if they could be implanted at sufficiently young an age, meaning before the onset or at a very early stage of the linguistic development. For this to become possible, it would be crucial to detect congenital hearing losses at a very early stage and to develop proper diagnostic tools to gain certainty about the type and degree of hearing loss.

Fortunately and in parallel with the development of cochlear implants, new techniques became available to easily detect hearing losses in newborns. These techniques were based on the otoacoustic emissions that were discovered as a physiological entity in the late seventies (Kemp 1978). Commercial equipment became available in the late eighties and this was the incentive to start thinking of universal neonatal screening programs in order to detect all congenital hearing losses immediately after birth (White 1993). Once detected, protocols for diagnostic work-up and therapeutic intervention had to be and were defined. These include not only audiological and rehabilitative strategies, but also new diagnostic investigations like genetic examinations and medical imaging techniques. Finally and equally important, new audi-

ological tests were developed for the selection of those infants that would be better off with a cochlear implant.

The last decade thus has been marked by a revolution with respect to congenital hearing loss. To date, universal neonatal hearing screening is a fact in several regions in the world, including Flanders. Infants with congenital hearing loss are receiving elaborate diagnostic work-up and they typically receive their first hearing aids by the age of 3 months. Audiological tools exist that allow early selection for cochlear implantation, which can be safely done before the age of 1 year and the first results show that 90 % of these children will have good speech and language development and will be integrated in the mainstream educational system.

This dissertation will illustrate some of the contributions to this evolution by the author and his colleagues at the University ENT Department of the St.-Augustinus Hospital in Antwerp, Belgium.

Some historical notes on cochlear implants

Any historical overview of cochlear implants starts by referring to Alessandro VOLTA (1745-1827) who had developed electric batteries and connected them up to two rods which he inserted into his ears. This provoked "une secousse dans la tête" with a clear auditive sensation (like the boiling of thick soup). It was not before 1950 that Lundberg directly stimulated the auditory nerve in man during a neurosurgical operation. Subsequently, many researchers tried to optimise the stimulation in an attempt to get acceptable understanding by the patient. Important break-troughs are the use of multiple-electrodes (Djourno and Eyries, 1957) and of intracochlear stimulation (Doyle 1964, Simmons 1965). The first commercially marketed implant (1972) was the House 3M ® single-electrode device developed by William House in California (House 1973). All actual implants have multi-electrode arrays that are inserted into the cochlea. The first such an implant (Nucleus ®) was implanted in 1978 by Graeme Clark in Australia (Tong 1979, Clark 2000). Since then, different types of implants, all based on the same "multi-electrode intracochlear" principle have been developed and marketed: Med-El ® in Austria (Hochmair 1979), Laura™ in Belgium (Peeters 1985, Offeciers 1991), Clarion ® in California (Schindler 1992). The pioneering work of the ENT-surgeon, the late Prof J Baron Marquet and the engineer Prof Stef Peeters at the University of Antwerp has enthused a generation of students in medicine, engineering, speech and language technology, audiology, physics, etc., many of which have become strongly involved and experienced in this field to date.

The interests of 3M ® and Laura™ have been bought by the Cochlear Ltd Company, and this company's device (Nucleus ®) is to date's market leader.

Anatomy and physiology of the cochlea

The ear is a sensory organ. Its function is to receive mechanical waves, called sound, and to transform this into neurological, i.e. electrical signals that ultimately lead to perception. As a sensory organ, the ear typically contains receptor cells and these are the inner hair cells in the cochlea or inner ear. The inner ear contains many more cells and structures, some of which are discussed further in this chapter. The outer ear and middle ear are no receptors in an electrophysiological sense. They serve as filter and impedance-matching device to improve the sound transmission from the surrounding air into the fluids of the cochlea.

THE INNER HAIR CELLS: PHYSIOLOGY

The inner hair cells behave essentially like any other receptor cell in the body. They have a transmembranous **resting potential** (the Nernst potential), which is an electrical potential between the intacellular and the extracellular space of the cell in its unstimulated or resting situation. This resting potential is typically -45 mV for the inner hair cell. On top of the hair cells are a few rows of so-called stereocilia (Figure 1). From a histological point of view, these are microvilli-like extensions. Deflection of these stereocilia towards one side (the side of the longest sterocilia) results in a depolarisation of the cell to a transmembranous potential of typically some -20 mV. This is called the **receptor potential** and is caused by ion flows, mainly a K^+-influx, through ion channels in the sterocilia. As a result of this depolarisation, vesicles in the basal part of the cell containing neurotransmitter (mainly glutaminic acid), release their content in the synaptic cleft at the base of the cell. This neurotransmitter binds to receptors of the postsynaptic membrane of the afferent nerve fibre (N. acousticus) where they elicit action potentials.

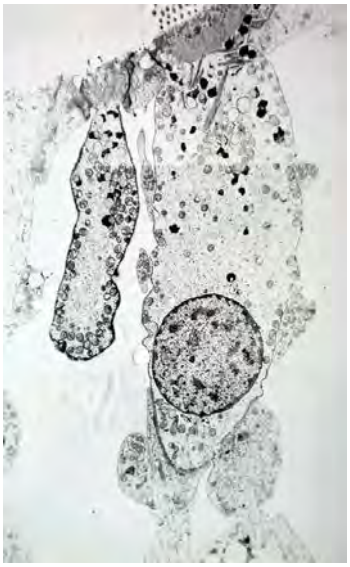


FIGURE 1. Transmission electron micrograph of a human outer hair cell with the stereocilia on top of it. (P Govaerts, unpublished data)

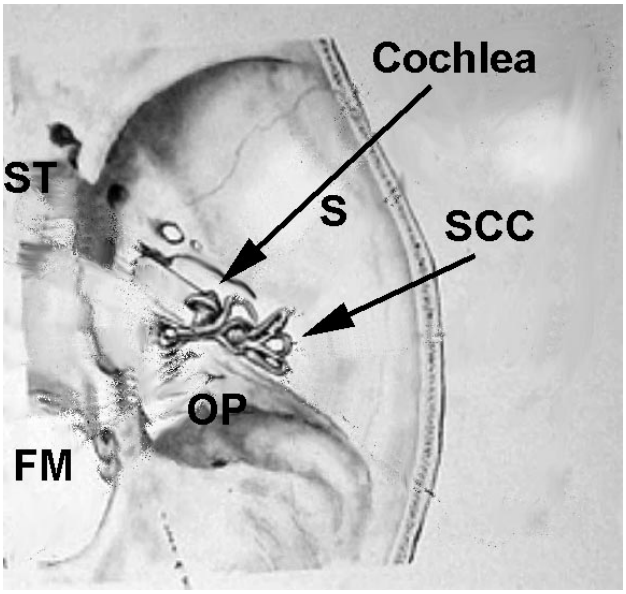
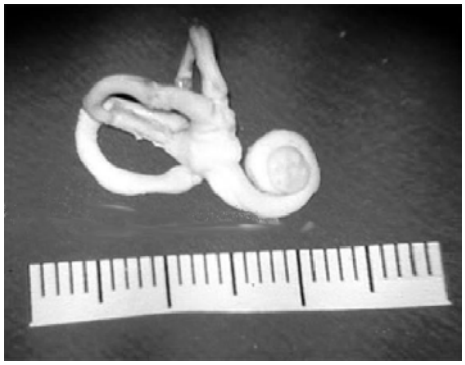


FIGURE 2. Position of the cochlea in the petrous part of the temporal bone. OP: os petrosum; S: squama ossis temporalis; SCC: semicircular canals; ST: sella turcica; FM: foramen magnum.

THE COCHLEA: ANATOMY

The cochlea is a bony structure, lying in the petrous part of the temporal bone (Figure 2), with the typical form of a snail's shell (Figure 3). Inside this bony structure is a tunnel spiralling around the central axis (modiolus). The start of the cochlea is known as the base or the basal end, while the other end is known as the apex or the apical end. The tunnel is divided by two membranous structures (the basilar membrane and Reissner's membrane) into three compartments, the scala tympani, scala media and scala vestibuli (Figure 4) (Michaels 1988).



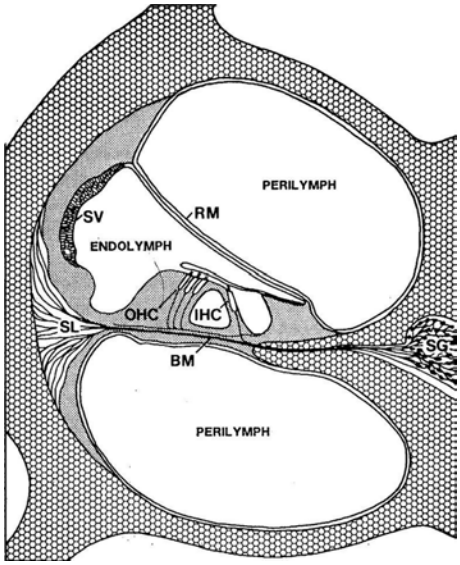


FIGURE 3 (left). Resin cast of the labyrinth with the snail's shell-like cochlea and the three semicircular canals (figure from Th Somers, by permission).

FIGURE 4 (right). Schematic representation of a section through one turn of the cochlea showing the partition into three scalae. BM: basilar membrane; RM: Reissner's membrane; IHC: inner hair cells; OHC: outer hair cells; SV: scala vestibuli; SL: spiral ligament; SG: spiral ganglion; endolymph: the endolymphatic fluid inside the scala media; perilymph: the perilymphatic fluid inside the scala tympani (lower scala) and the scala vestibuli (upper scala). (Figure from P Govaerts 1990a).

At the apex there is a small opening (the helicotrema) between the basilar membrane and the walls of the cochlea, which connects the scala vestibuli and the scala tympani. All scalae are filled with fluid, which is called endolymph in the scala media and perilymph in the two other scalae. The content of these fluids is different, the endolymph roughly resembling intracellular fluid (high

K^+) and the perilymph extracellular fluid (high Na^+). The cochlea is connected to the middle ear by two openings, the oval and the round window. The oval window is located at the basal end of the scala vestibuli and is sealed by the stapes (the third middle ear ossicle) and the round window is located at the basal end of the scala tympani and is sealed by a thin membrane. The round window therefore is an "obvious" place to enter the cochlea from the middle ear, like for introducing an electrode.

The basilar membrane is a collagenous membrane attached medially to the modiolus and laterally to the spiral ligament. Its structure shows graded differences along the cochlear length (Hunter-Duvar & Harrison 1988). Situated on this basilar membrane is a papillary epithelial mound, called the organ of Corti, which is composed of sensory cells (hair cells), supporting cells and nerve fibres (Figure 5). The inner hair cells are the genuine receptor cells, as explained before. In the human cochlea, some 3000 inner hair cells are localized as a single row along the basilar membrane, adjacent to the three rows of outer hair cells (Lim 1986). Their apical surface supports the rootlets of approximately 60 sensory hairs or stereocilia (Hunter-Duvar & Harrison 1988). During embryology the inner hair cell also has a kinocilium, which later disappears. A large number of horizontal cross-links of elastine-like proteins (Osborne 1990) join stereocilia of the same and different rows together laterally, some distance below their tips. Also the tip of each shorter stereocilium on the hair cell gives rise to a fine extension that joins the taller stereocilium of the next row. The internal structure of the stereocilia consists of axial microfilaments, which are tightly packed in a hexagonal array and have been identified as F-actin (Santi 1988). The base of the inner hair cell connects to about 10 afferent nerve endings (Nadol 1983). These afferent nerves form the cochlear nerve, which runs, together with the vestibular nerve, from the modiolus to the cochlear nucleus in the brainstem.

The outer hair cells are no real receptor cells, but they play a major role in the cochlear amplifier, which is an important physiological feature of the well functioning cochlea, as will be explained later. The outer hair cells are organized in three to five rows in the human ear. Like the inner hair cells, their surface contains stereocilia, typically arranged in W-shaped rows. The tips of the tallest stereocilia are embedded in the tectorial membrane (Pujol 1989). Most of the lateral surface of the outer hair cell is lined by the subsurface cisternae, a specialized endoplasmic reticulum structure that is in close proximity to the inner leaflet of the plasma membrane (Lim 1986). There are thin filamentous or tubular structures extending from the infracuticular region to the synaptic region, becoming especially evident near the latter. The outer hair cells are in contact with mainly efferent nerve endings.

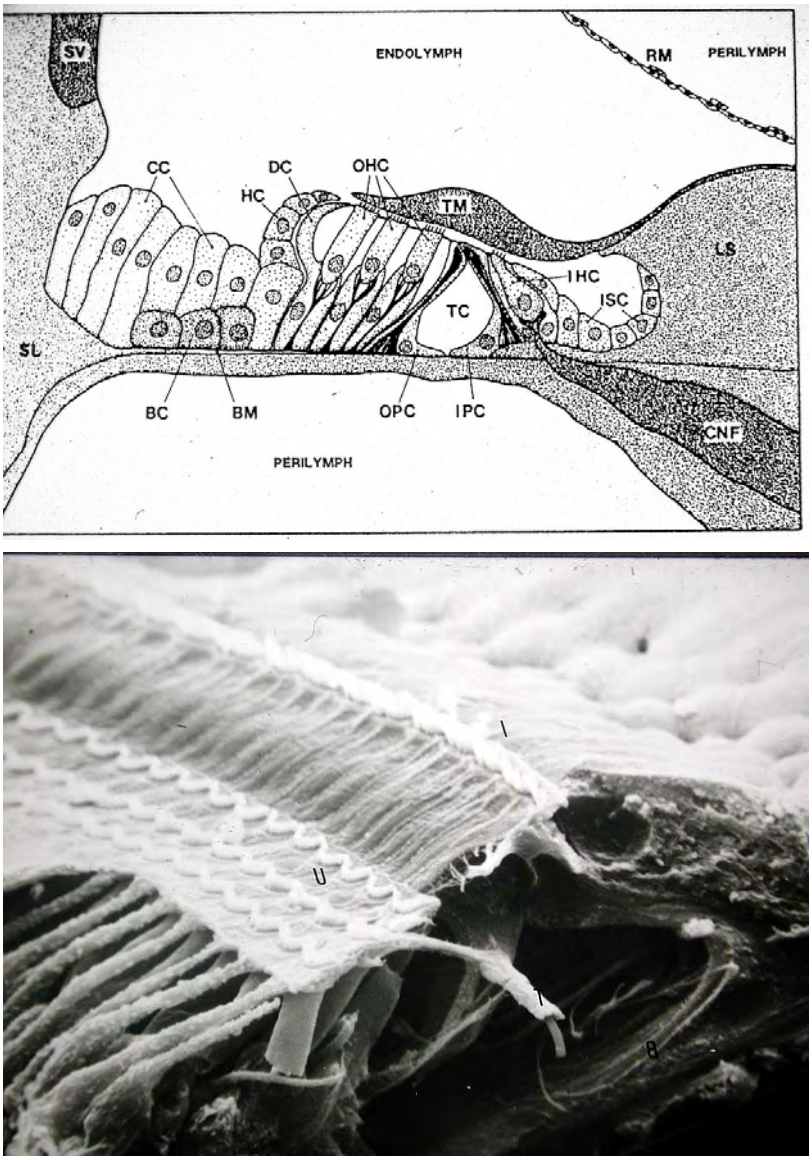


FIGURE 5. Schematic representation of the organ of Corti (top, from Govaerts 1990b) and a micrograph of the same organ by scanning electron microscopy (bottom, courtesy Th Somers). BM: basilar membrane; IHC: inner hair cells; OHC: outer hair cells; RM: Reissner's membrane; SL: spiral ligament; LS: limbus spiralis; SV: stria vascularis; TM: tectorial membrane; TC: tunnel of Corti; DC: Deiter cells; HC: Hensen cells; CC: Claudius cells; BC: Böttcher cells; IPC: inner pillar cells; OPC: outer pillar cells; CNF: cochlear nerve fibres.

THE COCHLEA: PHYSIOLOGY

Sound is transmitted through the middle ear and the stapes into the fluids of the cochlea. The motion of the stapes footplate applies a pressure difference across the basilar membrane, causing this basilar membrane to move. In response to sinusoidal stimulation, this movement takes the form of a travelling wave from the base towards the apex. The envelope of the travelling wave shows a maximal amplitude at a specific place along the basilar membrane and this point depends on the frequency of the stimulus. High-frequency sounds produce a maximum displacement of the basilar membrane near the oval window and low-frequency sounds near the apex of the cochlea. Each point on the basilar membrane thus has its "characteristic frequency", which is the frequency of sound that elicits maximum displacement of the basilar membrane at this point (Figure 6). The cochlea thus behaves like a spectral or a Fourrier analyser. This is a passive phenomenon, i.e. it doesn't require additional energy, and it is the result of the mechanical properties of the basilar membrane (Moore 2001).

If the basilar membrane is sufficiently displaced in a given region, the stereocilia of the inner hair cells in this region will be sufficiently deflected to elicit a receptor potential that in turn will elicit action potentials in the afferent fibres, as explained before. The phenomenon that the place of activation is defined by the frequency of the stimulus, is known as the tonotopic organization or the tonotopy of the cochlea. From a physicist's point of view, each point on the basilar membrane can be considered as a bandpass filter with the characteristic frequency as the centre frequency (Fletcher 1940, Moore 1986). The width of the band can be measured at its 10 dB down points, i.e. the frequencies at which the output of the filter has fallen by 10 dB relative to the output in the passband (Figure 7). The bandwidth at different points on the basilar membrane is inversely related to the frequency-resolving power of the basilar membrane (Moore 1986).

An interesting way of looking at this is to look at the tuning curve of a given point at the basilar membrane. A tuning curve plots the minimum level of sinusoidal sounds of different frequencies to elicit a response on the point of interest on the basilar membrane. This response can be a displacement of the basilar membrane, or alternatively the response of the inner hair cells at this point or the afferent fibres connecting to these hair cells. Figure 8 could be the tuning curve that corresponds to the situation in Figure 7.

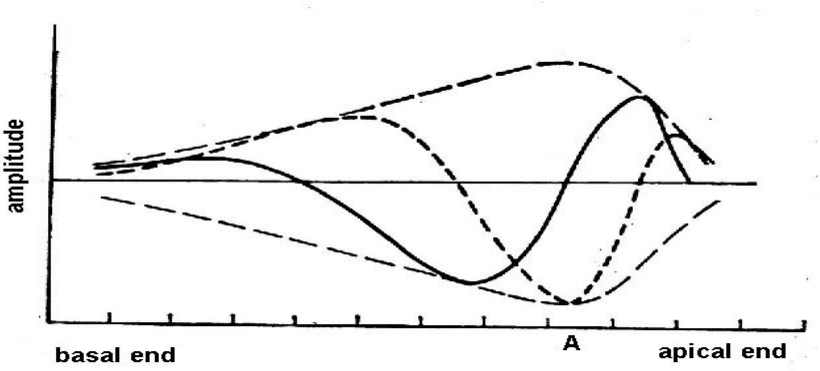


FIGURE 6. Travelling wave along the basilar membrane. The interrupted line is the envelope of the displacements of the basilar membrane over time. The solid and the dotted lines represent the instantaneous displacements at two successive moments. Point A on the basilar membrane is the place with the highest envelope-amplitude for the given stimulus. It is said that the "characteristic frequency" of point A is equal to the frequency of the stimulus. A point on the basilar membrane to the left of point A would have a higher characteristic frequency and a point to the right of A would have a lower characteristic frequency (figure modified after von Békésy 1947).

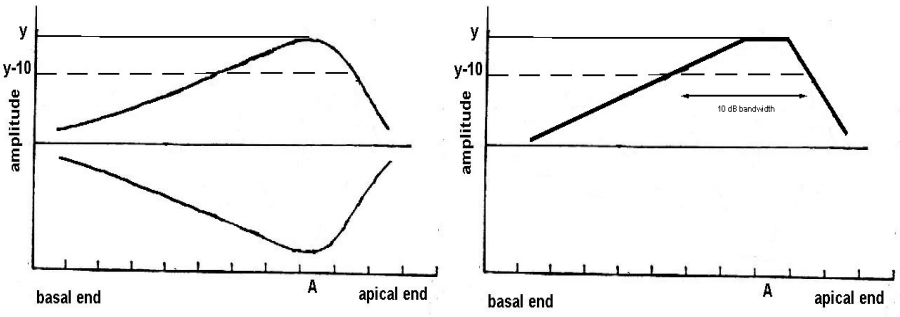


FIGURE 7.Bandpass characteristics of a point on the basilar membrane. The left figure shows the envelope from Figure 5. The maximum amplitude is y and the two places with a 10 dB smaller displacement are shown. The right figure shows this in terms of a bandpass filter with centre frequency A and with the same -10 dB bandwidth.

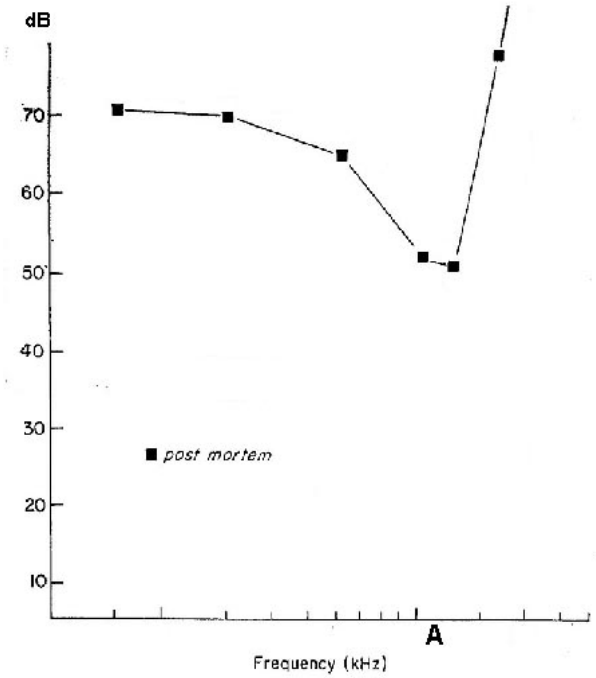


FIGURE 8. A typical tuning curve of a non-vital cochlea. The curve shows the thresholds (Y-axis) of sinusoidal sounds of different frequencies (X-axis) to elicit responses at point A on the basilar membrane. (figure modified after Sellick 1982)

So far, only passive processes have been described, i.e. processes that depend solely on the intrinsic mechanical characteristics of the cochlea. In a living cochlea in good physiological condition however, an active mechanism adds to the above-mentioned processes. This active mechanism is taken care of by the outer hair cells. As explained earlier, the outer hair cells also react to vibrations of the basilar membrane. Their stereocilia are embedded in the tectorial membrane and deflection results in depolarisation of the cell. Unlike inner hair cells, outer hair cells do not respond to this depolarisation by releasing neurotransmitter, but rather by contracting as a result of calcium release out of intracellular reservoirs (Yamashita 1990). There is evidence that this contraction actively influences the mechanics of the cochlea, so as to produce high sensitivity (approximately 50 dB gain) and sharp tuning (Figure 9)

(Khana 1982, Sellick 1982, Leonard 1984, Robles 1986, Slepecky 1989, Ruggero 1992). The sharp tuning enhances the spectral resolution of the cochlea. Both features add significantly to the proper functioning of the normal cochlea and they are the first to be lost in cochlear hearing deficits. Their effect is more pronounced at low level sounds than at higher levels and this causes nonlinearity in the input/output function of the cochlea (Sellick 1982, Ruggero 1992). A side effect of this contraction of the outer hair cells is the emergence of a very local mechanical wave in the fluids of the inner ear, that travels along the basilar membrane towards the oval window and moves the middle ear ossicles before leaving the ear as a low level sound, called an otoacoustic emission (Kemp 1978).

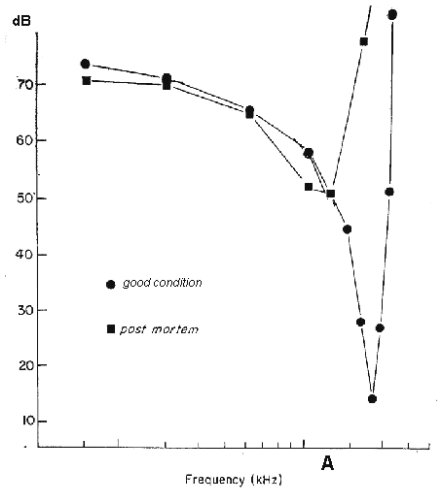


FIGURE 9. Typical tuning curve of a cochlea in good physiological condition. When compared to the tuning curve post mortem, it is clear that the sensitivity has increased (lower thresholds, especially near the characteristic frequency) and that the tuning has become sharper. This is the result of the active outer hair cell mechanism (figure modified after Sellick 1982).

CHAPTER I

Detection

neonatal hearing screening

“L’avancement des idées au cours du dernier siècle est l’œuvre d’une infime minorité de bons esprits; la masse demeure ignare, féroce quand elle le peut, en tout cas égoïste et bornée.”

Until 1998 the average age of detection of a child with congenital hearing loss was 2-4 years in western countries (Mehl 1998, Coplan 1987). In most of these countries different screening programmes existed to detect hearing losses at different ages. A behavioural distraction and observation technique (known in Belgium as the Ewing-test, after Ewing 1961) was most commonly used for universal screening, and this was done at the age of approximately 9 months (Vohr 1996). Time and again, this test was repeatedly reported to have a disappointing yield with poor coverage, sensitivity and specificity (Mott 1994, Robertson 1995, Wood 1997). Figure 1 shows an inventory of all children younger than 6 years that could be retrieved in 1993 as registered in any of the Flemish institutes for the hard of hearing. It shows that in these days, we had to wait for a birth cohort to become 5 years of age, before the number of children with an identified permanent hearing loss was as high as the number that was expected to have a congenital hearing loss, which was then thought to occur in 1.2 per thousand newborns. By that age, the children were supposed to have passed three routine screening moments, namely at the age of 9 months (the Ewing screening), and at the entrance and the exit of kindergarten. Although these screening programmes were considered to be universal, apparently they only yielded approximately 30 % of their target.

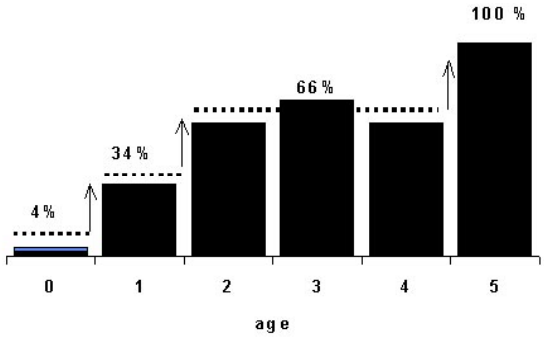


FIGURE 1. Results of a nationwide (Flanders) inventory in 1993 showing all children under the age of 6 years that were registered with hearing loss, as a percentage of the number expected per annual birth cohort based on an alleged incidence of congenital hearing loss of 1.2 per thousand newborns. It can be readily seen that only at the age of 5 years almost 100 % of all children with alleged congenital hearing loss, had been identified. The arrows represent the screening moments (see text) (P Govaerts, unpublished data).

In the same year 1993, audiograms were obtained form 116394 supposedly normally hearing children aged 3 to 6 years and attending the mainstream kindergarten (P Govaerts & W Aelvoet. Informatiseringsgegevens van het medisch schooltoezicht, schooljaar 1992-1993, Ministerie van de Vlaamse Gemeenschap, Depotnr D/1996/3241/044). This represented 44 % of all children attending the kindergarten in Flanders. In the age cohorts 3 and 4 years, approximately 7.5 per 10000 children appeared to have bilateral hearing losses exceeding 50 dB HL in the better hearing ear. These data were complimentary to those from Figure 1 and confirmed the idea that a significant number of Flemish children with a moderately severe bilateral hearing loss or worse were attending mainstream kindergarten without being identified as hard of hearing.

As mentioned in the introduction, it was clear that this average age of detection was too late and resulted in substantial and often irreversible developmental problems. But unfortunately no earlier detection was possible simply because no suitable technique or test existed that would be widely applicable, affordable, and sufficiently sensitive and specific. The western world had to wait for the discovery of the otoacoustic emissions (Kemp 1978) and the commercial availability of valid equipment to record these emissions (Bray 1987).

Otoacoustic emissions are thought to originate in the outer hair cells of a cochlea in good condition (Khanna 1986, Sellick 1982). Different types of otoacoustic emissions have been described, namely spontaneous emissions, transient evoked emissions, and distortion product emissions (Norton 1994). To date, transient evoked otoacoustic emissions (or TEOAEs) are widely used for universal neonatal screening purposes. These are emissions that are generated in response to click sounds and that are measurable in essentially all normally hearing persons with normal middle ears and normal cochleas (Kemp 1978, Johnsen 1982, Johnsen 1983). Because almost all congenital sensorineural hearing losses are cochlear hearing losses and because the outer hair cells are affected in almost all cochlear hearing losses, the absence of otoacoustic emissions is a very sensitive indicator of sensorineural hearing loss. Generally, a sensorineural hearing loss exceeding 30-40 dBHL will result in the absence of TEOAEs (Kemp 1986).

Soon after the release of validated equipment to measure otoacoustic emissions, it became clear that this was potentially a powerful tool for large-scale neonatal hearing screening. The first nationwide programme was set up in 1990 in Rhode Island, USA (White 1994). On January 1, 1993, a European concerted action on otoacoustic emissions started, in which the University ENT Department of the St.-Augustinus Hospital took part (project leader: F

Grandori, a project from the Commission of the European Communities, Directorate General XII - Science, Research and Development, Biomedical and Health Research Programme). Also in 1993, Govaerts and colleagues introduced neonatal hearing screening with otoacoustic emissions in the maternity ward of the St.-Augustinus Hospital (Daemers 1996). In the same year, the National Institute of Health published a recommendation in favour of universal neonatal hearing screening (NIH 1993). A similar recommendation was published one year later by the Joint Committee on Infant Hearing Screening (Joint Committee 1994).

Algemeen Ziekenhuis
Sint-Camillus / Sint-Augustinus
Campus SINT-AUGUSTINUS

UNIVERSITAIRE DIENST N. K. O.
Prof. Dr. F. E. OFFECIERS
Dr. Th. SOMERS
Dr. P. GOVAERTS

Dr Vandenberghe
Administrateur-Generaal - KIND & GEZIN
Hallepoortlaan 27
1060 Brussel

Uw kenmerk :
Ons kenmerk :

2610 WILRIJK,
Oosterveldlaan 24 13/11/95

Geachte Collega,

Betreft: Neonatale gehoor-screening

Zoals U misschien weet, bestaat sinds enige jaren de mogelijkheid van neonatale gehoorscreening.

Het is reeds lang duidelijk dat de spraak- en taalontwikkeling van het jonge kind sterk afhangt van een goed gehoor vanaf de leeftijd van 3 à 6 maand. Daarom bestaat er internationaal een consensus rond de noodzaak van tijdige detectie en apparellering cq intensieve vroegbegeleiding van het gehoorgestoorde kind. Nu de mogelijkheid van universele neonatale screening bestaat, ziet men internationaal programma's ontstaan om dit op punt te stellen.

In het St Augustinus-ziekenhuis te Antwerpen loopt sinds een tweetal jaar een piloot-project hierrond en dit in het kader van een Europese geconcerteerde actie. De eerste analyse hiervan is geschied en dit heeft enkele interessante gegevens opgeleverd mbt de techniek, de set-up van een dergelijk programma en de epidemiologie van congenitale slechthorendheid.

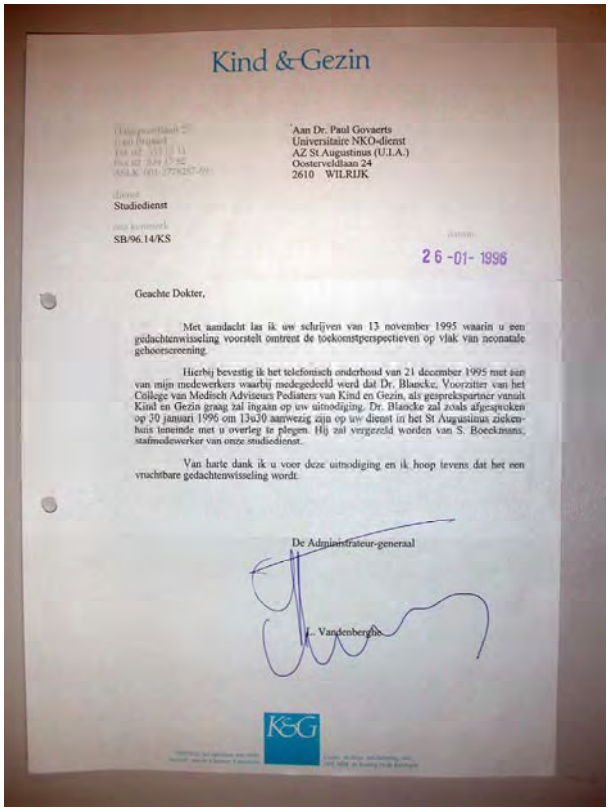
Ongetwijfeld zal Kind & Gezin in de toekomst geconfronteerd worden met de vraag naar neonatale gehoorscreening. Het komt mij trouwens voor dat dit volledig kadert in de maatschappelijk rol van Kind & Gezin. Daarom zou ik U willen vragen of het niet mogelijk is een onderhoud met U te krijgen ten einde hierover van gedachten te wisselen. Zou ik eerstdaags Uw secretariaat mogen contacteren om een afspraak te maken?

Met dank en hoogachting.

Dr. Paul Govaerts
Universitaire NKO-dienst
AZ St Augustinus (U.I.A.)
Oosterveldlaan 24
B-2610 Antwerpen-Wilrijk

Tel 03/443 36 14
Fax 03/443 36 11

FIGURE 2a. Facsimile of the first correspondence between Govaerts and the Flemish Well Baby Organisation (*Kind en Gezin*). In his letter of 13 November 1995, Govaerts informs *Kind en Gezin* of the new developments with respect to neonatal hearing screening and he suggests that *Kind and Gezin* gets involved in it.



Kind & Gezin

Aan Dr. Paul Govaerts
Universitaire NKO-dienst
AZ St.Augustinus (U.L.A.)
Oostervelddaan 24
2610 WILRIJK

Studiedienst

SB/96.14/KS

26-01-1996

Geachte Dokter,

Met aandacht las ik uw schrijven van 13 november 1995 waarin u een gedachtenwisseling voorstelt omtrent de toekomstperspectieven op vlak van neonatale gehoorscreening.

Hierbij bevestig ik het telefonisch onderhoud van 21 december 1995 met een van mijn medewerkers waarbij medegedeeld werd dat Dr. Blaecke, Voorzitter van het College van Medisch Adviseurs Pediaters van Kind en Gezin, als gesprekspartner vanuit Kind en Gezin graag zal ingaan op uw uitnodiging. Dr. Blaecke zal zoals afgesproken op 30 januari 1996 om 13u30 aanwezig zijn op uw dienst in het St Augustinus ziekenhuis teneinde met u overleg te plegen. Hij zal vergezeld worden van S. Boeckmans, staflmedewerker van onze studiedienst.

Van harte dank ik u voor deze uitnodiging en ik hoop tevens dat het een vruchtbare gedachtenwisseling wordt.

De Administrateur-generaal

L. Vandenberghe

K&G

FIGURE 2b. Mr Vandenberghe, head of *Kind en Gezin*, replies on 26 January 1996 and confirms a first meeting to be held in January 1996.

In 1995, Govaerts and colleagues contacted the Flemish Well Baby Organization (*Kind en Gezin*) to inform them of this new and exciting evolution (Figure 2). They also invited Prof Karl White, the pioneer of the Rhode Island project, to Antwerp to teach on the management of universal neonatal hearing programmes (December 9, 1995. Postacademisch programma Hoorwetenschappen, UIA, coordinated by S Peeters and P Govaerts). Also the public was sensitised, e.g. with information leaflets (Figure 3) and an instructional video for the parents that was released in 1997 ("Neonatale gehoorscreening door middel van oto-akoestische emissies". PJ Govaerts et al.).

Neonatale gehoorscreening: een recht van elk kind

"Surdus et mutus". Van oudsher wordt doofheid als vanzelfsprekend geassocieerd aan stomheid. Stomheid zowel in de betekenis van 'onvermogen tot spraak' als in zijn intellectuele connotaties. Want ongeacht de intrinsieke intellectuele capaciteiten, leiden slechthorendheid en slechte spraakontwikkeling tot problemen bij de ontwikkeling van het abstracte denken, tot problemen bij de sociale, intellectuele en professionele integratie.

Voor het eerst bestaat de hoop dat die dramatische consequentie geen vanzelfsprekendheid meer zal zijn. Recent werd het namelijk mogelijk al van bij de geboorte het gehoor van het kind op eenvoudige en goedkope wijze te controleren.

Per duizend neonati zijn er 1 à 3 ernstig slechthorend. Deze kinderen hebben absolute nood aan hoortoestelaanpassing en adequate auditieve en logopedische revalidatie. Nochtans leren epidemiologische studies ons dat hooguit een derde van de zwaar slechthorende kleuters bekend is in het circuit van de auditieve hulpverleners. Diegenen die bekend zijn, werden bovendien als dusdanig gediagnosticeerd rond de leeftijd van 18 maanden. Dit is veel te laat in het licht van de auditieve ontwikkeling. Kinderen beginnen normaal te spreken rond de leeftijd van één jaar. Voordien hebben de auditieve banen zich gevormd, is het auditieve geheugen gevuld met geluiden, klanken, intonaties, woorden. Dit 'voorbereidende' werk start al op de leeftijd van enkele maanden en is cruciaal voor de eigenlijke spraakproduktie. Een goed gehoor is hiervoor natuurlijk een eerste vereiste. Aangezien de plasticiteit van de hersenen en met name van de auditieve cortex snel afneemt, zal het verlies van auditieve ontwikkeling nooit meer volledig ingehaald kunnen worden. Zwaar slechthorende kinderen die pas hoorapparaten en revalidatie krijgen op de leeftijd van 12 tot 18 maanden, zullen ***NOOIT*** *komen tot een normale spraakontwikkeling. Deze kinderen zijn veroordeeld tot de marge van de maatschappij.*

Sedert meerdere jaren bestaat de mogelijkheid het gehoor van neonati te testen d.m.v. 'oto-acoustische emissies'. In het slakkenhuis waren er al langer niet-lineaire fenomenen bekend, die bleken te berusten op contractiele eigenschappen van een deel van de haarcellen, met name de buitenste haarcellen. Deze fenomenen zijn belangrijk voor het gehoor en vooral voor het spraakverstaan. Het is fylogenetisch een late ontwikkeling die bijgevolg weinig robuust is en die bij zowat alle vormen van perceptief gehoorverlies aangetast is. Eén van de aspecten van dit fenomeen is dat het slakkenhuis zelf geluid produceert zodra er een stimulus wordt gegeven. Dit geluid wordt een oto-acoustische emissie genoemd en kan met behulp van een microfoontje in het oor opgevangen worden. De aanwezigheid van emissies is tekenend voor een goed gehoor.

Ofschoon de onderliggende fysiologie en de interpretatie van de signalen redelijk complex zijn, is de technische uitvoering van de test eenvoudig, snel en onbelastend voor de testpersoon. Concreet wordt een plastic dopje geplaatst in het oor van de slapende neonatus. Hierdoor wordt een stimulus gegeven op matige intensiteit, waarna de emissies geregistreerd worden. Bij vlot verloop duurt dit hooguit enkele minuten per oor.

De test is dermate onbelastend en de sensitiviteit en specificiteit zo gunstig dat alle gezaghebbende internationale organisaties (Joint Committee on Infant Hearing Screening, National Institute of Health, Bureau International d'Audiophonologie) nu reeds oproepen tot universele neonatale gehoorscreening.

In het Sint-Augustinus Ziekenhuis zijn de Universitaire Dienst NKO en de diensten Pediatrie en Neonatologie in 1993 gestart met de invoering van deze vorm van gehoorscreening. Aan de ouders wordt een informatiefiche gegeven, waarna zij beslissen of zij het onderzoek wensen te laten uitvoeren. Bij de neonati met 'indicatoren van slechthorendheid' wordt het onderzoek automatisch uitgevoerd als onderdeel van de andere diagnostische testen.

Als een kind tweemaal 'faalt' op het gehooronderzoek, wordt een BERA-onderzoek onder narcose gepland om de slechthorendheid te bevestigen en de graad ervan te bepalen. Dit is nodig bij 6 op 1000 kinderen. De helft hiervan blijkt zwaar slechthorend en wordt onverwijld doorverwezen naar een revalidatiecentrum voor hoortoestelaanpassing en intensieve vroegbegeleiding (streven = vóór 6 maand leeftijd). Er bestaan nu reeds veel aanwijzingen dat een dergelijke aanpak ons in staat zal stellen deze kinderen een veel betere spraak- en taalontwikkeling te bezorgen en hen wellicht in het gewone onderwijs te integreren. Met de evolutie van de cochleaire implantatie wordt deze hoop nog versterkt en wordt de noodzaak tot vroegtijdige detectie en revalidatie alleen maar bevestigd.

Vanuit het Sint-Augustinus Ziekenhuis wordt met een aantal andere grote Europese centra samengewerkt in een Geconcerteerde Actie (AHEAD) van de Europese Gemeenschap om de expertise, de ervaring en de resultaten te bundelen ten einde op termijn te komen tot een universele neonatale gehoorscreening bij alle Europese borelingen. De consensus groeit dat elk slechthorend kind in een maatschappij met ons niveau van beschaving het aangeboren recht heeft op een vroegtijdige detectie met het oog op maximale integratie. Dit recht te realiseren is het voorwerp van onze gezamenlijke inspanning.

FIGURE 3. This information that was published in the newsletter of the St.-Augustinus Hospital in 1996, was one of the first attempts to sensitise the public of the importance of universal neonatal hearing screening in Belgium.

In 1998 the first seminar on this topic was organized in Belgium at the University of Antwerp (Figure 4) and the first European Consensus Conference on Neonatal Hearing Screening was held in Milan, Italy (Figure 5). As a member of the steering committee of this European Consensus Conference, Govaerts prepared a contribution on the cost of screening programmes. That year the Flemish Well Baby Organization (*Kind en Gezin*) launched a universal neonatal hearing screening programme which became fully operational in 1999. With this, Flanders turned out to be the first region of that size (approximately 60000 newborns per year) in Europe to have an operational universal neonatal hearing screening programme.

FIGURE 4 (next page). Programme of the first seminar in Belgium to introduce and promote universal neonatal hearing screening with otoacoustic emissions.

SEMINARIE NEONATALE GEHOORSCREENING
door middel van
OTO-AKOESTISCHE EMISSIES

Onder de auspiciën van de Belgische Vereniging voor Audiologie

17JANUARI 1998

Organisator: Dr Paul Govaerts
Universitaire Dienst NKO
AZ St.-Augustinus

PLAATS
Aula Maior - U.IA

Wetenschappelijk Programma

09.30-10h30	**Rationale van neonatale gehoorscreening** J Bamford (Manchester, U.K.)
10h30-11h00	**Technologische aspecten van OAE** BGA van Zanten (Rotterdam, NL)
11h00-11h30	koffie-pauze
11h30-11h50	**Vroegappareillering in Vlaanderen** V Standaert (Antwerpen-Wilrijk, B)
11h50-12h15	**Vroegbegeleiding in Vlaanderen** G Lichtert (Antwerpen, B)
12h15-14h00	lunch
14h00-14h45	**Universele screening in de U.S.A.** K White (Utah, USA)
14h45-15h10	**Vroegtijdige cochleaire implantatie** FE Offeciers (Antwerpen-Wilrijk, B)
15h10-15h45	koffie-pauze
15h45-16h00	**Het screening-programma in het AZ St-Augustinus** G De Ceulaer (Antwerpen-Wilrijk, B)
16h00-16h15	**Sensibilisatie en leercurve** K Daemers (Antwerpen-Wilrijk, B)
16h15-16h45	**Ronde tafel** B Vinck (RU Gent), L Feenstra (KU Leuven), F Gordts (VU Brussel), FE Offeciers (UIA), P Van De Heyning (UZA)

Europese Consensus-verklaring over neonatale gehoorscreening

Gehouden te Milaan, op 15 en 16 mei 1998.
Congres Voorzitters: Ferdinando Grandori, Mark E. Lutman

1. Permanente vroegkinderlijke slechthorendheid of doofheid(1) is een ernstig volksgezondheidsprobleem, dat tenminste één per duizend babies treft. Behandeling wordt het meest succesvol geacht, als deze in de eerste levensmaanden begonnen wordt. Daarom kunnen de levenskwaliteit en de maatschappelijke kansen van een slechthorend kind verbeterd worden door vroegtijdige opsporing, door middel van screening kort na de geboorte.

2. Doeltreffende programma's voor behandeling en begeleiding zijn genoegzaam voorhanden.

3. Methoden om permanente vroegkinderlijke slechthorendheid of doofheid al vlak na de geboorte aan te tonen behoren nu tot de algemeen aanvaarde klinische praktijk. Ze zijn doeltreffend en maken identificatie van tenminste 80 %kinderen met een permanent gehoorverlies mogelijk, terwijl ze maar 2-3 % van de goedhorende babies foutief als mogelijk slechthorend aanwijzen, in goed gecontroleerde screeningsprogramma's.

4. Neonatale screening in kraamklinieken of materniteiten is doeltreffender en goedkoper dan screening op de leeftijd van 7-9 maanden met behulp van gedragsmatige reacties op geluidstimulatie.

5. Het beperken van neonatale gehoorscreening tot de kinderen, die een verhoogd risico(2) op slechthorendheid of doofheid hebben, reduceert wel de kosten van screening, maar zal op zijn best leiden tot het identificeren van 40-50 % van de aangedane babies. Het screenen van alleen de hoog-risico kinderen vlak na de geboorte en daarnaast van alle kinderen op de leeftijd van 7-9 maanden met gedragsmatige methoden is duurder en minder effectief dan universele neonatale screening.

6. Gehoorscreening vlak na de geboorte kan geen later verworven of later intredende en progressieve slechthorendheid identificeren. Andere methoden van opsporing zijn vereist om deze 10-20 % van de kinderen met permanente gehoorverliezen te identificeren.

7. Nadelen verbonden aan neonatale gehoorscreening zijn onder andere onnodige angst bij een vals positief screeningsresultaat en ook een mogelijk verlate diagnose bij een vals negatief screeningsresultaat. Deze nadelen zijn aanvaardbaar gezien de te verwachten voordelen.

8. Neonatale gehoorscreening moet beschouwd worden als het eerste stukje van een habilitatieprogramma voor slechthorende en dove kinderen met daarin ook voorzieningen voor diagnostiek en gehooronderzoek.

9. Een systeem voor kwaliteitszorg is een essentiele component van een neonataal screeningsprogramma. Kwaliteitszorg houdt ook in de training van personeel en controle van de uitvoering van het programma. Een persoon, verantwoordelijk voor de kwaliteitscontrole, moet als zodanig aangeduid zijn.

10. Alhoewel de gezondheidszorg binnen Europa van land tot land verschilt wat betreft de organisatie en financiering, mag de invoering van neonatale gehoorscreening niet langer uitgesteld worden. Dit zal nieuwe Europese burgers betere vooruitzichten bieden op een hogere levenskwaliteit in het volgende millenium.

(1) Gedefinieerd als een tweezijdig permanent gehoorverlies van gemiddeld 40 dB of meer bij de frekwenties 0.5, 1, 2 en 4 kHz.

(2) Bijvoorbeeld door intensieve neonatale zorg of door een positieve familiegeschiedenis van vroegkinderlijke slechthorendheid.

FIGURE 5. Dutch translation of the European Consensus Statement of 1998.

In the mean time and over the years, efforts were made to optimise the screening procedure, the technique, the decision criteria, the different steps of procedure, etc. The results of these efforts have been published and are given in detail in the following chapters. The paper by Daemers et al. (1996) reports on the first results, those of the screening years 1993 and 1994, and on some modifications to the test protocol to improve the outcome figures. It was originally written in Dutch, but the policy of the Acta Otorhinolarynologica Belgica happened to change in that period and the publisher had the manuscript translated into English by a French-speaking editor without the author's consent. The Babel-like confusion adds a folkloric flavour to the final paper, but because of its place in the history of universal neonatal hearing screening in Belgium, it was judged to be an essential part of this dissertation and it has been added with some editorial modifications (sic!). The paper by Dirckx et al. (1996) summarizes the numerical scoring criteria that were used by different screening teams worldwide and pleads for a consensus. The contribution of Govaerts (1998) to the European Consensus Conference has been added. It shows that from a cost-benefit perspective, universal screening programmes based on otoacoustic emissions are to be preferred. The paper by De Ceulaer et al. (1999) gives an update of the situation and the impact of different procedural modifications on the outcome. The paper by Govaerts et al. (2001) reports on the most recent screening model that was evaluated in a joint pilot study with the Flemish Well Baby Organisation (*Kind en Gezin*) and that yielded unprecedented quality figures with a coverage of 99.3 %, a sensitivity of approximately 100 % and a false referral rate of 1/1000. The total time investment per child was less than 15 minutes.

Papers by PJ Govaerts related to this topic

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Neonatal hearing screening with otoacoustic emissions : an evaluation

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ABSTRACT

For several years now, it is possible to test the cochlear function immediately after birth in an easy way by means of click evoked otoacoustic emissions. Thanks to this early detection, hearing aid fitting and appropriate hearing rehabilitation can now be started at a very young age, which significantly enhances the possibility of integration of the congenitally hard of hearing in society. An international consensus is growing to endorse a universal neonatal hearing screening in western societies. Setting up screening programs necessitates good preparation, continuous quality control and regular analysis of procedures and results. The present paper evaluates the procedure as organised from January 1993 till December 1994 in the University ENT-Department of the St.-Augustinus Hospital. Of the 907 included neonates who were considered not to be at risk for hearing loss, 81 % passed the test immediately, and 93 % passed after maximum 3 tests. Some changes in the initial procedure increased the prevalence of emissions from 69 % to 84 %. The practical problems of the screening program and especially the importance of a stringent follow-up procedure in case of failure are discussed.

Key words: Neonatal hearing screening; otoacoustic emissions

INTRODUCTION

Epidemiological studies have shown that the incidence of congenital bilateral neurosensory deafness in Western countries is between 0.5 and 1 per 1000 live births. Other types of hearing loss probably occur in 1.5 to 6 neonates per 1000 (Watkin 1991, White 1993, Kuhl 1992.). The effect of this on the speech and language development of the child and on the social and professional situation is important. Auditory deprivation leads to severe problems in several learning processes, especially wit respect to speech and language development. Because language, spoken as well as written, is a very important vector of knowledge in our society, hearing loss is bound to influence the social, emotional and cognitive development of the affected person. Early detection, treatment and follow-up are essential to minimize these consequences (3).

For the moment, screening in Belgium is carried out by means of the Ewing test, which is performed at the age of 9 months by the Well Baby Clinics. This screening programme is operational since 1976 and is the first attempt to come to a nationwide screening. A disadvantage is that is is relatively late in terms of speech- and language development. Another problem is the limited epidemiological coverage; only 78 % of newborns were screened in 1993. This, however, is not a problem typically related to the Ewing-test, but rather a problem of every home-based screening. The problem of follow-up is similar in nature; after failures on the first screening, the parents do not always show up for the retest or in case they have it done elsewhere, they fail to provide the Well Baby Clinic with the results. Therefore follow-up is lacking in 30 % of children during the year 1993. With this in mind, it is very difficult to draw conclusions about the sensitivity of the Ewing test as it is currently organized.

If the Ewing test aims at detecting all children with impaired hearing (hearing loss of more than 30 dB) including transmission disorders, then specificity is estimated to be 96 %. If, however, the intention is to track only perceptive losses, then specificity is estimated to be no higher than 88 %. These estimations are based on the follow-up data after a 2 or 3 consecutive failures on the screening. The pass percentage after the first test is 76 % (*Kind en Gezin* Antwerp, personal communication).

The first apparatus for the measurement of otoacoustic emissions became available in 1986. Otoacoustic emissions are sound waves that are generated in the cochlea as a consequence of its non-linear characteristics. They are almost certainly caused by the functioning of the outer hair cells, which possess

contractile characteristics. An incoming sound wave causes contractions of these cells, causing amplification of the sound waves over a very limited area of the basilar membrane and thereby ensures “tuning” in the frequency area. A by-product of this function is the creation of a new wave in the cochlea, which in an inverse way, i.e. via the middle-ear, reaches the outside world where it can be detected. This emitted wave is known as otoacoustic emission (OAE) and it provides evidence of well functioning outer hair cells and, of course, evidence of a well functioning conductive middle ear.

Because the outer hair cells are the first to be affected by most hearing disorders, the detection of the otoacoustic emission is useful as a hearing evaluation. Evidence exists that the presence of OAE's indicates hearing with levels better than about 30dB HL at the best frequency. Thus a hearing loss of more than 30 dB HL, be it sensorineural or conductive, leads to the absence of emissions (Kemp 1990, Kok 1993).

Because of the relative simplicity and speed of tests, OAE's are currently being introduced as screening instruments for hearing problems. The fact that they can already be taken at neonatal age, provides an extra advantage in the field of early diagnosis and therapy. A lot more research is still necessary to evaluate the merits of OAE's as screening instruments.

A screening program was started in the St.-Augustinus Hospital in 1993. This paper reports the measured results of the screening, utilizing click evoked otoacoustic emissions taken from regularly born neonates over a period of 2 years. The practical problems associated with the set-up of a screening experiment are discussed.

MATERIAL AND METHODS

During the years 1993 and 1994, 907 neonates were tested by the University ENT department of the St.-Augustinus Hospital by means of an examination using non-linear click evoked OAE's. All examinations were carried out with the Otodynamics IL088 apparatus. The Quick Screen Test was used.

The test procedure was according to Bray & Kemp (1987). Briefly, a neonatal probe with a rubber cap was inserted into the auditory canal and the probe tone adjusted. The maximum stimulus level was 90 dB SPL. The probe was positioned in such a way that the click did not cause any resonance in the auditory canal (see Figure 1 window "stimulus") and the frequency spectrum was as flat as possible (see Figure 1 window "power analysis stimulus").

A number of 20 to 260 recordings was made. The examination was stopped when emissions were present. If, after 50 recordings the response was insufficient (see below), then the probe was refitted and a new test was started. Under favourable circumstances the registration lasted less than one minute per ear, but in exceptional cases, it could last longer than a quarter of an hour.

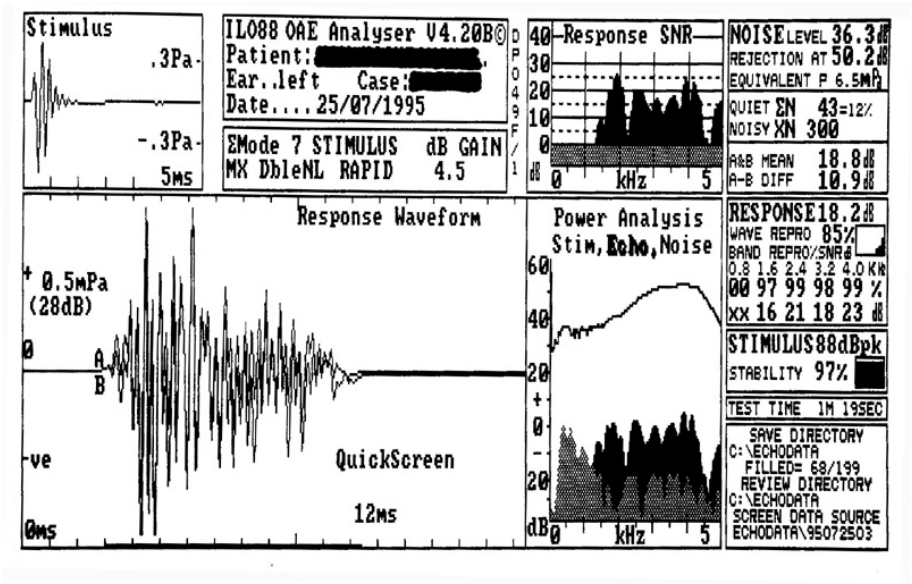

FIGURE 1. Print-out of the computer screen of the ILO 88. In the window "stimulus" we observe a representation of the sound measured by the microphone of the probe. The window “power analysis stimulus” shows the frequency spectrum of the stimulus. Below this the response is depicted. In this window we can read the S/R ratio for each frequency band, with centre frequencies 0.8, 1.6, 2.4, 3.2 and 4.0 kHz (stimulus = black; noise level = grey).

The neonates were tested in a sound-proof cabin or a quiet room at the Audiological Centre of the University ENT department. The neonates were brought to the test room by their mothers, about one and a half hours after feeding.

The parents of every newborn were informed of this new opportunity to have their baby tested. This was done in written form with a brief explanation and a simple registration slip. All NICU children were systematically tested but, because they form another target group, they were not taken into consideration for the purpose of this paper.

From January until April 1993 the examination took place immediately after registration. From May 1993 emissions were systematically tested on the last

working day before leaving hospital. This means that, at the earliest, the neonates were tested at the age of three days. This change in the procedure was important. In the rest of the report reference will be made to periods 1 and 2.

Until the end of 1993 the presence of emissions was assessed on the basis of a qualitative evaluation from the Fourier spectrum. A criterion was established that for frequencies between 1 and 4 kHz the average emission response had to significantly exceed the noise level. From February 1994 onwards, the new software (version 3.94) was at our disposal. With this, the signal to noise ratio (S/R ratio) in different frequency bands can be determined and thus the application of a numeric criterion became possible. We concluded that OAE's were present in case of an S/N ratio of 6 dB or more in the three frequency bands with centre frequencies 2.4 kHz, 3.2 kHz and 4 kHz and an S/R ratio of 3 dB at 1.6 kHz. If these criteria are met, a general reproducibility of more than 50 % is achieved. In case of doubt, the visual score was applied with a qualitative assessment of the Fourier spectrum.

In case of unilateral or bilateral failure, the parents were invited for a re-test 3 weeks later. If they failed to show up within 6 weeks they were contacted once or twice in writing. In the last quarter of 1994, this follow-up strategy was substantially intensified. The parents were already contacted after four weeks and in the absence of response, the family doctor was contacted and asked to get in touch with the parents. If necessary, both the parents and the family doctor would be contacted once again in writing.

RESULTS

Of the 907 neonates 13 % (118) failed unilaterally on the first test. The percentage of bilateral failures on the first test was 6 % (53). In 81 % (736) of the tested neonates OAE’s were found to be present during the first test.

Based on an interim analysis after a first period of four months the procedure was modified as explained above. These modifications did not influence the coverage. Both in the first and the second period, 19 % of the neonates were presented for examination (151/798 and 756/3979 respectively). On the other hand, the modifications clearly influenced the outcome of the screening. Unilateral failures dropped from 22.5 % in the first period to 11 % in the second period, and bilateral failures from 8.5 % to 5.3 % respectively. Thus, the prevalence of OAE’s increased from 69 % to 83.7 %. Table 1 summarizes the results of the screening.

The results of the follow-up of the failures are shown in Figure 2. From the 118 unilateral failures, 88 neonates were tested a second time. The other 30

received no second examination, despite the fact that their parents were invited several times to repeat the test. From the 88 retested neonates, 73 passed the second test and in 15 cases emissions remained unilaterally absent. From these 15 unilateral failures, 7 neonates were examined a third time, 8 were not. Six out of these seven turned into a pass at the third test.

There were 53 bilateral failures. Of these, 40 neonates were retested and 13 not. Of the 40 retested neonates, 23 showed a bilateral pass at the second test, 5 a unilateral pass and 12 a bilateral fail. Two neonates with unilateral failures were retested a second time and passed the test, but three were not retested. Only four neonates with bilateral failure were retested; 3 passed the test and 1 failed bilaterally. This neonate was referred for diagnostic workup and appeared to have glue ears. OAE's were present after ventilation tubes were placed.

TABLE 1. The screening results of the first test of 907 neonates, screened in 1993 and 1994.

	1/1/1993 to 30/4/1993 n = 151	1/5/1993 to 31/12/ 1994 n = 756	Total n = 907
OAE present	69 % (104)	93,7 % (632)	81 % (736)
OAE bilaterally absent	8,5 % (13)	5,3 % (40)	6 % (53)
OAE unilaterally absent	22,5 % (34)	11 % (84)	13 % (118)

Results in terms of percentages and absolute numbers (between brackets) of the screening in two different periods (first and second column) and the total values.

The number of failures at the first test was 171, of which 118 unilateral and 53 bilateral failures. In case of unilateral failure, 32.2 % were lost to follow-up *(*4.2 % of the total population of 907 neonates) and in case of bilateral failure, this figure was even 45.3 % *(*2.6 % of the total population).

It has to be mentioned that three neonates with a bilateral fail on the first test, turned into a unilateral fail on the second test. This brings the actual percentage of bilateral failures without follow-up after the first or second failure to 39.6 % (2.3 % of the total population), and the percentage of unilateral failures without follow-up after the first or second failure to 34.7 % (4.5 % of the tested population).

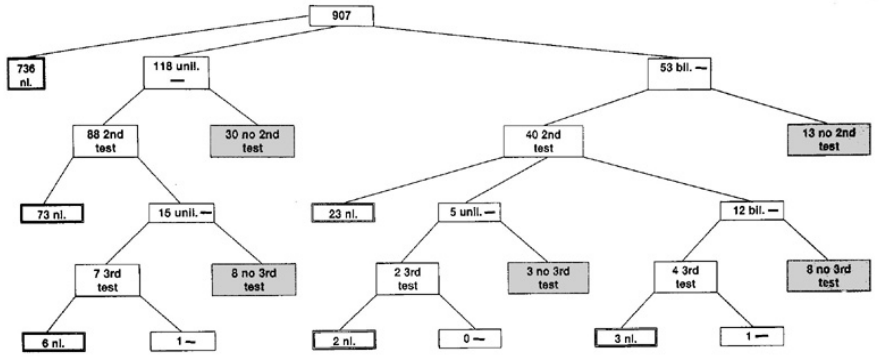

FIGURE 2. Results of the first OAE test and of the follow-up results in case of failure. nl: bilateral presence of OAE's ("pass"), unil- : unilateral fail, bil-: bilateral fail. The shaded blocks indicate neonates that were lost to further follow-up. A thick frame indicates the final presence of 0AFs and thus indicates normal hearing.

Of the 907 neonates, 6.8 % did not complete the follow-up after failure in the first or second OAE examination.

Finally, this means that, after 2 or 3 tests, OAE's were present in 93 % of the tested population.

Table 2 summarises the results after a maximum of 3 tests.

DISCUSSION

The annual birth rate in the St.-Augustinus Hospital is approximately 2400. Since 1993, the parents are offered the opportunity to have the hearing of their neonates tested. Since 1994 this is done systematically for the NICU-children since they are considered to be at risk. This group is not taken into consideration in the present report. Our population is therefore not representative of the total population of newborns. Thus the reported incidence of hearing problems in this report may be underestimated.

After childbirth, mother and child generally remain in hospital for about five days. In the first phase of our project, the test was arbitrarily planned during that week. Because there were indications that the prevalence of OAE's increased during the first few days after birth (Kok 1993), the screening was postponed until the last working day of the hospitalisation period during the second phase of the project. Moreover, the interpretation of the results became more certain, thanks to the new software described in "Material and Me-

thod". These modifications, together with the increased experience of the examiners, have led to an increase of detected OAE's from 69 % to 84 %.

TABLE 2. The screening results after a maximum of 3 tests of 907 neonates in 1993 and 1994 as a function of the result of the first test.

result 1st test	pass after max. 3 tests	fail after 2 or 3 tests	Lost to follow-up
Unilateral fail, n = 118	67 (8,7)	0,8 (0,1)	32,2 (4,2)
Bilateral fail; n = 53	52,8 (3)	1,9 (0,1)	45,3 (2,6)
Pass; n = 736	100 (81,3)		
Total	93	0,2	6,8

The figures are percentages within each group (- row). The numbers in brackets are the percentages within the total population (n = 907)

In comparison with other authors this prevalence is rather low. For example, Kok, among others, found a 99 % prevalence in neonates older than 108 hours (Kok 1993). Many authors, however, give little information on the composition of the experimental group. It is not unlikely that in some experiments only measurements were done in case of easy probe fitting.

Clinical practice teaches us that OAE's often require repeated attempts to place the probe.

Prevalence figures are presumed to be influenced to a large degree by factors such as the size and curvature of the auditory channel. The IL088 system only provides information concerning the stability of the probe. Information regarding the positioning of the probe in relation to the wall of the auditory channel cannot be obtained. These technical problems also have repercussions on the prevalence figures. Other research groups have also encountered these problems (Morlet, Collet, personal communication). It is therefore possible that new probe designs and feedback about the probe placement can increase the prevalence figures.

Within the present set up, the follow-up of failures was a major problem. During the first test there were 171 newborns that failed the test. Of the unilateral fails, 32.2 % were lost to follow-up and of the bilateral fails, even 45.3 % was lost to follow-up (see Table 2). Considerable efforts were made to “trace and chase” the parents. The value of a screening programme stands or falls with a good follow-up. It is therefore of the utmost importance to sensitise the entire medical and paramedical staff around the child and its parents and to get their full commitment. A general policy for the detection of hearing problems is necessary.

In comparison with the Ewing screening, our figures show a better pass-rate after the first test (81 % compared with 76 %). If specificity is defined in relation to perceptive losses, the present results are 5 % more specific than the Ewing-screening. After 2 or 3 tests the specificity of the Ewing-screening in our hands is known to be 88 %, whereas the specificity of the screening with OAE's is 93 %. If specificity relates to all kinds of hearing losses, the Ewing appears to be more specific (96 % compared to 93 %).

The most important advantage of screening with otoacoustic emissions is undoubtedly the timing. Various authors have already stressed the importance of early detection (White 1993).

OAE's make it possible to test neonates in a simple and reliable way, so that treatment can start between the ages of 3 and 6 months. It is clear that the impact of the hearing problem can be reduced by early detection followed by early intervention and this can only have a positive influence on the integrating into society. In some states of the USA the right to undergo a hearing screening is established by law. In our present study of 907 neonates, no bilateral hearing losses were found, but since the end of the study, some have already been detected and helped by hearing aid fitting and enrolment in early rehabilitation programmes.

The technology of conventional hearing aids and cochlear implants is evolving rapidly. They enable early stimulation of the auditory pathways, which is of the utmost importance.

Whether hearing screening of all neonates is justified is a question for debate. Although this is a political rather than a medical question, we would like to add a couple of points to the discussions. It is up to the medical world to use all available means in its endeavour to integrate the hearing impaired into the mainstream school and social live. This objective has not yet been achieved. The hard of hearing still faces enormous difficulties to integrate. Most of them still have no choice but to be part of the world of the deaf. In this world, and despite all good intentions and care, they become isolated from the hearing society. Fortunately, science is making great progress, both in the diagnostic field (e.g. genetic examination of deafness), and in the therapeutic field (e.g. cochlear implantation). Early detection leads to early therapy and we are becoming more and more aware that the earlier the therapy, the greater the chance of social integration. In Belgium there are still too many children in whom congenital hearing loss is only detected at the age of 2 or 3 years. In the present state of science and social welfare, this can no longer be morally justified.

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Numerical assessment of TOAE screening results: currently used criteria and their effect on TOAE prevalence figures

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ABSTRACT

The literature on neonatal hearing screening by means of otoacoustic emissions (OAE's) presents various prevalence figures, and gives little quantitative information on the procedure used to score the recordings. If the OAE test is to be interpreted by users who do not have the opportunity to develop intuitive interpretation skills through extensive training, a clear numerical decision criterion is needed. The present paper discusses the scoring procedure used by 25 teams, which together screen 22,356 neonates annually. More than 60 % of the groups involved in this study use visual interpretation of the recorded OAE response, together with numerical criteria. Amongst the teams, 21 different ways of numerical scoring are used. It is shown that for a given set of OAE recordings, prevalence varies from 61 % to 90 %, depending on the numerical decision criterion being applied. We conclude that at this moment no consensus exists regarding the numerical criterion to be used when assessing OAE screening results. In view of the strong effect of criteria on the outcome of OAE screening, such consensus is urgently needed, but should be based on sensitivity and specificity figures for each scoring technique.

Key words: otoacoustic emissions, specificity, neonatal.

INTRODUCTION

Following Kemp's first publication (1) on the recording of transient otoacoustic emissions (TOAE's), a number of authors published figures of TOAE prevalence. Some authors agreed on an extremely high prevalence rate, up to 100 % (e.g. Kemp 1978, Wit 1979, Johnsen 1982, Probst 1986, Bonfils 1988). Others found figures that were a bit less optimistic (e.g. Stevens (1988): 97 %, Rutten (1980): 90 %, and Grandori (1983): 90 %), and some workers even encountered quite a low number of ears in which emissions could be recorded (e.g. Zwicker (1983): 70 %, and van Dijk (1987): 40 %). In these first years of OAE research, many different recording techniques were used and the recording apparatus was not standardised, which can be one reason for the large range of prevalence figures reported. Measurements were also done in different populations, and were not focused on neonatal groups. The number of measured ears was quite small, usually less than 50 (except Bonfils (1988): 131, and van Dijk (1987): 210).

Following the pioneering work on OAE's, figures became available on OAE recordings in large (> = 100) neonatal populations. For example, Elberling (1985) and Johnsen (1988) reported a prevalence of 100 % in groups of respectively 100 and 200 neonates, Bonfils (1990) found 98 % prevalence in a group of 100 neonates. More recently, Kok (1993) measured a prevalence rate of 93.4 % in a group of 1,036 healthy new-borns, and Stevens (1994) measured a prevalence of 95.9 % in a population of 1,367 babies. Both Kok and Stevens based their OAE scoring on "visual interpretation" of the response.

Many reports are the result of a research project, and figures have therefore not been obtained in daily clinical practice where recording time is limited and a noise free environment is not always available. Such factors will inevitably have a negative result on OAE screening outcome.

In a recent 5-year field study, Meredith (1994) found a prevalence figure of only 72.3 % in a population of 772 babies. The screen was targeted on neonates with one or more risk factors. Follow-up confirmed hearing loss in 2.2 % of the cases, so the OAE screening gave a falls positive result in 25.5 % of the cases. The decision criterion for OAE presence was described by the authors as: "correlations … along with signal to noise measure and subjective assessment of the waveforms", without any numerical values being specified.

At this moment it is unclear whether any consensus exists about the criterion to be used by the clinician to decide upon TOAE pass or fail. Salomon (1994)

have shown, for linear clicks recorded in 378 neonatal ears, that a correlation of more than 0.7 is present in only 80.4 % of the cases, while correlation of more than 0.5 is present in 90.7 % of the cases. Changing the criterion for required correlation to give a pass on OAE testing from 0.5 to 0.7 will therefore change the prevalence by 10 %. The lack of information about the criterion used makes it very difficult to compare prevalence figures obtained in different studies, as long as a standardised decision criterion is not generally accepted.

It is not possible for all private practitioners or small screening teams to gain experience in "visual interpretation" of OAE curves. For these users, who will become a fast growing group as price of equipment goes down, a clear and well defined numerical criterion is needed. If one wants to come to automated decision making (as implemented in some of the newest commercial apparatuses), or if one wants the screening to be done by non-specialised personnel, numerical scores will have to be used rather than intuitive decision making (based on visual inspection of curves) which can only be obtained after extensive training. As pointed out by Kemp (1991), good automatic scoring should be based on multiparameter analysis.

In this paper we will address the question whether at this moment a consensus exists amongst screening teams concerning the numerical decision criterion to be used in the scoring of OAE screening results. We will give an overview of decision criteria currently used by a number of screening teams, and we will show the effect on prevalence figures when these different criteria are applied to a given set of OAE measurements obtained in daily clinical practice.

MATERIAL AND METHODS

In November 95, a questionnaire was sent to 95 groups who appeared on the mailing list of the European Concerted Action on Otoacoustic Emissions. The questionnaire was accompanied by a letter, explaining that we wanted to obtain an overview of the criteria that are currently in use, and proposing that all participants in the enquiry would obtain an overview of the results. The questionnaire contained the following questions:

- How many patients do you test annually for OAE's (adults, babies)?
- Which OAE system do you use?
- Which number of averagings is applied?
- Which kind of clicks do you use (linear, non-linear, both)
- Does the baby pass only if both linear and non-linear clicks give an OAE response, or it is sufficient that the linear clicks give an OAE?

- Do you use visual interpretation of the response curves? If so, how is this done?
- Which criteria do you use for the numerical scores 'global reproducibility, reproducibility in several bands, global S/N ratio, S/N ratio in several bands, correlation'?
- Specify any other methods used than those mentioned?

The questions were ordered in a table on one A4 page, using boxes to indicate the answers, and using multiple choice indicating boxes where possible. The page contained return address and fax number. We think it is a fair guess to say that filling out the form took no more than 10 min.

Of the 95 questionnaires sent, 3 were returned to sender because the address in the mailing list was wrong. Of the other 92, 40 groups sent the answering page back by mail or fax. We waited 4 months to obtain the last answer (up till now).

As the letters were directed towards groups that are active in the field of OAE screening, we did not explain the concepts such as "reproducibility" or "linear clicks", as this is common knowledge for those involved in OAE work. For the not specialised reader, we will shortly explain the terms used.

To eliminate stimulus and middle ear artefact from the ear canal response, two responses following clicks of the same polarity and amplitude are added to the response following a click with reversed polarity and double amplitude. All linear components in the response will disappear in this sum, as they will be twice as large and of inverse sign for the third click. Due to the saturating nature of the OAE response, the non-linear residue will remain. This process is referred to as non-linear click OAE testing. It has the advantage that linear artefacts in the response cannot be mistaken for OAE's. The subtraction process, however, also eliminates part of the OAE response itself, leading to a smaller signal to noise ratio. Therefore, if a non-linear OAE response is found, a linear response is also due to be present.

To improve the signal to noise ratio in the final response, a number of responses is averaged (usually between 25 and 1,000). A standard procedure to differentiate between OAE response and noise uses the acquisition of two sub averages. In one buffer, the average is made of the responses following the even numbered clicks, and in a second buffer the average is made of the responses following the odd numbered clicks. (In the non-linear measurement mode, these responses are in fact the result of three clicks. The sum of the three measurements is regarded as one response, which is added to one of the average buffers.) At the end of the measurement the content of the two buffers is displayed on the same graph. If an OAE signal is present, the two curves will overlap well. If the signal only contains noise there will be no

systematic overlap. Interpreting this quality of overlapping is referred to as visual interpretation of the OAE response.

To eliminate noise in the measurement, the user will set a rejection level. Responses with higher amplitude than this level are rejected, and will not be added to the averaged response, as they are regarded as artefacts. A lower rejection level will decrease the noise in the measurement, but will increase measurement time.

Using the two buffers which each contain an average, commercial OAE testing equipment performs a number of calculations to estimate the amount of noise and of OAE signal in the measured response. The result is displayed as "global correlation" or "global reproducibility". If the two buffers overlap perfectly, "global reproducibility" will be 100 %. On the basis of overlap and non-overlap of the buffers, an estimate is made of the global signal to noise ratio in the response. The ratio is expressed in dB.

The apparatus also performs a Fourier transform on the measured time data, and displays a spectrum of the response and of the estimated noise. Evaluation of this spectrum can also be incorporated in the visual interpretation of the result. The correlation between the two buffers and signal to noise ratio is also calculated and displayed in a number of separate frequency bands (e.g. five bands, with centre frequencies 800 Hz, 1.6 kHz, 3.2 kHz and 4 kHz). For a strong OAE response, global correlation and signal to noise ratio will be high, as well as the correlation and signal to noise ratio in the different frequency bands. For a smaller response, the global correlation will diminish, and sometimes correlation will be high in some frequency bands, and low in others.

To determine whether an OAE is present, one can use a minimal threshold value for the global reproducibility or signal to noise ratio, or (and) one can use criteria for the correlations in the different frequency bands (such as a minimal value that has to be present in at least a certain number of bands). In the following, criteria based on calculations in different frequency bands will be referred to as "band criteria", while criteria based on calculations on the whole of the response will be referred to as "global criteria".

RESULTS

From the answers we obtained we learned that 4 groups were about to start screening, but did not perform OAE measurements at this moment. Five researchers were on the mailing list, but were not practising OAE measurements. Four groups only made measurements on adults, one group used only

distortion products, and one group used a special complex analysis system, which did not fit with the questions we asked. As a result, 25 answers were obtained that could be used in the present study.

From the answers we learned that 22 groups are using the ILO system. Seven amongst them have the ILO 92 available, and run the IL088 software for their TOAE screening. The ILO system is a commercial OAE testing device, produced by Otodynamics ltd. The ILO 88 system can only record TOAE's and spontaneous emissions, while the ILO 92 can also be used to record distortion product emissions. For neonatal screening, the ILO 92 is used in ILO 88 mode, to record TOAE's. Two groups work with the POEMS system, and one group did not specify the apparatus being used. The POEMS, or Programmable Measurement System, is another commercially available device, suitable for TOAE testing.

As to the number of averagings being applied, 19 groups work with (up to) 260 averagings, while four favour (up to) 500 averagings.

Together, the 25 teams screen 22,356 babies per year. One group screens half of the babies in this study. Specifying the number of emissions scored by a certain criterion would therefore be strongly biased by the attitude taken by this one major group. On the other hand, it would neither be sensible to take into account only the number of groups following a certain procedure, thereby giving just as much weight to a group screening 50 babies per year as to a group screening 10,000 babies per year. For this reason we will note both the percentage of groups and the percentage of babies annually screened, for each parameter discussed.

Let us first consider the TAOE recording procedure being used. Four percent of the groups (accounting for 0.4 % of the babies) use linear clicks only. Another 16 % (11.8 % babies) apply both linear and non-linear clicks. Regarding decision criteria, 12 % of the groups (11.6 % babies) find that the response from linear clicks is sufficient to decide whether OAE's are present, while the other 88 % (88.4 % of the babies) want to see non-linear click evoked OAE's. Since the non-linear click calculation scheme reduces the measured emission result (only the non-linear residue remains), one can rest assured that the linear click process will always give a result when a non-linear result can be obtained. The question therefore arises what is to be learned (in terms of screening purposes) from measuring both linear and non-linear clicks if the final decision is being made on the mere presence of the linear measured emissions.

Further we learned from the questionnaire that 64 % of the groups (39 % babies) use some kind of visual interpretation together with the numerical interpretation. The explanation given about this visual interpretation varies from

group to group. Some compare the results of the two buffers containing the averaged time signals to see whether there is "good agreement over an acceptable range". Others make a "visual inspection" of the Fourier spectrum of the response to see if the S/N ratio is large enough. It is difficult to sum up a consensus in the answers about the visual inspection. We can only state that 64 % of the screening groups found that a mere numerical decision criterion does not suffice to establish the presence of OAE's. The one general consensus in the answers is that the visual interpretation of the time signal or of the spectrum is based on experience of the clinician. Clearly, it is not easy to pass on such experience if it cannot be described in terms of well-defined decision rules.

A summary of the numerical criteria used to decide upon the presence of OAE's is presented in Table 1. The groups are ordered according to the number of babies they screen annually. One group, using the POEMS system, applies a 66 % management score as decision criterion. The management score is calculated by the POEMS system on the basis of correlation and F_{sp} (which is a ratio between variance of estimated evoked response and variance of background noise (Don 1984)). The other groups use correlation values, signal to noise ratios or reproducibility scores. The groups which will give a pass when a linear response is detected are marked with an asterisk.

To avoid any confusion about terms, the questionnaire gave the possibility to fill out "global reproducibility" and "correlation" separately. Strange enough, one group (1.8 % babies) gives different answers for both scores: on the one hand they find it necessary to have a global reproducibility of 50 %, while on the other they maintain that correlation needs only be higher than 20 %. In Table 1, and in the evaluation of the OAE results in the next section, we have taken their more stringent criterion (reproducibility 50 %) into account. One group (2.2 % babies) used global correlation, but did not specify the numerical criterion they apply (indicated with question mark in Table 1).

From Table 1 we can derive that 56 % of the groups (29.2 % babies) apply only global criteria (global reproducibility, global S/N ratio, global correlation or global management score). Another 36 % of the groups (22.9 % babies) monitor both global and frequency band criteria. Eight percent of the groups (47.9 % babies) do not use global scores but find it sufficient that reproducibility and/or S/N ratio exceeds a certain value in at least 3 different frequency bands.

What we essentially learn from Table 1 is that the 25 groups use 21 different ways of numerical TOAE result scoring. Those using global criteria (on its own, or combined with band criteria) all apply global reproducibility (or cor-

TABLE 1. Overview of the numerical decision criteria used by the groups involved in the present study

Babies (n)	Babies (%)	Pass on linear OAE	Global repro (%)	Band repro (%)	Global S/N ratio (dB)	Band S/N ratio (dB)	Management score (%)
10	0.04		50		0		
20	0.09		60		3	3	
50	0.22		?				
86	0.38	*	75		5		
90	0.40		50				
100	0.45		60	60			
100	0.45		50				
100	0.45		60				
100	0.45		55				
100	0.45		50				
150	0.67		50	50	5	3	
200	0.89		70				
250	1.12		60		5		
300	1.34		50			6	
300	1.34		50				
400	1.79		50	50	3	3	
500	2.24	*					66
700	3.13		70		3		
700	3.13					3	
900	4.03		50	60			
1200	5.37		60		5	5	
2000	8.95	*	50				
2000	8.95		50		3		
2000	8.95		70	70			
10000	44.73			75		3	

The first two columns respectively show the number and percentage of babies screened annually by each group. Groups giving a pass on the basis of a linearly recorded OAE response are indicated with an asterisk. The last 5 columns show the values required to give a pass on the applied numerical criterion: Global repro: percentage global reproducibility or correlation; Band repro: percentage reproducibility in at least three frequency bands; Global signal to noise ratio: global signal to noise ratio in dB; Band signal to noise ratio: signal to noise ratio in at least three frequency bands, in dB; Management score; percentage of management score, as defined by the commercial POEMS system. Further explanation of these terms is given in the section Material and Methods.

relation), sometimes combined with global signal to noise ratio, but the correlation values used differ from 50 % to 70 %. Of the two groups using band criteria only, one group (3.1 % babies) found it sufficient to have 3 dB S/N ratio in 3 frequency bands, while the other (having the largest screening program of all participants: 44.7 % babies) wanted to see 3 dB S/N ratio and 75%

of reproducibility in at least 3 frequency bands to decide upon the presence of TOAE's. It is therefore hard to infer from Table 1 a consensus on numerical decision criteria.

Effect of different numerical scores on the pass/fail decision

As the follow-up results of the screened babies are not yet available it is not possible to calculate specificity and sensitivity figures for each of the different decision criteria in use. Neither do we want to deduce the prevalence rates obtained by the different groups. What we will do is to calculate the OAE prevalence that is obtained by applying the different criteria to a given set of OAE measurement results. When looking at the figures, one should not forget that more than half of all the clinicians who answered the questionnaire used visual interpretation of the time and/or frequency signals to make their final evaluation.

To get an idea of the effect of different numerical decision criteria upon the prevalence number of TOAE's we have taken 100 subsequently recorded TOAE results from our own screening program. Since we work with the non-linear click method we will only apply the criteria used by the 21 groups who base their decision on the non-linear method. From Table 1 we see that these groups screen 19,720 babies annually, and that they use 18 different numerical scores. The percentages of babies and groups mentioned in the present paragraph, and in Figure 1, will be given with regard to the 21 groups and 19,720 babies, respectively.

The 100 emissions were recorded in mature babies, all between the third and the sixth day after birth. Recordings were done in an ordinary, not specially sound treated room, using the IL092 apparatus, in IL088 mode. All babies were asleep or very quiet, and were held in the mother's arms. The ILO hardware was delivered (by the company representing Otodynamics in Belgium) in an ordinary PC, with a fan and a hard disk that produce a not negligible amount of noise. Though this set-up is certainly not ideal, we think it is representative for many actual clinical situations today.

The noise floor in the measurements was 38 dB on average, and never exceeded 44.5 dB. Measurements were performed by skilled personnel, trained in OAE screening and performing over 500 emission measurements per year. Positioning of the probe, and adjustment of the reject level was done following the indications proposed by Kemp (1990). Non-linear clicks were applied in the "Kwickscreen" setting of the ILO88. Stimulus intensity was automatically adjusted in the probe fit procedure, and varied for different recordings

between 85 dB SPL and 89 dB SPL. Probe stability was always better than 80 % (and in most cases higher than 90 %).

Before going into the figures presented in Figure 1, we want to emphasise that at present 66 % of the clinicians involved in this study use some visual interpretation on top of the numerical scores. The figures obtained therefore only show which prevalence results would be obtained if screening were to be based on pure numerical scores, using one of the decision criteria in use. At present, only 34 % of the groups are performing screen result scoring purely in that way.

Figure 1 shows the results of assessing our 100 recordings with the 18 different numerical criteria. Because so many groups use global reproducibility, we have ordered the decision criteria on this basis. To simplify the figure, criteria based on the same global reproducibility and leading to the same prevalence are registered in the same category. Because different prevalence rates are found by adding to the 50 % global reproducibility score one or several supplementary criteria, these results are split into several categories. Finally, the two purely band based scores are added as separate categories. In total, we obtain in this way eight main categories of numerical decision criteria. The exact composition of each category is explained below. Figure 2*a* shows for each category the percentage of groups following that way of decision making, and Figure 2*b* shows for each category the percentage of babies screened annually on the basis of these criteria.

The lowest prevalence figure is obtained by applying the criterion of 70 % global reproducibility, on its own or combined with global S/N ratio of 3 dB or band reproducibility of 70 %. This way of decision-making is used by 14.3 % of the groups (14.7 % babies), and leads to a prevalence of 61 %. The global reproducibility score was the decisive factor in all cases; there were no results that would have a pass for 70 % reproducibility, and then fail for the band criteria that are added by some groups.

The criterion of 60 % global reproducibility, be it or not in conjunction with other global or frequency band scores, delivers a prevalence figure of 72 %. This scoring is used by 23.8 % of the groups (8.5 % babies). The criterion of 55 % reproducibility leads to the same prevalence figure, and is used by one group or 4.8 % (0.5 % babies). In total, 28.6 % of the groups (9 % babies) use 60 % or 55 % global reproducibility.

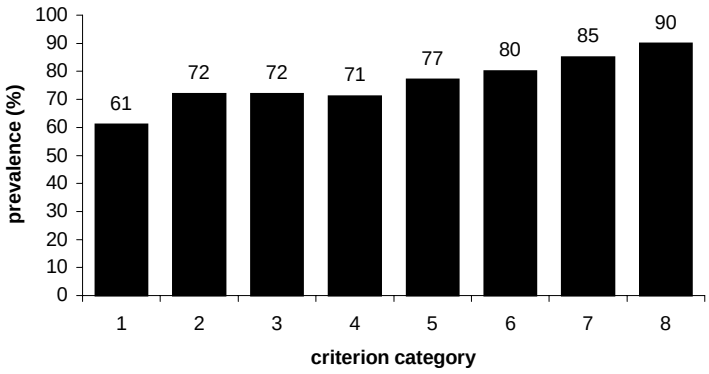

FIGURE 1. Prevalence rates obtained by applying different categories of numerical decision criteria to a given set of OAE results. The composition of the categories is briefly as follows (more details in the text):

(1) 70 % reproducibility	(+70 % band reproducibility, + 3dB band S/N)
(2) 60 % reproducibility	(+ 60 % band reproducibility, + 3 dB band S/N, + 5 dB S/N)
(3) 55 % reproducibility	
(4) 50 % reproducibility	+ 6 dB band S/N
(5) 50 % reproducibility	+ 50 % (60 %) band reproducibility (+5dB S/N)
(6) 50 % reproducibility	(+3 dB S/N, + 0 dB S/N)
(7) 75 % band reproducibility	
(8) 3 dB band S/N	

When using 50 % global reproducibility, together with a S/N ratio of 6 dB in at least 3 frequency bands, we obtained a prevalence figure of 71 %. One group, or 4.8 %, (1.5 % babies) uses this decision score.

Fifty percent global reproducibility, together with 50 % or 60 % reproducibility in at least 3 frequency bands, leads to 77 % prevalence. This procedure is used by two groups. One more group adds global S/N ratio of 5 dB and S/N ratio of 3 dB in at least 3 frequency bands. This criterion leads to the same prevalence figure. Taken as a whole, we see that 50 % global reproducibility, together with 60 % (or 50 %) reproducibility in three bands, gives a prevalence of 77 % and is used by 14.3 % of the groups (7.4 % babies).

Using 50 % global reproducibility on its own leads to a prevalence figure of 80 %. As stated above, 5 groups share this way of working. Combining 50 % global reproducibility with 3 dB global S/N ratio or with 0 dB S/N ratio, each used by one group, does not alter the obtained prevalence figure. In total, therefore, 28.5 % of the groups (13.2 % babies) base their decision on the 50 % global reproducibility criterion.

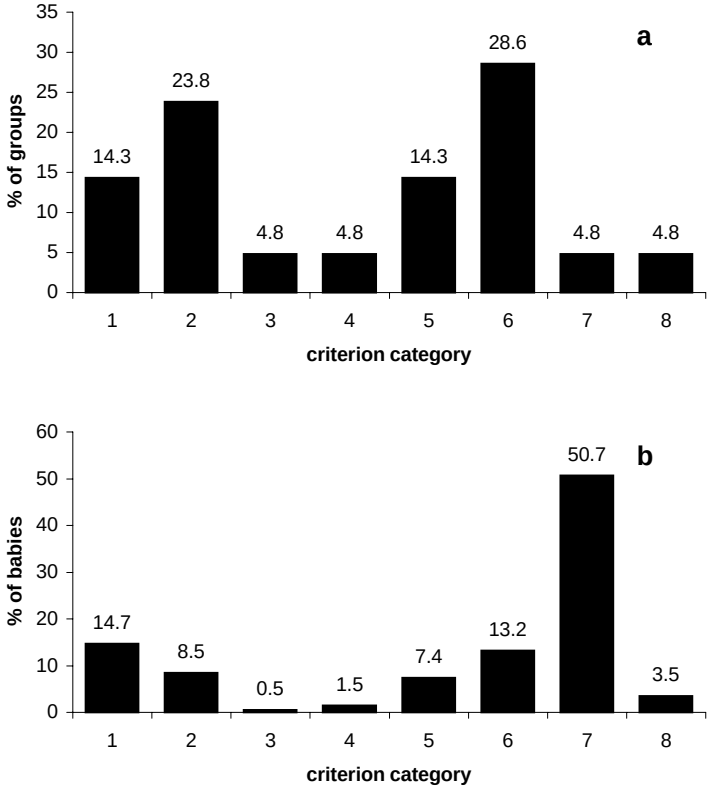

FIGURE 2. (*a*) Percentage of groups per category of decision criteria. (*b*) Percentage of babies screened annually on the basis of a category of decision criteria. The composition of the categories, and the legend to the figure, is the same as in Figure 1.

Finally, there were two groups that did not apply global criteria. One group, the one which screens nearly half of the babies involved in this study (50.7 % babies) wants to have 75 % reproducibility and 3 dB of S/N ratio in at least 3 frequency bands. The criterion leads to a prevalence figure of 85 %. The other group (3.5 % babies) uses only 3 dB of S/N ratio in at least three frequency bands. This criterion produces a prevalence figure of 90 %.

In summary, we see that the different ways to interpret the numerical score, when applied to a set of randomly chosen emission results, lead to prevalence figures varying from 61 % to 90 %.

CONCLUSIONS

From the reactions given by 25 teams, we learn that many differences exist in the ways neonatal OAE screening and scoring is performed at this moment. Although most groups base their decision on non-linear clicks, some groups find a linear answer to be sufficient. More than 60 % of the groups incorporate in their decision process some visual interpretation of the curves. As to numerical scores, some groups base their decision purely on global scores, while others use both global and frequency band scores, and still others only take into account frequency band based criteria. Amongst the 25 teams, 21 different ways of numerical scoring are used.

When emission results, obtained in an everyday, non ideal but realistic clinical set-up, are evaluated with the different numerical scores, the obtained prevalence figures range from 61 % to 90 %. These prevalence figures are less optimistic than the figures reported by other authors.

We conclude that at this moment there is no consensus amongst screening teams with regard to the numerical decision criterion to be used in scoring OAE screening results. When assessing a given set of OAE recordings, changing the criterion clearly has a dramatic effect on the obtained prevalence figure. The effect of scoring procedure on sensitivity will only become clear when for each scoring procedure figures become available of follow up of large numbers of babies who passed the OAE screen.

If OAE testing is to be performed by untrained personnel, a clear and simple, numerically based assessment of the measurement result is needed. At this moment, a consensus on the criterion to use does not exist. With the proliferation of the OAE test, clear guidelines on the scoring procedure to be used is urgently needed. This consensus has to be based on figures of specificity and sensitivity for each procedure currently in use.

Acknowledgement

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Costs of screening programmes (*)

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The European Consensus Statement on Neonatal Hearing Screening.
Grandori F, Lutman M (Eds.). Milan 1998.

Project AHEAD - Advancement of Hearing Assessment Methods and Devices.
European Commission, Directorate-General XII, Biomedicine and Health Programme.

(*) This is not a peer-reviewed scientific paper, but one of the sixteen contributions to the final report for the European Community Project AHEAD.

The report is based on original data and data from Davis 1997, Maxon 1995, Mehl 1998, Turner 1991, Turner 1992, and Weirather YP 1997.

INTRODUCTION

Things of value have a price. Modern medicine is reaching the upper plateau-phase of the sigmoidal cost-benefit curve, which means that the cost to obtain any further improvement in the health situation of our society is becoming very high. Society as well as its political representatives should be aware that no increase in health is to be expected without due investment.

Clearly the decision as to which benefit justifies which cost is a political one. The task of the medical world is primarily to demonstrate the benefit of a given intervention in terms of health parameters. For this the medical world has conceived strict scientific rules that are widely accepted. A new task that is demanded from clinicians is to calculate the cost of any new intervention. This is about to introduce a revolution in our way of thinking. In addition to expressing our outcomes in terms of health parameters, we are now forced to do so in terms of financial parameters as well. And it is only natural that we feel uncomfortable in doing so, not only because we lack the competence and proper instruments but also because we dislike the idea of health being of secondary importance when compared to money.

Already now, ample evidence exists to state that the direct cost of neonatal hearing screening is known, that neonatal hearing screening can be one of the cheapest screenings, and that the cost is justifiable and relatively low when compared to other screening programs for congenital diseases.

COST ANALYSIS

Costs can be categorized in many ways, such as health costs, individual costs, family costs and social costs. The topic here is primarily health costs.

Health costs can be calculated following two major approaches: the bottom-up model and the top-down model.

The bottom-up approach collects data on all subcomponents for a specific service. This approach yields rigorous data, but it takes a lot of time and an obsessive sense for detail to scrutinize all aspects of the service involved. The top-down approach collects aggregated data on costs and estimates individual costs for particular services. This approach is easier and cheaper than the bottom-up approach, but the data are inferred from group data and thus less rigorous.

In defining the health costs of a service like hearing screening, it is essential to identify all the program elements and to estimate the costs of each ingredient accurately. This requires a complete description of the program and its components. Researchers should be most careful in estimating the costs of equipment and supplies, personnel, including screeners, clerical staff, coordinator and audiologists, fringe benefits and overhead. It is equally important not to underestimate the cost of resources. An appropriate measure of a resource's cost is its best alternative value. This means that if a program uses a room free of charge, but the room would otherwise be used by someone else, then there is a so called "opportunity cost" even if the program does not pay for it. A similar "opportunity cost" must be accounted for in case the screening program uses resources that are included in another program's budget. Calculating the cost of a screening program should also cover all stages that precede referral to a diagnostic centre such as the initial screen, the rescreen, the scheduling, tracking and referral procedure.

FACTORS THAT INFLUENCE THE COST OF HEARING SCREENING

Good cost-analyses are available and the main sources of information are from the USA and the UK.

The issue of cost relates to the type of screening strategy. Basically the choice can be made between neonatal versus screening at 9 months of age; between targeted screening versus universal screening and between maternity-unit based versus home based programs.

Three cost parameters are commonly used and will also be used here.

(1) The **"cost per child tested**" covers the cost of the screen and rescreen and is a measure of how much should be **charged** for screening a child.

(2) The "**cost per 1000 births**" is a measure of what it **costs to implement** the program and reflects what politicians or health economists are most interested in and

(3) The "**cost per child detected**" is a measure of **cost-effectiveness** and is therefore interesting to compare screening programs for two different health problems.

The cost of a screening program depends on several factors. I will try to summarize them in three categories:

(1) Epidemiological factors, mainly the prevalence

(2) Test-specific factors

(3) Protocol specific factors.

The prevalence obviously does not influence the implementation cost of a program (Figure 1). The screening has a certain cost and this does not change whether children are being detected or not.

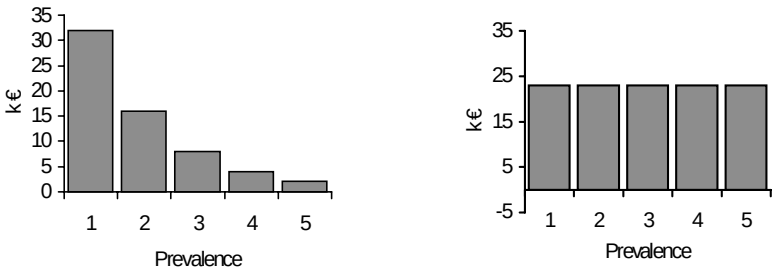

FIGURE 1. Influence of the prevalence (expressed as cases per thousand births) on the implementation cost (left: cost per 1000 births) and on the cost-effectiveness (right: cost per child detected)

In contrast the prevalence does have a significant influence on the cost-effectiveness (Figure 1). The higher the prevalence, the lower the cost per child detected. For instance in the case of neonatal hearing screening, a prevalence of 1.2 per 1000 makes a cost of approximately 25 k€ per child detected, whereas a prevalence of 3 per 1000 reduces this to approximately 10 k€.

Test-specific factors that influence the cost of a program are related to equipment and supplies, to personnel and to the site of testing. As an example of the impact of equipment and supplies, I have taken some rough figures to compare TEOAE and AABR: the equipment costs 8000 € and 10000 €, respectively; for TEOAE the supply costs are approximately 1 € per child for disposable probe tips and probe replacement compared to 8 € for AABR to cover disposable earphones and electrodes. As it will be discussed below, this difference accounts for a 40 % higher cost per child screened with AABR instead of with OAE.

It has been calculated that personnel costs represent some 70 % of the total costs and this is important because personnel costs differ substantially between different countries.

It is self-evident that maternity-based screening is far less expensive than home based screening, but to the best of my knowledge, no published data are available to quantify this difference.

Then there are protocol-specific factors that influence the cost of a program.

A targeted program aims at testing 6 to 10 % of all infants. This is far less than a universal program, aiming at some 95 %. Consequently, even if the cost of an individual "targeted" screen is higher than that of an individual "universal" screen, the total cost of a targeted program may still be substantially less than of a universal program. As we shall see later, the only problem with targeted screening is the good definition of a target.

Is a unilateral "pass" considered a pass or a fail? If it is considered a fail, we must be prepared to screen some 10 % additional children. This means that, although the impact of a unilateral hearing loss is much less than the one of a bilateral loss and although possibly no "early" intervention is needed for a unilateral loss, the cost for finding it is almost the same as for finding a bilateral loss. We must ask ourselves whether the cost-benefit for such a child with unilateral hearing loss is still positive.

The referral algorithm will also influence the total cost. The cost of a diagnostic work-up is usually much higher (factor 5-10) than the cost of a re-screen. Reducing the referral rate by re-screening some 3 weeks after the initial fail will reduce the total cost.

If the referral rate can be kept lower than 1 %, the impact of the diagnostic work-up on the total cost will be minimal (Figure 2). But if the referral rate gets higher, the impact of the diagnostic work-up will become substantial.

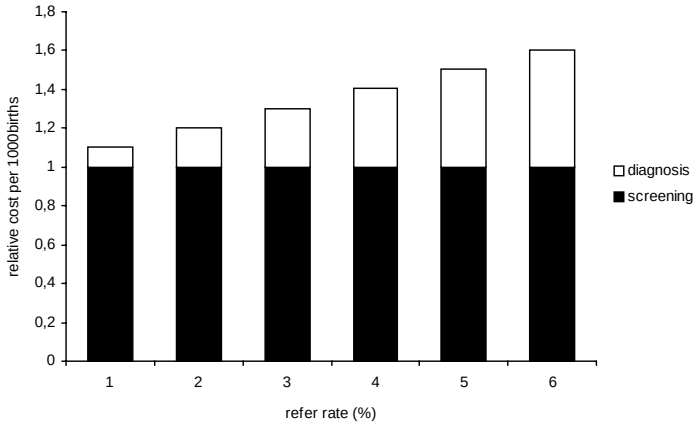

FIGURE 2. Effect of refer rate on the implementation cost of a screening program.

Another cost-determining factor is the number of patients that are "lost to follow-up". This does not significantly influence the total cost, but the cost-effectiveness will be negatively influenced, mainly because the prevalence of hearing loss in these children is obviously much higher than in the whole group. Loosing children during the re-screen-process is not as dramatic as loosing them during the referral procedure. But even in the re-screen-procedure, the number of children that does not show up any more should not exceed 10 %. During the referral procedure, loosing as few as 3 children per 1000 increases dramatically the cost per child detected. It is therefore of crucial importance to invest a good deal of money in tracking these children.

COST OF HEARING SCREENING

Published reports show different cost-data. This can be explained by the factors previously described. A comprehensive summary of different screening programmes in their most typical form is given here.

The distraction test has been the standard so far. The child is tested at the age of approximately 9 months by typically two trained testers. The cost per 1000 births is about 20 to 40 k€, provided that 90 % of infants are tested. This coverage is certainly not reached in all regions of Europe. There is a low yield, partly because by the age of 6 to 9 months several hearing impaired children have already been referred through targeted neonatal screening programs or

professional or parental concern. The test is also characterised by a low sensitivity and specificity. The low yield results in a bad cost-effectiveness. It costs approximately 130 k€ to detect a single hearing impaired child. In addition the detection is relatively late thus producing extra long-term costs. The targeted neonatal screening that often precedes the distraction test has not even been considered in this cost analysis.

The cost of this type of screening is clearly high. In an attempt to reduce these costs, the Joint Committee on Infant Hearing has published a list of "risk factors" or as they are now called "indicators of hearing loss" that aim at reducing the number of children to be screened. Children with one of these indicators are typically tested by ABR. This is an expensive test, but since only some 8 % of children have to be tested, the implementation cost is rather low (8 k€ per 1000 newborns) and the cost-effectiveness is good (18 k€ per child detected). It should be stressed here that only 50 % of hearing impaired children fall into at least one of these risk categories and that consequently only half of the hearing impaired children can be detected by a targeted screening.

The implementation cost of a universal neonatal screening program is approximately 20 k€ in case of an OAE-based screening and 28 k€ in case of an AABR-based screening. The cost-effectiveness equals that of the targeted screening. Again it is important to note that approximately 95 % of hearing impaired children are detected by universal screen and that these children are detected at a very early stage, offering quite a few additional advantages.

TABLE 1. Overview of cost data (expressed in €; k= x1000 €).

	Distraction test	Targeted Neonatal	Universal Neonatal (OAE)	Universal Neonatal (AABR)
Cost per child tested	37	109	18	25
Cost per 1000 births	30k	8k	20k	8k
Cost per child detected	135k	18k	7-25k	9-35k

Clearly the most cost-effective programs are neonatal programs, both targeted and universal. The implementation of a targeted program is definitely cheaper than a universal screening program, but as has already been said, in a targeted program 50 % of hearing impaired children remain undetected.

When we compare the cost of a universal neonatal program to other operational screening programs for congenital anomalies such as hypothyroidism, phenylketonuria (PKU), cystic fibrosis and sickle cell anaemia, screening for

hearing loss appears to be more expensive as such, but the cost-effectiveness is amongst the best, due to the high prevalence of sensorineural hearing loss.

TABLE 2. Comparative data of different screening programmes

	SNHL	Hypo-thyroid	PKU	Cystic Fibrosis	Sickle cell anaemia
Prevalence / 100.000	240	23	6	45	12
Cost per screen (€)	23	3	3	3	3
Cost per child detected (€)	9000	10000	37000	5500	21000

SNHL: sensorineural hearing loss; PKU: phenylketonuria

A net balance of costs and savings is hard to make, but in an attempt to do so, costs consist of the actual screening costs, the costs of follow-up and confirmatory evaluation and the cost of early intervention; and savings consist of averting costs of late diagnostic tests, of rehabilitation and of pre-school and school-age educational programs. In an estimate as close to reality as possible, net savings occur only 10 years after implementation of a neonatal screening program.

In conclusion, one must realize that the cheapest option is not to screen at all. Screening infants is a commitment based on definite medical, cultural and ethical arguments. It takes a lot of money to do so, but it also takes quite a good deal of money not to screen. If Society decides to screen, neonatal programs are by far the most cost-effective and as such even cheap in comparison with other operational screening programs for congenital diseases. The implementation cost of a targeted program is less than of a universal program, but a targeted program is bound to detect at most 50 % of hearing impaired children, compared to approximately 90-95 % detected by a universal program. Not identifying half of the children also implies a great cost, not only in medical and human terms, but also in economical terms, because of the additional costs of late detection and because of the need to have another program running to catch this remaining half at a later stage.

Thus, universal, neonatal, maternity-based hearing screening is the only program that can identify approximately 90-95 % of the hearing impaired children at an early stage and at a cost of about 20 k€ per 1000 newborns. Community can count on net savings only 10 years after the implementation of such a program.

Neonatal hearing screening with transient evoked oto-acoustic emissions: a learning curve

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ABSTRACT

The present paper reports on the implementation of a neonatal hearing screening programme in a private Hospital in Belgium. A maternity-based neonatal hearing screening project with transient evoked otoacoustic emissions (TEOAEs) was started in 1993. The cost of the test was not covered by the public health insurance, so the parents had to pay the full cost for screening their child (approximately 30 €). Since 1993 the programme strategies have been changed on several occasions to improve the quality and efficacy. A retrospective analysis was performed on: (1) the test pass rate: (2) the coverage: and (3) the number of children who become 'Lost to follow-up' after failing the initial test. The data show a steady learning curve with a time course of several years. They also demonstrate that it is worthwhile and feasible to run a high-quality screening programme in a private establishment.

Key words: otoacoustic emissions, Neonatal hearing screening, hearing tests, hearing-impaired persons, congenital hearing loss

INTRODUCTION

Retrospective epidemiological studies on the prevalence of' bilateral congenital permanent hearing impairment (PHI) in Europe have indicated estimates of 1.12 to 2.07 per 1000 live births (Fortnum 1997, Davis 1994, Parving 1993). In these cases auditory deprivation has a serious effect on the speech and language development and thus on the social, emotional and cognitive development of the child. Several authors have demonstrated the benefit of an early identification and intervention (with hearing aids) on the later outcome of language skills in hearing-impaired children (Yoshinaga-Itano 1998, Robinshaw 1995, Eilers 1994, Kuhl 1992).

Over the last decade two major new technologies have emerged which make it possible to take objective measures to estimate the likelihood of adequate hearing function in newborn babies: the evoked otoacoustic emissions (EOAEs) and the automated auditory brainstem response (AABR) testing. Furthermore, when compared to the classical infant distraction test which is only possible from around the age of nine months, these new neonatal screening programmes have produced better figures of sensitivity and specificity (Davis 1997).

A consensus is growing that neonatal hearing screening is important (European Consensus Statement 1998). Several programmes are being implemented throughout the Western world. In many countries people are still looking for a feasible programme that fits with the national health care system. By necessity most programmes will still be based on existing ones, with slight modifications to cope with the local circumstances. It is essential that these programmes are reported, in order to share the different experiences and to facilitate the organization of new programmes. One such neonatal screening programme, using transient otoacoustic emissions (TEOAEs), was started in St.-Augustinus Hospital, Antwerp in 1993.

TEOAEs are low intensity sounds that can he measured by a microphone coupled to the external auditory meatus. They result from energy from the stimulated cochlea passing back into the air contained in the external ear canal. This energy is thought to originate from the outer hair cells whose contractile motions ensure amplification and sharp tuning of the basilar membrane vibration when it is activated by sound. These outer hair cells are the first to be effected by most hearing disorders and ample evidence exists that the presence of EOAEs indicates hearing levels better than 30 dB HL for the frequency range tested (Vohr 1993, Kemp 1990).

The goal of a hearing screening programme is the early detection and referral of every hearing-impaired child, as defined in the European Consensus Statement on Neonatal Hearing Screening (1999). In order to accomplish this goal, a screening programme needs to include: (1) a high test pass rate; (2) a high coverage; and (3) a stringent follow-up and management.

This paper reports on the evolution of the screening programme and its performance parameters from the start of the programme in 1993 until the end of 1997. It tries to analyse whether the modifications made to the screening protocol actually served the final goal of improving the screening practice. To do that the test pass rate, the coverage and the number of 'Lost to follow-up' (LTFU) neonates are reviewed at different periods in time.

MATERIAL AND METHODS

From 1993 until the end of 1997, 3751 neonates were tested by the University ENT department of St.-Augustinus Hospital by means of recording non-linear click evoked TEOAEs. All procedures were made using the IL088 or IL0288 apparatus (Otodynamics Ltd, England).

The test method was adopted from Bray and Kemp (1987). After insertion and fitting of the neonatal probe with a rubber tip in the outer ear canal, the intensity of the eliciting click resulted in stimuli with a peak sound pressure level in the range of 77-83 dB peSPL. Attention was paid to a low stimulus ringing in the outer ear canal and a flat stimulus frequency spectrum.

The TEOAE recording consisted of a minimum of 20 and a maximum of 260 averaged recordings. The recording was stopped when emissions were sufficiently present to meet the pass criteria, which will be described below. If, after 50 recordings, there was clearly an insufficient response, the test was discontinued and, instead of waiting for 260 recordings, the probe was refitted and the test was restarted.

The opportunity to request an examination was given to the parents of every newborn child by means of a letter, which gave a brief explanation and included a simple registration slip.

In order to anticipate possible parental anxiety in case of test failure, we explained at different stages, both before and after the testing, the relative value of the test result at that stage and what would follow in case of failure.

The initial screening protocol in 1993 was as follows: the neonates were tested in a soundproof cabin or a quiet room at the Audiological Centre of the University ENT depart: typically the neonates were brought to the test loca-

tion by their mother, about 1.5 hours after feeding; testing was done as soon as possible after the parents registered for the test; the pass fail criterion was a test of qualitative visual scoring based on the Fourier spectrum of the TEOAE wave; in the case of bilateral failure of the first test, the parents were immediately and verbally invited for a re-screen three weeks later; if after six weeks no re-screen had been done, a letter was sent once or twice to the parents to urge them to make an appointment; if a child failed the TE0AE test twice it was referred for a diagnostic ABR test at the age of three months.

Since then, the screening protocol has been changed on several occasions to improve the test pass rate of the first test, the coverage and to reduce the rate of children who become LTFU after failing the first test. These chronological changes are summarized in Figure 1 and divide the total five-year evaluation period (1993-1997) into seven discrete periods, which will be referred to in the rest of the report as periods 1 to 7.

Chronologically these changes were the following:

1. From May 1993 onwards, the test was done on the last working day before the child left the hospital. This means that, at the earliest, the neonates were tested at the age of three days (period 2).
2. From February 1994, the new software (ILO88 V3.94 Quickscreen Test) was available. It allowed numerical assessment of the signal to noise ratio (S/N ratio) in different frequency bands and thus a numerical pass-fail criterion became possible. We concluded that TEOAEs were sufficient if S/N ratio in the frequency bands with centre frequencies 2.4, 3.2 and 4 kHz exceeded 6 dB and S/N ratio in the frequency band with centre frequency 1.6 kHz exceeded 3 dB (period 3). The standard use of a low-frequency cut-off filter was also implemented at that time.
3. In June 1994 a consensus was reached with the Neonatal Intensive Care Unit (NICU) to have all their babies screened with TE0AEs. This group consisted of 679 children out of the total of 3751 tested children; 49 per cent of those NICU babies were low or medium care; the other 51 per cent were high care. So, from then on, non-NICU and all NICU neonates were screened (period 4).
4. In October 1994 the follow-up strategy was changed. If after four weeks (instead of six) no re-screen had been performed, the parents were urged by letter to do so. If there was still no reaction, then the family doctor and/or the paediatrician were contacted to alert the parents (period 5).
5. In December 1995 an information session for general practitioners and paediatricians was organized (period 6).
6. In January 1997 the portable IL0288 apparatus became available. From then on neonates could be tested ‘on-site’ in the maternity ward or inten-

sive care unit. The pass/fail criterion was also changed to an S/N ratio 0f 6 dB in at least three neighbouring frequency bands drawn from the upper four bands (1.6, 2.4, 3.2 and 4 kHz) and an overall reproducibility exceeding 50 per cent (period 7).

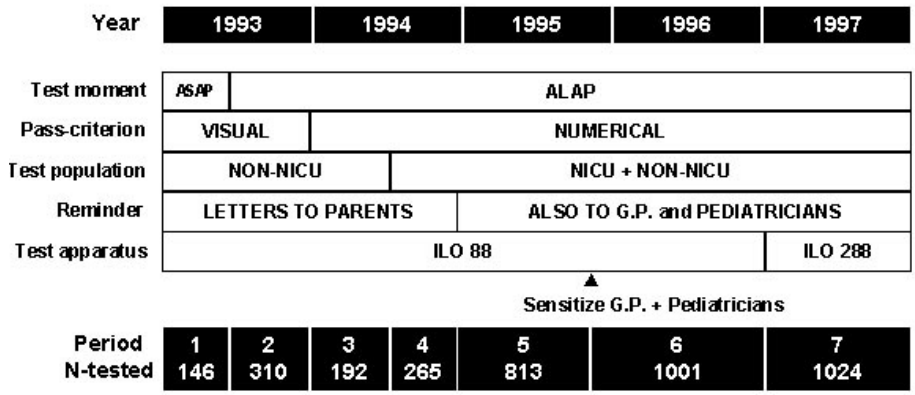

FIGURE 1. Changes to the screen protocol over the years. ASAP: as soon as possible; ALAP: as late as possible; NICU: neonatal intensive care unit; G.P: general practitioners.

In order to evaluate the efficiency of the test and the whole screening, the 'test pass rate' and 'screen pass rate' will be used in the present report. The test pass rate of a hearing screening test is defined as the percentage of children who meet the screening pass criterion at the first test. The screen pass rate of a hearing screening programme, on the other hand, is defined as the percentage of the children who pass at the initial test and the children who, after an initial bilateral failure, pass at the re-screen test which takes place three weeks later.

Although there is still no evidence that detecting unilateral hearing impairment at a very young age is beneficial, both ears were routinely tested. However, in the case of a unilateral fail, we did not encourage the parents to make a new appointment for a re-screen but, if they insisted, they could do so. In the report a 'pass' means that the screening criterion was met unilaterally or bilaterally.

RESULTS

Table 1 and Figure 2 summarize the test pass rate of the initial test with TEOAEs for the NICU, the non-NICU and the total population. For the first

three periods there are no pass rate figures available for the NICU population because the systematic screening in the NICU was not then operational.

TABLE 1. Test pass rate (per cent) in the different evaluation periods for the NICU, non-NICU and total population. A 'pass' means that the screening criterion was met unilaterally or bilaterally.

	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7
NICU	N.A.	N.A.	N.A.	92.0	95.7	96.4	96.3
non-NICU	93.2	94.8	92.2	95.3	97.0	97.5	97.6
Total	93.2	94.8	92.2	94.3	96.7	97.3	97.4

N.A.=not available

For the total population, the differences in pass rates from one period to the next are visible but not statistically significant. Figure 3, on the other hand, shows the linear regression statistics for the test pass rate evaluated on a monthly basis over the whole period of five years. The regression line has a slope value of 0.085 per cent per month which significantly differs from zero ($p<0.001$). This means that over a period of five years, the annual increase in pass rate was approximately 1 per cent. During the last 24 months, test pass rates, except on one occasion were always over 95 per cent with an average of 97.3 per cent.

The test pass rate in the non-NICU population was always slightly higher than in the NICU population. The average difference in pass rate for periods 5, 6 and 7 is 1.2 per cent but this difference is not statistically significant (CHI-square, $p>0.05$).

The screen pass rate is the overall pass rate of screen+rescreen and is summarized in Table 2. This pass rate was always high: $\geq$ 99.4 per cent, with an overall average of 99.6 per cent.

Figure 4 shows the evolution of' the coverage of the screening for NICU and non-NICU populations. At the start of the programme, the coverage was only 18.3 per cent of all live births in the hospital. This number steadily grew to 49.5 per cent for the last evaluation period. The impact of the systematic screening in the NICU is clearly visible on this figure. Its introduction (period 4) added some 7 to 9 per cent to the coverage.

The results for the number of' children who were lost to follow-up (LTFU) after failing the initial test are shown in Figure 5. At the start of the programme (periods 1 and 2) the percentage of LTFU was unacceptably high at 50 per

cent. From period 3 fewer children were lost and in period 7 this occurred in only 11 per cent of the neonates who failed the initial test bilaterally.

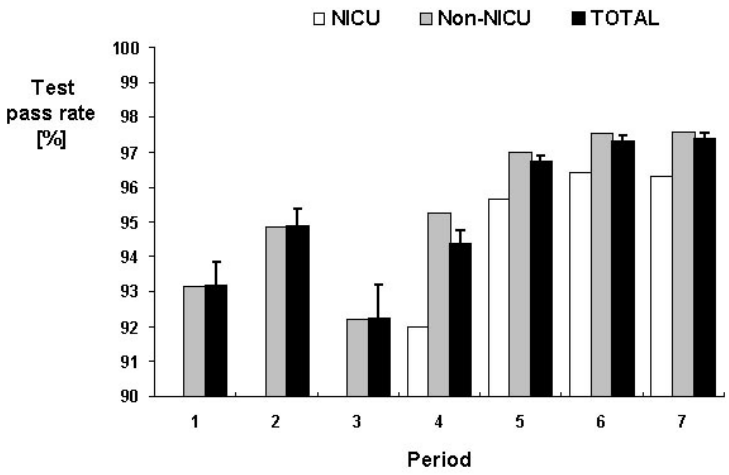

FIGURE 2. Evolution of the test pass rate for the initial TEOAE test in the NICU, non-NICU and total population. The standard error of the mean is shown for the total population. A 'pass' means that the screening criterion was met unilaterally or bilaterally. NICU: neonatal intensive care unit.

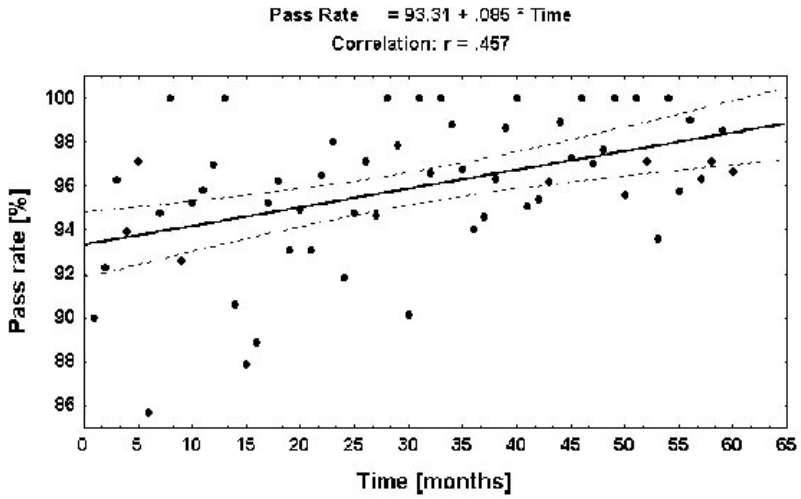

FIGURE 3. Linear regression statistics on the test pass rate evaluated on a monthly base for the whole evaluation period (five years). A 'pass' means that the screening criterion was met unilaterally or bilaterally.

TABLE 2. Screen pass rate (per cent) (test + retest) for the total population for the different evaluation periods. A 'pass' means that the screening criterion was met unilaterally or bilaterally

	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7
TOTAL	100.0	100.0	100.0	99,6	99.4	99.6	99.4

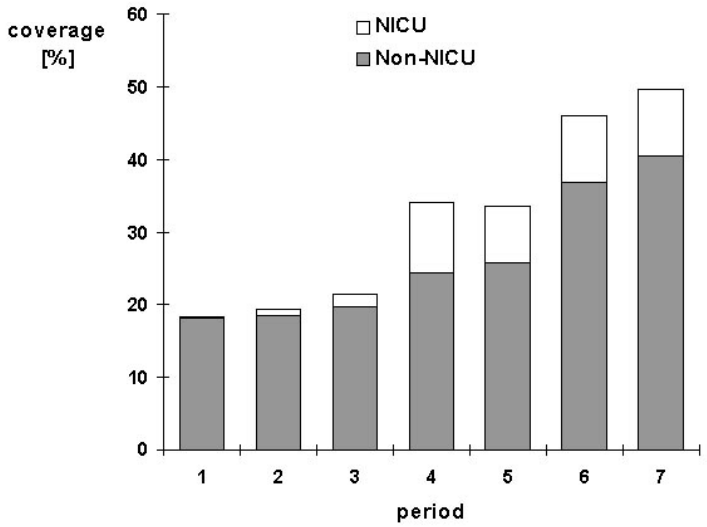

FIGURE 4. Screening coverage for the different evaluation periods. Black bars represent the coverage attributable to the non-universal screening in the non-NICU ward; the white bars represent the coverage attributable to the universal screening in the NICU ward. As mentioned in the test, all NICU children were screened from period 4 onwards. (NICU: neonatal intensive care unit).

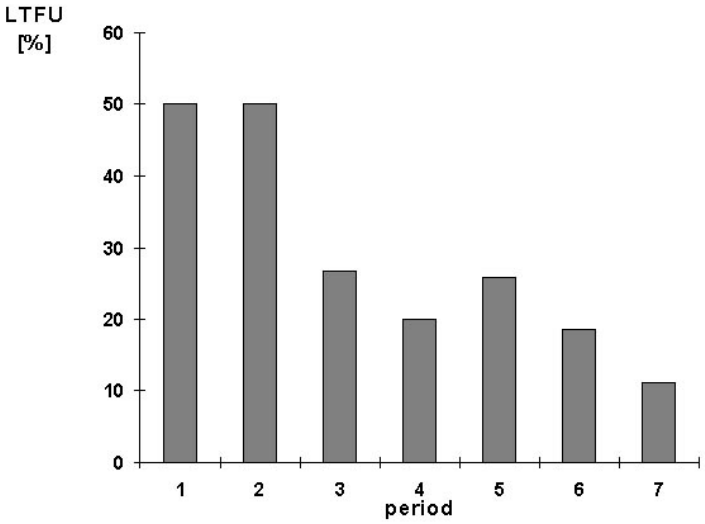

FIGURE 5. The percentage of neonates who became LTFU after failing the initial TEOAE test for the different evaluation periods (LTFU: lost to follow-up).

DISCUSSION

The present paper evaluates the implementation of a neonatal hearing screening programme with TEOAEs in a private maternity hospital. It reports on the successive modifications that have been implemented throughout the years and on the learning curve in terms of: (1) pass rate; (2) coverage; and (3) number of children lost to follow-up.

Test Pass Rate

The test pass rate is an important parameter to assess the efficiency of a screening test to improve this test pass rate, the test moment was delayed from testing as soon as possible after birth to testing as late as possible, i.e. on the last working day before the child leaves the hospital which was typically at about day 4. This is probably the main factor to explain the test pass rate increase from 93.2 to 94.8 per cent for the total population. Other authors have confirmed this finding (Van Zanten 1995, Smurzynski 1994, Kok 1993). Debris and vernix are thought to obliterate the external meatus and middle ear in some cases during the first one to three days of life.

After changing from a visual to a more rigid numerical pass criterion a decrease of test pass rate (from 94.8 to 92.2 per cent) was observed. From periods 3 to 6 the pass rate grew to around 97 per cent, although no relevant changes took place during these periods. This increase is thought to be due to a learning effect of the testers. In particular, testers had to learn by experience how the test probe is optimally fitted in the external meatus of the neonate's ear. According to Culpepper, this probe fit is the single most important factor to maintain low refer rates (Culpepper 1997). Recommendations on the insertion of the probe into the ear canal include: the use of the largest probe tip that can be inserted; the pulling of the pinna outward and upward; and the use of a slight twisting motion.

The test pass rate in the NICU group was always slightly lower then in the non-NICU group. This may be because these neonates were tested at an older age, which is associated with the production of more internal noise. Other studies indicate lower test pass rate figures for the NICU population.

Compared with other studies, these test pass rate figures (NICU and non-NICU) are very high. A possible explanation for this may be that in Belgium, in contrast to most other countries, neonates typically reside for five days in the maternity ward and thus the test could be performed as late as day 4 or 5. By that time. the prevalence of obliteration of the external meatus and middle ear becomes extremely low. The fact that all testers were dedicated and trained audiologists may be a second factor to explain these high figures when compared with other studies.

The screen pass rate, which evaluates the efficacy of the total two-stage-screening programme, was always high (> 99 per cent) with a total mean of 99.6 per cent. This means that only 4 per 1000 screened needed to undergo further diagnostic ABR testing. Half of those were found to be hearing impaired, so only 2 per 1000 screened neonates had a false positive screening result.

Coverage

For a screening programme that requires parents to pay to have their child screened, the coverage is obviously an important factor.

The initial coverage of about 20 per cent rose to around 50 per cent in the last period. The starting of the systematic screening in the NICU in period 4 added some 10 per cent to the total coverage. The organization of an information session to sensitise general practitioners and paediatricians probably caused an increase in coverage of another 10 per cent (period 5 to 6). General

awareness of the public about the test and for the ease of testing was probably responsible for the continuous slight increase in coverage. Although a coverage of 50 per cent is not bad in view of the fact that the screening is not free of charge, it is still low from an epidemiological point of view and is considered to be insufficient for a screening programme. The fact that the cost of the test was not covered by the general health insurance and thus had to be charged to the parents is considered to be the main reason for this low coverage.

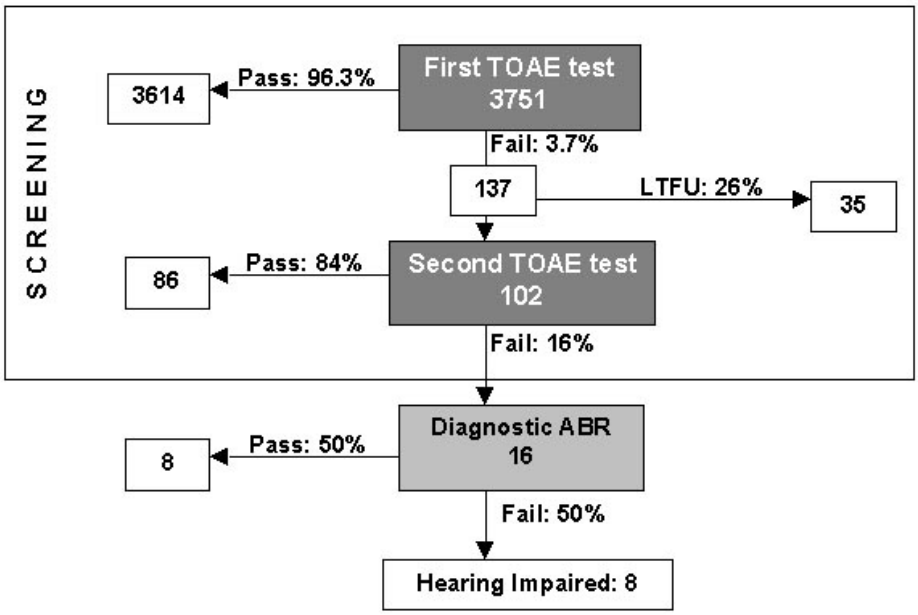

FIGURE 6. The two-stage screening protocol and diagnostic ABR testing. The pass, fail and LTFU rates are shown for the total of all neonates tested. (LTFU: lost to follow-up).

Lost lo Follow-up (LTFU)

The number of children who became LTFU after failing the first test was the major problem in the beginning. One of the children who became LTFU in period 2 was later identified as bilaterally deaf. After identification of this problem (period 2) a more strict follow-up strategy was instigated and this resulted in a drop of LTFU from 50 per cent in periods 1 and 2 to about 25 per cent for periods 3 and 4. Contacting the family doctor or paediatrician to sensitise the parents in period 5 did not immediately result in a decrease in

LTFU. The effect of these two changes became visible only in the last period when the LTFU became as low as 11 per cent.

The global evaluation of the screening programme for the whole period, from 1993 until 1997, is shown in Figure 6. Up to the present, 16 of the 3751 screened neonates were referred for diagnostic ABR testing. Half failed this test and were identified as being bilaterally hearing impaired. Of those eight children two were found to have a profound hearing impairment (> 95 dB HL), one was severely impaired (loss of 70 dB HL) and five had a moderate hearing impairment (loss of 40-50 dB HL). Three out of these eight neonates (38 per cent) came from the NICU population, the other five from the non-NICU population. All were referred for early rehabilitation and intervention. The other eight children (0.2 per cent) underwent ABR and proved to have normal hearing. One might argue that, in these eight children, unnecessary morbidity could have been caused. This would, however, be limited to complications of ABR and general anaesthesia, which are known to be extremely rare. In our 16 children no such complications occurred.

CONCLUSIONS

It is our experience that starting a neonatal hearing screening programme requires permanent quality control and daily efforts to improve the outcome. We believe that our results clearly show that the case is worth the investment and the enthusiasm. A steep learning curve is the result of continuous attention being given to even the smallest details. High quality figures can be reached and reasonable coverage is feasible in a private establishment. The authors believe that this should encourage all clinicians who are in charge of maternity units not to wait for the health care system to implement nationwide programmes, but to start immediately in their own unit. The hearing-impaired child can only benefit from it.

Acknowledgments

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A two-stage bipodal screening model for universal neonatal hearing screening.

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ABSTRACT

A model is proposed for universal neonatal hearing screening. It is two-staged since it consists of a first test and, in case of failure (1.4 % of the subjects) of a retest three weeks later. It is bipodal because it involves both the hospital audiological department and a central Well Baby Organization. The idea is to have a maximal number of newborns tested during their stay in the maternity ward by trained audiologists and to have the Well Baby Organization trace and chase the missing subjects. This model has been evaluated during one calendar year (1999) in a maternity with 2012 newborns. The result is a coverage of 99.3 %. Most newborns (97.3 %) were tested at the maternity ward with a total time investment of less than 15 minutes per child. The actual test time is 2 minutes, 12 seconds (median value) when using the more user-friendly of two equipments tested. The Well Baby Organization keeps track of all the results and has to test no more than 2 % of the newborns. Sensitivity and specificity were not the primary outcomes of this evaluation, but they were of the same order of magnitude as shown in a previous study evaluating the screen procedure on a larger scale, giving a sensitivity of approximately 100 % and a false alarm rate of 1 per thousand.

Key words: universal neonatal screening, sensorineural hearing loss, neonatal abnormalities

INTRODUCTION

The implementation of screening for any disease or impairment requires several prerequisites. Screening and early detection must lead to early intervention with substantial benefit for the patient compared with late intervention (Thomson 1999); the equipment for screening must be available on a large scale and must be affordable (Mehl 1998); the screening procedure must guarantee detection of a majority, if not all, of the subjects with the impairment (Downs 1995); and the procedure must be feasible (White 1995).

For congenital hearing impairment, it has been shown that early detection is possible and that early intervention leads to significantly better outcome in terms of hearing and speech and language development than in the case of late intervention (NIH 1993, Yoshinaga-Itano 1998b and 1998c, Moeller 2000), that the equipment to do this is available (otoacoustic emissions or automated auditory brainstem response) and relatively cheap when compared with other screening programs (White 1995, NIH 1993, Maxon 1996), and that the only way to detect almost all children with hearing impairments is by a universal neonatal screening (White 1995, NIH 1993, Parving 1999, Fonseca 1999, Aidan 1999). The actual issue in most western countries is to find a feasible procedure that meets the specific national situation with regard to maternity care. This procedure should combine a minimal cost with a maximal screening efficacy. The cost relates to the equipment used and to the procedure (how to reach newborns and perform a single or multiple tests before referring) (Downs 1995, Fonseca 1999, Stevens 1998, Weirather 1997). The efficacy relates to a maximal coverage and good sensitivity and specificity figures (Wessex Group 1998, De Ceulaer 1999).

In most western countries a majority of the babies is born in maternity wards, and it needs no explanation that testing them there is more cost efficient than visiting them at home or inviting them to come to a screening centre once they are home. In addition, testing in the maternity ward may have the advantage that professional audiologists may do the screening and that their expertise may serve both the efficacy and the counselling of the parents if needed. Disadvantages of testing in the maternity ward are that it is difficult to reach full coverage either because not all babies are born in maternities or because they leave maternity too early, that a substantial number of babies gets lost to follow-up because maternity wards have no experience in tracing subjects once they have left, and that the data are not centralized for quantitative and qualitative control (De Ceulaer 1999, Daemers 1996).

Because of these considerations, the authors have run a pilot project together with the Flemish Well Baby Organization (*Kind en Gezin*) to try to combine the expertise of both a well-functioning centralized controlling organization and a large maternity department (approximately 2000 births per year) in a hospital that hosts an audiological department with professional audiologists. The involvement of these two parties is expressed by the term *bipodal*. The term *two-stage screening* is used because the screening consists of an initial test at the maternity ward and a second test three weeks later in case of failure. Only a failure on the second test is called a *screen fail* and leads to referral to a specialized audiological centre for further diagnostic work-up (De Ceulaer 1999). The aim of this project was primarily to evaluate the feasibility of this type of cooperative screening, the coverage, the number of subjects that get lost to follow-up and the time investment of the audiologists. The project also included a comparison of two screening devices, both based on the registration of transiently evoked otoacoustic emissions, with one (Echocheck; Otodynamics, Ltd., Hatfield, UK) being more user-friendly and portable (palmtop) than the other (Echoport; Otodynamics, Ltd.), which is a more complicated laptop version.

MATERIAL AND METHODS

During the calendar year 1999, an attempt was made to screen all the newborns in St-Augustinus Hospital of Antwerp, Belgium, both at the maternity ward and the neonatal intensive care unit (NICU).

The technique, equipment, procedure, and decision criteria have already been described elsewhere (16). Briefly, non-linear click-evoked transient otoacoustic emissions were recorded with either the Echoport or the Echocheck devices. Both devices were alternated on a weekly basis. The Echocheck is a fully automatic device giving a pass or a fail based on a fix algorithm. The Echoport yields a large number of numerical and visual data on the basis of which the examiner has to score the tested ear. Our criteria have been described and evaluated before (De Ceulaer 1999, Daemers 1996, Dirckx 1996) and can be summarized as an signal to noise ratio of 6 dB in at least three neighbouring frequency bands drawn from the upper 4 bands (1.6, 2.4, 3.2, and 4 kHz) and an overall reproducibility exceeding 50 %. An audiologist or a supervised audiologist in training did all tests. The subjects were screened as late as possible, which was on the last working day before the child was supposed to leave the hospital, which was typically at postnatal day 3-5. A fail was defined as a bilateral fail. In such cases a retest was scheduled 3 weeks later. If the child failed this test as well, an Auditory Brainstem Re-

sponse (ABR) with air and bone conduction was scheduled at the age of 3 months. In case of proven hearing loss, the child was referred for hearing aid fitting with the aim to have the hearing aids operational by the age of 6 months.

To assess the total time involved in this screening, 3 time registrations were done at the maternity ward: 1) the total time that the audiologist spent daily for the screening, which includes the collecting of the list of newborns, putting these data in a database, performing all the tests at the maternity wards or NICU, informing and counselling the parents, distributing pre-printed reports for the paediatrician or family doctor, putting all the results in the database, and establishing the weekly contacts with the Well Baby Organization; 2) the room time for each child, which is the time that the audiologist stayed in the room of each newborn; and 3) the test time, which is the time for testing both ears. A Mann-Whitney test is used to compare test times between the Echoport and the Echocheck, and a Chi-square test with Yates correction is used to compare pass rates between the two devices.

The Flemish Well Baby Organization (*Kind en Gezin*) coordinated and sponsored the project (approximately $ 11.08 or 12.4 €/screen). All results were reported to this organization on a weekly basis. For this, two lists were faxed, one with the names of the children who passed the test and one with the names and coordinates of the children whom we missed and should be "chased" by the Well Baby Organization. The latter situation could arise for different reasons: The child was missed for the first test because he or she left the hospital earlier than planned or because of administrative problems, the parents of the child may have refused the screening, or the child failed the first test and was not brought to the second test scheduled for three weeks later. These children were actively traced and chased by the Well Baby Organization, and they were tested by means of an automated ABR (ALGO; Natus Medical, Inc., San Carlos, CA, USA) at the Well Baby Centres or at home if necessary. The Flemish Well Baby Organization provided us with feedback on all the children whom they had to chase to complete our database and to allow full analysis.

RESULTS

During calendar year 1999, a total of 2012 children were born in the St-Augustinus Hospital, 1781 in the maternity ward and 231 in the NICU. Approximately 60 % of infants born in the NICU were high care, and approximately 40 % were low and medium care. Four children born in the NICU

died while still in the hospital. They were not tested and were excluded from the analysis. Coverage data are shown in Table 1.

Of the 1954 newborns tested in the hospital, 49.8 % were tested by means of the Echoport and 50.2 % by means of the Echocheck. The test results of the first screen are shown in Table 2. All 41 children tested by the Well Baby Organization passed the test (40 bilaterally and 1 child from the NICU unilaterally). Pass rates did not differ between the Echoport and the Echocheck (the bilateral pass rates were 95.4 and 94.4 %, respectively; $p > 0.05$).

TABLE 1. Coverage of the neonatal hearing screening*

	Total	Maternity ward		NICU	
Number of newborns	2008	1781		227	
Tested in the hospital	97.3 %	1742	(97.8 %)	212	(93.4 %)
Tested by Well Baby Organization	2 %	30	(1.7 %)	11	(4.8 %)
Not tested	0.7 %	9	(0.5 %)	4	(1.8 %)
Refused the test		4		2	
Lost to follow-up		5		2	

* Numbers and percentages of newborns tested in either the maternity ward or the neonatal intensive care unit (NICU).

TABLE 2. Pass and Fail rate of the first test*

	Total	Maternity ward		NICU	
Number tested	1995	1772		223	
Pass	98.6 %	1745	(98.5 %)	222	(99.6 %)
Bilateral		1679		213	
Unilateral		66		9	
Fail	1.4 %	27	(1.5 %)	1	(0.4 %)

* Numbers and percentages of newborns that passed or failed the first test. NICU, neonatal intensive care unit.

From Table 2 it can be inferred that 28 children needed a retest. Twelve (43 %) were brought for this retest at St.-Augustinus Hospital; the others (57 %) had to be chased by the Well Baby Organization. All were found and retested. In case of failure, an ABR was performed at the age of 3 months and approximate audiometric hearing levels were deduced from the ABR thresholds. The results are summarized in Table 3. Figure 1 shows the extrapolated results for the two-stage bipodal screening as calculated for 1000 new-

borns. The results of the time registration at the maternity ward are shown in Figure 2 and Table 4.

The median times show that with the Echocheck the test takes 2 minutes, 12 seconds and that the audiologist stays 5 minutes, 41 seconds in the room with the newborn. With the Echoport, this takes more than 1 minute extra. This difference is statistically significant ($p < 0.001$).

The average total time spent per child, including the administrative work, is 17 minutes, 36 seconds. After finishing this study, total time registration has been continued for 150 newborns in order to eliminate the additional time spent for study-specific tasks, such as timing the different steps. For these 150 newborns, the average total time spent per child is 14 minutes, 38 seconds.

DISCUSSION

The development of a device to measure otoacoustic emissions (ILO; Otodynamics, Ltd., Hatfield, U.K.) some 20 years ago triggered a new wave of interest in universal neonatal hearing screening. Since then, different types of equipment have been developed that are essentially based on the principle of either otoacoustic emissions (Paludetti 1999, Hatzopoulos 1999, White 1994, Meredith 1994, Salomon 1993) or automated ABR (Doyle 1998, Oudesluys-Murphy 1996). This has made it possible to easily test the hearing of newborns. It had been speculated before that early detection and early intervention would substantially improve the fate of the child with congenital hearing loss. Soon after the introduction of hearing screening and early intervention programs, it could be demonstrated that the communicative skills and speech-language development of children with hearing impairments indeed changed dramatically (NIH1993, Salomon 1993, Doyle 1998, Oudesluys-Murphy 1996). It was equally clear that only universal screening programs would be able to detect all or most of the children with congenital hearing impairments. Attempts to limit the screening to a targeted subpopulation by the use of checklists of indicators of hearing impairment failed because only about half of the hearing-impaired children seemed to have one of these indicators. The Rhode Island project showed that it was feasible to establish such a universal neonatal hearing screening program with the use of the ILO otoacoustic emission analyser (White 1995, NIH 1993). A coverage of 95 % with a high sensitivity (almost 100 %) and a low false alarm rate (less than 5 %) could be obtained. These figures proved that for the first time ever it is possible to organize a hearing screening program for very young children with good screening parameters. This prompted several international authorities to strongly advocate the implementation of universal neonatal hearing screening

cate the implementation of universal neonatal hearing screening (NIH 1993, Joint Committee 1994, European Consensus Statement 1999).

TABLE 3. Pass and fail rate of the retest*

	Total	Maternity ward		NICU	
Number retested	28	27		1	
Pass	79 %	21	(78 %)	1	(100 %)
Bilateral		21		0	
Unilateral		0		1	
Fail	21 %	6	(22 %)	0	(0 %)
Mild (< 40 dB)		2			
Moderate (40- 60 dB)		2			
Moderately severe to Profound (> 60 dB)		2			

* Numbers and percentages of newborns that passed or failed the retest that was typically performed 3 weeks after failing the first test. NICU, neonatal intensive care unit.

TABLE 4. Time registration for the first test in the maternity ward*

	Echoport		Echocheck	
	room-time	test-time	room-time	test-time
Upper extreme	850	540	676	418
Upper quartile	559	306	437	224
Median	439	208	341	132
Lower quartile	365	150	278	94
Lower extreme	197	63	132	33

* Time (seconds) spent in the maternity room (room time) or just for testing (test time) with the Echoport and the Echocheck. For both systems approximately 7 %-9 % outliers exist beyond the upper extremes.

Other countries since then consider implementing some type of neonatal hearing screening, and they are facing problems to fit this in existing structures like the Well Baby Organizations and maternity wards. A universal screening program seems to be the natural responsibility of a nationwide Well Baby Organization. Such organizations have expertise in keeping large databases, in tracing newborns, and in controlling screening programs. However, they lack expertise in hearing evaluation and, in consequence, in counselling parents properly, especially in case of hearing problems. In addition, they experience problems in establishing sufficient coverage (Kanne 1999, Davis 1997). In contrast, maternity wards seem to be the natural place to look for newborns, and even if not all of them are born in a maternity ward (in Belgium, more

than 99 % are born in maternity wards), testing those who are at the maternity ward should save a lot of money and effort. It seems reasonable to expect a high coverage.

The pilot study that has been reported on in this paper has evaluated a bipodal screening program. The different steps of the screening procedure with the decision criteria to define pass and fail were established and optimised over the years and were published separately (De Ceulaer 1999, Dirckx 1996). The cooperation between the two parties starts with the audiologists trying to test as many newborns as possible at the maternity ward. They give full weekly reports to the Well Baby Organization, including the data of the babies that passed the test and of those that were not tested for any reason. The Well Baby Organization thus keeps track of all newborns having passed the test and of those that still have to be tested by their own structure. In case of fail at first test, a retest is immediately scheduled 3 weeks later. If the parents fail to show up for this retest, the data of the child are immediately added to the weekly report so that the Well Baby Organization knows that this child should be actively chased.

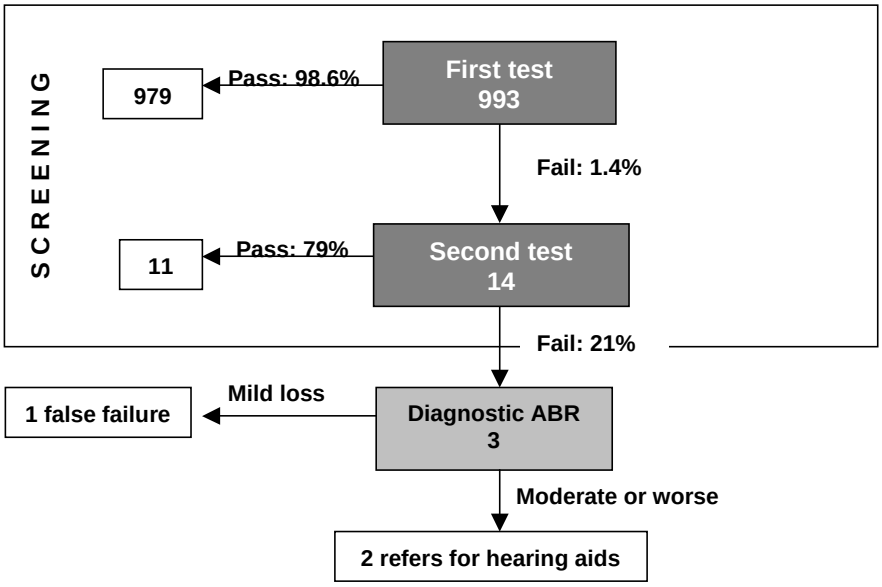

FIGURE 1. Flowchart and results of a typical screen calculated for 1,000 newborns. Because 7 are missed (see text), only 993 undergo the first test. When the screening is defined as the combination of the first test and the retest, the screen pass rate is 99.7 %. ABR, auditory brainstem response.

The results show that a high coverage of 99.3 % is obtained by this bipodal system. Half of the remaining 0.7 % are missed because the parents refused screening. Such coverage has never been reported before for a universal screening program (Daemers 1996). In addition 97.3 % of the newborns could be tested at the maternity ward, taking no more than 15 minutes in total per child when the Echocheck was used, which has become the standard in our department. So the Well Baby Organization can focus all its energy to the remaining 2.7 % of neonates, resulting in an additional 2 % coverage. In this particular setting, the intervention of the Well Baby Organization was required to complete a minimal fraction of the first stage (41 newborns, or 2 % of the cohort) and a larger fraction of the second stage (16 babies, or 57 % of the ones who failed the first test). Of the children that failed the first test, no one was lost to follow-up. Although this study was too small to evaluate test sensitivity and specificity, a hit rate of more than 2 hearing-impaired newborns per 1,000 and a false alarm rate of less than 1 per 1,000 are in line with a previous study on a larger population. These figures seem also exceptionally good and the authors believe that this is at least partially because of different procedural factors such as the moment of testing (3-5 days after birth), the decision criteria (unilateral fail = pass), and the fact that trained audiologists perform the test. Trained audiologists are not more expensive than nurses in Belgium. The authors feel that their expertise in handling hearing-impaired people adds to the quality of the screening and certainly to the quality of counselling the parents in case of a fail. This results in an important reduction of the parental anxiety in comparison to counselling by others.

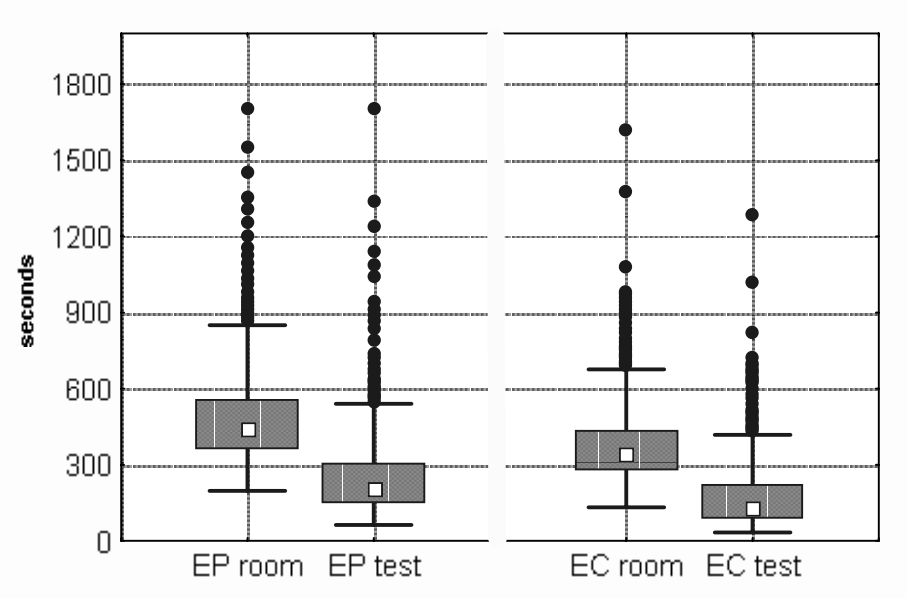

FIGURE 2. Time spent in the room and time spent for the actual testing for the Echoport (EP room, EP test) and the Echocheck (EC room, EC test). In the box- and whisker plots, the central dot represents the median time, the box represents the upper and lower quartiles (P25 and P75) and the whiskers represent the lower and upper extremes. The outliers are depicted as individual dots above each plot. The exact values can be read in Table 4.

It is obvious that a high-quality screening program alone is not sufficient but should rather be followed by a well-structured and widely available diagnostic follow-up and an early intervention program. In Belgium, a limited number of diagnostic centres are recognized by the Well Baby Organization for the diagnostic workup after referral. This diagnostic workup includes full audiological assessment with bone and air conduction ABR, connexin-26 analysis, ophthalmologic examination, electrocardiogram and medical imaging. By the time the child has reached the age of 3 months, the diagnostic assessment is to be completed, and the child is referred to a specialized centre for hearing aid fitting and early educational and developmental intervention. By the age of 10-12 months, the auditory performance with hearing aids is assessed by means of audiometry and phoneme discrimination tests. On the basis of these results, it is decided whether the child continues with hearing aids or is referred for cochlear implantation. Thanks to this tight scheme, the age of implantation has shifted from 2-3 years to below 2 years.

In conclusion, the present bipodal model is the result of multiple modifications to existing techniques and of an attempt to combine the specific competencies of two involved parties. It is applicable in many situations and can fit in most local situations. It may result in universal screening with better coverage, sensitivity and specificity than those reported in other studies (White 1995, Stevens 1998, Wessex group 1998, Oudesluys-Murphy 1997, Vohr 1998, Watkin 1999, Van Straaten 1999, Kennedy 1999).

Acknowledgements

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CHAPTER II

Diagnosis

workup protocol

"La profession de médecin m'aurait plu; je me passionnai pour cette science trop proche de nous pour n'être pas incertaine, sujette à l'engouement et à l'erreur, mais rectifiée sans cesse par le contract de l'immédiat et du nu."

It has already been mentioned in the introduction that the incidence of congenital bilateral hearing loss is estimated to be 1.2 to 5.7 per 1000 live births. During the last decade, important progress was made in the etiologic workup of these patients. Ten years ago, hardly any diagnosis could be based on solid evidence. It was accepted that interdisciplinary assessment was mandatory (Parving 1985). But even in case of extensive and interdisciplinary diagnostic workup, most causes remained unknown or speculative (Das 1988). Table 1 summarizes different reports referring to data from some ten years ago. Although the results of these studies are not always very straightforward, critical analysis learns that the aetiology of congenital hearing loss was proven in less than 10-20 % of the cases (Das 1986, Das 1988, Dereymaker 1991, Parving 1994, Drews 1995, Vartiainen 1997, Fortnum 1997, Van Naarden 2000). In a number of cases, some indirect evidence could be suggestive of a given cause, such as a positive familial history, perinatal morbidity, etc. and with flexible interpretation, this could account for some additional 30-50 %. The aetiology of the remaining 40-60 % of cases was classified as "unknown".

TABLE 1. Alleged aetiology of congenital hearing loss approximately 1 decade ago

	Das 1988	Dereymaker 1991 (*)	Parving 1994	Drews 1995	Vartiainen 1997	Fortnum 1997
Unknown	40	38	30	55	22	43
"Genetic"	25	27	43	30	58	43
Acquired						16
infectious	10	23	13	15	8	
perinatal	16	12	10		12	

Numbers refer to the prevalence in %. The references are given at the top of each column. Some of the data have been recalculated after the original publication to exclude hearing losses that were obviously not congenital, such as meningitis. Genetic refers to positive familial history, chromosomal abnormalities etc. (*) only data for Belgian ethnicity were adopted.

During the last decade, significant progress in the diagnostic tools has made it possible to routinely perform a number of investigations that allow a more accurate diagnosis. The diagnostic workup of a congenital hearing loss is described in the next chapter. The two most important non-audiological investigations are the genetic evaluation (mainly the connexin-26 gene mutations) and the high-resolution medical imaging.

A survey in the paediatric cochlear implant database of the St.-Augustinus Hospital shows that in the years 2000-2001 only 25 % of congenital hearing

losses remain without diagnosis, 10 % have an uncertain diagnosis (positive familial history with negative genetic examination) and the remaining 65 % have proven aetiology (Table 2, Govaerts, unpublished data).

TABLE 2. Alleged aetiology of congenital hearing loss in the last two years

	Govaerts unpublished
Unknown	25 %
Genetic	
connexin-26	25 %
familial history	10 %
Labyrinthine malformation	20 %
Acquired	20 %
infectious	
perinatal	

Govaerts, et al (unpublished data)

It is remarkable that congenital Rubella infections no longer appear in the aetiological lists of congenital hearing loss, and this is due to vaccination. Also, ototoxicity doesn't seem to play a major role any longer and this is due to better dosing schemes and an overall lesser toxicity of the chemical molecules being prescribed (Govaerts 1990).

Hence, the first cause of congenital hearing loss appears to be genetic (at least 35 %, which is in line with other data from literature, such as Cohen 1995). The mode of inheritance is autosomal recessive in approximately 80 %, autosomal dominant in 15 % and X-linked in 2-3 % of cases. The first locus has been published in 1992 (DFNA1, Leon 1992). Since then many more have been reported, some of which by researchers from the University of Antwerp (Coucke 1994, Van Camp 1995, Verhoeven 1997, Van Laer 1998). A continuous update can be found on the Hereditary Hearing Loss Homepage (Van Camp 1996). Table 3 gives an overview of the number of loci and genes as reported so far.

TABLE 3. Number of published loci and genes for congenital hearing loss.

	Autosomal recessive DFNBn	Autosomal dominant DFNAn	X-linked DFNn
Loci	30	41	8
date of first publication	1994	1992	1994
Genes	9	12	1
date of first publication	1997	1997	1995

From: http://www.uia.ac.be/dnalab/hhh/ (Van Camp 1996)

The first genes for autosomal hearing loss have been identified in 1997 and other have followed during the subsequent years. One of these is TECTA, which has been described in 1998 (Verhoeven 1998, Govaerts 1998) and which has been found to be involved in an autosomal dominant mid-frequency hearing loss.

The most frequent genetic cause of congenital hearing loss appears to be a bi-allelic mutation in the connexin-26 gene (GJB2). Connexin-26 protein (Cx26) is one of several gap-junction proteins found in different tissues throughout the body. In the cochlea, connexin-26 is found in the stria vascularis, basement membrane, limbus and spiral ligament (Lefebvre 2000), and a potential role in the endolymph potassium recycling has been put forward (Rabionet 2000). Immunohistochemical studies have shown that Cx26-reactivity in the foetal cochlea appears at an early prenatal age, together with the cochlear development and maturation (Kammen-Jolly 2001). A first mutation in the gene has been reported recently as the cause of congenital hearing loss (Kelsell 1997) and this and other Cx26-mutations have subsequently been shown to be the most common cause of congenital hearing loss to date (Dahl 2001, Kenna 2001). The carrier frequency of connexin-26 mutations is estimated to be approximately 1/54 in the general population, half of which are 35delG mutations (Dahl 2001). An analysis of 100 hearing impaired children confirms a 25 % prevalence of connexin-26 mutations (Govaerts, unpublished data). The majority (approximately 60 %) of connexin-26-gene related hearing losses are due to homozygote 35delG mutations. Homozygote 312del12 mutations and compound heterozygocity (35delG and another mutation, such as the V95M and the V37I mutations) are sporadic findings. In the same unpublished series of 100 children with hearing loss, biallelic connexine-26 mutations give profound hearing loss in 82 % of the cases, severe hearing loss in 6 % and moderate hearing loss in 12 %.

The second most frequent cause of congenital hearing loss can now be unequivocally attributed to cochleo-vestibular anomalies. Thanks to improved medical imaging techniques over the last decade these anomalies are now

found in 20 % of congenital hearing losses (Table 2). The most frequent congenital anomalies are an enlarged vestibular aqueduct and an aplasia or hypoplasia of the cochleo-vestibular nerve. An enlarged vestibular aqueduct was first described in 1978 (Valvassori 1998), but the diagnosis was often missed either because no imaging was performed, or because the anomaly was overlooked. The audiological findings of this congenital anomaly were published in 1999 (Govaerts 1999). To date over 50 patients with an enlarged vestibular aqueduct are being followed at the St.-Augustinus Hospital. Many of them have moderate to moderately severe hearing losses and receive regular -and often successful- treatment for sudden deterioration. Others have already evolved into severe hearing loss and have been implanted. Aplasia and hypoplasia of the cochleo-vestibular nerve as cause of congenital hearing loss has first been described in 1997 (Casselman 1997) and a classification has been suggested based on the embryological development of this nerve. Since this first description sixteen patients with aplasia or hypoplasia have been detected in the St.-Augustinus Hospital (Table 4).

TABLE 4. Distribution of different types of aplasia and hypoplasia of the cochleovestibular nerve

	Type I	Type IIa	Type IIb
Bilateral	18 %	35 %	6 %
Unilateral	12 %	18 %	12 %

Govaerts, et al. (unpublished data), based on 17 cases.

The next chapter describes the state-of-the-art diagnostic workup of congenital hearing loss (Govaerts, 2002) and is followed by a few chapters on the different contributions of Govaerts and colleagues to these new developments in genetic (Verhoeven 1997, Govaerts 1998, Verhoeven 1998) and imaging (Casselman 1997, Govaerts 1999) diagnostics.

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Audiometric tests and diagnostic workup

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In: PJ Willems (Ed.) Genetic Hearing loss. M Dekker, New York 2002 (in press).

ABSTRACT

Children with suspected congenital hearing loss are referred for audiological and diagnostic workup. The suspicion is often based on parental anxiety, but more and more children are referred after a fail on neonatal hearing screening.

The audiological workup aims at establishing the type and degree of hearing loss. Pure tone audiometry is the standard test in daily clinical practice. The technique of pure tone audiometry is explained and some issues that are useful for a good interpretation of audiometrical reports are highlighted. Standards are given for age-related deterioration of hearing. In addition, attention is paid to objective tests, such as ABR (Auditory Brainstem Responses), oto-acoustic emissions and tympanometry. These tests play an important role in assessing the hearing of infants or otherwise uncooperative people.

The diagnostic workup of hearing loss also aims at both refining the diagnosis, excluding associated pathology in case of syndromic hearing loss, and identification of the molecular defect. To exclude associated pathology means looking for syndromes. Typical features such as facial anomalies may be indicative of a syndrome. A thorough clinical examination focusing on any signs of an underlying syndrome is therefore mandatory. In addition several organs are known to be at risk in case of a congenital hearing problem. These are mainly the kidneys (e.g. BOR syndrome), the heart (e.g. long Q-T syndrome), the thyroid (e.g. Pendred syndrome) and the eyes (e.g. Usher syndrome). Special attention should therefore be given to these organs.

Key words: audiometry, ABR, OAE, diagnosis, genetics, syndromes

PURE TONE AUDIOMETRY

Pure tone audiometry is the standard test to assess hearing and hearing loss. It is a way to measure hearing thresholds at different frequencies and at both ears. It is a subjective test as it involves the cooperation of the test person and this is in contrast to objective tests like Brainstem Evoked Audiometry (ABR) or otoacoustic emissions.

Technique

The technique of measuring hearing thresholds is standardized (ANSI, American National Standards Institute). The thresholds are expressed in "decibels hearing level" (dBHL), whereby zero dBHL at a given frequency is defined as the lowest sound level that a normal person of 18 years is just able to hear. A hearing loss of e.g. 30 dB means that the intensity of sound has to be 30 dB above the zero level before the subject starts hearing it (the average intensity of conversational speech is 50-60 dB).

In general hearing is tested in a sound proof room with a calibrated audiometer and earphones that present sounds of varying intensity and frequency to each ear separately. Different test procedures exist. Conventional procedures use attenuation steps of 5 dB or more, thus introducing a minimum error of ± 5 dB. The test frequencies used are 125, 250, 500, 1000, 2000, 4000 and 8000 Hz. Once the threshold at a given frequency is assessed, it is plotted with a specific symbol on the audiogram. Both the graphical representation and the symbols are defined in international recommendations (ASHA, ANSI, Table 1). For unmasked air conduction thresholds the symbols are O for the right ear and X for the left ear (Figure 1).

TABLE 1. Common symbols used for audiometric representation (ASHA 1990)

	Right ear	Left ear
Air conduction (ear phones)		
unmasked	O	X
masked	Δ	□
Bone conduction (mastoid)		
unmasked	<	>
masked	[	]

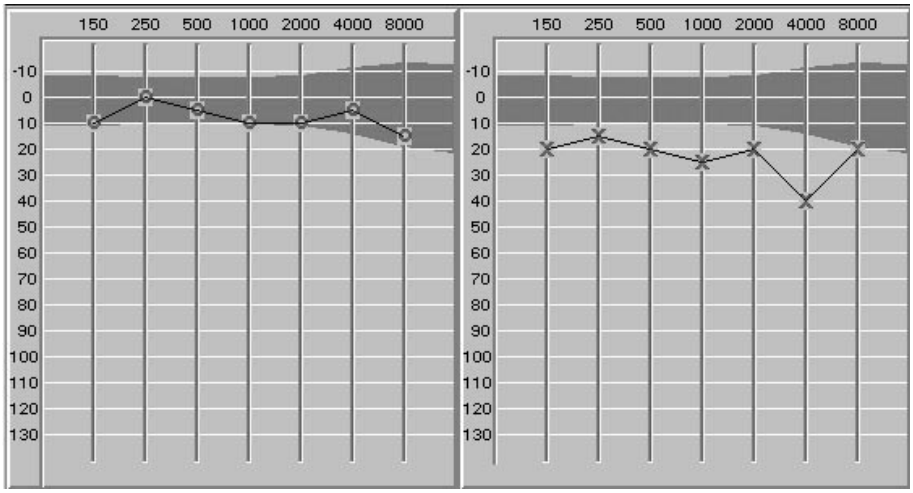

FIGURE 1. Typical audiogram showing the air-conduction thresholds of the right ear (depicted with the symbol 0 at the left pane) and the left ear (depicted with the symbol X at the right pane). The dark grey area is the 95 % confidence region for an 18 year old person.

Air conduction (AC) audiometry uses earphones to present the different sounds. Bone conduction (BC) audiometry uses a bone-conducting vibrator that is positioned on the mastoid of each ear. Air-conducted sound reaches the auditory nerve through the external, the middle and the inner ear. Bone-conducted sound bypasses the external and the middle ear and reaches the auditory nerve directly through the inner ear. The symbols for unmasked BC-thresholds are < for the right and > for the left ear.

Conductive, sensorineural and mixed hearing loss

Anomalies of the inner ear and/or the central auditory pathways (from the auditory nerve via the brainstem to auditory cortex) result in a “perceptive” or “sensorineural” hearing loss and will affect both AC and BC thresholds (Figure 2, left ear). Many forms of congenital hearing loss and most types of non-syndromic hearing loss are sensorineural.

Anomalies of the outer and middle ear will only affect AC thresholds. The difference between AC and BC threshold is called the “air-bone gap” and reflects a middle or outer ear problem. This is called a “conductive” hearing loss (Figure 2, right ear). This type of hearing loss is found e.g. in congenital atresias of the outer ear canal, malformations of the middle ear ossicles and stapedial ankylosis due to otosclerosis.

Problems at different levels (e.g. middle and inner ear) may result in a "mixed" hearing loss, with a sensorineural component given by a BC loss and a conductive component given by a superimposed air-bone gap. This type can be found for instance in otosclerosis affecting both the cochlea and the stapes.

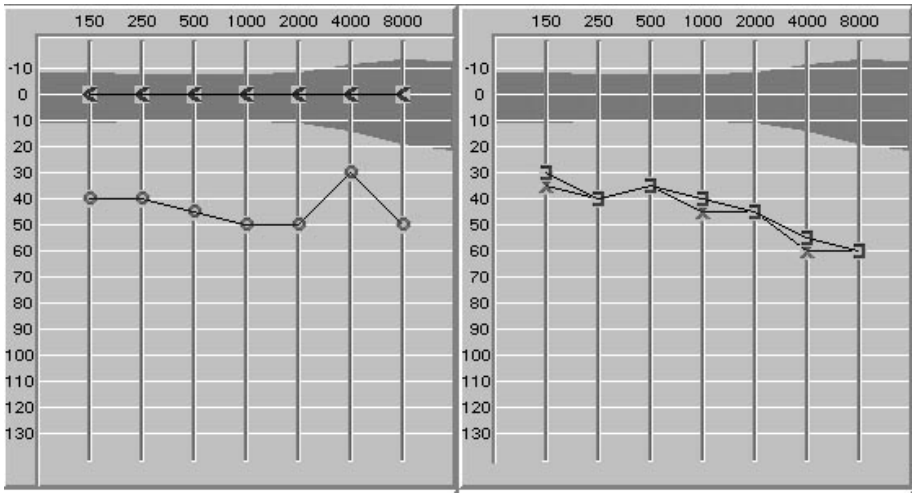

FIGURE 2. Typical audiograms of a conductive hearing loss at the right ear (left pane) and a sensorineural hearing loss at the left ear (right pane). The right ear shows normal bone-conduction thresholds (PTA 0 dBHL) and abnormal air-conduction thresholds (PTA 47 dBHL). The left ear shows abnormal bone- and air-conduction thresholds with a PTA of 40 dBHL and 43 dB respectively.

Masking

Sound that is presented to one ear may also reach the contralateral ear, which should be avoided. The interaural attenuation of AC and BC sound is known for the different test frequencies and in case a risk of crossover exists, the nontest ear should be "masked". Masking is difficult and both the decision whether to mask and the execution of it should not be underestimated and, although strict criteria and guidelines exist, it should be left to audiologists. Masking leads to corrected AC and BC thresholds and special symbols exist to represent these.

PTA or Fletcher index

In order to summarize the audiometrical findings several indices have been introduced, amongst which the Pure Tone Average "PTA" or "Fletcher index"

is the most commonly used. The PTA is the average of the AC thresholds at the frequencies 500, 1000 and 2000 Hz. For instance, the audiogram in Figure 2 has a PTA of 47 dBHL for the right ear and 40 dBHL for the left ear. Hearing losses are often described in a qualitative way that is based on the PTA. Different classifications exist. The WHO recommends the classification of Table 2. In addition one may describe the curve of the audiogram, like "down-sloping, or U-shaped etc.

TABLE 2. Grades of hearing impairment

Grade of impairment	Corresponding audiometric ISO value (Average of 500, 1000, 2000, 4000 Hz) of the better ear	Performance
0 No	25 DB or better	No or very slight hearing problems. Able to hear whispers.
1 Slight	26-40 DB	Able to hear and repeat words spoken in normal voice at 1 metre.
2 Moderate	41-60 dB	Able to hear and repeat words using raised voice at 1 metre
3 Severe	61-80 dB	Able to hear some words when shouted into better ear;
4 Profound	81 dB or greater	Unable to hear and understand even a shouted voice

From: World Health Organization (http://www.who.int/pbd/pdh/Docs/GRADESTable-DEFs.pdf). Adopted from the Report of the informal working group on prevention of deafness and hearing impairment programme planning WHO, Geneva, with adaptations from the Report of the first informal consultation on future programme developments for the prevention of deafness and hearing impairment, WHO, Geneva.

Feasibility

Since pure tone audiometry requires a well-responsive person, it may be unfeasible in children or in persons that are not able to give reliable responses because of mental or other problems. For small children special observational or conditioning techniques exist that allow fairly reliable audiometrical results from the age of approximately 2 years onwards. At younger ages, more than one session may be required or alternative techniques, like ABR (see below) may be used.

ISO 7029

A special issue of interest is the definition of “normality” in hearing. Zero dBHL is defined as the average threshold in 18-year-old persons with a history free of otological disease. It is however known that hearing deteriorates with age and a hearing loss of 25 dBHL at 500 Hz and even 80 dBHL at 8000 Hz is not abnormal for a 70-year-old man. The age- and gender-related distribution of hearing thresholds is defined by the International Organization for Standardization (ISO) 7029 standard (ISO 7029 [1984], “Acoustics - threshold of hearing by air conduction as a function of age and sex for otologically normal persons” [International Organization for Standardization, Geneva]). The hearing threshold of any given patient can therefore be expressed as the number of standard deviations below or above the median value for the given age and gender. The corresponding percentile can be derived from these data in any table of a normal distribution. For example, the median hearing loss at 500 Hz for a normal male of 70 years is 8 dBHL according to the ISO 7029 standard with a positive standard deviation of 10 dBHL. A hearing loss of 25 dBHL can be expressed as 1.7 standard deviations (= 25 dBHL/10dBHL) above the median and this corresponds to the 96th percentile (or P96). If normality is defined as the group between P2.5 and P97.5, this is to be considered normal (Govaerts 1998, Figure 3) Since genetic hearing losses affect different generations in one family, it is important to bear in mind this concept of normality and abnormality.

Supraliminal audiometry

So far only “pure tone” audiometry has been discussed. This is called “liminal” audiometry since it assesses the threshold of hearing. Hearing however is far more complex than simply detecting low-level sounds. In order to understand the sounds one needs to discriminate different sounds. These supraliminal aspects of hearing can be assessed by other tests, such as speech audiometry. Supraliminal tests in general are less standardized than liminal audiometry and they are most often language-dependent. In addition, they assess not only hearing but also higher cognitive and other functions. This renders them less applicable for genetic research.

Cochlear conductive loss

A rare finding is the so called "cochlear conductive hearing loss". This is typically found in an enlarged vestibular aqueduct (Govaerts 1999) but it may

also be found in other types of cochlear anomaly. It shows a conductive hearing loss on audiometry (an air-bone gap). Tympanometry (see below) shows normal middle ear pressure but stapedial reflexes are absent. These audiometric findings are commonly interpreted as an ossicular problem (ossicular malformation or fixation) but exploratory tympanotomy or high resolution CT-scan do not reveal any such condition. Although the underlying mechanism is not quite understood, it is thought that the minor cochlear malformation impedes the travelling wave within the cochlea to proceed smoothly. Although the sound is well transferred through the middle ear and thus reaches the cochlea without problems, it encounters a mechanical resistance within the fluids of the cochlea itself before arriving at the inner hair cells. This should explain the relatively normal BC thresholds and abnormal AC thresholds.

AUDITORY BRAINSTEM RESPONSES

The evaluation of Auditory Brainstem Responses (ABR), also called "Evoked Response Audiometry (ERA)" or "Brainstem Evoked Response Audiometry (BERA), refers to an objective technique of assessing hearing thresholds. It is objective since it doesn't require the cooperation of the test person. It can even be done under anaesthesia. It is based on the recording of electrical responses from the cochlea and the auditory nerve after acoustical stimulation either via AC or via BC. An averaging paradigm is used with a short stimulus (typically a click of 100 μsec) that is presented some 1000 to 2000 times in order to allow averaging of the response. Although the test is objective, physical principles allow it merely to assess the thresholds at the higher frequencies (2000 and 4000 Hz). The thresholds at other frequencies are far less reliable. In addition, the confidence interval of the thresholds is higher than the ±5 dB of the pure tone audiometry. This renders ABR a test of second choice that should only be used in case regular audiometry is not feasible or reliable, e.g. in infants, mentally disabled persons, etc.

Special devices have been developed to record ABR and to automatically interpret the responses in terms of hearing thresholds. The output is either "pass" or "fail" meaning normal hearing or, respectively, a hearing loss of at least 20-30 dBHL. These are called AABRs (Automated ABRs) and are used for screening purposes and especially for neonatal hearing screening.

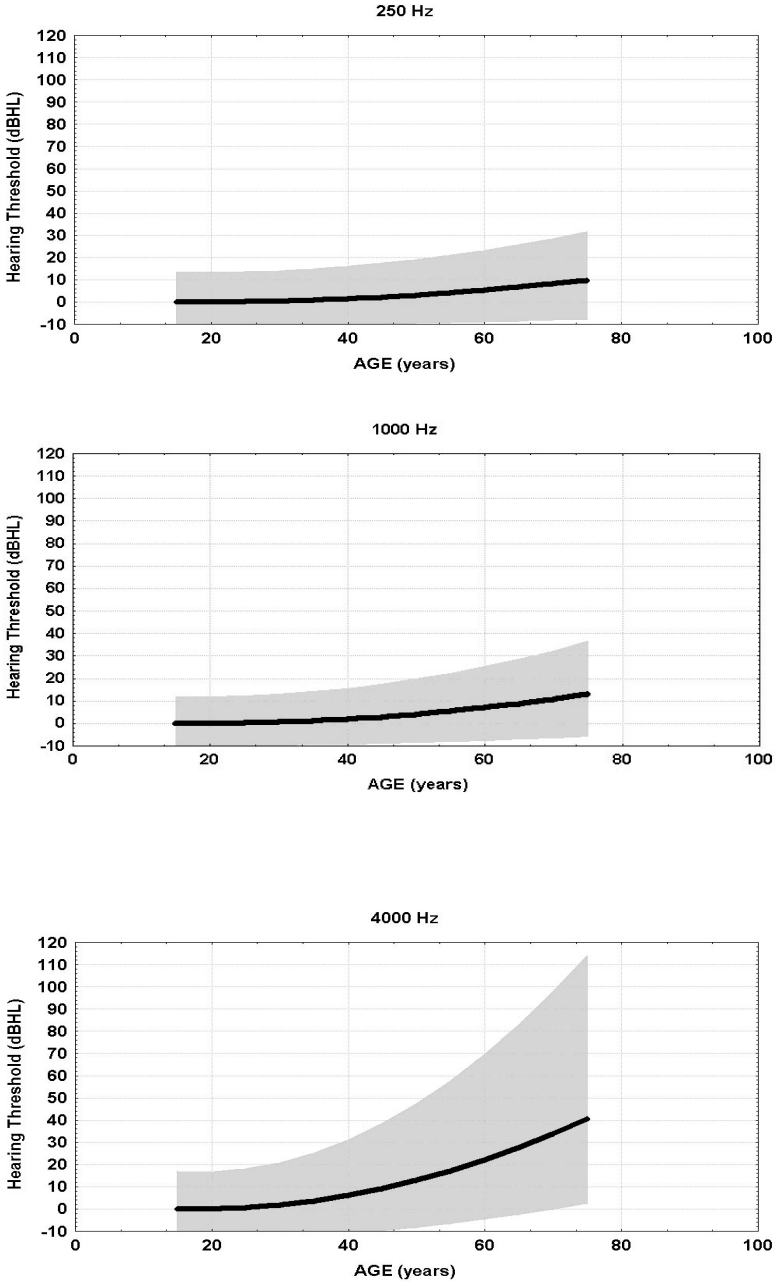

FIGURE 3. Evolution of normal hearing thresholds for 250 Hz (top), 1000 Hz (mid) and 4000 Hz (bottom) in function of age according to the ISO 7029 formula (see text for details). The solid lines are the median hearing thresholds and the grey areas represent the 95 % confidence interval.

OTOACOUSTIC EMISSIONS

Otoacoustic emissions are acoustic signals that are emitted from the ear (Kemp 1978). Different types exist, but in clinical practice, the so-called Transient Evoked Otoacoustic Emissions (TEOAEs) are most commonly used. They are produced by the outer hair cells if they are in good physiological condition and stimulated by an external sound (Khanna 1986, Sellick 1982). The technique and interpretation is well established. If no TEOAEs can be elicited, this is interpreted as a hearing loss of 30 dBHL or more. Presence of TEOAEs means normal or near-normal hearing. The only exception to this rule is the so-called auditory neuropathy, which is a rare condition of hearing loss in the presence of normal TEOAEs. The TEOAE-test is fast and no cooperation of the test person is needed. On the other hand, it is rather aspecific, since both sensorineural and conductive hearing loss will result in the absence of TEOAEs and hardly any frequency information can be derived. However, it is a high-quality screening tool and as such it is widely used for neonatal and other hearing screening. Thanks to the many nationwide ("universal") neonatal hearing screening programs, early detection of congenital hearing loss is becoming more and more common practice (White 1994, Govaerts 2001)

TYMPANOMETRY

Tympanometry is a test to register the acoustic impedance of essentially the middle ear. It reflects the pressure within the middle ear cavity and as such it is often used to detect middle ear ventilation problems. A special feature is the possibility to record stapedial reflexes, which are small movements of the stapes, due to a contraction of the stapedial muscle as a response to high intensity sounds. The movement of the stapes makes the incus, the malleus and the tympanic membrane move which can be measured with an external probe. The test is simple and gives information on the mobility of the ossicular chain. An immobile chain fails to give recordable stapedial reflexes. This typically occurs in otosclerosis and also in different types of congenital ossicular malformation with fixation of one of the ossicles.

BLOOD EXAMINATION, INCLUDING CONNEXIN 26

Thanks to the universal neonatal hearing screening programs, an increasing number of neonates are referred for diagnostic work-up. The amount of blood

that is available for laboratory tests is limited. Therefore, not all tests that may contribute to the diagnosis may be done. In the absence of indications for specific underlying pathologies, genetic (connexin 26) and serological examinations may suffice.

Thyroid hormone tests are not useful. Patients with Pendred syndrome are euthyroid at birth. Only half of them become hypothyroid with the development of a goiter after the age of 10 years (Reardon 1999).

GENETIC EXAMINATION

In case of syndromic hearing loss, either karyotyping or specific biochemical and molecular investigations may be useful. Even in the absence of phenotypic indications suggestive for an underlying syndrome, it is recommended to actively exclude the three most frequent syndromes, namely the autosomal recessive Usher and Pendred syndromes and the X-linked Alport syndrome. The former two syndromes typically have negative familial histories. Ophthalmologic examinations with electroretinography (at the age of 5 years), medical imaging and urine examination are required.

An increasing number of genes causing non-syndromic hearing loss has been described (see web-page V Camp 1996). At present it is not possible to routinely search for many of these mutations for practical reasons. Mutations in the connexin 26 gene (GJB2) account for probably 20 % of the non-syndromic congenital hearing losses (Dahl HH 2001, Kenna 2001, Milunsky 2000). In some populations this figure may even be higher (e.g. 80 % in Jewish Ashkenazi children, Morell 1998, Lever 2000). The most common mutations are the 35delG and the 162delT mutations and these can be routinely found by simple and inexpensive restriction enzyme analysis. Additional mutations should be ruled out by sequencing the gene.

A frequent anomaly found in congenital non-syndromic hearing loss is an enlarged vestibular aqueduct (Govaerts 1999). This may account for over 20 % of all congenital hearing losses (Zhang 1997). A number of them (15 %, Scott 2000) has been shown to be related to mutations in the Pendred syndrome gene (PDS). In case an enlarged vestibular aqueduct is found by medical imaging, it may be worthwhile investigating this gene

SEROLOGICAL EXAMINATION

Maternal or congenital infections are becoming rare as cause of congenital deafness in the Western world.

Thanks to widespread vaccination, the rate of confirmed congenital rubella syndrome has decreased to approximately 0.05 per 10.000 life births (Zimmerman 2001). In areas where Rubella vaccination is no common practice, serologic examination is probably justified.

Cytomegalovirus (CMV) is a frequent cause of congenital infections (0.4-2.3 % of life births, Witters 2000) and may cause congenital hearing loss. Prenatal diagnosis is possible and provides the optimal means for both diagnosing foetal infection and identifying foetuses at risk of severe sequels (Azam 2001). Serological evaluation is possible on blood samples and PCR diagnosis is possible on urine samples.

IMAGING

Refining the diagnosis means searching for the aetiology.

Middle ear problems often consist of atresia and/or ossicular malformations. In most cases these can be readily seen on high resolution CT scan (Figure 4). Therefore, a congenital conductive hearing loss makes a CT scan mandatory. This can be done under sedation or anaesthesia if necessary. Sensorineural hearing losses are mainly caused by cochlear problems (Large Vestibular Aqueduct, Mondini dysplasia, semicircular canal malformations) and to a lesser extent by central auditory lesions, situated in the auditory nerve (aplasia or hypoplasia), the auditory pathways or the auditory cortex. Magnetic Resonance (MR) imaging (Figure 5) may elucidate the details and is often complimentary to CT, especially in the study of inner ear malformations (Casselman 2001). Routine T2-weigted spin-echo images of the brain are ideally suited to exclude white matter disease or other lesions in the cochlear nuclei and along the auditory pathways. Only MR can demonstrate the abnormal course, hypoplasia or aplasia of the vestibulocochlear nerve and facial nerve (Casselman 1997). MR techniques have to be adapted for inner ear malformations.

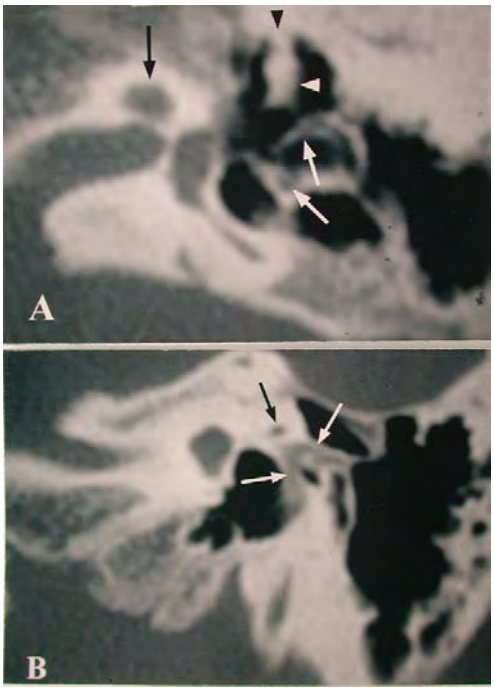

FIGURE 4. CT-scan for congenital conductive hearing loss (courtesy J Casselman). Axial and coronal CT image with bone window through the left middle and inner ear of a patient with congenital conductive hearing loss related to the Branchio-Oto-Renal syndrome. (A) The malleus and incus are fused (white arrowhead) and are fixed against the anterior wall of the middle ear cavity (black arrowhead). The facial nerve descends in an abnormal position through the middle ear cavity and splits n two descending branches (white arrows). Note the hypoplastic cochlea with absence of a normal modiolus. (B) The facial nerve leaves its normal position under the lateral semicircular canal (black arrow) and gives rise to two branches, which are descending, through the middle ear cavity (white arrows).

Only heavily T2-weighted gradient-echo sequences as three-dimensional Fourier transform constructive interference in steady state (3DFT-CISS), true-fast imaging with steady precession (true-FISP) or 3D-fast spin-echo (3D-FSE) sequences are suitable for this purpose (Casselman 1993). Moreover, some changes inside the membranous labyrinth can only be seen on sub-millimetric ($\leq$ 0.7 mm thickness) heavily T2-weighted MR images. A CT can be complimentary to evaluate the abnormal internal auditory canal or facial nerve canal. Thin CT images (reconstructed 1 or 1.25 mm thick images every 0.5 or even 0.1 mm) yield detailed information on the bony labyrinth, including modiolus and even the osseous spiral lamina, but they do not give any information on the fluid in the labyrinthine compartments, which can only be seen on MR images.

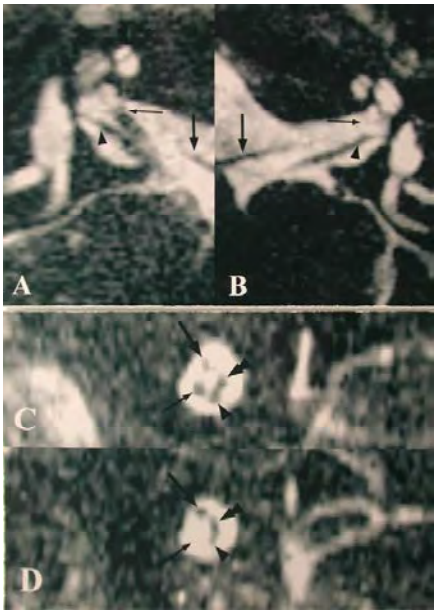

FIGURE 5. MRI for congenital sensorineural hearing loss (courtesy J Casselman). Axial 0.7 mm thick T2-weighted gradient-echo images and sagittal reconstructions perpendicular to the course of the nerves made at the level of the fundus of the internal auditory canal (IAC) through both the right (A, C) and the left (B, D) inner ear in a patient with congenital deafness on the left side.
(A) Normal facial nerve (large black arrow), inferior vestibular (black arrowhead) and cochlear (small black arrowhead) branch of the VIIIth nerve can be seen near the floor of the IAC.
(B) The facial nerve (large black arrow) and inferior vestibular branch of the VIIIth nerve (black arrowhead) can again be distinguished, the cochlear branch of the VIIIth nerve is however absent (small black arrow).
(C) The facial nerve (large black arrow), superior vestibular (double arrowhead), inferior vestibular (arrowhead) and cochlear (small black arrow) branch of the VIIIth nerve can all be seen on the reconstruction made at the fundus of the right IAC.
(D) The facial nerve (large black arrow), superior vestibular (double arrowhead) and inferior vestibular branch (arrowhead) of the VIIIth nerve can again be seen. This image confirms the congenital absence of the cochlear branch of the VIIIth nerve (small black arrow).

OPHTALMOLOGIC EXAMINATION WITH FUNDOSCOPY

One of the most frequent ocular problems linked with congenital hearing loss, is retinitis pigmentosa (Usher syndrome). This is seen on fundoscopy. The first signs of retinitis however appear no sooner than at the age of a couple of years and often even much later. Therefore, a negative ophthalmologic exam is no proof of the absence of Usher syndrome. Electroretinography may provide early diagnosis from the age of 2 years onwards and some authors claim that all children with severe to profound, prelingual sensorineural hearing loss should be screened by ophthalmologic examination including electroretinogram (Metz 2000).

Other syndromes may consist of early onset eye problems, like retinopathy, optic atrophy, iridal or corneal anomalies, etc.

ECG

An ECG is routinely taken to exclude the long Q-T syndrome (Jervell and Lange-Nielsen syndrome).

ULTRASOUND EXAMINATION OF THE RENAL SYSTEM

Ultrasound examination of the kidneys is important to rule out any renal structural malformation, like e.g. in the Branchio-Oto-Renal syndrome (BOR).

URINE

Urine examination should exclude microscopic haematuria and proteinuria, although this latter is uncommon in children. It is also useful for detecting cytomegalovirus by PCR-techniques.

Aplasia and hypoplasia of the vestibulocochlear nerve: diagnosis with MR imaging

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ABSTRACT

In seven patients with congenital deafness or unexplained sensorineural hearing loss, MR imaging enabled diagnosis of aplasia or hypoplasia of the vestibulocochlear nerve (VCN). Axial (0.7-mm) three-dimensional Fourier transformation-constructive interference in steady state (3DFT-CISS) images and parasagittal reconstruction images perpendicular on the course of the VCN were obtained. Twenty normal inner ears were also studied as controls. The facial nerve and inferior and superior vestibular and cochlear branches of the VCN were identified on the MR images in all controls. Aplasia of the VCN was detected in two patients with normal labyrinths but with a severe stenosis of the internal auditory canal. A common VCN with absence of the cochlear branch was found bilaterally in two patients with a congenital malformation of the labyrinth. A common VCN with absence or hypoplasia of the cochlear branch was found in three patients with normal internal auditory canals and labyrinths. It is concluded that submillimetric gradient-echo images (e.g., 3DFT-CISS) in two planes should always be used to exclude aplasia or hypoplasia of the cochlear branch of the VCN in all cochlear implant candidates and patients with congenital deafness.

Key words: Ear, abnormalities; ear, anatomy; ear, MR; magnetic resonance (MR), pulse sequences; magnetic resonance (MR), thin section; nerves, abnormalities.

INTRODUCTION

Magnetic resonance (MR) imaging is accepted as the method of choice to look for abnormalities in patients with sensorineural hearing loss and/or vertigo (Mark 1993, Mark 1994, Mark 1992,, Casselman 1994, Casselman 1996b). Moreover, gradient-echo MR imaging proved its value in patients with congenital inner ear malformations (Casselman 1996a) and especially in candidates for cochlear implantation (Klein 1992, Marst-Dupuch 1995, Harnsberger 1987). The MR demonstration of a normal cochlea, with a fluid-filled scala tympani and vestibuli, indicates that these patients are ideal candidates for implantation. Nevertheless, in some of these patients the cochlear implant did not result in auditory perception, although the implant itself worked and was not causing the problem (O'Donoghue GM, personal communication, 1996). A possible explanation could be an absent or abnormal cochlear branch of the vestibulocochlear nerve (VCN). With the advent of submillimetric T2-weighted gradient-echo images, these nerves and nerve branches can be visualized in a reliable way inside the internal auditory canal and cerebellopontine angle (Casselman 1993). In the internal auditory canal, the facial nerve, the cochlear branch, inferior vestibular branch and superior vestibular branch of the VCN are best recognized on axial three-dimensional Fourier transformation-constructive interference in steady state (3DFT-CISS) images and can be confirmed on parasagittal reconstruction images (Casselman 1996b).

The purpose of our study was to introduce aplasia or hypoplasia of the VCN as a possible cause of sensorineural hearing loss or congenital deafness and to identify the MR imaging characteristics of this entity with use of the 3DFT-CISS sequence.

MATERIAL AND METHODS

Subjects

During a period of 24 months (from February 1994 to January 1996), the diagnosis of aplasia or hypoplasia of the cochlear branch of the VCN was made at MR imaging in seven patients (six male patients, one female patient; age range, 2-42 years; average age, 11 years). The common clinical finding that led to computed tomography (CT) and MR imaging was sensorineural hearing loss. The sensorineural hearing loss was congenital and bilateral in three pa-

tients (who were part of a cochlear implantation selection program) and congenital and unilateral in three patients, and sudden hearing loss occurred in one patient. More details of the clinical presentation of these patients are listed in Table 1.

TABLE 1. Clinical and imaging data of the affected inner ears of the seven patients with aplasia or hypoplasia of the VCN

Patient No/Sex/ Age (y)	Clinical Presentation	Side	CT	MR		
				Labyrinth	IAC	Nerves
1/F/2	Parental concern at 9 months; diagnosis of bilateral deafness at 14 months with audiogram and ABR; normal VII;	Right	IAC stenosis	Normal	Stenosis	Aplasia of VCN
		Left	IAC stenosis	Normal	Stenosis	Aplasia of VCN
2/M/42	Bilateral aplasia of EAC, normal VII, BAHA on the right side, with completely deaf ear on the left	Left	Stenosis, separate canal for facial nerve	Normal	Stenosis, separate canal for facial nerve	Aplasia of VCN
3/M/2	Parental concern at 6 months; diagnosis at 18 months with ABR and audiogram; electric promontory stimulation: response on left ear; potential cochlear implant candidate	Right	CC, abnormal SCCs	CC, abnormal SCCs	Normal	Common VCN
		Left	CC, abnormal SCCs	CC, abnormal SCCs	Normal	Common VCN
4/M/10	Bilateral congenital deafness confirmed with audiogram; electric promontory stimulation is planned; potential cochlear implant candidate	Right	CC, IAC stenosis, partial development of sSCC	CC, partial development of sSCC	Stenosis	Common VCN
		Left	CC, IAC stenosis, partial development of sSCC	CC, partial development of sSCC	Stenosis	Common VCN
5/M/6	Congenital hearing loss on the left side since birth; confirmed as deafness at 6 years, normal hearing on the right side	Left	Normal	Normal	Normal	Rudimentary vestibular nerve, absent cochlear branch
6/M/5	Congenital deafness on the right side since birth, only mild hearing loss on the left; completely deaf ear on the right confirmed with audiogram	Right	Not applicable	Normal	Normal	Rudimentary vestibular nerve, absent cochlear branch
7/M/12	Congenital high frequency hearing loss on the left side confirmed with audiogram; normal hearing on the right	Left	Normal	Normal	Normal	Hypoplasia of the cochlear branch

ABR = auditory brain-stem response, BAHA = bone-anchored hearing aid, EAC = external auditory canal, IAC = internal auditory canal, CC: common cavity, SNHL = sensorineural hearing loss, SCC: semicircular canal; sSCC = superior semicircular canal; VII = facial nerve function.

Imaging Protocol

All patients underwent MR imaging performed with a 1-T, active-shielded superconductive system (Magnetom SP 42; Siemens, Erlangen, Germany). A standard circular polarized head coil was used to allow simultaneous imaging of both inner ears. All patients underwent a routine inner ear study with an axial, 7-mm-thick, T2-weighted spin-echo sequence (2,000/16, 90 [repetition time msec/echo time msec], one signal acquired) of the brain and a selective, axial, 3-mm-thick, contiguous, T1-weighted spin-echo sequence (500/14, four signals acquired) with and without administration of an intravenous gadolinium chelate. Their temporal bones were also examined with a coronal gadolinium-enhanced T1-weighted sequence. A dose of 0.1 mmol/kg gadoterate meglumine (Dotarem; Guerbet Laboratories, Aulnay-sous-Bois, France) or gadopentetato dimeglumine (Magnevist; Schering, Berlin, Germany) was used. The patients were also examined with a 3DFT-CISS gradient-echo sequence. The details of this gradient-echo sequence have been published previously (Casselman 1994, Casselman 1993). The most important parameters of this sequence are the following: 15/21, 65° flip angle, one axial slab of 22.4-mm thickness, 32 partitions, 256 x 256 matrix, 170-mm field of view, two signals acquired. This results in 0.7-mm axial sections with an in-plane resolution of 0.66 x 0.66 mm and a total acquisition time of 8 minutes 6 seconds. The absence of nerves or nerve branches was always checked on parasagittal 3DFT-CISS reconstruction images. These reconstruction images were made through the cerebellopontine angle and middle and lateral thirds of the internal auditory canal and were angled perpendicular on the course of the nerves (Figures 1, 2a, 2b).

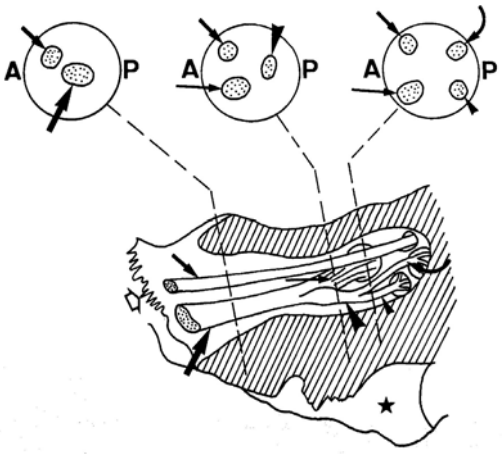

FIGURE 1. Diagram shows the nerves in the internal auditory canal. The posterior wall of the internal auditory canal is removed, and cross sections (top) through the cerebellopontine angle-porus region (left), middle third of the internal auditory canal (middle), and lateral third of the auditory canal (right) were made. Facial nerve (small thick arrow), VCN (large arrow), common vestibular nerve (large arrowhead), inferior vestibular branch (small arrowhead), superior vestibular branch (curved arrow), and cochlear branch (thin arrow) of the VCN are indicated. *A* = anterior, *P* = posterior, ★ = jugular foramen, open arrow = petro-occipital fissure.

In six of the patients, 1.5-mm-thick axial CT sections also were obtained every 1 mm, and in two patients (patients 2 and 4) additional coronal CT scans were acquired.

Control Group

Twenty normal inner ears were also studied with 0.7-mm-thick 3DFT-CISS images. The selected 3DFT-CISS examinations were free of movement or flow artefacts and therefore allowed adequate evaluation of the nerves in the cerebellopontine angle and internal auditory canal. The reliability to distinguish the facial nerve and the inferior vestibular, superior vestibular, and cochlear branches of the VCN in the cerebellopontine angle and internal auditory canal was checked on these axial images and on the parasagittal 3DFT-CISS reconstruction images, made perpendicular on the course of the nerves in the cerebellopontine angle and in the middle and lateral thirds of the internal auditory canal. The thickness of the nerves in relation to one another was evaluated on the parasagittal reconstruction images. Especially, the

thicknesses of the VCN (in the cerebellopontine angle) and its cochlear branch (in the internal auditory canal) were compared with the thickness of the facial nerve.

RESULTS

Control Group

The facial nerve, the cochlear branch, inferior vestibular branch, and superior vestibular branch of the VCN (Figure 1) could be visualized on the axial 3DFT-CISS images in all 20 normal inner ears (Figure 2a, 2b). On the parasagittal reconstruction images made at the level of the cerebellopontine angle, both the facial nerve and VCN were always visible. At this location, the VCN was 1½-2 times larger in diameter than the facial nerve in 19 of the 20 normal inner ears (Figure 2c). In one inner ear, they were the same size. In 19 inner ears, the facial nerve and the cochlear branch of the VCN and the common vestibular nerve (the vestibular branch of the VCN, not yet bifurcating into a superior and inferior branch) could be distinguished on the parasagittal reconstruction images made through the middle third of the internal auditory canal. The three branches of the VCN and the facial nerve could be separated from one another on the parasagittal reconstruction images made near the fundus of the internal auditory canal. In only one patient was it difficult to visualize the facial nerve because this nerve probably was small and adjacent to the wall of the internal auditory canal; the three branches of the VCN were clearly visible.

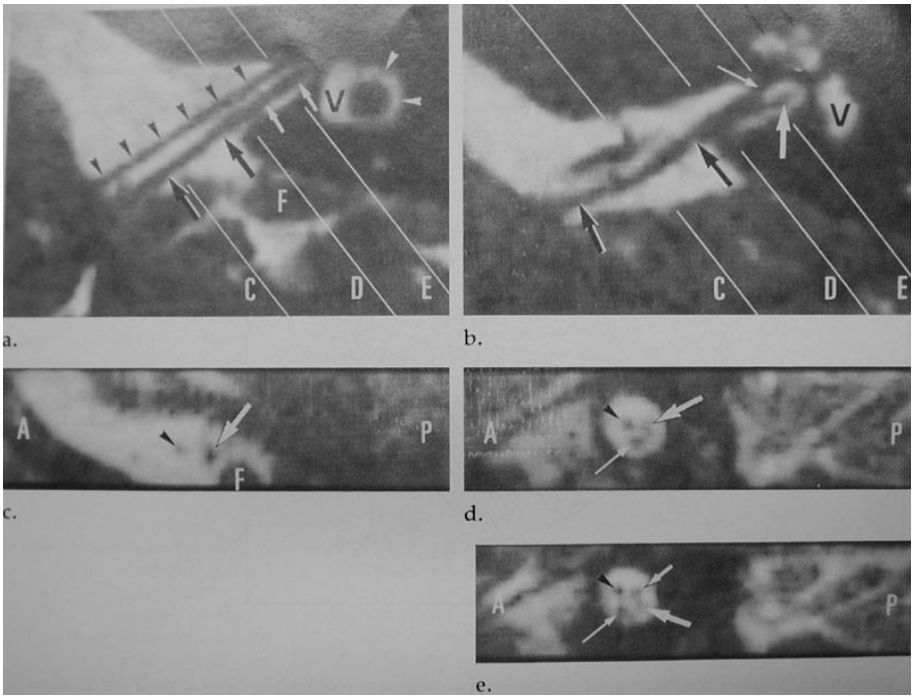

FIGURE 2. Normal facial nerve and VCN in the cerebellopontine angle (CPA) and internal auditory canal (IAC). **(a)** Axial 0.7-mm-thick 3DFT-CISS image (15/21, 65° flip angle) obtained through the superior part of the left IAC shows the total course of the facial nerve (black arrowheads) from the brain stem to the fundus of the IAC. At this level, the facial nerve is always parallel to the VCN (black arrows), which becomes the superior vestibular branch (white arrows) of the VCN in the lateral part of the internal auditory canal. *F* = flocculus, *V* = vestibule, white arrowhead = lateral semicircular canal. **(b)** Axial image like in (see a) obtained through the inferior part of the left IAC. A typical bifurcation of the VCN into the cochlear (thin white arrow) and inferior vestibular (large white arrow) branches is always visible on the images through the inferior half of the IAC. The VCN can be seen in the cerebellopontine angle and medial third of the IAC (large black arrows). *V* = vestibule, thin black arrows = cochlea. Lines *C*-*E* represent the perpendicular lines along which the reconstruction images *c*-*e* were obtained. **(c)** Parasagittal 3DFT-CISS reconstruction image obtained perpendicular to the course of the nerves at the level of the CPA (along line C in a and b). The VCN (arrow) and the facial nerve (arrowhead) can always be recognized at the level of the CPA, and at this site the VCN is nearly always 1½-2 times larger in diameter. *A* = anterior, *F* = flocculus, *P* = posterior. **(d)** Parasagittal image (see c) obtained perpendicular to the course of the nerves at the level of the middle third of the IAC (along line D in a and b). The VCN has divided into a cochlear branch (thin white arrow) and a common vestibular branch (large white arrow). The facial nerve (arrowhead) is visible in its normal high and anterior position in the IAC. *A* = anterior, *P* = posterior. **(e)** Parasagittal image (see c) obtained perpendicular to the course of the nerves at the level of the lateral third of the IAC (along line E in a and b). Near the fundus of the internal auditory canal, the facial nerve (arrowhead) and the cochlear branch of the VCN (thin white arrow) are still visible in the anterior part of the IAC and have the same size, which can be normal, but more frequently the cochlear nerve is the larger one. At this level, the common VCN has split into superior (small white arrow) and inferior (large white arrow) branches. *A* = anterior, *P* = posterior.

On these images made through the internal auditory canal, the cochlear branch of the VCN was larger than the facial nerve in 12 inner ears, was as large as the facial nerve in five inner ears, and was smaller than the facial nerve in only three inner ears (Figure 2d, 2e).

Patients

In all patients, the T2-weighted spin-echo images of the brain were normal, and the unenhanced and gadolinium-enhanced T1-weighted images of the inner ear helped confirm only the stenosis of the internal auditory canal (five inner ears [three patients]) and the malformations of the osseous and membranous labyrinths (four inner ears [two patients]). However, these inner ear malformations were far easier to visualize on the 3DFT-CISS images. The absence of gadolinium enhancement in the cerebellopontine angle, internal auditory canal, and membranous labyrinth ruled out an acoustic neuroma or acute labyrinthitis as the cause of the deafness or hearing loss. Chronic labyrinthitis was ruled out on CT scans (no calcifications) and on the 3DFT-CISS images (no fibrous obliteration of the intralabyrinthine fluid spaces). Both inner ears were involved in three of the seven patients.

Two patients (three inner ears) had normal osseous and membranous labyrinths but had very narrow internal auditory canals. One of them (patient 2) even had a separate bony canal for the facial nerve, parallel to the internal auditory canal. In these two patients, the VCN was completely absent, and only a facial nerve was visualized on the gradient-echo images (Figure 3).

Associated malformations of the osseous and membranous labyrinths were seen in only two patients (four inner ears [patients 3 and 4]), and in one of them, the internal auditory canal was also stenotic on both sides. These patients had a common VCN, without trifurcation into cochlear, inferior vestibular, and superior vestibular branches (Figure 4).

Three other patients (three inner ears) had normal internal auditory canals and labyrinthine structures. Two of them (patients 5 and 6), however, had a common VCN running toward the vestibular labyrinth, and in both patients the cochlear branch of the VCN was absent (Figure 5). In the other patient (patient 7), hypoplasia of the cochlear branch of the VCN was found (Figure 6). All MR and CT findings are listed in Table 1.

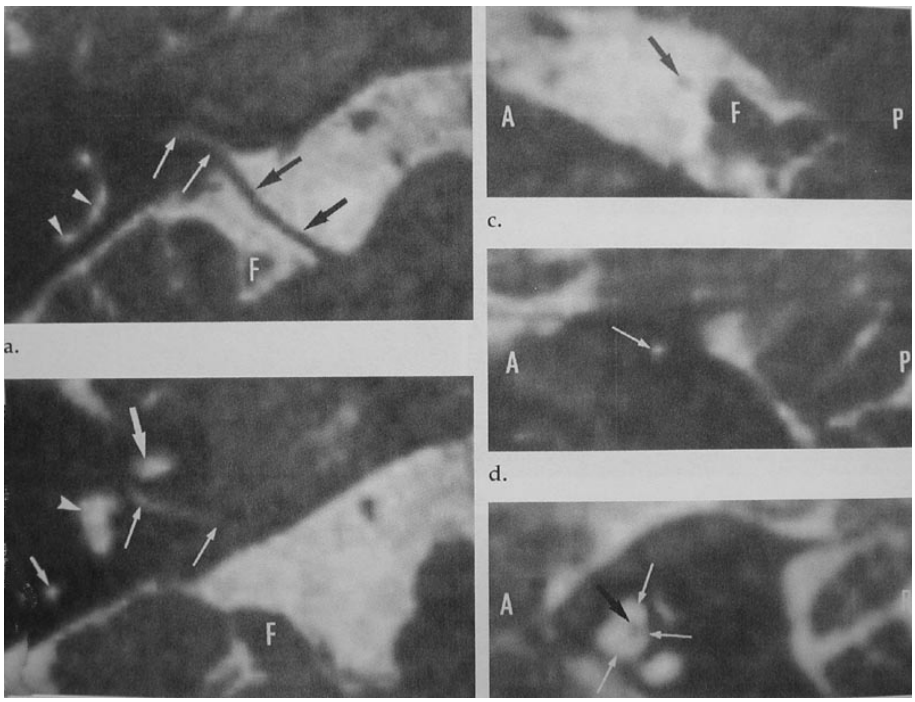

FIGURE 3. Patient 1. Type 1 malformation of the VCN (aplasia).
(a) Axial 0 7-mm-thick 3DFT-CISS image (15/21, 65° flip angle) obtained through the upper part of the right stenotic internal auditory canal (IAC). Only very little cerebrospinal fluid can be seen in the stenotic IAC (white arrows), and it is impossible to demonstrate the presence or absence of nerves in such a narrow canal. Only one nerve, the facial nerve (black arrows), can be recognized in the cerebellopontine angle. *F* = flocculus, arrowheads = intralabyrinthine fluid in the common crus. **(b)** Axial 0.7-mm-thick 3DFT-CISS image (15/21, 65° flip angle) obtained through the lower part of the right stenotic IAC. Again, little cerebrospinal fluid is visible in the stenotic IAC (thin white arrows). High-signal-intensity intralabyrinthine fluid is seen in the cochlea (large white arrow), posterior semicircular canal (small white arrow), and vestibule (arrowhead). *F* = flocculus. **(c)** Parasagittal 3DFT-CISS reconstruction image obtained perpendicular to the course of the IAC and facial nerve at the level of the right cerebellopontine angle. At the level of the cerebellopontine angle, only the facial nerve (arrow) can be recognized anterior to the flocculus (F). In normal ears, two nerves are always present at this site (Figures 1, 2c). Therefore, parasagittal reconstruction images through the cerebellopontine angle are very reliable to demonstrate the absence of the VCN in patients with congenital deafness and normal facial nerve function. *A* = anterior, *P* = posterior. **(d)** Parasagittal 3DFT-CISS reconstruction image obtained perpendicular to the course of the IAC at the level of the middle third of the IAC shows the very narrow IAC filled with cerebrospinal fluid (arrow). It is impossible to recognize nerves in this narrow canal. *A* = anterior, *P* = posterior. **(e)** Parasagittal 3DFT -CISS reconstruction image obtained perpendicular to the course of the IAC at the level of the lateral third of the IAC. At the level of the fundus, the IAC is wider (white *arrows*) and this allows visualization of the facial nerve (black arrow); the three branches ot the VCN are absent. *A* = anterior, *P* = posterior.

DISCUSSION

For years, CT was the best technique to look for congenital malformations of the inner ear in patients with congenital deafness. With the advent of MR imaging, it became possible to exclude abnormality along the acoustic pathway and in the auditory cortex on T2-weighted spin-echo images. Later on, gadolinium-enhanced T1-weighted spin-echo images were used in these patients to exclude acoustic neuromas, labyrinthitis, and other possible pathologic conditions in the cerebellopontine angle, internal auditory canal, and membranous labyrinth (Mark 1993, Mark 1994, Mark 1992, Casselman 1994, Casselman 1996b). In recent years, T2-weighted gradient-echo techniques have been used more and more to study the inner ear. These gradient-echo images are needed to evaluate the very small structures of the inner ear and to detect some of the abnormalities in the cerebellopontine angle, internal auditory canal, and membranous labyrinth (Casselman 1994, Casselman 1996b, Casselman 1996a). Good gradient-echo images must provide high contrast between the cerebrospinal fluid-intralabyrinthine fluid, nerves, and bone, and the sections must be very thin. In this study, axial 0.7-mm-thin 3DFT-CISS images were used because they provide excellent contrast between the different inner ear structures, and even the cerebrospinal fluid around the brain stem remains completely white on these images (Casselman 1993). Similar results were reported with other gradient-echo techniques, including 3D gradient-recalled acquisition in the steady state (Schmalbrock 1993), contrast material-enhanced fast acquisition in the steady state (Tien 1993), and 3D fast imaging with steady-state precession (Tanioka 1991), and even a fast spin-echo (Tien 1992) sequence proved to be beneficial in the study of the inner ear. The congenital malformations, detectable with CT, could now also be recognized on these gradient-echo images. The big advantage, however, was that it now became possible to detect unexpected inner ear malformations in patients with sensorineural hearing loss and/or vertigo by using MR alone, obviating an additional CT study (Casselman 1996a).

CT and MR imaging could now be used to confirm the presence of a normal cochlea in candidates for cochlear implantation and to exclude calcifications in the cochlea (at CT) and/or fibrous obliteration in the membranous labyrinth (at MR imaging). In the absence of calcifications and fibrous obliterations, it is possible to introduce a cochlear implant into the cochlea. It is, however, obvious that the next important structure to be checked in these patients is the cochlear branch of the VCN. However, the MR technique must be fine-tuned to be useful for detection of nerve aplasias or hypoplasias. These malformations can be detected only on thin-section T2-weighted gradient-echo images (e.g., 3DFT-CISS, etc) or comparable fast spin-echo images.

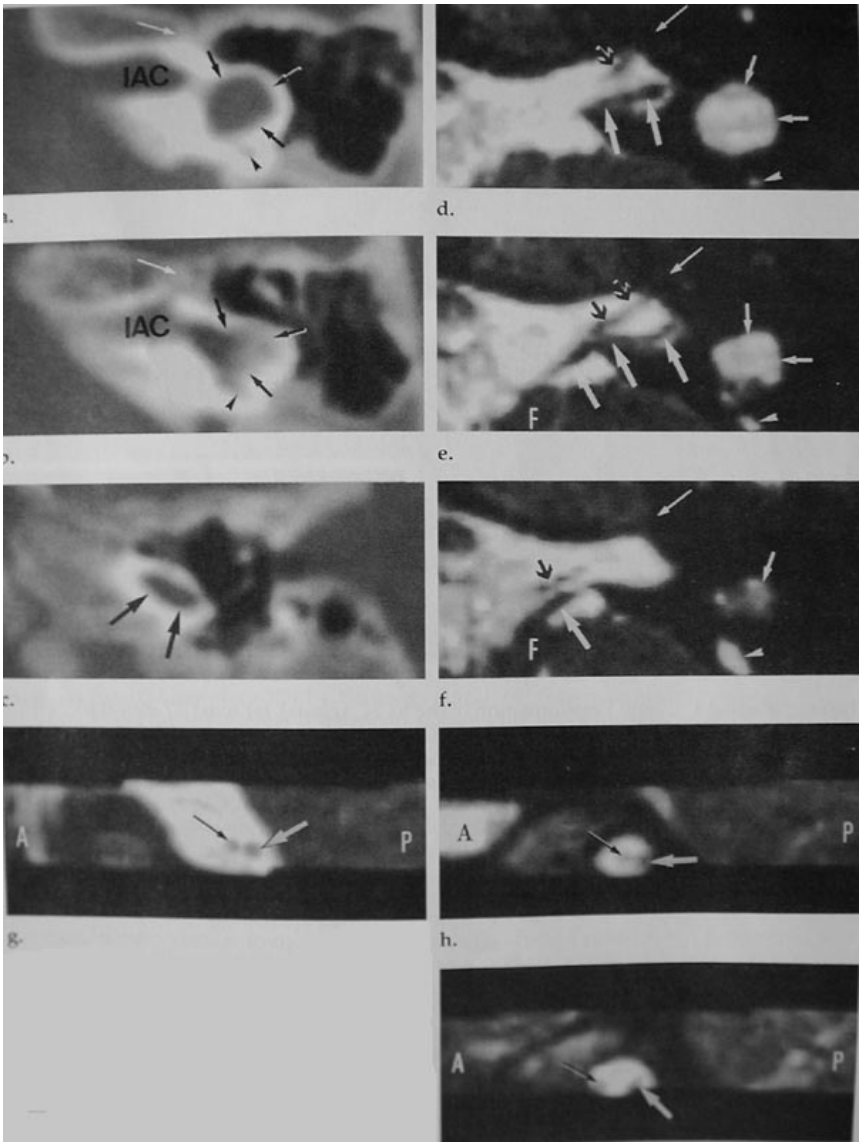

FIGURE 4. Patient 3. Type 2A malformation of the VCN (common VCN with aplasia of its cochlear branch in the presence of a labyrinthine malformation). **(a)** Axial 1.5-mm-thick CT scan of the left inner ear obtained through the upper part of the internal auditory canal (IAC) shows only a single cavity (black arrows). The cochlea cannot be found at its normal site (white arrow), and in this patient, the cochlea and the vestibule formed a single or "common cavity". A partially developed and malformed posterior semicircular canal (arrowhead) can be seen. *IAC* = IAC. **(b)** Axial 1.5-mm-thick CT scan of the left inner ear obtained through the lower part of the IAC. The absence of the coch-

lea (white arrow) and the presence of a common cavity (black arrows) and a partially developed posterior semicircular canal (arrowhead) are confirmed at this level. *IAC* = IAC. **(c)** Axial 1.5-mm-thick CT scan of the left inner ear obtained through the base of the abnormal labyrinth. At this level, an oval inferior extension of the common cavity can be recognized (arrows) and mimics a basal turn of a cochlea. **(d)** Axial 0.7-mm-thick 3DFT-CISS image (15/21, 65° flip angle) obtained through the upper part of the left IAC. The facial nerve (black arrow) and a vestibular nerve (large white arrows) can be depicted just under the roof of the IAC. No fluid is seen at the site where one normally finds the cochlea (thin white arrow), and a fluid-filled common cavity (small white arrows) and posterior semicircular canal (arrowhead) are the only labyrinthine structures that can be visualized. The upper part of the posterior semicircular canal was missing on the adjacent images (not shown) made higher through the inner ear. **(e)** Axial 0.7-mm-thick 3DFT-CISS image (15/21, 65° flip angle) obtained through the middle part of the left IAC. Both the facial nerve (black arrows) and the vestibular nerve (large white arrows) can be followed toward the porus of the IAC where they come close together and touch the posterior lip of the porus. No fluid is found in the cochlear region (thin white arrow). A fluid-filled common cavity (small white arrows) and malformed posterior semicircular canal (arrowhead) are noted. *F* = flocculus. **(f)** Axial 0.7-mm-thick 3DFT-CISS image (15/21, 65° flip angle) obtained through the inferior part of the left IAC. The cochlear and inferior vestibular branch of the VCN cannot be found. At this level, the facial nerve (black arrow) and a “common vestibular nerve” (large white arrow) can be recognized in the cerebellopontine angle just anterior to the flocculus (*F*). The nerve is called a common vestibular nerve because no separate superior and inferior branches of the VCN are present in this patient. The absence of fluid in the normal region of the cochlea (thin white arrow) and the presence of a fluid-filled abnormal broad posterior semicircular canal (arrowhead) and "common cavity” (small white arrow) are confirmed. **(g)** Parasagittal 3DFT-CISS reconstruction image obtained at the level of the left cerebellopontine angle. Two nerves can be seen in the cerebellopontine angle, and the VCN (white arrow) is larger than the facial nerve (black arrow), which is a normal finding. *A* = anterior, *P* = posterior. **(h)** Parasagittal 3DFT-CISS reconstruction image obtained at the level of the middle third of the left IAC. At this level, the cochlear branch of the VCN is missing, and only a common VCN (white arrow) posteriorly and a facial nerve (black arrow) can be recognized. *A* = anterior, *P* = posterior. **(i)** Parasagittal 3DFT-CISS reconstruction image obtained at the level of the lateral third of the left IAC. Near the fundus of the IAC, the common VCN (white arrow) is still seen instead of the three branches of the VCN that should be seen at this level. The facial nerve (black arrow), seen in the anterior part of the IAC, has an abnormal low position inside the IAC. *A* = anterior, *P* = posterior.

Visualization of the Nerves in the Internal Auditory Canal

It is crucial to use images with a thickness of 1 mm or less to visualize the facial nerve and the three branches of the VCN separately inside the internal auditory canal. Nerve visualization becomes more accurate when, for instance, 0.7-mm-thick sections are used instead of 1.0-mm sections (Casselman 1993). The four nerves could be visualized in the internal auditory canal on the axial 0.7-min-thick 3DFT-CISS images in all 20 normal inner ears and on the parasagittal reconstruction images in 19 of them. This proves that in the absence of movement artefacts, in cooperative patients, this technique is reliable enough to demonstrate the four nerves (Figure 2). Verification of the nerves in a second plane makes the technique even more reliable. It can also happen that a nerve is lying against the anterior or inferior wall of the medial part of the internal auditory canal, and in these patients the parasagittal recon-

struction images can help in the demonstration of a nerve that is difficult to see on the axial images.

The thickness of the nerves inside the internal auditory canal can be measured, but these nerves are too small to be measured in a reliable way on images with an in-plane resolution of 0.66 x 0.66 mm and a thickness of 0.7 mm. The voxels are nearly isotropic or cubically shaped when these in-plane and section-thickness dimensions are used, and the use of such voxels will result in good quality multiplanar reconstruction images. The diameter of the common vestibular nerve and its superior and inferior vestibular branches is difficult to evaluate. Sometimes the bifurcation is seen only near the fundus of the internal auditory canal, and in the region just medial to the bifurcation, the nerve then becomes shaped like a figure eight and therefore has a large craniocaudal diameter. The diameters of the cochlear branch and the facial nerve were easier to depict inside the internal auditory canal (on the parasagittal images and were more constant in size. Most frequently, the cochlear branch of the VCN was larger than the facial nerve, although the latter can be as large or even larger. The findings were more constant in the cerebellopontine angle, where the facial nerve and the VCN are found, and the latter was nearly always 1½-2 times larger than the facial nerve and was never smaller. These findings can be used as a reference when the nerves in the cerebellopontine angle and internal auditory canal have to be checked.

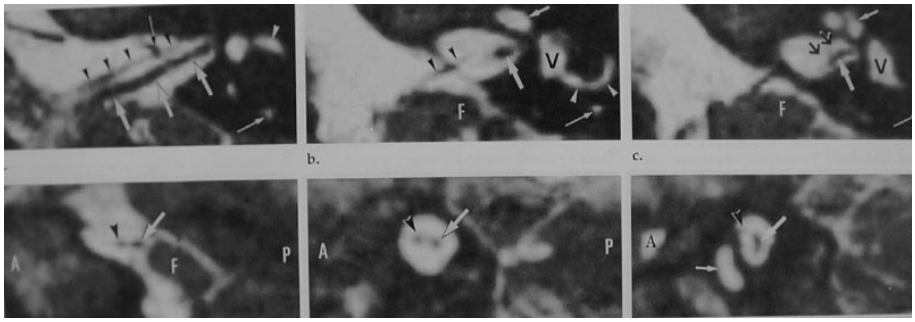

FIGURE 5. Patient 5. Type 2B malformation of the VCN (common VCN with aplasia of its cochlear branch in the presence of a normal labyrinth).
(a) Axial 0.7-mm-thick 3DFT-CISS image (15/21, 65° flip angle) obtained through the upper part of the left intenal auditory canal (IAC). The facial nerve (black arrowheads) and a common VCN (large white arrows) are seen high in the IAC; a vascular loop (black arrow) is crossing the facial nerve deep in the IAC. Fluid is noted in the lateral (white arrowhead) and posterior (white arrow) semicircular canals. **(b)** Axial 0.7-mm-thick 3DFT-CISS image (15/21, 65° flip angle) obtained through the middle part of the left IAC. The facial nerve (black arrowheads) can be followed toward the cerebellopontine angle, and part of the "common VCN" (large white arrow) is depicted. A cochlear branch of the VCN cannot be demonstrated. High-signal-intensity intralabyrinthine fluid is noted in the cochlea (small white arrow) and lateral (white arrowheads) and posterior (thin white arrow) semicircular canals. *F* = flocculus, *V* = vestibule. **(c)** Axial 0.7-mm-thick 3DFT-CISS image (15/21,65° flip angle) obtained through the inferior part of the left IAC. Part of the common VCN (large white arrow) is still visible near the floor of the IAC. The cochlear branch of the VCN is again absent (black arrows). Fluid is noted inside the cochlea (small white arrow) and the posterior semicircular canal (thin white arrow). *F* = flocculus, *V* = vestibule. **(d)** Parasagittal 3DFT-CISS reconstruction image obtained perpendicular to the course of the nerves, at the level of the left cerebellopontine angle. The facial nerve (arrowhead) and the VCN (arrow) have the same size at the level of the cerebellopontine angle, which is a rare finding in normal inner ears. Moreover, in this patient, the VCN was twice as large as the facial nerve on the opposite normal side (not shown), which supports the diagnosis of hypoplasia of the VCN. *A* = anterior, *F* = flocculus, *P* = posterior. **(e)** Parasagittal 3DFT-CISS reconstruction image obtained perpendicular to the course of the nerves at the level of the middle third of the left IAC. The cochlear branch of the VCN cannot be recognized, confirming the findings in b and c. Therefore, the two nerves seen on this image must be the facial nerve (arrowhead) anteriorly and a common VCN (arrow) posteriorly. A = anterior, P = posterior. **(f)** Parasagittal 3DFT-CISS reconstruction image perpendicular to the course of the nerves at the level of the lateral third of the left IAC. Near the fundus of the IAC, the facial nerve (arrowhead) occupies its normal position. However, a separate superior and inferior vestibular branch of the common VCN and a cochlear branch cannot be demonstrated. Instead, a single common VCN continues deep in the IAC and gets larger in craniocaudal diameter (large arrow) near the fundus, explaining why this nerve could be identified (in three contiguous 0 7-mm, thick axial images a-c. *A* = anterior, *P* = posterior, small arrow = high-signal-intensity intralabyrinthine fluid in the cochlea.

Aplasia of the complete VCN and aplasia or hypoplasia of its cochlear branch were demonstrated on MR images in seven patients (10 inner ears). These abnormalities occurred isolated or in association with a stenosis of the internal auditory canal and/or congenital malformation of the labyrinth. A possible explanation for these isolated and associated nerve abnormalities can be sought in the embryologic development of the labyrinth and VCN.

The development of the human cochlea starts with the appearance of the otic placode at the third embryonic week. This placode transforms into the otic vesicle that gives rise to the endolymphatic duct, the utriculus, sacculus, semicircular canals, and cochlea. At 9 weeks, the cochlear windings are fully developed and the appearance of the neural epithelium has started. Neuroblasts of the cochlear ganglion separate from the otic epithelium. Fibres from these ganglion cell bodies grow peripherally back into the otic epithelium and centrally into the brain stem (Hemond 1991). The first afferent fibres entering the undifferentiated otic epithelium are seen at 9-10 weeks (Pujol 1991). In the avian embryo, an abundant neuronal population invades the epithelium (Lefebvre 1990, Lefebvre 1990). This is followed by the disappearance of many redundant fibres, which may lead to a 25 % reduction in the number of fibres. This reorganization is called "neural stabilization" (Lefebvre 1989). Although it has been thought that the cochlear development or differentiation depends on the innervation, this has been proven not to be the case. Explants of chicken otic vesicles that lack neuronal fibres give rise to inner ear sensory structures with normal morphologic features in vitro. This implies that the inner ear development is not dependent on any neuronal trigger or stimulus or trophic effect (Van De Water 1976). Also, the differentiation of the hair cells is controlled by location-specific cues that originate in the ear itself. Conversely, the developing inner ear appears to have an important trophic effect on the survival and the cytodifferentiation of the afferent neurones. The otic vesicle releases a nerve growth factor-like substance that is essential for the survival of the neurones and for "neuronal stabilization" (Lefebvre 1990).

These data can explain why the VCN or its cochlear branch can be absent in patients with an abnormal or absent cochlea. It is equally conceivable that a disturbance in the trophic effect that the cochlea exerts on the cochlear neurones may result in a well-developed cochlea without a surviving cochlear nerve. The association of an absent VCN and a stenosis of the internal auditory canal is not explained by these findings, but a possible hypothesis is that a normal internal auditory canal is formed only in the presence of a normal nerve. Therefore, a disturbance in the trophic effect of the cochlea can result

in loss of too many or all neuronal fibres, and in these patients, the internal auditory canal formed around the initial neuronal fibres will not develop further and eventually will be stenotic.

Classification Proposal

The MR findings in the seven patients with aplasia or hypoplasia of the cochlear branch of the VCN were in accordance with the clinical findings (Table 1) but as yet cannot be confirmed with surgery or at pathologic examination. The authors believe that the presented cases represent different stages or grades of developmental anomalies of the VCN. According to the CT, MR imaging, clinical findings and with respect to embryologic knowledge, we propose the following classification.

Type 1: Aplasia of the VCN
Associated with Stenosis of the Internal Auditory Canal

Bilateral stenotic internal auditory canals (patient 1) and a left-sided stenosis (patient 2) were recognized on CT scans and on the axial 3DFT-CISS images and parasagittal 3DFT-CISS reconstruction images. Both patients had normal labyrinths. It was, however, impossible to look for nerves in the extremely narrow internal auditory canals in these two patients (Figure 3). Nevertheless, the cerebellopontine angle could still be evaluated in these patients, and both the axial and reconstructed parasagittal gradient-echo images showed the presence of a single nerve-the facial nerve. As already mentioned, the absence of the VCN in the presence of a normal cochlea can be explained by a disturbance of the trophic effect (nerve growth factor) that the cochlea exerts on the cochlear neurones (Lefebvre 1990). The hypothesis for the associated stenosis of the internal auditory canal is that the absence of a normally developing VCN causes the stenosis of the internal auditory canal. The internal auditory canal is formed around the neuronal fibres of the VCN, but these fibres can again disappear when there is a disturbance in the trophic effect of the cochlea (nerve growth factor) on these fibres. This excessive loss of fibres or loss of all fibres probably results in an arrest of the development of the internal auditory canal. A separate canal for the facial nerve was detected on CT-scans and gradient-echo MR images in patient 2. This shows that abnormal development of the nerves can even be associated with more severe and rare abnormalities of their canals.

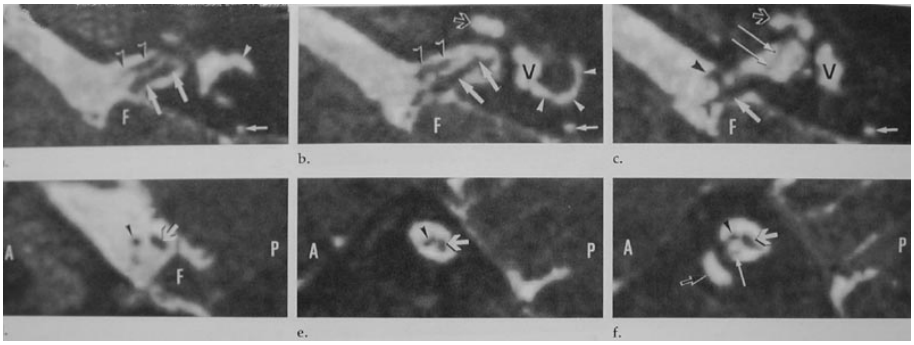

FIGURE 6. Patient 7. Type 2B malformation of the VCN (common VCN with hypoplasia of its cochlear branch in the presence of a normal labyrinth).
(a) Axial 0.7-mm-thick 3DFT-CISS image (15/21, 65° flip angle) obtained through the upper part of the left internal auditory canal (IAC). The facial nerve (black arrowheads) and a common VCN (large arrows) are seen parallel to one another in the upper part of the IAC. Intralabyrinthine fluid is noted inside the lateral (white arrowhead) and posterior (small arrow) semicircular canals. *F* = flocculus. **(b)** Axial 0.7-mm-thick 3DFT-CISS image (15/21, 65° flip angle) through the middle part of the left IAC. The facial nerve can be followed toward the porus of the IAC (black arrowheads), and the common VCN (large white arrows) is still visible in the IAC and near the porus. High-signal-intensity fluid is seen in the cochlea (black arrow), the lateral semicircular canal (white arrowheads), the posterior semicircular canal (small white arrow), and the vestibule (V). *F* = flocculus. **(c)** Axial 0.7-mm-thick 3DFT-CISS image (15/21, 65° flip angle) obtained through the inferior part of the left IAC. The facial nerve (arrowhead) and the common VCN (large white arrow) are seen in the cerebellopontine angle on this image made just above the floor of the IAC. A very thin cochlear branch of the VCN (thin white arrows) can be depicted deep in the IAC, compatible with a hypoplastic cochlear branch. Intralabyrinthine fluid is noted inside the cochlea (black arrow), posterior semicircular canal (small white arrow), and vestibule (V). *F* = flocculus. **(d)** Parasagittal 3DFT-CISS reconstruction image obtained perpendicular to the course of the nerves at the level of the left cerebellopontine angle. The common VCN (arrow) is twice as large as the facial nerve (arrowhead). This is a normal finding at this site, and therefore no malformation is suspected on this image. *A* = anterior, *F* = flocculus, *P* = posterior. **(e)** Parasagittal 3DFT-CISS reconstruction image obtained perpendicular to the course of the nerves at the level of the middle third of the left IAC. Only two nerves, the facial nerve (arrowhead) and a common VCN (arrow), are recognized. A separate cochlear branch, normally already visible at this site, is absent. *A* = anterior, *P* = posterior. **(f)** Parasagittal 3DFT-CISS reconstruction image obtained perpendicular to the course of the nerves at the level of the lateral third of the left IAC. Near the fundus of the IAC, the facial nerve (arrowhead) is seen in its normal position high and anterior in the IAC. A common vestibular nerve (thick white arrow) is seen instead of two separate branches deep in the IAC, and a very thin hypoplastic cochlear branch (thin white arrow) is depicted. Deep in the IAC, the cochlear branch can be smaller than the facial nerve but the size always remains close to the size of the facial nerve in normal inner ears. This is not the case in this patient. Moreover, the diameter of the cochlear branch of the opposite normal inner ear was larger than the diameter of the facial nerve (not shown). This finding supports the diagnosis of a hypoplastic cochlear branch of the VCN. *A* = anterior, *P* = posterior, black arrow = high-signal-intensity intralabyrinthine fluid in the cochlea.

In these patients, the findings on the parasagittal 3DFT-CISS reconstruction images made through the cerebellopontine angle are very reliable in the exclusion or confirmation of aplasia of the VCN. Partial volume effects cannot explain the disappearance of a nerve in this plane, and in normal inner ears, both the facial nerve and VCN were always visible anterior to the flocculus (Figure 2). Therefore, it is advisable to look for aplasia of the VCN at this level in patients with congenital hearing loss and associated stenosis of one or both internal auditory canals.

The MR demonstration of the absence of a VCN might predict that a cochlear implant will not work. Nevertheless, it could be interesting to perform an electric promontory stimulation test and functional MR imaging of the auditory cortex to exclude the presence of very thin cochlear fibres, too thin to be detected on MR images. However, it seems unlikely that a completely invisible VCN on MR images would possess enough fibres to result in worthwhile hearing.

Type 2: Common VCN with Aplasia or Hypoplasia of Its Cochlear Branch

Type 2A*: type 2 in the presence of a labyrinthine malformation.* - In two patients (patients 3 and 4), the cochlea and vestibule formed a single, large, fluid-filled cavity, known as a common cavity (Jackler 1987). They also had associated malformations of the semicircular canals (Table 1). In both patients, the axial gradient-echo images and the parasagittal reconstruction images, showed that the cochlear branch of the VCN was absent (Figure 4). As mentioned above, the absence of a normal developing cochlea can impede the survival or cytodifferentiation of the afferent neurons (cochlear branch) and can explain this combination of malformations. The absence of the cochlear branch was initially overlooked on the axial MR images of one of these patients (patient 3), and at that time, parasagittal reconstruction images were not made. The diagnosis was made only several months later when the images were reviewed for a study on congenital malformations. In the meantime, electric stimulation of the left ear had elicited clear subjective hearing sensation, and as a consequence, the ear surgeon (F.E.O.) placed a cochlear implant (LAURA™; Antwerp Bionic Systems, Antwerp, Belgium) into the inferior part of the common cavity, which looked like a basal turn of the cochlea (Figure 4c). The postoperative electro-audiogram was within the normal range and stable throughout the 6-month postoperative period, and the child showed clear signs of auditory progress (voice control, auditory behaviour). The most probable explanation or hypothesis is that the single common VCN probably carries some fibres projecting into the auditory cortex. These results make it, of course, difficult to make a decision in the second patient (patient 4), with

similar malformations on both sides and bilateral stenoses of the internal auditory canal. The results of the electric promontory stimulation can guide the surgeon, and in the future, functional MR imaging of the auditory cortex might become the technique of choice. Only this imaging modality has the potential to demonstrate whether "cochlear fibres" connect an abnormal labyrinth with the brain stem and auditory cortex, even in the absence of a cochlear branch of the VCN.

Type 2B*: type 2 in patients with a normal labyrinth.* - Three patients presented with completely normal labyrinths and internal auditory canals. The axial and parasagittal gradient-echo images showed an absent cochlear branch of the VCN in two patients (patients 5 and 6), and in these patients, the common vestibular nerve could be followed to the fundus of the internal auditory canal without a clear bifurcation or a very late (not visible on MR images due to partial volume effect with the fundus) bifurcation in a superior and inferior vestibular nerve (Figure 5). In a third patient (patient 7), a very thin cochlear branch could be seen on the axial and parasagittal gradient-echo images (Figure 6). In these three patients, a disturbance in the trophic effect (nerve growth factor) that the cochlea exerts on the cochlear neurones could once again explain the hypoplasia or complete absence of the cochlear branch of the VCN. Of course, these findings had no clinical consequences as these three patients had a normal functioning contralateral ear. Nevertheless, the MR findings correlated well with the unilateral hearing loss. However, in patients with normal labyrinths and bilateral aplasias of the cochlear branch of the VCN, electric promontory stimulation and/or functional MR imaging should be used as a selection tool for cochlear implant candidacy.

The absence of the cochlear branch can be recognized on thin-section gradient-echo images, although once again, parasagittal reconstruction images are mandatory to confirm the findings seen on the axial images. The danger exists that the cochlear branch lies adjacent to the floor of the internal auditory canal and is therefore not seen on the axial gradient-echo images due to partial volume effects. The parasagittal plane is better suited to study this region and can be used to exclude partial volume effects. The diagnosis of hypoplasia of the cochlear branch is more difficult. In three of the 20 normal inner ears, the cochlear branch of the VCN inside the internal auditory canal was smaller than the facial nerve. But even in these cases, the diameters of both nerves were nearly the same. In patient 7, the diameter of the cochlear branch was much smaller than the diameter of the facial nerve, whereas on the opposite normal side the cochlear branch was much larger than the facial nerve.

Type 3?*: Presence of a Common VCN with Aplasia or Hypoplasia of the Vestibular Branch(es)*

Theoretically, a third type of VCN aplasia or hypoplasia with only absence of the vestibular branches but with a normal cochlear branch could be conceived. To our knowledge, such a type of VCN malformation has not yet been detected on MR images. Since the vestibule develops at an earlier stage than the cochlea, one may expect that a vestibular malformation will always lead to an associated cochlear malformation. In such a case, a type 1 aplasia would be the result. Therefore, the authors speculate that an isolated aplasia of the vestibular branch or type 3 aplasia of the VCN may not exist.

A gene for autosomal dominant nonsyndromic hearing loss (DFNA12) maps to chromosome 11q22-24

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ABSTRACT

We performed linkage analysis in a Belgian family with autosomal dominant midfrequency hearing loss, which has a prelingual onset and a nonprogressive course in most patients. We found LOD-scores >6 with markers on chromosome 11q. Analysis of key recombinants maps this deafness gene (DFNA12) to a 36-cM interval on chromosome 11q22-24, between markers D11S4120 and D11S912. The critical regions for the recessive deafness locus DFNB2 and the dominant locus DFNA11, which were previously localized to the long arm of chromosome 11, do not overlap with the candidate interval of DFNA12.

Key words: hereditary hearing loss, nonsyndromic hearing loss, autosomal dominant hearing loss, midfrequency deafness, chromosome 11q, genetic linkage

INTRODUCTION

Nonsyndromic hearing loss is a very common sensory disability. It can be classified in two groups: prelingual and postlingual. Prelingual hearing loss occurs at a frequency of 1/1000 births, and has a monogenic origin in approximately 50 % of cases (Morton 1991). Prelingual hereditary hearing loss has a recessive mode of inheritance in 75 % of cases and a dominant inheritance pattern in 20-25 % (Cohen 1995). However, prelingual hearing loss makes up only a small part of the hearing loss in the total population as postlingual hearing loss is much more frequent. At the age of 65 years, nearly 10 % of the Western population has a significant hearing loss, and this figure rises to approximately 50 % at the age of 80 years (Morton 1991). In most cases, postlingual hearing loss is probably a multifactorial disease, caused by an interaction of environmental and genetic factors. However, there are families with purely genetically determined postlingual hearing loss. With few exceptions these families have an autosomal dominant mode of inheritance (Cohen 1995). These families present an ideal opportunity to identify the genes responsible for postlingual hearing impairment by linkage analysis and positional cloning.

At present 4 loci for X-linked hearing loss, 11 loci for autosomal dominant hearing loss and 11 loci for autosomal recessive hearing loss have been reported. A review of the gene localization's for nonsyndromic hereditary hearing loss can be found in the Hereditary Hearing loss Homepage (Van Camp 1996). These 26 loci clearly illustrate the genetic heterogeneity of hearing loss. Linkage to regions on the X chromosome has been found in families with X-linked profound prelingual hearing loss and in families with mixed conductive and sensorineural hearing loss. The dominant families for which linkage has been found, originate from a great number of countries and most of them show a postlingual, progressive hearing loss. However, both a French family (DFNA3) (Chaib 1994) and an Austrian family (DFNA8) (Kirschhofer 1995) have a moderate to severe stable hearing loss with prelingual onset. The recessive families, on the contrary, are all consanguineous, and originate from ethnic isolates. The hearing loss in these recessive families is always characterized by a prelingual onset and a profound and stationary disease pattern, with the exception of DFNB8 (Veske 1996). The hearing loss in this family is postlingual and progressive, although the onset is early, and progress is rapid as compared to most dominant families.

Until now only two genes for hereditary nonsyndromic hearing loss have been identified. Mutations in the POU3F4 gene are responsible for X-linked mixed

hearing loss with stapes fixation (DFN3) (de Kok 1995), and a mutation in the myosin VIIA gene on chromosome 11q13.5 is responsible for DFNB2 (C. Petit, personal communication). Previously, mutations in the myosin VIIA gene had already been shown to be responsible for Usher syndrome type1B, a recessively inherited combination of prelingual deafness and progressive retinitis pigmentosa (Weil 1996).

In this study we mapped a new gene for autosomal dominant hearing loss to chromosome 11q, telomeric to the previously localized DFNB2 and DFNA11 genes.

MATERIAL AND METHODS

Clinical diagnosis

A family pedigree was constructed at the St.-Augustinus Hospital, and audiograms and blood samples from the family members were obtained after informed consent was granted. We performed pure-tone audiometry on all family members with air conduction at 250, 500, 1000, 2000, 4000, 6000 and 8000 Hz, and with bone conduction at 500, 1000, 2000 and 4000 Hz. Family members were considered to be affected if they had a bilateral sensorineural hearing loss at the mid- and high frequencies below the 95th percentile of an age- and sex-dependent control curve of the general population (International Organization of Standardization 1984). Information on deceased members of the pedigree obtained from relatives indicated that 3 individuals in the older generation had manifested hearing loss. Family members were considered to be unaffected if their hearing thresholds (at most frequencies) were better than 20 dB HL or above the 50th percentile (International Organization of Standardization 1984). Patients with a hearing loss suspected to be caused by other than genetic causes, patients with an audiogram atypical for this family, and patients with threshold values between the 50th and 95th percentile, were given an uncertain affection status and were excluded from the genetic analysis.

Genetic analysis

Genomic DNA was extracted from blood samples by standard techniques. Microsatellite markers were amplified using the polymerase chain reaction

(PCR) and separated on polyacrylamide gels (Hughes 1993). All markers used are listed in the most recent Généthon map (Dib 1996).

Linkage analysis

Linkage analysis was carried out using the LINKAGE 5.1 program package (Lathrop 1984) and the FASTLINK computer program (Cottingham 1993). MLINK two-point linkage analysis was performed between the disease gene and each marker. The deafness was coded as a fully penetrant autosomal dominant trait with a gene frequency of 0.0001. Equal recombination frequencies between males and females were assumed. For each marker the number of alleles in the LOD-score calculations was set at the observed number of alleles in the pedigree (N), and allele frequencies were set equal at 1/N. Changes in the allele frequencies resulted in only minor alterations of the two-point LOD-scores and did not alter the conclusions of the study.

RESULTS

Family pedigree

In this family, bilateral, sensorineural hearing loss is transmitted in an autosomal dominant way. Fourteen tested family members between the age of 6 and 85 years were considered to be affected. Nine tested family members were considered to be unaffected, and nine family members were excluded from the linkage studies due to an uncertain affection status. Examination of the audiograms of the 14 affected individuals showed a mild to moderately severe hearing loss (21 - 80 dB Best Ear HL), mainly in the middle frequencies (500 Hz to 2000 Hz). There was no correlation between the severity of hearing loss and age. No hearing loss was found exceeding a Fletcher index of 73 dB HL. The history and records of most of the patients suggested a prelingual onset (at birth or in the first years of life) with no progression over the subsequent decades.

Seven affected family members had complaints of tinnitus. There were no family members with a history of dizziness or vertigo. Because no further abnormalities were found, the deafness was classified as nonsyndromic.

Linkage analysis

Linkage to known deafness loci, DFNA1 - DFNA10 and DFNB1 - DFNB9, was investigated in our family with the markers listed in the Hereditary Hearing loss Homepage (Van Camp 1996). Negative LOD-scores were obtained for each of these chromosomal regions, with the exception of DFNB2 on chromosome 11q. Suggestive LOD-scores of approximately 2.0 were obtained for DFNB2 with D11S937 and D11S911. Therefore, additional markers spanning the DFNB2 region were analysed. Figure 1 shows the relative position of these markers on the Généthon map (Dib 1996). Two-point LOD-scores over 6 were obtained with several markers 20 to 40 cM telomeric to DFNB2. The LOD-scores for linkage of the deafness locus in our family with the 11q markers are given in Table 1.

The most likely 11q haplotype was constructed for the family (Figure 2). In all affected family members, the linked haplotype was found. Three key-recombinants were identified. In patient IV-2 a recombination is present between D11S912 and D11S4151, mapping DFNA12 centromeric to marker D11S912. This localization is confirmed by a recombination between the same markers in individual III-1. Another important recombinational event is present in individual III-8 between D11S4120 and D11S1778, mapping DFNA12 telomeric to D11S4120. His two affected daughters (IV-9 and IV-10) have inherited this recombinant chromosome, confirming the localization of DFNA12 telomeric to D11S4120. Combining the information from these recombinants indicates that the critical region containing the DFNA12 gene is a 36-cM region between D11S4120 and D11S912.

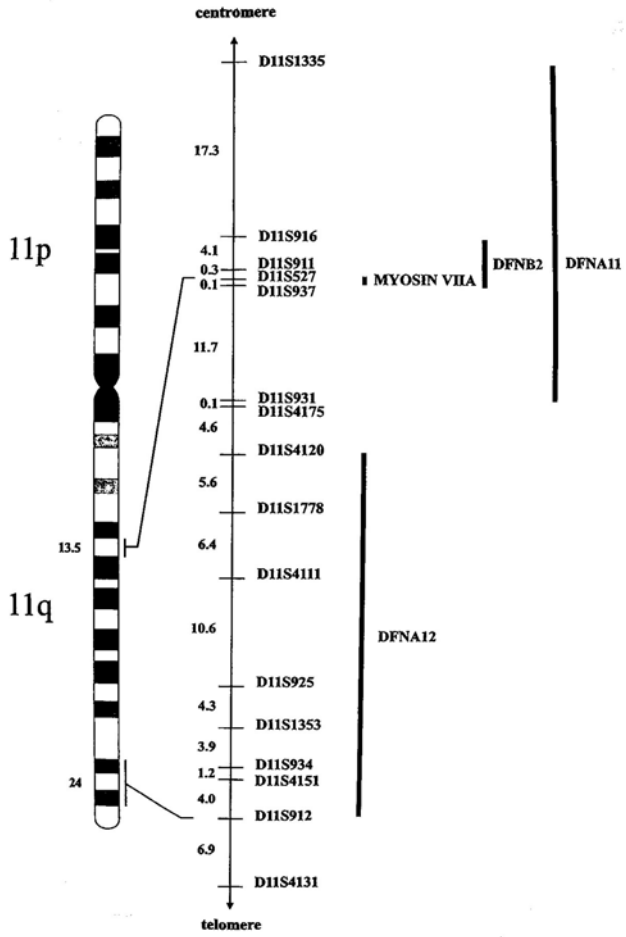

FIGURE 1. Map of chromosome 11q containing the DFNB2, DFNA11 and DFNA12 candidate regions, and the myosine VIIA gene. Genetic distances between the markers are given in cM. The links between the genetic and the cytogenetic maps were inferred from the report of the fourth international workshop on the mapping of human chromosome 11 (van Heyningen and Little 1995).

DISCUSSION

We found linkage to markers located on chromosome 11q in a family with autosomal dominant hearing loss. The hearing loss is nonsyndromic and sensorineural, affecting the midfrequencies. Three other genes for hearing loss have been localized to 11q : (i) Usher syndrome type 1B, characterized by recessive inheritance of prelingual profound deafness and retinitis pigmentosa (Smith 1992), (ii) a form of nonsyndromic recessive profound prelingual deafness (DFNB2) Usher 1B and DFNB2 have recently been shown to be caused by mutations in a single gene, the myosin VIIA gene (Weil 1995; C. Petit, personal communication). However, myosin VIIA is not located in the DFNA12 candidate region (Figure 1). Since the candidate region for DFNA12 is defined by more than one recombinant on both sides, myosin VIIA can reliably be excluded as a candidate gene for DFNA12. The candidate region for the deafness gene in our family (DFNA12) does not overlap with the candidate region in the previously reported Japanese family with a postlingual progressive hearing loss (DFNA11) (Figure 1). (Guilford 1994), and (iii) a form of dominant nonsyndromic postlingual progressive hearing loss involving all frequencies in a Japanese family (DFNA11) (Tamagawa 1996).

TABLE 1. Two-point LOD-scores between DFNA12 and chromosome 11 markers.

	LOD-score at Θ =						
Locus	0	0.01	0.05	0.1	0.2	0.3	0.4
D11S4175	$-\infty$	4.34	4.64	4.42	3.60	2.52	1.24
D11S4120	$-\infty$	4.08	4.39	4.19	3.42	2.40	1.18
D11S1778	6.07	5.97	5.55	5.00	3.81	2.50	1.10
D11S4111	5.35	5.26	4.91	4.44	3.44	2.34	1.10
D11S925	6.53	6.43	6.01	5.45	4.27	2.94	1.45
D11S1353	5.22	5.13	4.79	4.34	3.37	2.30	1.10
D11S934	6.41	6.31	5.89	5.35	4.18	2.88	1.41
D11S4151	5.57	5.48	5.11	4.63	3.60	2.46	1.19
D11S912	$-\infty$	1.68	2.72	2.86	2.48	1.77	0.85
D11S4131	$-\infty$	-0.67	1.14	1.66	1.73	1.33	0.67

However, the telomeric side of the DFNA11 candidate region was defined on the basis of a recombination in a single unaffected individual of unspecified age. It can never be excluded that this individual is non-penetrant or too young to be affected. Therefore, the possibility that the hearing loss in our DFNA12 family and in the Japanese DFNA11 family is caused by the same gene cannot be completely excluded at present. The hearing loss in the Japanese DFNA11 family has a postlingual onset and shows a subsequent gradual progression, while the hearing loss in the Belgian DFNA12 family is prelingual and stable in most patients. These phenotypic differences support the hypothesis that DFNA11 and DFNA12 are different genes localized to separate regions on 11q. The Belgian family in this study is the third linked autosomal dominant family containing patients with prelingual stable hearing loss, after previous reports of a French family (Chaib 1994) and an Austrian family (Kirschhofer 1995). Although postlingual progressive hearing loss was reported in many more autosomal dominant families for which linkage has been found (compiled in the Hereditary Hearing loss Homepage, Van Camp and Smith, 1996), this suggests that prelingual stable hearing loss is not infrequent in families with autosomal dominant hearing loss.

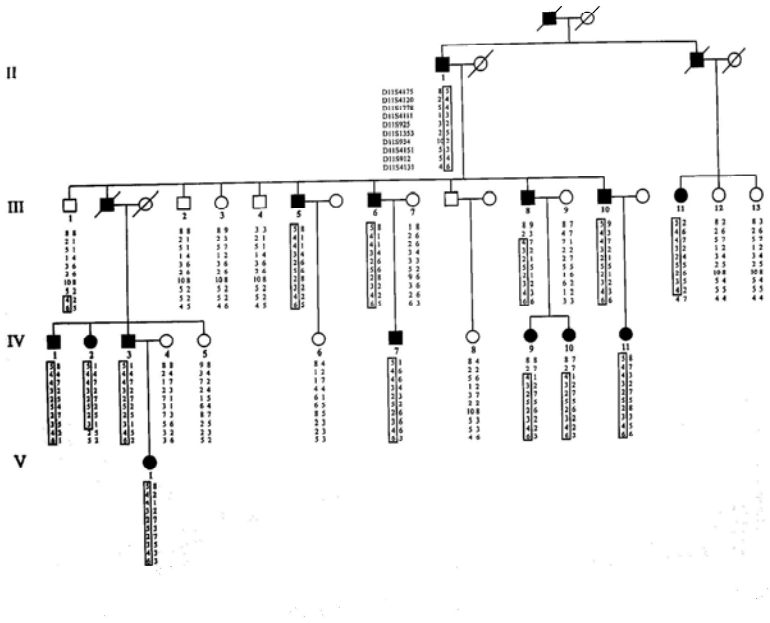

FIGURE 2. Pedigree of the Belgian family with autosomal dominant hearing loss, showing the most likely haplotypes for the chromosome 11 markers. Only family members of whom DNA was analyzed, are numbered. The haplotype linked to DFNA12 is boxed.

Although many genes have been mapped to chromosome 11q22-24 (OMIM 1996), it is difficult to select functional candidate genes. The only two non-syndromic deafness loci whose gene products have been identified are a POU and a myosin gene, in DFN3 and DFNB2 respectively. Members of these two gene families obviously deserve special attention. None of the currently known myosin genes maps to 11q. However, one of the POU genes, Pou2f3, is located on mouse chromosome 9 in the syntenic region of human chromosome 11q21-24 (DeBry 1996). Pou2f3 was mapped in the mouse between the gene for the neural cell adhesion molecule (Ncam) and the gene for friend leukaemia virus integration factor 1 (FLI1), for both of which the human homologues are located in the DFNA12 candidate region (Goldsborough 1993). However, before this gene can be screened for mutations, the human homologue of Pou2f3 has to be cloned. Another possible candidate gene in the DFNA12 candidate region is the POU gene associating factor POU2AF1 (Junker 1996). The POU2AF1 gene codes for a protein that specifically associates with POU transcription factors to regulate immunoglobuline transcription in the B-lymphocyte (Gstaiger 1995; Strubin 1995). However, this highly specific function in the lymphocyte makes it a less likely candidate gene for DFNA12.

The mouse mutant variable spotting (vs) is characterized by hearing loss and absence of pigment on the abdomen in a large ventral patch, a head blaze, white feet and tail tip in the homozygotes (Bailey 1988; Mouse Genome Database 1996). As crossing experiments localized the *vs* mutation on mouse chromosome 9 between the Ncam and Apoa-1 genes, both of whom have a human homologue in the DFNA12 candidate region (Bailey 1988), the *vs* mouse possibly represents a mouse model for DFNA12. However, the affected members in our DFNA12 family did not show obvious pigmentation abnormalities.

DFNA12 represents the twelfth locus associated with autosomal dominant nonsyndromic hearing loss, clearly illustrating the genetic heterogeneity of this type of hearing loss. However, none of the responsible genes have been identified so far. It is to be expected that several of these genes will be cloned over the next few years. The functional analysis of these genes will, it is hoped, provide new insights in the molecular mechanisms of hearing and hearing loss.

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A new autosomal dominant locus (DFNA12) is responsible for a nonsyndromic, midfrequency, prelingual and nonprogressive sensorineural hearing loss

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ABSTRACT

This study reports on the audiologic findings of a nonsyndromic autosomal-dominant hearing loss of which the gene (DFNA12) recently was found to map to chromosome 11q22-24. This paper also proposes and evaluates an algorithm based on the audiometric findings to discriminate between affected and unaffected family members before genetic linkage analysis. A total of 17 genetically affected and 54 unaffected family members were studied retrospectively. The type and degree of hearing loss as compared to age and gender-dependent values according to the ISO 7029 standard were measured. For this comparison, the variable "hearing standard deviations" (HSD) is introduced and is defined as the number of standard deviations that a hearing threshold is lying above the age and gender-related median at the given frequency. A description of the algorithm and an evaluation in terms of α- and β- error also were measured. The hearing loss is nonsyndromic, sensorineural, moderate-to-moderately severe (PTA 51 dB at 18 years), with an early onset (probably prelingual) and no progression. It affects all frequencies but mainly the midfrequencies (500, 1000 and 2000 Hz).

Key words: Sensorineural hearing loss – Genetics – Midfrequency – Autosomal dominant – Audiology.

INTRODUCTION

In a recent article, we reported the results of a genetic analysis in a family with nonsyndromic autosomal-dominant hearing loss. Genetic linkage analysis was performed, and the gene was found to map to a 36-cM interval located on chromosome 11q22-24. The candidate region for the gene did not overlap with other known deafness loci on this chromosome, and the novel gene locus was named DFNA12 (Verhoeven 1997). Only one family has been linked to this locus by now.

The prevalence of congenital hearing loss is approximately 1-3 per 1000 births (NIH 1993, Joint Committee 1994), half of which is assumed to be of genetic origin. In addition, an unknown fraction of the postlingual types of hearing loss also is of genetic origin (Morton 1991). In recent years, several loci for inherited hearing loss have been reported, a review of which can be found on the hereditary hearing loss homepage (Van Camp G, Smith RJH. http://dnalab-www.uia.ac.be/dnalab/hhh). Hearing losses can be classified into prelingual versus postlingual or stable versus progressive. Mostly those categorizations are performed by audiologists or otologists. Yet, no strict criteria exist, and the heterogeneity of the phenotypes makes it difficult to ensure whether the hearing loss is prelingual or not and whether the hearing loss is progressive or not. Several criteria have been suggested (Martini 1997, Gorlin 1995), but they are based merely on empiric interpretations, and they fail to provide a solid statistical rational. The current article reports on a statistical analysis of the audiologic data of the DFNA12-affected patients in an attempt to define the type of hearing loss on more solid grounds.

In addition, when performing genetic linkage analysis, each family member has to be labelled "affected" or "unaffected" before the actual genetic linkage analysis. For all gene localization studies in hereditary deafness published up to now, this labelling has been based solely on the "expert" analysis of the audiometric findings. This expert analysis is subject to error, especially because in most hereditary hearing losses, the degree of hearing loss is not extreme but rather moderate. The current article proposes a mathematical algorithm to discriminate between affected and unaffected family members.

MATERIAL AND METHODS

Family collection

A pedigree of 10 generations and 238 members of a Belgian family with autosomal-dominant hearing loss was worked out, starting from a propositus who presented with familial sensorineural hearing loss. Audiograms and blood samples were obtained after informed consent. Pure-tone audiometry was performed, and air and bone conduction thresholds were established according to routine procedures. In case of hearing loss, anamnestic data were obtained and previous audiograms were collected if available.

Statistical analysis

The audiometric data were statistically analysed. Five-parameter statistics and box-and-whisker plots were used as descriptive statistics (Govaerts 1998). Pure-tone averages (PTA) were defined as the average of the thresholds at 500, 1000 and 2000 Hz. To label an audiogram in terms of normality, the thresholds were compared to the age- and gender-related distribution as defined by the International Organization for Standardization (ISO) 7029 standard (ISO 7029 [1984], "Acoustics-threshold of hearing by air conduction as a function of age and sex for otologically normal persons " [International Organization for Standardization, Geneva]). Thus, for each frequency, the threshold can be expressed as the number of standard deviations below or above the median value for the given age and gender (further called hearing standard deviations [HSD]). From this number of standard deviations, the corresponding percentile can be found in any table of a normal distribution. For example, the median hearing loss at 500 Hz for a normal male at age 70 years of age is 8 dB according to the ISO 7029 standard with a positive standard deviation of 10 dB. A hearing loss of 25 dB can be expressed as 1.7 HSD, namely 1.7 standard deviations (=17 dB) above the median, and this corresponds to the 96th percentile (or P96). Nonparametric statistics (Mann-Whitney *U* test) were used to compare the hearing thresholds of affected patients to those of unaffected patients.

Before linkage analysis can be done, the audiometric results of all the family members have to be labelled affected or unaffected. This has always been done visually by trained otolaryngologists. In an attempt to find out whether the expert interpretation of the audiometric results can be replaced by a calculated categorization, a tentative algorithm was evaluated. It is assumed that a

genetic hearing loss is present with a preference for some frequencies. The algorithm is meant to detect the patients that are affected, based on the audiogram. The algorithm is a two-staged procedure: 1. Look for the audiometric frequency with the highest interindividual variability; 2. Find the patients with a big hearing loss at this frequency, expressed as HSD's in such a way that only affected patients are withheld.

RESULTS

Genetic analysis

Of the 238 members of the pedigree, 163 belonged to the family and 75 were related by marriage. A pure-tone audiogram was obtained from 76 members, and the blood of 70 members was collected for genomic DNA analysis.
The diagnosis of sensorineural hearing loss was based on expert analysis of the audiograms. This expert analysis was based roughly on the following criteria:
1. Family members were considered to be affected if they had a bilateral sensorineural hearing loss exceeding the 95th percentile of an age- and gender-dependent control curve of the general population (ISO 7029 standard).
2. Family members were considered to be unaffected if their hearing thresholds were better than 20 dB HL or better than the 50th age- and gender-related percentile.
3. In case of an abnormal audiogram that was atypical compared with that of other patients of this family, in case of doubt on the genetic cause of the hearing loss, or in case of a hearing loss between the 50th and 95th percentile, the patient was labelled "uncertain" regarding his or her affected status.

Of the 76 family members who were investigated audiometrically, 15 were scored as definitely affected and 45 as definitely unaffected. Only the blood of these members was further processed for linkage analysis. This analysis showed 17 patients to carry the DFNA12 gene. Table 1 lists the correlation between the audiometric analysis and the DNA status.

Anamnestic family data

The anamnestic data and, if available, the audiometric history of the affected family members are summarized in Table 2. Three patients (18 %) were not aware of any hearing loss; three patients (18 %) reported the onset of their

hearing loss at ages ranging from 35-47 years. Four patients (24 %) reported a hearing loss from primary school onward, and seven patients (41 %) presumed their hearing loss to be prelingual. Of four patients, an audiogram before the age of 10 years was available. The hearing loss ranged from 50-70 dB, and no deterioration was measured during a follow-up time ranging from 2-14 years.

TABLE 1. Correlation between audiometry and DNA status

	DFNA12 +	DFNA12 -	
Audio +	15	0	15
Audio +?	1	7	8
Audio -?	1	2	3
Audio -	0	45	45
Audio NA*	0	3	3
Total	17	57	74

DFNA 12+, carrier of the DFNA12 gene; DFNA12-, not a carrier of the DFNA12 gene;
*NA, not available.

TABLE 2. Patient history

Actual age (years)	Reported age of onset (years)	Age of first audiogram (years)	First PTA* (dB)	Evolution
40	0			
85	0			
36	0			
17	0	3.5	55	no deterioration
19	0	5	70	no deterioration
15	0	6	50	no deterioration
6	2.5	4	55	5 dB deterioration
47	10y			
70	< 12			
33	< 12			
34	< 12			
52	35			
53	40			
49	47			
44				
22				
23				

*PTA, pure tone average.

Statistical analysis

The audiometric results of the patients genetically diagnosed as affected are plotted in Figure 1, which shows a midfrequency sensorineural hearing loss of 57 dB as PTA. At all frequencies, the hearing loss of the genetically affected patients is significantly worse than that of the unaffected patients (Mann-Whitney *U*, $p<0.001$). To eliminate the gender- and age-effect in the interindividual variation, the hearing loss of each individual was compared to the age- and gender-related median (refer to Material and Methods section for details). Table 3 lists the hearing loss of the affected patients expressed as HSD. Here, also, the hearing loss is significantly worse than that of the unaffected patients (Mann-Whitney *U*, $p<0.001$).

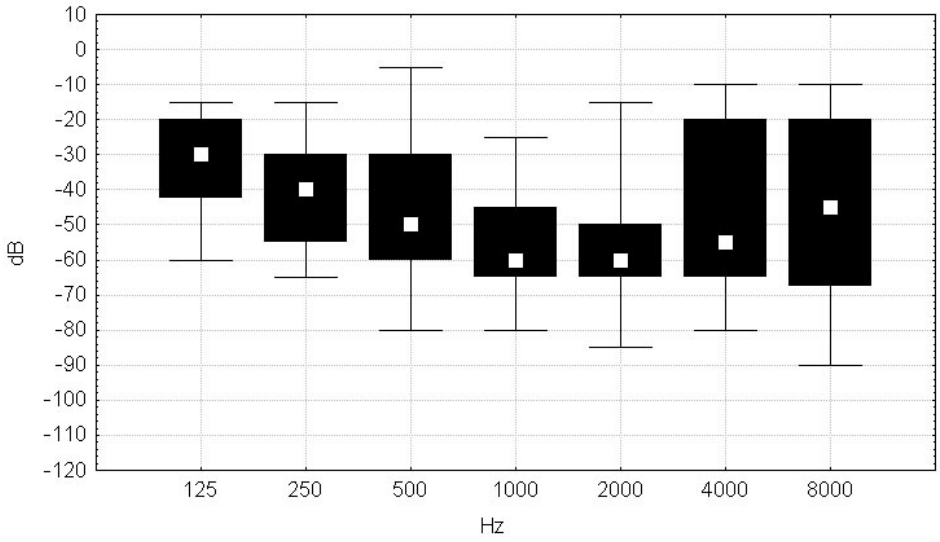

FIGURE 1. Box-and-whisker plot of the audiometric data of 17 affected family members. Bars: minimum tot maximum; large rectangles: 25-75 %; small squares: median values. The hearing loss is highest over the midfrequencies (500-2000 Hz).

Because this study reports on a cross-sectional audiometric evaluation, it is not possible to give the exact time course of the hearing for each individual. Yet, plotting the hearing threshold of each individual on an age-hearing loss plot gives a good approximation of the evolution with age. This is done for frequencies 250, 1000 and 4000 Hz in Figure 2. The best linear fit can be calculated according to the ISO formula:

$$H_{md,Y} = \alpha\,(Y-18)^2 + H_{md,18}$$

where the median hearing threshold for a person of age Y ($H_{md,Y}$) is expressed as a function of age $(Y-18)^2$ with $H_{md,18}$ being the median hearing threshold at age 18 years and α being the slope of the linear function (expressed as deterioration in decibels/year^2).

Table 4 resumes the values of the coefficient α for each frequency compared with the ISO values of α for males and females.

TABLE 3.
Hearing loss of affected patients

Freq. (Hz)	HL* (HSD**)
125	4.2
250	5.0
500	6.9
1000	7.6
2000	5.9
4000	3.2
8000	2.1

***HL: hearing loss;**
**HSD: hearing standard deviations.

It can be readily seen that the values of coefficient α are lower in the affected patients than in the normal population, from which it can be inferred that the average hearing deterioration with age in the affected patients does not exceed the normal deterioration with age.

For the evaluation of the tentative algorithm, the interindividual variation for each frequency was determined in the entire study population (affected and unaffected patients). The results are listed in Table 5. Because the interindividual variation was maximal at 1000 Hz, the hearing loss at this frequency was compared between the genetically affected and the unaffected group. This is shown in Figure 3.

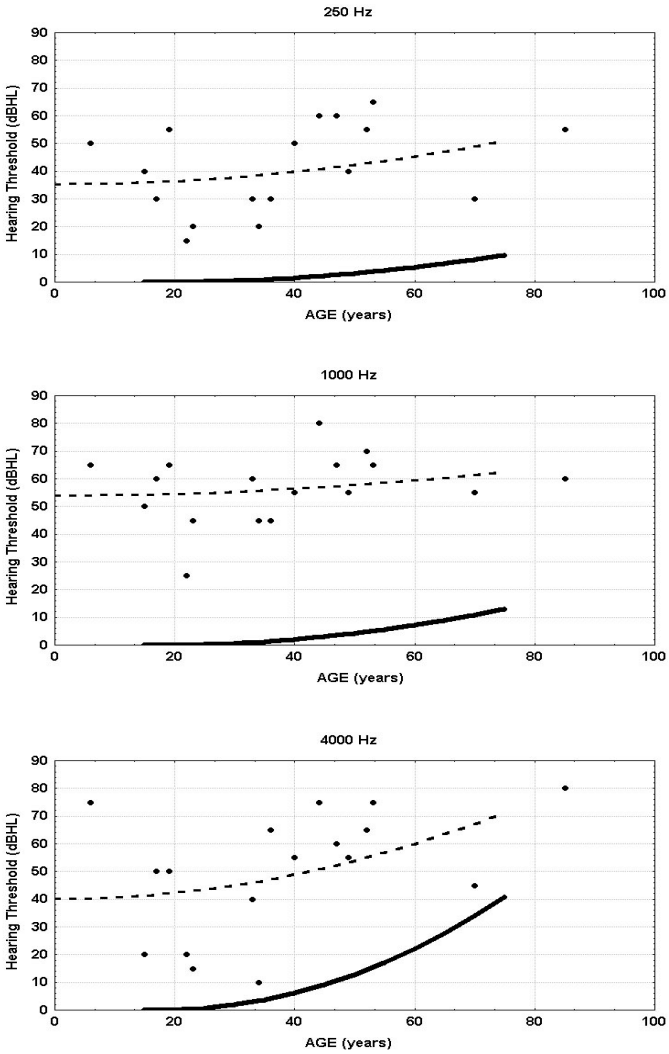

FIGURE 2. Hearing thresholds (dBHL) for 250 Hz (top), 1000 Hz (mid), and 4000 Hz (bottom) plotted in function of age. The dots represent the thresholds of the affected patients. The dotted line is the best linear fit through the affected patients according to the International Organization for Standardization (ISO) 7029 formula (refer to text). The solid line is the best linear fit of the normal population according to the IS0 7029 standard. At all frequencies, the slope of the dotted line is similar to the slope of the solid line. Thus, the hearing deterioration of the affected patients does not exceed the normal hearing deterioration with age. The "onset" hearing loss is likely to be the same as the hearing at age 18 years and is 38 dB at 250 Hz, 55 dB at 1000 Hz, and 43 dB at 4000 Hz.

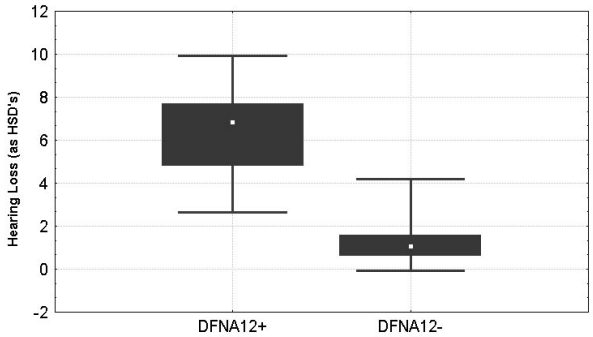

FIGURE 3. Box-and-whisker plot of the hearing loss at 1000 Hz (expressed as HSD; refer to Material and Methods section) in the affected (DFNA12+) and the unaffected (DFNA12-) family members. Bars, minimum to maximum; large rectangles, 25-75 %; small squares, median values. No unaffected patients have a hearing loss of >4 HSD, whereas all but one (16 of 17) of the affected patients have a hearing loss exceeding 4 HSD at 1000 Hz.

DISCUSSION

A Belgian family with nonsyndromic autosomal-dominant hearing loss was investigated. The disease gene was named DFNA12 and was found to map to chromosome 11q22-24. This paper focused on the analysis of the audiological data.

Hearing evolution with time

It is impossible to draw definite conclusions on the evolution of the hearing loss based on a cross-sectional examination. Yet, we believe our analysis yields approximate values for both the "onset" hearing loss and the slope of the hearing deterioration with age. The onset hearing loss can be inferred from the value of $H_{md,18}$, as calculated by the linear fit according to the ISO formula. This is the hearing loss at age 18 years. In the normal population, $H_{md,18}$ equals 0 dB at all frequencies. In the affected patients, $H_{md,18}$ equals between 31 and 55 dB, with an average of 51 dB as PTA (Table 4). To be comparable with the ISO 7029 data, the onset age was set at 18 years. Yet, when the calculations are performed with an age of onset being 0 year, the results are quite alike, with the same hearing loss at onset (PTA, 51 dB). In addition, anamnestic data confirm the early onset. A majority of patients (11/17, or

65%) mention the hearing loss to be first noticed before or at the primary school, and where audiometric data at this age are available, they show hearing losses of >50 dB (age, 3.5-6 years) with no further deterioration (Table 2).

TABLE 4. Slope α of hearing deterioration

	α			
Freq. (Hz)	Normal males	Normal females	Affected patients	$H_{md,18}$ (dBHL)* affected cases
125	0.0030	0.0030	0.0040	31
250	0.0030	0.0030	0.0040	38
500	0.0035	0.0035	0.0020	45
1000	0.0040	0.0040	0.0020	55
2000	0.0070	0.0060	0.0030	54
4000	0.0160	0.0090	0.0090	43
8000	0.0220	0.0150	0.0150	33

*$H_{md,18}$: median hearing loss at age 18 years, expressed in dB Hearing Level.The hearing loss is sensorineural and most prominent in the midfrequencies, although all frequencies are affected. The slope of the linear fit is slightly less than the slope of the linear fit of the normal population (Table 4). This means that the hearing deterioration in the affected patients does not exceed the normal age-dependent hearing deterioration. Consequently, the current hearing loss may be labelled as nonprogressive. This is in line with the anamnestic data, because most affected persons mention no or only slight progression with age. In addition, when audiometric follow-up data are available, no deterioration is seen.

Audiometric definition of the affection status

Statistical analysis of audiometric data is not only important in the characterization of the type of hearing loss but may also contribute to a more reliable diagnosis of affected patients. For genetic linkage analysis to succeed, it is important that affected and unaffected patients are distinguished without error. Labelling an unaffected person as affected is an α-type of error, and labelling an affected person as unaffected is a β-type of error. In families with nonsyndromic hearing impairment, the only material that is available for a more objective evaluation is the audiogram. So far, the interpretation of the audiogram was a matter of expertise. For the current study, the ISO P95 values were plotted on top of each audiogram, and three otologists with experience in family investigation for genetic purposes were asked to agree on labelling each audiogram as positive (+), negative (-), positive with doubt (+?) or negative with doubt (-?). As listed in Table 1, the labels (+) and (-) correlated perfectly with the genetic diagnosis, whereas only 13 % and 66 % of the labels (+?) respectively (-?) appeared to correspond with the final genetic diagnosis (Table 1). However, we still are uncertain regarding this expert audiometric

diagnosis because one mistake may jeopardize gene localization studies. That is why an attempt was made to find a more objective way to interpret the audiogram by developing an algorithm. For this algorithm, the age-and gender-dependent variances are ruled out to not have them interfere with the genetically induced variance. For this purpose, the hearing of each individual is expressed in terms of age- and gender-corrected values, as defined by the ISO 7029 standard. Thus, the concept of HSD was introduced.

A hearing loss of 1 HSD means that the hearing of a given person is 1 standard deviation worse than the age- and gender-matched median, or that the hearing of the given person is situated at the 84th percentile. The actual algorithm then is based on the idea that a family with inherited hearing loss is a mixed population with affected and unaffected persons, resulting in an increased statistical variance in the audiometric results when compared with those of a normal population. If the genetic hearing loss has a preference for certain frequencies (e.g., the high frequencies), then the increased variance will be most prominent at these frequencies and these frequencies are more sensitive for the genetic effect. Therefore, the first step of the algorithm is to analyse the variances at the different frequencies (hearing expressed as HSD). If a marked pattern is seen (e.g., the variance is larger at the high frequencies), then it is assumed that the genetically affected patients will differ most explicitly from the unaffected patients at these frequencies. The second step of the algorithm then is to define an upper and a lower cut-off level. Hearing losses above the upper cut-off level are labelled as affected, those below the lower cut-off level as unaffected, and those between the lower and the upper cut-off level as uncertain. Setting the upper cut-off level high will result in too few persons labelled as affected, but setting it low will result in too large an α-error. Similarly, setting the lower cut-off level low will result in too few persons labelled as unaffected, but setting it high will result in too large a β-error. It is up to the geneticist to decide how many persons with a positive or negative affection status he or she needs for the linkage analysis and which α- an β-error he or she is prepared to accept. An elegant method is to present the family members ranked according to their hearing loss at the most sensitive frequency, expressed as HSD.

TABLE 5. Analysis of variance

Freq. (Hz)	Mean (HSD)	Variance (HSD^2)
125	2.5	2.5
250	2.7	4.7
500	2.8	8.0
1000	2.9	10.1
2000	2.5	7.7
4000	1.9	3.7
8000	1.2	1.9

HSD, hearing standard deviation.

To define the affected persons, one may count down from the persons with the worst hearing to those with the best hearing. The geneticist will decide how far one is allowed to count down and will need enough patients to be labelled as affected, but he or she will be limited in counting down by the increasing risk of labelling unaffected patients as affected. This risk is the α-error and can be assessed by the cut-off level that defines the affected patients. With a cut-off level at 4 HSD, the α-error will be <0.01 %. The α-error is 0.14 % at 3 HSD and 2.3 % at 2 HSD (data derived from a standard normal distribution with one-side testing). In the current family, the variance was most prominent in the midfrequencies with a maximum at 1000 Hz (Table 5). No genetically unaffected patients showed hearing losses exceeding 4 HSD at this frequency (Figure 3). In contrast, 16 (94 %) of 17 affected patients had hearing losses of >4 HSD. Thus, defining the cut-off threshold at 4 standard deviations above the age- and gender-correlated median would yield an excellent selection of affected patients without the risk of erroneously labelling patients as affected. Four HSD may seem high and therefore too strict, but one must take into account that one is evaluating the most sensitive frequency. Thus, the likelihood of finding such extensive hearing losses at this frequency is higher than one might expect to find when examining all frequencies or merely the PTA. It would be interesting to evaluate this cut-off level in other families with a genetic hearing loss.

Similarly, one may label the persons as unaffected by counting up, starting from those with the better hearing. The β-error can not be calculated, however, because the genetically affected subpopulation is not yet know at this moment in the procedure. On the other hand, it is less critical, because the study population will consist of many unaffected persons, such that even a lower cut-off level will yield enough persons, whereas the β-error will remain low. For the current family, a hearing loss of <0 HSD or 1 HSD at 1000 Hz could be used to label the members as unaffected.

CONCLUSIONS

The phenotypic expression of the DFNA12 gene is a nonsyndromic, sensorineural hearing loss, affecting all frequencies, but especially the midfrequencies. The hearing loss is moderate-to-moderately severe, with a most probable onset at a prelingual age and without progression. The median hearing loss is 51 dB (PTA) at onset. The inheritance is autosomal dominant and fully penetrant. An algorithm is proposed for a more objective analysis of the audiogram. This may lead to a more reliable diagnosis of affected patients. The authors propose this algorithm to be evaluated further in other families with inherited hearing loss.

Acknowledgments

The authors thank Dr. T. Cox, Dr. P. Lemkens, and Dr. L. Van Dijck for putting at their disposal the former audiograms of some of the family members.

Mutations in human α-tectorin (TECTA) cause autosomal dominant nonsyndromic hearing impairment (*DFNA8/DFNA12*)

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Nature Genetics 1998; 19: 60-62.

ABSTRACT

The tectorial membrane is an extracellular matrix of the inner ear that contacts the stereocilia bundles of specialized sensory hair cells. Sound induces movement of these hair cells relative to the tectorial membrane, deflects the stereocilia, and leads to fluctuations in hair cell membrane potential, transducing sound into electrical signals. Alpha-tectorin is one of the major non-collagenous components of the tectorial membrane (Richardson 1987, Legan 1997). Recently the gene encoding mouse α-tectorin (*Tecta*) was mapped to a region of mouse chromosome 9, which shows evolutionary conservation with human chromosome 11q (Hughes 1998), where linkage was found in two families, one a Belgian (*DFNA12*) (Verhoeven 1997) and the other, Austrian (*DFNA8*) (unpublished data) with autosomal dominant nonsyndromic hearing impairment. We determined the complete sequence and the intron-exon structure of the human *TECTA* gene. In both families, mutation analysis revealed missense mutations which replace conserved amino-acid residues within the zona pellucida domain of *TECTA*. These findings indicate that mutations in *TECTA* are responsible for hearing impairment in these families, and implicate a new type of proteins into the pathogenesis of hearing impairment.

As mouse *Tecta* is only expressed in the inner ear (Legan 1997), and human *TECTA* maps to the genetic linkage interval for both *DFNA8* and *DFNA12* (Hughes 1998), we considered *TECTA* a candidate gene for the nonsyndromic hearing impairment in both families (Hughes 1998). We therefore determined the sequence and the intron-exon structure of the human *TECTA* gene by genomic sequencing. Human genomic *TECTA* sequence was aligned with the mouse *Tecta* cDNA sequence. In regions where the homology between the mouse cDNA and the human genomic sequence diverged, the presence of splice-site consensus sequences was evaluated, and consensus values (CV) were calculated (Krawczak 1992). We found a total of 23 exons, ranging in size from 65 to 602 bp.

The composite DNA sequence, comprising all exons of *TECTA*, defines a single open reading frame of 6465 bp, displaying 88 % identity to mouse *Tecta*. *TECTA* encodes a protein of 2155 amino-acids, with 95 % identity to mouse α-tectorin (Figure 1). Nearly all structural features of TECTA are conserved between man and mouse (Figure 1). Alpha-tectorin has an amino-terminal hydrophobic signal sequence for translocation across the membrane, and a carboxy-terminal hydrophobic region characteristic of precursors for glycosylphosphatidylinositol-linked membrane-bound proteins. The protein is probably released from the membrane by proteinase cleavage at a conserved tetrabasic sequence upstream of the predicted acceptor for the glycosylphosphatidylinositol anchor (Legan 1997) (residue 2091; Figure 1). Alpha-tectorin is further processed into three polypeptides: a module containing a region homologous to the G1 domain of entactin (Durkin 1988), a module similar to zonadhesin (Hardy 1995), and a module consisting of a zona pellucida domain (Bork 1992). These three polypeptides are crosslinked to each other by disulfide bridges and interact with β-tectorin to form the non-collagenous matrix of the tectorial membrane.

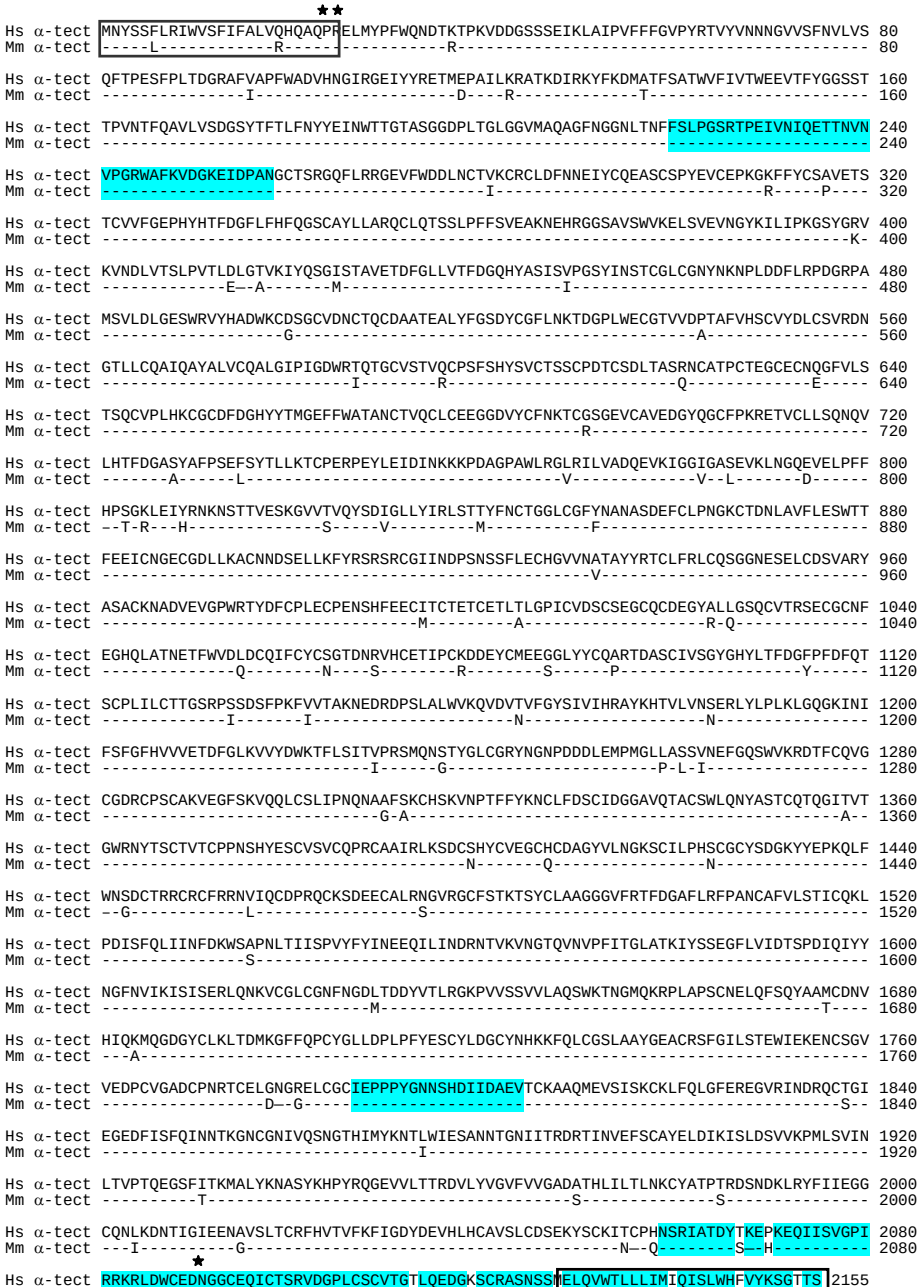
In the mouse, RT-PCR of *Tecta* cDNA amplified two splice variants, the larger variant encoding a protein containing 5 amino-acids (RPLAP) (Legan 1997) not found in the smaller variant. The exact nature of the alternative splicing, however, could not be determined. In the human *TECTA* genomic sequence, exon 15 was found to contain two possible 5' splice sites 15 bp apart, with CV values of 0.76 and 0.90, respectively (Figure 2). Use of the first splice site would lead to the insertion of an RPLAP peptide in the same position as in the mouse. These data suggest that in man as well as in mouse, both splice sites are used, giving rise to two isoforms with and without the RPLAP peptide (Figure 2).

We found no gross rearrangements in *TECTA* by Southern blot of DNA from either family studied. We then conducted exon-by-exon scanning using Sin-

gle Stranded Conformation Polymorphism (SSCP) analysis. Mutation analysis of *TECTA* in the Austrian family revealed an A→G missense mutation at nt 5876 (Table 1, Figure 3). This mutation replaces the tyrosine at residue 1870 with a cysteine (Y1870C). The Y1870C mutation segregated in 8 affected family members and was not found in any of the 6 unaffected family members, 50 Belgian controls or 50 Austrian controls living in the same region as the *DFNA8* family.

Mutation analysis of all 23 exons of *TECTA* in the Belgian *DFNA12* family revealed two mutations in exon 17. The first mutation, C→T at nucleotide position 5725, results in phenylalanine replacing leucine residue 1820 (L1820F) (Table 1, Figure 3). The second mutation, G→A at nt 5738, leads to a substitution of aspartic acid for glycine at residue 1824 (G1824D) (Table 1, Figure 3). These two mutations are only 12 base pairs apart (Figure 3). Eighteen affected members of the *DFNA12* family had both mutations, but neither was present in any of the 40 unaffected family members or 100 control. It is possible that one mutation is a rare polymorphism, while the other one is the disease-causing mutation. Alternatively, they might have a synergistic effect, neither being capable of producing disease by itself.

FIGURE 1 (next page)**:** Amino-acid sequence alignment of human (Hs) and mouse (Hm) α-tectorin. Identical amino-acids are indicated with (-). Positions showing no homology to any known protein sequence are darkly shaded. The first 219 amino-acids show homology with the G1 domain of entactin. Thirty-nine amino-acids separate this domain from a 1528-amino-acid domain (amino-acids 259-1786) which is homologous with zonadhesin. The third conserved region (amino-acids 1805 to 2057) is the zona pellucida domain. The NH2- and COOH-terminal hydrophobic sequences are boxed. Two stars (**) indicate the cleavage site of the signal peptide. One star (*) indicates the most likely acceptor of the glycosylphosphatidylinositol anchor. The tetrabasic putative endoproteinase cleavage site is underlined.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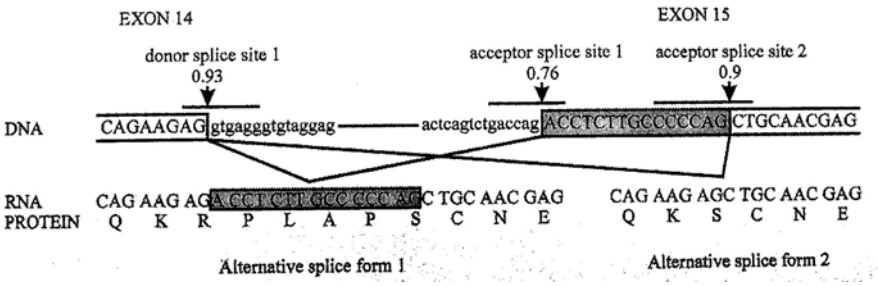

FIGURE. 2. Alternative splicing of *TECTA*. Intron sequences are given in lower-case letters; exon sequences are given in upper-case letters and are boxed. Splice site consensus sequences with their CV value are indicated above the DNA sequence. Use of the first acceptor splice site gives rise to 15 extra nucleotides in the mRNA, leading to 5 extra amino-acids (RPLAP). When the second acceptor splice site is used, the protein lacks the RPLAP amino-acids.

TABLE 1. TECTA mutations in families with hereditary hearing loss

Exon	Domain	DNA	Protein	Family
17	ZP∗	5459C→T	L1820F	Belgian (*DFNA12*)
17	ZP∗	5472G→A	G1824D	Belgian (*DFNA12*)
18	ZP∗	5610A→G	Y1870C	Austrian (*DFNA8*)

∗ZP: zona pellucida domain

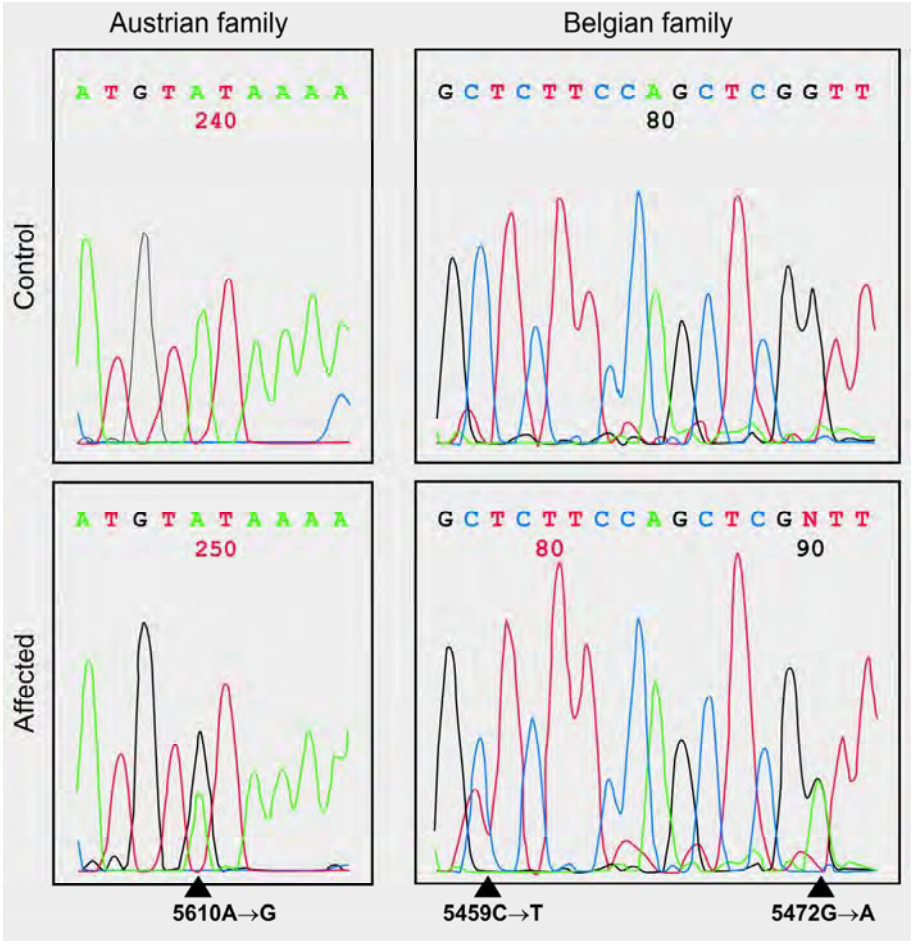

FIGURE 3: DNA sequences with *TECTA* mutations in *DFNA8/DFNA12* families. Electropherograms for the regions immediately surrounding the *DFNA8/DFNA12* mutations are shown. For each family, an affected patient and a control person is depicted. Arrows indicate the positions of the mutations.

To investigate the evolutionary conservation of the amino-acids changed by the missense mutations found in the *DFNA8/DFNA12* families, we searched the GenBank database for protein sequences homologous to the zona pellucida domain of TECTA (residues 1805 - 2057) using BLASTX computer program at the National Centre for Biotechnology Information (NCBI). Alignment of the 10 genes with the highest homology in the BLAST results showed that all 3 amino-acids changed by the missense mutations were evolutionary conserved (Legan 1997, Hession 1987, Prassan 1995, Fukuoka 1991, Yu 1994, Fukuoka 1992, Wong 1996) (Figure 4).

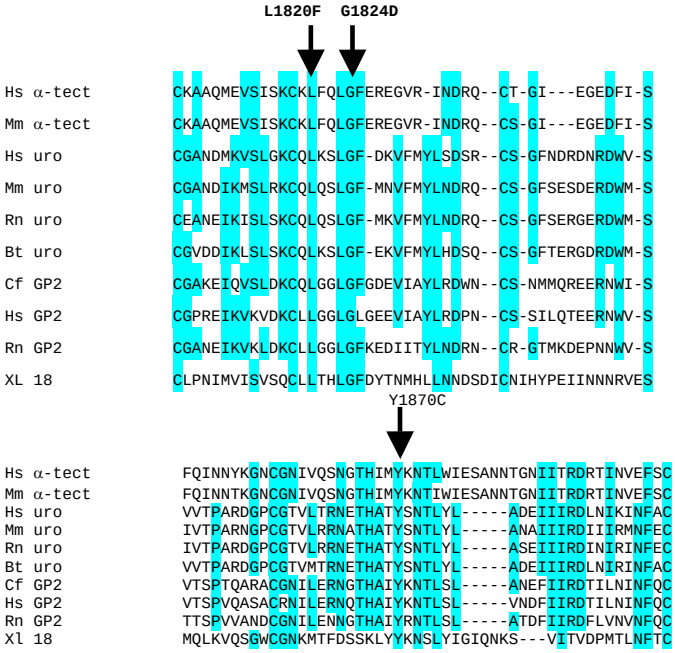

FIGURE 4. Multiple amino-acid alignment of proteins homologous to the TECTA zona pellucida domain. The alignment includes TECTA (Hs α-tect), Tecta (Mm α-tect) (Hughes 1998), human uromodulin (Hs uro) (Krawczak 1992), mouse uromodulin (Mm uro) (Durkin 1988), rat uromodulin (Rn uro) (Hardy 1995), bovine uromodulin (Bt uro) (Bork 1992), dog glycoprotein 2 (Cf GP2) (Hession 1987), human glycoprotein 2 (Hs GP2) (Prasasan 1995), rat glycoprotein 2 (Rn GP2) (Fukuoka 1991) and frog thyroid regulated glycoprotein 18 (XL18) (Yu 1994). Only a short region surrounding the three different missense mutations in the zona pellucida domain is shown. Positions with conservation in at least 6 out of 12 sequences are shaded. Arrows indicate the 3 mutations in *DFNA8/DFNA12*.

The mutations in the zona pellucida domain of TECTA may have dominant negative phenotypes that disrupt the interactions between the different tectorin polypeptides, and as a consequence, disrupt the structure of the tectorial membrane. A deficient tectorial membrane is expected to lead to inefficient transmission of sound to the mechanosensitive stereociliary bundles of the hair cells, resulting in hearing impairment. It is also possible that a mutation causes mRNA instability or the degradation of α-tectorin, reducing the amounts of this protein in the tectorial membrane.

The hearing impairment in both families is prelingual in onset. The fact that the human tectorial membrane is formed between the twelfth and twentieth week of embryonic development is consistent with a defect of the tectorial membrane in these families (Sulik 1995). Furthermore, α- and β-tectorin are only expressed transiently during cochlear development in the mouse. CT scans of the temporal bones of affected members of the *DFNA8* family and magnetic resonance imaging of the inner ear of *DFNA12* patients (unpublished results) did not reveal any gross structural abnormalities. These in vivo imaging methods are inadequate to visualize the structure of the tectorial membrane. Definitive proof of the disease-causing nature of the α-tectorin mutations must, therefore come from further experiments investigating the effects of the missense mutations in TECTA on the structure and the function of the tectorial membrane.

METHODS

DFNA12 and DFNA8 families.

The Belgian *DFNA12* family has already been described clinically (Govaerts 1998) and genetically (Verhoeven 1997). All 8 affected members of the Austrian *DFNA8* family showed a moderate-to-severe hearing deficit (60-80 dB) involving all frequencies. The hearing impairment was prelingual and the patients reported no change in hearing over time. Linkage results have localized the gene responsible for *DFNA8* on the long arm of chromosome 11, in the same region as *DFNA12*. A detailed description of the *DFNA8* family will be published elsewhere.

Identification of cosmid clones.

Cosmids containing *TECTA* DNA sequences were identified by screening an arrayed chromosome-11-specific cosmid library (Lerach 1990) with the mouse *Tecta* cDNA sequence as a probe. Five positive clones were obtained from the Resource Centre of the German Human Genome Project, and grown overnight in LB medium containing 25 μg/ml kanamycin. Cosmid DNA samples were digested with restriction enzymes, electrophoresed through a 0.8 % agarose gel and transferred to a Hybond N+ membrane (Amersham) using standard procedures. The membranes were consecutively hybridized with four overlapping *Tecta* cDNA fragments.

Shotgun cloning of cosmid clones.

DNA from four selected chromosome-11-specific cosmid clones (ICRFc107F1132D1, ICRFc107C05177D1, ICRFc107A0652D1, ICRFc107F06171D1) was sonicated into fragments between 400 bp to 1.5 kb, blunt-ended and shotgun-cloned into a plasmid. From each cosmid, 768 plasmid subclones were picked in two 384-well microtiter plates. Replicas were made on Hybond N+ membranes (Amersham) using a 384-pin replicator (Genetix). The membranes were hybridized with four overlapping fragments of the mouse *Tecta* cDNA as probes, and positive plasmid clones were sequenced.

Mutation Analysis.

All 23 exons were amplified by PCR using primers flanking the different exons (primers sequence available from author on request) if the corresponding PCR products were smaller than 200 bp. Otherwise, additional primers were designed to generate several overlapping fragments comprising the whole exon. SSCP analysis was carried out using 0.5 X MDE gels (FMC) as described (Orita 1989). DNA was sequenced on an ABI 377 automated DNA sequencer (Perkin Elmer), using Thermo Sequenase (Amersham) and Big Dye (Perkin Elmer) dye terminator cycle sequencing kits. Rapid mutation screening was carried out by restriction enzyme digestion of PCR-amplified exons followed by polyacrylamide gel electrophoresis. To analyze the Y1870C mutation in exon 18, a modified forward primer was designed ('5-CCAATGGCACGCATATCATGT-3'), to create an *NdeI* site (Boehringer Mannheim). To analyze the L1820F substitution in exon 17, a second modified forward primer was designed ('5-GTGTCCATATCTAAGTGCGAG-3'), to create an artificial restriction site for *SacI* (Boehringer) in the wild-type allele. The G1824D mutation in exon 17 creates a new restriction site for *TaqI* (Life Technologies).

Genbank accession numbers

TECTA genomic sequences, AF055114 to AF055136.

Acknowledgements

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Audiological findings in the large vestibular aqueduct syndrome

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ABSTRACT

An enlarged vestibular aqueduct is a congenital disorder causing early onset and progressive hearing loss in children. This paper presents the audiological findings at first presentation and the audiological evolution in 10 consecutive cases presenting with hearing loss and showing a large vestibular aqueduct on imaging. The reported onset of the hearing loss is within the first few years of life. Most of the cases (80 %) showed bilateral involvement. The sex ratio was 1. Patients presented on average at age 5 with a median hearing loss of 62 dB at the speech frequencies. The hearing loss was essentially asymmetrical with an interaural difference of 33 dB and it was a mixed type of hearing loss in 90 % of the cases. The authors claim that the conductive component of this hearing loss is a pure cochlear conductive loss which may be pathognomonic for the disease. The presence of a conductive component in a child is easily misinterpreted as a middle ear ventilation problem or in case of good ventilation as an ossicular problem (type otosclerosis). In addition and in contrast to most literature data, the authors did not find evidence for stabilization of the hearing loss but they found a steady decrease of the hearing at an average rate of 4 dB/y.

Key words: Large Vestibular Aqueduct, Congenital Malformation, Sensorineural Hearing Loss, Cochlear Conductive Hearing Loss; Progressive

INTRODUCTION

Large Vestibular Aqueduct Syndrome was first described as a morphological and clinical entity in 1978 by Valvassori and Clemis (Valvassori 1978).

The vestibular aqueduct is the bony canal originating on the medial wall of the vestibule and extending towards the cerebellar face of the petrous pyramid (Arcand 1991). It contains a vein, an artery and the endolymphatic duct. Enlargement of the vestibular aqueduct is considered to be a minor dysmorphology belonging to the family of Mondini dysplasias. Since in the series of Valvassori this enlargement was often accompanied by other dysmorphologies, such as an enlarged vestibule, an enlarged semicircular canal or a hypoplastic cochlea, Valvassori introduced the term "Large Vestibular Aqueduct Syndrome". An enlarged vestibular aqueduct is found in almost all Pendred syndromes, but it is more frequently found as an isolated entity.

The diagnosis is made by imaging and different criteria may be used. On CT a vestibular aqueduct with a diameter larger than 1.5 mm is considered abnormal (Emmett 1985) On MRI, in general and as a rule of thumb, a vestibular duct and/or sac which exceeds in diameter that of the posterior semicircular duct may be considered to be an enlarged vestibular duct and/or sac (Eelkema 1989).

The clinical picture is most often that of a child or a youngster presenting with a sensorineural hearing loss. Some variability exists in the audiological features between the different reports (Valvassori 1978, Emmett 1985, Jackler 1989, Lacombe 1989, Zalzal 1995). The hearing loss is generally reported as sensorineural, although some authors mention a mixed hearing loss in a minority of their patients (27 % (5), 17 % (3), 38 % (Lacombe 1989)). Bilateral involvement is reported in 59-94 % of cases and in these cases symmetrical hearing is suggested (Arcand 1991). The hearing is often reported to be stable (64 % (Zalzal 1995), 81 % (Emmett 1985)). Yet many papers also report a deterioration which may be stepwise and associated with minor head trauma (Okumura 1995). Jackler reported an average deterioration of 25 dB in 6 years (Jackler 1989).

The present paper consists of a report on 10 consecutive cases with emphasis on the audiological findings.

MATERIAL AND METHODS

Ten consecutive cases in which a large vestibular aqueduct was diagnosed were studied retrospectively. Several parameters were registered, namely sex, age at first presentation, reported age of onset, family history, history of head trauma.

Audiometry and speech audiometry were performed in a soundproof room with an audiometer calibrated according to ISO (International Standards Organization) standards. Transient click-evoked oto-acoustic emissions were recorded with the Otodynamics ILO88 equipment. Auditory Brainstem Responses (ABR) and electrocochleography were recorded with the Madsen ERA 2250 system.

All patients were studied using enhanced and Gadolinium enhanced 3-mm contiguous T1-weighted images, 500/15/4 (repetition time/echo time/excitations). A three-dimensional Fourier transformation-constructive interference in steady state (3DFT-CISS) gradient-echo sequence was also used and enables detailed evaluation of the membranous labyrinth. The parameters of this sequence are: 0.7 mm thick slices, in plane resolution of 0.66 x 0.66 mm (field of view of 170 mm and a 256 x 256 matrix), repetition time of 15 ms, echo time of 21 ms, two acquisitions, flip angle of 65° and a total acquisition time of 8 minutes 6 seconds.

Parametrical data are expressed as mean and range. Audiometrical data are expressed in terms of five-parameter statistics (Govaerts 1998). A linear regression analysis was performed for the evaluation of the deterioration of hearing over time.

In case of bilateral involvement only one ear was included in the statistical analysis in order to respect the requirement of independency of data. In such a case a random choice was made as to which ear to include.

RESULTS

Ten consecutive cases were included, 5 males and 5 females. The age at first ENT-visit averaged 5 years (range 0-8 years). All cases presented with hearing loss, two unilateral and eight bilateral. In all cases the diagnosis of Large Vestibular Aqueduct was made on MRI (Figure 1).

The mean follow-up was 6 years (range 3 months - 13 years).

One child with bilateral involvement had a father and a mother who were both bilaterally deaf due to a Large Vestibular Aqueduct, as confirmed on MRI (Figure 2). The pedigrees of two other children were reported to each contain another case of congenital hearing loss, but further information was lacking.

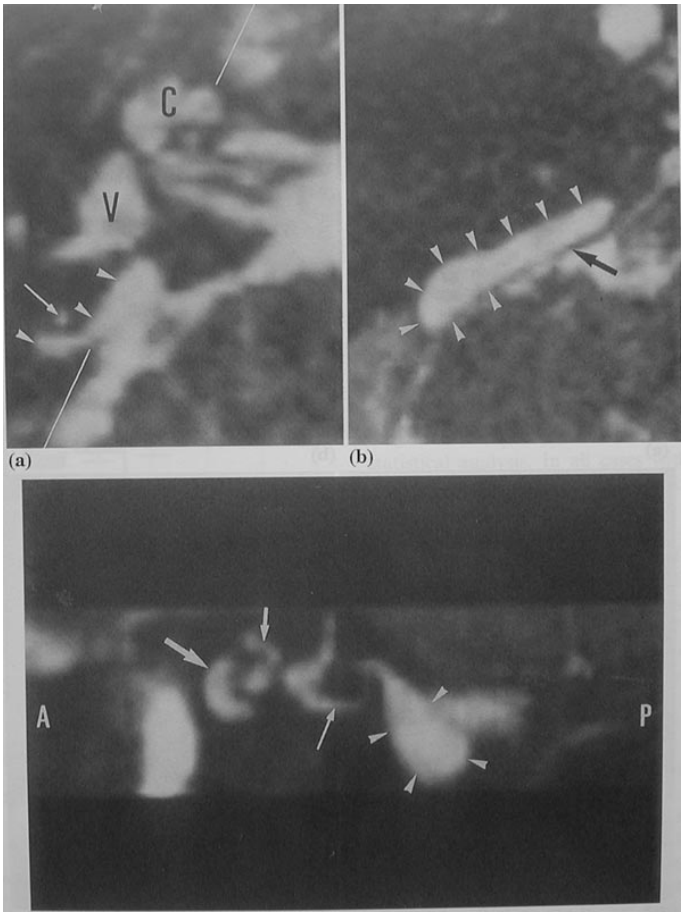

FIGURE 1. Axial 0.7 mm thin 3DFT-CISS images (a,b) and a para-sagittal multiplanar reconstruction (c) through the right membranous labyrinth in a 33-year old man, with an enlarged vestibular duct and sac bilaterally. (a) The endolymphatic duct and sac (white arrowheads) are dilated and their diameter is larger than the diameter of the posterior semicircular canal (long white arrow). Fluid filled cochlea (C) and vestibule (V). (b) Axial image at the level below the membranous labyrinth. The extension of the endolymphatic sac (white arrowheads) in the posterior fossa can be seen on this image. The sac is separated from the cerebrospinal fluid surrounding the cerebellum by the dura mater (large black arrow). This dura mater and the fluid in the enlarged endolymphatic duct and sac can only be seen in a reliable way on thin T2-weighted images (e.g. gradient-echo images, fast spin-echo images etc.). (c) The extension of the endolymphatic sac in the posterior fossa (white arrowheads) can be recognized on this para-sagittal reconstruction made along the white line in Figure 1a. Cochlea (large white arrow), internal auditory canal (small white arrow), posterior semicircular canal (long white arrow), A = anterior, P = posterior.

As to associated congenital anomalies, one case showed mild anomalies of the vestibulum (slightly dilated), one case showed a torsion-anomaly of the kidney and one case showed a hypofunction of the thyroid, of which no further data were available

The audiometrical results at the first visit are shown in Figure 3 and Table 1. A median hearing loss of 62 dB was recorded at the speech frequencies (Pure Tone Average or PTA = average of 0.5, 1 and 2 kHz). In all cases the audiogram was down-sloping. The better ear showed a median loss of 54 dB and the worse ear of 87 dB at speech frequencies.

In 9 cases the type of hearing loss was mixed with a distinct conductive component. Tympanometry was performed in 6 cases and a type A tympanogram was found in all of them. Click evoked oto-acoustic emissions were examined in 4 cases and were absent in all of them. Speech audiometry was performed in 4 cases and ABR in 3 cases and neither of both added any further information. Electrocochleography was performed in one case with unilateral involvement and showed an enlarged negative summating potential with an SP/AP-ratio of 0.70 in the involved ear and a normal summating potential with an SP/AP-ratio of 0.22 in the non-involved ear.

The evolution of the hearing is displayed in Figure 4. Linear regression analysis shows a linear deterioration of 4 dB/y with an average correlation coefficient of .60 %. As can be seen on the figure, many cases show episodes of more pronounced hearing loss, which recuperates totally or partially. This sometimes occurred after minor head trauma, but often without any evidence of head trauma. Most episodes were not associated with vestibular problems. As explained in the Material and Methods section, only one ear per patient was included in this statistical analysis. In all cases with bilateral involvement, the evolution of the other ear was similar to the evolution of the ear that has been included.

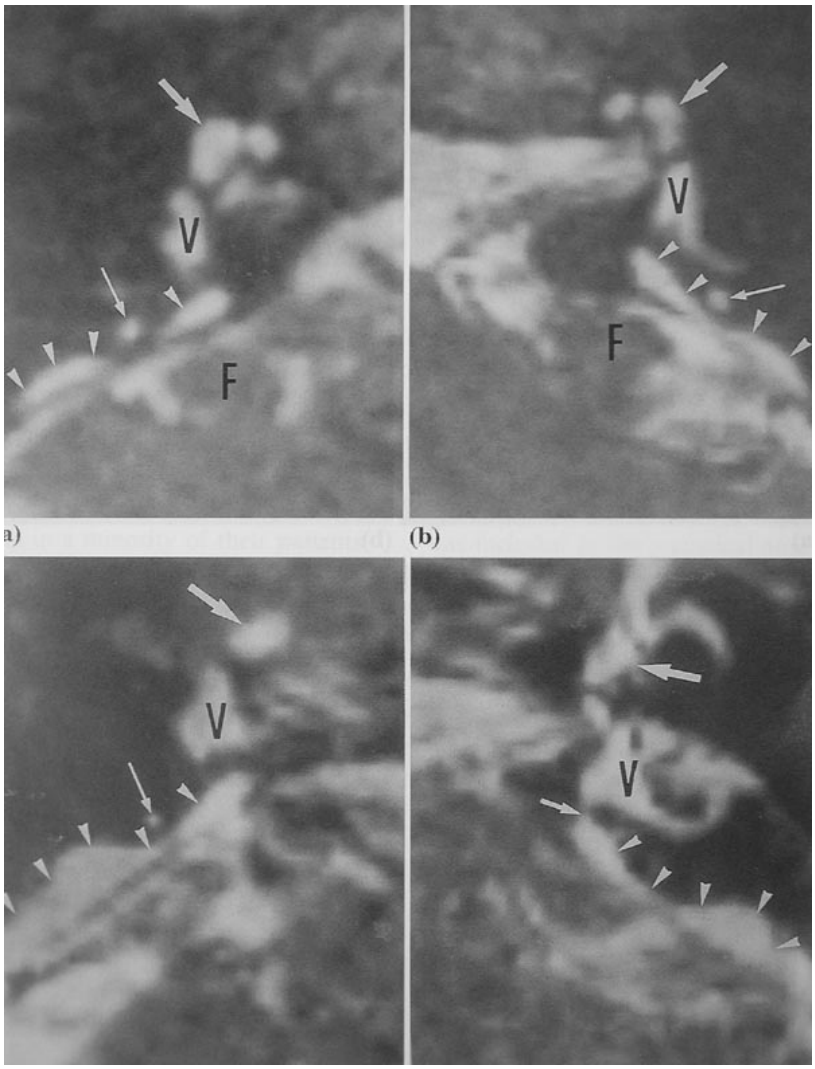

FIGURE 2. Axial 0.7 mm thin 3DFT-CISS images through both membranous labyrinths in the wife (a, b) and child (c, d) of the man illustrated in Figure 1. (a, b) The large fluid filled endolymphatic sacs (white arrowheads) can be depicted posterior to the vestibule (V), then pass the posterior semicircular canal (long white arrow) which has a smaller diameter, and then reach the posterior fossa. Fluid filled cochlea (large white arrow), F = flocculus. (c, d) Again the enlarged endolymphatic sacs (white arrowheads) can be followed behind the posterior semicircular canal (long white arrow) and reach the posterior fossa on both sides. On the left side one can even recognize the endolymphatic duct or connection with the vestibule (small white arrow).. Cochlea (large white arrow), vestibule (V).

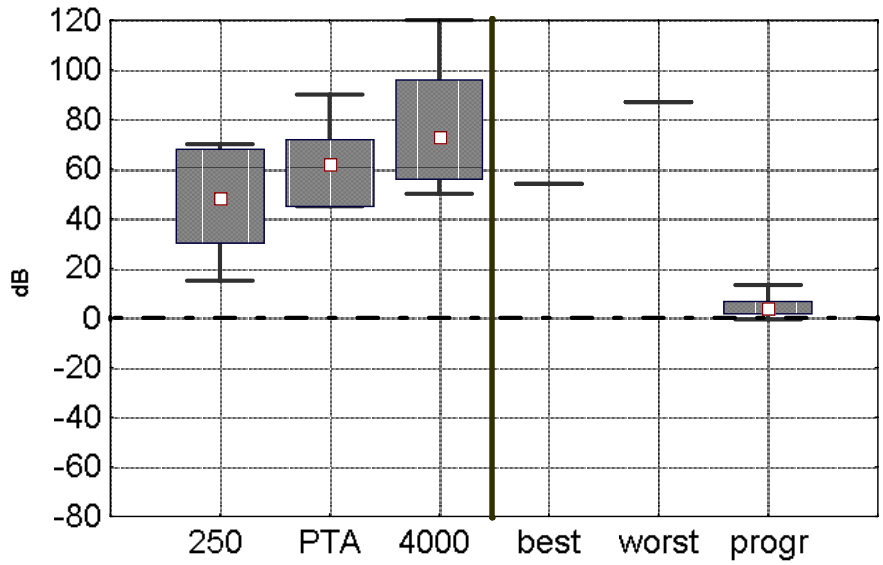

FIGURE 3. Box and whisker plots representing some audiometrical variables. 250, PTA, 4000: hearing thresholds (dBHL) at first ENT-visit at 250 Hz, Pure Tone Average and 4000 Hz respectively. Best, worst: PTA at the better respectively the worse hearing ear. Progr: deterioration of the hearing expressed as db/year at the PTA. Bars = minimum to maximum; large rectangles = 25 % to 75 %; small squares = median value.

TABLE 1. Numerical data of the box and whisker plots in Figure 3, representing some audiometrical variables.

	250 Hz	PTA	4000 Hz	progr
Maximum	70	90	120	13
Upper quartile	68	72	96	6.5
Median	48	62	73	4
Lower Quartile	30	45	56	1.4
Minimum	15	45	50	-0.6

250 Hz, PTA, 4000 Hz: hearing thresholds (dBHL) at first ENT-visit at 250 Hz, Pure Tone Average and 4000 Hz respectively.
Progr: deterioration of the hearing expressed as dB/year at the PTA. Five parameters as in Govaerts (1998).

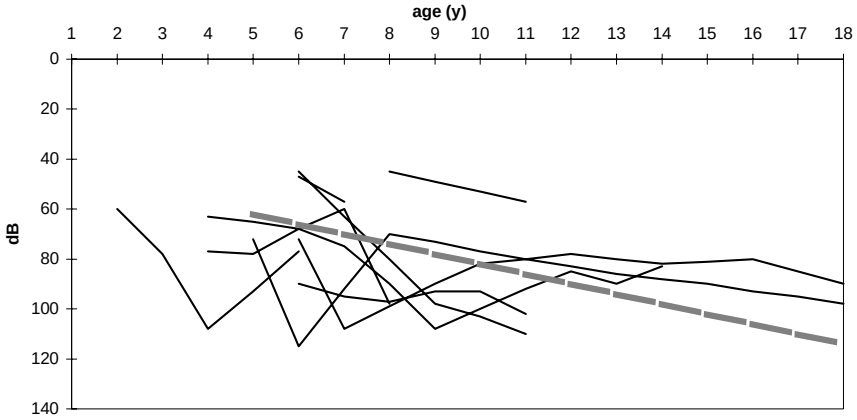

FIGURE 4. Evolution of hearing thresholds of nine children with a follow-up of at least 1 year. The lines represent the hearing thresholds (dBHL) at PTA of one child in function of age. The interrupted line is the median of the individual best linear fit curves, showing that on average children present at age 5 with a hearing loss of 62 dB that deteriorates with age at a rate of 4 dB/y, resulting in a severe hearing loss or deafness by age 18.

Two cases were operated upon for middle ear inspection. In both cases the middle ear showed no anomaly, the ossicular chain was intact and its mobility was absolutely normal. The only noteworthy observation that was found in both operation records was the absence of a "round window reflex", which means that the round window membrane could not be displaced by moving the stapes in the oval window.

One case was operated upon and received a LAURA™ Cochlear Implant. The same findings were recorded as in the former two cases. In addition, upon the opening of the basal cochlear winding before the insertion of the cochlear implant electrode, a profuse perilymph leaking was observed, reflecting the higher than normal pressure in the cochlea.

DISCUSSION

The large vestibular aqueduct syndrome was first described in 1978 (Valvassori 1978). It was diagnosed on radiological tomography of the inner ears of 50 patients presenting with hearing loss. In subsequent years and with the introduction of other medical imaging techniques, the diagnosis has become more common and several papers have reported on this new clinical entity (Valvassori 1978, Arcand 1991, Emmett 1985, Jackler 1989, Lacombe 1989,

Zalzal 1995, Okumura 1995, Valvassori 1983, Belenky 1993, Levenson 1989). It has been called a syndrome because of its frequent association with other inner ear anomalies such as enlarged vestibule, enlarged lateral semicircular canal, hypoplastic cochlea etc (Valvassori 1978). The term syndrome may however be illegitimate, since the associated anomalies are localized in the same organ and since "isolated" large vestibular aqueducts are frequently encountered as well, with the same clinical symptoms. The present authors support the suggestion by Emmett to consider a large vestibular aqueduct as a minor variant of a Mondini deformity (Emmett 1985).

The large vestibular aqueduct can be recognised on CT (Emmett 1985), but only MR images can demonstrate the extension of the large endolymphatic sac in the posterior fossa (Eelkema 1989, Casselman 1996). However this malformation and its extension in the posterior fossa can only be recognised in a reliable way when T2-weighted gradient-echo (e.g. 3DFT-CISS) or fast spin-echo sequences are used. Only these images are thin enough and provide enough contrast between intralabyrinthine fluid (white) and bone (black) so that all details of the malformation become visible. These images even enable visualisation of the dura mater between the endolymphatic sac and cerebrospinal fluid surrounding the cerebellum. Routine T1-weighted spin-echo images are not sensitive enough. In our experience they can depict a large endolymphatic duct/sac in only 26 % of these patients and should therefore not be used as the only sequence to detect congenital inner ear malformations (Casselman 1996).

In agreement with the literature data, the present series shows mainly bilateral involvement (80 %). So far, not much attention has been given in literature to the symmetry of the hearing loss. We found a median interaural difference of 33 dB, with thresholds of 54 dB in the better hearing ear at the time of first presentation.

The average age of presentation was 5 years, which is in line with other reports. Zalzal (1995), Levenson (1989), Arcand (1991) and Belenky (1993) mentioned an average age of resp. 4.9y, 4.5y, 3.1y and 3.5y at initial presentation. The mean age at the first ENT-visit was higher in other papers: 11y (Jackler 1989, Okumura 1995), 16y (Lacome 1989), 20y (Emmett 1985). The reported age of onset of the symptoms (hearing loss) is even lower and can be assumed to be prelingual.

The type of hearing loss is commonly being reported as sensorineural (Zalzal 1995, Okumura 1995, Belenky 1993, Levenson 1989), although some papers mention a mixed type of hearing loss in a minority of cases: 27 % (Jackler 1989), 33 % (Valvassori 1978), 38 % (Lacombe 1989). In our series, 9 patients out of 10 showed a mixed type of hearing loss. In 6 cases tympanome-

try was performed and showed a type A curve, meaning that the conductive component could not be explained by middle ear impedance problems (such as effusion). In addition, middle ear inspection in 3 cases showed normal mobility of the ossicular chain and absence of a round window reflex. The latter finding is suggestive of a cochlear mechanical problem. This was confirmed in one case where an excessive perilymph leakage was observed upon opening the basal cochlear turn for the insertion of a cochlear implant electrode. A similar finding was also reported by Schessel (1992). In addition electrocochleography was performed in one patient and showed an enlarged negative summating potential and this was also reported to be the case in 4 out of 14 patients in another study (Emmett 1985). All these findings contribute to the idea of an intrinsic cochlear conductive hearing loss. The cause of this functional anomaly is still unknown, but it seems reasonable to speculate that an enlarged vestibular aqueduct with an enlarged endolymphatic duct may cause mechanical endocochlear problems, either by volume or by pressure effects.

The hearing loss is said to be stable (though fluctuating) in most cases and progressive in some. The present data give evidence of a steady decrease of the hearing over time. Sudden attacks of hearing loss (10-20 dB) may occur, sometimes following minor head trauma. In most cases the hearing recovers to its former level. Since many patients may present just after a sudden hearing loss, their thresholds may be assumed to be at their worst and to recover in the next few days or weeks. If afterwards the hearing slowly goes down at a rate of 4 dB/y, as suggested by our data, it may take a couple of years before the thresholds will reach the same level as the level at presentation. During this period the observer will believe the hearing to remain stable. The present authors therefore believe that the idea of a stable hearing may be untrue and may be due to too short a follow-up period. They feel confirmed by the data of Jackler (1989), who reported an overall deterioration of 25 dB over a median follow-up period of 6 years in 12 patients.

In general a large vestibular aqueduct is believed to be congenital, yet not inherited. In this regard it is remarkable that in one family, both father and mother and their only child have bilateral large vestibular aqueducts with associated hearing loss. This finding may be a coincidence but it may also be some evidence of an autosomal recessive trait. The family history did not report consanguinity. No audiometric or imaging results are available from the rest of the family, but the family history does not mention other members with hearing loss. On the other hand the relatively closed community of the deaf may increase the likelihood of two affected homozygotes meeting one another. Recently a report has been published on two brothers with large vesti-

bular aqueducts (Griffith 1996) and of several families with large vestibular aqueducts in one generation (Tong 1997), which may also be suggestive for an autosomal recessive way of inheritance.

In conclusion the authors believe that the clinical picture of a large vestibular aqueduct may be refined on the basis of the present data. They advocate the clinical entity should not be named a syndrome. It is rather a congenital anomaly that may be considered a minor variant of the Mondini dysplasia and that is characterized by a prelingual hearing loss that is probably mild in the first few years of life, but that deteriorates at a rate of 4 dB/y, resulting in severe hearing loss or deafness by adulthood. Episodes of sudden hearing loss may occur and they usually recover totally or partially. The hearing loss is basically asymmetrical with an interaural difference of approximately 30 dB and it is mixed with its conductive component being due to cochlear mechanical disturbances. Some evidence exists that it may be inherited in an autosomal recessive way and that it may be associated with thyroid dysfunction.

CHAPTER III

Therapy

cochlear implantation

“Je vois une objection à tout effort pour améliorer la condition humaine : c’est que les hommes en sont peut-être indigne.”

As mentioned before, congenital hearing loss can be both conductive and sensorineural and the degree can vary from a mild unilateral loss to a profound bilateral loss. The therapeutic options for conductive hearing loss are hearing aids or reconstructive and plastic surgery, but this is not within the scope of the present dissertation. For sensorineural hearing loss the therapy exists of conventional hearing aids in case of moderate to severe losses and cochlear implants for severe to profound losses.

Conventional hearing aids are basically amplifiers of sound. The amplified sound still has to be processed by the cochlea before the cochlear nerve can transfer the signal to the brainstem and the auditory cortex. The function of the cochlea has been explained in the introduction and it should be clear that the two major functions of the cochlea are amplification and frequency-resolution. This is expressed by the tuning curve (Figure 9 of the introduction). In case of sensorineural hearing loss, the outer hair cells are virtually always affected. Only in rare cases of isolated retrocochlear types of hearing loss, this may not be the case. If the outer hair cells are affected, the tuning curve shows a higher threshold and a broader tip. The higher threshold results in an elevated threshold on pure tone audiometry. The broadened tuning curve results in a lower frequency resolving power of the cochlea, which is more difficult to assess in the clinical setting. Conventional hearing aids don't interfere with the tuning, they only amplify the sound. Figure 1 shows how this affects the tuning curve. The result for the patient is that the detection level of sound decreases but that the frequency resolution of his hearing does not really improve. The patient will therefore report to hear sound better with a hearing aid, without necessarily better understanding the words.

Cochlear implants in contrast not only amplify the sound, but they also aim at a (partial) restoration of the frequency resolution of the cochlea. This is achieved by the spatial selectivity of the stimulation at different points in the cochlea. A cochlear implant has an electrode array with multiple electrode contacts. The Nucleus® 24 device (from Cochlear Ltd, Australia) will be described to illustrate this. This implant has 22 intracochlear and 2 extracochlear electrodes. Different stimulation modes are possible, of which the monopolar mode is commonly used. This means that the current flows between the intracochlear and the extracochlear electrodes. In consequence the spatial current spread at the site of the electrode is small and results in a local stimulation of the cochlear nerve. The smaller the spatial spread, the more selective the stimulation will be. This should be reflected in the tuning curves.

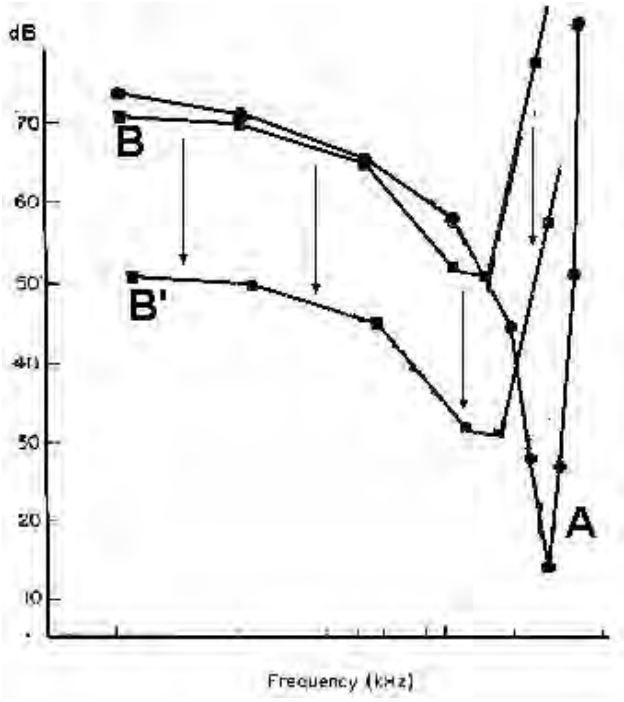

FIGURE 1. Effect of a hearing aid on the tuning curve of a cochlea. This Figure is based on Figure 9 of the introduction. The sharply tuned curve (A) is the typical curve of a normal cochlea. Curve B is of a hearing impaired cochlea with elevated thresholds and broad tuning. With a hearing aid, this curve shifts downwards but the shape does not change (B'). The effect is that the cochlea will detect sound at lower levels, but that the frequency resolving capacity of the cochlea does not improve.

Neuronal tuning curves cannot be obtained in the living human for obvious reasons, but psychoacoustic and psychoelectric tuning curves are feasible in a patient and are thought to mimic the electrophysiological tuning curves rather well. An example of psychoacoustic tuning curves in a hearing impaired adult with and without hearing aids, is given in Figure 2. The thresholds of the tuning curves correspond well with the audiometrical thresholds and it is readily seen that the tuning is not as sharp as in the normal cochlea.

With a cochlear implant, tuning curves not only show better thresholds, they also show remarkably fine tuning (Figure 3 and Figure 4). This is the major advantage of a cochlear implant over a hearing aid. Hearing aids are doing fine as long as the hearing loss is not too severe and cochlear tuning is still acceptable. In such a case, amplification alone is sufficient. If dynamic com-

pression strategies (e.g. wide dynamic range compression), noise suppression paradigms and other quality-improving features are added, modern -often digital- hearing aids may serve the moderately to severely hearing impaired patient well. But as soon as the cochlear tuning becomes deficient, amplification alone doesn't suffice any longer and cochlear implants may yield better results.

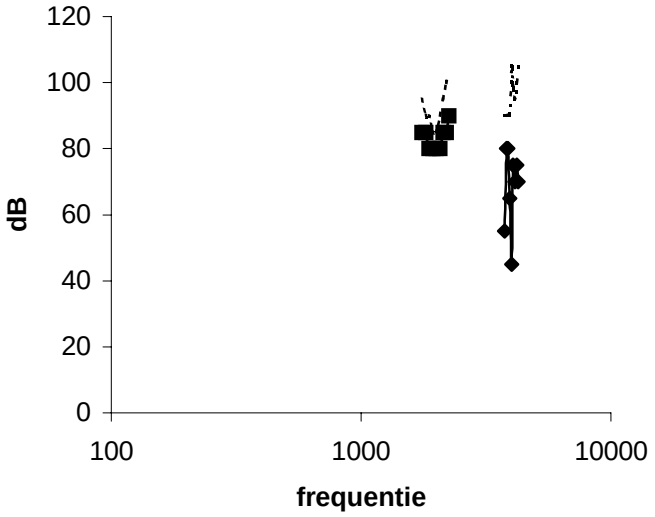

FIGURE 2. Psychoacoustic tuning curves of a patient with a hearing aid. Tuning curves with probe frequencies at 2000 and 4000 Hz and a forward masking paradigm are shown, without (dotted lines) and with hearing aids (solid lines). It can be inferred from the figure that the thresholds at 2000 Hz are approximately 80 dB HL and that they don't really improve with hearing aids; at 4000 Hz, the thresholds are approximately 90 dB HL without hearing aids and 50 dB HL with hearing aids. In addition, the shape of the tuning curve is not as sharp as in Figure 1. (Govaerts, Collaerts, et al. unpublished data).

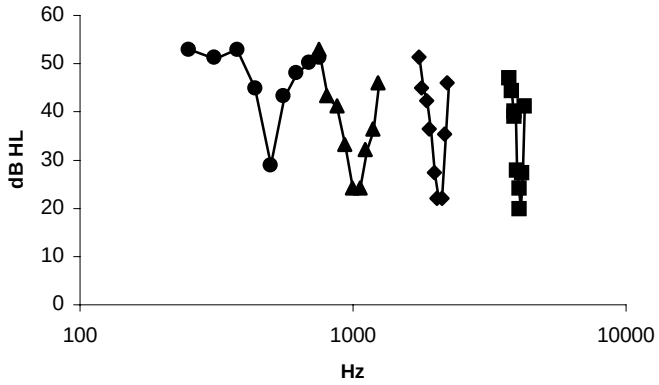

FIGURE 3. Psychoacoustic tuning curves of a patient with a Nucleus® 24 multichannel cochlear implant in monopolar stimulation mode. Tuning curves with probe frequencies at 500, 1000, 2000 and 4000 Hz and a simultaneous masking paradigm are shown. It can be inferred from the figure that the thresholds are approximately 25 dB HL and that the tuning is sharp (Govaerts, Jespers, et al. unpublished data).

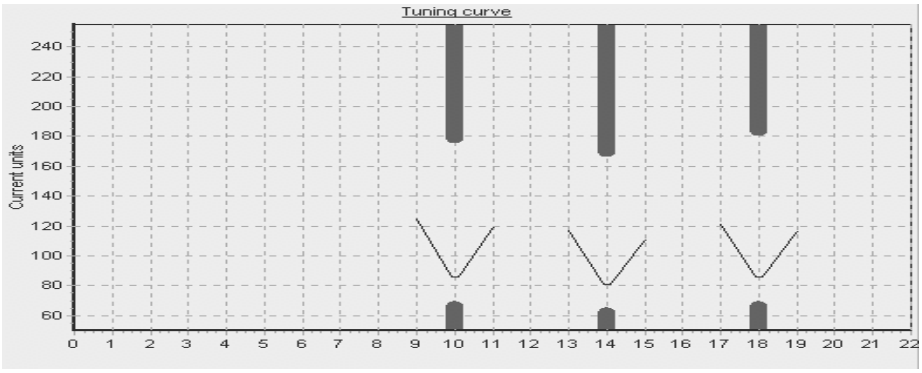

FIGURE 4. Psychoelectric tuning curves of a patient with a Nucleus® 24 multichannel cochlear implant in monopolar stimulation mode. Tuning curves with probes on electrodes 10, 14 and 18 are shown. These tuning curves are obtained with a home-made software tool, written by G De Saegher and A Symoens. The vertical bars represent the lower and upper borders of the dynamic range. A forward-masking paradigm was used with a masker on the neighbouring electrodes of the probe electrode. (Govaerts, Deman, et al. unpublished data)

The challenge for the therapist is to decide when a cochlea's resolving power has diminished sufficiently to justify a cochlear implant. It is obvious that this cannot be based on the hearing thresholds alone, be it aided or unaided. Tests that measure this frequency resolving power accurately, are indispensable for an accurate selection. Psychoacoustic tuning tests would be ideal for this purpose. Unfortunately they are not easy to obtain, they are not routinely used in the clinical setting and no normative data or standards exist. In severe hearing loss, they also have the disadvantage that stimulation intensities exceeding the hearing threshold are difficult to apply, which renders the test hardly feasible. Also, it is impossible to obtain psychoacoustic tuning curves from a child or an infant, and especially this group needs proper audiological tools for the selection in view of cochlear implant candidacy. Therefore, other tests had to be developed. It would make no sense to put all efforts in early detection and in developing cochlear implants for the very young, without having the proper tests to know which infant or child would benefit from such an implant more than from conventional hearing aids. One could argue that word intelligibility tests give an idea of the frequency resolution of the auditory system, but these tests depend on the linguistic development of the child. No such tests exist for children younger than approximately 3-4 years of age and since almost all hearing-impaired children are retarded in their language development, one even has to wait for them to be 4-6 years before these tests can be done. Therefore it was mandatory to develop other tests that would assess the frequency resolving power of the cochlea and would be feasible in the very young child. The following chapter (Govaerts, et al., 2002, in preparation) will report on the APE™, which is a phoneme-based evaluation tool that meets these criteria. It has taken several years to develop the APE™ and to date it is routinely used in the University ENT Dept of the St.-Augustinus Hospital and it has allowed a significant age shift in the cochlear implant indication (Figure 5). The first children below 6 years of age were implanted in 1994, below 2 years in 1996 and below 1 year in 2000. This steady shift in the age of implantation has resulted in a significant improvement in outcome. The outcomes are reported in one of the next chapters (Govaerts, et al., 2002, in press). Briefly, in children with congenital severe to profound hearing loss, implantation above the age of 4 years gives a moderate auditory performance (even in the long run) with no more than 33 % of the children being able to integrate in the mainstream educational system. Implantation between 2 and 4 years of age gives good auditory performance, be it with a significant delay of 2-3 years, and a mainstream integration in two out of three. Implantation at 12-18 months gives immediate high auditory performance with an integration rate of 90 % already in the first year of the kindergarten.

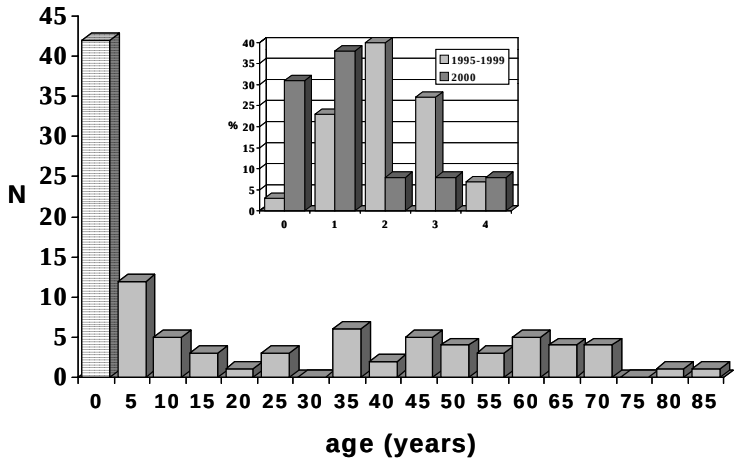

FIGURE 5. Age distribution of the cochlear implantees at the University ENT Department of the St.-Augustinus Hospital. For the period 1995-2000. The small Figure zooms in on the youngest group (less than 5 years) and it shows that the age distribution in this group has clearly shifted to the younger than 2-year-old children in 2000. (Govaerts, et al, unpublished data).

The growing confidence in the selection tools, together with the ever-improving performance of the implants, has made the number of implants performed at the University ENT Department increase exponentially over the years (Figure 6).

In the beginning of the cochlear implant programme, cochlear anomalies were considered a contra-indication for implantation. After a first and successful implantation of a 12-year-old child with Mondini dysplasia of her inner ears in 1995, this restriction was abandoned. Improvements in medical imaging (CT scan and MRI) made it possible to judge cochlear anomalies in a more detailed and accurate way. Even aplasia or hypoplasia of the cochleovestibular nerve is not a formal contraindication for cochlear implants, as is explained in one of the following chapters (Govaerts, et al. 2002, submitted). As said before, cochlear implants are electronic devices to restore hearing in profound cochlear hearing loss. The development of the Antwerp LAURA™ multichannel implant and the surgical procedure of the implantation have been exhaustively described by Offeciers in his PhD-dissertation in 1991. At that moment the first nine patients had been implanted. The basic technology has not significantly changed over the years. A cochlear implant still consists of an external (Figure 7) and an internal part (Figure 8 and Figure 9), but both have been substantially reduced in size.

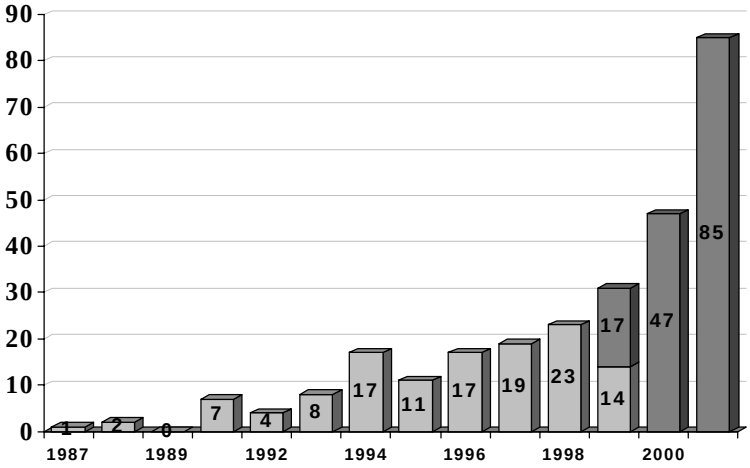

FIGURE 6. Annual number of cochlear implants at the University ENT Department of the St.-Augustinus Hospital. Light grey: LAURA™ implants; dark grey: Nucleus® 24 implants

FIGURE 7. External part (ESPrit™ 3G) of the Nucleus® 24 (Cochlear Ltd, Sydney, Australia) multichannel cochlear implant. The microphone and speech processor are in the behind-the-ear box and the external induction coil is fixed to the head with a magnet and sends the information to the internal coil.

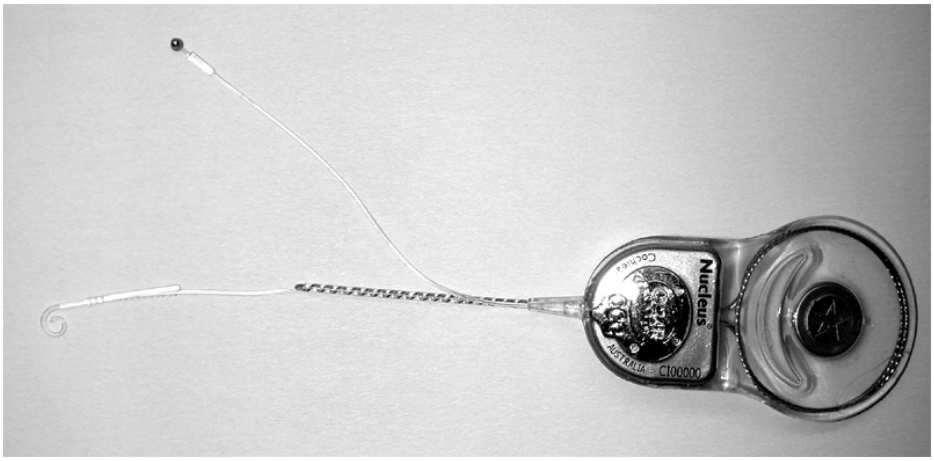

FIGURE 8. Internal part of the Nucleus® 24 Contour™ multichannel cochlear implant. The internal coil receives the information from the external coil. The titanium box contains the internal chip with the current sources. The curled electrode array is inserted in the cochlea and contains 22 electrodes and electrode contacts

The internal part consists of a coil and a titanium box that contains the internal chip and the current sources. These are placed in the mastoid of the temporal bone through a retroauricular incision. The electrode array leaves the titanium box and is inserted in the cochlea through a posterior tympanotomy and a cochleostomy that is drilled in the basal turn of the cochlea.

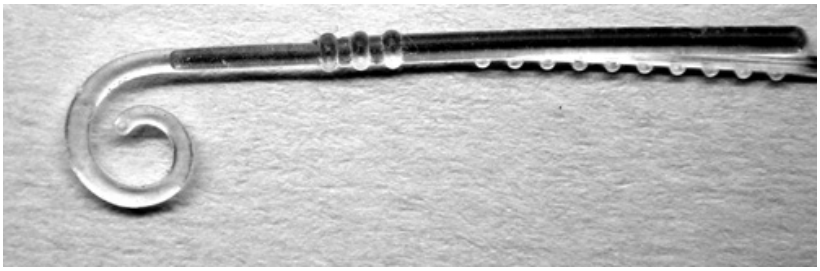

FIGURE 9. detailed view on the intracochlear electrode array of the Nucleus® 24 Contour™ multichannel cochlear implant

The electrode array is gently pushed in the scala tympani of the cochlea (Figure 10), and the cochleostomy is sealed with bone wax. Inside the cochlea, the electrical current will flow from one electrode to another. This very local electrical field will depolarise the afferent neurons (dendrites if still present, otherwise ganglion cells or axons), and this will give rise to action potentials

on the afferent nerves to the brainstem and further to the higher central auditory pathways.

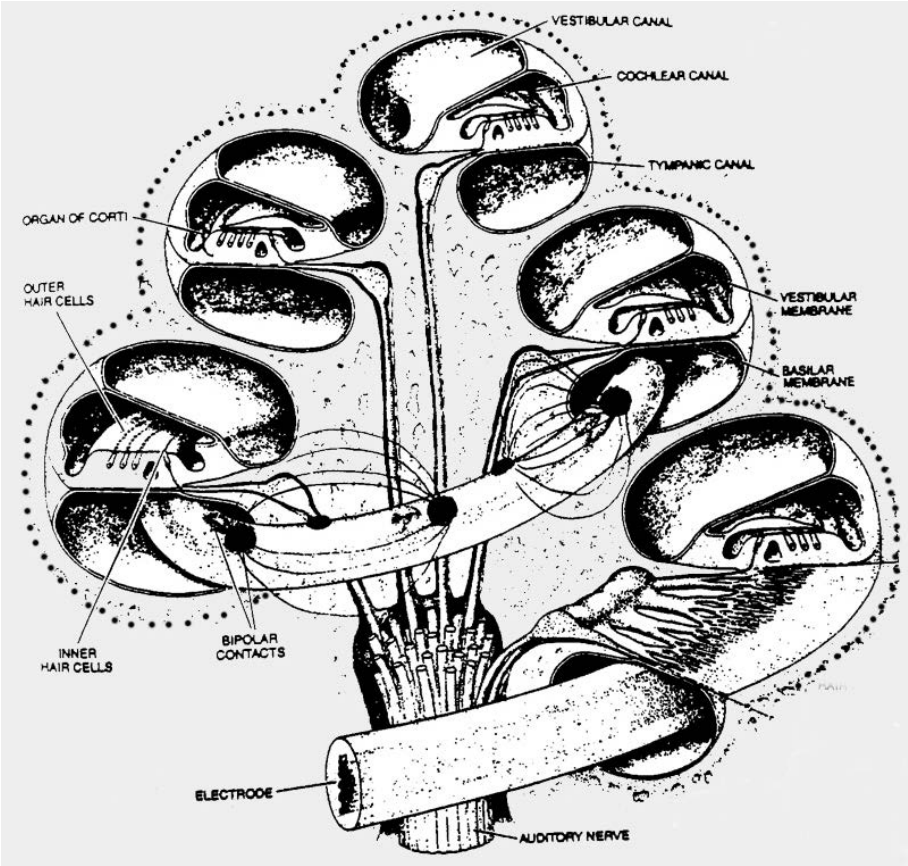

FIGURE 10. Insertion of the electrode array in the scala tympani of the cochlea. (courtesy FE Offeciers, 1991)

One of the technical problems of cochlear implants is the electrical impedance at the interface between the electrode and the surrounding cochlear tissue. This impedance depends on the static electrical impedances of the elements involved, but also on dynamic electrochemical and histological processes at the level of this interface. High impedances lead to high voltages generated across the electrode-electrolyte interface, which may cause the current sources to saturate at low current levels. Also, high voltages and a low charge storage capacity of the electrode contacts increase the risk of irreversible electrochemical reactions at the interface, altering the composition of the tissue fluid

and inducing changes in pH and the emergence of toxic reaction products. Finally, high impedances increase the energy consumption of the implant, which is to be avoided especially with future developments such as totally implantable devices in mind. The static impedance of the interface depends mainly on the electrode surface. This surface is very small and future developments aim at even reducing it in an attempt to increase the total number of electrodes and the spatial selectivity. The only way to increase the actual surface of the electrode without changing its diameter, is to introduce irregularities in the electrode surface. Govaerts and colleagues have tried out several sputtering and electrochemical procedures to achieve this with the LAURA™ spherical electrodes.

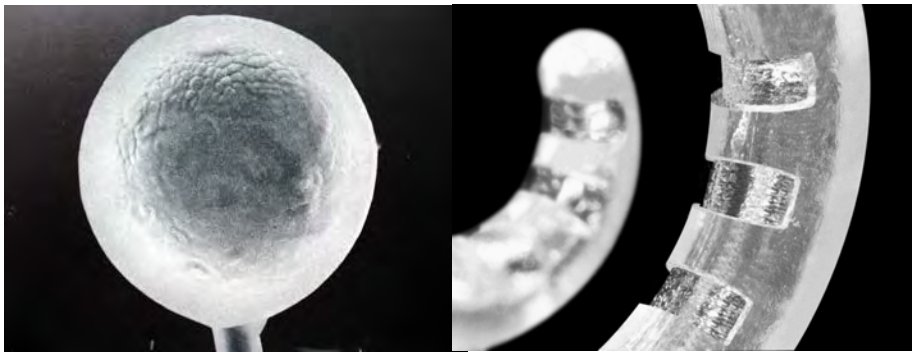

FIGURE 11. Details of the intracochlear electrode contacts. Left: scanning electron micrograph of the LAURA™ 180 µm diameter ball contact (Govaerts, unpublished data); Right: light micrograph of the Nucleus® Contour™ half-ring contacts (courtesy Cochlear Ltd).

The application of a non-catalytic electrochemical coating of the electrode contacts with iridium oxides has proven to reduce the impedances significantly (Peeters 1998). Iridium oxides form a multilayer deposit that allows for reversible valence transitions and proton and hydroxyl ions transfers between the layers, increasing immensely the charge storage capacity of the interface. Electrochemically deposited iridium coating is resistant to mechanical friction, stable in time and stable under biphasic electrical stimulation. Microscopically it is an inhomogeneous deposit forming islands of 1-3 µm, separated with grooves 2-4 µm deep and 1-2 µm wide. The redox potential of the electrode decreases with 370-410 mV. Chemical micro-analysis gives evidence that the exact nature of the coating is Ir_2O_3 (iridium sesquioxide). The effect of the coating on the impedances after implantation is shown in Figure 12.

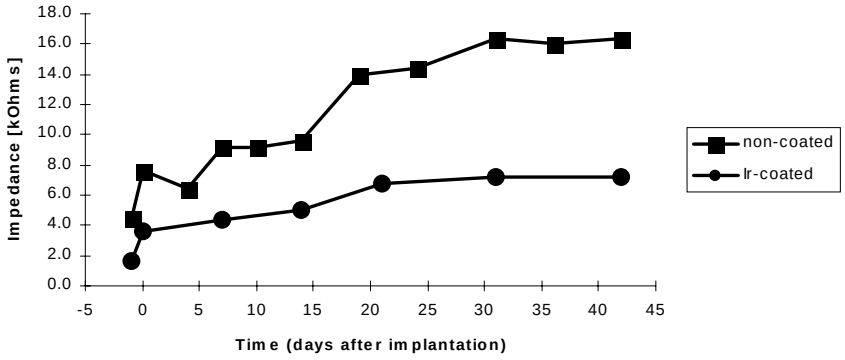

FIGURE 12. Median impedance course of coated and non-coated subcutaneous electrodes in function of days after implantation. Note that day '0' = day of implantation, and day '-1' = measurements done in saline, before implantation. (from Peeters 1998)

Based on these and other findings, the producer of the LAURA™ cochlear implant (Philips Hearing Implants, Antwerp, Belgium), started applying this coating systematically to all LAURA™ electrodes. Another way of interfering with the impedance is related to the dynamic component of the fibrous tissue layer that surrounds the electrodes after implantation. This is the result of the inflammatory process following the (micro-)trauma of the electrode insertion. Steroids are known to impede this reactive process in part and they, together with other products with potentially similar effect, have been tried out in the lab. It was shown that steroids have a powerful immediate and long-term effect on the impedances (Figure 13).

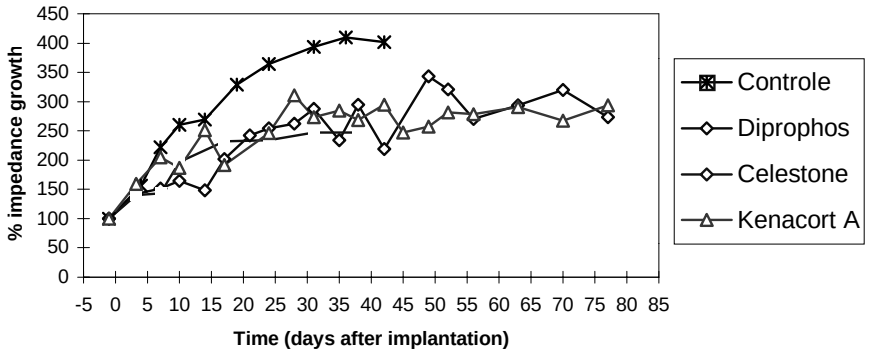

FIGURE 13. Impedance course of non-coated subcutaneous electrodes treated with Kenacort A (40mg/ml), Celestone Chronodose (7mg/ml), Diprophos (7mg/ml), and saline (control) in function of days after implantation. All measurements were first converted to percentages referring to the starting value (=100 %) of each electrode (at day -1), as measured in saline before implantation. The medians, expressed as %, are shown in this graph. Note that day '0' = day of implantation, and day '-1' = measurements done in saline, before implantation. (from Peeters 1998)

Based on these results, steroids were introduced in the human cochlear implant surgery. They are now routinely used at the University ENT-department of the St.-Augustinus Hospital and the paper by De Ceulaer (2002, in preparation) resumes the positive results of a follow-up study during one year after implantation.

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22/9/2001	Panel on cochlear implant candidacy. 1st European Consensus Conference on Cochlear Implants. Padua, Italy
19-23/1/02	Congress Committee "23rd Annual Meeting of the Politzer Society", Courchevel, France.
4-6/9/2002	Organising committee 7th International Cochlear Implant Conference, Manchester, UK.

Auditory phoneme evaluation: a new test with phonemes to assess detection, discrimination and identification in hearing impairment

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Paper in preparation

ABSTRACT

This paper describes a set of new supraliminal tests for the auditory evaluation of the hearing-impaired child, which is available as a software package (APE™). It uses isolated phonemes as test material for a discrimination, identification, and detection test and is specifically suited to test preverbal children. All tests allow strict analytical interpretation. The test material and procedures are described. The discrimination test has been normalized in 11-month-old normally hearing infants and the identification test in 33-month-old normally hearing children. Their use in clinical audiology is illustrated. The authors conclude that supraliminal tests are feasible in the preverbal child allowing analytical evaluation of the auditory capacities. These tests are complementary to the detection tests that are routinely used and add significantly to the evaluation of the hearing in preverbal children. The authors recommend the phoneme discrimination test for selection of cochlear implant candidates and for the evaluation and fitting of cochlear implants.

Key words: hearing loss, hearing aid, cochlear implant, supraliminal audiological test, phoneme discrimination, phoneme identification

INTRODUCTION

Cochlear implants are computerized prostheses that partially replace the function of the cochlea. They transduce sound energy into electrical signals to the neural cells in such a way that the information is meaningful at the level of the auditory cortex (Balkany 1996). Since their introduction two major evolutions have necessitated the development of new analytical behavioural test procedures. First the lower age limit for implantation is shifting progressively towards a younger age, and second, new devices have ever-increasing facilities for programming and fine-tuning (Balkany 1996, Lenarz 1998). Fitting these devices in young children as well as measuring their auditory capacities is difficult and audiological tests are needed that allow analytical evaluation at supraliminal levels.

One of the challenges in handling the pediatric hearing-impaired population is the assessment of hearing. Pure tone audiometry, otoacoustic emissions, automated brainstem audiometry etc. only assess hearing at its detection level. This may be sufficient to know whether a hearing problem exists or not, but it hardly reflects the capacity of the hearing impaired child to discriminate or identify language. So far, little attention has been given to the fact that hearing impairment means both an increase in detection threshold and a loss of frequency discrimination. Consequently, improving the detection threshold to "within the speech zone" (e.g. 40 dB) does not imply that the aided subject also discriminates the phonemes presented at or above this sound level. Although this limitation has always existed, cochlear implants have forced us to look for supraliminal evaluation techniques. These are needed both in the selection of cochlear implant candidates and the evaluation of cochlear implantees. Supraliminal features of hearing are discrimination and identification of sounds. Tests for discrimination or identification of words and sentences exist, but especially in the preverbal child the results are strongly biased by their individually variable language impairment or cognitive skills. A "preverbal" child is a child with no or very limited functional speech, both comprehensive and productive. Normal hearing children use to become verbal by the age of 1 year (Barrett 1994, Gillis 2000). In hearing impaired children this age is very variable. It depends on the level of hearing loss and the type and intensity of stimulation. Their preverbal stage may typically last till the age of 4-5 years. Tests for this "preverbal" population are difficult and should be conceived in such a way that the dependence on the child's linguistic and cognitive skills is minimal and that no reading and speech skills are required. Furthermore, the distinctive features should be very clear and unambiguous so as to leave no doubt which features are perceived by the child and which are not

(Boothroyd 1997). At least some of the tests should provide the fitter with phoneme-based analytical information to guide the fine-tuning of the cochlear implant.

A common way to investigate auditory performance is the identification test. In a previous study we found that normal hearing Flemish speaking "verbal" children (i.e. 2 years and older) were able to perform 2- to 4-choice words and sentences identification tests (Daemers K, et al. Oral communication 3rd European Conference on Audiology in Prague 1997). However, hearing-impaired children of that same age group can still be preverbal and it has been shown that their scores on these tests vary significantly depending on the degree of hearing loss and on possible additional learning problems. A substantial percentage of these children was even unable to perform these identification tests (Hodgson 1994, De Sloovere M, et al. Oral communication 4th European Symposium on Paediatric Cochlear Implantation in 's-Hertogenbosch 1998). Identification tasks presuppose knowledge of both stimulus and distracting words as well as the complex abilities to remember the stimulus, to match it with the auditory image of the distracting words, to take a decision etc (Dillon 1995, Boothroyd 1995). This degree of linguistic knowledge and higher functions is not always present in the hearing impaired child. In consequence these children tend to score too low on this type of tests when compared to their real auditory capacities. Thus most of the existing identification tests are only fit for verbal children. In normal hearing children they are feasible from the age of 2-3 years onwards but in deaf children or children with additional problems in language development they cannot be done at this young age.

Another and possibly more correct way to test preverbal children with minimal bias related to the level of linguistic development is testing discrimination instead of identification. No knowledge of the stimulus is required. The child has to discriminate between two or more successive stimuli and has to show a behavioural response (Dillon 1995, Bochner 1992). A disadvantage of conventional discrimination tests may be the lack of behavioural response to small perceptive differences and it has been reported that these tests are not feasible below the age of three years or even later in hearing impaired children (Daemers K, et al. Oral communication 3rd European Conference on Audiology in Prague 1997; De Sloovere M, et al. Oral communication 4th European Symposium on Paediatric Cochlear Implantation in 's-Hertogenbosch 1998). Furthermore, these tests are boring and cognitively demanding (Boothroyd 1997). On the other hand, when conventional discrimination tests were modified for the younger children to visually reinforced discrimination audiometry, some proved to be feasible (Eilers 1977, Moore

1995, Dawson 1998). An additional advantage of discrimination tests as part of a test battery is that they allow for the assessment of the cause of systematic confusions as they may occur in identification tests. Indeed, if a child fails to identify a given stimulus while it can be shown that the discrimination of the same stimulus is present, it can be concluded that the identification problem is not due to auditory perceptive deficiencies (Dillon 1995). Identification in such a case cannot be improved by changing the fitting or programming parameters of the implant. In contrast, an identification problem of a given stimulus that can be shown not to be discriminated properly, is obviously due to bad discrimination and thus to an auditory perceptive deficiency. In the latter case better identification may be achieved by optimising the fitting or programming parameters of the implant.

This paper describes the Auditory Phoneme Evaluation (APE™, ©Melakos nv, Antwerp, Belgium), which is an audiological evaluation tool that uses strictly defined phonemes as stimulus material for detection, discrimination and identification tests. The APE™ was designed as a lexicon-independent test that would yield supraliminal information on the auditory function with as little cognitive bias as possible. The main purpose of the test was to evaluate the discriminatory power of the cochlea of very young, preverbal hearing-impaired children with hearing aids. It was hoped that the results of such a test could be used in the selection and the evaluation of cochlear-implant candidates. Hence, the reasons to choose phonemes were the following: (1) phonemes can be presented at supraliminal intensities; (2) phonemes are basically language-independent (although not entirely, as discussed below); (3) phonemes can be constructed with exact duration and intensity, thus limiting the potential cues and (4) they can be used for discrimination, thus eliminating the cognitive abilities that are required for e.g. speech audiometry; (5) phonemes are more attractive to infants and children than either pure tones or synthetic material; (6) the frequency spectrum of phonemes can be measured and this can be used for analytical evaluation of the test results. The construction of the test material, the test procedure, normative data and the clinical applications are described in what follows.

APE™ IN GENERAL

The APE™ (Auditory Phoneme Evaluation, ©Melakos nv, Antwerp, Belgium) is an audiological evaluation tool that was constructed at the University ENT-Department of the St.-Augustinus Hospital in Antwerp. The stimuli are phonemes. In a first stage the phonemes were recorded on CD and the response and tester forms were on paper. In a second stage, the whole test-

procedure was written in a software-package, which was released in August 2001 (www.melakos.net). All phonemes were recorded by one female speaker of the Flemish dialect. The selection of the phonemes will be discussed for each test (detection, discrimination and identification) separately.

Loudness balancing

All phonemes were digitally trimmed to the same length of 625 msec, rms-balanced and recorded as *.wav-files on CD (16 bit stereo 48k sample rate). Then, each phoneme was loudness-balanced with reference to the /a/ in 6 normally hearing adults. For this purpose, each phoneme was presented in free field at random intensities (between an upper and a lower fence, see below) and alternated with the /a/ which was presented at 70 dBSPL. The test person was asked whether the test phoneme sounded louder, softer or equally loud as the /a/. If a given intensity was scored “louder than /a/” for three consecutive presentations, this intensity was considered to be too loud and defined the upper fence for the time being. The same was true for intensities that were scored “softer than /a/” for three consecutive presentations and that defined the temporary lower fence. The step size decreased from 3 dB in the beginning to 0.8 dB at the end of the test. In this way, the intensity range between upper and lower fence was narrowed until all remaining intensities resulted in ambiguous comparisons with the /a/. This was typically the case for three or four remaining intensities of the test phoneme. Then the test phoneme was presented seven times at each of these remaining intensities, again in random order and alternating with the same /a/ at 70 dB SPL. For each presentation, the score was recorded and at the end, the intensity with the most frequent score “sounds equally loud as /a/” was saved as the loudness-balanced intensity of that particular phoneme. The intensity of all phonemes was modified according to this algorithm. Thus all phonemes were loudness balanced with reference to /a/ at 70 dB SPL and with a precision of 0.8 dB. Finally, the /a/ was loudness-balanced according to the same algorithm with reference to a 1kHz narrow-band noise at 70 dB HL and all phonemes were adjusted accordingly. In consequence the intensity of the phonemes can be expressed in “dB HL (re 1kHz narrow band noise)”.

Intensity Roving

The precision of this loudness balancing was 0.8 dB since this was the minimum step-size used in the test procedure. In addition the temporal profile of the phonemes may still contain intensity cues that would help discrimination

between two phonemes. In order to eliminate these possible intensity-cues, the APE™ is designed in such a way that a random gain is added to the intensity of all phonemes. This gain varies randomly between an upper and a lower limit, which can be defined by the tester. Limits of +3dB and -3dB respectively. are recommended and set as default values. This introduces a random variability in the intensity of the phonemes that overrules any possible intensity differences between two phonemes. In consequence the test-person is "deconditioned" to take notice of any possible intensity cues.

PHONEME DISCRIMINATION TEST

The phoneme discrimination test is an oddity test in which two phonemes are presented and the infant is conditioned to react to the odd phoneme. The details of the procedure are described below.

The phonemes for the APE™ were selected to be "linguistically representative". This means that for the vowels the 3 cardinal vowels /a/, /I/ and /u/ were selected as well as /E/, /y/ and /o/ which are situated in between the three cardinal vowels in the vowel triangle, and the centrally positioned /œ/ (Peterson 1952). For the consonants, phonemes were selected that differ only in one feature (like voicing (/z/-/s/), articulation place (/v/-/z/ and /s/-/ʃ/)) or in several features (like articulation place and mode and nasality (/m/-/z/), articulation place and mode and nasality and voicing (/m/-/f/ and /m/-/r/)). This selection also includes the Ling-sounds (/a/-/I/-/u/-/s/-/ʃ/). From the many combinations that can be possibly constructed, a "basic set" of 22 phoneme pairs was selected (Table 1) in such a way that most contrasts are represented.

TABLE 1. "basic set" of phoneme pairs that were tested for discrimination

a-r	u-o	œ -E	m-z
u-ʃ	œ -a	œ -I	m-r
u-I	œ -u	y-I	s-ʃ
I-a	œ -o	u-y	v-z
u-a	E-a	z-s	
o-a	I-E	m-f	

The first phoneme of a pair is presented as the background phoneme and the second as the odd phoneme. The black fields represent the phoneme pairs of the "minimal set", see text.

Test procedure

Since the phoneme discrimination test can be used for both adults and children, the test procedure is given in general terms. It is basically an oddity procedure (Figure 1). For each pair of phonemes (Table 1), the first serves as background and the second as odd phoneme. All test sessions begin with a training or conditioning phase in which the test persons are trained (adults) or conditioned (children) to react to the odd phoneme. The training or conditioning procedure is the same as the actual test procedure; only the odd phoneme is much longer (between 1941 and 3261 msec). The background phoneme is repeated at regular intervals (typically 850 msec, although this can be varied from 500 to 3000 msec). Every now and then, the background phoneme is replaced by the odd phoneme and if the test person responds to this in a consistent way, it is concluded that the contrast between the background and the odd phoneme is well discriminated.

All 14 phonemes can be used as background phoneme and 11 as odd phoneme (Figure 2).

Conditioning track

O O O O O O XXXX O O…
O O O O XXXX O O O O…
O O O O O XXXX O O O…
O O O O XXXX O O O O….

Test Track

O O O O O X O O O…
O O O O X O O O O…
O O O O O O X O O…
O O O O X O O O O….
O O O O O O X O O…
O O O O O X O O O…
O O O O X O O O O…

FIGURE 1. Example of the conditioning and test tracks of the APE™ to test the discrimination of a stimulus phoneme in a background of a repeated other phoneme. Each line represents a track consisting of a series of the background phonemes(O) which is replaced by the stimulus phoneme (X) at random positions. The duration of the background phonemes and of the stimulus phonemes X is 625 msec. The duration of the stimulus phonemes XXXX varies from 1941 to 3261 msec.

Normative data

Since the main purpose of the phoneme discrimination test is to have a supra-liminal test that can be used in infants, the phoneme discrimination test was carried out in 10 normally hearing infants aged 11 months (average 10.6 months, range 9.2-12.3 months). Al children had hearing thresholds of 20 dB or better at 500, 1000 and 2000 Hz with presence of transient evoked oto-acoustic emissions. All children were evaluated for the 22 phoneme pairs (Figure 1). On average this took 3 sessions (range 2-5) spread over 5 weeks (range 1-12 weeks). Each phoneme pair took approximately 6 minutes to be assessed. All phonemes were presented in free field at an intensity of 70 dB HL (re 1 kHz narrow band noise) with the loudspeaker positioned at 1 m from the child either at the left or the right side.

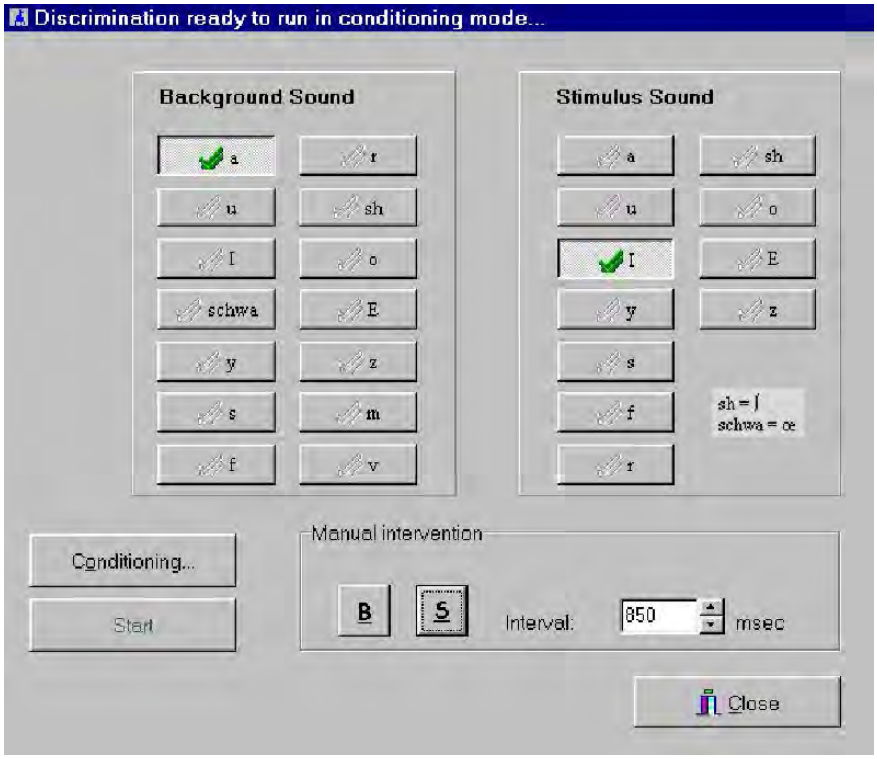

FIGURE 2. Test screen of the APE™ phoneme discrimination test. The fourteen background phonemes and eleven odd phonemes are represented by buttons. The tester selects one of each (in this case /a/ and /I/ respectively), switches to conditioning or test mode (in this case conditioning mode) and defines the interval between the phonemes (in this case 850 msec).

The children were tested by two test audiologists (tester and distracter) in a sound proof testing booth. The infant was sitting in a seat with his/her caregiver (mostly the mother) sitting behind but not touching him/her. The primary infant's reaction that was looked for was a head turn, although the audiologists were allowed to judge other reactions also as orientation reflexes. Only if both audiologists agreed in their judgement, a positive reaction was scored. Visual reinforcement was used to reward the infant both during the conditioning and the test procedure (Eilers 1977). The odd phoneme was presented eight times and the reaction was scored as positive (orientation reflex) or negative (no orientation response). For each phoneme pair and for each infant, the number of orientation reflexes (on eight presentations) was calculated as well as the maximal number of consecutive orientation reflexes. For example, a child that showed the following reactions to the eight presentations of the odd phoneme

no - no - reflex - no - reflex - reflex - no - reflex

would score 4 reflexes on eight and a maximal of 2 consecutive reflexes. Several decision criteria were evaluated in terms of how many of these ten normally hearing children would pass the discrimination test when a given decision criterion would be used. The decision criteria and the results are shown in Figure 2.

TABLE 2 decision criteria and results of the discrimination test.

Phoneme pairs (*)	1/8	2/8	3/8	2 consecutive	3 consecutive
a-r	10	10	10	10	10
u-ʃ	10	10	10	10	10
u-I	10	10	9	10	8
I-a	10	10	10	10	8
u-a	10	10	10	10	9
o-a	10	10	9	9	8
u-o	10	10	9	9	8
œ -a	10	10	8	9	7
œ -u	9	8	6	8	3
œ -o	10	10	9	9	7
E-a	10	10	9	10	5
I-E	10	10	10	10	8
œ -E	10	10	9	9	9
œ -I	10	9	9	7	4
y-I	9	8	7	6	4
u-y	9	9	9	9	7
z-s	9	9	7	7	6
m-f	10	10	10	10	8
m-z	10	10	10	10	10
m-r	10	10	10	10	8
s-ʃ	10	10	10	10	9
v-z	10	9	9	9	9

(*) see Figure 1. Each field shows the number of infants (out of 10) that would pass the discrimination test for a given phoneme pair if the decision criterion would be used that is defined at the top of each column. The following decision criteria were evaluated: 1/8, 2/8 and 3/8: one, two or three correct reflexes on eight presentations; 2 and 3 consecutive: a maximal number of two or three consecutive reflexes in the series of eight. For instance, for /y/-/I/ discrimination, 9 children showed at least one correct reflex, 8 children at least two and seven at least three, and 6 had two consecutive reflexes and 4 had three consecutive reflexes in the series of eight presentations. The black fields represent the phoneme pairs of the "minimal set", see text.

Based on these results, the phoneme pairs can be ordered with respect to the ease or the difficulty with which infants react to the difference. This is shown in Figure 3. In consequence, if the discrimination of a phoneme pair is tested, Figure 3 gives the decision criteria that would yield a "pass" in normally hearing children.

TABLE 3. Hierarchy of the phoneme pairs in order of ease of discrimination

Decision criterion that is met by all children	Phoneme pair (*)
3 consecutives	a-r
	u-ʃ
	m-z
2 consecutives and 3 in total	u-a
	s-ʃ
	I-a
	I-E
	m-f
	m-r
2 consecutives	u-I
	E-a
2 in total	œ -E
	o-a
	u-o
	œ -o
	œ -a
1 response	v-z
	œ -I
?	u-y
	z-s
	y-I
	œ -u

(*) see Figure 1. The upper phoneme pairs are most easily discriminated by the infant. For instance, in all infants, three consecutive orientation reflexes can be elicited in a series of eight presentations of the odd phoneme /r/ against a background of /a/. The question mark (?) means that no decision criterion was able to make all infants pass the discrimination test of the given phoneme pairs. The black fields represent the phoneme pairs of the "minimal set", see text.

In conclusion, the normative data show that it is feasible to use the phoneme discrimination test of the APE™ in infants as young as 11 months. In daily practice, even younger infants (6-7 months) have been tested with success. Some phoneme pairs appear to be "easier" than other pairs to elicit good orientation reflexes from the infant. Therefore different "pass criteria" may be used for different phoneme pairs (Figure 3). However, testing infants of such a young age is seldom a matter of solid test circumstances and robust statistical interpretation, but rather of good judgement by experienced testers. Thus the pass criteria of Figure 3 should not be used too strictly but should provide some guidance to the testers. In addition, testing these young infants requires a lot of time, which may not always be available. Therefore a "minimal set" of phoneme pairs is suggested. This is an arbitrary selection of seven phoneme pairs (see Tables 2 an 3) in which the cardinal vowels are represented, as well as contrasts in voicing (/z/-/s/), place of articulation (/s/-/ʃ/ and /v/-/z/) or combinations (/m/-/z/). As can be seen in Figure 3, the seven phoneme pairs of the minimal set are also well distributed over the hierarchical scale. The minimal set can often be assessed in a single test session for even the very young infants.

Use in clinical audiology

The discrimination test of the APE™ is routinely used to evaluate the cochlear function in hearing impaired children and adults. As a measure of the frequency resolving capacity of the aided cochlea (with hearing aids), it has become an essential tool in the selection of cochlear implant candidates. If the patient fails to discriminate several phoneme pairs, it is anticipated that his/her discrimination will be better with an implant. If all 22 phoneme pairs of the basic set are assessed, discrimination of less than 19 pairs is an indication to consider cochlear implantation. If only the minimal set of 7 phonemes is assessed, discrimination of less than 6 is an indication to consider cochlear implantation. The phoneme pairs that are often the first fall-outs in hearing aid wearers, are /z/-/s/, /m/-/z/, /u/-/I/ and /v/-/z/. Obviously the phoneme discrimination is not the only selection criterion for cochlear implant and the results should be combined with other audiological and other results before a final decision is made.

The discrimination test of the APE™ is also routinely used for the evaluation of cochlear implants. This information adds to other outcome measures and is essential as feedback for the selection of new candidates. Figure 3 shows a typical cochlear implant patient file. Figure 4 shows the results of an unpublished analysis of the APE™-results (basic set) of 45 children aged 4 to 10

years. Twenty-two children were hearing-aid wearers for at least one year and were divided into three groups defined by the unaided pure tone average (PTA) of their better ear. The first group (A) had a PTA between 60 and 79 dB HL (N=9), the second group (B) had a PTA between 80 and 99 dB HL (N=7) and the third group (C) had a PTA of 100 dB HL or more (N=6). Twenty-three children were cochlear implant wearers for at least one year. The Figure shows the number of phoneme pairs (on a total of 22) that were NOT discriminated by these children. It can be seen that the results of the cochlear implant group are comparable to the hearing-aid group A. They are slightly better than hearing-aid group B and significantly better than hearing aid group C. No cochlear implantee failed on more than 6 phoneme pairs and 75 % of them even made no more than 3 errors.

In addition the APE™ is also routinely used to adjust the fitting of the cochlear implant. As mentioned before, an implant has multiple channels (22 in case of the Nucleus® 24 device), each representing a specific frequency band. Each channel needs to be fitted to the psychophysical features of the nerve and the auditory pathways. This is done manually by an audiologist. The results of the APE™ can help the audiologist in finding out which channels need readjustment. For this purpose, a frequency analysis can be made of the phoneme pairs that are not or not well discriminated by the patient (Figure 5). The spectral difference between the two phonemes can be linked to the frequency table of the implant and the channels where the largest spectral difference is situated, are the ones that need to be readjusted.

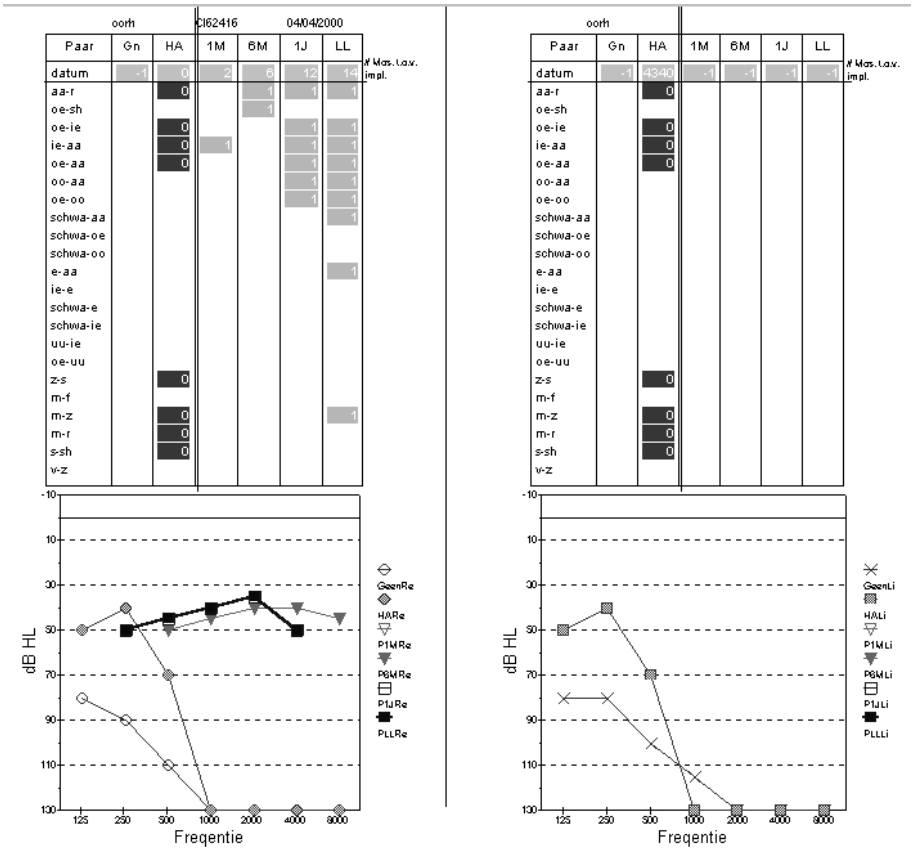

FIGURE 3. Typical cochlear implant patient file as routinely used in the University ENT-Department of the St.-Augustinus Hospital. The file represents the right ear (left pane) and the left ear (right pane) of a baby with congenital deafness due to connexine-26 mutations and who was implanted at the age of 14 months. The upper Figure lists the results on the discrimination test of the APE™. The thick vertical line in the middle of the Figure represents the moment of implantation. The column to the left of this line (marked HA) contains the APE™ results with hearing aids prior to the implantation. The fields are red (black on B&W with an 0 inside) in case no discrimination was found on the given phoneme pair and green (grey on B&W with a 1 inside) in case discrimination was found. The columns to the right of the vertical line are the results at different moments after implantation, as marked on top of the column. The lower Figure gives the audiometrical results without hearing aids ("GeenRe" and "GeenLi" for right and left respectively), with hearing aids ("HARe" and HALi" for right and left respectively) and with the implant at several moments, namely 1month ("P1MRe" and "P1MLi"), 6 months ("P6MRe" and "P6MLi"), 1 year ("P1JRe" and "P1JLi") after the implantation and at the latest moment available ("PLLRe" and "PLLLi").

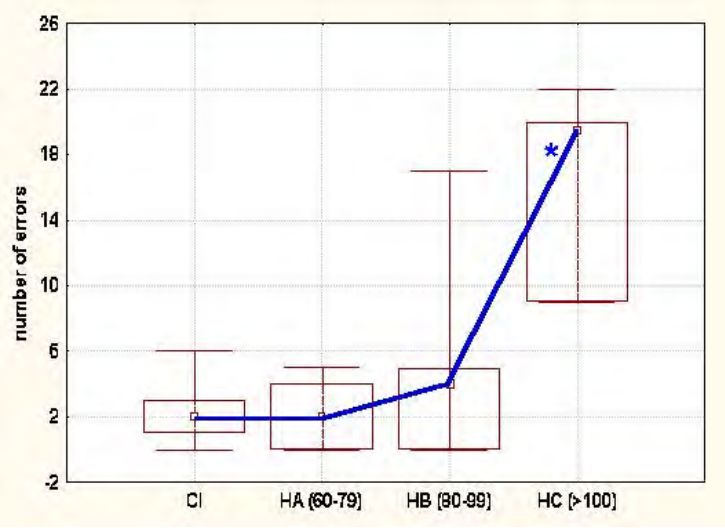

FIGURE 4. Number of phoneme pairs that were NOT discriminated by four groups of children aged 4-10 years. CI: cochlear implant wearers; HA, HB and HC: hearing aid wearers group A, B and C respectively (see text). The results are given in box and whisker plots (Govaerts 1998) showing the minimum to maximum values (bars), 25th to 75th percentiles (large rectangles) and median values (central dots). (Daemers & Govaerts, unpublished data)

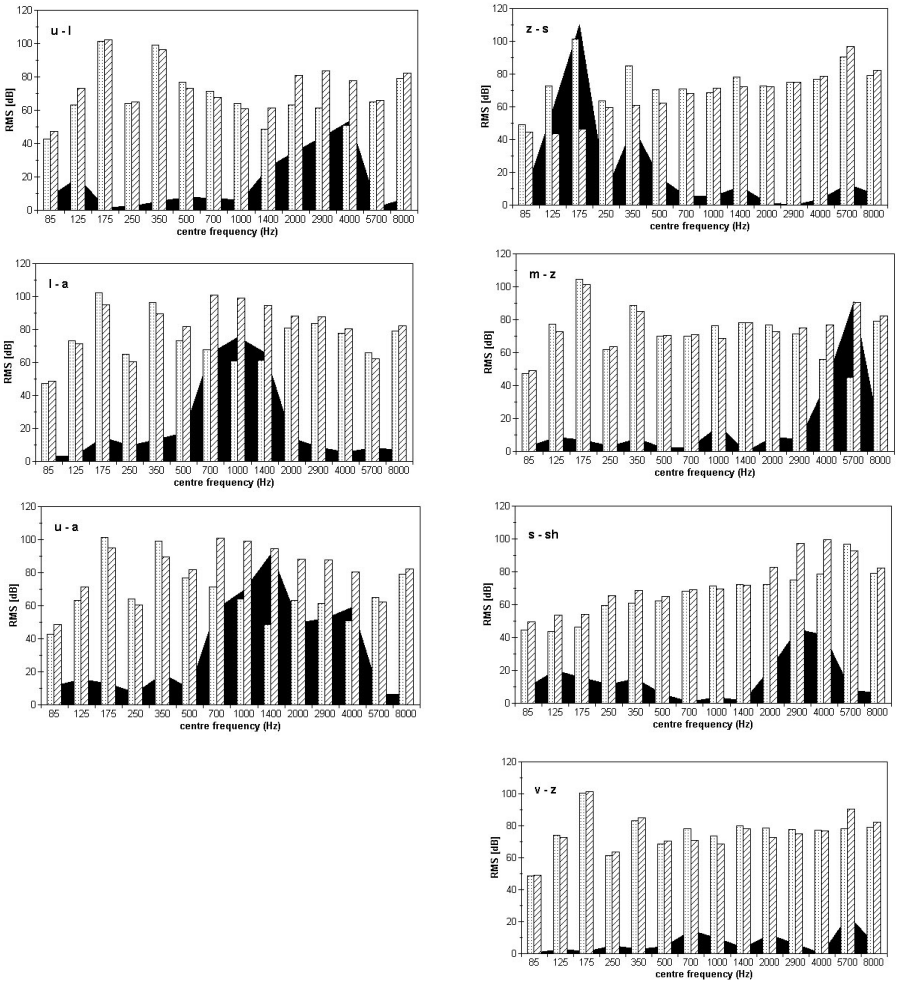

FIGURE 5. Spectral analysis of the seven phoneme pairs of the "minimal set" (Table 1). For each frequency band, the first box (dotted) depicts the energy content of the first phoneme and the second box (shaded) the energy content of the second phoneme. The black graph shows the spectral difference between the two phonemes in each frequency band. It can be readily seen that the seven phoneme pairs cover the whole frequency range of the auditory spectrum. Linking these data with the cochlear implant frequency table of a patient, shows which channels need to be readjusted.

PHONEME IDENTIFICATION TEST

The phoneme identification test is a 2- or more forced-choice phoneme identification test with a picture-pointing response. The details of the procedure are described below.

The same phonemes as for the discrimination test were selected, with the exception of /y/ and /œ/. Both phonemes are situated either intermediately or centrally in the vowel triangle (Peterson 1952), and it is not easy to find pictures (onomatopoeia or mouth images, see further) that clearly represent these phonemes. For all twelve remaining phonemes, pictures were made that unambiguously represent the phoneme. Two types of pictural representations were made, the first type based on onomatopoeia (Figure 6) and the second type based on the mouth image of the phoneme (Figure 7). Onomatopoeia are commonly used by speech therapists and teachers of the deaf to elicit phonation and auditory attention in hearing impaired children. The phonemes or syllables have to refer to a known object or situation. A set of such onomatopoeia had earlier been developed by the Royal Institute for the Hearing and Speech Impaired in Hasselt, Belgium (Koninklijk Instituut voor Doven en Spraakgestoorden) and was adapted and recorded for the APE™. Mouth images are also familiar to hearing impaired children, since they start reading lips from birth and continue to use this spontaneous faculty. From the many phoneme-combinations that can be possibly constructed, a limited number of multiple-choice sets were selected in such a way that the number of test phonemes ranged from 2 to 6 (Figure 8).

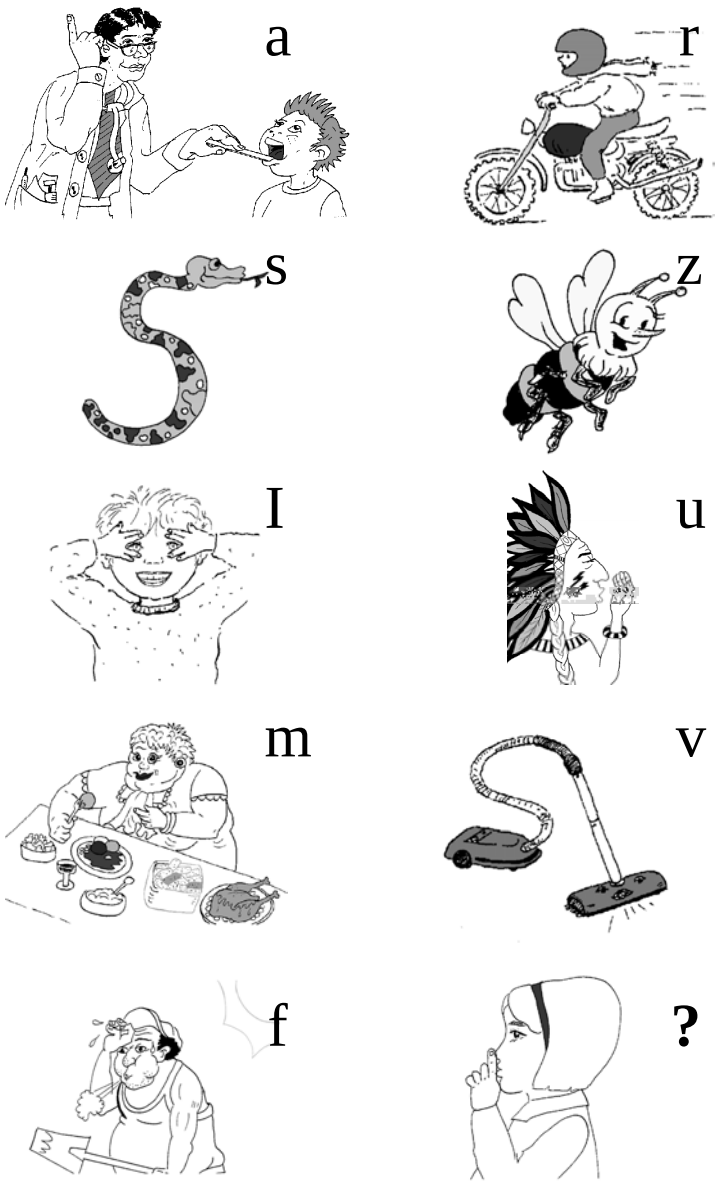

FIGURE 6. . Pictures of the onomatopoeia of the phonemes for identification.
(pictures by Marijke Duffhaus)

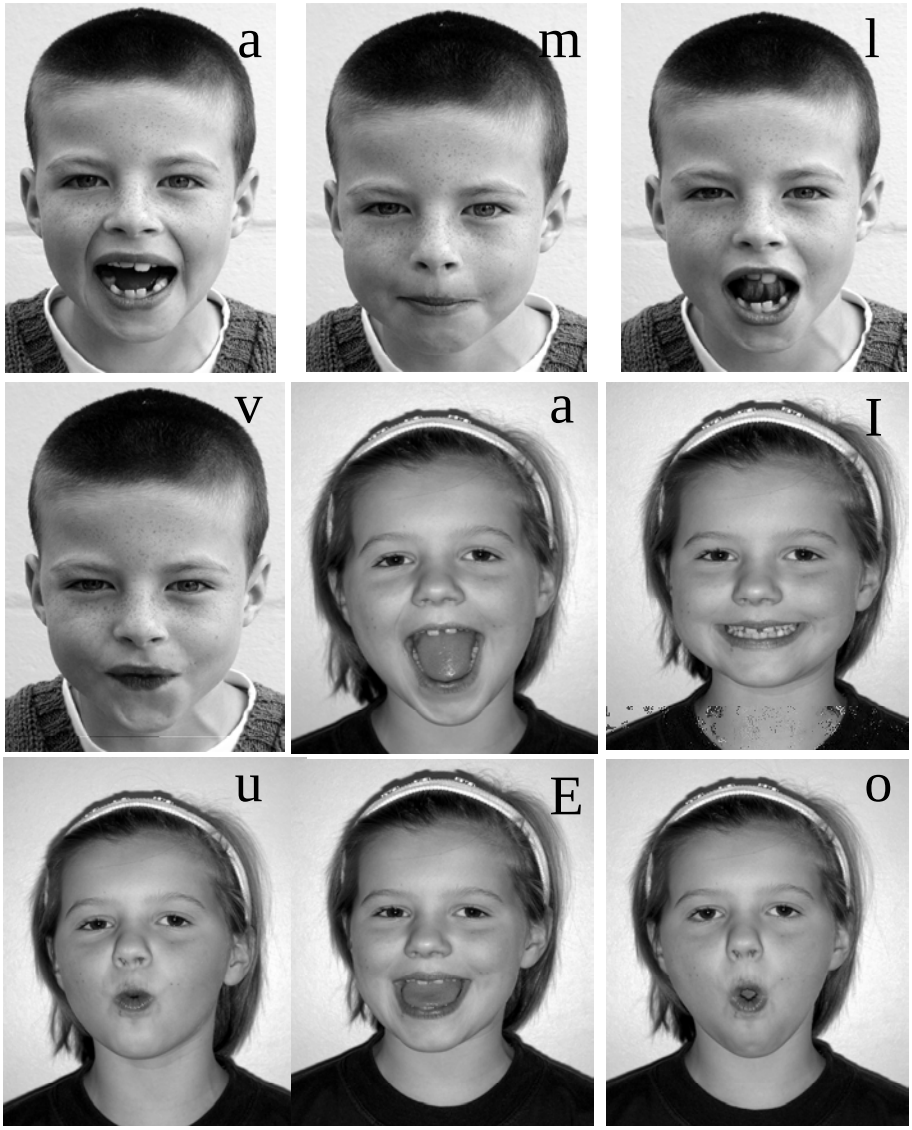

FIGURE 7. Pictures of the mouth images of the phonemes for identification. Note that hearing-impaired children are used to read lips, which may facilitate the test.

Test procedure

Since the phoneme identification test can be used for both adults and children, the test procedure is given in general terms. It is basically a forced-choice procedure (Figure 8). Phonemes are combined in sets of 2, 3, 5 or 6. The tester can chose how often each phoneme has to be presented (range 3 to 6 times). The order of presentations is randomised. After a phoneme is presented, the test person has to identify it, either by just repeating it (adults), or by pointing to the correct picture (children). This choice is registered and the next phoneme is given. The test stops when all phonemes of the set are given the predefined number of times. The number of correct responses and the confusion matrix of all errors is given in the report, as well as the overall score. The overall score is a yes or no score, meaning that the given set of phonemes is correctly identified or not. This is based on binomial statistics with a significance level of 0.05.

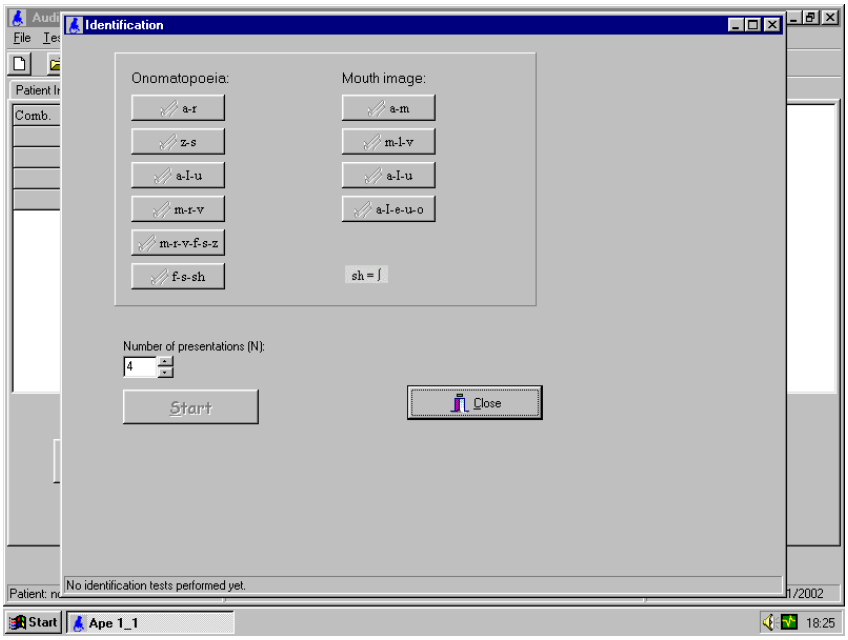

FIGURE 8. Test screen of the APE™ phoneme identification test. The six multiple choice tests with onopatopoeia and the four multiple-choice tests with mouth images are represented by buttons. The tester can choose how often each phoneme has to be presented (in this case 4 times). The report form will say whether the test person has identified the phonemes correctly with a statistical significance based on real-time binomial statistical calculations.

Normative data

It is known that identification tests in clinical practice are feasible in children from 3.5 to 4 years onwards provided that adequate test material is used (Jerger 1982, Hodgson 1994). Play audiometry, which is a detection test requiring active responses from the child, is feasible at younger ages. It has been shown that 70 % of children between 2 and 2.5 years and 90 % of those between 2.5 and 3 years are capable of doing play audiometry. The discrepancy in feasibility between this detection test and identification tests is due to the dependence of the identificaton test on the language development and cognitive skills of the child. It could be speculated that a phoneme identification test is less demanding in terms of linguistic skills and that the lower age limit for the feasibility would be lower than for classical identification tests. Therefore, normative data for the phoneme identification test of the APE™ were obtained from two groups: (1) 30 normally hearing children aged 2.8 years (average 34 months, range 30-36 months) and (2) 6 normally hearing children aged 3.5 years (median 44 months, range 41-47 months). All children were evaluated for the ten sets of phonemes (Figure 8). The number of presentations of each phoneme was 5 for 2-choice tests, 4 for 3-choice tests and 3 for 5- and 6-choice tests. All phonemes were presented in free field at an intensity of 70 dB HL (re 1 kHz narrow band noise) with the loudspeaker positioned at 1 m in front of the child. The children were tested by one audiologist in a quiet room. The response was a forced picture-pointing response (see test procedure and Figure 6 and 7). For each set of phonemes, the number of children was calculated that showed an identification score above the statistical significance level. Also, the average score on each set of phonemes was compared to the significance level of that set. The results are given in Tables 4 and 5. These results show that the phoneme identification test yields significant results in 67 to 97 % of normally hearing 2.8-year-old children and in 100 % of normally hearing 3.5-year-old children. Only /z/-/s/ and /m/-/l/-/v/ gave worse results. These figures are in the range of the earlier mentioned results in play audiometry and they are better than classical identification tests. Still, for the 2.8-year-old group, the 95 % confidence interval is not situated above the level of significance for most of the phoneme sets. Only the score on /a/-/I/-/u/ has a 95 % confidence interval of 7.9 - 13.6, which is above the significance level of 7.2.

TABLE 4. Normative data of the identification test (2.8-year-old group)

	a-r	*z-s*	*a-I-u*	*m-r-v*	*m-r-v-f-s-z*
% children	67	37	83	70	93
Score	9.0 (1.3)	7.3 (2.3)	9.1 (2.0)	8.8 (2.7)	10.1 (2.1)
S.L.	8.1	8.1	7.2	7.2	6.1

	f-s-ʃ	*a-m*	*m-l-v*	*a-I-u*	*a-I-E-u-o*
% children	77	70	57	97	90
Score	8.5 (1.7)	9.1 (1.5)	8.6 (3.0)	10.8 (1.4)	10.0 (2.7)
S.L.	7.2	8.1	7.2	7.2	6.04

The columns represent the sets of phonemes. % children: the percentage of the children (N=30) with statistically significant identification ($p<0.05$); Score: the average score (+ standard deviation) of the children on the set of phonemes; S.L: significance level above which the score has to be to conclude that the phonemes are identified in a significant way.

TABLE 5. Normative data of the identification test (3.5-year-old group)

	a-r	*z-s*	*a-I-u*	*m-r-v*	*m-r-v-f-s-z*
% children	100	50	100	100	100
Score	10.0 (0.2)	8.5 (1.3)	10.5 (2.2)	12.0 (1.7)	14.0 (2.1)
S.L.	8.1	8.1	7.2	7.2	6.1

	f-s-ʃ	*a-m*	*m-l-v*	*a-I-u*	*a-I-E-u-o*
% children	100	100	33	100	100
Score	10.5 (3.0)	10.0 (0.7)	6.5 (3.3)	11.0 (1.1)	12.0 (2.4)
S.L.	7.2	8.1	7.2	7.2	6.04

See Table 4 for legend. Since these data refer to only 6 children, they should be interpreted with caution. The standard deviations are only indicative and are calculated based on the interquartile difference (see Govaerts 1998).

This means that the score on the identification test in this age group only has a positive predictive value. Indeed, if a child achieves a score above the significance level, one may conclude that the identification of the given phonemes is OK. On the other hand, if the score stays below the significance level, one is not entitled to conclude that the identification is not OK. It is remarkable to note the influence of the age on the results, even within the lim-

ited age range of the test group (30-36 months). Figure 9 gives the linear regression line and its 95 % confidence interval and this shows a statistically significant age effect ($p<0.001$). Table 6 shows the sets of phonemes that were well identified by all 3-year old children (N=10). This is in line with the findings in the 3.5-year-old group (Table 5). In consequence it can be concluded that there is a transition zone which is lying somewhere around 3 years. Before this age, the phoneme identification test of the APE™ can only be interpreted in a positive direction. Only part of these children (between 67 and 97 %) will perform well. Beyond this age, all phoneme tests, except /z/-/s/ and /m/-/l/-/v/ can be used in both directions. All children should perform well at this age.

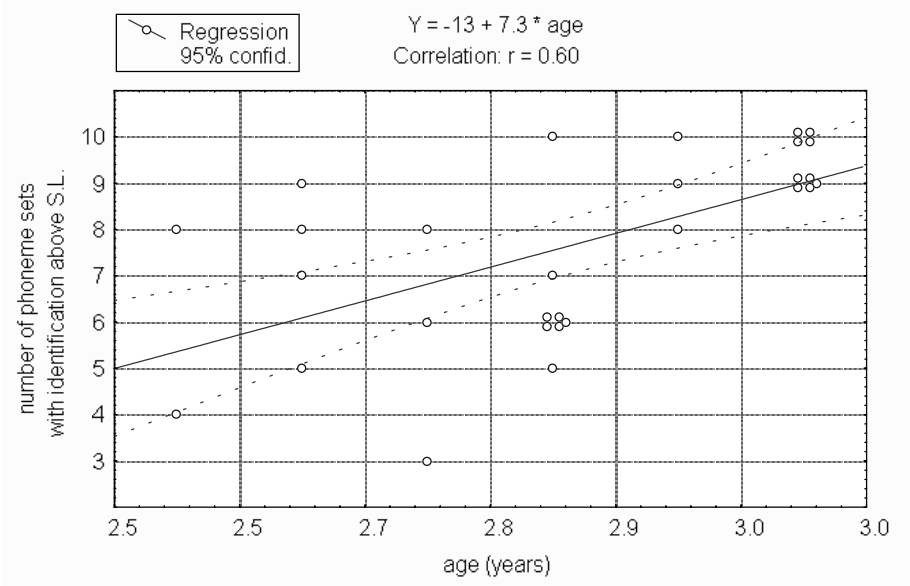

FIGURE 9. Linear regression between the age at which the APE™ phoneme identification test was taken and the number of phoneme sets that were identified above the level of significance. It can be inferred that at the age of 2.5 years, approximately 5-6 sets (out of 10, see Figure 8) are well identified by normally hearing children. At the age of 3 years, this has gone up to approximately 9 sets out of 10.

TABLE 6. Sets of phonemes that are identified by all(*) normally hearing children of 3 years

Identified by all	not identified by all
a-r	z-s
a-I-u (onomatopoeia)	f-s-ʃ
m-r-v	m-l-v
m-r-v-f-s-z	
a-m	
a-I-u (mouth images)	
a-I-E-u-O	

(*) N=10

Use in clinical audiology

The identification test of the APE™ is not routinely used in clinical practice. The reason therefore is that it requires not only good discrimination of the phonemes, but also good cognitive processing and this is not the primary scope of the audiological evaluation. A discrimination test assesses the cochlear frequency resolving function in a purer way. On the other hand, an identification test is less boring than a discrimination test and this may be interesting for some patients. In addition, an identification test can be helpful in case the discrimination of phonemes is difficult but not impossible. In such a case, it may be interesting to know whether this hardly discriminated phonemes result in distinct identifications or not. This knowledge adds nuances to the audiologist's interpretation of the audiological performance of a person, e.g. for the selection of cochlear implant candidates.

The identification test of the APE™ can also be used for the evaluation of cochlear implants. This information adds to other outcome measures, although its quantitative information is limited.

Finally, the identification test is sometimes used to adjust the fitting of the cochlear implant. The results contain a confusion matrix indicating which phonemes are easily confused with which other phonemes. Spectral analysis of two such phonemes can help the audiologist in finding out which channels need readjustment.

In combination with the phoneme discrimination test, the results can help the rehabilitative therapist to focus and train on specific phonemes that are discriminated but not identified as distinct phonemes.

PHONEME DETECTION TEST

The phoneme detection has been added to the APE™ on the request of several users. As said before, the primary purpose of the APE™ was to have a supra-liminal test. Detection of sound can be tested by routine audiometry using pure tones, warble tones, narrow band noise etc. These are well calibrated, validated and are part of every basic audiological test equipment. Assessing the detection thresholds for the phonemes of the APE™ can be useful as an internal control to check the response thresholds of the child, and to check the equipment and hearing aid used.

All consonants of the basic set (Table 1) were selected, together with the vowels /a/, /o/ and /I/. The other vowels have been left out since the /a/, /o/ and /I/ sufficiently cover the whole frequency range of human hearing. In addition the stop consonants /t/, /p/, /k/, /d/, /b/ have been added as experimental tools on the request of several audiologists and to be used at their own discretion.

Since the phonemes of the basic set had been loudness-balanced at a level of approximately 70 dB HL, a rebalancing was carried out at threshold-levels for the detection test. For this purpose, thresholds were determined for all phonemes in six normally hearing adults. The threshold of a 1 kHz narrow band noise was used as reference. This yielded the correction factors that were used to modify the intensity of each phoneme. The phonemes have been loudness balanced in such a way that the normal thresholds are 25 dB HL on a calibrated audiometer (hence, this is 0 dB HL re 1 kHz narrow band noise).

Test procedure

Since the phoneme detection test can be used for adults and children, the test procedure is given in general terms. It is basically the same as any detection test aiming at defining the hearing threshold. The same strategies can be used as for audiometry and a 5-up, 10-down procedure may be preferred by most audiologists. Phonemes are presented three times after the proper button has been pushed (Figure 10).

The test person is asked to give a response when the phoneme is heard. Depending on the age this can be an oral response, a conditioned instrumentation response or an orientation reflex. The tester records whether the test person has detected the phoneme or not and proceeds to the next phoneme.

Normative data

Normative data for the phoneme detection test of the APE™ were obtained from 30 normally hearing adults. All phonemes were presented to the test persons in free field with the loudspeaker positioned at 1 m in front of the test person. The detection thresholds were registered with a 5 dB up, 10 dB-down procedure. Table 7 shows the thresholds for each phoneme.

TABLE 7. Thresholds of the phonemes for the detection test

Phoneme	Threshold (dB HL)	Standard deviation (dB HL)
a	25	5
t	24	2
I	27	3
p	23	3
k	23	5
s	26	5
f	24	3
d	26	3
r	24	4
ʃ	22	5
o	25	4
b	27	4
z	28	5
m	24	5
v	24	3

Use in clinical audiology

As mentioned before, the phoneme detection test does not constitute the primary goal of the APE™. It is not routinely used in clinical practice, since detection thresholds are better assessed by means of classical audiometry. On the other hand, phonemes may have specific advantages. Like for the other phoneme tests, phonemes are more attractive to many infants and children than pure tones and it may be easier and time-saving to work with phonemes. Phonemes also cover all frequencies, and in case of hearing aids or implants,

it is not always obvious how the electronic device modifies these frequencies. Hence, it may be interesting to know the detection threshold for a given phoneme rather than for a specific tone.

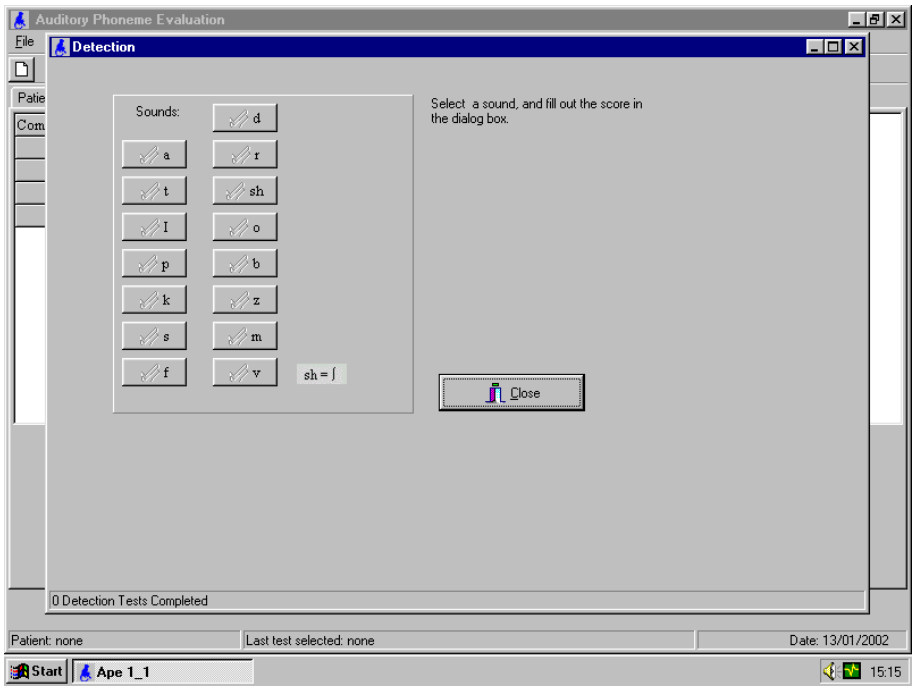

FIGURE 10. Test screen of the APE™ phoneme detection test. The phonemes are represented by buttons. After having selected a phoneme, the phoneme will be presented three times and the tester will be asked whether the test person has detected it. The results are listed on the report form.

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Outcome of cochlear implantation at different ages from 0 to 6 years

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ABSTRACT

A retrospective longitudinal and cross-sectional analysis of paediatric cochlear implant patients has been carried out to evaluate the outcome of cochlear implantation in young children in relation to the age of implantation. All children with congenital deafness who were implanted before the age of 6 years (N=48 for the longitudinal analysis and N=70 for the cross-sectional analysis) were included. Two outcome measures were registered: (1) the CAP-score (categories of auditory performance) and (2) the integration in the mainstream school system. For all children the CAP-score increased after implantation. Implantation beyond the age of 4 years hardly ever resulted in normal CAP-scores or in integration in the mainstream primary school (20-30% of the cases). Implantation between the age of 2 and 4 years always resulted in normal CAP-scores after 3 years with a 66 % probability of integration in the primary school. Implantation before the age of 2 years resulted always in immediate normalization of the CAP-scores with a 90 % probability of integration in the mainstream kindergarten, well before entering the primary school. In conclusion, all children with congenital deafness who were implanted before the age of 6 years appear to benefit from their implant. However, these data add evidence to the importance of early implantation (before the age of 2 years). Intervention before 4 years of age seems to be critical to avoid irreversible auditory performance losses and intervention before 2 years seems to be critical to achieve optimal results.

Key words: Paediatric Cochlear Implant, Children, Outcome, Integration, Hearing Loss, Early intervention

INTRODUCTION

Cochlear implants are widely used to treat profound perceptive hearing loss. Based on growing evidence of positive outcomes, the indications are steadily shifting both in terms of degree of hearing loss and age of implantation (Miyamoto 1999, Nikolopoulos 1999, Illg 1999). Mainly as a result of the implementation of universal hearing screening programs, the age of detection of congenital hearing losses is substantially decreasing. Infants with congenital hearing loss are nowadays referred by the age of 1 to 3 months for diagnostic work-up and therapeutic intervention (Govaerts 2001). The question whether cochlear implantation in these infants is relatively urgent or not, is important.

Although it can be assumed that early implantation and in consequence early (partial) restoration of hearing may yield better results than late implantation, the evidence for this is only slowly being built up. One of the reasons for this is that it is difficult to reliably assess the auditory performance of very young children. Pure tone audiometry is the only measure available that is widely acknowledged as reliable, but it is not really valid as an outcome measure of cochlear implantation. Therefore indirect measures may have to be used, such as scores of speech and language development, the CAP-score (Categories of Auditory Performance (Archbold 1995, Archbold 1998) and the eventual integration in the mainstream school system.

The pediatric cochlear implant program of the St.-Augustinus Hospital started in 1994. The authors started implanting children younger than 2 years of age in 1996 and younger than 1 year in 2000. This paper reports on the results in relation to the age of implantation.

PATIENTS AND METHODS

This paper deals with two study groups (a longitudinal and a cross sectional study group) and one control group.

Longitudinal study group

All congenitally deaf children implanted between January 1994 and August 1999 that were between 1 and 6 years old at the time of implantation were included in this group. All these children thus have a follow-up of at least two years. In addition, all children that were implanted before the age of 1 year

were also included, regardless of the follow-up time. Children with severe mental retardation or with cochlear malformations were excluded.

All children received a multichannel bipolar LAURA™ cochlear implant (Philips Hearing Implants, Edegem, Belgium, now Cochlear Technology Centre Europe) (Peeters 1989, Offeciers 1991) with the phase-locked continuous interleaved speech coding strategy (Peeters 1993).

The CAP-score (see below) was determined at regular intervals, namely before and at 3, 6, 12 and 24 months after the intervention.

In addition, for each child the moment of the first hearing aid fitting was recorded and whether and when he or she was integrated in the mainstream kindergarten or primary school.

The children were grouped by age of implantation. Six age- cohorts were defined, namely those implanted between 0 and 12 months of age, between 13 and 24 months, etc. until the last cohort of children implanted between 61 and 72 months of age. Median values and the ranges were used to describe the results.

Cross sectional study group

All congenitally deaf children implanted between January 1994 and August 2001 that were between 9 months and 6 years old at the time of implantation were included in this group. Children with severe mental retardation or with cochlear malformations were excluded.

Children that were implanted before August 1999 received a multichannel bipolar LAURA™ cochlear implant (Philips Hearing Implants, Edegem, Belgium, now Cochlear Technology Centre Europe) (Peeters 1989, Offeciers 1991) with the phase-locked continuous interleaved speech coding strategy (Peeters 1993). Children that were implanted after August 1999 received a multichannel monopolar Nucleus® 24 cochlear implant (Cochlear corp, Sydney, Australia) with the ACE™ coding strategy.

The CAP-score (see below) was determined at regular intervals, namely before and at 3, 6, 12, 24, 36 and 48 months after the intervention. At each interval, this CAP-score was compared with the normal CAP-scores at the given age (data from the control group) and the percentage of children falling within the normal range was calculated. Since no normative data are available for children over 36 months of age, the normal range was taken to be CAP-score 6-7.

Control group

Four control groups were evaluated with CAP-scores. The control groups consisted of normal hearing children aged 12, 18, 24 and 30 months. For each group the median CAP-score and its range were calculated.

CAP-score

CAP is a global outcome measure of auditory receptive abilities (5, 6). It comprises a nonlinear, hierarchical scale on which children's developing auditory abilities can be rated in eight categories of increasing difficulty. The categories are:

(score 0) describing no awareness of environmental sound

(score 1) awareness of environmental sounds

(score 2) responds to speech sounds

(score 3) recognizes environmental sounds

(score 4) discriminates at least two speech sounds

(score 5) understands common phrases without lipreading

(score 6) understands conversation without lipreading with a familiar talker

(score 7) can use the telephone with a familiar talker.

The score is calculated, based on the responses to a questionnaire by the parents and the professional therapist that follows the child.

RESULTS

Control group

The control group consisted of 113 children. Table 1 shows the numbers, age distribution and CAP-results of each group.

TABLE 1. Control group

Age group	N	Median age (months)	Range (months)	CAP mean	CAP range
12	26	12	11-14	2	1-5
18	28	18	17-19	5	1-7
24	36	24	22-26	6	3-7
30	23	30	29-32	7	5-7

Numbers, ages and CAP-scores for the different age groups (12, 18, 24 and 30 months) of the normal hearing children.

Longitudinal study

The longitudinal study group consisted of 48 children. Table 2 shows the numbers and age distribution of the children in each group. Each cohort consists of at least 6 children. All children have a full two-year follow-up after implantation, with the exception of the youngest cohort, as explained in the Material section. Figure 1 shows the consecutive CAP-scores for each age group at different moments after implantation. Table 3 shows the age at which the first hearing aids were given to the child and the percentage of the children that were partially or fully integrated in the mainstream school at the moment of the study. Some children, who were not yet integrated at the moment of the analysis, are doing sufficiently well so that they can be expected to integrate within the near future. The number between brackets shows the sum of those already integrated and those that are likely to get integrated in the near future as judged by professional therapists.

TABLE 2. Longitudinal study group

Age group	N	Median age (months)	Range (months)
0	6	8	5-10
1	9	19	13-23
2	7	30	25-35
3	13	40	37-47
4	7	56	50-60
5	6	70	63-71

Numbers and ages for the different cohorts (0 to 5 years of age at the time of implantation).

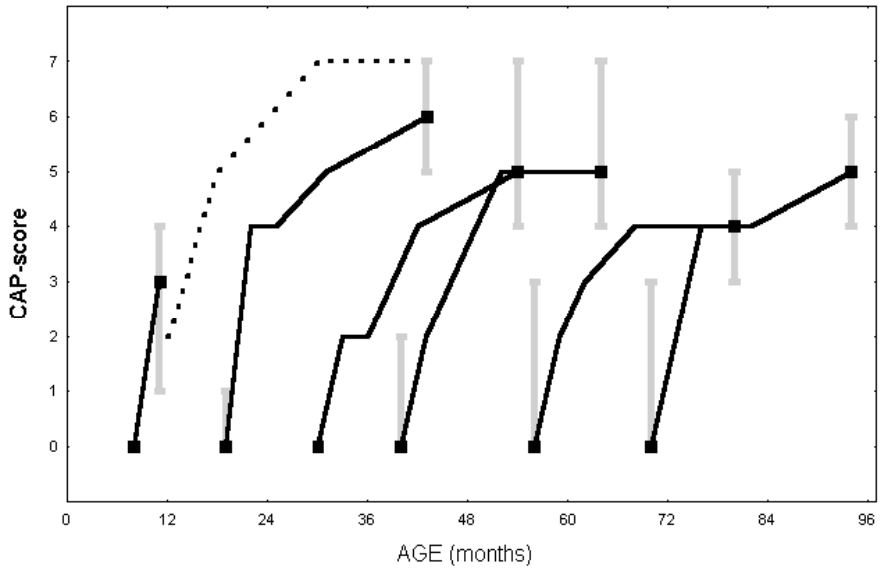


FIGURE 1. Longitudinal group. This figure shows the consecutive median CAP-scores for the six age cohorts. Five cohorts have a follow-up of two years. For each cohort, the range of the CAP-score is given preoperatively and 2 years postoperatively. The dotted line is the median CAP-score of the control group.

TABLE 3. Longitudinal study group

Age group	Age (with range) of first hearing aids (months)	Mainstream integration (%)	Age of integration (months)
0	2 (1-4)		
1	7 (3-12)	67 (89)	37
2	13 (9-21)	57 (63)	67
3	13 (3-32)	23 (54)	96
4	15 (10-37)	17 (33)	79
5	20 (10-44)	14 (14)	84

The figures in the third column refer to the percentage of children that have been integrated in the mainstream school system so far. The figures between brackets are the same ones plus those that are anticipated to be able to integrate in the near future.

Cross-sectional study

The cross-sectional study group consisted of 70 children. These children were categorized according to the age of implantation into 7 categories. Table 4 shows the numbers and age distribution of the children in each group.

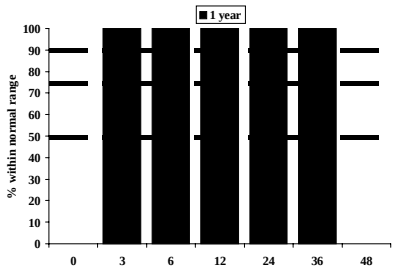
TABLE 4. Cross sectional study group

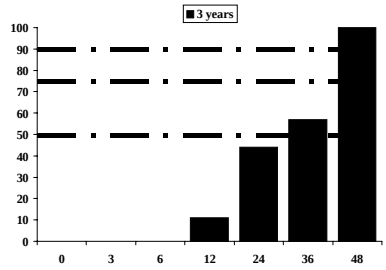
Age group	N	Median age (months)	Range (months)
12	10	13	9-15
18	11	18	16-20
24	7	23	22-26
30	4	29	28-30
36	9	37	34-39
42	9	42	40-45
48+	20	58	47-71

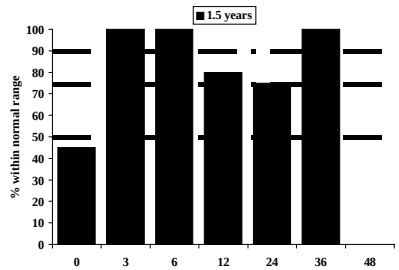
Numbers and ages for the different age groups (12 to over 48 months at the time of implantation).

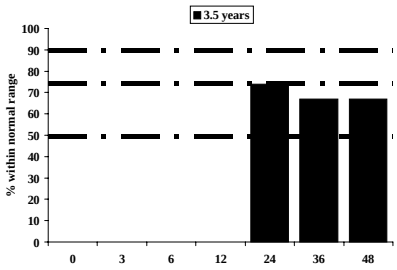
Figure 2 shows the percentage of children from each age group that reaches "normal" CAP-scores with respect to normal hearing children of the same age.

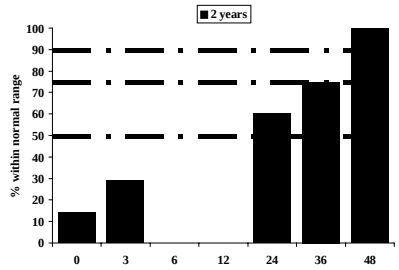
FIGURE 2 (next page). Percentage of children from each age group (1 to over 4 years at implantation) that reaches CAP-scores within the normal range, at different moments after implantation (from 0 to 48 months). The horizontal dotted lines show the 50 %, 75 % and 90 % borders. It can be readily seen that the older the age of implantation, the longer it takes to catch up with the normal children. Implantation before 2 years of age results in all children obtaining normal CAP-scores 3 months after implantation. Implantation beyond the age of 3 years leaves over 25 % of the children not obtaining normal CAP-scores within the first 48 months after implantation.

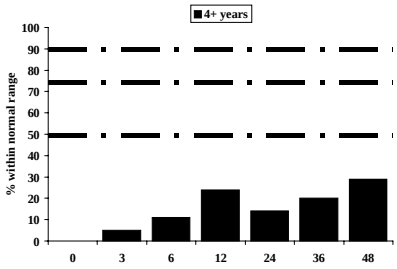

1 year
% within normal range
0 10 20 30 40 50 60 70 80 90 100
0 3 6 12 24 36 48


3 years
0 10 20 30 40 50 60 70 80 90 100
0 3 6 12 24 36 48


1.5 years
% within normal range
0 10 20 30 40 50 60 70 80 90 100
0 3 6 12 24 36 48


3.5 years
% within normal range
0 10 20 30 40 50 60 70 80 90 100
0 3 6 12 24 36 48


2 years
% within normal range
0 10 20 30 40 50 60 70 80 90 100
0 3 6 12 24 36 48


4+ years
% within normal range
0 10 20 30 40 50 60 70 80 90 100
0 3 6 12 24 36 48

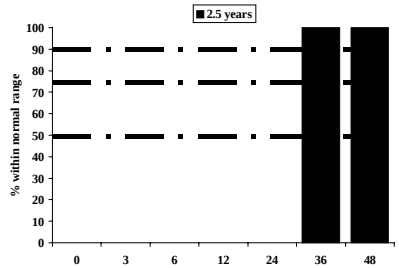

2.5 years
% within normal range
0 10 20 30 40 50 60 70 80 90 100
0 3 6 12 24 36 48

Table 5 shows the time it takes for 50 %, 75 % and 90 % of implanted children to reach normal CAP-scores.

TABLE 5. Cross-sectional group

	T50	T75	T90
12 (N=10)	3	3	3
18 (N=11)	3	3	3
24 (N=7)	24	36	48
30 (N=4)	36	36	36
36 (N=9)	36	48	48
42 (N=9)	24	never ?	never ?
>48 (N=20)	36	never ?	never ?

Time (months) to reach normal CAP-scores for 50 % (T50), 75 % (T75) and 90 % (T90) of the children implanted at different ages (12 to over 48 months of age at implantation). As an example, it takes a median time of 48 months before 75 % of children implanted at the age of 36 months reach normal CAP-scores.

DISCUSSION

This study shows that the auditory outcome of cochlear implantation in children with congenital deafness decreases with the age of implantation. Also, the integration in the mainstream school systems tends to decrease with the age of implantation.

The CAP-score is used as outcome measure of auditory performance (Archbold 1995, Archbold 1998). This is a global measure and the reduction of the auditory performance to only eight levels implies poor accuracy and little detail. On the other hand and in contrast to pure tone audiometry, it measures supraliminal performance and this reflects everyday auditory performance in a more realistic way. In addition, CAP is the only supraliminal auditory receptive outcome measure that is applicable to all children irrespective of their age. This is important for studies like this, where children of different ages from 0 to 6 years are followed up for two years and compared between different age groups. Speech audiometry would not be suitable, because this is not possible for the very young children and even for the older group, different speech lists should be used at different ages, making the results incomparable. The interobserver reliability of the CAP has been formally confirmed (Archbold 1998) and normative data are provided in this study, for which a control group of 113 normally hearing children aged 11 to 32 months were as-

sessed. All normally hearing children achieve a CAP-score of 6 or 7 (use of the telephone) by the age of 24 to 36 months.

An indirect measure of success is the integration in the mainstream school system. In Belgium all children with severe to profound hearing impairment are referred to specialized rehabilitation centers. These centers provide hearing rehabilitation and scholar education throughout the educational career of the child. However, the centers are also stimulated and financially supported to promote the integration of a hearing impaired child in the mainstream kindergarten or primary school.

This study shows that only children implanted before the age of 4 years have a chance of reaching CAP-level 7 within two years after implantation. This is the highest possible CAP-level, but does not imply normal hearing.

No children from the longitudinal group that were implanted after the age of 4 years, reached this highest CAP-level within the first two years after implantation (Figure 1). In the cross-sectional study with a follow-up of more than two years for some of the children, only some 20 % reached normal CAP-scores (score 6 or 7) after a long postoperative interval (Figure 2). Also only 33 % of these children are likely to ever be integrated in the mainstream school system and this will only occur by the age of six to seven years (median 79 months), which is approximately 2 to 3 years after surgery (Table 3). Parents of these children should therefore be counseled appropriately and the realistic expectations should not be set too high.

Children implanted between the age of 2 to 4 years seem to level of at a median CAP-score of 5 two years after surgery (Figure 1). This corresponds to understanding of common phrases without lip-reading. The cross-sectional data however show that the auditory performance of these children tends to further increase after two years. At least half of them have normal CAP-scores after 3 years and all have normal CAP-scores after 4 years (Figure 2). In addition about 60 % have integrated or will probably integrate in the mainstream school system at the age of about 7 years (median 67-96 months), which is approximately 3 years after surgery (Table 3). In consequence, implantation between the ages of 2 to 4 years may yield a good auditory outcome but it may take 3 to 4 years for this to happen.

Implantation before the age of 2 years results in normal CAP-scores as early as 3 months after implantation (Figure 1 and Table 5). It seems that children, who receive their implant at about 18 months of age, lag a bit behind their normally hearing peers whereas those receiving their implant in their first year of life follow the normal line. It is shown that 67 % attend mainstream school at the age of 3 years (which is the first class in the kindergarten) and it is an-

ticipated that about 90 % will ultimately be able to integrate before entering primary school.

A possible sampling bias exists in the fact that the early implanted children appear to be those who also received their hearing aids at a significantly earlier stage (Table 3) in their life than those who have been implanted later. This probably reflects the impact of the universal neonatal hearing-screening program that started in 1998 in Flanders, Belgium (Govaerts 2001). This, together with many sensitization campaigns over the last couple of years, has increased the awareness of the public and amongst professionals and has boosted the early intervention programs. Thus one might speculate that the better results of early implantation are not due to the implant as such, but to the early enrolment of these children in intervention programs. This would be in line with other reports claiming that early intervention of whatever kind is beneficial to the child (Yoshinaga-Itano 1998, Downs 1999, Moeller 2000). Although our numbers are insufficient to draw any firm conclusions, this bias does not seem to be entirely true. Indeed, some children that received early intervention with hearing aids (started in the first year of life) were nevertheless implanted at an older age. Three such children received their implant between the age of 2 to 3 years and only two of them (66 %) have integrated or will integrate. Of six such children who received their implant between 3 and 4 years, only 1 is anticipated to become integrated (17 %). One such child received its implant between 4 and 5 years and will not integrate (0 %) and another received its implant between 5 and 6 years and has just been integrated in a mainstream primary school (100 %). This suggests that children that received their implant at a relatively late age, even if they had been enrolled at a very young age (first year of life) in an intervention program with hearing aids, did not perform any better with their implants than children that were implanted at the same age but that did not receive hearing aids at such a young age. Thus the relatively poor results of cochlear implants at later ages do not seem to be caused by a late-detection effect. This finding therefore is very suggestive for a real beneficial effect of early cochlear implantation, i.e. before the age of 2 years, in comparison to cochlear implantation at a later age.

In conclusion, this study provides evidence in favor of early implantation (before 2 years of age). It provides data that may be helpful in counseling the parents of implant-candidates in a realistic way. All children in this age group (0-6 years) with congenital deafness seem to benefit from cochlear implantation. A child older than 4 years of age has a small chance (roughly 20-30 %) of reaching normal CAP-scores and of being integrated in the mainstream school system, and if this happens, it will only be at the age of six to seven

years. A child between 2 and 4 years of age will most probably reach a normal CAP-score but this will take 3 years and only two out of three may be able to integrate. A child below the age of two is very likely to immediately reach normal CAP-levels after implantation and almost all (90 %) of these children will probably be able to integrate in the mainstream kindergarten.

The LAURA multichannel cochlear implant in a true Mondini dysplasie

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ABSTRACT

A congenitally deaf child with bilateral Mondini dysplasias of the inner ear was successfully implanted with a LAURA™ multichannel cochlear prosthesis. This is the first report of a patient with a Mondini dysplasia in whom a LAURA™ multichannel cochlear prosthesis was successfully implanted. The cerebrospinal fluid leakage typically occurring after cochleostomy in similar patients was readily controlled, indicating that the deformity present was not a contra-indication for cochlear surgery. The audiological results obtained are described in detail. Since the internal unit of the LAURA™ prosthesis is very flexible, various speech processing strategies, such as continuous interleaved and phase-locked continuous interleaved strategies, can be tried and evaluated.

Key words: Sensorineural hearing loss - Congenital cochlear diseases - Mondini dysplasia - Perilymph gusher - Cochlear implant

INTRODUCTION

The Mondini dysplasia is a congenital malformation of the inner ear that is characterized by a normal basal turn communicating with a distal sac. The middle and apical windings are missing (Phelps 1990). The dysplasia seen can be associated with other diseases, such as Pendred syndrome, anencephaly, brancho-oto-renal dysplasia, Klippel-Feil syndrome, trisomy and Di George's syndrome, but it may also occur as an isolated finding (Miyamoto 1986, Schuknecht 1980). In general, affected patients have severe sensorineural hearing losses, but some patients may present with minimal hearing impairments.

True Mondini dysplasia is believed to arise from an arrest of inner ear embryogenesis during the 7th week of gestation (Jackler 1987b). This causes an incomplete partition of the developing cochlea, which subsequently forms one and a half turns instead of two and three fourths.

Profound hearing loss in patients with Mondini dysplasia justifies cochlear implantation. However, this indication is controversial because of a continuing conviction that Mondini dysplasia bears a great risk for cerebrospinal fluid (CSF) leakage and recurrent meningitis.

There has been much confusion about the term "Mondini dysplasia," as virtually all congenital malformations of the bony labyrinth have occasionally been mislabelled as such. This terminology is mainly due to a lack of reliable classification of congenital inner ear deformities. Jackler (1987b) and Phelps (1992) have suggested a better differentiated classification, in which true Mondini dysplasia can be better distinguished from more severe inner ear malformations. These latter deformities bear a much greater risk for complications when compared to a true Mondini malformation (Phelps 1990, Phelps 1991). Based on radiological classification, it is now possible to implant the majority of congenital inner ear malformations and more objectively assess potential risks (Jackler 1987c, Maingabiera-Albernas 1983, Phelps 1992, Silversstein 1988).

Successful implantation of multichannel cochlear prostheses in a patient with Mondini dysplasia has been reported only by Silverstein (1988). A number of other cases have been presented at international conferences, but to our knowledge have not been published. This paper is the first to report a LAURA™ multichannel cochlear implantation in a patient with a congenital inner ear malformation. This latter implant is known to be highly flexible regarding stimulation modalities (Peeters 1989), validating its utility in cases such as ours.

CASE REPORT

A 12-year-old girl with profound congenital bilateral deafness presented to our department for consideration of cochlear implantation. Hearing loss was believed to be due to maternal rubella infection during pregnancy. The patient had been attending a school for the deaf. She was wearing hearing aids and was trained in speech reading. She was able to understand suprasegmental information but without achieving speech discrimination. Although she had always been considered a communicative child, speechreading capabilities were poor and she had no pure oral speech recognition. The use of written language and finger spelling was necessary to support language acquisition and oral communication.

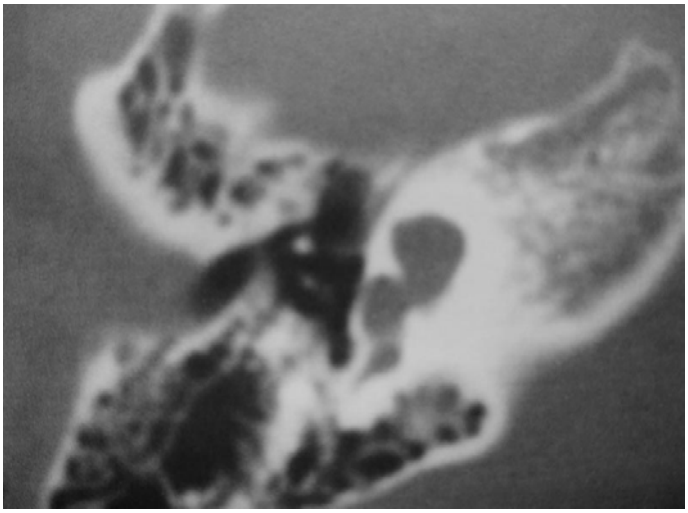
Except for hearing loss physical examination, including otoscopy, was unremarkable. Audiometric evaluation revealed bilateral profound sensorineural hearing losses. There was some residual hearing in mid-frequencies (500-2000 Hz) that averaged 115 dB HL. The dynamic range was reduced, with a level of discomfort at 120 dB HL.

Computed tomography (CT) with axial and coronal sections was performed, demonstrating bilateral symmetrical deformities of the inner ear. There was no distinct visualization of the apical and middle turns of the cochlea, which seemed to form a common sac (Figure 1). The basal turn was enlarged and was in wide communication with the fundus of the internal auditory canal (Figure 2). The vestibule was also enlarged and the semicircular canals shortened.

Magnetic resonance imaging was performed and also showed symmetrical cochleovestihular malformations (Figures 3 and 4). The cochlea was devoid of clear distinctive median and apical turns. The basal turn, however, was present and was clearly enlarged, as were the vestibule and the internal auditory canal. The facial nerve, both branches of the vestibular nerve and cochlear nerve appeared to be normal. The cochlea was filled with fluid without fibrous obliterations.

A multichannel LAURA™ cochlear device (Antwerp Bionic Systems, Edegem, Belgium) (Offeciers 1991, Peeters 1989)] with a monopolar configuration for this particular case was surgically implanted in the right ear by the senior author (F.E.O.), using a transmastoid facial recess approach. A cochleostomy was performed near the anterior lip of the round window. Although there was a profuse flow of CSF ("gusher") from the cochleostomy, this was controlled by bone dust and fibrin glue (Tissucol) after complete introduction of the electrode into the cochlea. The impedances of the implant

channel were measured after completion of the surgical intervention and were fully satisfactory. The facial nerve was never stimulated peroperatively. The reference electrode was placed in the middle ear near the helicotrema.



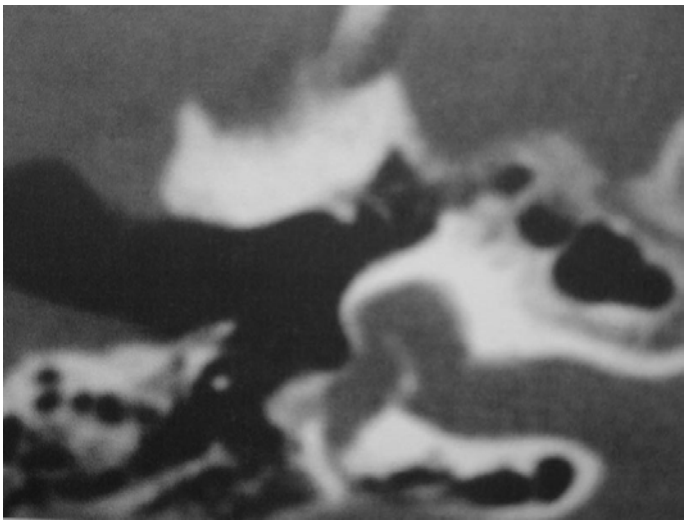


FIGURE 1 (top)**.** Computed tomography (CT) of the right ear in an axial plane at the level of the oval window and stapes showing a Mondini dysplasia. Note the common distal sac.

FIGURE 2 (bottom). CT of the right ear in an axial plane at the level of the internal auditory canal. Note the dilated implantation of the semicircular canals. The abnormally enlarged basal turn of the cochlea reduces the bony separation with the internal auditory canal to a minimum

To prevent further possible leakage of CSF, the whole middle ear cavity was filled with fat, fascia and bone dust. Forty-eight hours postoperatively the child developed a slight facial paresis at the corner of the mouth (House-Brackman score 2) that spontaneously disappeared after a few weeks. Postoperative radiographs showed good positioning of the implant and electrodes. No signs of CSF leakage or meningitis were observed.

One month after implantation the LAURA™ speech processor was programmed, using the phase-locked continuous interleaved strategy (Peeters 1993). Dutch auditory tests for children were used to objectively compare pre- and postoperative performances. Postoperative testing was undertaken at 3 months post-fitting and was conducted at a most comfortable loudness level of 70 dB SPL. Tests on three perception levels were performed (Figure 5).

Performances on everyday sound signals (4-choice test) improved from zero to 67 % (8/12). Good performance on a suprasegmental level was determined by the 3-choice "number of syllables" test (80 % correct) as well as the 4-choice "number of words in a sentence" test (95 % correct). There was still poor performance on the 3-choice voice recognition test (40 % correct).

At a segmental level, monosyllabic word 4-choice identification improved from zero to 50 % and 4-choice spondee testing improved from zero to 60 %. Closed-set identification of 12 words representing stress pattern categories increased from 17 % to 37 % pure word score, while the prosodic score remained at 50 %. Closed-set 4-choice testing of sentences increased from zero to 50 %.

Auditory rehabilitation started with basic sound and speech awareness, followed by selective attention to specific sounds and speech. Training of suprasegmental cues comprised different prosodic features of speech, including rhythm, duration, accentuation and intonation, followed by segmental cues based on phonemes, syllables, words and sentences.

By training auditory memory the opportunity was given to the patient to enlarge closed sets of phonetic interpretation and to make the identification exercises more difficult. The patient also learned to connect auditory speech perception skills with speechreading information and to integrate this multisensorial information into different efficient conversation strategies.

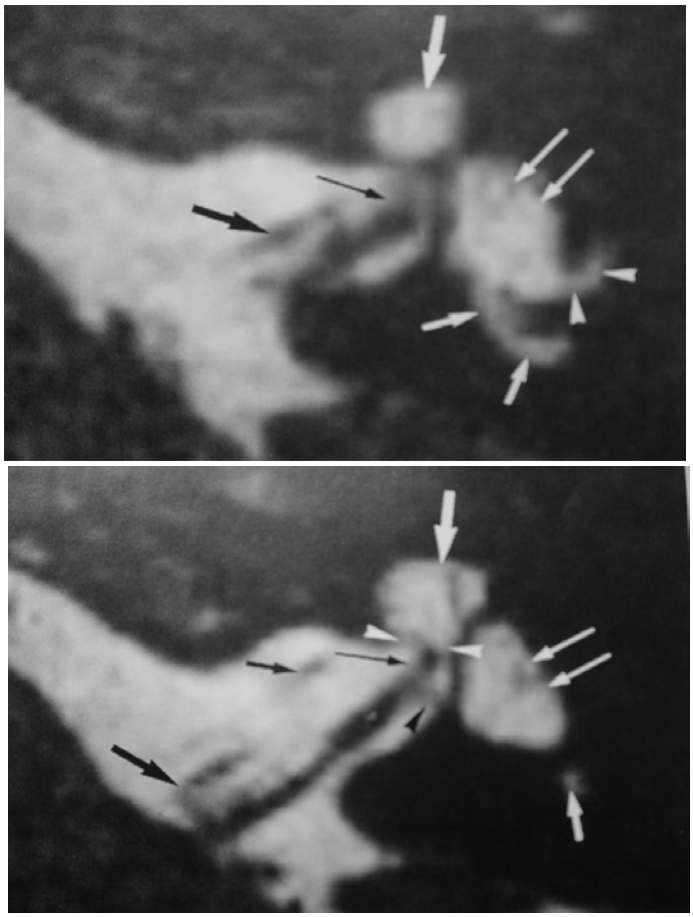


FIGURE 3. Axial 0.7-mm-thick three-dimensional Fourier transformation constructive interference in steady state (3DFT-CISS) MR images made at the level of the superior part of the internal auditory canal. Both the facial nerve *(large black arrow)* and superior vestibular branch of the vestibulocochlear nerve *(long black arrow)* are visible. The vestibule is enlarged *(long white anows)* and the lateral *(white arrowheads)* and posterior *(small white arrows)* sernicircular canals are short. The cochlea can be recognized as a cystic fluid filled structure *(large white arrow).*

FIGURE 4. Axial 0.7-mm-thick 3DFT-CISS MR images made at the level of the inferior part of the internal auditory canal. The cochlea has no second or apical turns and the modiolus is absent, making the cochlea appear as a cystic fluid-filled structure *(large white arrow).* The enlarged vestibule is again seen *(long white arrows)* and a broad connection between the abnormal cochlea and the broad fundus of the internal auditory canal is visible *(white arrowheads).* These findings indicate a potential "gusher ear". The cochlear branch *(long black arrow)* and inferior vestibular branch of the vestibulocochlear nerve *(black arrowhead)* are visible on this image. Also seen are the facial nerve *(large black arrow),* vascular loop in the internal auditory canal *(small black arrow)* and postenor semicircular canal *(small white arrow).*

At present audiological training is being continued both at school and at home. Long-term goals include increasing the patient's communication skills such as speech-reading, monitoring her own voice, sharpening her ability to discriminate similar auditory stimuli and consistently being alert to meaningful sounds and speech. All clinicians involved in our patient's cue have noticed better oral communication as a result of significant progress in speech-reading and improved voice and speech quality after implantation. Academically, these improvements have turned our patient into a capable student in an oral class setting.

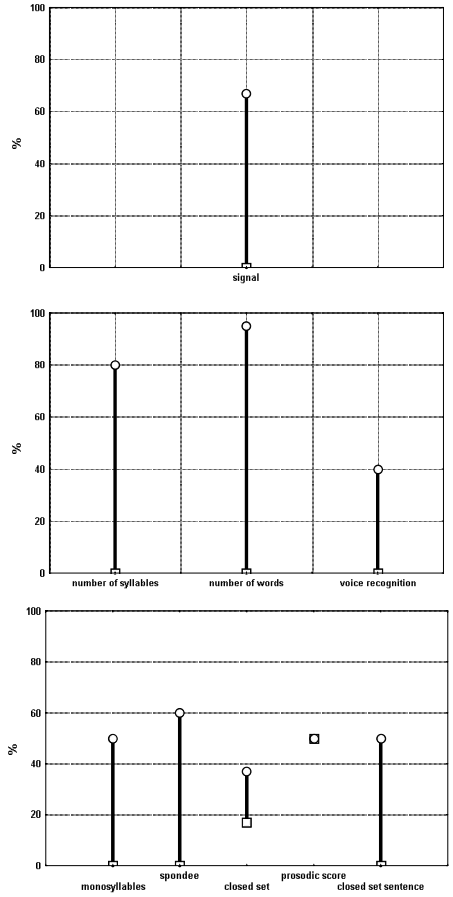


Figure 5. Patient's results of pre- and 3 months postoperative auditory tests on three perception levels: A signals, B suprasegmental, C segmental. See text for detailed comments. The preoperative suprasegmental cues are not available, since these tests are not routinely performed on children at the St.-Augustinus Hospital.

DISCUSSION

Successful implantation of patients with true Mondini dysplasia has been reported in the recent literature (Jackler 1987c, Maingabiera-Albernaz 1983, Schuknecht 1980, Silverstein 1988). According to some authors, pseudo-Mondini dysplasias and other more severe malformations of the inner ear are not candidates for cochlear implantation because of the greater risk for accidental penetration of the electrode through the fundus into the internal auditory canal, especially in cases with an enlarged basal turn and minimal bony separation from the internal auditory canal. Extension of the subarachnoid space into the middle ear in creases the risk for spontaneous and/or iatrogenic CSF leaks and recurrent meningitis (Phelps 1992, Phelps 1991).

All reports of congenital inner ear anomalies implanted so far are listed in Table 1. It should be stressed that a "perilymph gusher" is relatively common, even in true Mondini dysplasias, which are considered to be rather safe regarding spontaneous CSF leaks. We would emphasize that such an amount of fluid flowing out of the cochlea should not be called perilymph "flow," as the inner ear contains only a few microliters of endo- and perilymph, but rather CSF leakage. This occurrence has never caused major complications in implanted cases in our experience.

The LAURA™ multichannel intracochlear device has been developed to provide maximal flexibility regarding stimulation modalities (Offeciers 1991, Peeters 1989, Peeters 1993). In case of a cochlear anomaly, this feature has already proven to be of great benefit several times. The multichannel mode may especially provide superior stimulation characteristics in Mondini-like dysplasias when compared with any other type of stimulation.

Due to our patient's profound congenital deafness and lack of any auditory experience, performance on open-set recognition and comprehension levels was rather poor and insignificant. Although our objective tests demonstrated only a modest gain at this stage, the patient's immediate acceptance of the device and improved communication proved to be clinically gratifying.

We believe that implantation with the LAURA™ cochlear device will play an important role in this patient's future development, especially as an important aid towards communication, language and speech acquisition and integration in a hearing society.

TABLE 1. Summary of all published congenital inner ear anomalies implanted with a cochlear device

Year	Patients' age (years)	Anomaly	Type of implant	Complications	Results	Re
1988	31	Mondini	Nucleus multich.	Self-limited gusher	Lower threshold user	1
1982	22	Mondini	3 M/House singlech.	Implant revised due to inadequate position of electrode	Not available	2
1984	5	Pseudo-Mondini (CC)	3 M/House singlech.	Gusher sealed with connective tissue plug	Lower threshold user	3
1985	7	Mondini	3 M/House singlech.	Facial twitch	Tactile perception; non-user	4
1983	5	Pseudo-Mondini (CC)	3 M/House singlech.	Facial twitch	Higher threshold non-user	4
1985	7	Cochlear hypoplasia	3 M/House singlech.	Not specified	Lower threshold user	4
1984	9	Cochlear hypoplasia	3 M/House singlech.	Not specified	Lower threshold user	4
1994	12	Mondini	LAURA™ multich.	Gusher (sealed with bone dust and fibrin glue); Facial paresis (self-limited)	Lower threshold user	

CC: Common cavity; multich: multichannel, singlech: single channe; RE1-: references (1) Silverstein 1988, (2) Mangabiera-Albernaz 1983, (3) Miyamoto 1986, (4) Jackler 1987

Cochlear implants in aplasia and hypoplasia of the cochleovestibular nerve

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Otol Neurotol 2001 (submitted)

ABSTRACT

So far, only few patients with aplasia or hypoplasia of the cochleovestibular nerve (CVN) have been implanted with a cochlear implant, with variable results. This paper reports on four patients with this anomaly who have received a cochlear implant. The four patients represent different types of aplasia/hypoplasia: type I aplasia, type IIa aplasia and hypoplasia and type IIb aplasia. All patients had corner audiograms even with hearing aids. Three patients received a LAURA™ multichannel implant, and one patient a Nucleus® 24 implant. The patients with type I and type IIb aplasia did not have auditive perception with their implant and became non-users. Both are now in a total communication educational setting. The patients with type IIa aplasia and hypoplasia had moderate audiological results with the implant with audiometrical thresholds of approximately 40-60 dB HL (PTA), moderate phoneme discrimination and poor word discrimination. One child is in a total communication educational setting and the other in an oral educational setting, but the preferred mode of communication remains total communication for both. Both appear to benefit from the implant nevertheless. It is concluded that aplasia/hypoplasia of the CVN should be counselled with caution with respect to cochlear implantation, but that particular circumstances may justify the intervention. At present these circumstances seem to be a type IIa aplasia or hypoplasia in which the end organ (cochlea or common cavity) still connects to a neural structure on MRI.

Key words: aplasia, hypoplasia, cochlear implant, sensorineural hearing loss

INTRODUCTION

Congenital bilateral sensorineural hearing loss (>30 dB HL) occurs in approximately 1.2 to 3.2 per 1000 live births (White 1993, Davis 1994, Northern 1994). One of the causes is an aplasia or hypoplasia of the cochleovestibular nerve (CVN). This radiological entity was first described in 1997 (Casselman 1997). It was shown that MR images (axial (0.7 mm) three-dimensional Fourier transformation-constructive interference in steady state (3DFT-CISS) images) with parasagittal reconstruction images perpendicular on the course of the VCN allowed identification of the facial nerve and of the VCN with its cochlear and inferior and superior vestibular branches. A classification was suggested, based on the affected branch of the nerve and the related labyrinthine dysplasia (Table 1 and Figure 1). It was anticipated that the cochlear branch would always be involved in this anomaly and to date, no isolated hypoplasia or aplasia of the vestibular nerve, in the presence of a normal cochlear nerve, has already been described. Although one would assume that aplasia and hypoplasia of the cochlear nerve would be a contraindication for cochlear implantation, some reports claim good results after implantation. In most of these cases, the diagnosis of aplasia or hypoplasia of the CVN was made after the implantation. These reports justify a more detailed analysis of the results of cochlear implantation in the different types of aplasia/hypoplasia of the CVN. In our series of 17 cases of aplasia/hypoplasia of the CVN, four received a cochlear implant and they represent four different types of aplasia/hypoplasia. Three patients had an aplasia (type I, IIa and IIb) and one a hypoplasia (type IIb) of the CVN. The results will be discussed.

TABLE 1. Classification of hypoplasia and aplasia of the CVN

Type	Affected nerve on imaging	remarks
I	Cochleovestibular nerve	The labyrinth may be normal or dysplastic, the internal auditory canal is stenotic
IIa	Cochlear branch with labyrinth dysplasia	Labyrinth dysplasia ranges from a minor dysplasia, like in case 3, to a common cavity
IIb	Cochlear branch with normal labyrinth	
III ?	Vestibular branch	was anticipated not to exist as an isolated aplasia and has not been reported so far

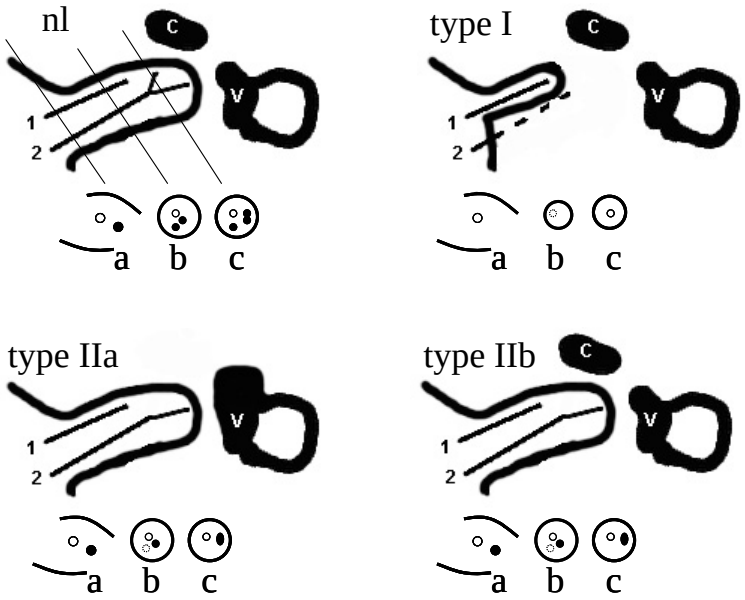

FIGURE 1. Schematic representation of the MR images of the normal situation (**nl**), and the different types of hypoplasia/aplasia of the cochleovestibular nerve (type **I**, **IIa** and **IIb**). Each figures contains two schemes, the upper representing the axial image through the middle part of the left internal auditory canal; and the lower representing the parasagittal reconstructions perpendicular to the course of the nerves at three levels: (**a**) cerebellopontine angle, (**b**) middle third and (**c**) lateral third of the internal auditory canal.
In the **normal** situation, the facial nerve (**1** on the axial image**, circle** on the parasagittal image) and the CVN (**2** on the axial image**, dot** on the parasagittal image **a**) are present in the inner auditory canal. The CVN contains a cochlear branch and a common vestibular branch. This can be seen at level (**b**) where in clockwise direction, the facial (**circle**), the common vestibular nerve and the cochlear branch (**dots**) are seen. At level (**c**), the common vestibular nerve has split into a superior and inferior branch.
Type I is recognized by a stenotic internal auditory canal in which no CVN can be seen. The facial nerve runs in a separate canal and is seen at level (**a**) and (**c**). At level (**b**) the canal can be too narrow to allow visualization of the facial nerve. The labyrinth may be normal or dysplastic.
Type IIa is recognized by the absence of the cochlear branch at level (**c**) and sometimes at level (**b**) in the presence of a dysplastic labyrinth.
Type IIb is similar to type IIa, but with a normal labyrinth.

PATIENTS AND METHODS

A retrospective case study was carried out on four patients that are known in our department with aplasia/hypoplasia of the cochleovestibular nerve and that have been implanted with a cochlear implant. No other patients of the

seventeen patients with aplasia/hypoplasia of the CVN that have been diagnosed to date by the authors, have been implanted.

The diagnosis of the deafness was made with routine techniques of clinical audiology, such as pure tone audiometry with and without hearing aids, auditory brainstem responses (ABR), and transient otoacoustic emissions. In addition, prior to surgery all children underwent an electrical trial stimulation, either with subjective responses or with brainstem evoked responses. For this, an active electrode was placed in the outer ear canal, which was filled with physiological fluid, or at the round window. The reference electrode was placed on the skin of the mastoid. Biphasic pulses (150µsec per phase) of varying intensities (200-1400 µA) and repetition rates (30-200 Hz) were given as stimulus and the responses were registered.

The diagnosis of aplasia/hypoplasia of the CVN was made on MR imaging with axial (0.7 mm) three-dimensional Fourier transformation-constructive interference in steady state (3DFT-CISS) images and parasagittal reconstruction images perpendicular on the course of the VCN (Casselman 1997). Only for the first case, no parasagittal reconstructions were made, because this was a later development.

A LAURA™ multichannel cochlear implant (Antwerp Bionic Systems, Antwerp, Belgium) was given to the first three cases and a Nucleus® 24M multichannel cochlear implant (Cochlear Ltd, Sydney, Australia) for the last case and for reimplantation.

Postoperative audiograms are given, as well as the results on the phoneme discrimination test, which is part of the APE™ (Auditory Phoneme Evaluation, Melakos nv, Antwerp, Belgium, for details see www.melakos.net). This test is an essential part of the routine test battery that is used by our department for the selection and evaluation of cochlear implantees.

RESULTS

Case 1. aplasia type IIa.

Case 1 is a boy who was born after an uncomplicated pregnancy. At the age of 13 months he was referred for hearing evaluation because of parental concern. Otoscopy was normal. Conditioned orientation audiometry did not show any hearing thresholds. Transient evoked otoacoustic emissions were bilaterally absent. Auditory Brainstem Responses (ABR) were absent at 120

dB click stimulation. No mutations were found in the connexin-26 gene. Medical imaging (CT scan and axial 3DFT-CISS images) revealed a cochleovestibular dysplasia with a common cochleovestibular cavity with dysplastic semicircular canals. At that moment, no anomalies were diagnosed at the level of the CVN. Only later, after thorough re-evaluation of the images, the CVN that was present in the inner ear canal, did not appear to divide into separate cochlear and vestibular branches. The common nerve made contact with the common cavity. At the age of 15 months the boy received hearing aids and was enrolled in an early rehabilitation program. The auditory rehabilitation was unsuccessful. Aided thresholds were high (70-120 dB) at the low frequencies (125, 250 and 500 Hz) and absent at the frequencies above 500 Hz. A trial with a multichannel vibrotactile stimulator (Tactaid™, Audiological Engineering corp, Sommersville MA, USA) was not tolerated by the patient. Electrical stimulation with an outer ear canal electrode could elicit responses at both ears. After thorough counselling the decision was made to implant the left ear. In September 1995, at the age of 3 years, a LAURA™ multichannel cochlear implant was placed in the left ear. Only four electrodes could be inserted in the common cavity. Because of the cochleovestibular dysplasia, a monopolar configuration was selected. Postoperatively, electrical stimulation with the implant yielded good subjective perception with a flat audiogram at 65-70 dB HL three months after the operation. During the following years, the audiometric thresholds improved to 40 dB HL and the boy made good progress in terms of social behaviour and speech development, although his main mode of communication remained sign and body language in a total communication educational setting. Four years after implantation he was able to discriminate the majority of a set of phoneme pairs that is routinely used by our department (Table 2). After five years (July 2000), the implant had to be removed because of technical failure (electrical leakage) and was replaced with a Nucleus® 24M multichannel implant of which 12 electrodes could be inserted. The audiogram after one year showed thresholds of 45 dB HL and all phoneme pairs of Table 2 could be discriminated, except /u/-/o/, /u/-/y/ and /y/-/I/. The word score on a closed set identification test (Erber 12) was 50 %. The boy has been moved to an oral educational setting.

TABLE 2. Case 1: results on the phoneme discrimination test (*)

Able to discriminate	Unable to discriminate
a-r	œ -a
u-ʃ	E-a
u-I	œ -E
I-a	v-z
u-a	
o-a	
u-o	
œ -u	
œ -o	
I-E	
œ -ie	
y-I	
u-y	
z-s	
m-f	
m-z	
m-r	
s-ʃ	

(*) The phoneme discrimination test is part of the APE™ (Auditory phoneme evaluation, Melakos nv, www.melakos.net). The first phoneme of a pair is presented as the background phoneme and the second as the odd phoneme. The phonemes are presented at 70 dB HL (re 1kHz narrow band noise)

Case 2. aplasia type I.

Case 2 is a girl who was born after a pregnancy of an insulin-dependent diabetic mother with multiple episodes of vaginal bleeding during gestational weeks 8 to 12. Infancy was uneventful and the girl entered the kindergarten at 2;6 years, where she received speech therapy for delayed speech development. At the age of 4;6 years, a profound sensorineural hearing loss was diagnosed and the child was referred to a school for the deaf, where she received hearing aids. Oral education failed to improve the communication and at the age of 6 years the girl was moved to a total communication class. She was considered mentally retarded with autistic behaviour. With total communication, the be-

haviour changed dramatically, the girl became a very good student with an open and communicative character. At the age of 10 years, she was referred for cochlear implantation. Otoscopic examination was negative at the left side, and revealed a cholesteatoma the right side (which was surgically removed). Audiometry showed a corner audiogram. Aided thresholds showed no responses at 1000 Hz or higher frequencies, with elevated thresholds (80-110 dB HL) at the low frequencies (125, 250 and 500 Hz). Click evoked otoacoustic emissions were present at the left ear, absent at the right ear. Medical imaging (CT scan and axial 3DFT-CISS images) showed a type I aplasia of the CVN. Both internal auditory canals were stenotic and a CVN could not be visualized. Both labyrinths were normal and the facial and trigeminal nerve were present. Electrical stimulation with an outer ear canal electrode could elicit responses at the left ear. After thorough counselling and in the absence of precedents in the literature, the decision was made to implant the left ear. In January 1997, at the age of 11;3 years, a LAURA™ multichannel cochlear implant was placed in the left ear. Postoperatively, electrical stimulation with the implant failed to elicit subjective perception. Electrically evoked brainstem responses could not be elicited. The patient discontinued wearing the speech processor. A vibrotactile aid (Tactaid™) was tried but not tolerated by the girl.

Case 3. hypoplasia type IIa.

Case 3 is a boy who was born at 31 weeks gestational age due to a premature dehiscence of the placenta. At birth it was noted that the auricles were small and displaced inferiorly with supernumerary ear tags at the right side. No other deformities were withheld. The child did not pass the neonatal screening with transient otoacoustic emissions and was referred at the age of two months. ABR with air-conducted clicks of 120 dB HL did not show responses, but with bone-conducted clicks, responses were recorded at 50 dB HL. Medical imaging (CT scan and axial 3DFT-CISS images) showed a stenotic outer ear canal at the right side with major ossicular malformations at both ears. Both cochleas had a normal aspect, the vestibula were slightly dysplastic and the semicircular canals were normal. At both sides, the CVN could be visualized, the vestibular branch appeared to be normal but the cochlear branch was very hypoplastic. No connexin-26 gene mutations were found. The boy received hearing aids at the age of 5 months and was enrolled in an early rehabilitation programme. The auditory rehabilitation was unsuccessful and based on the working hypothesis of a mixed hearing loss, a bone anchored hearing aid (BAHA™) was given at the age of 3 years and after a positive 3-month trial with a conventional bone conducting hearing aid. Soon

after the placement of the BAHA™, the bone conduction thresholds were reported to go down and the boy did not seem to benefit form the device. Electrical stimulation with an outer ear canal electrode could elicit responses at both ears and based on these results, a cochlear implant was given in April 1998, at the age of 3;9 years. A LAURA™ multichannel cochlear implant was placed in the left ear. Postoperatively, electrical stimulation with the implant yielded good subjective perception with thresholds of 65-70 dB HL at 500-4000 Hz three months after the operation. Electrically evoked brainstem responses could be elicited at the five most basal channels. The boy made moderate progress in terms of audiological performance and speech development, and his main mode of communication remained sign and body language in a total communication educational setting. Three years after the implantation, the LAURA™ device had to be removed because of technical failure (electrical leakage) and was replaced with a Nucleus® 24 multichannel cochlear implant. Six months later, audiometry showed thresholds of 65 dB HL at the low frequencies and 45 dB at the frequencies 1000-4000 Hz) with discrimination of some phonemes (Table 3).

TABLE 3. Case 3: results on the phoneme discrimination test (*)

Able to discriminate	Unable to discriminate
a-r	z-s
u-I	m-z
I-a	
u-a	
s-ʃ	

(*) see Table 2 for legend. Only the "minimal set" of the APE™ is used for this patient.

Case 4. aplasia type IIb.

Case 4 is a girl who was born with the Goldenhar syndrome (oculoauriculovertebral dysplasia) after an uncomplicated pregnancy. ABR did not show any responses to air conducted clicks of 120 dB HL. Medical imaging (CT scan and axial 3DFT-CISS images) revealed a normal labyrinth (cochlea, vestibulum and semicircular canals) with a narrow internal ear canal in which a cochleovestibular nerve could be visualized with a vestibular branch but no cochlear branch. No mutations in the connexin-26 gene were found. The girl received hearing aids at the age of 9 months, but the aided thresholds were

never better than 80-100 dB HL at 250 and 500 Hz without responses above 500 Hz. She was enrolled in an early intervention program with total communication. She was referred for cochlear implantation at the age 19 months because of the poor audiological and speech developmental progress. Electrical promontory stimulation with ABR could elicit a reproducible peak at 3.8 msec, which was interpreted as an auditory brainstem response. Based on these results and after careful counselling, the girl received a Nucleus® 24M multichannel cochlear implant in February 2000, at the age of 2;2 years, with full insertion of the electrode array. During the fitting sessions, no responses could be elicited and the girl did not appear to benefit from her implant. One year later, she discontinued wearing her implant and received a vibrotactile aid (Tactaid™) which appears to contribute to her level of communication and comfort of life.

DISCUSSION

After the first report on the MR diagnosis of aplasia and hypoplasia of the cochleovestibular nerve (Casselman 1997), many other authors have confirmed this diagnosis and have stressed the importance of systematic use of MR imaging in the workup of congenital profound sensorineural hearing loss (Gray 1998, Weber 1998, Rech 1999, Maxwell 1999, Furuta 2000, O'Leary 1999, Bamiou 1999, Van 2000, Acker 2001, Bamiou 2001, Colletti 2001). Recently, aplasia of the CVN was also histopathologically confirmed in two cases (probably type I and IIb) (Nelson 2001). In the first publication, a classification was proposed based on the affected branch of the nerve and the related labyrinthine dysplasia (Table 1). Since then, seventeen cases with aplasia/hypoplasia of the CVN have been diagnosed in our department and their distribution is shown in Table 4.

TABLE 4. Distribution of different types of aplasia and hypoplasia of the cochleovestibular nerve

	Type I	Type IIa	Type IIb
Bilateral	18 %	35 %	6 %
Unilateral	12 %	18 %	12 %

Govaerts, et al. (unpublished data), based on 17 cases.

All reported cases had profound sensorineural hearing loss and would meet the commonly used criteria for cochlear implantation. As could be expected, several papers report bad results after implantation (Gray 1988), and some authors claim that aplasia/hypoplasia of the CVN is a formal contraindication

for cochlear implantation (Weber 1998, Maxwell 1999). It has been suggested that these patients could benefit from a brainstem implant (Colletti 2001). Yet, other papers report good results with cochlear implantation (Ito 1999, Bamiou 1999, Acker 2001).

In our series of seventeen cases, four received a cochlear implant. Two patients appear to benefit from it and the other two are non-users. In the first case, the aplasia was overlooked and was only diagnosed after implantation. The next three cases represent different types of aplasia/hypoplasia and this justified the implantations. Obviously, the parents were carefully counselled and were aware of the potential lack of effect. An encouraging argument was the positive electrical stimulation that was performed in all four candidates prior to surgery. One test was even done under anaesthesia with evoked brainstem responses and the result was interpreted positively. This was probably a misinterpretation of a myogenic response. Electrical stimulation has been abandoned in our department because of its poor prognostic value in general (Nikolopoulos 2000). A common feature of all four children was the corner audiogram, with little audiometrical improvement with hearing aids. This is obviously in line with the little benefit that was achieved with hearing aids. It is noteworthy that transient otoacoustic emissions were present in one patient (case 2). This was the case in only one ear, but the contralateral ear suffered from middle ear problems. The inner ears were normal on imaging.

Despite early detection and rehabilitation in three children, none developed speech or oral communication. The cochlear implant had no effect in two patients, one with a type I aplasia (case 2) and one with a type IIb aplasia (case 4). Both have discontinued wearing their implant. The second child appears to benefit from her vibrotactile device. A brainstem implant is being considered, especially for the younger of both (case 4). The other two patients do benefit from their implant, be it with moderate auditory outcome. The reason for this is probably that in both cases, the cochlear implant electrode is situated in the vicinity of an afferent nerve, containing auditory fibres. In case 1 (type IIa aplasia), this is because the labyrinth is so dysplastic, that only a common cavity remains, from where the common (cochleo?-)vestibular nerve runs to the brainstem. In case 3 this is because the cochlear nerve is hypoplastic, which means that even on MR imaging, neural tissue can be recognized at the place of the cochlear branch. Probably the remaining neural fibres suffice to provide reasonable detection and frequency discrimination of sound.

In conclusion, these data have led us to believe that aplasia/hypoplasia of the CVN is not a formal contraindication for cochlear implantation. Medical imaging may be of important prognostic value. If the local anatomy is such that the electrode cannot be located in the close vicinity of the nerve, it may not be

justified to proceed with implantation. This is the case in type I and type IIb aplasia. If, in contrast, the electrode can be positioned in the close vicinity of the nerve, it may be worthwhile implanting the child. This is the case in type IIa hypoplasia or in a type IIa aplasia with major labyrinthine malformation, such as a common cavity. The authors recommend the routine use of this classification in case of hypoplasia or aplasia of the cochleovestibular nerve.

Long-term evaluation of the effect of intracochlear steroid deposition on electrode impedance in cochlear implants patients.

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ABSTRACT

A retrospective study was carried out comparing the impedances of cochlear implant electrodes with and without a single application of steroids in the cochlea. The impedances of Nucleus® electrodes, either straight or Contour™, were measured at regular intervals (12 months after surgery for the straight electrodes and 6 months for the Contour™ electrodes. Ninety-nine implanted children with an average age of 5 years (range 0.7-16 years) were divided in four groups according to the type of electrode and the use of steroids or not. In addition the impedances of five children who required a reimplantation are reported. Two months after surgery, the impedances in the steroid groups are significantly lower than in the non-steroid groups (straight electrodes: 3.9 vs. 4.7 kOhm resp.and Contour™ electrodes 5.4 vs. 6.5 kOhm resp.). This reduction remains stable over time for the straight electrodes, but for the Contour™ electrodes, it seems to disappear after six months. The impedances after a second implantation are significantly higher than after a first implantation (median value 8.8 kOhm after two months).

It is concluded that the application of a single dose of a steroid-solution reduces the electrode-impedances significantly and that for the straight electrodes this effect seems to last. It seems justified to reimplant with caution because this seems to increase the impedances substantially.

Key words: cochlear implant impedances, steroids, outcome

INTRODUCTION

In cochlear implants the energy of the processed signals is transferred from the electrode contacts onto the nerve fibre endings through the electrode interface.

One of the technical problems of cochlear implants is the electrical impedance at the interface between the electrode and the surrounding cochlear tissue. This impedance depends on the static electrical impedances of the elements involved, but also on dynamic electrochemical and histological processes at the level of this interface. High impedances lead to high voltages generated across the electrode-electrolyte interface, which may cause the current sources to saturate at low current levels and to a decreased dynamic range of the stimulation. Also, high voltages and a low charge storage capacity of the electrode contacts increase the risk of irreversible electrochemical reactions at the interface, altering the composition of the tissue fluid and inducing changes in pH and the emergence of toxic reaction products. Finally, high impedances increase the energy consumption of the implant, which is to be avoided especially with future developments such as totally implantable devices in mind

Today's electrode designs tend to have more electrode contacts with smaller dimensions. There is also a tendency towards more space filling electrode arrays and/or closer contact with the modiolar tissue ("modiolus hugging"). These evolutions obviously will cause the intra-cochlear impedance of an individual electrode contact to be higher when compared to larger surface and less tissue-surrounded designs. Strategies to control the impedance of the electrode interface have already been and continue to be an important issue.

There are basically two ways to improve the electrode impedance. The first is to increase the electrode surface. This is in contrast with the trend to build smaller electrodes, but a solution may be to roughen the surface. This can be done by etching, sputtering, electrochemical coating techniques etc. (Peeters 1998) and increases the real surface substantially without changing the diameter of the electrodes. A second way is to prevent the increase in impedance that is routinely seen postoperatively. That is speculated to be the result of two effects, namely (1) electrochemical phenomena at the electrode-tissue interface and (2) fibrotic tissue growth around the electrode (Walsh 1982). The first effect may be counteracted by electrically stimulating the electrode (Platia 1986). The second effect, if it is truly due to reactive fibrosis, may be counteracted by steroid application, which is known to have a strong anti-inflammatory action. To test this working hypothesis, our group in Antwerp started to apply steroids in the cochlea during implantation. This fibrosis-

inhibiting product should possibly lower the impact of the inflammatory reactions after electrode insertion and thus lower the electrode contact impedance (Peeters 1998). Guinea pigs experiments and a pilot study on patients implanted with the LAURA™ cochlear implant device (former Philips Hearing Implants, Edegem, Belgium) showed a 50 % reduction in impedance growth when steroids were used (Peeters et al. 1998). This paper describes a restrospective comparative study with a longer follow-up time and comparing patients who received intra-cochlear deposits of steroids right before insertion of the cochlear implant with subjects who did not.

MATERIAL AND METHODS

Study groups

All subjects described in this paper were implanted with Nucleus® 24 types of implant (Cochlear Ltd., Sydney, Australia) using a soft surgery technique (Lehnhardt 1993). Only children receiving their first implant and with a normal cochlear anatomy without ossification were included in the study. Four groups were defined by the type of the electrode (straight or Contour™) and the use or non-use of steroids.

The straight electrodes refer to the Nucleus® 24 M or k implants and Contour™ electrodes to the Nucleus® 24 Contour™ implants. All Nucleus® 24 implant types have 2 large extracochlear electrode contacts: one ball contact (MP1) and 1 plate contact situated on the implant box (MP2). The dimensions of the intracochlear electrode contacts is different for the different types. The straight electrodes have 22 intracochlear ring contacts with average surface dimensions of 0.5 mm^2. The electrode carrier has diameter dimensions going from 0.6 mm (basal) to 0.4 mm (apical). The Contour™ electrode also has 22 intracochlear half-a-ring contacts with average surface dimensions between 0.23 to 0.21 mm^2 (from basal to apical electrodes). The electrode carrier has diameter dimensions going from 0.8 mm (basal) to 0.5 mm (apical).

The steroid Test groups consist of children that were implanted in Antwerp at the University ENT Dept of the St.-Augustinus Hospital. In these groups the cochlea was perfused with a mixture of the lubricant Healon® (Pharmacia Corporation, Peapack, N.J., U.S.A., Donnelli 1995) and the steroid product, Kenacort A® (1 ml of a 40 mg/ml triamcinolonacetonide solution, Bristol-Myers Squibb AG, Baar, Switserland), just before the electrode insertion. The electrode carrier itself was also immersed in this mixture before insertion.

The Control groups consist of children that were consecutively implanted at the Dept. of Otolaryngology of the University of Nottingham. In these groups the cochlea and electrode carrier were not lubricated at all.

Table 1 summarises the children in the different groups.

TABLE 1. Study groups

Electrode Size	Steroids	
	Yes	No
Straight (Nucleus® 24M/k)	**Test Group 1** N =24 Age = 5 years* (range 0.7 – 16)	**Control Group 1** N =30 Age =5 years* (range 2 – 11)
Contour™ (Nucleus® Contour™)	**Test Group 2** N =27 Age =5 years* (range 0.7 – 13)	**Control Group 2** N =18 Age = 5 years* (range 2 – 14)

* average age

Cases

In addition to these group data, five case studies were included in this study. These five children were reimplanted with a Nucleus® 24 implant after device failure of their first implant (LAURA™ flex type, former Philips Hearing Implants, Edegem, Belgium). All of them received intracochlear deposits of the Healon®-Kenacort A® mixture at the time of their first implantation as well as at the reimplantation. Table 2 describes these cases in terms of age at first implantation, age at reimplantation and reimplanted device type.

TABLE 2. Individual patients

Case	Device Type (all Nucleus®)	Age at first implantation (years)	Age at reimplantation (years)
1	24 Contour™	2	6
2	24 Contour™	4	7
3	24 Contour™	4	11
4	24 M	9	16
5	24 Contour™	13	17

Methods.

Impedance measures were done by delivering biphasic pulses using a 25μs phase width and a current level of 100 units CL (approximately 85 μA). Voltages created between the stimulated electrode contacts were measured and registered using back-telemetry, a detailed description of this technique was published elsewhere (Swanson 1995). Briefly, RF bursts are sent from the speech processor to the implant, the implant returns coded information to the programming system about the voltage developed on the electrode during stimulation, and these voltages are measured at 4 points on the stimulus waveform and are encoded as four pairs of RF pulses; the time interval between each pair is proportional to the measured peak-to-peak voltage created across the electrode interface.

The Nucleus® 24 implant system allows stimulation and impedance measurements in four different modes: (1) in Common Ground (CG) mode, where the impedance is measured between an intra-cochlear electrode contact and all other intracochlear electrodes coupled in parallel; (2) in Monopolar 1 (MP1) mode, where the impedance is measured between the intra-cochlear electrode contact and an extra-cochlear ball electrode situated at the temporal muscle; (3) in Monopolar 2 (MP2) mode, where the impedance is measured between the intra-cochlear electrode and an extra-cochlear electrode plate situated on the implant box under the skin; and (4) in Monopolar 1+2 (MP1+2) mode, where the impedance is measured between the intra-cochlear electrode and MP1 and MP2 coupled in parallel. In all patients, CG, MP1, MP2 and MP1+2 impedances were measured. MP1+2 impedances are relevant since this is the routine stimulation mode of the implant. On the other hand CG impedances reflect better the purely intracochlear resistance/capacitance and this is what the steroids are expected to interfere with. Since the intracochlear impedances can be suspected to be orders of magnitudes higher than the extracochlear impedances, it can be anticipated that the CG impedance corresponds very well with the MP1+2 impedance, the first only differing from the second

by a small negative constant which represents the extracochlear impedance. To verify this, a linear regression analysis was performed on paired CG - MP1+2 measures taken from 4328 individual electrode contacts from Test Group 1.

Impedance measures for the groups were made at different time-intervals: (1) intraoperatively, immediately after the electrode insertion in the cochlea; (2) 3 to 4 weeks after implantation, just before the first fitting; (3) 3 to 4 weeks after implantation, after the first fitting; (4) 2 months; (5) 3 months; (6) 6 months and (7) 12 months after implantation. For the Groups 2 the measures at 12 months post-implantation were not yet available.

To verify whether the extracochlear impedances change over time, linear regression analysis was performed on 528 paired CG - MP1+2 measures from Test Group 1 in period (2) and compared with a similar analysis on the data from period (5) and (7).

For all cases, impedance measures were available for the same intervals up to 3-month follow-up. Their results will also be expressed in terms of percentile value referred to their non-reimplanted peers.

Statistical analysis.

Shortcut or open-circuit electrodes are not considered for data analysis, as these contacts are not operational contacts and thus not stimulated. The upper and lower boundaries for an electrode contact to be functional have been determined by the manufacturer to be respectively 0.7 and 20 kOhm.

Linear regression statistics were used to determine the relationship between CG and MP1+2 impedance values for paired measures.

To check for normality of the data distribution, a Shapiro-Wilks' W test was performed on all group data series.

For normally distributed group results paired t-tests with a significance level of 0.05 were used to compare dependent data, such as impedance measures at the different time intervals. For the groups that are not normally distributed, Wilcoxon tests for paired data were used. For independent data, normal t-tests were used to compare between normally distributed group data and Mann-Whitney U tests for not normally distributed group data.

RESULTS

Linear regression statistics performed on the 4328 paired CG - MP1+2 impedance measures show a highly significant linear correlation between the MP1+2 impedance and the CG impedance (R^2=0.96 / p<0.00001 Figure 1). MP1+2 always tends to be 1.55 kOhms greater then CG impedance ($impedance_{MP1+2}$= 1.55+0.96 $impedance_{CG}$). The intracochlear impedance thus accounts for the major part of the MP1+2 impedance as expected (see Material and Methods). The intercept of the linear regression line from the 520 paired CG - MP1+2 impedance measures (Group 1) remains very stable over time (1.55 kOhm for the prefitting measures, 1.43 kOhm 3 after implantation and 1.46 kOhm 12 months after implantation).

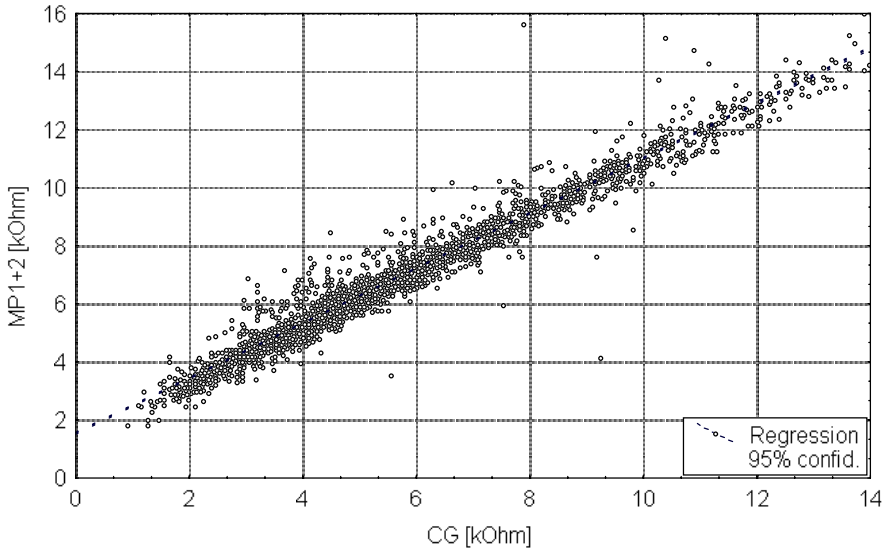

FIGURE 1. Linear regression analysis plot of paired MP1+2 - CG impedance measures of 4328 electrode contacts.

All but 7 data series passed the Shapiro-Wilks' W test for normality (p>=0.05) (19 out of 26).

Group data.

All group data are summarised in Table 3 in terms of mean and standard deviation and in Figure 2 in terms of mean and standard error of the mean.

TABLE 3. Impedances of the study groups over time (kOhm)

Group	Intraop	Pre-fitting	Postfitting	2 months
Test Group 1	4.57 ± 1.42	5.31 ± 1.56	4.41 ± 1.10	3.94 ± 0.89
Control group1	3.83 ± 1.54	6.58 ± 1.09	5.01 ± 1.05	4.71 ± 0.80
P value (t-test)	0.07	0.001	0.07	0.005
Test group 2	8.78 ± 1.48	8.54 ± 2.30	6.02 ± 1.57	5.35 ± 1.04
Control group 2	6.82 ± 1.67	9.59 ± 1.17	7.16 ± 1.23	6.52 ± 1.41
P value (t-test)	0.0001	0.08	0.008	0.004

	3 months	6 months	12 months
Test Group 1	3.94 ± 0.67	4.15 ± 0.76	4.49 ± 0.71
Control group1	4.59 ± 0.80	4.85 ± 1.17	5.10 ± 1.20
P value (t-test)	0.003	0.04	0.04
Test group 2	5.33 ± 1.09	5.49 ± 1.26	
Control group 2	6.10 ± 1.10	5.55 ± 0.88	
P value (t-test)	0.01	0.4	

Mean and standard deviation of CG impedance for the different groups under study and for the different evaluation periods

At the time of the operation the impedance tends to be higher for the Test Groups when compared to their Control Groups (4.57 versus 3.83 kOhm for Groups 1 and 8.78 versus 6.82 kOhm for Groups 2). This difference is not significant (p=0.07) for Groups 1 but is significant for Groups 2 (p=0.0001).

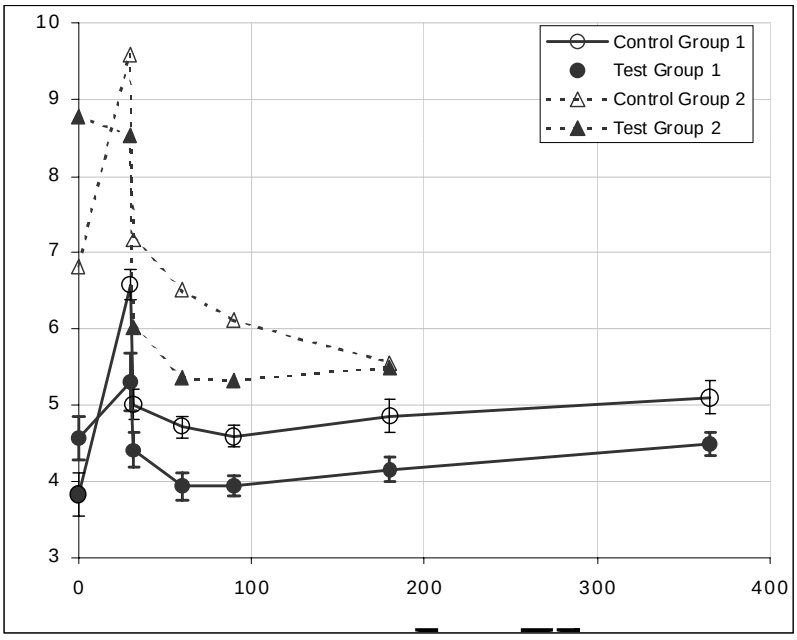

FIGURE 2. CG impedance values as a function of the post-operative time for the different study groups. The different symbols represent the mean values; the error bars represent the standard error of the mean.

In all series, the impedance values reach their maximal values at the time before the first fitting. There is a significant difference between Test and Control Group 1 ($p=0.001$) but not between Test and Control Group 2 ($p=0.08$). The rise in impedance postoperatively is significantly higher in the Control Groups compared to Test Groups (2.75 versus 0.74 kOhm for Groups1 and 2.77 versus 0.24 kOhm for Groups2, $p<0.05$).

At the second fitting session impedances have dropped significantly in all 4 groups. The decrease is 0.91 and 1.57 kOhm for Test and Control Group1 respectively and is even greater for Test and Control Group 2 were it is 2.52 and 2.43 kOhm respectively. The values for the Test Groups remain lower than the Control Groups. The differences are not significant ($p=0.07$) for Groups 1 but are significant for Groups 2 ($p=0.008$).

Impedances continue to decrease (2 months postoperatively) in all groups and all, except Control Group 2, attain their minimal values 3 months post-implantation. The differences between Test and Control Group are significant for the 2 and 3-month evaluation times ($p<0.05$).

In Test and Control Groups 1, impedance tends to increase from 3 months to the 6 and 12 months evaluation time. In these groups, the differences between Test and Control groups remain almost equal and significantly different until the end (12 months) of the follow up ($p<0.05$).

In Groups 2, impedance tends to remain the same for Test Group 2, but seems to decrease further for Control Group 2 until the end of the evaluation (6 months post implantation). There is no significance difference between Test an Control Group 2 at the end of the evaluation ($p=0.4$).

Case Data.

The results of the five reimplanted cases are given in Table 4 and shown in Figure 2. For all post-fitting evaluation periods the intracochlear impedances are significantly higher when compared their non-reimplanted peers ($p<0.05$). This is true in all but one case. Only for case 3, the impedance lies within the range of its non-reimplanted peers.

TABLE 4. Impedance data [kOhm] for the 5 reimplanted patients

Case	Intraop	Pre-fitting	Postfitting	2 months	3 months	6 months
1	15.19	13.40	11.83	10.78	10.97	11.43
	p<0.0001	p=0.02	p=0.0001	p<0.0001	p<0.0001	p<0.0001
2	10.80	10.33	9.34	8.92	9.58	9.15
	p=0.09	p=0.2	p=0.02	p=0.0003	p=0.0001	p=0.002
3	7.59	3.59	4.05	4.22	4.24	3.82
	p=0.2	p=0.02	p=0.1	p=0.1	p=0.2	p=0.1
4	6.43	9.66	9.25	9.64	10.92	8.49
	p=0.1	p=0.003	p<0.0001	p<0.0001	p<0.0001	p<0.0001
5	10.54	11.11	8.70	8.21	10.80	7.71
	p=0.1	p=0.1	p=0.04	p=0.003	p<0.0001	p=0.04

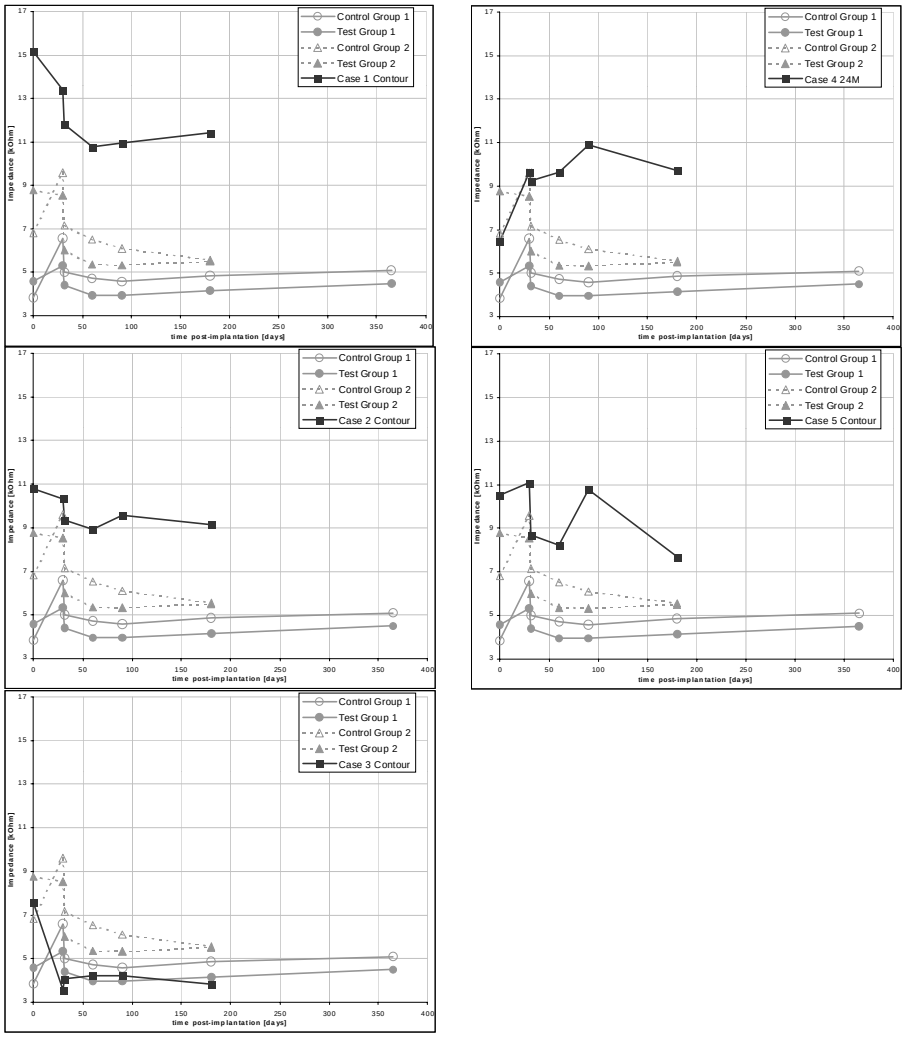

FIGURE 3. CG impedances of the 5 reimplanted cases (black) and the group data from Figure 4 (grey).

DISCUSSION

The intracochlear impedance has been shown to account for the major part of the MP1+2 impedance. The extracochlear part of the overall MP1+2 impedance is small (1.5 kOhm) and appears to vary very little over time.

The intracochlear impedance changes over time. Part of this is due to the electrical stimulation. This is most clearly seen when comparing the values just before the onset of the stimulation (during the first fitting) and a couple of weeks later. This shows a dramatic decrease in impedance in all groups. Such an effect was already reported earlier (Dorman 1992) ans is also known from pacemaker stimulation (Platia 1986).

Another part of the impedance changes over time, is thought to be due to reactive fibrosis at the site of the electrodes. This would contribute in a negative sense to the impedances and it is worthwhile trying to reduce this effect. Since steroids are know to strongly inhibit the reactive processes of inflammation and scar formation, it would make sense applying these drugs to try to interfere with the postoperative impedance growth. This study evaluates the effect of a single administration of steroids, applied locally in the cochlea at the time of implantation.

A first conclusion that can be drawn from this study is that the perfusion of the cochlea with a turbid mixture of Healon® and Kenacort A® causes an immediate increase of the intracochlear intraoperative impedance. This is true for both the large Nucleus® M and k electrodes and the small Contour® electrodes. A possible explanation can be the introduction of more air bubbles by mixing the two components or an intrinsic lower conductivity of the mixture. It has been shown that a film of Healon on its own has no influence on the electrical impedance (Mens 1997).

A second conclusion is that the impedances increase during the first weeks after surgery, as long as the implant has not been turned on, and that this increase is smaller when steroids are used. Thus, after a couple of weeks, the impedances in the steroid-groups are significantly smaller than in the other groups ($p<0.05$). This difference in impedance between the Test and Control Groups will further be referred to as the ‘steroid effect’. Indeed, it has been shown earlier that the use of Healon® alone does not contribute to this effect. It has been reported earlier, in a similar study comparing the impedances after applying a Healon/steroid mixture (Antwerp group) with impedances after applying Healon alone (Melbourne group), that similar differences could be found (De Ceulaer et al., oral communication at the Pediatric Cochlear Implant Congres, Antwerp 2000). In consequence, the fact that the electrodes in

the Control Groups in this study were not lubricated with Healon® is probably not important.

A third conclusion is that this steroid effect last at least twelve months when the larger electodes are used. In fact, over time, the impedance curves for Test and Control Group 1 tend to run parallel from the second fitting until the end of the follow up. If the steroid effect is due to the anti-inflammatory effect of the steroids, It may seem difficult to explain such a long-term effect after a single application of the drug. But the authors speculate that the traumatic event as such is also limited in time (only the introduction of the electrode) and in consequence no inflammatory reaction is to be expected later on. The single dose of steroids may very well suffice to prevent or decrease the immediate inflammation due to the surgical insertion of the electrode.

A fourth conclusion is that this steroid effect may not last as long when the Contour™ electrodes are used. This group is smaller in number and the follow-up is only 6 months, so more data are needed. Still, it is remarkable not only that the impedances are higher, which is probably due to the smaller surfaces, but also that the steroid effect seems to fade out 6 months after implantation. The authors did not expect the steroid effect to disappear in Group 2, 6 months after implantation and it remains unclear how to explain this. One interpretation could be that with the Contour™ electrodes, the fibrosis remains active during the months following surgery. A single administration of steroids would then have an immediate effect (as is the case), but this effect would disappear over time and the fibrosis would go one. Why the fibrosis would continue with a Contour™ electrode and not with the straight electrodes of the Nucleus® 24 M and k types, remains a matter of speculation. The modiolus-hugging design with a close and permanent contact between the electrodes and the modiolus, could play a role in this phenomenon.

A final conclusion relates to the reimplantations. Four out of five patients who required a new implant because of failure of the former implant, showed significantly higher impedances than the “virgin” peers and these high impedances remained high during the six-month follow-up after the reimpantation. This is most likely due to the additional trauma of the second intervention. Although the group is too small and the follow-up too short for definite conclusions, this could become an important issue for the future. Especially children, who will probably need more than one implant in their life, may experience problems with the second or third implant if the impedances become too high. Both the implant surgeon and the manufacturer should take this possibility into account.

Summary

Congenital permanent and bilateral sensorineural hearing loss occurs in approximately 1 out of every 400 newborns. It affects the communication, the speech- and language development, and the social, educational and emotional development of the child to varying degrees, depending on the level of hearing loss. Deaf-mutism is the most extreme expression of this.

No longer than ten years ago, hardly any diagnostic or therapeutic possibilities were available. The origin of the hearing loss could be retrieved with certainty in less than 10% of the cases. Therapy was limited to hearing aids, which could be frustrating especially in severe and profound hearing loss. The reasons for the poor results were multiple. Late detection resulted in irreversible retardation in the speech- and language development and conventional hearing aids could only partially correct the deficient cochlear functions that they were meant to replace.

During the last decade, this situation has drastically changed.

An important issue has been the worldwide emergence of universal neonatal hearing screening programmes, based on the new technique of transient evoked otoacoustic emissions. The implementation and optimisation took several years of technological, audiological and epidemiological evaluation and fine-tuning. Flanders is the first European region with a population of 6 million that has implemented such a program, which became operational in 1998. The different steps towards a screening model with high coverage, sensitivity and specificity are being discussed in the first chapter of this dissertation.

After failure on the screening, newborns are referred for diagnostic workup. This workup also underwent significant progress over the last decade, mainly due to new developments in genetic research and in medical imaging. Mutations in the connexin-26 gene are thought to be the most frequent genetic causes of congenital deafness, but other mutations are known as well. Mutations in the α-tectorin gene are reported to give a congenital non-progressive mid-frequency hearing loss. The different steps towards the discovery of this gene and its mutations are dealt with in the second chapter. The radiological diagnosis of aplasia/hypoplasia of the vestibulocochlear nerve was first reported in 1997 and appears to be a common cause of congenital deafness. It has also been covered in detail in chapter 2. Finally, the audiological features

of the large vestibular aqueduct syndrome are described. This minor cochlear anomaly is a frequent cause of congenital progressive hearing loss. As a result of these new developments in the diagnosis of congenital hearing loss, certainty about the origin of such a hearing loss is obtained in 65-75% of cases to date.

In line with this evolution, cochlear implants have become an obvious therapeutic option in the treatment of severe to profound congenital sensorineural hearing loss. In view of the critical time-window of the speech- and language development of the child, it is important to implant at a young age. Evidence is growing that this should be done before the age of 2 years, probably even 1 year. Therefore, audiological tools are needed to enable the indication for implantation in infants. The “Auditory Phoneme Evaluation” is a test battery based on phonemes to assess infants below the age of 1 year. The test construction, normative data and results of early implantation are given in the third chapter of this dissertation. In addition, implantation in difficult cases, such as Mondini dysplasia and aplasia/hypoplasia of the vestibulocochlear nerve, is also discussed. Finally an important technical issue is addressed, namely the reduction of the electrical impedances of the implant electrodes. This is of special interest in the young child, not only to reduce the power consumption to a degree necessary for miniaturisation, but also to maximize the future options for re-implantation and by doing so to secure the long-term chances of the child.

One decade ago, children with a congenital hearing impairment were detected late, a diagnosis could be made only in few cases and the common educational setting would be the school for the deaf, with inevitable severe problems in speech- and language development, and even verbal mutism. To date most of these children can be detected at birth, a diagnosis can often be made and early treatment is available and leads to integration in the mainstream educational setting for the majority of cases.

Samenvatting

Ongeveer 1 op 400 kinderen wordt geboren met een congenitaal permanent bilateraal neurosensorieel gehoorverlies. Afhankelijk van de graad van gehoorverlies kan dit leiden tot meer of minder uitgesproken problemen in de communicatie, de taal- en spraakontwikkeling, de sociale, schoolse en emotionele ontwikkeling. In zijn meest extreme vorm leidt dit tot doofstomheid.

Tien jaar geleden waren de diagnostische en therapeutische mogelijkheden in dit kader bijzonder beperkt. Slechts in een tiental procent der gevallen kon een zekerheidsdiagnose gesteld worden. Therapeutisch waren we beperkt tot hoortoestelaanpassing, maar zeker bij ernstige vormen van slechthorendheid waren de resultaten daarvan onbevredigend. De reden daarvan was meervoudig. Vooreerst was de gemiddelde leeftijd van detectie relatief laat, waardoor de spraak- en taalontwikkeling onomkeerbare achterstand opliep. Bovendien ligt de oorzaak van een congenitaal neurosensorieel gehoorverlies bijna steeds in het slakkenhuis en kan een hoortoestel de deficiënte functie daarvan slechts ten dele corrigeren.

Tijdens de laatste tien jaar is deze situatie grondig gewijzigd.

Belangrijk daarbij is dat er wereldwijd programma's zijn ontstaan van universele neonatale gehoorscreening, dankzij de nieuwe techniek van de transiënt geëvokeerde otoakoestische emissies. De introductie van deze techniek voor neonatale gehoorscreening heeft vele jaren van technologische, audiologische en epidemiologische evaluatie en bijsturing gevergd. In Europa is Vlaanderen de eerste regio van die omvang waar, sinds 1998, een programma van universele neonatale gehoorscreening loopt. De verschillende stappen naar een uiteindelijk screeningsmodel met hoge dekkingsgraad, sensitiviteit en specificiteit, worden in het eerste hoofdstuk van dit proefschrift uitgewerkt.

Borelingen waarbij de neonatale screening een gehoorverlies doet vermoeden, worden verwezen voor diagnostische oppuntstelling. Ook daarin zijn de laatste decade grote stappen vooruit gezet, vooral dankzij nieuwe ontwikkelingen in het genetisch onderzoek en in de medische beeldvorming. Mutaties in het connexine-26 gen zijn wellicht het talrijkst, maar andere genetische oorzaken komen ook voor. Mutaties in het α-tectorine gen blijken een congenitaal mid-frequent gehoorverlies te geven dat stabiel blijft in de

tijd. De verschillende stappen naar de ontdekking van dit gen en zijn mutaties worden uitvoerig beschreven in het tweede hoofdstuk van dit proefschrift. De radiologische diagnose van aplasie en hypoplasie van de nervus cochleo-vestibularis werd voor het eerst beschreven in 1997 en blijkt een van de belangrijkere diagnoses te vormen. Zij is eveneens opgenomen in het tweede hoofdstuk van dit proefschrift. Tot slot is een verbreed vestibulair aqueduct een frequente oorzaak van een aangeboren en progressief neurosensorieel gehoorverlies en worden de audiologische kenmerken en evolutie daarvan beschreven. Dankzij deze nieuwe diagnostische inzichten, kan momenteel een zekerheidsdiagnose gesteld worden bij 65-75% van de congenitale doofheden.

In het verlengde van dit alles, is cochleaire implantatie een vanzelfsprekende therapeutische optie geworden bij kinderen met een ernstige aangeboren neurosensoriële slechthorendheid. Aangezien de spraak- en taalontwikkeling van het kind kritisch tijdsafhankelijk is, is het van belang tijdig te implanteren. Vele inzichten wijzen erop dat dit voor de leeftijd van twee, wellicht één jaar optimaal is. Te dien einde is het nodig over audiologische instrumenten te beschikken om de indicatie tot cochleaire implantatie te stellen bij zeer jonge kinderen. De “Auditory Phoneme Evaluation” is een testbatterij die gebruik maakt van fonemen, de bouwstenen van onze spraak, om kinderen jonger dan één jaar te testen. De constructie en normering van deze test, alsook de resultaten van vroegtijdige implantatie, worden besproken in het derde hoofdstuk van dit proefschrift. Ook implantatie bij moeilijke indicaties, zoals een Mondini-afwijking of een aplasie en hypoplasie van de cochleo-vestibulaire zenuw, komen aan bod. Tot slot wordt een belangrijk technisch onderwerp behandeld, namelijk het beperken van de toename van de electrische impedanties van de cochleair implant-electroden. Zeker bij jonge kinderen is dit belangrijk, niet enkel om het stroomverbuik te beperken, wat nodig is voor de miniaturisatie, maar ook om de mogelijkheden tot herimplantatie open te houden en dus de lange-termijn kansen van het kind te vrijwaren.

Tien jaar geleden werden ernstig slechthorende kinderen laat gedetecteerd, werd zelden een diagnose gesteld en kwamen zij in principe in het bijzonder onderwijs terecht met een ernstige spraak- en taalachterstand en vaak zelfs verbale stomheid. Momenteel kunnen de meeste van deze kinderen reeds bij de geboorte gedetecteerd worden, kan er vaak een diagnose gesteld worden en kan er tijdig therapeutisch worden ingegrepen waardoor het grootste deel van hen geïntegreerd kan worden in het normale onderwijs.

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