DILEMMAS AND PITFALLS OF INDICATING COCHLEAR IMPLANTATION IN PEDIATRIC DEAFNESS CAUSED BY KNOWN AND UNKNOWN INNER EAR LESIONS

Ph.D. thesis

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CONTENTS

1. INTRODUCTION AND AIMS OF THE THESIS

Cochlear implantation (CI) is a surgical procedure developed for the treatment of bilateral sensorineural hearing loss (SNHL) where the failure lies within the organ of Corti. The loss of hair cell function is replaced by a device surgically implanted into the vicinity of the spiral ganglion cells. The implant uses electric impulses derived from the transformed, processed and encoded sounds of the patient's surroundings to stimulate the acustic nerve and consequently the central auditory system, thus "reproducing" the mechanoelectric transduction which is the function of a healthy cochlea.

Ever since CI was devised as a concept and procedure, its field of indications has been continuously expanding. In the beginning only *postlingual* (onset after language development) *totally deaf adults* were implanted, but during the ensuing years the indications were broadened to include *children*, *partially deaf* patients, *prelingual* (onset before language skills are acquired) deaf patients and any combination of these criteria plus some more. This expansion of indications was enabled by a growing knowledge about these patients, the realisation of neural plasticity, the observation of the implants' effects on the cochlea, acustic nerve and central nervous system, the discovery of CI complications, device development (hardware and software both) and through these all the better understanding of the mechanisms of normal and impaired hearing and speech development. These processes – both our learning about what it means to hear and to give back hearing, and the further extension of indications – keep happening in the present.

The aims of my thesis are the following:

1. The introduction of genetic screening brings about the better understanding of the genetic background of deafness, and leads to a more accurate identification of implant candidates meaning a more accurate and better established surgical indication. My aim was to work out and to demonstrate the practical feasibility of a non-invasive procedure which enables us to screen for known deafness-causing genetic mutations without drawing blood in any age group (primarily in little children) in order to gain an early, accurate genetic diagnosis for a proper indication of CI and for full patient (re)habilitation.

2. With the growing number of implanted patients more so-called special cases get to be operated, as well. With the presentation of three extraordinary cases from our department's implantees I set out to demonstrate that with proper professional caution it is worth

performing the CI of children healed from an earlier malignant tumorous disease, and that we should accept the potential surgical difficulties and risks of implanting patients with unusual, unclassified inner ear malformations for the sake of enabling audition.

3. My purpose was to map the foreseeable routes the development of CI will take. I set out to illustrate how a laboratory research method can contribute to the development of implants, to the expansion of the indications of CI and to a better understanding of the pathomechanism underlying certain postimplantation complications, e.g postimplantation meningitis.

2. THE HISTORY OF COCHLEAR IMPLANTATION

In truth the history of cochlear implantation begins with the discovery of the electrical excitability of the auditory system. Having inserted a metal electrode into both his ears, Alessandro Volta lead a direct current with approximately 50 Volts through his head in 1800, upon which he had an acustic experience lasting for seconds [186]. In 1801 Ritter repeated Volta's experiment on himself [147]. Volta's experiment were followed by several similar attempts throughout the next half century [153] until Duchenne discovered in 1855 that auditory stimulation performed with alternating current provides a longer lasting subjective sound more similar to real sounds [48].

Brenner published a detailed study in 1868 about the effect of the polarity, frequency, strength of the stimulating alternating current and the position of the electrodes on the quality of the acustic sensation [15].

In 1950 N. Lundberg stimulated the acustic nerve with sinusoidal current during a neurosurgical operation. His patient reported on hearing a noise [59].

The implantation of the first electric acustic nerve stimulator is credited to André Djourno and Charles Eyriès in Paris. Preceding the pioneer work, Djourno studied the electrophysiology and telestimulation of nerves [38, 39], mentioning the chance of electrically stimulating the acustic nerve as a treatment of deafness in an article in 1954 [43]. Being an ear surgeon, Eyriès was interested in the treatment of facial nerve injuries [129], so he was called upon by his colleagues to help a patient suffering from a bilateral iatrogenic peripheral facial nerve palsy. A partial temporal bone resection had been performed on the left ear of the patient because of a large cholesteatoma several years before, leading to deafness and

peripheral facial nerve palsy on the left. His right ear necessitated the same operation due to cholesteatoma in February 1957, also resulting in deafness and facial paralysis. Eyriès attempted a surgical reconstruction of the right facial nerve unsuccessfully, hence he was planning a second operation. Electric diathermy applied during the first reconstruction attempt (performed in local anaesthesia) caused hearing sensations to the patient who reported this to Eyriès [41]! Eyriès contacted Djourno knowing about his work on nerve stimulation. Djourno suggested that the hearing should be surgically improved (by implanting his nerve stimulator) along with grafting of the facial nerve.

The operation was performed on February 25, 1957. After a successful reconstruction of the facial nerve with graft, Djourno and Eyriès implanted a stimulating electrode into the stump of the acustic nerve. The electrode was connected to an induction coil, thus the implant could be made to work in a transcutaneous (not percutaneous!) fashion. A few days after surgery the patient was able to differentiate sounds with different pitch [41]. Later he was able to recognize a few simple words and his implant provided him considerable help with lipreading by transmitting the rhythm of speech [40, 42].

Months later the implant stopped functioning because of a broken electrode, so Djourno and Eyriès replaced it in another operation. Unfortunately the second implant also suffered the same fate after a while. Eyriès – blaming Djourno, maker of the implants – would not perform a third operation. The relationship of Djourno and Eyriès terminated here [50].

In 1958 Djourno and Roger Maspetiol performed another implantation. This time a stimulating electrode was implanted in the neighbourhood of the round window of a young woman who was deafened by streptomycin. They achieved similar results to the first implantation [44, 45].

In 1958 Djourno also built a sound analyser (a contemporary ”speech processor”, actually) which was capable of a real-time frequency analysis of human speech, channeling the different frequencies into separate stimulating channels [37, 46]. This work practically displays the idea of a multichannel cochlear implant. After this, however, Djourno cound not carry on with his research due to a lack of funding [61].

Hearing about the work of Djourno and Eyriès [71] William House (Ear Research Institute, Los Angeles, California, USA) inserted a single channel electrode into the cochlea (scala tympani) of two patients and a multiple channel electrode into that of one patient in 1961, which were able to evoke an acustic experience by electrical stimulation. The patients, however, were unable to tolerate these intracochlear implants in the long run, so they had to be removed later [72].

Blair Simmons (Stanford University, Palo Alto, California, USA) stimulated the acustic nerve of a volunteering patient with bipolar electrode during a craniotomy done in local anaesthesia because of a recurring cerebellar ependymoma in 1962. The patient was able to determine the length of stimulation and differentiated between sounds with different pitch [162]. In light of the results Simmons introduced an array of six electrodes into the modiolus of a patient suffering from bilateral, severe hearing loss in 1964. He carried out investigations with the patient for one and a half years [161].

Robin Michelson (University of California, San Francisco, California, USA) implanted permanent, single channel electrodes into patients' cochleae [111, 112]. His patients were later followed up by Merzenich and coworkers [154].

In 1962 Doyle and coworkers (Loma Linda University, Loma Linda, California, USA) implanted a stimulating array of four electrodes into the cochlea. The patient was able to repeat certain words upon hearing [47].

In 1963 Zöllner and Keidel (Freiburg, Germany) stimulated the cochlea of patients suffering from unilateral deafness caused by Ménière's disease in local anaesthesia. Based on their results and theoretical considerations (tonotopic structure of the cochlea and the spiral ganglion) Zöllner and Keidel proposed the development of an array which would be inserted into the cochlea up to the second turn through the round window and which would tonotopically stimulate the cochlea with 20-100 electrodes to ensure adequate speech perception [200].

A common problem of the first cochlear implants was their rapid rejection due to the unsolved issue of biocompatibility. Further research and inventions resulted in the production of chronically tolerable cochlear implants by the end of the sixties [72].

Following the pioneer steps in the fifties and sixties the development of cochlear implants started in several centres of the world in a parallel fashion during the seventies.

In 1972 House's group produced the first induction coil and portable speech processor to be worn with their single channel implants. The *House 3M* implant (Minnesota Manufacturing and Mining Company) and its processor was implanted in great numbers from the beginning of the seventies. Producer of the House 3M later ceased to be and care of these patients were taken over by Cochlear Corporation.

At the University of Melbourne (Melbourne, Australia) Graeme Clark began the development of a multichannel intracochlear implant. He performed the first implantations in 1978 and 1979 [25]. Development in association with the firm Nucleus in Sydney (today Cochlear Corporation) brought about the first *Nucleus* implant to be put to the market in 1982.

A multichannel cochlear implant was developed at the University of California as a result of the work of Michelson, and later Merzenich and Schindler in association with the firm Storz [154]. That device is no longer being produced but the cooperation of the same research group with Advanced Bionics Corporation gave birth to the *Clarion* implant which was commercialized in 1991.

Eddington and Brackmann at the University of Utah (Utah, USA) begin developing a multichannel cochlear implant in 1975 [49]. Electrodes of the device named *Ineraid* (Symbion, Inc.) were in permanent percutaneous connection with their speech processor. Although results with this device were promising, due to worries raised by the percutaneous connection the FDA did not approve the use of this device.

In Paris Chouard – who worked in the facial nerve laboratory of Eyriès at the time of the implantation by him and Djourno – carried out research with a multichannel intracochlear implant named *Chorimac*. He performed a cochlear implantation on 21 patients by 1975 [22]. The electrodes communicated with the outer world through a percutaneous teflon connector. This setup, however, lead to skin infections so the research group switched to transcutaneous signal transmission. The successor of Chorimac today is the *Digisonic* implant produced by MXM/Neurelec in France.

Bánfai in Cologne and Düren, Germany experimented with a multichannel extracochlear implant. Its eight electrodes were placed in holes drilled on the promontory as deep as the endosteum (without penetrating it) [6]. The percutaneous connection of the implant with the outer world, however, later led to problems. None of the *Banfai-Hortmann* implants produced by the German Hortmann company are functional today.

Offeciers and Peeters at the University of Leuven (Leuven, Belgium) developed a multichannel intracochlear implant from the middle of the eighties [126, 133] which was manufactured under the name *Laura* (Antwerp Bionic Systems, later Philips). Laura implants are no longer produced, the patients are taken care of by Cochlear.

In Vienna, Austria Hochmair, Burian and Hochmair-Desoyer experimented with both extra- and intracochlear, single- and multichannel implants during the seventies [18]. Later they decided on developing a multichannel intracochlear device. Their first such implant was implanted into human in 1977. They founded Medical Electronics Corporation in Innsbruck in 1989 which today produces the *MED-EL* implants.

3. THE HISTORY OF COCHLEAR IMPLANTATION IN HUNGARY

In 1979-80 Jenő Hirschberg performed one CI in Düren, Germany and three more implantations in the Pál Heim Children's Hospital of Budapest with Banfai-Hortmann extracochlear devices.

In 1985 CI was introduced by Ottó Ribári as an organised programme at the Department of Otorhinolaryngology and Head & Neck Surgery of the Semmelweis Medical University, Budapest with the Banfai-Hortmann devices [145]. The Budapest centre later switched to the intracochlear implantation method with multichannel implants. Today their programme is directed by Gábor Répássy.

This pioneer work was followed ten years later, in 1995 by the foundation of the second Hungarian Cochlear Implantation Centre at the Department of Otorhinolaryngology and Head & Neck Surgery of the Albert Szent-Györgyi Medical University of Szeged (today named University of Szeged) under the chairmanship of Jenő Czigner and later József Jóri [32, 85]. The Szeged centre implanted multichannel intracochlear devices from the beginning.

Witnessing the success of the first two centres the National Health Insurance agreed to CIs performed at the otorhinolaryngological departments of the other two Hungarian universities with a medical faculty, too, in 2002. The CI programme started at the Department of Otorhinolaryngology and Head & Neck Surgery of the University of Pécs under József Pytel and at the Department of Otorhinolaryngology and Head & Neck Surgery of the University of Debrecen under István Sziklai.

At the time of the first cochlear implantations in Budapest the scientific "debate" between advocates of the extracochlear and intracochlear implant was not yet settled. In another few years, however, the direction to be followed became evident in the leading centres of the world: multichannel intracochlear implants should be used. Hence – apart from the Budapest centre's work in the first years – cochlear implantation in Hungary could adopt settled and scientifically proven precepts and easily applicable surgical techniques. Thanks to this, members of the Hungarian CI centres could turn their attention toward various clinical investigations and CI-related research beside performing CI according to internationally acclaimed standards. Publications were born about medical/surgical and biophysical/engineering observations which helped expanding the aspects of patient selection and the field of indications. The question of implantability of certain special groups of patients (patients with malignant tumors, epilepsy, or unusual cochlear malformations) is becoming clear [172, 173, 174, 178, 180]. Beside genetic examinations at the Debrecen and

Szeged centres Hungarian specialist developed cooperation with internationally acknowledged foreing centres (Debrecen – Tübingen [182], Szeged – Hannover [181]). Thanks to these common programmes of scientific research a better knowledge and recognition of patients (on the genetic level) is possible. It also became possible for Hungarian researchers to be involved in laboratory work related to the development of the new, would-be generation of cochlear implants at the Department of Otolaryngology of the Hannover Medical University.

4. THE INDICATIONS OF COCHLEAR IMPLANTATION

The first cochlear implantation in the world was performed on a postlingually deafened adult by Djourno and Eyriès. Following the direction of their pioneer work House and more and more researchers after him also carried out investigations and implantations on postlingual deaf adults. *Cochlear implants were originally designed for the treatment of bilateral postlingual total deafness in adults*. In 1980, however, House performed the first CI in the world on a prelingual deaf child, thus opening the gate of hearing (re)habilitation for another group of patients [74].

It would be impossible to cover the ever-expanding field of indications of CI with the consideration of just one aspect (e.g. the age of the implanted patients, or the cause of deafness or the time of its onset). In my thesis I will attempt to discuss the various indications viewed from several aspects, at the same time also trying to depict the history of how they came to be established.

4.1. Age, time of the onset of deafness, the degree of hearing loss

4.1.1. Adults

The first indication of CI was bilateral total deafness (anacusis, >121 dB HL) in adults with postlingual onset. The development of implants and implantation techniques soon enabled broadening of the indication field from total deafness to bilateral profound deafness (91-120 dB HL). In light of the spectacular results indications were further extended to the group of severe-to-profound deaf (pure tone average around 90 dB HL), where high-performance conventional hearing aids provide only minimal speech understanding beside a

certain degree of pure-tone threshold improvement. Results proved to be very satisfying in this group of patients, too.

Balkany and his group forecast the further expansion of the indication field in 1997 when they prognosed the introduction of CI in patients with severe hearing impairment (70-90 dB HL) a.k.a. patients with residual hearing [69]. According to research by other authors the presence of residual hearing is a possible predictor of good performance with CI [92, 149, 184]. This is explained by the stronger presence of surviving hair cells in the cochlea in case of residual hearing, which in turn results in a greater number of viable spiral ganglion cells that can be stimulated electrically [149].

In 1999 Klenzner et al reported on their satisfactory results of CI in five patients with residual hearing [94]. Their patients suffered from severe hearing impairment, their speech discrimination in the Freiburg monosyllable word test was 5-30% at 70 dB SPL with conventional hearing aids.

According to the most recent data in literature CI is indicated even in cases of severe bilateral hearing loss where speech discrimination in open-set word test is lower than 40% at 65 dB HL with optimal hearing aids [33].

There is no upper age limit of CI for postlingual deaf adults apart from considering the general state of health. CI in elderly patients is regarded as safe and generally satisfactory [17, 88, 176]. It is, however, important to emphasize – and not only in case of elderly patiens, but concerning every CI candidate – that the length of time between the onset of deafness and CI may have a considerable influence on results achieved with the implant: the shorter this time is, the better hearing rehabilitation may be expected from CI. The explanation partially lies in the cross-modal reorganisation of the brain enabled by neural plasticity and caused by auditory deprivation [98]: having lost its acustic stimuli (meaning: having lost its *function*) the auditory cortex falls prey to ”colonisation” by neighbouring cerebral areas – fortunately rather slowly in postlingually deafened adults. The advancement of this process determines how well the acustic input restored by CI can be utilised. On the other hand, the number of hair cells and their trophic effect on spiral ganglion cells will be dramatically reduced in a deafened cochlea, and the latter will bring about the reduction of spiral ganglion cell numbers in the long run. Hence, the longer the deafness is sustained, the lower the number of electrically stimulatable ganglion cells will be in the cochlea [123, 149].

It is best to discuss the other major adult group, prelingually deafened adults on the apropos of plastic brain reorganisation. In this group of patients the functional specialisation of the cortical region ”destined” for hearing does not happen until the onset of deafness.

Considering that a child's brain (prelingual deaf adults lose their hearing in childhood!) is definitely more plastic, cross-modal reorganisation in the absence of acustic stimuli will occur faster and to a greater extent at the expense of the auditory cortex.

At the beginning of CI operations were performed on prelingual deaf adults, too. In 1979 House reported on the first such implantation [72] and in 1981 he summarized his results on several prelingual deaf adult CIs with optimism [74]. The majority of his patients regarded CI as a factor positively influencing their lives, highlighting the appearence of sound hearing or its considerable improvement, the end of isolation from their environment etc. The dynamic development of CI in the ensuing years and the unexpectedly remarkable postoperative results of certain groups of implanted patients, however, soon raised the expectance of both physicians and patients from implantation. In light of these, the results achieved with prelingual deaf adults – similar to those of House's patients – were no longer so encouraging [166, 190, 201], hence implantation in this group of patients was practiced only seldom after the initial enthusiasm. From the end of the '90-es papers with more optimism began to appear again, reporting on better results than previously [130, 156, 189, 191]. These results are probably related to the emergence of newer speech encoding strategies, the greater number of deaf people using auditory-verbal (oral) communication, the growing experience of hearing (re)habilitation centres and a more appropriate patient selection [142]. It is very important to emphasize that – beside other factors – individual abilites and motivation have a determining influence on postimplantation results in this group [33]. The latter is also corroborated by the nice results achieved with a few prelingual deaf adults at our department. Hence, *nowadays – with appropriate patient selection, reserved optimism and expectations – we indicate CI for prelingual deaf adults, as well*.

4.1.2. Children

The first pediatric CI was performed in 1980 by House on a prelingual deaf child [74]. Seeing the success of surgery and postoperative rehabilitation House and his group implanted 12 deaf children during an 18-month pediatric cochlear implantation pilot study [73]. In light of the fine results they launched their pediatric CI programme.

The first European pediatric CI programme was initiated in 1988 in Hannover, Germany [100]. The Hannover group implanted postlingual deaf children in the first time, then began to operate on prelingual deaf kids, too, and reported on good results with both groups [99, 100].

While the time elapsed between the onset of deafness and CI is an important factor in postlingual deaf children, it is not all-important concerning rehabilitation results. In these children – like postlingual deaf adults – the functionally already specialized auditory cortex is somewhat protected from cross-modal reorganization between cortical areas of different functions, and the ability for speech production and speech perception is preserved without acustic input. Still, for the sake of vocabulary, personality and interpersonal relationship development CI is better be performed as soon as possible.

In prelingual deaf children the length of time between the onset of deafness and CI is a critical, all-important factor from the aspect of hearing and speech development. In this group – and also in prelingual deaf adults, who will become of prelingual deaf children without CI – the cerebral area originally destined to develop as auditory cortex will quickly (in a few years) and irrevocably come to serve other cortical modalities to a large extent without acustic stimuli due to the extraordinary plasticity of a child's brain. Beside this, the lack of acustically generated trophic effect (delivered by hair cells in a healthy cochlea) will cause a continuous decrease of the number of stimulatable ganglion cells until the time of CI (when the stimulation of ganglion cells is restored) [123]. While a prelingual deaf child implanted in good time may learn to speak and understand speech flawlessly with the aid of his CI, a patient undergoing a delayed implantation will achieve considerably weaker results – though this depends highly on personal abilites and commitment.

In 1994 the Hannover group defined the lowest age for CI in prelingual deaf kids at 3 years [100]. At the same time, they emphasized in the same paper that in certain pressing circumstances (e.g. meningitis causing deafness, see later in detail) this age limit might be pushed considerably lower. The same group reported in 1999 about implanting children below the age of 2 years as their everyday practice [102]. Govaerts et al published a study in 2002 stating that while 60% of kids implanted between 2 and 4 years of age may participate in mainstream education from the age of 7, 67% of those implanted under 2 will enter mainstream kindergarten/school already at 3 years of age [60].

In 2004 the lower age limit of pediatric CI was – apart from exceptional cases – 1 year [26]. However, a 2007 report about the indications of CI [33] cites many authors according to whom children implanted under 1 year of age will show better speech development results than their counterparts operated between 1 and 2 years. Schauwers et al examined the effect of very early CI on prelexical speech development (speech development preceding the use of actual words) [152]. Observing the babbling and CAP (Categories of Auditory Performance) of children implanted between 5 and 20 months of age they found that

kids implanted under the age of 1 year showed a prelexical speech development with dynamics equalling their hearing counterparts, while those implanted later lagged behind healthy controls to some extent for months.

At the beginning of pediatric CI only children with bilateral total deafness were operated [2, 99, 100]. In 2000 Walch and coworkers published a study about the educability of kids with various degrees of hearing impairment in kindergarten and school and found that bilateral profound deafness (>91 dB HL) does not make the education of kids in conventional kindergarten or school (a.k.a. integrated education) possible, only education in a special institution (deaf school). The paper suggests CI for these children [188].

The field of indications in pediatric CI expanded in the direction of children with residual hearing in recent years, just as in the case of postlingual deaf adults. Following the scheme of the implantation of selected adults with residual hearing (severe hearing loss, 70-90 dB HL) Hodges et al prognosed the same tendency for children already in 1997 [69]. Cowan et al predicted the same in the same year [28]. In 2000 Gantz and coworkers performed CI on a small group of children with residual hearing and measured significiantly better postoperative open-set word recognition than in children implanted with no preoperative word recognition at all [55]. Mondain published in 2002 about the CI of prelingual deaf children with residual hearing above the age of 4 whose open-set word recognition was 30% at most with conventional hearing aids [115]. 12 months after CI he experienced an exceptionally marked development (speech recognition >60%) in every child. He proposed further similar studies to determine whether the indication limit of 30% preoperative open-set word recognition could be raised to 40% in prelingual hearing impaired kids with residual hearing. In 2004 Quaranta quoted several authors who suggested CI for selected cases of children with residual hearing [142]. Brademann definitely proposed the CI of children with residual hearing at the 8th International Conference of the European Society of Paediatric Otorhinolaryngology organised in June 2008 in Budapest, Hungary [14].

According to Deggouj's 2007 article [33] *pediatric CI is indicated in cases of bilateral hearing loss exceeding 85 dB HL*. At the same time Deggouj and other authors, as well, emphasize that the degree of hearing loss and the usability of residual hearing (or the absence of its usability) with conventional hearing aid must be determined with utmost care before CI is indicated. The problem is, that this is becoming more and more difficult with the continuous decrease of the lower age limit of CI. The conclusion of the papers cited by Quaranta is that under 4 years in case of residual hearing CI can only be indicated with the greatest possible caution [142]. As speech perception can be determined properly only from 5

years of age with the presently available methods, new speech audiometry approaches need to be developed and other assessment modalities introduced to enable the indication of surgery without a doubt.

4.2. Labyrinthitis ossificans

The essence of this phenomenon is an inflammatory process leading to the bony obliteration of the inner ear. It can be triggered by a meningitis causing deafness. If a meningitis leads to deafness, the latter develops parallel with the former or right afterwards. Ossification of the cochlea, however, takes months, or sometimes years and means a partial or complete obliteration of the cochlear lumen. *The surgical treatment of deafness is CI in such a case, too*, which is technically more challenging but never contraindicated (as opposed to the beginning of the CI era, when it *was* contraindicated). Implanting surgeons recognized early that it's better to precede the obliterative process with CI. This was the illness where surgeons first dared to push the lower age limit of CI under the age of 2, though Lehnhardt in 1994 [100] called for extreme caution yet: he suggested CI under 2 years of age only if bilateral deafness was present without a doubt and CT showed the first signs of bony obliteration. Naturally, the tendency of continuously lowering the age limit of CI in recent years also meant its lowering in cases of obliterative labyrinthitis. According to a 2004 paper of Cohen CI under the age of 1 year in this disease is generally accepted and the youngest child implanted for this reason at the otolaryngology department of the New York University School aged 6 months [26]. At the same year the author of the present thesis had the chance to witness professor Thomas Lenarz of the Department of Otolaryngology of the Hannover Medical University performing a bilateral cochlear implantation on a 4-month-old baby suffering bilateral deafness from meningitis to precede the obliterative process and to enable full audiological rehabilitation. Of course, CI in infants raises several technical difficulties and chances for complication [26], which, however, can be avoided with a proper surgical technique.

It should be mentioned that the bony obliteration of the cochlea may rarely occur as a result of some other illness (autoimmune inner ear disease, invasion by tumor, temporal bone fracture, chronic middle ear inflammation, obliterating otosclerosis, Ménière's disease) [87].

4.3. Inner ear / temporal bone malformations

Developmental disorders of the labyrinth meant a contraindication at the beginning of the CI era. Thanks to the growing experience with the anatomy of the temporal bone and its imaging *CI is performed in several minor and major anomalies of the inner ear nowadays*. Mondini's dysplasia, common cavity malformation, cochlear hypoplasia and other developmental disorders require special attention and surgical experience and often also the modification of standard CI techniques (see Case report in Chapter 7). In some malformations (e.g. stenosis of the internal auditory canal with absence of the 8th cranial nerve or cochlear aplasia) CI is not an option but auditory brainstem implantation may be attempted.

4.4. Additional handicaps – multiple handicap

Handicaps accompanying bilateral total, profound or severe deafness – like blindness or impaired sight, slight mental retardation, psychiatric problems, motor disabilities, behavioural problems – were a contraindication of CI in the beginning. The fact that CI is performed in an ever younger age and that it is more and more difficult to diagnose slight mental/motor/psychiatric disturbances in a younger age shed new light on this matter [192]. *Nowadays multiply handycapped deaf patients are indicated for CI more freely – though with utmost caution* – and promising results were reported in several combinations of multiple handicaps [103, 150]. The implantation of a patient with deafness and blindness, one with osteogenesis imperfecta and one with grand mal epilepsy should be mentioned from our department's experience [172, 173, 174].

4.5. Bilateral cochlear implantation

The first report on bilateral cochlear implantation came in 1978 from Johnsson, House and Linthicum [84].

Bilateral CI has been performed in increasing numbers worldwide recently. From the side of implant producers there is partly a financial driving force behind this, obviously. On the other hand, benefits derived from binaural hearing (better sound localisation, better speech understanding in noise) as opposed to monaural hearing are well known, and studies so far have justified the reasoning of those ear surgeons who expected the same benefits from bilateral CI [105, 122, 155, 185].

However, while we may speak about indications concerning unilateral CI, we can't do the same for bilateral CI. Or to be more accurate: *the indications for a bilateral CI are the same as those for a unilateral one*. If the indication for a (unilateral) CI exists in case of a given patient (and bilateral CI is technically feasible), then it is only the health care situation of the given country, the decision of the surgeon and the wish of the patient that determines whether a unilateral or a bilateral CI will be performed. We have to accept that bilateral CI raises serious economical questions. Certain heath insurance companies will not finance two implants for a patient, and in certain countries the national health care budget for CI is centrally decided and limited. In the latter situation, when the number of patients needing implantation is bigger than the number of centrally allocated implants, it is reasonable both from the humane and the economic point of view to help the greater number of patients with unilateral CI [26].

4.6. Residual hearing, electroacustic stimulation

The presence of residual hearing needs to be discussed from another point of view beside the indication or contraindication of CI (see 4.1.1. and 4.1.2.), one that in part lies beyond the questions of CI. It was von Ilberg who first defined and demonstrated electroacustic stimulation (EAS) as a phenomenon and a procedure for hearing rehabilitation [187] in 1999. Not much later Gantz et al presented the first hibrid/bimodal implant capable of EAS [55, 56, 58].

The essence of the procedure is that a special type of implant is inserted into the ear with residual hearing which will provide electric stimulation only in the frequency range which cannot be improved with conventional hearing aid. The hearing residuum of the same ear is stimulated acustically with a hearing aid at the same time – parallel with electric stimulation. The fact that these patients can greatly benefit from their cochlear implants can be partly explained with the lack of auditory deprivation and partly with the fact that a great number of nerve elements exist in their cochleas that can be stimulated electrically (as well) [30].

What makes the procedure feasible in practice is that the human ear and central auditory system is able to intergrate information gained from a simultaneous electric and acustic stimulation [56, 187], and that residual hearing can be preserved in the implanted ear with adequate, minimally traumatizing implantation technique [5, 58, 64, 69, 82, 91, 187].

Today EAS is indicated for patients who have considerable residual hearing in the lower frequencies in both ears while their hearing thresholds reach deafness or its equivalent with dramatic steepness toward middle frequencies ("left corner" audiogram) [26]. Until 2007 only reports about EAS in adults were published. In 2007, however, Skarzynski and his group published a study about CI and subsequent EAS in children with considerable residual hearing in the lower frequencies (left corner audiogram) [165]. Their results prove that residual hearing can be preserved in children, too, with adequate surgical technique and that a combined electric-acustic stimulation will provide good results comparable to that of adults in this group, also. Based on these observations, *the previously described indication of EAS applies not only to adults but also to children*.

5. A NON-INVASIVE METHOD FOR SCREENING FOR KNOWN GENETIC MUTATIONS BEHIND DEAFNESS

5.1. Introduction

Hearing impairment is the most common sensory disorder. It is the prelingual manifestation of HL that has the most dramatic impact on the life of the affected individual and his/her family. Congenital hearing impairment (the most frequent form of prelingual HL) affects 0.1% of children born in developed countries [96, 119].

Recent advances in the genetics of deafness show that at least 50% of the congenital cases have a genetic background (mostly inherited genetic disorders, seldom newly occuring mutations) [96].

Hereditary hearing loss may be conductive, sensorineural (not only peripheral but also central) and mixed type. It may have a prelingual, perilingual or postlingual onset. It may be associated with other inherited disorders as a syndromic HL (30 %) or may present on its own as a nonsyndromic HL (70 %). According to our present knowledge a mutation in any of several hundred known genes may lead to hereditary hearing impairment, with mutations in the GJB2 gene being by far the most frequent cause [96]. This gene – localized at 13q11-q12 – encodes the Connexin-26 protein [66]. Cx26 (also named GJB2 meaning *g*ap *j*unction *b*eta-*2*) is a protein, one of the several connexins expressed in cell membranes in the cochlea [36]. Connexins aggregate in groups of six forming a unit called a connexon with a pore of 2.3 nm diameter at its centre. A connexon of one cell covalently bonds with a connexon of a

neighbouring cell, thus forming a channel which bridges the adjoining cell membranes connecting the two cytoplasms. Connexons built from one type of connexin are called homomeric, those made up of different connexin molecules heteromeric. A gap junction channel composed from two identical connexons is homotypic, otherwise heterotypic. Connexon channels aggregating in large numbers can be seen with an electronmicroscope as a gap junction (Fig. 1).

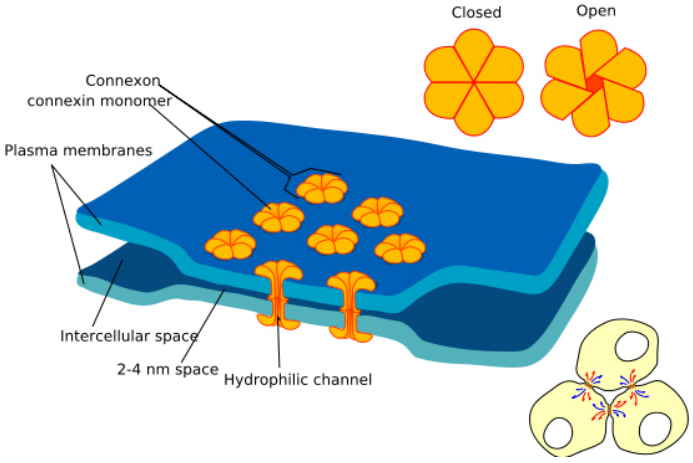

Fig. 1: Connexin, connexon and gap junction (from: en.wikipedia.org/wiki/Gap_junction)

In the cochlea Cx26 is present in the gap junctions of both the epithelial cellular network (nonsensory supporting cells of the organ of Corti and adjacent epithelial cells) and the connective tissue network (fibrocytes of the spiral ligament plus basal and intermediate cells of the stria vascularis but no marginal cells). Gap junction channels allow the transmission of several ions and low-molecule-weight species including potassium ions (K^+), calcium ions (Ca^{2+}) and signalling molecules such as cAMP and $InsP_3$ (inositol triphosphate) [35, 67] (Fig. 2). They seem to play a key role in the K^+ circulation between the hair cells, endolymph and stria vascularis during mechanoelectric transduction [93] and its spatial buffering after mechanoelectric transduction.

Mutations of Cx26 are considered to inhibit the normal function of gap junctions, affecting the K^+ recirculation, thus leading to HL. Earlier models considering the role of Cx26 gap junctions *solely* in K^+ recirculation, however, cannot explain why healthy Cx30 gap junctions – coexpressed in the epithelial cellular network (see below) along with mutant Cx26 gap junctions – are unable to compensate the defect of Cx26, thus preventing the development of deafness. Current research *and theory* implies that the mutations of Cx26 will inhibit Cx26 gap junction permeability to the Ca^{2+}-mobilizing second messenger $Ins(1,4,5)P_3$, which will result in the lack of a regenerative wave of Ca^{2+} throughout the supporting cells of the organ of Corti that should be necessary for pumping the excess K^+ out of these cells into the

endolymph [10, 16]. Accummulation of K^+ in the supporting cells (travelling here from the endolymph through the hair cells during mechanoelectric transduction) causes the excitotoxic death of hair cells. Cx26 mutations present as a degeneration of hair cells and an agenesia of the stria vascularis during histological examination [86].

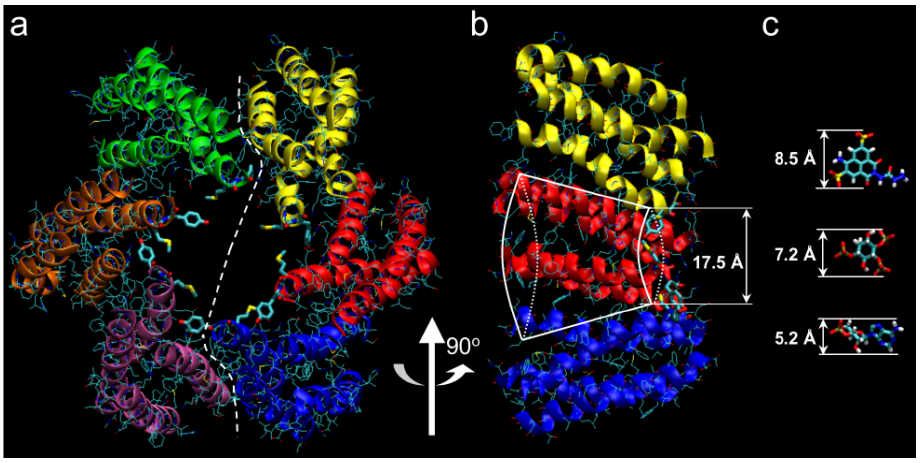

Fig. 2: Structural model of the human Cx26 connexon. a/ Extracellular view of the transmembrane part of the hemichannel, each composing connexin depicted in different colour. Residues Met151 and Tyr152 that determine the maximum constriction belt are drawn with thick lines. White dashed line indicates the dissection surface of the cross section. b/ Cross section. c/ Minimal dimensions of some permeating molecules: Lucifer Yellow, InsP3 and cAMP from top to bottom. Figure adopted from Hernandez et al [68].

Several dominant mutations of the GJB2 gene have been described so far. In one dominant mutation the damaged Cx26 protein with an altered secondary structure seems to partially block the activity of the coexpressed wild type (normal) Cx26 [107], in another the oligomerisation / channel formation of the mutant Cx26 is disturbed leading to nonfunctional channels (Fig. 3) [118]. The resulting SNHL in dominant mutations is prelingual in onset and is characterized by a progressive deterioration of high frequency thresholds.

Recessive mutations of the gene GJB2 encoding the protein Connexin-26 cause a (usually) stable SNHL with prelingual onset. More than 70 such mutations have been identified so far. The majority of them lead to loss of Cx26 function by lack of expression (e.g. R184P), inappropriate membrane sorting (e.g. G12V, S19T, 35delG) or impaired channel formation (e.g. V37I, W77R, S113R, 235delC) (Fig. 3). The most common autosomal recessive mutation among the European population is the frameshift mutation 35delG that leads to an early termination of Cx26 synthesis. Thus, only a shortened Cx26 protein is synthesised that is not functional. The resulting congenital HL is usually a bilateral, non-progressive profound deafness which shows neither improvement, nor fluctuations [63]. In a minority of cases the same mutation may cause less severe problems, leading to mild or moderate HL, and in 10-20% of the patients progression of the HL has also been demonstrated [63].

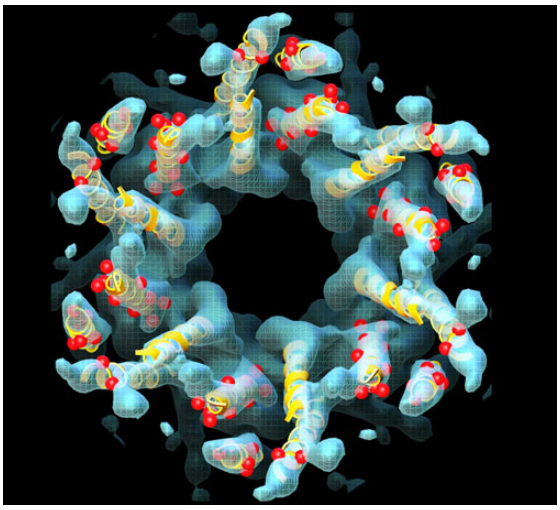

Fig. 3: Computer graphic model of a gap junction channel derived by combining the results of biochemical studies, a computational analysis of connexin sequences and electron cryocrystallography. Yellow ribbons stand for the membrane spanning domains of the hemichannels. Red spheres mark mutations in the sequences which may disrupt helix-helix packing. Figure adopted from M. E. Pique and M. Yeager; www.scripps.edu/newsandviews/ e_20041025/yeager.html

As the mutations of the Cx26 gene may account for as much as 60% of autosomal recessive nonsyndromic HL in some countries [34, 199], the screening of Cx26 mutations is suggested as the most promising initial test in any genetic analysis of genetically caused deafness [76]. Several reliable methods have been suggested for the screening of mutations of the Cx26 gene [3, 19, 53, 143, 163], all based on the analysis of genetic material gained from the most commonly used DNA source, peripheral whole blood (leukocytes). Drawing blood from an adult usually poses no challenge, whereas gaining blood from very young children, however, does. It often proves to be a time consuming maneuver which is an undesired trauma for both the patient and the parent. Hence, an easily accessible alternative DNA source was required. In principle, any nucleated tissue may serve as DNA source for analysis, but until recently only few articles reported on the practical use of anything else than peripheral blood for the detection of Cx26 mutations.

Mucosal surfaces provide a convenient source of nucleated cells, with the oral mucosa being the most easily accessible. In 2006 we reported on a qualitative *and* quantitative comparison between DNA gained from buccal smears and DNA isolated from blood samples [181]. The objective of our study was to demonstrate the feasibility of the use of buccal smears as adequate DNA source for screening 35delG mutations of the Cx26 gene and to show the advantages of buccal smears versus blood in the genetic analysis of deafness in very young children.

5.2. Material and methods

For the purpose of our study we chose hearing impaired patients who were preevaluated for cochlear implantation at the Department of Otolaryngology and Head & Neck Surgery of the Hannover Medical University, as in these patients a higher than average mutation rate of the Cx26 gene could be expected. Patients were referred to the department for cochlear implantation preevaluation based on the observation of HL or audiological examinations performed at other audiological centres. From October 2004 to February 2005 a total of 60 patients were assessed, all of whom were proven to be deaf (either prelingual or postlingual) during the cochlear implantation preevaluation process (including otomicroscopy, electrocochleography, brainstem response audiometry, otoacustic emission). Ages of the patients ranged from 1 to 72 years with the mean age of 15.8 years. As the aim of our study was to demonstrate the feasibility and the usefulness of buccal smears in very young children, we divided our patients into two groups. Patients aged 3 years or less formed Group 1 (29 patients, mean age: 1.5 years). Patients above the age of 3 years formed Group 2 (31 patients, mean age: 29.1 years). Peripheral blood and buccal smears were collected from every patient. Throughout the collection of both buccal smears and blood the examiner wore sterile gloves to avoid contamination of samples with his own DNA. The patients or their parents signed a written consent prior to the genetic examination and the study was permitted by the local ethical committee.

5.2.1. Collection of buccal smears

Prior to the harvesting of buccal smears patients were asked not to take food for eight hours to avoid sample contamination by DNA originating from any food. Smears were gathered with sterile cotton swabs rubbed against both sides of the buccal mucosa and the upper gingiva at least four times. Although firm pressure was applied during the collection, attention was paid not to cause any bleeding. Every patient was awake during the procedure. The swabs were put into a tube with 400 µl of PBS (phosphate-buffered saline, 0.1 mol/l, pH 7.4) each and used immediately for genomic DNA (gDNA) isolation or stored at –80 °C and used later.

5.2.2. Collection of blood samples

Children above the age of twelve and adults were awake when their blood was drawn. Blood from children under twelve was taken under general anaesthesia during the process of

cochlear implantation preevaluation. Blood was drawn into tubes containing EDTA to prevent clotting, and used immediately or stored at –80 °C for later use.

5.2.3. Isolation of genomic DNA from blood samples

The DNA isolation from blood samples was performed according to the manufacturer`s guide (QIAamp® DNA Mini Kit and QIAamp DNA Blood Mini Kit, QIAGEN). Once isolated, the gDNA was stored at +4 °C or analysed immediately. Sterile gloves were worn all the time by the examiner to avoid contamination of the samples with his own DNA.

5.2.4. Isolation of genomic DNA from buccal smears

The DNA isolation from buccal smears was performed according to the manufacturer`s guide (QIAamp® DNA Mini Kit and QIAamp DNA Blood Mini Kit, QIAGEN). Once isolated, the gDNA was stored at +4 °C or analysed immediately. Sterile gloves were worn all the time by the examiner to avoid contamination of the samples with his own DNA.

5.2.5. Quantitative analysis of gDNA isolated from blood and buccal smears

gDNA concentration of the final filtrates gained from both the blood samples and buccal smears was measured using a UV meter (Eppendorf BioPhotometer). Concentration of gDNA was calculated from the 260 nm light absorption of the samples. The 260 nm light absorption of Buffer AE was used as reference.

DNA concentration from blood samples in Group 1 was compared to those in Group 2 to statistically test for age dependency of DNA amounts. Statistical comparison of DNA amounts isolated from buccal smears was likewise performed between Group 1 and Group 2.

5.2.6. Qualitative analysis of gDNA isolated from blood and buccal smears

Polymerase chain reaction (PCR):

Detection of the 35delG mutation was performed according to Storm et al [169]. 10 µl of gDNA gained from blood or buccal smears was mixed in an Eppendorf tube with 25 µl of Taq polymerase mix (Ready Mix ™ REDTaq™ PCR reaction mix with MgCl2, Sigma), 5 µl of Connexin-26-1 primer (Con 26-1, 5`-GGT GAG GTT GTG TAA GAG TTG G-3`, MWG-Biotech AG), 5 µl of Connexin-26-2 primer (Con 26-2, 5`-CTG GTG GAG TGT TTG TTC CCA C-3`, MWG-Biotech AG) and 5 µl of water (Water PCR reagent, Sigma). The mixture was placed in a PCR Express cycler (Thermo Hybaid, U.K.) and gDNA was amplified by

PCR. The PCR product was then immediately submitted to enzymatic digestion or stored at +4 °C for later analysis. All samples were processed three times.

Enzymatic digestion:

12 µl of the amplified gDNA (PCR product) were diluted in an Eppendorf tube with 0.95 µl water (Water PCR reagent, Sigma), 1.5 µl NE-Buffer 3 (10x concentrate, New England BioLabs, Inc.), 0.15 µl bovine serum antigene (Purified BSA 100x 10 mg/ml, New England BioLabs, Inc.) and 0.4 µl restriction endonuclease BSI Y1 (New England BioLabs, Inc.). Enzymatic digestion was enabled by placing the mix in a PCR Express cycler (Thermo Hybaid, U.K.). The restriction product was then analysed immediately by agarose gel electrophoresis.

Electrophoresis:

During the digestion process agarose gel was prepared: 100 ml 10x TBE (TRIS-borat–EDTA buffer: TRIS-borat 1 mol/l, pH 8.3; EDTA 20 mmol/l) were thoroughly mixed with 900 ml destilled water. 3.75 g 2.5% Broad Range Agarose (Carl Roth GmbH) were dissolved in 150 ml of the mixture by heating and mixing, and after complete dissolvation 7.5 µl ethidium bromide 1% (10 mg/ml, Carl Roth GmbH) were added. Once the gel hardened in its tray, the remaining buffer was poured on it. Restriction products (15 µl each) were loaded into the slots of the gel, and submitted to electrophoresis with 100V, 100 mA, 20W for 2 hours (Power Ease 500, Novex, San Diego, CA, U.S.A.). For every electrophoresis a sample of water previously submitted to PCR and restriction (as if it were a gDNA sample) was used as negative control indicating that no false PCR product was generated in the absence of an original DNA template. Also, to every electrophoresis a positive control (amplified and digested gDNA of an individual known to be homozygote for the 35delG mutation) and 3 µl pUC19/Msp I DNA marker (50 µg/500µl, Carl Roth GmbH) were added. DNA bands were observed under UV light in a UV light chamber (Biostep Co.), photographed with an Olympus C4040 Zoom camera and stored on a computer using the Argus X1 software (Biostep Co.).

5.3. Results

Blood and buccal smears gained from a total of 60 cochlear implant candidates were analysed in our study. Each patient provided a blood as well as a buccal smear sample. For the quantitative analysis of the DNA yield a statistical comparison of the gDNA amounts isolated

from blood samples was performed between patients ≤ 3 years (Group 1) and > 3 years (Group 2). The comparison was done likewise with gDNA isolated from buccal smears.

5.3.1. gDNA quantity gained from blood samples

gDNA concentration of the samples isolated from blood in Group 1 was 15.9 ± 1.8 µg/ml (mean ± s.e.). In Group 2 gDNA concentration in the blood-derived samples was 14.6 ± 1.9 µg/ml (mean ± s.e.) (Table 1). Two-Sample t-Test comparison showed no significiant difference (p=0.63) between the blood-derived gDNA concentrations of Group 1 and Group 2, indicating that the amount of gDNA gained from blood was not age dependent.

5.3.2. gDNA quantity gained from buccal smears

gDNA concentrations gained from buccal smears were 9.5 ± 1.4 µg/ml and 8.6 ± 1.4 µg/ml in Group 1 and 2, respectively (mean ± s.e., Table 1). Two-Sample t-Test comparison showed no significiant difference (p=0.67) between the buccal gDNA concentrations of Group 1 and Group 2 proving that the gDNA yield of buccal smears was not age dependent.

	gDNA concentration isolated from blood samples (mean ± s.e., µg/ml)	gDNA concentration isolated from buccal smears (mean ± s.e., µg/ml)
Group 1 (age ≤ 3 years)	15.9 ± 1.8	9.5 ± 1.4
Group 2 (age > 3 years)	14.6 ± 1.9	8.6 ± 1.4

Table 1. Mean gDNA concentration of the samples isolated from blood and buccal smears

5.3.3. Comparison of gDNA quantities gained from blood samples and buccal smears

Table 1 shows that blood samples yielded considerably higher concentrations of gDNA than buccal smears in both groups. The amount of gDNA gained from buccal smears, however, was still sufficient in quantity and quality for PCR and subsequent genetic analysis.

5.3.4. 35delG detection in gDNA isolated from blood samples and buccal smears

Qualitative gDNA analysis was based on the detection of the 35delG mutation of the Cx26 gene. For this purpose we used PCR-mediated site-directed mutagenesis followed by a BSI Y1 digestion [169]. Using specifically designed primers we first amplified the GJB2 sequence by PCR. We then submitted the PCR products to enzymatic digestion by the enzyme BSI Y1. Only PCR products containing the 35delG mutation presented a restriction site for the enzyme which produced two GJB2 fragments (181 and 26 bps). These fragments clearly size-separated during electrophoresis from the wild GJB2 allele unaffected by the BSI Y1. Fig. 4 shows representative results.

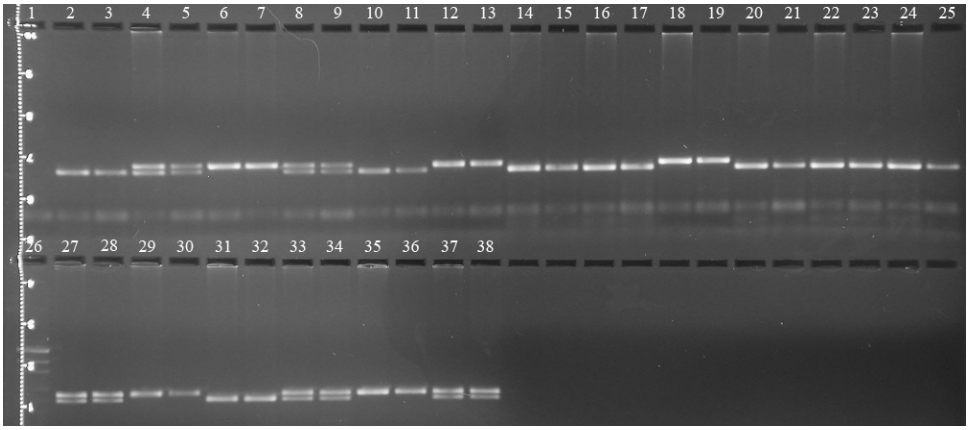

Fig. 4: Representative picture of electrophoresis results. Slot numbering starts at upper row going left to right, then continues at lower row likewise. Slot 1: negative control (water, previously submitted to PCR and restriction). Slot 26 was loaded with pUC19/Msp I DNA marker. Samples are paired as PCR-amplified, restricted gDNA of the same patient from blood (left) and buccal smear (right). Slots 2-3, 10-11, 14-15, 16-17, 20-21, 22-23, 24-25, 31-32 indicate 35delG homozygote patients. Slots 4-5, 8-9, 27-28, 33-34, 37-38 indicate 35delG heterozygotes. Slots 6-7, 12-13, 18-19, 29-30, 35-36 stand for individuals with no 35delG mutation.

Table 2/a: Group 1	gDNA analysis from blood samples	gDNA analysis from buccal smears
Homozygotes (age ≤ 3 years)	6	6
Heterozygotes (age ≤ 3 years)	3	3

Table 2/b: Group 2	gDNA analysis from blood samples	gDNA analysis from buccal smears
Homozygotes (age > 3 years)	2	2
Heterozygotes (age > 3 years)	2	2

Table 2: Number of 35delG homozygote and heterozygote cases based on gDNA analysis from blood and buccal smears in a/ Group 1 and b/ Group 2

Analysis of DNA isolated from blood samples and buccal smears detected 6 homozygote and 3 heterozygote patients in Group 1, and 2 homozygote and 2 heterozygote patients in Group 2 regarding the 35delG mutation in the Cx26 gene (Table 2).

Both Fig. 4 and Table 2 demonstrate that in the case of all examined patients qualitative analysis of the DNA isolated from buccal smear revealed the same result as DNA originating from blood.

5.4. Discussion

In our study gDNA isolated from the blood samples and buccal smears from 60 deaf patients was analysed quantitatively and qualitatively. Our results of quantitative gDNA measurement proved that the gDNA yield of neither blood samples nor buccal smears was age dependent. Both sources provided sufficient amounts of DNA for PCR analysis and genetic examination

(Table 1). Our data also showed that the 35delG detection results from blood samples and buccal smears were identical in all examined patients, proving that buccal smears were a reliable source of good quality gDNA for genetic analysis.

The 35delG mutation of the Cx26 gene usually leads to a congenital, prelingual, severe to profound bilateral HL in the homozygote form. However, also mild and moderate, as well as progressive hearing loss has been associated with the presence of mutations in the Cx26 gene. Thus, screening hearing impaired children for 35delG may be of importance because this knowledge might affect family counselling or the initiation of early treatment for a hearing impaired patient in the future.

Evaluating the results of genetic screening is, however, difficult for a number of reasons. Genetic examination cannot replace audiological assessment. For example, a negative screening result for the 35delG mutation cannot exclude other possible genetic causes of HL. In addition, progression of HL cannot always be predicted as there may be other genetic and non-genetic contributors, too, apart from incomplete penetrance etc.

Screening for the 35delG mutation from blood is a reliable and fast method. It, however, needs the drawing of blood from the individual, which itself sometimes poses a challenge and might occassionally also lead to complications. Especially drawing blood from very young children is often not easy. Buccal smears have been reported as a good alternative source of genomic DNA [151, 170]. Our study focused on the usability and feasibility of buccal smears for 35delG screening in very young children. We performed not only a qualitative but also a quantitative analysis of the gDNA gained from buccal smears. Our study demonstrated that the gDNA isolated from buccal smears was adequate in all cases, both in quantity and in quality, for PCR and further genetic analysis. Schade et al. [151] reported that in a number of their patients they could not gain sufficient amounts of DNA from the buccal smears. In our study we showed that the amount of gDNA gained from buccal smears was not only sufficient to be analysed for gene mutations, but in addition we demonstrated that DNA content of buccal smears was not age dependent.

Harvesting buccal smears from the oral cavity proved to be an easy, fast, non-invasive method for gathering material for 35delG screening that invariably works even in very young children, causes less stress to the patient and is without any risk of complications. Our results also proved that screening for the 35delG mutation in the Cx26 gene from buccal smears was exactly as reliable and sensitive as screening from peripheral blood. Our study focused on the 35delG mutation of the Cx26 gene as this is the most common mutation and thus is suggested as an ideal starting point for any genetic analysis of deafness [76]. As, however, we positively

demonstrated that buccal smears yielded gDNA in sufficient quantities, it can be stated that from the same source of genetic material a series of different mutations of different genes known to cause HL may be screened for in a parallel fashion.

Hereditary hearing loss of any kind demands early audiological intervention: the prescription of conventional hearing aids, the performance of various types of corrective ear operations, the implantation of a BAHA or a cochlear implant. In case of a questionable/unconfirmed audiological diagnosis – and we may more often have such an unsure diagnosis as the lower age limit for cochlear implantation is continuously decreasing – the certain knowledge of the presence of a mutation known to cause HL will definitely help establishing the diagnosis of HL itself. Hence, genetic screening of HL may add a considerable piece of information to indicating an early CI or initiating any other type of early audiological intervention. Buccal smears can help in this in a non-invasive way which is especially important in very young children.

6. COCHLEAR IMPLANTATION IN PATIENTS WITH A PREVIOUS MALIGNANT TUMOR

6.1. Introduction

Certain criteria of patient selection for pediatric and adult cochlear implantation are set but several details are debated worldwide. Opinions on evaluating multihandicapped patients for implantation are especially diverse [110, 174, 192]. People also suffering from other congenital or acquired maladies beside hearing impairment are in disadvantage already when getting on the waiting list. The primary question in such cases is whether hearing and speech development is possible at all. Such illnesses as osteogenesis imperfecta [75, 172], epilepsy, Waardenburg's syndrome [131] etc. also sometimes pose a challenge in making decisions. Until a few years ago only one report could be found in the internationally accessable literature about a cochlear implantation indicated for deafness in a patient previously treated with a malignant tumor [52].

Hearing impairment can set on pre-, peri- and postlingually in relation to the process of speech learning. Adults, and children who become deaf after they have learned to speak (postlingually deafened patients) will not lose their speech as a result, though it will most

probably suffer deterioration to some degree. Once the Broca's area is developed, it will keep functioning even if the Wernicke's region no longer gets sensory input.

Prelingually deafened children, however, will never develop their hearing and speech centres properly if their brain gets no acustic information. In such cases the organisation of the Wernicke's and Broca's area can be enabled and quasinatural language development may be achieved if we provide acustic input via cochlear implants, but considering the age-related diminishing of brain plasticity we had better perform the implantation as early as possible. The age limit of maximum six years for prelingually deafened children suggested by many authors at the beginning of the cochlear implantation era [100] is nowadays not considered an absolute limit, but it is general understanding that the later we implant a child the less satisfactory speech perception and production will be achieved, though sound perception will in most cases be excellent. This finding can be partly explained by the phenomenon called cross-modal reorganization (see also Chapter 4): the lack of functional specialization of the auditory cortex presents a kind of vulnerability and enables the expansion of the afferent neural network of other sensory systems into the auditory region. Once these plastic changes happen, the patient will show a worse prognosis after cochlear implantation [98] – the auditory brain will not be able to fully reconquer its original territory. Beside this, due to the absence of the trophic effect that should originate from functional and functioning hair cells, the number of stimulatable ganglion cells will continuously decrease until CI (when the stimulation of ganglion cells is restored) [123]

A hearing impairment of perilingual onset will prolong the time of brain plasticity (at least with regard to hearing and speech), pushing the "age limit" at 6 years somewhat higher, allowing for better speech perception and production results even if cochlear implantation is performed at a later age. In perilingual deafness we already have the rudiments of the developing Wernicke's and Broca's area when the acustic input ceases, and the functional (re)organisation of these brain regions will be easier and more complete even if the flow of acustic information is restored after considerable delay [62, 140]. However, even this period of prolonged brain plasticity will come to an end eventually, and if hearing is not restored by that time, speech will devolve leaving the child deaf and mute. Thus in order to achieve good hearing and speech rehabilitation we should not wait endlessly with implanting a perilingually deafened child [110].

All considered, we have to state that the sooner a child is provided with a cochlear implant after the onset of deafness, the better (re)habilitation results can be expected. It is not possible, however, to follow this logic if the cause of hearing loss is the treatment of a

malignant disease, or any other potentially fatal illness which has a tendency to recur. It is well known that a patient treated with a malignant tumor should be considered oncologically healed only after a tumor-free period of 5 years. Because of this, it is not customary to perform operations of considerable magnitude (and a costly CI is certainly considered one of these) that are unconnected with the malignancy itself until the fate of the patient is decided from the oncological aspect.

It is an extremely difficult situation for the cochlear implant team to evaluate such a case when the patient is a perilingually deafened child: the oncologically guaranteed tumor free state of the child must be weighed against the fact that an incredibly costly implantation should be performed as soon as possible to get the best rehabilitation results. While we wait for 5 years after the oncological treatment in order to declare the child oncologically healed, the previously mentioned plasticity of the brain decreases, which forecasts modest speech development even in spite of a probable good hearing rehabilitation after implantation.

Should we then not implant children who have been deprived of acustic information for such a long time, but give the expensive device to some other, more promising child? Or should the operation of a good implant candidate be postponed and months of his development delayed or partially lost in order that we could give one of the limited number of devices to a patient who might prove to be a failure in rehabilitation?

The date of cochlear implatation is not such a pressing issue if deafness develops postlingually in a child (or in an adult). In this case, the patient has a fully functional auditory and speech centre by the time of hearing loss, and these centres will stay functional even if the brain gets no auditory imput. Cross-modal plastic changes *do* happen in these patients, too, as evidenced by Lee et al. [98], but the process is slow with a late onset, forecasting good rehabilitation results even if implatation is done after years of auditory deprivation.

In August 2002 and June 2005 our cochlear implant centre reported on two children, both of whom suffered from a malignant disease and who received a cochlear implant once they were considered oncologically healed [178, 180]. Prior to our publications only one such report was found in the internationally accessable literature [52].

6.2. Case 1: Cochlear implantation after successful treatment of a rhabdomyosarcoma

6.2.1. Introduction: Rhabdomyosarcoma

According to December 2007 data of the American Cancer Society (www.cancer.org) rhabdomyosarcoma represents 3% of all childhood malignancies, and is the most common

type of soft tissue sarcoma in children. The embryonal variant is more common, the alveolar type is rarer. This tumor has a tendency of growing fast and thus responds well to chemotherapy and radiotherapy. Its prognosis is favorable, 2/3 of all rhabdomyosarcoma children can be healed. A combination of cisplatin and etoposide is suggested [21, 134].

6.2.2. Case report

D.Gy. was born from an uneventful pregnancy without complication on September 25, 1990. His hearing was good and his speech development was undisturbed in his first years. In September 1992 the right upper eyelid of the 2-year-old child began to droop. Detailed assessment revealed a solid mass in his right orbita and right frontobasal region, documented with CT (Fig. 5) and MR scans. The tumor originating in the right orbita, extending into the frontobasal, extradural region was removed by transfrontal craniotomy in January 1993. Histology diagnosed an embryonal rhabdomyosarcoma. The postoperative period was uneventful, the child recovered without complications.

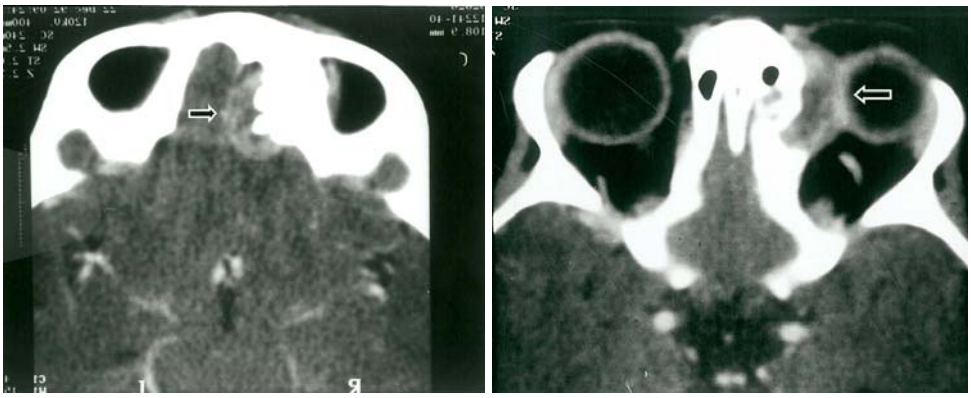

Fig. 5: CT of the rhabdomyosarcoma in the right frontobasis and orbita. Arrows indicate the tumor.

Considering the delicate localisation of the tumor the child was submitted to postoperative combined chemotherapy: he received etoposide-vincristin-actinomycin-D-ifosfamide-adriablastin until January 1994. Two weeks after the last cycle of the 11-month cytostatic treatment the child developed a limp, started to drag his left leg, his gait became wide-based. Neurologists suspected meningitis. The child underwent lumbal puncture, and a purulent meningitis was diagnosed (a mixed infection of Haemophilus influenzae and Streptococcus pneumoniae). The three-and-a-half-year-old child recovered thanks to ceftriaxon and adjuvant treatment. As a complication of the meningitis, however, a bilateral profound hearing loss developed. The child became perilingually deafened.

He received stereophonic hearing aids soon after recovery. The aids helped with hearing loud noises, but were insufficient for everyday communication. The child's voice

became distorted, nasal, his speech considerably diminished in a few months and he started to rely more and more on natural gestures. Soon the child started an intensive hearing and speech therapy in the Deaf School of Budapest. The 5-year intensive training put a stop to his speech deterioration, and he even started to pick up new words. His speech (re)development, however, was very slow and relied mostly on lipreading as he had no benefit from the high-performance hearing aids in speech understanding.

In the autumn of 1998 members of our team gave a presentation for teachers and parents in the Deaf School about cochlear implantation. Hearing about implantation there for the first time, the child's mother visited our department later to have his child enrolled in the implantation programme.

We suggested cochlear implantation after evaluating the child's candidacy. We contacted the institute which did the oncologic treatment and the follow-up; the specialists confirmed that after 6 years of follow-up the child had been declared free of tumor (Fig. 6).

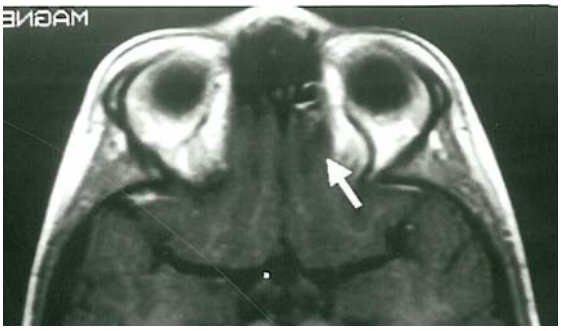

Fig. 6: MRI showing no residual or recurring tumor. Arrow indicates the region the tumor occupied before treatment.

Otorhinolaryngological examination revealed no pathologic finding. Pure-tone audiometry showed a threshold of 100-110 dB HL on both sides (Fig. 9/a) which could be improved with Starkey A 675442 stereophonic hearing aids – this, however, meant only pure-tone and noise hearing, and not speech understanding. Type A tympanogram was registered on both sides. Stapedius reflex could not be evoked on either side. Distortion product otoacoustic emission (DPOAE) revealed no outer hair cell activity in either ear. Auditory Brainstem Response (ABR) examination found no acustically evoked brainstem potentials. Inner ear high resolution CT showed an open cochlea (Fig. 7) on both sides (no obliterative complication of the purulent meningitis). No psychopathologic symptoms were found by the pediatric psychiatrist. Good background was available in the Deaf School for postoperative surdopedagogic training.

On June 10, 1999 we performed a cochlear implantation in the child's left ear with a Nucleus 24 M device (Fig. 8). One month after the operation the child was given the speech

processor and he has been using his implant ever since. He attends our clinic every two months for fitting and testing his speech development.

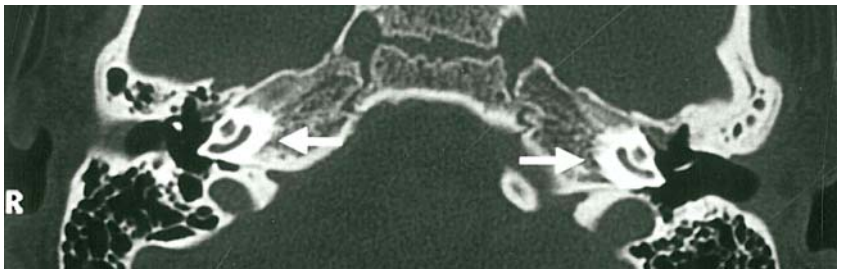

Fig. 7: Inner ear CT prior to CI. Arrows indicate an open cochlea on both sides.

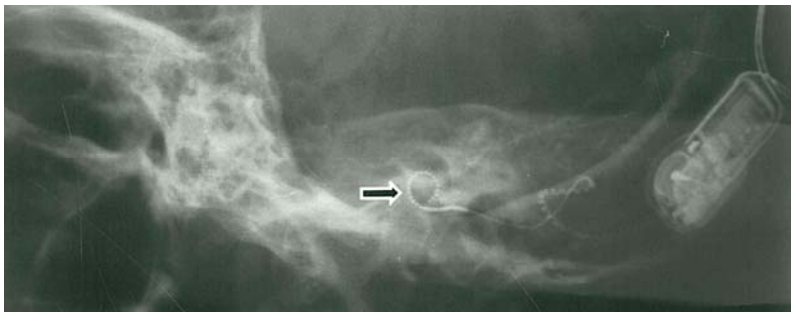

Fig. 8: Stenvers' view after CI depicting the array in the basal turn of the cochlea.

Since the operation the child has shown very good hearing rehabilitation results, being able to hear even very soft noises. His pure-tone threshold can be improved to the level of 25-35 dBs depending on the programme in the processor (Fig. 9/b). His sound recognition and speech understanding improved considerably. He is able to differentiate consonants and dissonants, and recognizes and gives back all six sounds of Ling's test. He shows more moderate results in speech rehabilitation. His voice became natural but his speech is arrhythmic. His vocabulary has been slowly but steadily growing.

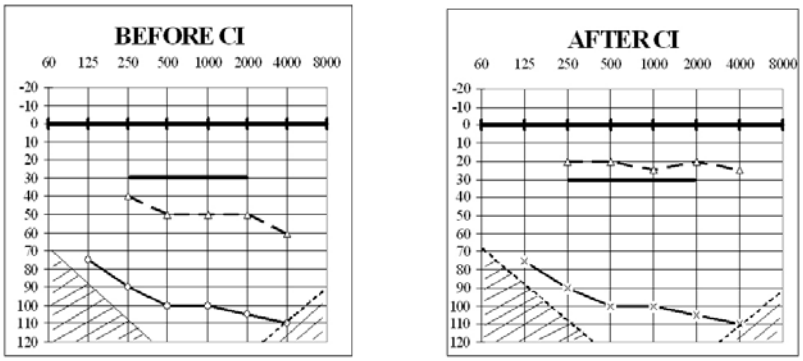

Fig. 9: Pure-tone threshold audiogram. a/ and b/: continuous line shows the preoperative average hearing threshold of the child's ears. a/ Jagged line indicates threshold with bilateral hearing aids. b/ Jagged line stands for threshold with cochlear implant.

6.2.3. Discussion of Case 1

In the case of this child operation and postoperative chemotherapy was enough for recovery from his rhabdomyosarcoma. The child did not receive the planned radiotherapy after the cytostatic treatment because of the purulent meningitis. We have to consider his meningitis a complication of chemotherapy. It is known that a prolonged chemotherapy causes neutropenia and thus a transitory state equivalent with immune suppression [160]. In the case of this child eleven months of cytostatic treatment resulted in an immune compromised state which let an intercurrent infection turn into a severe purulent meningitis. It is known that purulent meningitis quite often causes internal ear damage and irreversible hearing impairment or deafness through the liberation of inflammatory mediators [79] or via a descending, meningogenic labyrinthitis (see also the Introduction of Chapter 7). Although the direct ototoxic effect of cytostatic agents is well established in literature [13, 21, 120, 134, 159, 171], in this situation we still have to regard chemotherapy an indirect cause of the child's hearing impairment.

6.3. Case 2: Cochlear implantation after successful treatment of a Langerhans cell histiocytosis

6.3.1. Introduction: Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH, previously referred to as histiocytosis X) is a neoplastic proliferation of histiocytes with an unknown etiology. Its incidence is 5 per million with a predilection for males (male:female ratio 3.7:1) and most cases occur in childhood [80]. Depending on the sites of involvement it can be divided into three clinical variants. One is the eosinophilic granuloma which is a unifocal disease, mostly affecting bones. Another variant is Hand-Schüller-Christian disease, a multifocal, unisystem illness which involves several sites of one organ system, again mostly bones. The third clinical type is Letterer-Siwe disease which is a multifocal, multisystem malady, attacking several organ systems at the same time. The most important factor that determines prognosis seems to be the number of affected organs. The overall survival of patients with unifocal disease is above 95%, which drops to 75% in cases with two organs involved and continues to drop with the increasing number of affected sites.

The treatment of LCH remains problematic. The unifocal type, eosinophilic granuloma may be treated with either surgery or radiotherapy, but for the multifocal variants chemotherapy is the best choice of treatment. Gadner, Minkov and coworkers [54, 113, 114]

suggest an intensive initiation with etoposide, prednisone and vinblastine lasting for six weeks, and a prolonged continuation with the same agents plus mercaptopurine lasting for one year, and report on high 5-year survival rates.

Chemotherapy, however, rises the problem of its own complications, one of which is hearing impairment. The ototoxic effect of several cytostatic agents is a well established fact in literature [13, 21, 120, 134, 159, 171], and this question demands even more attention in the case of LCH which affects mostly children at various stages of their hearing and speech development.

6.3.2. Case report

B.P. was born from an uneventful pregnancy in 1988. Her hearing and speech development was undisturbed during her first years. In 1991 a protrusion of her left eye presented. Conventional X-ray (Fig. 10) and CT revealed a multifocal destruction localised in her left orbita, ethmoid and sphenoid bone and other bones of her skull. Histological examination of these lesions diagnosed Langerhans cell histiocytosis. The disease was classified as the Hand-Schüller-Christian clinical variant. Polychemotherapy with mercaptopurine, prednisone and vinblastine was started but the child's illness kept on progressing. Hence, the intensity of the treatment was enforced in the beginning of 1993: according to the scheme described by Gadner, Minkov and coworkers the child was given an initiation of several cycles of prednisone, vinblastine and etoposide followed by a prolonged continuation of the same agents plus mercaptopurine until the spring of 1994. The child responded favourably to this treatment, her histiocytosis went into complete remission.

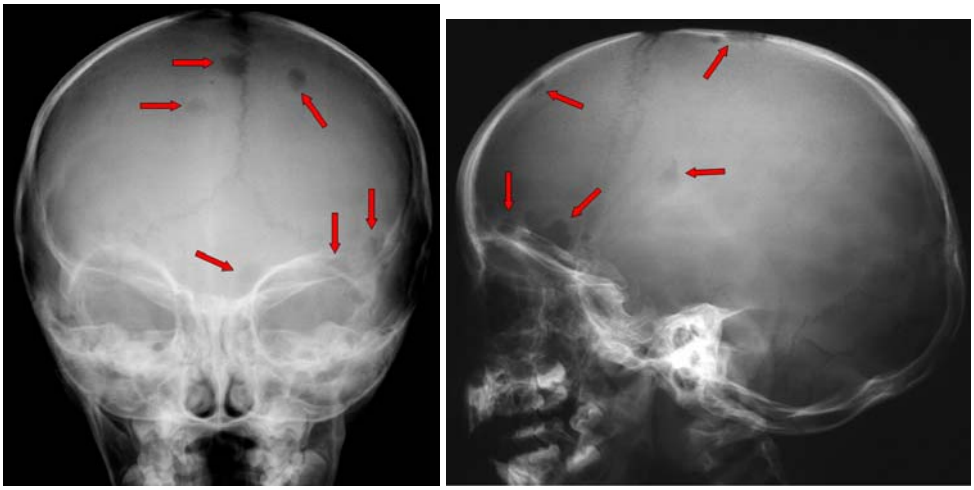

Fig. 10: AP and lateral skull view with arrows indicating lytic lesions typical of LCH

Unfortunately, during the prolonged chemotherapy a progressive hearing loss presented in both ears. The girl, who used to have good hearing and had already learned to speak received conventional hearing aids for both ears in 1994. The progression of her hearing impairment, however, did not stop with the end of chemotherapy. By 1995 the child's high performance hearing aids could only help with the perception of loud noises. During the process of her progressive postlingual hearing loss the girl learned lipreading and preserved and even developed her speech skills which enabled her to go to a normal hearing school after kindergarten.

The child's parents came to our clinic only in 2001 enquiring about the possibility of CI. We found the girl a candidate for cochlear implantation. Pure-tone audiometry showed anacusis on her right ear and a threshold of 90 dB HL on her left ear (Fig. 11). Type A tympanogram was registered on both sides. Stapedius reflex could not be evoked. No outer hair cell activity could be registered with DPOAE. We found no acustically evoked brainstem response on either side with ABR. A patent cochlea showed on both sides with high resolution CT and MR (Fig. 12); there was no radiological sign of the previous histiocytosis. Oncohaematologists re-examined the child and declared her healed, as no sign of histiocytosis recurrence had presented since 1994.

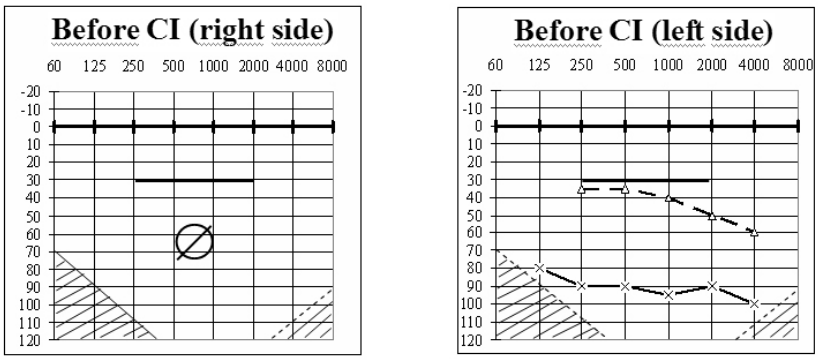

Fig. 11: Preimplantation pure-tone audiogram: Total deafness on the right side, profound hearing loss on the left aided with conventional hearing aid.

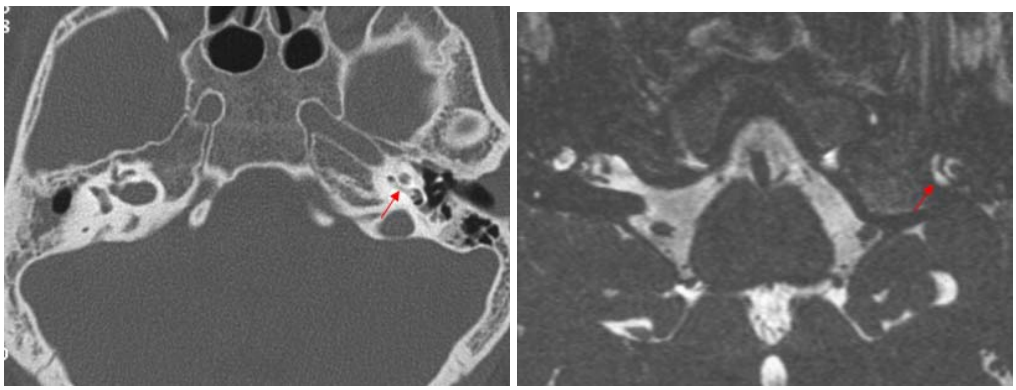

Fig. 12: Preimplantation CT and MR. Arrows indicate an open cochlea on the right side.

In October 2002 we performed a cochlear implantation on the girl's right ear with a Nucleus 24 M device. Fig. 13 shows the postoperative X-ray of the implant in situ.

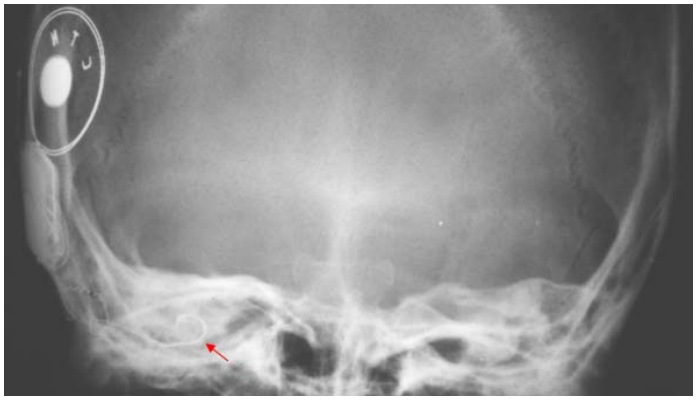

Fig. 13: Orbital temporal bone projection with the array in the basal turn of the cochlea indicated by arrow

The first fitting of the device took place one month after the operation. Three months later the girl was able to quit lipreading and rely on her cochlear implant for everyday communication. Fig. 14 illustrates the effect of the implant on her pure-tone hearing threshold. She recognizes five sounds of Ling's test.

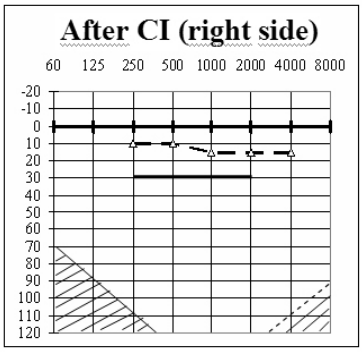

Fig. 14: Postimplantation pure-tone audiogram. Normal threshold on the right ear with implant.

6.3.3. Discussion of Case 2

The Hand-Schüller-Christian disease of the child we presented was successfully treated with polychemotherapy which altogether lasted for almost two years (including the first few months of unsuccessful treatment).

The ototoxic effect of several cytostatic agents have been reported. Of the medicines our child was given, etoposide and vinblastine have been described as having ototoxic side effects [13, 29, 120, 159]. Furthermore, the cumulative toxicity of drugs is also a well-known phenomenon [134], and more than 12 months' parellel treatment with two cytostatic agents

with proven inner ear destructive potential is enough to explain why a progressive hearing loss started in this girl at the age of 4.5 years.

The child might have become an implantee in 1999, when the 5 years needed for declaring her oncologically healed were over. However, her parents confessed that their fear of surgery took them an additional 2 years to overcome, hence the girl could be enrolled in the implantation programme only in 2001. In a country where the total number of cochlear implantations per year is controlled by the limited budget of the National Health Insurance, an additional year of waiting was needed as we could not favor her against smaller, prelingually deafened children who were also on our waiting list. This resulted in a cochlear implantation in 2002.

6.4. Discussion

Prior to our publications only one paper could be found in the internationally accessable literature about CI performed in a patient who survived a malignant tumor [52]. This paper, published in 1998, described the case of a 67-year-old man, who suffered from nasopharyngeal cancer. Surgical excision was first performed, then the patient received postoperative irradiation. As a complication of radiotherapy, a labyrinthitis and an acustic neuritis developed leading to a (postlingual) bilateral deafness. Two years after surgery the authors implanted a MED-EL Combi 40 in the patient, achieving satisfactory hearing rehabilitation.

We published our first paper about a CI after effective treatment of a malignant tumor in 2002 (Case 1). To the best of our knowledge, this was not simply the second such case published, but also the first that concerned a *child* who was in the process of speech development when his struggle with a malignancy began. The task our team had to face was very rare and thus indication of the implantation was an enormous dilemma and responsibility. Beside the fact that we had to exclude cochlear obliteration as a frequent late complication of purulent meningitis during the preoperative investigation, we also had to consider whether a 9-year-old child (who had had no hearing for the previous 5 years) could benefit well enough from the expensive cochlear implant paid by the National Health Insurance. Should we have given the implant to another, probably more promising congenitally deaf candidate with a much younger age? In Hungary, where the yearly number of CI-s is decided and limited by the Ministry of Health, the question is very similar to that raised by Cohen concerning bilateral CI: shall we implant more patients unilaterally or fewer

patients bilaterally [26] (see also Chapter 4). In a country where the budget available for cochlear implantation is less limited, this might have been a smaller issue from the financial point of view. However, ever in such a country, the question whether CI was worthwhile considering effectivity would have been a valid one. The fact, that this rare cochlear implantation was a success and that the effects of postoperative training are plain to see in the hearing and speech of the child, however, demonstrates that it was worth taking the responsibility of the decision.

In 2005 our first malignancy-CI report was followed by a second one (Case 2). Although we were by then treading on somewhat beaten path, the decision process were no less difficult. In this case we also had to consider that the child's malignancy was a system-wide illness. As such, special attention from the oncohematologist's side was important when the girl was assessed for recurrence prior to CI. Despite the fact that the CI was performed several years after the child lost her hearing, we achieved excellent results not only regarding pure-tone hearing thresholds, but also speech perception. This is due to the fact that the patient was deafened postlingually, and it proves that the development and maturation of the auditory cortex is practically over by the age of 4.5.

The success of our two reported cases proves that CI must not be excluded as a method of hearing rehabilitation in deaf patients who suffered and survived a malignant disease.

Since our two articles several reports have been published about CI in patients treated with malignant head and neck tumors. In 2006 Lin et al. [104] reported on a petroclival low-grade chondrosarcoma causing a slowly progressing bilateral SNHL over a period of 35 years, finally leading to a bilateral profound hearing loss. The authors gained a histopathologic diagnosis by frozen section of a biopsy taken via middle cranial fossa exposure, and at the same time implanted a Med-El Combi 40+ device in the right cochlea of the patient in 1999. As the malignancy was determined to be of low-grade and had a history of slow progression with several decades, no further therapeutic measures were taken, only regular CT follow-up. At 5 years after CI the size and extension of the tumor remained unchanged and no new symptoms associated with it presented.

Also in 2006 Low and coworkers reported on a retrospective study of four patients who received a curative dose of radiotherapy for nasopharyngeal cancer and were later implanted with Nucleus Contour devices between 2002 and 2005 due to bilateral profound SNHL developing as a complication of irradiation [109]. Their article was followed by two more in 2007, by Adunka et al [1] and Chua et al [23], both teams reporting on CI of a patient

who previously received radiotherapy for a tonsillar cancer and a nasopharyngeal cancer, respectively, and both of whom developed a bilateral SNHL thanks to the tumor treatment. These papers and that of Formanek [52] clearly established that CI is feasible both from the technical and the therapeutic point of view in an irradiated temporal bone, at the same time pointing out several pathological changes that may challenge surgeons. In a previous, experimental work, Low et al also demonstrated that in spite of considerable external, middle and inner ear damage human retrocochlear pathways remain functionally intact after receiving curative doses of radiotherapy, providing good functional outcome for CI [108].

In 2007 two teams published a case report each about CI performed in a patient with bilateral endolymphatic sac tumor (low-grade adenocarcinoma) [12, 81]. In both cases treatment of the tumors was performed by surgery and was followed by a rehabilitation of hearing (lost due to the disease itself and not its treatment) with CI. A follow-up of 3 years [12] and 2 years [81] showed both patients to be free of tumor and benefiting from their implants.

The boom of articles in recent years about successful CI after treatment of head and neck malignancies confirms our opinion that CI must not be excluded from the range of auditory rehabilitation measures after the successful treatment of malignancies that are complicated by bilateral hearing impairment. Based on our findings and that of others quoted here, severe to profound bilateral hearing loss caused by a head and neck malignancy or its treatment need to be added to the ever-expanding list of indications for CI. We believe surgeons must not shy away from this therapeutic measure even in cases of children deafened prelingually by the tumorous process or its treatment. Even if waiting for 5 years to declare the child oncologically healed means that some or most of the timeframe associated with adequate brain plasticity is lost, we suggest that CI should be performed as this is the only chance to reintroduce these patients to the world of sound and speech.

7. COCHLEAR IMPLANTATION IN A NEWLY DESCRIBED INNER EAR MALFORMATION

7.1. Introduction

Bacterial meningitis following CI has become a frequently visited entity in recent years. The first comprehensive study was published in 2002 [125] after reports about a few cases of

death caused by postimplantation purulent meningitis were released. The summary of papers published since 2002 about this phenomenon [144, 148, 193, 194] is that although CI does indeed increase the incidence of otogenic meningitis, this higher risk will, nevertheless, not contraindicate the procedure in light of the existing modern vaccines against meningitis and the advantages of CI – at least not in cases with normal inner ear anatomy.

The peculiar structure of the labyrinth and its closeness to the meninges provides two paths of ascending invasion for bacteria from the inner ear to the subarachnoidal space even in case of normal anatomy (and also for the propagation of infection in the opposite direction: let's consider descending purulent labyrinthitis developing as a complication of bacterial meningitis!). It is common knowledge that the inner labyrinthine surface is covered by endosteum and its space is filled with perilymph. The composition of perilymph does not differ from that of cerebrospinal fluid (CSF). The bony labyrinth is not a completely closed space: it is connected with the posterior cranial fossa by the vestibular aqueduct and with the skull base by the cochlear aqueduct. In the vestibular aqueduct (originating from the vestibule) runs the endolymphatic duct which contains endolymph, the fluid of the membraneous labyrinth. The endolymphatic duct ends in the endolymphatic sac which is located between sheets of the dura mater in a crevasse on the posterior surface of the pyramid bone. The narrow space between the bony wall of the vestibular aqueduct and the membraneous wall of the endolymphatic duct is filled with connective tissue which enables communication between the perilymphatic space and the subarachnoidal space of the posterior fossa, thus between perilymph and CSF. The cochlear aqueduct (also called perilymphatic duct) starts out from the base of the bony cochlea, from the vicinity of the round window and opens on the skull base between the fossula petrosa and the jugular fossa (near the jugular foramen). Here, the perilymph in the aqueduct may communicate with the CSF in the subarachnoidal space which follows the proximal portion of the glossopharyngeal nerve to some length [31].

Hence, the two aqueducts may both be considered as anatomically preformed routes of communication between the inner ear and the subarachnoidal space. These routes, however, can only be travelled by bacteria in case they first get into the perilymphatic space. Unfortunately, the main goal of CI is to open the bony wall of the cochlea enabling the insertion of an electrode array into the interior of the bony cochlea. The perilymphatic space thus opened is sealed off from the tympanic cavity with pieces of muscle tucked between the cochleostomy and the array once the array is inserted, but the result after healing is only a

boundary of scar tissue between the inner ear and the middle ear, the later a potential source of bacteria.

Besides the creation of a cochleostomy, CI may alter the anatomy of a healthy inner ear in other ways, too, establishing another – in truth iatrogenic – route of communication between the perilymphatic and the CSF space. The anatomic basis of this can be found in the relationship of the internal auditory canal (IAC) and the cochlea. A multitude of tiny foramen at the bony end of the IAC enables the nerve fibres reaching out from the spiral ganglion in the cochlear modiolus to pass into the IAC and form the acustic nerve. Here, the subarachnoidal space is quite often divided from the perilymphatic space only by the thin bone of the modiolus [137], and this bony partition, together with the osseous spiral lamina, is sometimes broken due to the intracochlear trauma of array insertion [27, 97, 146] (see Chapter 8, Fig 25/e). Thanks to the microfracture, CSF and perilymph can freely mix here, opening the gate for a potential future bacterial invasion.

Morphologic anomalies caused by a faulty development may mean further openings between perilymph and CSF beside widening the previously described potential routes of germ invasion. Thus, developmental disorders of the labyrinth greatly increase the risk of postimplantation meningitis. Several attemps to classify labyrinthine malformations can be found in literature, from which it is that of Jackler et al published in 1987 [78] that is generally considered as reference. Jackler and coworkers explain developmental disorders of the inner ear (osseous and membraneous labyrinths both) as a result of prematurely terminated (*arrested*) embryogenesis, and classify them based on cochlear involvement and according to the time of premature termination, thus the level of development.

7.1.1. Developmental disorders of the inner ear according to Jackler et al...

7.1.1.1. ...with an absent or malformed cochlea:

7.1.1.1.1. Complete labyrinthine aplasia (Michel deformity)

During the *3rd gestational week* the otic placode is formed on the lateral surface of the neural tube. If development of the inner ear is arrested at this time, a complete absence of the labyrinth will be the result.

7.1.1.1.2. Common cavity

During the *4th gestational week* the otic placode forms a simple cavity called the otocyst. The lack of differentiation beyond this stage will cause the common cavity deformity.

7.1.1.1.3. Cochlear aplasia

During the *5th gestational week* the otocyst grows three appendages which would later differentiate into the cochlea, the vestibular organ and the endolymphatic sac. If the development of the cochlear bud is arrested at this stage, a cochlear aplasia will be the result, while the vestibule and the semicircular canals will develop normally.

7.1.1.1.4. Cochlear hypoplasia

From the 6th gestational week the cochlear bud grows continuously until the end of the 8th week, reaching its full length (2 ¾ turns). If its maturation is arrested during the *6th gestational week*, various degrees of cochlear hypoplasia will be the result depending on the length of the so-far developed rudimentary cochlea. The vestibule and the semicircular canals may mature properly or become malformed, too.

7.1.1.1.5. Incomplete partition (Mondini deformity)

During the *7th gestational week* the cochlea grows to the length of approximately 1 ½ turns. If development is terminated here, it will not be properly partitioned due to the incomplete or absent interscalar septum and osseous spiral lamina. This anomaly was first described by Mondini in 1791 [116, 117]. Here the basal turn of the cochlea is developed, whereas the distal one and a half turn is replaced by a cystic cavity where the intracochlear partition is absent. The disorder of the cochlea is often accompanied by an enlarged vestibule and a widened vestibular aqueduct, dilated endolymphatic duct and sac. Unfortunately, several papers were published in the international literature which apply the term ”Mondini’s dysplasia” to various labyrinthine malformations differing from that originally described by Mondini and also from each other. Jackler [78], Phelps [137] and Lo [106] speak up against this erroneous use of ”Mondini’s malformation” as a collective noun, urging for a correct anatomical description of the various inner ear anomalies visualized by modern imaging procedures instead of incorrectly associating them with Mondini. The increased risk of postimplantation meningitis is explained by the dilated vestibular aqueduct in Mondini’s malformation.

7.1.1.2. ...with a normal cochlea:

7.1.1.2.1. Vestibule-lateral semicircular canal dysplasia

The semicircular canals develop from the vestibular appendage of the otocyst *from the 6th gestational week*. Failure of maturation affects the lateral semicircular canal most often and may result in a pocket-shaped canal confluent with an enlarged vestibule.

7.1.1.2.2. Enlarged vestibular aqueduct

The vestibular aqueduct grows from the third appendage of the otocyst *from the 5th gestational week* onwards, gradually narrowing in diameter. If its development is arrested, this narrowing will not occur, leaving an enlarged vestibular aqueduct [78, 141] which represents the radiologically most frequently diagnosed inner ear malformation [20]. The presenting illness is usually referred to as Large Vestibular Aqueduct Syndrome (LVAS) [9, 183] or Large Endolymphatic Duct and Sac syndrome (LEDS) [127]. It is mainly discussed in literature as the presence of LEDS means an anatomic situation that leads to SNHL in certain situations of life [95]. At the same time, the widened diameter of the vestibular aqueduct may lead to intraoperative perilymph/CSF ”oozer” (mild form) or ”gusher” (severe form) or may increase the risk of otogenic postimplantation meningitis by the previously described mechanism [195].

The logical system described by Jackler and coworkers, however, is not able to explain all kinds malformations described so far, as stated by the authors themselves. It is their opinion that malformations that cannot be explained with an arrested embrional development may be the result of an *aberrant* embryogenesis of the inner ear, or a combination of both.

Such a combination might be responsible for the development of an abnormally wide cochlear aqueduct, a rather rare entity, which increases the risk of intraoperative oozer and postimplantation meningitis the same way as an enlarged vestibular aqueduct [11, 70, 77, 121, 135, 137, 157, 195, 196].

A congenital absence of the bony wall between the IAC and the base of the cochlea may present by itself or associated with other inner ear dysplasias [31, 136, 138, 139] and increases the risk of both gusher and meningitis in case of CI.

It is evident that the indication of CI in an inner ear malformation associated with deafness is both a difficult professional challenge and an ethical responsibility. What would

the correct decision be? Shall we indicate CI and put the patient to a higher risk of meningitis, or shall we contraindicate CI and condemn the patient to lifelong deafness and muteness? By presenting an extraordinary labyrinthine malformation and discussing insights gained from its treatment, my thesis also seeks the answer to this dilemma.

7.2. Case report

N.K. male child was born from an uneventful dizygotic twin pregnancy as child ”A” on the 38th gestational week with uncomplicated delivery. He did not have any major illnesses during infancy. His hearing impairment was discovered by his GP when the child was 2 months old. ABR determined profound bilateral hearing loss and the child received conventional hearing aid on both ears. Family history regarding hearing loss is negative: his parents and his female twin have normal hearing.

The child was brought to our department for CI at the age of 1.5 years. Physical examination revealed no pathological findings. A pure-tone hearing threshold of 80-90 dB HL could be measured when aided with 2 conventional hearing aids (Fig. 21). Impedance audiometry registered normal (type ’A’) tympanogram on both ears; stapedial reflex could not be evoked on either side. No outer hair cell activity was demonstrated with DPOAE. No acustically evoked brainstem response was detected with ABR. Temporal bone CT showed labyrinthine dysplasia on both sides which we determined as cochlear hypoplasia (or maybe common cavity) according to the classification of Jackler et al (Fig. 17). MRI was not considered necessary. Based on our findings the child was enrolled in our CI programme. We prepared for the possibility of an intraoperative gusher.

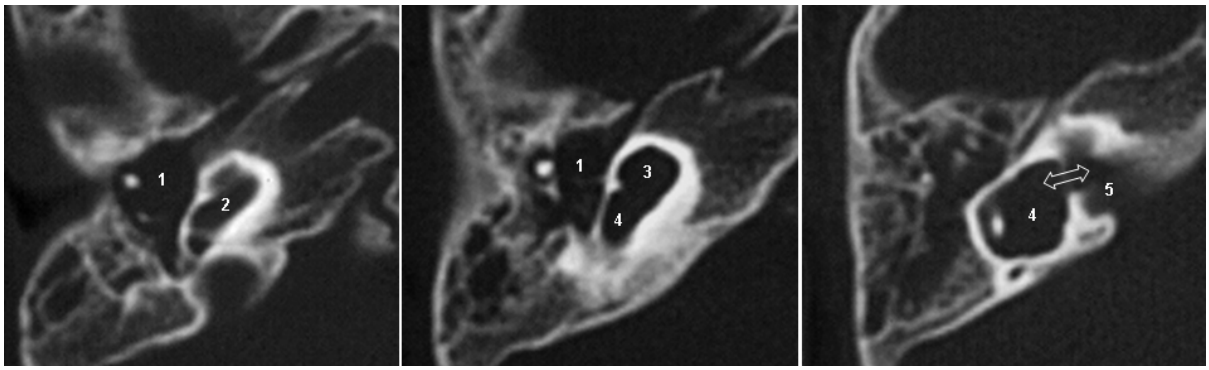

Fig. 15: Representative scans of the preoperative CT about the right middle and inner ear. 1: tympanic cavity; 2: unusually wide proximal portion of the basal turn; 3: undifferentiated distal part of the cochlea; 4: enormously wide vestibule, partially incorporating the horizontal semicircular canal; 5: pathologically wide inner auditory canal; ↔: perilymph-CSF communication through the deficient bony partition between labyrinth and IAC

Cochlear implantation on the child's right ear was performed in January 2006 at the age of 2 years. After standard mastoidectomy a cystic sac was found filling the aditus ad antrum with a transparent, blood vessel streaked wall containing clear watery fluid, bulging from the tympanic cavity to the aditus ad antrum (Fig. 16). We widened the antrum, identified the short process of the incus and opened the wall of the cyst for a better navigation in the aditus ad antrum and tympanic cavity. Opening of the cyst was followed by a profuse, pulse synchronous perilymph/CSF gusher which – somewhat reduced – continued till the end of the implantation. After posterior tympanotomy it was visible that the cyst completely filled the tympanic cavity. Having removed the cyst wall, the aditus ad antrum and the posterior tympanotomy were merged to reveal the tympanic cavity. A major portion of the bony labyrinthine wall was missing under the curve of an intact facial nerve canal and the endosteum sac (the „cyst") filled with perilymph bulged into the tympanic cavity and the aditus ad antrum through this defect. The malleus, incus and stapes showed normal anatomy. A standard cochleostomy was drilled on the promontory, through which a pulse synchronous perilymph gusher began. Stimulating electrode array of a Nucleus 24 R implant was introduced into the cochlea and its indifferent electrode under the temporal muscle and the periosteum. The body of the implant was embedded in a nest previously drilled on the temporal bone surface. Stapedial reflex could be evoked with the implant during the operation. Pieces of muscle were tucked between the cochleostomy and the array, then the defect of the labyrinthine wall was obliterated with muscle and Surgicell. The mastoid cavity was stuffed with fibrin sponge wrapped in Surgicell. No perilymph/CSF leak was detected after wound closure.

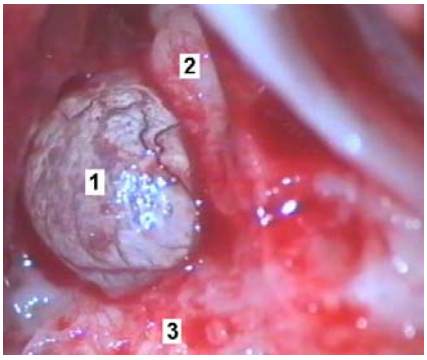

Fig. 16: Intraoperative photo about the endosteum sac filled with perilymph occuping the right aditus ad antrum (and tympanic cavity). 1: the transparent sac filled with watery fluid; 2: short process of the incus; 3: prominence of the bony lateral (horizontal) semicircular canal.

On the first postoperative day an otoliquorrhoea presented manifesting through the soaked but intact eardrum and also postnasally (via the Eustachian tube). A lumbal

depressurizing liquor drain was introduced and the liquorrhoea ceased on the fifth postoperative day. Throughout, the child was well and without fever. He was emitted on the tenth postop day after suture removal. Fig. 17 shows the intracochlear position of the stimulating array upon emission.

The implant was activated 4 weeks after emission by switching on the speech processor. The child tolerated the process well and have been using his implant ever since. Audiometry performed with the implant a few weeks later showed a considerable improvement of the pure-tone threshold (Fig. 21).

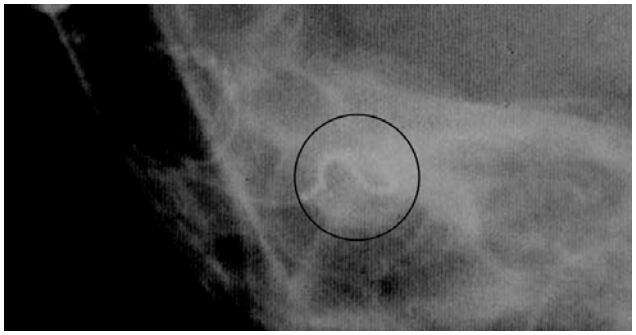

Fig. 17: Stenvers' view of the right temporal bone after implantation. Black circle marks the stimulating electrode array which makes an irregular loop in the undifferentiated cochlea.

6 months after CI, in July 2006 fever and a bad general state presented. Bacterial meningitis was diagnosed at the pediatric unit of the appropriate county hospital and the child was admitted. Microbiological examination of the CSF (gained with lumbal puncture) identified Haemophilus influenzae. Parenteral meropenem and supportive treatment healed the child. During the meningitis both ears were negative.

In November 2006, due to the development of a bilateral acut mastoiditis a remastoidectomy on the right and a mastoidectomy on the left ear was performed at the otolaryngological department of the same county hospital after a detailed consultation through telephone with our department. No pathology was found around the body of the implant in the right ear. Here, a tympanomeatal ventilation tube was inserted into the eardrum. During the mastoidectomy on the left the inflamed mastoidal cells and mucosa were removed. A cyst with a membraneous wall filled with clear watery liquid identical to that on the right was found in the left aditus ad antrum and left untouched. The operation was planned to be finished with the insertion of a ventilation tube into the eardrum as on the right side. Upon myringotomy, however, a profuse perilymph/CSF leak started, hence no ventilation tube was inserted. The child was administered parenteral ceftriaxon as an empirical preventive therapy (no bacterial cultures of the middle ear discharges were taken).

As days later the left side otoliquorrhoea seemed to have ceased, the child was emitted on the 10th postoperative day in good general state. In truth, however, the liquorrhoea must have persisted as the child was readmitted to the hospital 3 weeks later with bacterial meningitis. This time Streptococcus pneumoniae was identified from his CSF.

After the parenteral administration of meropenem the meningitis began to resolve, but as the otoliquorrhoea on the left persisted the child was transferred to our university's department of pediatrics in the middle of December 2006. At the time of transfer mucopurulent discharge through the ventilation tube and a per primam healed remastoidectomy wound could be seen on the right. Pseudomonas aeruginosa was cultured from the discharge. On the left the wound of mastoidectomy healed per primam. Through the site of myringotomy in the upper-anterior eardrum quadrant a continuous liquorrhoea was present.

The child got a lumbal depressurizing liquor drain which stopped the otoliquorrhoea in a few days. As parenteral meropenem was kept on being administered and was paired with ciprofloxacin, both the meningitis and the purulent discharge of the right ear ceased. We removed the tympanomeatal tube. To prevent further episodes of pneumococcal meningitis the child received PCV-7 (Prevenar) vaccine. A few days after removal of the lumbal liquor drain the otoliquorrhoea on the left returned. Considering the physical findings and the patient history an exploration of the tympanic cavity was decided.

We exposed the left tympanic cavity with an endaural incision in January 2007. The tympanic cavity and the aditus ad antrum was occupied by a membrane-walled sac filled with perilymph-CSF which bulged through the defective promontorial wall into the tympanic cavity (Fig. 18). The endosteum sac lay against the medial surface of the eardrum, explaining the liquorrhoea which presented after myringotomy. We opened the sac (Fig. 19) and removed its wall, thus causing a profuse perilymph-CSF gusher. In order to have a good exposition the long process of the incus was transected and removed with the stapes. The stapes footplate was only partially developed (Fig. 20) and the ligamentum anulare baseos stapedis was absent. The oval window was not identifiable, it was merged into the previously mentioned defect of the promontorial wall. We obliterated the vestibule and the tympanic cavity with muscle and closed the myringotomy of the eardrum with temporal fascia with underlaid technique. No liquorrhoea presented after the obliteration and the child was emitted after suture removal.

The child was admitted to his county hospital's pediatric unit once again in April 2007 because of yet another (the third) bacterial meningitis. Otolaryngological examination

performed there revealed an incipient otitis media in the left ear. Streptococcus pneumoniae was identified in the CSF. He was administered parenteral ampicillin and supportive treatment

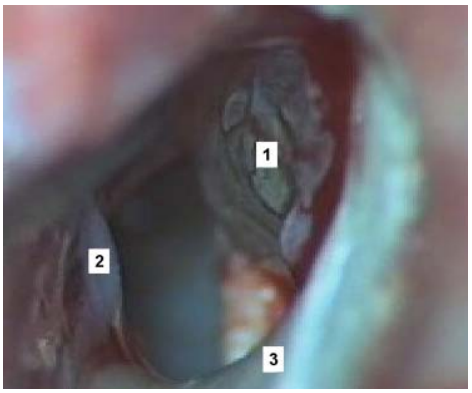

Fig. 18: Endosteum sac in the left tympanic cavity. 1: sac partially collapsed after puncture; 2: tympanic membrane folded sideways; 3: inner edge of the external auditory canal

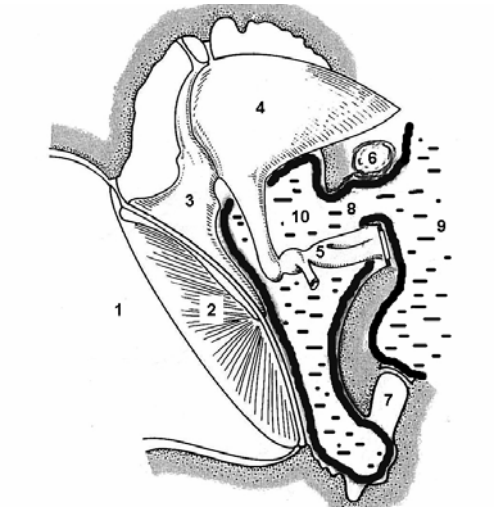

Fig. 19: Drawing of the endosteum sac filled with perilymph-CSF herniating into the left tympanic cavity (and aditus ad antrum). Thick black line marks the endosteum covering the wall of the bony labyrinth. 1: external auditory canal; 2: eardrum; 3: malleus; 4: incus; 5: stapes; 6: facial nerve; 7: niche of the round window; 8: defect on the bony labyrinth wall; 9: vestibule; 10: endosteum sac in the tympanic cavity filled with perilymph-CSF.

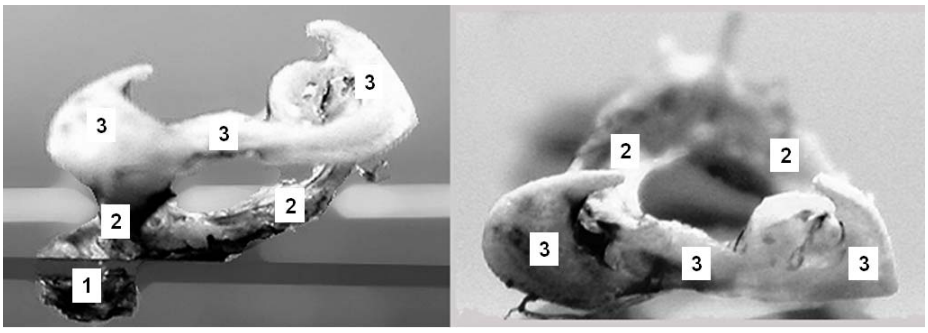

Fig. 20: Two views of the removed left stapes with its partially developed footplate. 1: head of the stapes; 2: crura of the stapes; 3: deficient footplate of the stapes

thanks to which his otitis and meningitis healed. He came to our department for follow-up in good general condition with eardrums and tympanic cavities free of inflammation. The

pediatrician responsible for his treatment suggested removal of the implant in order to prevent further episodes of meningitis but we refused (see Discussion).

After the third meningitis no such episode presented for a whole year. Bacterial upper airway infection occurred more than once but never lead to meningitis. In April 2008, however, yet another meningitis presented along with a bilateral acute purulens otitis media. The child was admitted to the pediatric unit of his county hospital again. This time Streptococcus pneumoniae and Haemophilus influenzae was cultured from his CSF. Parenteral meropenem cured the child from this fourth meningitis.

At the time this thesis is being written the child is over 4 years old. He has had no complaints since the last meningitis. He uses his implant every day, pays attention to his environment and is able to say several words with clear articulation (Fig. 21).

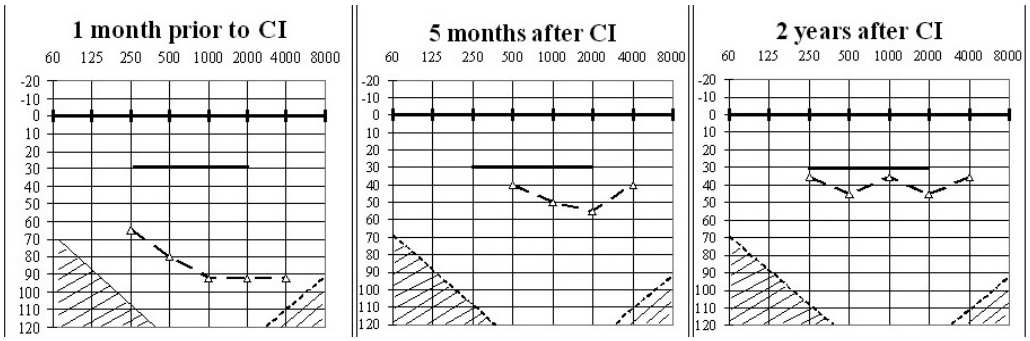

Fig. 21: a/ Pure-tone audiogram measured with the use of two conventional hearing aids 1 month prior to implantation. Without hearing aids no threshold could be registered. b/ Pure-tone hearing threshold measured with the implant 5 months after CI. c/ Threshold measured with the implant 2 years after CI.

7.3. Discussion

Several studies in international literature prove that the incidence of otogenic/labyrinthogenic meningitis is higher in certain inner ear dysplasias than in patients with normal inner ear anatomy [27, 137, 168]. In such cases usually a pathologic communication exists between the middle ear and the subarachnoidal space via the inner ear which enables – for instance in otitis media – bacteria to reach the meninges.

It poses a serious dilemma to indicate CI in a labyrinthine malformation associated with deafness. While in certain dysplasias the communication between middle ear and subarachnoidal space exists from birth, in others the communicating perilymphatic and CSF spaces are isolated from the middle ear until they are opened by the preparation of a cochleostomy during CI.

It is also known that CI performed in ears with normal anatomy increase the risk of bacterial meningitis – this, however, does not contraindicate CI in light of the benefits of implantation, the existence of modern antibiotics and vaccines against meningogenic bacteria [125, 144, 148, 193, 194].

We believe that the recurrent meningitis of our case is a consequence of the peculiar pathoanatomy of the child's inner ear. CI had only initiated the series of meningitis, but it could also have been initiated by a purulent otitis media or a myringotomy on either side. Our opinion is based on the following observations:

1./ We think that due to the peculiar inner ear malformation, episodes of recurrent bacterial meningitis associated with upper airway infection or otitis media would have presented sooner or later anyway. That the child had suffered no meningitis prior to CI may be explained by the fact that he – being raised at home during his two years of life – had never before had an otitis media.

2./ Due to the deficient bony partition between the IAC and the labyrinth, the perilymphatic space and the subarachnoidal space were in a permanent, wide communication (a similar route of communication may have been present via the widened vestibular aqueduct, too, but during the operations we always observed liquorrhoea from the direction of the IAC).

3./ Only the labyrinthine endosteum (and later scar tissue) stood between the middle ear (a potential source of bacteria) and the mixed perilymph/CSF; this is not an adequate microbiological barrier, hence presents a site of invasion for the infection.

4./ The labyrinthine malformation was present in both ears, not only in the implanted side.

5./ The second meningitis did not present at the same time as the bilateral mastoiditis, but only three weeks after the surgical sanation of the mastoiditis, when the persistent iatrogenic liquorrhoea on the left was already present.

6./ The third and fourth meningitis (which developed three and fifteen months after the obliteration of the left inner ear) were preceded by an acute, incipient otitis media on the left side associated with an upper airway infection and a bilateral acute purulent otitis media, respectively.

Having considered these statements we rejected the idea of implant removal which was put forward by pediatricians. We believe that a "plug-shaped" scar which would have developed in the cochleostomy after explantation would not have presented a safer barrier against a next possible bacterial invasion than either the current, "ring-shaped" scar around the array adhering to it sealing the cochleostomy, or the scar that developed from the muscle obliterating the defects of both labyrinthine walls.

Did we increase the risk of meningitis considerably with CI? Are the previously mentioned scars isolating the perilymphatic space from the middle ear on both sides less resistant to bacterial migration than the original endosteum in their place? We believe it is impossible to answer these questions objectively.

The indication of CI in certain inner ear dysplasias associated with deafness means a serious medical and ethical dilemma. This comes partly from the fact that CI increases the risk of postimplantation meningitis even in case of normal inner ear anatomy [125, 193, 194] and partly from the fact that certain labyrinthine malformations are associated with an increased risk of meningitis even without CI [31, 138, 139, 195]. When do we bring a correct decision? If we indicate CI to enable an adequate hearing and speech development and push the child toward an increased risk of meningitis at the same time? Or if considering that risk too high we contraindicate CI and condemn the patient to deafness and muteness for life? It is not help but rather a further difficulty in the decision process that the precise identity of certain labyrinthine malformations is only revealed during surgical exploration. In spite of the difficulties and pitfalls of the presented case, in light of the satisfying hearing and speech development, we believe that – having involved the parents in the decision process with detailed knowledge of the problems and potential complications – in similar situations we must indicate CI.

7.4. Summarizing description of a newly described bilateral labyrinthine malformation with congenital deafness producing a CSF-perilymph cele in the middle ear

We encountered an extraordinary labyrinthine malformation in both ears of the child. Hereby we present its detailed anatomical description (as suggested by Lo [106]) based partly on CT findings and partly on findings of the two operations we performed. The proximal half of the cochlea's basal turn was defined, but unusually wide and distally continued in an undifferentiated cavity. No modiolus had developed. The vestibule was enormously wide, partially incorporating ("devouring") the horizontal semicircular canal. The sagittal and frontal semicircular canal were well defined. The internal auditory canal was abnormally wide. The bony partition between the interior of the labyrinth and the IAC was deficient enabling a perpetual communication between CSF and perilymph (Fig. 15). A large segment of the lateral labyrinthine wall was absent (like an enormously wide oval window) and through the defect the endosteum of the labyrinth herniated into the tympanic cavity and the

aditus ad antrum in the form of a sac containing CSF-perilymph ("CSF-perilymph cele") (Fig. 19). The vestibular aqueduct was pathologically wide.

According to this description it is evident that the present dysplasia cannot be classified as one fitting in the system published by Jackler and coworkers which explains malformations with a prematurely terminated embryogenesis [78]. It must rather have been the result of an aberrant embryonal development which – considering a negative pregnancy history and the fact that the child's dizygotic twin has a normal inner ear with good hearing – was most probably not caused by a teratogenic agent but a genetic defect. The authors believe that the malformation they observed simmetrically in both ears of the child can not be identified with any labyrinthine dysplasia reported in literature so far. Our opinion is confirmed by the fact that the *International Journal of Pediatric Otorhinolaryngology* accepted this dysplasia as a newly described malformation for publication [177].

8. COCHLEA MICRO-GRINDING: A LABORATORY METHOD FOR VISUALIZING INTRACOCHLEAR SITUATION AFTER COCHLEAR IMPLANTATION

8.1. Introduction

CI is one of the most invasive of ear operations, where a biocompatible but foreign device is implanted for the rest of the patient's life into the perilymphatic space which is in indirect (or sometimes direct, see Introduction of Chapter 7) connection with the cerebrospinal fluid space. During the five decades that elapsed since the first, pioneer CI by Djourno and Eyriès in 1957 in Paris [41] CI has become a routine procedure and also a story of success in the majority of the world's otosurgical centres.

According to the University of Michigan about 100000 patients have received a CI so far (2006 data, http://www.umich.edu/news/index.html?Releases/2006/Feb06/r020606a), most of whom – due to the relatively short history of the procedure – are live implant users today. A whole new, multidisciplinary branch of science came to life for indicating and performing the operations, for the postoperative care, follow-up, hearing and speech training, for designing and developing implants etc. – of which otorhinolaryngology is only a segment.

Apart from the ever-broadening field of indications (see Chapter 4) progress in the science of CI is defined mainly by device development in the research laboratory. This is just

understandable as – while modifications in surgery always mean to find the ”ideal” method of implantation – implants based on new therapeutic concepts are always designed and built in laboratories... of course, involving ear surgeons willing to experiment.

One inevitable condition for this device development is that the position of implants can be detected in vitro, in vivo and ex vivo after implantation. Many imaging methods are available which are suitable for visualizing the implant (most importantly its electrode array) and its surroundings in all three ”modes” after insertion.

Postoperative X-ray is a routinely applied procedure in the everyday (hence in vivo) practice of ear surgery following CI. Of course, X-rays can be used very well in vitro and ex vivo, too.

CT is not routinely used for visualizing the device after CI. The reason is partly that the metallic implant definitely scatters X-rays generating visual artefacts disturbing the evaluation of pictures and partly that it means a greater load of irradiation for patients than conventional X-ray. While spiral CT (with the longest history) is able to depict the array inside the cochlea, the separate electrodes of the array (points of stimulation) are not discernible, the fine structures of the cochlea (eg. the osseous spiral lamina) can barely be made out, and the precise position of the array (scala tympani or vestibuli) not at all [90, 167]. The newer rotational CT (RT) is somewhat more suitable for clarifying the postoperative situation as on pictures it provides it is possible to decide which scala the array is in [4]. The newest method named flat panel volume CT (fpvCT) promises especially detailed, high definition pictures without artefacts [7].

The use of MRI is also limited after implantation. According to the majority of authors the high-energy electromagnetic field generated during MRI – beside its artefact-generating effect – may have various, damaging effects on the implanted device: it may demagnetize its magnetic components, cause warming, move the implant [124, 175]. Speaking of which, this might pose a serious problem in case MRI is necessary due to some other disease. For such a case, the magnet is removable from certain types of implants via surgical exposure and it can be replaced after MRI – but the procedure carries its own surgical risks. It should be noted, though, that some authors reported about the safety of MRI performed with low-induction (1-1.5 Tesla) magnetic field in vivo [8, 197]. The use of MRI in vitro and ex vivo is less limited.

The joint use of preoperative MRI and postoperative CT in case of CI is a promising method. The procedure have already been utilised in many others fields of medicine. The idea is that high definition preoperative MRI data and high definition postoperative CT data are superponated by a special 3D computer workstation. From the 3D fusion of data the position

of the electrode array in the cochlea is clearly visualized in case of either in vitro, in vivo or ex vivo specimen [124]. The procedure requires special computer hardware and software and superior quality MRI and CT devices. Even this imaging method, however, is incapable of accessing the submillimeter range in the cochlea. For this purpose two procedures are available for researchers.

One is conventional histology. Microtomic sectioning and histological examination of temporal bones removed from cadavers and afterwards implanted, or temporal bones removed from deceased implant users is both possible. A variety of methods are available. One is the classical fixation with formaldehide, embedding in celloidin, sectioning and tissue staining [89, 128, 198]. Another is embedding in metacrylate resin following formaldehide fixation, sectioning and staining [65, 146]. Yet another is histological examination of frozen sections [51]. Microanatomical pictures gained by any of these methods are wonderfully detailed and may be magnified up to the limits of light microscopes. They, however, lack ”depth”, the extra information provided by 3D, which can only partially be restored by histological sections arranged in order and examined thus.

Here I will present the other laboratory research method called cochlea micro-grinding which is uniquely capable of visualizing intracochlear situation following CI in vitro and ex vivo. This procedure can also access the submillimeter range, and the gained images do not lack the feeling of depth, the third dimension, beside providing high definition details.

It is used in the research laboratory of the Hannover Medical University Department of Otolaryngology and Head and Neck Surgery for examining the intracochlear behaviour and effects of various, novel cochlear implants designed with new therapeutic concepts in mind. Research with devices from the three major implant producer companies (Advanced Bionics, Cochlear, MED-EL) has been going on for years. I had the opportunity to join this work for a period of seven months. As the implants we tested are still under development and the project has not been closed yet, it was not possible to report on conclusive results in any scientific journal. A segment of my work in micro-grinding, however, was used as reference material in a joint line of research, where the previously mentioned flat panel volume CT procedure was adapted for depiction of the cochlea [7]. Hereby I will present the procedure to demonstrate how it helps with understanding the pathogenesis of postimplantation meningitis and to illustrate some of the directions the development of CIs intends to take in the near future.

8.2. Material and methods

I used human cadaver temporal bones for the procedure, meaning that it was an in vitro research. (It should be noted, however, that sometimes ex vivo material is also used when – fortunately rarely – an implant user person dies and his/her temporal bone with the CI in situ is delivered to the laboratory. Such a specimen will also be presented here.)

8.2.1. Cochlear implantation

A normal CI was undertaken on the temporal bones meaning that mastoidectomy, posterior tympanotomy, cochleostomy was performed; afterward the stimulating electrode array was inserted into the cochlea according to the specifications of the experimental implant in question.

8.2.2. Fixation and dehydration

Immediately after CI the temporal bone was fixated in phosphate (0.1 M, pH 7.4) buffered 4% glutardialdehyde. Having left the bone in the solution for 4 hours, it was placed into phosphate buffer for another 2 hours. After this it needed dehydration which was done by soaking in an ascending alcohol-acetone series as follows: 50% ethanol–3 hours; 70% ethanol –one night; 90% ethanol–3 hours; 100% ethanol–3 hours; 1:1 mixture of ethanol:acetone–3 hours. Afterwards the bone was placed in a 60 °C drying chamber for 16 hours.

8.2.3. Embedding

The completely dried temporal bone was embedded in epoxy resin (TekMek, Struers A/S, Ballerup, Denmark) by filling first the inner ear through the cochleostomy, then the tympanic cavity and mastoid cavity. Epoxy resin hardened in 8 hours.

The next step – excision of the labyrinth block from the embedded temporal bone – was done with a rotating-blade Labotom 3 machine (Struers A/S, Ballerup, Denmark). The alcohol-washed, dried block was then placed in a casting mould made of silicon rubber where it was re-embedded in freshly made epoxy resin. After 8 hours of hardening a translucent epoxy cylinder was retrieved from the mould, with the cochlea (and surrounding bone) in the middle, containing the array of the tested implant.

8.2.4. Micro-grinding

Micro-grinding of the epoxy cylinder was done with a grinder (LaboPol-5 – LaboForce-1, Stuers A/S, Ballerup, Denmark). The procedure resulted in an evenly ground surface, grinding away a layer of 200 μm thickness from the embedded cochlea every time. Diminishing of the epoxy cylinder height was checked with a Mitutoyo 500 ruler. After every grinding round the ground surface of the epoxy cylinder (the gradually revealed interior of the cochlea) was stained, examined with microscope and documented with a camera.

8.2.5. Staining

1% silver-nitrate was dropped on the freshly ground surface and the epoxy cylinder was put into a UV chamber for 1 minute. UV radiation speeded up the photochemical reaction of silver-nitrate causing the bony structures of the surface to stain silvery. The solution was washed off the surface with 40 °C water and the surface was let dry. Silver-nitrate was fixated with 2.5% sodium-tiosulphate dropped on the surface which was washed off with water 4 minutes later. Soft tissues of the ground surface were stained red (counterstaining) afterwards with fuchsin. The stain was washed off after 45 seconds.

8.2.6. Examination, documentation

The surface stained with silver-nitrate and counterstained with fuchsin was examined with a Leica M26 transmission light microscope and documented with a Canon Eos D60 digital camera.

After documentation another 200 μm thick layer was ground off the cylinder, the newly gained surface stained and counterstained, examined and photographed again as many times as it took to grind away the whole cochlea step by step.

Once the whole cochlea was processed, the photographs were examined in the order they were taken. The place, position, possible kinking or tip foldover of the tested array and the fine traumatisation of the soft and bony structures of the cochlea caused during array insertion could be assessed with extraordinary accuracy and in microscopic detail.

8.3. Results

Fig. 22 and 23 both show arrays (that are in everyday use today) inserted into a proper position.

Fig. 24 illustrates one of the frequent positional irregularities occuring during CI: tip foldover.

Fig. 25 shows various possible cochlear traumas caused by insertion. The least severe damage is elevation of the basilar membrane (a). The next stage in severity is rupture of the membrane (b) followed by the situation where the array itself also passes through the membrane perforation and gets into the scala vestibuli (c) or outside the membraneous cochlea altogether (d). Rarely the spiral osseous lamina and/or the modiolus is fractured (e).

Fig. 26 demonstrates an array which is designed based upon a new therapeutic concept, first suggested by Lehnhardt. It is called ”endosteal electrode” [101, 132].

Further array variations meant to preserve residual hearing are named ”slim lateral” (Fig. 27) and ”apical” (Fig. 28).

Fig. 29 shows the electrode ”array” of another device in experimental stage, the ”modiolus implant”. As its name suggests, it is inserted into the modiolus of the cochlea.

Fig. 30 is a photo from the micro-grinded ex vivo cochlea of a deceased implant user. It shows the properly inserted array of the device, also documented with X-ray taken during the life of the patient.

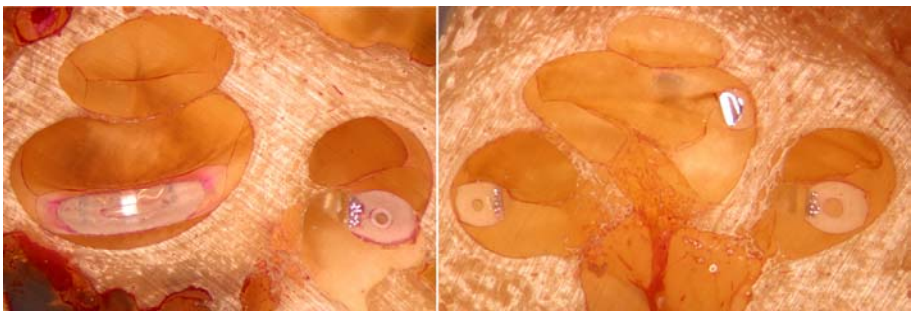

Fig. 22: Conventional array in the scala tympani. The ground surface is parallel with the axis of the cochlea (a) close to the cochlear wall and (b) inside the modiolus.

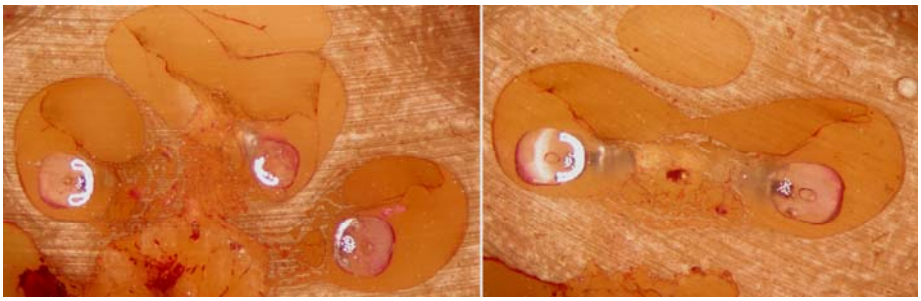

Fig. 23: Perimodiolar electrode array in the scala tympani (a) in the plain of the modiolus and (b) in the ”far” side of the coclea from the observer. It is easily recognizable that the electrodes of the array lie much closer to the modiolus than those of a conventional array in Fig. 22.

Fig. 24: Foldover of the array tip in case of two different types of implant.

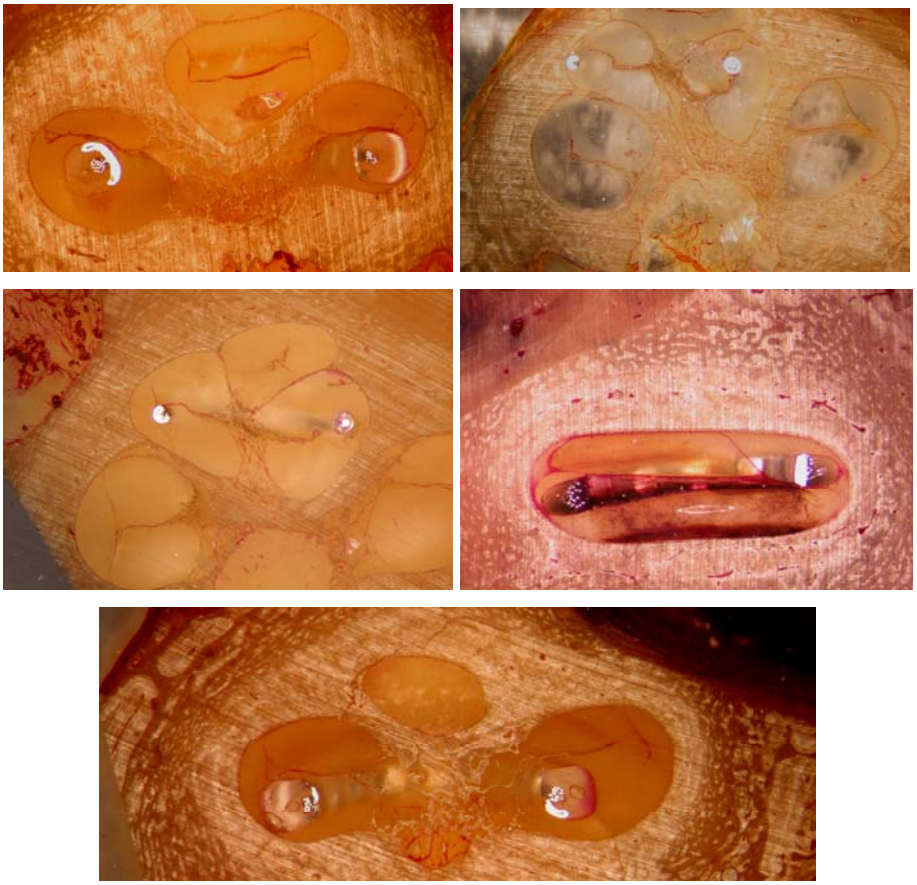

Fig. 25: Various types of intracochlear trauma. (a) Elevation of the basilar membrane on the left side of the photo. (b) Rupture of the basilar membrane on the right side. (c) Through the ruptured basilar membrane the array got into the scala vestibuli. (d) From the scala tympani the array got outside the membraneous cochlea. (e) The fine bony structure of the modiolus is fractured on the right side, the spiral osseous lamina is elevated, the basilar membrane is torn.

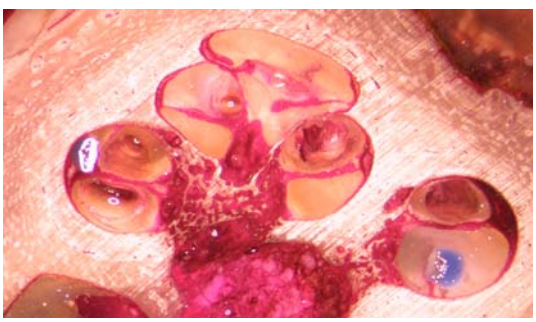

Fig. 26: ”Endosteal” electrode array. The array lies between the membranous cochlear wall and the endosteum in the proximal part of the basal turn.

Fig. 27: ”Slim lateral” array in ground specimen and on modified Stenvers’ view. The array lies in the outer/lateral part of the scala tympani filling the proximal half of the basal turn.

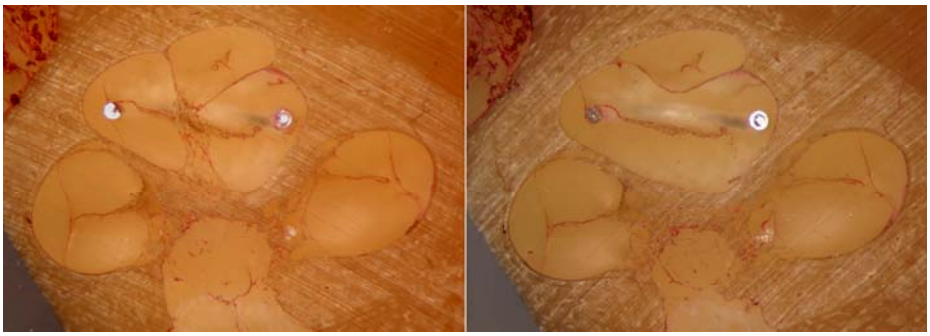

Fig. 28: ”Apical” array for electrically replacing the missing low-frequencies while preserving the residual high-frequency hearing. No array in the basal turn.

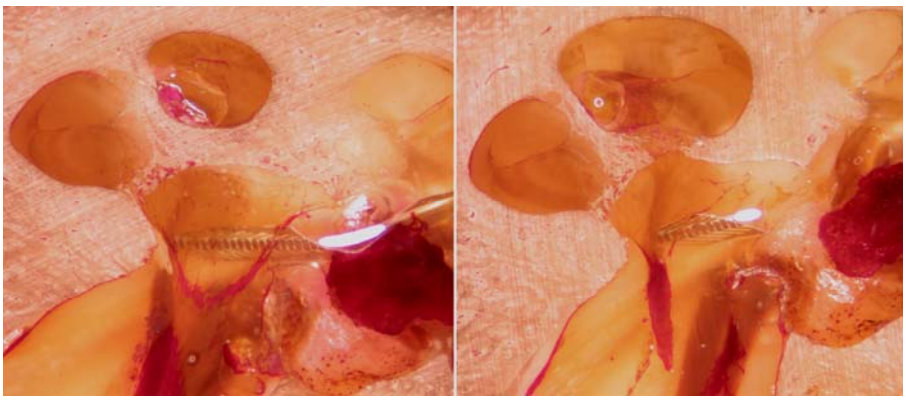

Fig. 29: ”Modiolus implant”. After the drilling of a special ”cochleostomy” the array is driven as a spear into the acustic nerve trunk branching in the modiolus.

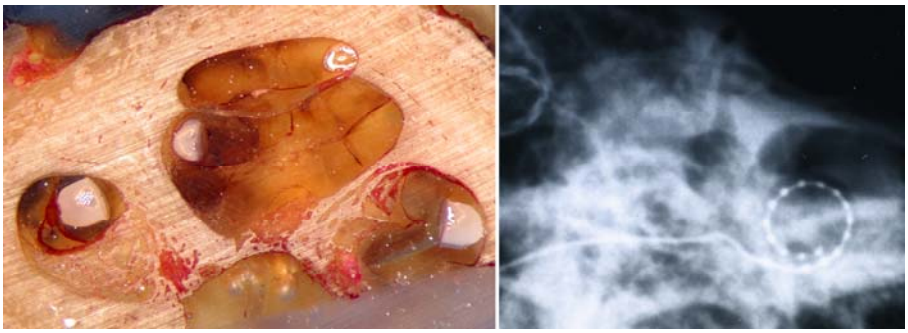

Fig. 30: Ex vivo ground cochlea. The specimen was made after the death of a patient using an implant for several years. Beside it a modified Stenvers’ view made when the same patient still lived.

8.4. Discussion

Knowledge of the intracochlear situation and electrode array position after CI is important both for ear surgeons and implant designers/developers. For the former a postoperative X-ray and feedback from a specialist checking the workings of the device are enough for making sure the operation was successful. A researcher, however, needs a more accurate view of events taking place in the cochlea.

Embedding of cochleae implanted in the laboratory in epoxy resin and their micro-grinding offers an ideal way of observing intracochlear situation. Examination of the bony cochlea opened by the procedure with a stereoscopic microscope offers both surface and in-depth visual assessment of structures, whereas playing the photoes made after each grinding round in order gives us a ”virtual endoscopic journey” from the cochleostomy to the far bony wall of the cochlea. Tissue fixation with glutardialdehyde, dehydration and subsequent filling with epoxy resin preserve structures of the membraneous cochlea in their anatomical position, enabling the observation of even microscopic traumas caused by array insertion.

The value of the method is proven by the fact that it was also used in developing other research procedures: during the adaptation of flat panel volume CT to the cochlea visual reference and proof for evaluating the CT findings were provided by micro-grinding and subsequent photography of the same cochlea specimens [7].

In ideal circumstances the electrode array is inserted into the scala tympani, in the neighbourhood of cell bodies of the spiral ganglion during CI. Fig. 22 documents a conventional array, Fig. 23 a ”modiolus-hugging” perimodiolar array; it is clearly visible how much closer the latter lies to the spiral ganglion cells reducing the energy needed for stimulation and ensuring better signal transmission. The figures nicely document the depth of insertion, too: both tips lie in the second turn of the cochlea.

In case a surgeon pushes the array with ”gentle violence” against intracochlear resistance (sometimes felt during CI) in order to achieve a deep insertion, the array tip may fold over. The situation on Fig. 24 explains why such a ”violated” array is not capable of a more effective signal transmission than an array inserted less deep but without excess force: although all of the stimulating array disappears in the cochlea, the electrodes farthest from the cochleostomy do not get ”higher” than a certain point, nevertheless. What’s more, due to the tip foldover the order of electrodes is mixed up necessitating extra attention and work when programming the device. Besides, the crumpling array may severely traumatize the cochlea.

Injury to the basilar membrane and other serious cochlear microtraumas (Fig. 25/a-d) may worsen the results of CI in the long run, as damaging of the spiral ganglion neurites can lead to retrograde nerve degeneration [158]. Microtraumas may also trigger scarry obliteration or ossification of the cochlear lumen, reducing the electrical excitability of the acustic nerve [24, 84]. Fracture of the osseuos spiral lamina or modiolus (Fig. 25/e) may enable a direct communication between CSF and perilymph, allowing the development of meningitis [97] – see also Introduction of Chapter 7.

The implant called ”endosteal electrode” by Lehnhardt [101, 132] is offered as a treatment for isolated high-frequency hearing loss with the preservation of the physiologic (acustic) hearing mechanism in the middle and low frequencies (which are not affected by the hearing loss). To achieve this, the array is inserted through the cochleostomy *between* the walls of the membraneous and bony cochlea (under the endosteum), and due to its short length it occupies only the first half turn of the cochlea according to the tonotopic arrangement of hair cells and spiral ganglion cells (Fig. 26). In this case it is especially important not to damage the membraneous cochlear wall upon insertion.

It should be noted that the theory and feasibility of simultaneous acustic and electric stimulation was first described and demonstrated by von Ilberg et al [187] (see also Chapter 4). Lehnhardt’s ”endosteal electrode” is one of many based on this principle [57, 164]. Further array variations meant to preserve residual hearing are named ”slim lateral” (Fig. 27) and ”apical” (Fig. 28).

Epoxy resin filling and micro-grinding of the cochlea is a uniquely adequate method for assessing the intracochlear situation after CI. Today it is an unavoidable – though time-consuming and expensive – research procedure for designing and developing implants with better positioning and less traumatizing arrays and implants based on new therapeutic concepts [179].

9. SUMMARY AND NEW FINDINGS

My involvement in otorhinolaryngological scientific research began in January 1999 when I became a junior member of the cochlear implantation team at the Department of Otorhinolaryngology and Head & Neck Surgery of the University of Szeged under the guidance of Professor Jenő Czigner and Professor József Jóri.

As the youngest *physician* in the team my duty was to perform the preevaluation of potential cochlear implantation candidates. This gave me the chance to get to know in detail all the examination procedures necessary to decide whether a person should be implanted or not, the process of CI indication itself and all the preoperative investigations. I also had the chance to do the follow-up of implanted patients from a physician's point of view which enabled me to see the (re)habilitation process and results of patients and – sometimes, unfortunately – also the early and late complications of CI.

As the youngest *surgeon* in the team my duty was to participate in the implantations themselves as an assistant, hence I could see the beauties of a routine operation and also the dilemmas, frustrations and improvisations when we had to break from routine.

My scientific publications originated partly from participation in the CI team's work and research done in relation with questions and concerns arising from everyday implant surgery.

From September 2004 till March 2005 I had the opportunity to do a 7-month-long scientific research at the Department of Otolaryngology and Head & Neck Surgery of the Hannover Medical University, Germany under the supervision of Professor Thomas Lenarz and Professor Timo Stöver. My focus there was on laboratory research, although I had the chance to see the working of their cochlear implantation centre, one of the most significiant in the word in this field. My scientific papers were born in part from the work I did in Hannover.

I managed to develop a non-invasive procedure for the screening of known deafness-causing genetic mutations without drawing blood **[181].** I demonstrated the feasibility of this method by comparing screening results for the presence of the 35delG mutation of the GJB2 gene gained from blood samples and oral mucosal smears of the same patients. This research proved that the use of buccal smears for the genetic screening of known deafness-causing mutations is exactly as reliable as the same screening done from blood samples. Thus we were able to offer an atraumatic way of finding a genetic diagnosis behind deafness for little children (for patients of any age, actually). Such genetic diagnoses may very well contribute to establishing a more accurate diagnosis of hearing loss which is getting more crucial as the proper assessment of the hearing of little children/infants gets more difficult with the continuous decrease of the lower age limit of CI.

Until 2005 – according to the almost total absence of such publications in literature – it was not customary to perform CI on hearing impaired patients who previously suffered from malignant tumors. With the presentation of the successful cases of two children we managed to demonstrate that CI must not be excluded as a means of hearing rehabilitation

after healing from a malignancy. The boom of articles by other authors reporting on further such cases after 2005 also implies that our CI team was right when we chose to implant these children. ***Hence, we managed to extend the field of indications of CI by including hearing loss in patients with a previous malignant disease*** **[178, 180].**

We suceeded in describing a new, previously unreported labyrinthine malformation for the first time in literature **[177].** With presenting the case of the patient we demonstrated our opinion that the surgical difficulties and risks of implantation in an unknown inner ear malformation are acceptable in light of the potential good audiological and speech developmental outcome.

In my thesis I sought to map the foreseeable directions the development of cochlear implants will take in the near future. I demonstrated how a laboratory research procedure contributes to device planning and testing and to a better understanding of how certain complications of CI develop. By showing some of the implants with new concepts behind them I illustrated which way the field of cochlear implantation's indications will probably be extended in years to come. ***My contribution to the process of CI development lies in testing a series of prototype novel arrays, most if which will show up in the hands of ear surgeons as final CI products in the near future*** **[179].** ***With my grinding work I also participated in the adaptation of fpvCT for imaging of the cochlea*** **[7].**

Today the surgical treatment of sensorineural hearing loss no longer belongs to the realm of Science Fiction so dear to the author of this thesis. Cochlear implantation is now science fact, the potentials of which we have barely started to discover.

10. ACKNOWLEDGEMENTS

This thesis took a long time coming. Some say it could have been written sooner, and they are probably right. It would, however, have been a much poorer work then, missing Chapter 7 altogether. I believe it was worth waiting until it became ripe enough for harvest.

I am grateful to Professor Jenő Czigner, former chairman of our department for involving me in the cochlear implantation team and for guiding my pen when it came to writing. He has been continuing to do so ever since, fortunately.

I express my gratitude to Professor József Jóri, now chairman of our department. He let me keep on working in the implantation team, offered professional and scientific insight both in practising medicine and writing science, and supported my research in Hannover in every possible way.

I thank the members of our department's cochlear implantation team (József G. Kiss, Alice Szamosközi, Ferenc Tóth, Éva Szabados, Attila L. Nagy, János Jarabin) and all the assistant staff for the support they gave me.

My sincere gratitude to Professor Thomas Lenarz and Professor Timo Stöver for welcoming me in Hannover. They blazed a wonderful path of research for me and showed me both how to travel this road and how to publish the results. Many thanks to Peter Erfurt for training and helping me in the lab.

And now my heartfelt thanks to my family. My wife Ági was there all the time, making and maintaining a warm, loving home for me – even in Hannover, accepting the monotony without relatives and friends. My daughter Dalma filled our life with constant joy, and as her intelligence blossomed, she gradually learned to accept that sometimes I do need to sit down and write stupid scripts instead of playing with her. Our younger one, Ádám made it just in time to join the last few months of my scientific endeavour. Welcome on board, my son!

I can only try to express my deepest gratitude to my parents and grandparents for the unwavering support they gave me from the beginning of my life. They have always been a fountain of love, knowledge, and humaneness guarding my path, and they keep on being there for us still. May Fate bless them!

I thank my brother Robi for sharing a considerable portion of my life, and for being my friend beside being my brother. I also thank my parents-in-law for all the help they gave and keep giving us.

And finally, my special thanks to my dear colleague László Rovó. While having a warm lunch in a ski ”Hütte” on Stuhleck he said to me: ”You have all the material. What are you waiting for? Write it!”. So I did.

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