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An Excursus into Hearing Loss

Edited by Stavros Hatzopoulos and Andrea Ciorba

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and **Andrea Ciorba**

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Meet the editors

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Contents

Preface

The objective of this volume is to diffuse the information related to hearing loss, which is among the most prevalent chronic disabilities worldwide. Nowadays, it is clear that the identification and rehabilitation of hearing impairment, when possible, have to be adequately and promptly managed because hearing loss can seriously interfere with psychosocial development, family dynamics, and social interactions.

This volume was made possible through the substantial contributions of 10 groups of authors.

The format of this volume is purely educational, targeting graduate courses in audiology, speech pathology and hearing science, and neurosciences and basic graduate course in otolaryngology. The authors have been asked to present a generous background of their topic in the introduction section of their chapter and an extensive list of technical terms used throughout each chapter.

The volume is divided into three main sections as follows:

1. Section I: "Hearing Loss and Its Etiology." In this section, the problems associated with various types of hearing impairment are presented, particularly focusing on the genetic background of hearing loss.
2. Section II: "Early Diagnosis and Prevention of Hearing Loss." This section focuses on the description of a newborn-hearing screening as an important tool to prevent problems resulting from hearing loss and on the assessment and prevention of ototoxicity (the various side effects of drugs related to cochlear-induced damage).
3. Section III: "Treatment Strategies for Hearing Loss." Hearing aids, cochlear implants, and implantable devices represent the currently used treatments for rehabilitation of patients affected by hearing impairment, and the specific indication of each solution is presented and discussed.

It was our intention to use multimedia material wherever possible, but for the majority of contributors, this was not feasible. Further developments (such as multimedia materials and updates) will probably appear on IntechOpen website (https://www.intechopen.com/).

We would personally like to thank all the contributing authors, the IntechOpen personnel, and specifically Ms. Renata Sliva and Ms. Dajana Pemac for their continuous and generous assistance during the preparation of this volume.

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Section 1

Hearing Loss and Its Etiology

Chapter 1

Effects of Genetic Background on Susceptibility and the Acceleration of Hearing Loss in Mice

Shumpei P. Yasuda, Yuki Miyasaka and
Yoshiaki Kikkawa

Additional information is available at the end of the chapter

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Abstract

Acquired hearing loss, which includes age-related hearing loss and noise-induced hearing loss, is a common hearing impairment and shows phenotypic variability. One reason for phenotypic variability is influence of genetic background. The modifiers underlying genetic background are modulated and advance the hearing phenotypes through gene-gene interactions with other etiological genetic factors. Moreover, the modifiers play a role in the susceptibility of environmental hearing risk factors, namely, the strength and weakness of environmental susceptibility often modulate and advance hearing phenotypes via gene-environment interactions. The complicated gene-gene and gene-environment interactions make genetic analysis of acquired hearing loss difficult. In particular, the effects of environmental factors cannot be completely excluded or controlled. Although genome-wide approaches to identify genetic modifiers have proven challenging in humans, the responsible genes and mutations are widely unknown. In this chapter, we suggest that mouse models are useful for studying genetic background effects for acquired hearing loss. The genetic analysis of mouse models identified the genetic modifiers. We review the genetic research in mouse models for acquired hearing loss to identify and confirm the modifiers by both forward and reverse genetics approaches.

Keywords: genetic background effects, mouse model, quantitative trait loci (QTL), genetic modifiers, genetic interaction, epistasis, genome editing

1. Introduction

Hearing loss is the most common sensory disorder, which affects approximately 0.1–0.2% of newborns [1]. A genetic etiology of congenital hearing loss accounts for an estimate of at least 50–60% of hearing loss cases, whereas the remaining 40–50% develops from a nongenetic etiology, such as effects of risk factors for neonates and birth conditions [1–3]. To date, many

mutations responsible for hearing loss have been recently identified in approximately 100 human genes [3, 4]. However, most mutations are primarily associated with congenital and severe hearing loss developed at newborn and childhood stages caused by a single gene. The identification of the more common "acquired hearing loss," such as age-related hearing loss (ARHL) and noise-induced hearing loss (NIHL) is currently understudied.

Acquired common hearing loss is a complex multifactorial disease influenced by genetic backgrounds and environments. In ARHL, an accurate estimation of the genetic etiology has not been reported. However, it is estimated that ARHL develops through the effects of genetic modifier(s) because the onset time and severity of hearing loss vary greatly among individuals [5, 6]. Moreover, there is a significant heritability of hearing phenotypes [6]. The heritability ranges from low to high [6–10], suggesting that multiple genetic modifiers and environmental factors contribute to the onset and severity of hearing loss. The documented risk factors of ARHL and acquired hearing loss are noise, smoking, alcohol consumption, diet and reduced exercise, complication of other diseases, and uses of ototoxic drugs [6, 11]. It is known that one major risk factor is exposure to loud noise, accounting for approximately 16% of the population worldwide [12]. Genetic factors from a genetic background might also play an important role in the susceptibility of NIHL [13]. However, the identification of genetic background effects in ARHL and NIHL is difficult in humans because of lower heritability of this phenotype and the influence of environmental risk factors mentioned above. In addition, genetic differences among individuals disturb genetic analysis.

To investigate genetic background effects associated with hearing loss, we propose that mouse models have several advantages to overcome weaknesses in the genetic analysis of ARHL and NIHL in humans. Mice can be controlled to avoid environmental risk factors. The techniques for evaluation of hearing, such as measurements of the auditory brainstem response (ABR) and distortion product otoacoustic emission (DPOAE), have been established [14–18]. Based on the techniques, it is known that there is phenotypic heterogeneity of ARHL and NIHL caused by genetic background effects [3, 6, 11]; therefore, the genetic background effects can be analyzed using the quantitative trait loci (QTL) analysis and genome-wide association study (GWAS) of experimental populations produced by mating susceptible and resistant strains of ARHL and NIHL. This chapter applies the advantages of a genetic analysis by using mouse models to study the genetic background effects of hearing loss.

2. What is a genetic background effect?

First, we will explain the basic mechanisms of background effect in phenotypic modification to readers in a way that they will understand the importance of this chapter.

2.1. Gene-gene interaction

A complex disease is one that lacks a one-to-one correspondence of mutation and phenotype [19, 20], namely, the expression of phenotype is influenced by genetic modifier(s) underlying the genetic background. **Figure 1A** shows a simple model of the genetic background

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effect. In most cases, the genetic background effects are revealed by the expression of different phenotypes caused by the same genetic mutation in different genetic backgrounds. Let us assume that a gene associated with hearing loss was mutated by gene targeting in mice (strain R). We performed the hearing test of knock-out (KO) mice using measurements of ABR. The KO mouse exhibited latency peak responses for peaks I–V as well as the wild-type mouse; however, the amplitudes of all the peaks were weak and delayed. Next, we performed the gene targeting of the same gene in mice of different genetic backgrounds (strain S). The mouse had no discernable ABR waveform, indicating that the hearing loss of the mouse became more severe due to variation in the genetic background. These results suggest the presence of a genetic modifier, which affects the phenotype developed by the mutation of the causative gene, with respect to the genetic background of strain R. Moreover, it is assumed that the modifier interacts with the causative gene in the acceleration of hearing loss. The genetic interaction could be separated into nonadditive and additive effects to

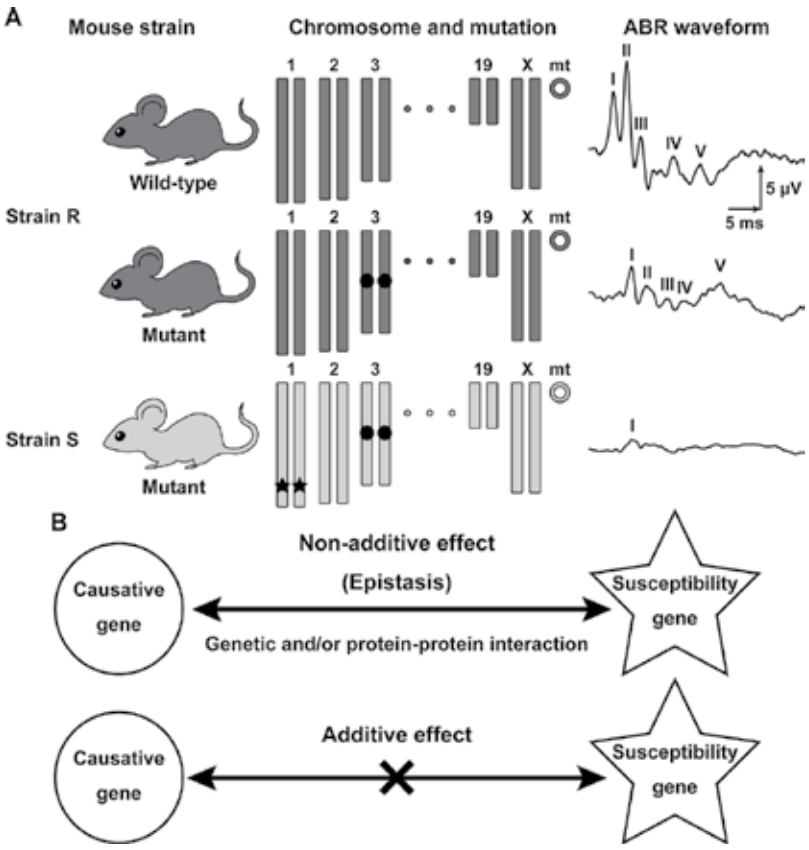

Figure 1. Simple models for genetic background effect in phenotypic modification. (A) Schematic representation of the genetic background effect in hearing of mice. Illustrations show the differences of auditory brainstem response (ABR) waveforms by the effects of the susceptible allele (black stars) in the hearing loss mutant. Black circles indicate mutation associated with hearing loss. The locations of ABR peaks I–V are indicated with ranges (μV) of the negative wave apex and latency (ms). (B) Definition of additive (top) and nonadditive (bottom) interaction in phenotypic modification.

evaluate whether the gene-gene, gene-protein, and protein-protein interaction are present in the regulatory pathway of the phenotype (**Figure 1B**). The nonadditive effect is called "epistasis" in technical terms of genetics, stating that there is a direct interaction between two or more genes [19, 20]. The additive effect states that phenotypic acceleration and modification occur by accumulation of mutations in genes of similar function in different molecular pathways (**Figure 1B**) [20].

2.2. Gene-environment interaction

In a complex disease, the expression of phenotype is also influenced by environmental factor(s), along with the interaction between the environment and genes in genetic background. A model is shown in **Figure 2A**. Let us assume that we performed an experiment of noise exposure to mice. We performed the experiment in strains R and S and then measured ABR. The ABR responses between the two strains were different. The peaks of the ABR

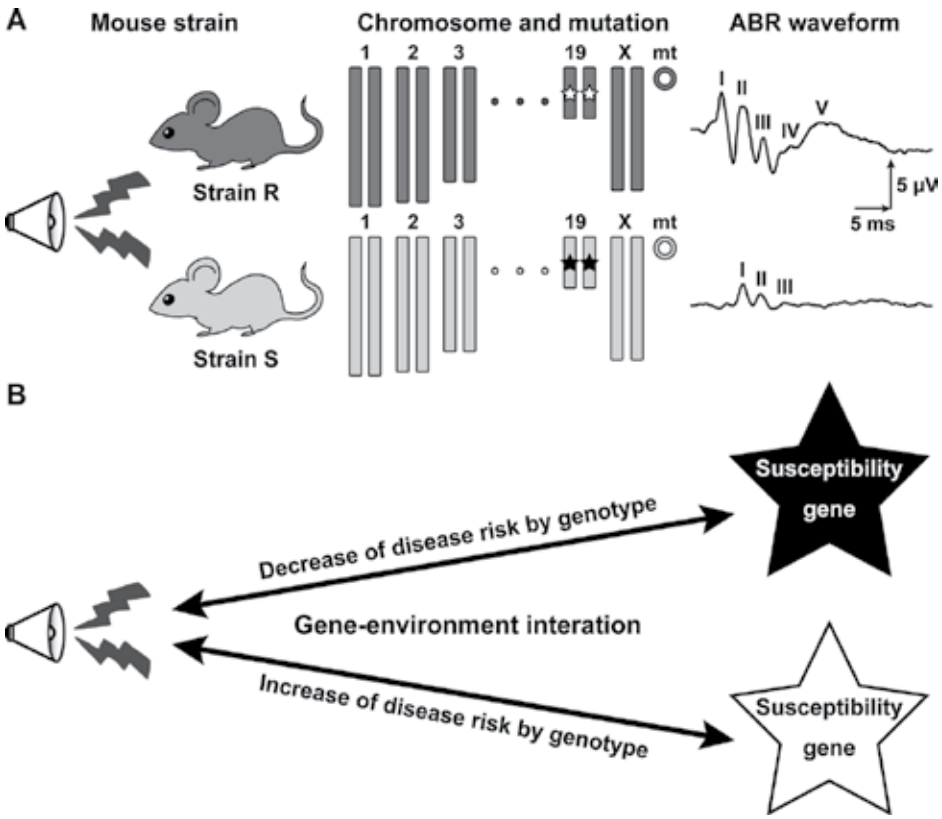

Figure 2. Simple models for genetic background effect in the susceptibility of environmental factors. (A) Schematic representation of the genetic background effect in noise-induced hearing loss of mice. Illustrations show the differences between strain R and S of ABR waveforms by the effects of the noise exposure and susceptible allele (black stars). The locations of ABR peaks I–V are indicated with ranges (μV) of the negative wave apex and latency (ms). (B) a model for genetic background effect in the susceptibility of environmental factors.

waveform in strain S were significantly lower than those in strain R. This result suggests that strain R is a noise-resistant strain, whereas strain S is a noise-susceptible strain. In addition, the genetic mechanism for noise sensitivity in both strains can be explained by the presence of resistance and susceptibility alleles in addition to the risk of noise exposure, namely, a gene-environment interaction contributes to the development of NIHL (**Figure 2B**) based on a genetic background effect. Thus, the genetic background effect is important in the study of the influence of environmental factors on complex diseases.

There is one thing to note. Although we explained the gene-environment interaction using a model that would be easy to understand, this model is admittedly simple because it only considers the effect of one gene and one environmental factor. In the case of human diseases, the gene-environment interactions are more complicated because the interactions involve multiple genes, multiple environmental factors, genetic heterogeneity, and heterogeneity of environmental exposure [20].

3. Phenotypic variations of hearing caused by genetic backgrounds in mouse inbred strains

Laboratory mice are one of the best experimental models to investigate the genetic background effect for ARHL as mentioned in Section 1. Moreover, the classical inbred strains have been established in large numbers and exhibit variable hearing ability and onset time of ARHL caused by genetic background [21, 22]. **Figure 3** shows the means of ABR thresholds to tone-pip stimuli at 4, 8, 16, and 32 kHz in mice from MSM/Ms, C3H/HeN, C57BL/6J, A/J, and DBA/2J at 4 months of age, as cited in our previous studies [23–25]. The hearing phenotypes of these strains can be classified into two groups: normal hearing and early onset ARHL. The MSM/Ms and C3H/HeN comprise the normal hearing group. The ABR thresholds are stable at all frequencies. The C57BL/6J mice also show normal ABR thresholds at 4, 8, and 16 kHz. However, the ABR threshold at 32 kHz of C57BL/6J mice is significantly higher than that of MSM/Ms and C3H/HeN mice, indicating that C57BL/6J developed high-frequency-specific ARHL. The A/J mice exhibit an ARHL that is more severe for high-frequency stimuli. In addition, the ABR thresholds of the A/J mice at other frequencies are clearly increased when compared with those of C57BL/6J mice. Moreover, the DBA/2J mice developed more severe hearing loss. The ABR thresholds of the DBA/2J mice exhibited levels of severe (71–90 dB SPL) and profound (<91 dB SPL) hearing loss in sound stimuli at 4/8 and 16/32 kHz, respectively, which were significantly higher than those of A/J mice at 4, 8, and 16 kHz.

The difference between the normal hearing and early onset ARHL groups can be explained by a mutation of the Cadherin 23 gene (*Cdh23*). The responsible $Cdh23^{c.753G>A}$ mutation was identified at one base before the splice-donor site, leading to partial skipping of a single exon [21, 24, 26] and age-related stereocilia degeneration in cochlear hair cells [23, 24, 27]. The A/J mice have another strain-specific mutation (p.His55Asn) in the citrate synthase gene (*Cs*) [28]. By identifying $Cs^{p.His55Asn}$ mutation, A/J mice were shown to have developed severe ARHL

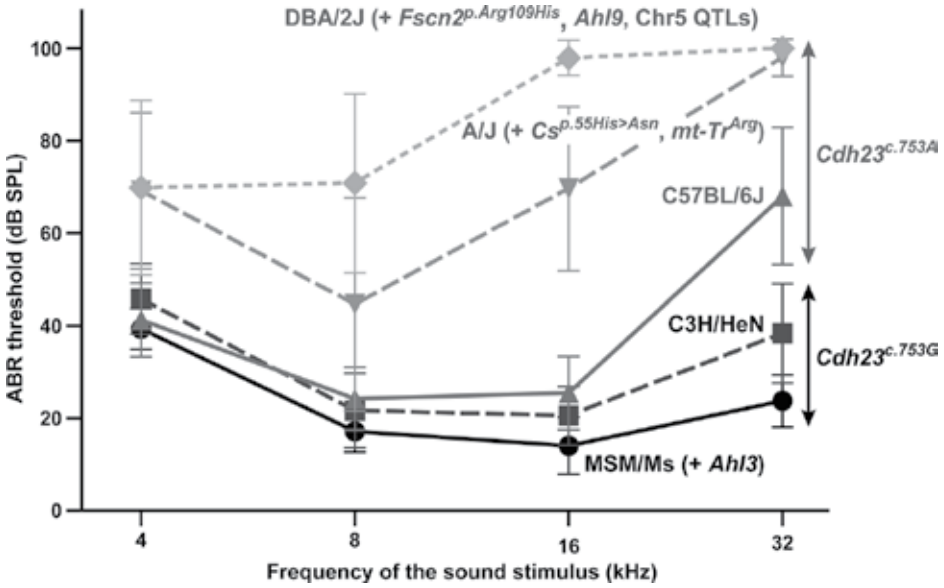

Figure 3. Comparison of hearing levels among the mouse inbred strains. The means (circles, squares, diamonds, and upper and lower triangles) and standard deviations (error bars) of ABR thresholds for 4, 8, 16, and 32 kHz sound stimuli are shown for MSM/Ms, C3H/HeN, DBA/2J, C57BL/6J, and A/J mice at 4 months of age. The graph was created by using data from our previous studies [23–25].

by interaction between *Cdh23*$^{c.753G>A}$ and *Cs*$^{p.His55Asn}$ mutations. The CDH23 is a member of the calcium-dependent cell-cell adhesion and tip link component [21, 29, 30]. In contrast, CS is the first enzyme of the tricarboxylic acid cycle, generating citrate and free coenzyme A [31]. Therefore, both proteins seem to contribute different functions in the inner ear for hearing, suggesting that A/J mice develop early onset hearing loss from additive effects of different functional mutations, as described in the previous section (**Figure 1B**). In addition, A/J mice carried a single adenine insertion in the mitochondrial tRNA-Arg gene (*mt-Tr*^{Arg}) [32]. CS is transported into the mitochondrial matrix and plays an important role in condensing mitochondrial acetyl-coenzyme A and oxaloacetate for transporting of acetyl-coenzyme A from the mitochondrial matrix to the cytosol [31], suggesting that mitochondrial dysfunction by epistasis (**Figure 1B**) between *Cs*$^{p.His55Asn}$ and *mt-Tr*^{Arg} mutations is accelerated in ARHL of A/J mice. The DBA/2J mice also have a strain-specific mutation (p.Arg109His) in the fascin 2 gene (*Fscn2*) [33]. DBA/2J mice exhibit progressive shortening of the stereocilia, and this phenotype only develops with homozygosity of both the *Cdh23*$^{c.753G>A}$ and *Fscn2*$^{p.Arg109His}$ mutations [34]. FSCN2 is an actin crosslinking protein and localizes along the length of stereocilia at especially high concentration around the stereocilia tips [33, 34]. Although the pathological mechanisms in the genetic interaction between the *Cdh23*$^{c.753G>A}$ and *Fscn2*$^{p.Arg109His}$ mutations are widely unknown, the degeneration of stereocilia in DBA/2J mice may be explained by epistasis. Moreover, the other QTLs related to ARHL were detected in DBA/2J mice. The QTLs, *Ahl9* [35] and *Chr5* QTL [25, 36], are likely to contribute to frequency-specific ARHL. Although the causative genes and mutations are still unknown, these QTLs lead to severe hearing loss by

additive or epistatic interaction with the *Cdh23*$^{c.753G>A}$ and *Fscn2*$^{p.Arg109His}$ mutations. Thus, the differences of hearing levels among the inbred strains are regulated by background effects through the epistatic and additive effects.

4. Identification of the genetic modifiers in mice

We have described in the previous section that several mouse inbred strains developed ARHL by genetic background effects. In this section, we introduce approaches to identify genetic modifiers and susceptibility loci of hearing loss underlying the genetic backgrounds.

4.1. Classical forward genetics approach

The forward genetics approach is phenotype-driven, with a foundation that associates the detection of chromosomal location with phenotype by linkage analysis. The start of the experiments included production of chromosomal recombinants, F_2 and N_2 mice, by crossing between the susceptible and resistant strains in phenotype (**Figure 4A**). The linkage analysis is based on meiotic recombination events that occur in sperm and egg precursor cells of F_1 hybrid, which have heterozygous chromosomes derived from both the susceptible and resistant strains. Accordingly, the F_2 and N_2 progenies were produced by intercrossing between F_1 mice and backcrossing of F_1 mice to one parental strain, respectively, and inherited chromosomes that underwent recombination events. The recombinant region on the chromosomes was detected by using a genetic marker, such as microsatellites and SNPs, which recognized genetic polymorphisms compared to parental strains. Finally, the phenotypes of F_2 and N_2 mice were investigated to determine whether there is linkage with the recombinant regions of F_2 and N_2 mice. This approach has been a powerful and productive method to identify QTL-associated ARHL. Johnson et al. [37] detected the first QTL *ahl* locus for ARHL that displayed a *Cdh23*$^{c.753G>A}$ mutation by using N_2 backcross mice between ARHL-susceptible C57BL/6J and -resistant CAST/Ei.

As mentioned earlier, there are many modifiers in the genome of inbred strains. To evaluate the effect of a single QTL identified in the mapping by avoiding the effects from other modifiers, congenic mice have become a powerful tool. Congenic mice are defined as having part of the mutation or a chromosomal segment from one inbred genetic background (donor) to another (host) [38] (**Figure 4B**). The creation of congenic mice is based on backcrossing the system for at least seven times. Although this process is long, the resolution of the phenotype greatly improves when compared with F_2 and N_2 mice. The most successful example of this strategy is the study of *moth1* locus [39, 40]. The *tubby* mice, which are a mutant of tubby bipartite transcription factor gene (*Tub*), exhibit severe hearing loss caused by cochlear degeneration in C57BL/6J background [39]. However, some F_2 mice produced by intercrossing with AKR/J and CAST/Ei showed normal hearing. Ikeda et al. [39] mapped the modifier, *moth1*, via linkage analysis using both F_2 mice and confirmed the locus by creating congenic mice. This study led to the successful identification of the association of the modification of hearing loss with a strain-specific mutation in microtubule-associated protein 1 gene (*Map1a*), which was the first elucidated causative gene caused by the background effect in hearing [40].

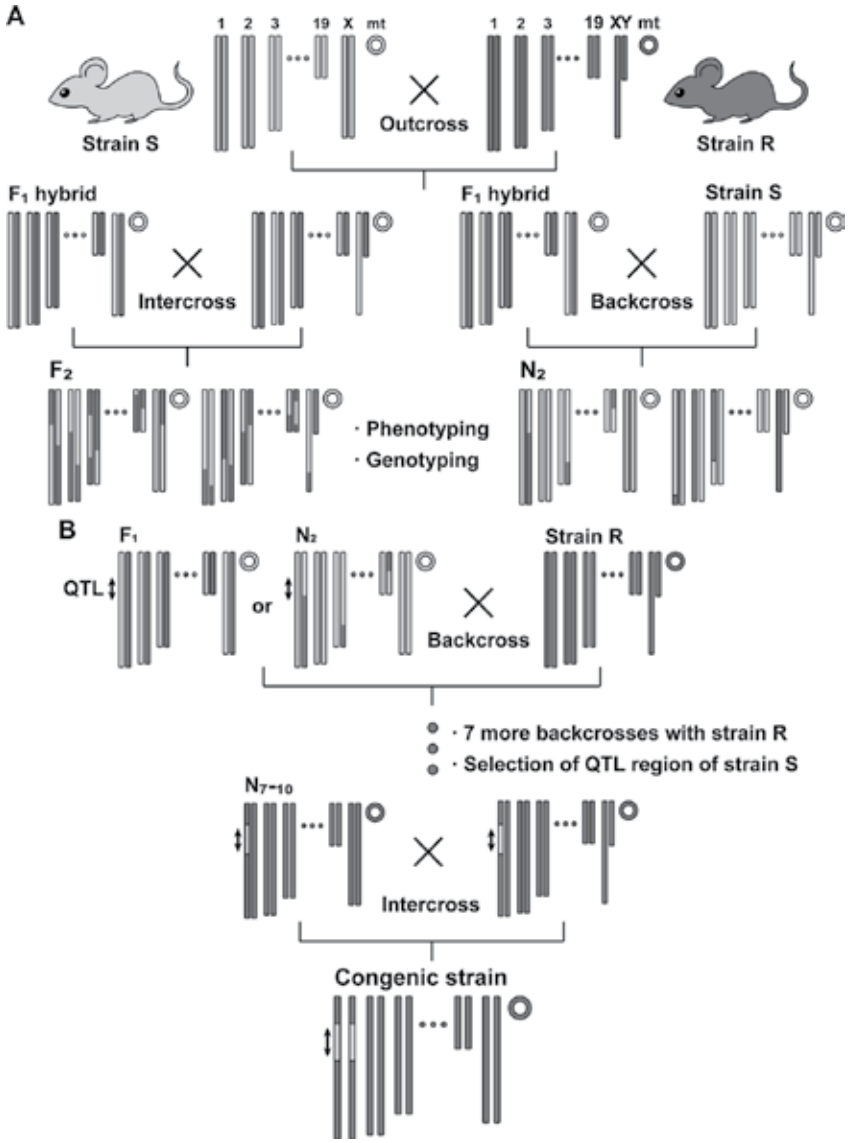

Figure 4. Schematic representation of the virtual genomic structures of experimental cross (F_2 and N_2) (A) for genetic mapping and congenic mouse (B). The rectangles and circles represent chromosome and mitochondrial DNA, respectively. The different strain-derived chromosomal regions are distinguished by light and dark gray colors. Bidirectional arrows indicate quantitative trait locus (QTL) regions.

4.2. Forward genetics approaches using genetic reference populations of mice

Currently, we believe that a classical forward genetics approach using F_2, N_2, and congenic mice is useful to identify the modifiers from genetic background in mice. However, productions of the F_2, N_2, and congenic mice consume great amount of time and costs for breeding. Large numbers of mice are required to increase mapping resolution. Moreover, the F_2 and N_2 mice must be used for genome-wide genotyping because their genome architectures are uniquely mixed between parental chromosomes. Therefore, the genotyping cost is enormous. Here, we

introduce the public genetic reference populations of mice. These populations have several advantages owing to established QTL mapping.

4.2.1. Recombinant inbred strain (RIS)

Recombinant inbred strain (RIS) panel is a genetic reference population of mice and can serve as a powerful tool for QTL mapping. It is produced by mating sibling F_2 mice until the resulting progeny, at least 20 generations later, is fully inbred and displays a mosaic of parental genomes (**Figure 5A**) [41, 42]. RIS panel has several advantages for QTL mapping; if the genotyping is performed once, it does not require genotyping in each individual and is available in public databases; individual, environmental, and measurement variability can be reduced; it has greater mapping resolution because the breakpoints in the genome are denser than those that occur in any one meiosis, such as F_2 and N_2 mice [41].

RIS panels have been successfully applied to several QTL mappings for ARHL. The strategy includes only evaluating the hearing abilities of each individual RIS panel performed by

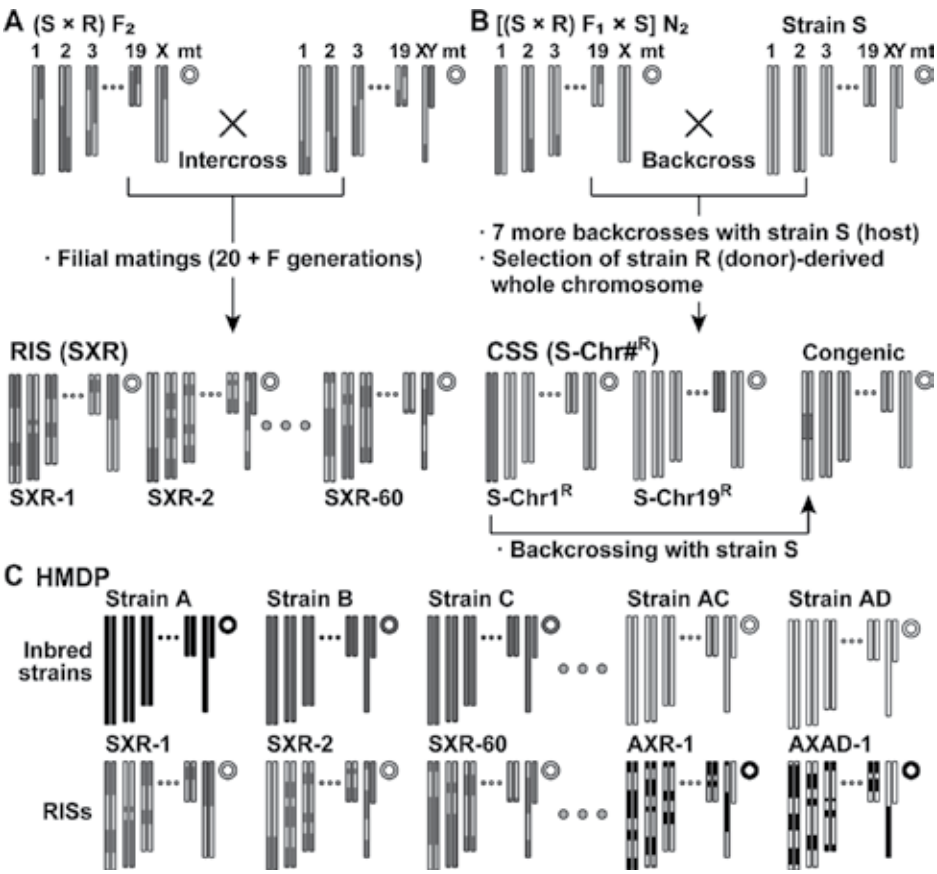

Figure 5. Schematic representation of the virtual genomic structures of the recombinant inbred strains (RIS) (A), consomic strain (CSS) (B), and hybrid mouse diversity panel (HMDP) (C) for QTL analysis and genome-wide association study (GWAS). The rectangles and circles represent chromosomes and mitochondrial DNA, respectively. Each strain-derived chromosomal region is distinguished by a different color.

measurements of ABR thresholds and then performing QTL linkage analysis using WebQTL [43], which collects genotypes of microsatellite and SNPs in each RIS panel. By this strategy, the QTLs *ahl4* (*Cs*$^{p.His55Asn}$) [44], *ahl8* (*Fscn2*$^{p.Arg109His}$) [45], *Ahl9* [35], and *Snhl* [18] were mapped using the AXB/BXA [46], BXD [47], BXD and LXS [48], and RIS panels, respectively (**Table 1**). The other RIS panels, such as CXB [49], BXH [50], and SMXA [51], have been established by sibling mating between several inbred strains and will become useful resources to identify new loci associated with ARHL and NIHL.

4.2.2. Consomic strains (CSS)

Consomic strains (CSS), also called chromosome substitution strains, are combined genomes of two founder inbred strains that have a substitution of one whole chromosome pair from the donor strain into the genetic background of the host strain (**Figure 5B**) [52, 53]. The productive strategy is the same with congenic mice. Usually, a full set of CSSs will consist of 22 strains, which includes 19 pairs of autosomal chromosomes, X and Y sex chromosomes, and a mitochondrial genome, although the introgression into the host background of a whole chromosome from the donor is difficult in some cases [53]. The main advantage of CSS is mapping of the phenotype to single chromosomes. The *Ahl3* [54] and *ahl4* [44] loci have

Population	Panel	Origin	QTL or QTN	Gene
Recombinant inbred strain (RIS)	AXB [46]	(A/J × C57BL/6J) F_1	*ahl4* [44]	*Cs* [28]
	BXA [46]	(C57BL/6J × A/J) F_1		
	BXD [47]	(C57BL/6J × DBA/2J) F_1	*ahl8* [45]	*Fscn2* [34]
			Ahl9 [35]	Unknown
	LXS [48]	* (ILS × ISS) F_1	*Snhl* [18]	Unknown
Consomic strain (CSS)	C57BL/6J-Chr#$^{A/J}$ [52]	Host: C57BL/6J, donor: A/J	*ahl4* [44]	*Cs* [28]
	C57BL/6J-Chr#$^{MSM/Ms}$ [53]	Host: C57BL/6J, donor: MSM/Ms	*Ahl3* [54]	Unknown
			*mjs*** [24]	*Cdh23* [24]
Inbred strain population	Hybrid mouse diversity panel (HMDP) [56]	30 classic inbred strains and 70 recombinant inbred strains	rs33652818 [17]	*Nox3* [17]
			rs37517079 [60]	Unknown
Outbred stock (OS)	Black Swiss [62]	NIH Swiss, C57BL/6J	*Ahl5* [63]	*Gipc3* [14]
			Ahl6 [63]	Unknown
	NIH Swiss [64]	NIH GP colony	*Hfhl1* [15]	Unknown
			Hfhl2 [15]	Unknown
			Hfhl3 [16]	Unknown

*Inbred long sleep (ILS) and inbred short sleep (ISS) mouse strains, which were derived from a multi-generation cross of eight inbred strains.

**Modifier of *js* (tentative symbol).

Table 1. Genetic reference population contributed for identification of the loci and SNPs associated with hearing loss underlying in genetic background of mice by QTL analysis and GWAS.

been mapped to a single chromosome by ABR measurements in CSSs of partial and full sets (**Table 1**). Moreover, congenic mice for QTL mapping can be easily and quickly produced by intercrossing (CSS × host strain) F_1 and backcrossing (CSS × host strain) F_1 × host strain (**Figure 5B**). The genotyping is only required in one chromosome for progeny. By this strategy, we have previously mapped the *Ahl3* [54] and a modifier [24] responsible for the acceleration of ARHL of heterozygotes of Jackson shaker mice (*Ush1g*^{js}) (**Table 1**).

In addition, CSS may be used to study epistasis in detail. An example is *Ahl3* [54], which was mapped to chromosome 17 using C57BL/6J-Chr17$^{MSM/Ms}$ CSS. The donor strain, MSM/Ms, is an inbred derived from the Japanese wild mouse, *Mus musculus molossinus*. By introgression of the genomic segment including *Ahl3*, the ARHL of C57BL/6J was dramatically suppressed despite having the homozygous *Cdh23*$^{c.753A}$ allele in the genome. Although we predicted that *Ahl3* is the resistance allele for ARHL in MSM/Ms mice, the resistant effects of *Ahl3* were not detected in the other mapping system of the C57BL/6J and MSM/Ms strain [24]. The genetic divergence between C57BL/6J and MSM/Ms is extremely high [55]; therefore, the resistant effect of *Ahl3* was caused by incompatibility by chromosomal substitution. We detected a similar situation in CSSs of another chromosome [54] (Yasuda et al. unpublished data). There is some possibility that the incompatibility is caused by a *cis*/*trans* change via chromosomal substitution; therefore, the analysis of CSS may allow for the study of cross talk between genes on different chromosomes, namely, *cis*- and *trans*-regulation of the variation of gene expression in hearing research.

4.2.3. Hybrid mouse diversity panel (HMDP)

Although the classical genetic crosses, RIS and CSS, are powerful tools to identify modifiers in genetic backgrounds, the phenotypic and genetic variations are low because of the inclusion of only two parental strains. Moreover, the low genetic variation is not suitable for GWAS. The hybrid mouse diversity panel (HMDP) was developed to increase the statistical power and resolution of the classical QTL mapping [56]. The HMDP consists of 30 classical inbred strains and four set of RISs (AXB/BXA, BXD, BXH, and CXB) (**Figure 5C** and **Table 1**), which are genotyped with 140,000 SNPs [57]. By using the HMDP, a high statistical power and high resolution of QTL mapping were provided from the RISs and classical inbred strains, respectively.

HMDP contributed to the identification of the gene and locus associated with NIHL. Lavinsky et al. [17] investigated the noise susceptibility in five-week female mice in 64 strains selected from HMDP. The noise susceptibilities of strains varied widely, and GWAS analysis picked up five quantitative trait nucleotides (QTNs) with statistically significant p values ($p < 4.1E{-}06$) [17]. Consequently, candidate genes were screened by expression QTL (eQTL) analysis after which NADPH oxidase-3 gene (*Nox3*) was selected as a candidate (**Table 1**). Moreover, the study identified that the *Nox3* KO mice showed noise sensitivity [17]. This is the first study to have reported the NIHL-related gene. Till date, noise sensitivity of 100 stock strains from HMDP has been reported [58], and phenotype data have also been collected continuously [59]. Additionally, a QTN at chromosome 6 associated with noise susceptibility was detected (**Table 1**) [60].

4.2.4. Outbred stock (OS)

QTL analysis using inbred strains is limited to the phenotypes and alleles associated with ARHL and NIHL. Although the genotyping is required, outbred stock (OS) is a colony with

maintained phenotypic and genetic diversity kept in laboratory settings and thus exhibits a high degree of both genetic and phenotypic diversity, allowing high-resolution genetic mapping for a wide variety of traits by crossing with another population [42, 61].

In a study of ARHL, Black Swiss [62], which is derived from NIH Swiss outbred stock and C57BL/6J, was first used in OS for QTL linkage mapping. Drayton and Noben-Trauth [62] performed QTL linkage mapping using [(Black Swiss × CAST/Ei) F_1 × Black Swiss] N_2 backcross mice and mapped two QTLs: *Ahl5* and *Ahl6*. Subsequently, the responsible mutation for *Ahl5* was detected in the GIPC PDZ domain containing family member 3 gene (*Gipc3*), which is associated with audiogenic seizures and sensorineural hearing loss in mice and humans [14]. The $Gipc3^{p.Gly115Arg}$ mutation was absent in inbred strain, indicating that OS is a powerful tool to identify new ARHL-related genes. Moreover, NIH Swiss mice [63] also contributed to the detection of three loci (*Hfhl1–3*) associated with high-frequency hearing loss (HFHL) (**Table 1**) [15, 16].

Heterogeneous stock (HS) and diversity outcross stock (DO) could be considered variants of OS and display a similar advantage with OS for QTL mapping [42, 61]. These populations are available and probably will contribute to the identification of QTL and genes responsible for ARHL and NIHL.

4.3. Elucidation of genetic background effects by using reverse genetics approaches

When the candidate gene and mutation are detected by forward genetics approach, the next step is elucidation of the real causative gene and mutation. The reverse genetics technique is immensely helpful with this elucidation. An approach is production and phenotypic analysis of KO mice of candidate gene *Nox3* as mentioned earlier [17]. However, rescue of phenotype is required for full proof.

Transgenic expression of bacterial artificial chromosome (BAC) clones in mice is commonly used for *in vivo* complementation tests. The test BAC contains wild-type allele and is simple since BAC contains the wild-type allele to be injected into the susceptible strain with the candidate mutation. The $Fscn2^{p.Arg109His}$ mutation of DBA/2J is confirmed by this complementation test [33]. The disadvantage of BAC transgenesis is that genes of large sizes exceeding the BAC clone (average size between 120 and 250 kb) cannot be rescued. Moreover, the rescue of the phenotype caused by dominant-negative and gain-of-function mutations is difficult. In addition, the strains of available BAC libraries are limited [64, 65].

An advanced approach is rescue by the knock-in (KI) method mediated by the CRISPR/Cas9 genome editing system. This system can efficiently and quickly repair the candidate mutation of the KI donor oligonucleotide containing the wild-type allele via a homology-directed repair (HDR) [66]. We previously reported utility of this method [24]. C57BL/6J-$Ush1g^{js/+}$ heterozygous mice exhibit severe early onset ARHL caused by progressive degeneration in the stereocilia of outer hair cells. We mapped a locus associated with early onset ARHL of $Ush1g^{js/+}$ mice in an interval of chromosome 10 that harbors the $Cdh23^{c.753G>A}$ mutation, which is also responsible for ARHL of C57BL/6J mice as mentioned above. We injected Cas9 mRNA, single guide RNA (sgRNA) and a donor oligonucleotide that contained $Cdh23^{c.753G}$ (**Figure 6A**) to produce KI mice. In KI mice, early onset ARHL and stereocilia degeneration were completely rescued (**Figure 6B**). This is the first report that confirms the phenotypic effect of modifiers at the mutation level in hearing research.

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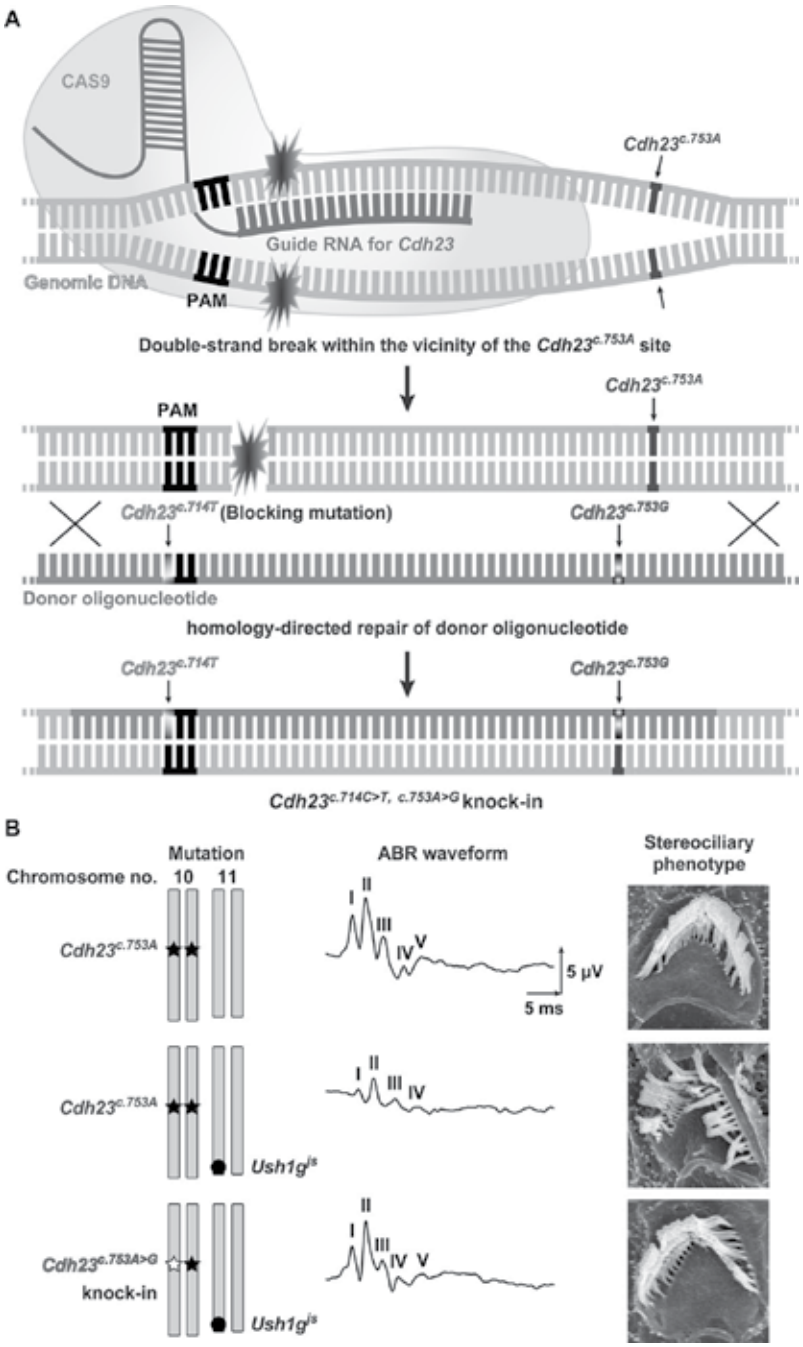

Figure 6. Phenotypic rescue of hearing loss in mice caused by genetic background effect using the CRISPR/Cas9-mediated KI method. (A) Schematic representation of the *Cdh23*$^{c.753A>G}$ KI using double-strand break within the vicinity of the *Cdh23*$^{c.753A}$ site of C57BL/6J mice by CRISPR/Cas9 and homology-directed repair of single-stranded donor oligonucleotide. The donor oligonucleotide was designed to include c.753A>G with a synonymous blocking of the c.714C>T mutation to avoid cleavage by Cas9 [24]. (B) Comparison of the hearing phenotypes among the C57BL/6J (top), C57BL/6J-*Ush1g*$^{js/+}$ (middle) and -*Ush1g*$^{js/+}$ *Cdh23*$^{c.753A/G}$ (bottom) mice. Illustrations of left panels represent combination of the *Cdh23*$^{c.753A>G}$ (★>☆) on chromosome 10 and *Ush1g*^{js} (●) on chromosome 11. Middle and right panels show ABR waveforms and stereocilia phenotypes, respectively, in each mouse.

5. Conclusions

In this chapter, we attempt to highlight several issues regarding the identification of background effects in mice. To identify the modifiers underlying genetic background effects, several strains were established for QTL and GWAS. Thus, the technologies for forward genetics in mice have enabled important breakthroughs and will contribute to the identification of new loci and genes associated with hearing loss. The reverse genetics approach has also been developed based on technological innovations, that is, genome editing and will be increasingly applied. An increasing number of studies have reported that the hearing loss phenotype resulting from a single gene mutation in humans is modulated by the genetic background in which the mutation is maintained (e.g., see [67].). Using genome editing, mutations discovered in the genetic background of patients with hearing loss can be conveniently manipulated in mice, and the effects of the candidate mutation can be confirmed *in vivo* by phenotypic analyses of mice.

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Index of technical terms

μV: microvolts

ABR: auditory brainstem response

ahl, *Ahl3*, *ahl4*, *Ahl5*, *Ahl6*, *ahl8* and *Ahl9*: loci for age-related hearing loss in mice

A/J, C3H/HeN, C57BL/6J, CAST/Ei, DBA/2J and MSM/Ms: mice inbred strains

ARHL: age-related hearing loss

AXB, BXA, BXD, BXH, CXB, LXS and SMXA: mice recombinant inbred strains

BAC: bacterial artificial chromosome

Black Swiss and NIH Swiss: mice outbred strains

C57BL/6J-Chr17$^{MSM/Ms}$: a consomic (chromosome substitution) strain, which contain MSM/Ms-derived chromosome 17 in the genetic background of the C57BL/6J strain

Cas9: CRISPR associated protein 9

Cdh23: cadherin 23 gene

Cdh23$^{c.753G>A}$: a guanine-to-adenine substitution at nucleotide position 753 of cadherin 23 gene

Chr5 QTL: QTL on chromosome 5

CRISPR: clustered regularly interspaced short palindromic repeat

Cs: citrate synthase gene

Cs$^{p.His55Asn}$: a histidine-to-asparagine substitution at amino acid position 55 of citrate synthase (CS) protein

CSS: consomic (chromosome substitution) strains

dB SPL: decibel sound pressure level

DPOAE: distortion product otoacoustic emission

DO: diversity outcross stock

eQTL: expression QTL

Fscn2: fascin 2 gene

Fscn2$^{p.Arg109His}$: an arginine-to-histidine substitution at amino acid position 109 amino acid of fascin 2 (FSCN2) protein

Gipc3: GIPC PDZ domain containing family member 3

GWAS: genome-wide association study

HDR: homology-directed repair

HFHL: high-frequency hearing loss

Hfhl1, 2 and *3*: loci for high-frequency hearing loss in mice

HMDP: hybrid mouse diversity panel

HS: heterogeneous stock

kHz: kilohertz

KI: knock-in

KO: knock-out

Map1a: microtubule-associated protein 1

moth1: modifier of tubby hearing

ms: milliseconds

mt-Tr^{Arg}: mitochondrial tRNA-Arg

NIHL: noise-induced hearing loss

Nox3: NADPH oxidase-3

OS: outbred stock

QTL: quantitative trait loci

QTN: quantitative trait nucleotides

RIS: recombinant inbred strain

sgRNA: single guide RNA

Snhl: a locus for sensorineural hearing loss in mice

SNP: single nucleotide polymorphism

Tub: tubby bipartite transcription factor gene

Ush1g: USH1 protein network component sans gene

Ush1g^{js}: Jackson shaker mouse

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[67] Vona B, Müller T, Nanda I, Neuner C, Hofrichter MA, Schröder J, Bartsch O, Läßig A, Keilmann A, Schraven S, Kraus F, Shehata-Dieler W, Haaf T. Targeted next-generation sequencing of deafness genes in hearing-impaired individuals uncovers informative mutations. Genetics in Medicine. 2014;**16**(12):945-953. DOI: 10.1038/gim.2014.65, 10.1038/gim.2014.65

Chapter 2

Genetic Basis of Hearing Loss

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Additional information is available at the end of the chapter

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Abstract

Etiology of hearing impairment (HI) is complex and comprises genetic and environmental factors. Currently, the background of genetic hearing impairment is an area of intensive research and we are witnessing fast progress in this field. The story has begun in 1997 when the DFNB1 locus was discovered with *GJB*2 and *GJB*6 genes causative for almost 50% of cases of recessive, profound, prelingual hearing loss. Nowadays, we have much more possibilities for dissecting the reason of HI, but proper assessment of clinical symptoms is essential for selecting the most optimal diagnostic pathway. In the first stage, the detailed characteristic of hearing loss including its level established by pure tone audiometry (PTA) or auditory brainstem responses (ABR), age of onset, and other helpful features as progressive or no progressive type should be provided. Subsequently, the presence or absence of accompanying symptoms should be established and followed by a detailed analysis of pedigree. In addition, modern assistive algorithms such as AudioGene, Face2Gene, and POSSUM are also discussed. Taking into account the variety of causative genes and pathogenic variants underling hearing loss, searching for causative genes, after exclusion of the DFNB1 variants, should be performed with multigenic panels based on next-generation sequencing technology.

Keywords: gene, pathogenic variant, phenotype, diagnostic, pedigree, next-generation sequencing

1. Introduction

The dynamic development of new DNA sequencing technologies in recent years has given us unprecedented insight into the information encoded in the human genome. Introduction of these techniques into a clinical practice has put the diagnosis of genetic disorders to a much more advanced level with a very high detection rate of pathogenic variants. Hearing loss (HL) has also greatly benefited from the technological revolution as it is a genetically

heterogeneous condition with more than 100 different genes being involved in its pathogenesis, and novel genes are still being discovered (www.herediataryhearingloss.org; accessed 10/2017). As compared to the strategy of sequential analysis of single genes, the application of high-throughput DNA sequencing has increased the diagnostic yield of genetic causes of HL by approximately four times [1].

At the same time, the technological advancements have brought us to a higher level of complexity. Searching for HL-causing variants, often hundreds of genes have to be analyzed and we are flooded by huge amounts of information that are difficult to interpret [2]. It is partially overcome by still-improving computational tools and growing data from population studies, but an indispensable part of better planning of genetic testing and understanding its results is the information gathered from a thorough clinical examination and family history. Sometimes, the primary clinical data collected prior to genetic testing do not completely match the phenotypic features that could be expected from molecular findings. In such cases, clinical reevaluation is needed to better delineate the phenotype and verify whether the identified genetic variants are indeed responsible for the observed clinical features [3, 4].

2. Pedigree construction and analysis

The fundamental and basic element of genetic evaluation in the consultation room is the creation of a precise and accurate family pedigree based on the detailed medical interview. A genetic pedigree is a diagram of genetic relationship enriched with an information about health history, which allows to easily trace the transmission of symptoms, estimate whether symptoms may be caused by genetic reason, and evaluate the risk for other family members (including unborn) of an inherited disorder. Although in the archival literature, readers may encounter many different systems of constructing pedigrees [5], the current, uniform, and precise guidelines in this area should be followed and applied in both clinical practice and publications. Taking into account the dynamic rise of genetic knowledge within the last years, triggered by new technologies such as next-generation sequencing (NGS), clinicians and scientists should be familiar with preparation and interpretation of a pedigree. This allows a proper interpretation of medical and genetic information of the studied family. At the time of writing, an authority dealing with the standardization of the terminology used to describe a pedigree is the National Society of Genetic Counselors (NSGC, http://www.nsgc.org) established in 1979 in the United States of America (USA), with its two official journals: "Journal of Genetic Counseling" and "Perspectives in Genetic Counseling." The Pedigree Standardization Work Group (PSWG) operating within the NSGC established unified recommendations for standardized human pedigree in 1995 [6, 7], and updated it in 2008 [8]. Regarding the fact that no alternative comprehensive, analogous recommendations have been proposed, along with lack of critical comments on the proposed system, the PSWG established rules have become an accepted and international symbolic language of human genetic clinicians and researchers.

The most commonly used pedigree symbols, definitions, and abbreviations in compliance with the PSWG revised recommendations are presented in **Figure 1**.

With the symbols listed in **Figure 1**, a family tree should be created according to the following rules:

- At the beginning, a shaded symbol (square for male, circle for female) denoting the proband (an affected person from a family who came for a medical consultation as first) should be placed. In the bottom left corner, an arrow and letter "P" should be placed to uniquely mark that this individual is the proband.
- Above the symbols for proband's, ancestors starting with parents should be placed. The symbol denoting male partner should be placed to the left of the female's one if possible. Furthermore, symbols denoting both parents should be connected by a horizontal line (relationship line) and doubled if the parents are consanguineous. The line of descent should be placed in the middle of the horizontal line, which connects parents with the offspring (sibship line).
- All symbols representing siblings should be placed in the birth order starting from the left side, at the same height as the proband's symbol. Vertical lines (individual's line), linking symbols to the horizontal line (sibship line) above the symbols, must be placed for all siblings' symbols.
- According to the above-described rules, symbols representing all remaining family members should be placed and joined with the appropriate lines.
- Some additional, useful information such as disease, age, age at death, initials, or the first name may be placed below appropriate symbols.

The pedigree line definitions and rules of placing them within the pedigree are presented in **Figure 2**.

Additional most common symbols, rules, and family situations are gathered in **Figure 3**.

Since drawing pedigrees, especially for large families, is complicated and time consuming, it is worth to use computer programs that facilitate and accelerate this task. There are many professional and public tools, which are useful in the process of creating accurate family diagrams for both, clinical and educational purposes, e.g., Genial Pedigree Draw (http://www.pedigreedraw.com/), Progeny Online Pedigree Tool (http://www.progenygenetics.com/online-pedigree/), and CeGaT Pedigree Chart Designer (http://www.cegat.de/en/for-physicians/pedigree-chart-designer/).

Understanding the elementary rules of inheritance is the key to appreciate how traits or diseases are passed on within a family. It should be reminded here that every individual has two copies of almost every gene localized on chromosome (autosome), one of them derives from biological mother and the second one from biological father. The situation is different in case of sex chromosomes—every male has only one X (inherited from mother) and Y chromosome (inherited from father). The Y chromosome is transmitted in its entirety exclusively from

	Female	Male	Gender unknown	Remarks
Healthy person				The age of the individuals should be placed below the symbol.
Affected person				The symbols may be partioned and filled with different pattern if ≥ two symptoms occurred. The used patterns must be defined in the legend.
Deceased person				The age at death should be placed below the symbol. If the cause of death is known it also should be indicated.
Proband	P	P		A first affected individual coming to the consultation.
Consultand				The person(s) referred for genetic counseling.
Multiple persons, number known	3	3	3	If the number is unknown or unstated the letter „n" should be used instead of a number.
Pregnancy	P	P	P	For affected individuals light shading should be used. Gestational age and karyotype should be denoted below the symbols.
Spontaneous abortion				Gestational age, gender should be denoted below the symbols
Termination of pregnancy				Gestational age, gender should be denoted below the symbols
Ectopic pregnancy			ECT	ECT should be given below the symbols

Figure 1. Most common pedigree symbols according to Bennett et al. [8].

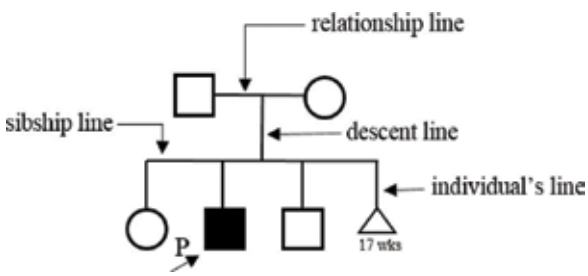

Figure 2. Definition of pedigree lines.

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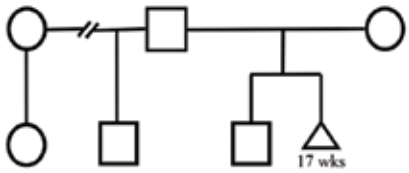
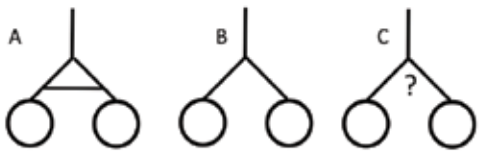
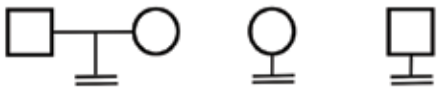
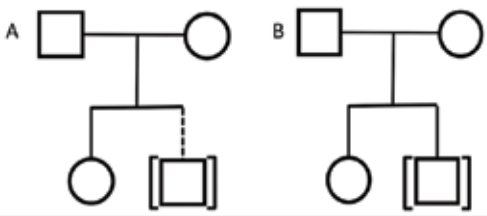
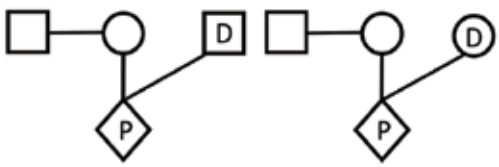
Definition	Symbols	Remarks
Consanguinity		Relationship which is not evident regarding pedigree should be described above relationship line
Relationship		A gap within relationship line denotes that relationship currently is not continued
Multiple gestation		A. Monozygotic B. Dizygotic C. Unknown
Infertility		If the reason is known, should be indicated below the symbol
Adoption		Biological parents are denoted by solid line, adoptive parents are denoted by dashed line. A. In B. Out
Carrier		The disease is not manifested
Asymptomatic or presymptomatic carrier		Individual without clinical symptoms at the time of completing the medical history
Sperm/ovum donor		The line of descent is solid denoting biologic relationship which may have influence to the fetus

Figure 3. Symbols useful in uncommon clinical situations.

father to son. In contrast, every female has two X chromosomes (inherited from both parents) [9]. Another derogation from basic inheritance rules is mitochondrial inheritance, in which the entire independent small genome is passed only from mother to offspring [10]. Typically,

there are four most common inheritance patterns, depending on the genomic localization and influence on the protein function of pathogenic variants or genes i.e., autosomal dominant (AD), autosomal recessive (AR), sex-linked, and mitochondrial [11]. Diseases caused by pathogenic variants localized in a single gene are mostly inherited in an AD or AR pattern and are referred to as Mendelian inheritance (tribute to Gregor Mendel, who first noted this pattern in pea plants).

The AD mode of inheritance occurs when a single copy of the disrupted (mutated) gene is causative of the disease. It should be emphasized that for AD disorders, a variety of inter and intrafamilial variability of symptoms may occur. Nevertheless, there are few substantial features, which make this mode of inheritance rather simple to distinguish. Dominantly inherited genetic diseases tend to occur in every generation of a family, they affect males and females equally; furthermore, the disorder may be transmitted from males and females. The risk for offspring to inherit the pathogenic variant is 50%. Due to the variability of symptoms severity, characteristic for this type of inheritance, the risk of becoming symptomatic may be less than 50%. A typical family tree representing the AD mode of inheritance is shown in **Figure 4**.

The AR type of inheritance requires two disrupted copies of a gene for a disease to occur. Thus, both parents of an affected individual are obligatory asymptomatic carriers (due to an assumption that heterozygotes do not manifest a disease). Furthermore, the symptoms are not typically seen in every generation. AR diseases are much more common in offspring of consanguineous pairs (which is evident within small, isolated populations e.g., Icelanders, Bedouins, or Amish [12]. In contrast to the AD inheritance mode, affected individuals present more consistent clinical picture. The risk for offspring to inherit both pathogenic variants is 25%, whereas the risk to inherit one heterozygous variant is 50%. It should be also noted that all children of an affected parent and a noncarrier partner, regardless of their gender, will be obligate carriers. A typical family pedigree illustrating the AR mode of inheritance is shown in **Figure 5**.

A sex-linked mode of inheritance consists of three subtypes: X-linked dominant (XLD), X-linked recessive (XLR), and Y-linked. Whereas the Y chromosome contains very limited

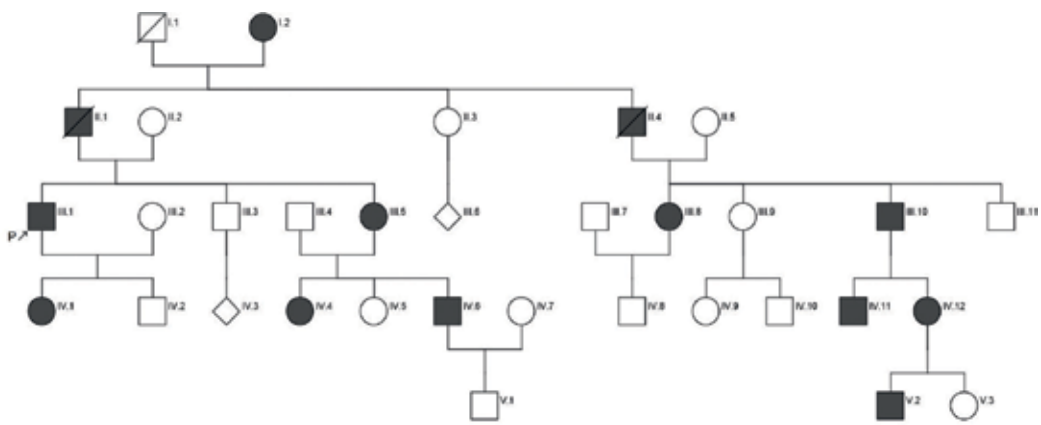


Figure 4. Pedigree of a family with the AD pattern of inheritance.

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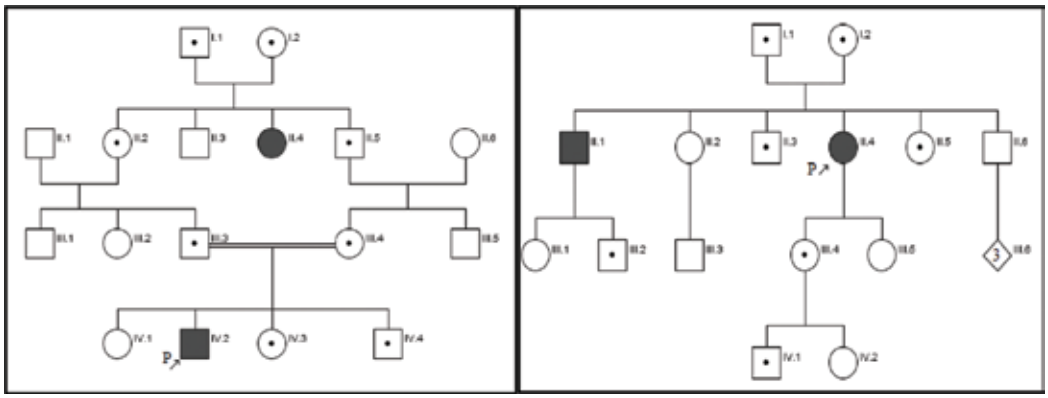

Figure 5. Two typical family trees representing the AR type of inheritance.

number of genes and there are only few Y-linked disorders, none of them related to hearing and speech disorders, this type of inheritance will not be described here. The XLD and XLR type of inheritance relate to genes located on the X chromosome, and for the occurrence of XLD symptoms, only one copy of a disrupted X-linked gene is required. XLD diseases usually manifest very severely in males, which may lead to spontaneous abortion or neonatal death. The characteristic feature for this type of inheritance is that there is no transmission of the disease from male to male, and all of the female offspring of affected male will inherit the pathogenic variant and the disease. A characteristic family tree for the XLD mode of inheritance is shown in **Figure 6**.

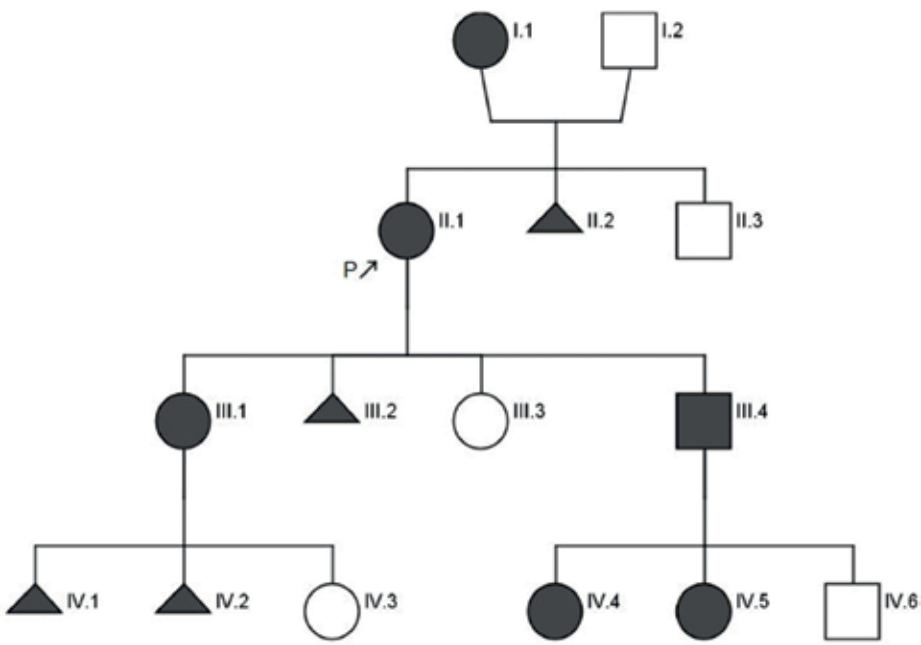

Figure 6. Exemplary pedigree of a family with the XLD type of inheritance.

For an XLR disease to occur in females, both copies of a gene must be impaired. Characteristic features for an XLR inheritance mode are affected males, but an extremely low number or no affected females, in every generation. A distinct feature of the XLR inheritance pattern is that the pedigree tree shows no male to male transmission of the disease. All males harboring a pathogenic variant in an X-linked gene present severe symptoms of the disease, whereas carrier females are in general unaffected or present significantly less severe symptoms. A typical family tree representing the XLR mode of inheritance is shown in **Figure 7**.

Although within small families, which currently are very common, especially in European countries, the recognition of an X-linked inheritance pattern is rather challenging and remains unknown until the results of genetic testing [4].

The mitochondrial mode of inheritance has distinctive features differentiating it from others. Briefly, this unique features come directly from mitochondrial DNA (mtDNA) specificity: mtDNA is a small, independent, circular genome; furthermore, an average human cell contains up to 1000 mitochondria and in every mitochondrion several copies of the mtDNA genome may be present. If all mitochondria in a given individual contain an mtDNA variant it is defined as homoplasmy. In contrast, heteroplasmy indicates the coexistence of more than one mtDNA type within an individual. As all mitochondria of offspring are of maternal origin, the pathogenic variants localized within mtDNA are exclusively passed from mother to children and they may affect males and females equally. Consistently, males do not transmit the mtDNA disorders to their offspring. A representative family tree demonstrating mitochondrial mode of inheritance is shown in **Figure 8**.

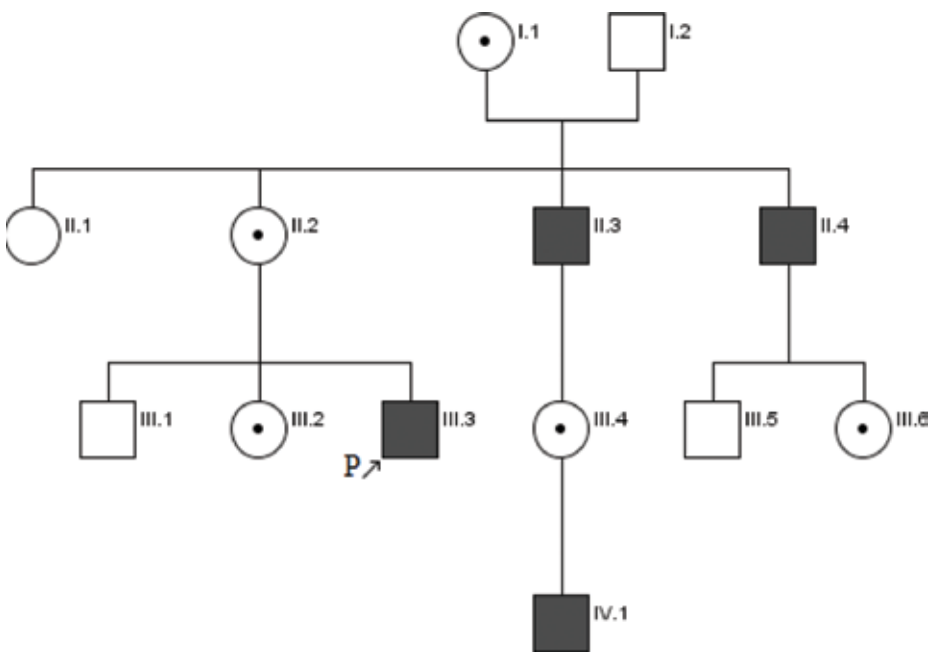

Figure 7. Pedigree of a family with the XLR pattern of inheritance.

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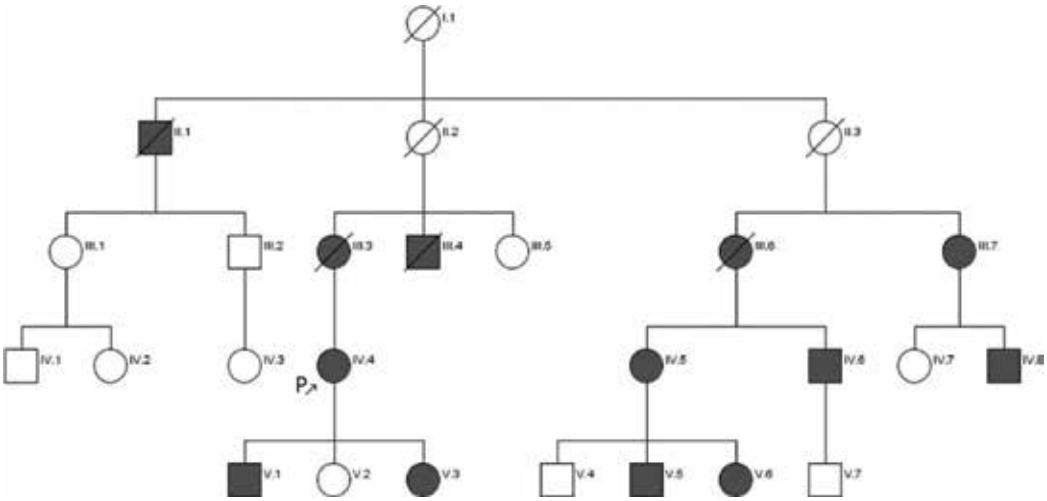


Figure 8. Pedigree of a family with mitochondrial mode of inheritance.

It should be emphasized that in many cases distinction between the mitochondrial and AD inheritance is a difficult task based only on the family tree analysis.

3. Nonsyndromic hearing loss

It has to be stressed that all patients with a positive family history of HL should be referred for genetic counseling. Over generations, an inherited disorder automatically raises a suspicion of a genetic underlying cause. A careful analysis of a family pedigree enables to identify or to presume the mode in which hearing impairment is inherited. This in turn is an important step in directing genetic testing at specific genes that are causally involved in the pathogenesis of autosomal dominant, recessive, X-linked, or mitochondrial HL. In case of marriages between individuals with hearing impairment or between individuals coming from families with hearing impairment, the family pedigrees should be analyzed especially carefully. In the offspring of such couples, different HL causative variants of different genes may be found. Interestingly, in a study of 80 deafness genes, the DNA samples of HL patients were significantly enriched in potentially pathogenic variants [13]. One possible explanation of the phenomenon may the above-mentioned marriages between hearing impaired individuals. Attention should also be paid to the consanguinity between parents, which is common in certain populations. Looking for a genetic cause of HL in offspring of a consanguineous couple, the autosomal recessive mode of inheritance with pathogenic variants in a homozygous state is primarily expected.

A diagnostic challenge represents an HL patient without other affected family members, also referred to as a sporadic case. Here, a family history of HL is negative and a genetic cause is strongly suspected after exclusion of environmental factors, such as prenatal infection (with toxoplasmosis, rubella, cytomegalovirus, and herpesvirus—"TORCH" organisms), postnatal infections (mainly bacterial meningitis, mumps), prematurity, traumatic injury, blood vessels

or autoimmune disease, Meniere's disease, acoustic neuroma, exposure to chemical agents, or noise that may be responsible for HL development. While describing HL, four major terms related to its presentation such as (I) the age of onset, (II) the type, (III) the degree of HL, and (IV) stability are usually used. The onset of HL can be congenital, prelingual (before a child develops speech), postlingual (after the acquisition of speech and language, usually after the age of six), adult-onset or age-related late-onset (presbyacusis). The different types of HL (conductive, sensorineural, or mixed) indicate which part of the ear is affected. Genetically determined HL is usually bilateral although families with asymmetric and unilateral HL are also reported [14, 15].

It has been estimated that about 80% of prelingual HL results from genetic factors. It is most often inherited as an autosomal recessive feature without other accompanying medical problems The second most common inheritance pattern of prelingual HL is autosomal dominant (20%), while X-linked and mitochondrial constitute together approximately 1–1.5% [16]. Most of the reported families with nonsyndromic postlingual HL present an autosomal dominant pattern of inheritance. Currently, 36 different genes causally involved in autosomal dominant HL have been identified (www.hereditaryhearingloss.org; accessed 10/2017) and only a few of them are associated with prelingual HL [17].

If hearing impairment represents an isolated finding that can be associated with abnormalities of the middle and/or inner ear but is not accompanied by visible abnormalities of the outer ear or any other medical problems, it is referred to as nonsyndromic or isolated. The major cause of prelingual severe-to-profound autosomal recessive nonsyndromic HL in many populations are pathogenic variants of the *GJB*2 gene. The *GJB*2 and *GJB*6 genes, contained within the *DFNB*1 locus, should be tested in the first line in patients with nonsyndromic bilateral sensorineural HL of the prelingual onset [18].

Pathogenic *GJB*2 variants are also identified as the second most frequent cause of mild-to-moderate autosomal recessive HL. The most common causes of HL in this group of patients are pathogenic variants of the *STRC* gene and the third causative gene in this category is *TECTA*, but the prevalences vary among different ethnic groups [13, 19].

Discussing the genetic causes underlying partial deafness, defined as normal or slightly deteriorated thresholds involving low frequencies combined with profound HL in high frequencies [20], pathogenic variants localized within mtDNA and *TMPRSS*3 should be considered for diagnostic purposes [21, 22]. Nevertheless, the contribution of other genes should be also taken into account.

Inheritance pattern	Genes and loci involved
AD	*COCH* (DFNA9), *WFS*1 (DFNA6/14/38), *MYO*6 (DFNA22), *GJB*2 (DFN3A), *MYO7A* (DFNA11)
AR	*GJB*2 (DFNB1A), *SLC*26*A*4 (DFNB4), *MYO*15*A* (DFNB3), *TMC*1 (DFNB7/11), *TMPRSS*3 (DFNB8/10), *STRC* (DFNB16)
X-linked	*POU3F*4 (DFNX2), *PRPS*1 (DFNX1), *SMPX* (DFNX4), *COL*4*A*6 (DFNX6), *AIFM*1 (DFNX5)
Mitochondrial	*MT-TL*1, *MT-TK*, *MT-TS*1, *MT-TE*, *MT-RNR*1

Table 1. Genes involved in the pathogenesis of hearing disorders grouped according to the type of inheritance—examples.

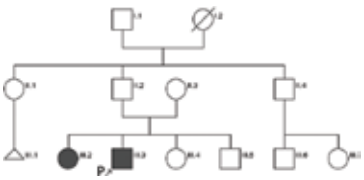
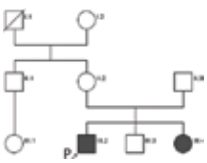
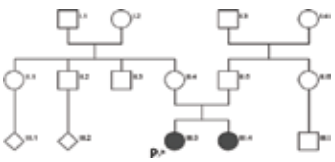
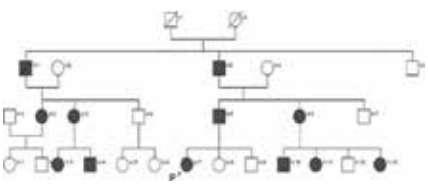
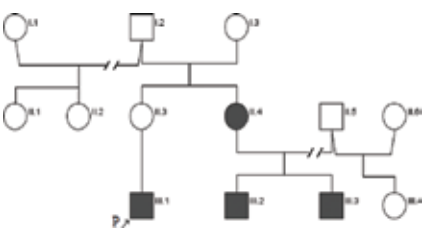
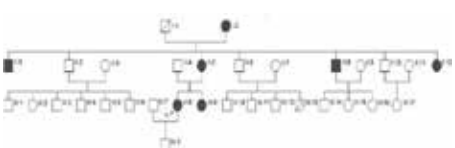
Locus DFNB1, gene *GJB2*, inheritance type: AR		**Remarks**
Truncating pathogenic variants (e.g., c.35delG)		Congenital, bilateral, profound HL [23]
Nontruncating pathogenic variants (e.g., p.Met34Thr)		Postlingual, bilateral, mild-to-moderate HL [24]
Locus DFNB4, gene *SLC26A4*, inheritance type: AR		**Remarks**
Nontruncating, pathogenic variants (e.g., p.Glu29Gln)		Enlarged vestibular aqueduct, vestibular dysfunction, Mondini malformation, early-onset, fluctuating HL [25]
Locus DFNA6/14/38, gene *WFS1*, inheritance type: AD		**Remarks**
Nontruncating, pathogenic variants (e.g., p.Asp771His)		Postlingual, low-frequency HL, deteriorating with time [26]
Locus DFNX2, gene *POU3F4*, inheritance type: X-linked		**Remarks**
Truncating pathogenic variants (e.g., p.Glu187*)		Congenital, profound, sensorineural HL (may be accompanied by a conductive component). Inner ear IP3 type malformation—comprises of enlarged internal auditory canal and vestibular aqueduct, underdeveloped cochlear modiolus and malformations of the vestibule. Due to the inner ear malformation perilymphatic gusher may occur during inner ear surgery [4]
Gene *MT-TS1*, inheritance type: X-linked		**Remarks**
Pathogenic variants (e.g., m.7511T>C)		Postlingual, high-frequency HL [27]

Table 2. Pedigrees and audiometric features characteristic for different genes and pathogenic variants causative of HL.

Considering the significant contribution of genetic factors to HL and the recent guideline for clinical evaluation and etiologic diagnosis of HL, one may conclude that single-gene testing is justified if a specific genetic etiology of HL is suspected. If there are no specific clinical indications, testing for the DFNB1-related HL should be performed. If the investigations do not provide conclusive results, HL genes may be analyzed by the NGS approaches such as multigene panels, whole exome or whole genome sequencing [16]. All known nonsyndromic deafness loci (locus denotes the position in the genome linked with the disease) are labeled as DFN (DeaFNess) and classified according to the type of inheritance (DFNA: autosomal dominant; DFNB: autosomal recessive; DFNX: X-linked) followed by a number indicating the order of locus discovery. In **Table 1**, some of the most common HL causative loci are gathered.

As it was previously stated, HL is a genetically heterogenous disease; nevertheless, there are some common, characteristic features, which may be a valuable asset in the process of dissecting the genetic reason of HL. Examples of pedigrees, characteristic audiometric features, and additional remarks for some common HL genes are shown in **Table 2**.

Despite quite a large number of genes causative for HL, the first step in the diagnostic approach should be the analysis of the DFNB1 locus, as the testing is inexpensive and fast [28]. Apart from obvious clinical indications, such as IP3 malformation for the *POU3F4* gene analysis, the remaining cases should be rather streamed to wide, multigenic analysis.

4. Syndromic hearing loss

In contrast to the nonsyndromic hearing impairment, the syndromic hearing impairment is defined as a part of a syndrome, and it is associated with malformations of the external ear, malformations of other organs or other medical problems. HL is identified in more than 400 different syndromes [29]. The most common type of autosomal dominant syndrome with sensorineural HL is **Waardenburg syndrome** (WS types 1-4; OMIM#193500, #193510, #148820, and #277580), an auditory-pigmentary syndrome caused by pathogenic variants in *PAX*3, *MITF*, *EDNRB*, *EDN*3, or *SOX*10 genes and characterized by the presence of pigmentary anomalies of skin, hair, and eyes. The second most common are **branchiootorenal spectrum disorders** (OMIM#113650, #610896 #602588, #166780), where conductive/sensorineural HL is accompanied by branchial cleft cysts or fistulas, malformations of outer ear, preauricular pits, and renal anomalies resulting from pathogenic variants in *EYA*1, *SIX*1, or *SIX*5. The third most common cause of autosomal dominant syndromic hearing impairment is **neurofibromatosis type 2** (NF2, OMIM#101000), a multiple neoplasia syndrome with HL secondary to the usually bilateral vestibular schwannomas (acoustic neuroma) and other tumors of the central nervous system (meningioma, schwannoma, glioma, or neurofibroma). NF2 is caused by heterozygous pathogenic variants in a gene-encoding neurofibromin-2 (NF2 gene) [30].

The **Stickler syndrome** (STL) is a connective tissue disorder with eye findings (high myopia, vitreoretinal degeneration, retinal detachment, and cataract) being the most constant traits. Other features are sensorineural or conductive HL, midline clefting (cleft palate, bifid uvula), Pierre Robin sequence, flat midface, mild spondyloephiphyseal dysplasia, and

early-onset osteoarthritis [31]. Currently, four types of STL syndrome are distinguished—autosomal dominant STL1 (OMIM#108300) and STL2 (OMIM# 604841) caused by pathogenic variants in *COL2A1* and *COL11A1*, and autosomal recessive STL4 (OMIM#614134) and STL5 (OMIM#614284) due to pathogenic variants in *COL9A1* and *COL9A2* genes, respectively. The **Usher syndrome** (USH) is a combination of HL and visual impairment as a consequence of retinitis pigmentosa. The autosomal recessive condition is classified into three types: USH1 (OMIM#276900) with severe-to-profound deafness and defective vestibular function, USH2 (OMIM#276901) with mild-to-severe hearing impairment and normal vestibular function and USH3 (OMIM#276902) with progressive postlingual HL and vestibular dysfunction. Pathogenic variants in one of six genes (*MYO7A*, *USH1C*, *CDH23*, *PCDH15*, *USH1G*, or *CIB2*) may lead to USH1 [32], in one of three genes (*ADGRV1*, *WHRN*, or *USH2A*) to USH2 and in one of two genes (*CLRN1* or *HARS*) to USH3. The second most common autosomal recessive syndrome with sensorineural HL is the **Pendred syndrome** (PDS, OMIM#274600), characterized by severe-to profound deafness that is congenital or develops in early childhood and euthyroid/hypothyroid goiter that arises in early puberty or adulthood. It is associated with developmental abnormalities of the cochlea (Mondini dysplasia or enlarged vestibular aqueduct) that can be diagnosed by a CT examination of temporal bones. The cause of the PDS is pathogenic variants in the *SLAC26A4* gene encoding an anion transporter named pendrin. The third most common autosomal recessive syndrome with deafness is the **Jervell and Lange-Nielsen syndrome** (JLN), which is marked by congenital profound sensorineural HL and prolongation of the QT interval (corrected QT (QTc) > 440 msec), syncopal episodes due to ventricular arrhythmias and a high risk of sudden death. In patients with JLNS1 (OMIM#220400) pathogenic variants in *KCNQ1* and in patients with JLNS2 (OMIM#612347) pathogenic variants in *KCNE1* are found.

The two following autosomal recessive syndromic forms of HL represent rare metabolic disorders that, however, should not be missed out as their symptoms may resolve by appropriate treatment and dietary modifications. The **Biotinidase deficiency** (BTD, OMIM#253260) is a form of multiple carboxylase deficiency characterized by primarily neurologic (seizures, hypertonia, developmental delay, ataxia) and cutaneous (skin rash, dermatitis, alopecia) features. Patients lose vision and three-fourth of those who become symptomatic have some degree of HL. Laboratory findings show organic aciduria, mild hyperammonemia, and biotinidase deficiency. The BTD begins usually within the two first years of life and results from recessive pathogenic variants in the *BTD* gene. Treatment with biotin resolves neurologic and cutaneous manifestations, while HL and optic atrophy are usually irreversible.

The **Refsum disease** (OMIM#266500) is an inborn error of lipid metabolism with anosmia and early-onset retinitis pigmentosa being two universal findings. Other variable clinical features include neuropathy, ataxia, progressive severe HL, ichthyosis, cardiac, and skeletal (metacarpals/metatarsals shortening) involvement. Increased serum concentration of phytanic acid establishes the diagnosis. The symptoms present an insidious onset usually during the late first through third decades of life. Causative recessive variants are found in the *PHYH* and *PEX7* genes. In the medical care, diet modifications aimed at reduction of chlorophyll from the diet (exclusion of green vegetables (phytanic acid), and animal fat (phytol), and plasmapheresis) are used.

Syndromic X-linked HL is represented by the **Alport** (OMIM#301050) and **Mohr-Tranebjaerg** (MTS, OMIM#304700) **syndromes**. The Alport syndrome is characterized by glomerulonephropathy leading to progressive renal failure, varying severity of progressive sensorineural HL (occurs typically after 10 years of age and affects mainly high frequencies), and variable ocular anomalies. In 85% of patients with Alport syndrome, dominant pathogenic variants in the *COL4A5* gene on the X chromosome are found. Approximately 15% of patients develop Alport syndrome due to recessive variants in the *COL4A4* or *COL4A3* genes, cases with autosomal dominant inheritance, have also been occasionally reported.

In the Mohr-Tranebjaerg syndrome, also known as progressive deafness syndrome with blindness, dystonia, fractures and mental deficiency, progressive pre- or postlingual sensorineural deafness occurs in the early childhood and is a presenting symptom. MTS is caused by recessive variants of the *TIMM8A* gene.

Mutations in the **mitochondrial genome** can lead to HL that is an isolated feature or part of genetic syndrome, i.e., mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERFF) or Kearns-Sayre syndrome (KSS), a mitochondrial myopathy, characterized by ptosis, ophthalmoplegia, muscle weakness, cerebellar ataxia, diabetes mellitus, and/or endocrinopathies [33]. Aminoglycoside ototoxicity has been associated with pathogenic variants in *MT-RNR1* [34]. Pathogenic variant m.3243A > G in the *MT-TL1* gene, which is causative of MELAS, was found in patients with diabetes mellitus and HL or HL exclusively [35]. The data raise questions on mitochondrial variant penetrance, tissue specificity, and heteroplasmy level.

5. Assistive algorithms

Regarding the heterogeneity of genetically related HL, the precise evaluation of its cause is a challenging task. Apart from some, rather rare, unquestionable phenotypic manifestations, many of the cases of possibly genetically related HL (syndromic and nonsyndromic) are hard to distinguish. It should be noted that there is a group of useful, assistive algorithms, which are helpful for both: establishing the diagnosis and targeting a diagnostic approach.

The Face2Gene (http://suite.face2gene.com/) is a collection of phenotyping applications, which enable accurate and comprehensive assessment of a patient based on characteristic dysmorphic facial features. As the variations in the face and skull are very common and are present in about 40% of genetic disorders, they are very useful in identification of the disorder. Briefly, the picture of patient face is uploaded to an application, than the quantification of the similarity is calculated with the usage of the algorithm database. The result is the list of syndromes with analogous morphology. The algorithm Face2Gene is accessible free of charge to all healthcare specialists.

The AudioGene (http://audiogene.eng.uiowa.edu/) predicts the genes underling autosomal dominant nonsyndromic hearing loss (ADNSHL) based on the audiometric data. This algorithm also takes into account the age of the patient, which is essential in the ADNSHL study

due to characteristic deterioration of hearing during patient's life. The algorithm is based on the computational analysis of specific audiometric data deposited in the database. Furthermore, the machine-learning method is applied to select and prioritize possibly causative genes for pathogenic variant screening [36, 37].

The Pictures of Standard Syndromes and Undiagnosed Malformations (POSSUM) (https://www.possum.net.au/) is a comprehensive dysmorphology database designed for the diagnosis of multiple malformations, metabolic, teratogenic, chromosomal, and skeletal syndromes as well as their images. This database consists of information on over 4000 different syndromes and searching is based on the selected features and results in a specific list of possible diagnoses [38].

6. Next-generation sequencing technology in dissecting the background of hearing loss

In almost all genetically related diseases (included hearing impairment), there is a need for tailored diagnostic strategies in searching for their molecular background. The milestone in this research area was the development of the method for the DNA sequencing by Frederick Sanger in 1975 [39]. Whereas the direct sequencing (called also Sanger sequencing—tribute to its inventor) allows to debunk the molecular cause of disease in a limited number of genes, e.g., when HL background analyses were limited to the *GJB*2 gene, there was a significant gap in our knowledge and diagnostic capabilities. This gap has been filled out by introducing NGS technology, also called massive parallel sequencing (MPS) or high-throughput DNA sequencing. The NGS developed over the last decade has revolutionized the genetic research and diagnostic practice, mainly because of reducing costs and time of DNA sequencing. This technology gives a unique opportunity to analyze in one experiment the sequence of more than 1 million base pairs, thus sequencing of the whole genome or thousands of genes simultaneously in a few days has become possible [40]. The most commonly used forms of NGS in searching for pathogenic variants underling HL are whole exome sequencing (WES) and multigene panels.

An undisputable advantage of the WES is the possibility of simultaneous sequencing of the whole coding DNA sequence (protein coding part within all human genes ~20,000) regardless of the disease studied. This makes WES a universal test for almost all known genetic diseases. The multigene panel sequencing is a more economical solution, especially dedicated for the diagnostic purpose. It should be noted that with the panel sequencing, only already known genes associated with a given disease are analyzed. Although the targeted NGS has many advantages, whole-genome sequencing (WGS) is still the state of art approach with its high cost representing a main drawback. The application of high-throughput DNA sequencing methods generates a vast amount of information, which accelerated the discovery of new, causative genes for many diseases. Also in the field of genetically related HL, with the NGS technology, novel genes have been discovered for all modes of inheritance described above. The important, newly discovered genes causative of recessive HL are: *ADCY*1, *BDP*1, *SYNE*4, *ELMOD*3, *CABP*2, *GRXCR*2, *OTOGL*, *TPRN*, and *TSPEAR*. For dominant HL, the *CEACAM*16, *P2RX*2, and *OSBPL*2 genes

were revealed, also gene for the DFNX4 locus (i.e., *SMPX*) was identified. Another remarkable achievement obtained by the NGS technology is the identification of genes incorrectly classified as pathogenic, the examples of such events are: *MYO1A* and *RAB40AL* [41–43].

For the clinical diagnostic purpose, there are many commercial tests based on NGS, which differ in technologies and numbers of genes included. Heretofore, at least 20 commercially available tests, based on the NGS technology, focused on genetically related HL may be applied [1]. Due to the constant reduction of costs and availability, diagnostic approach based on the NGS technology in the nearest future will become a standard, which will significantly improve the level of patient care.

Index of technical terms

Autosomal dominant inheritance (AD)—type of Mendelian inheritance of a trait in which a defective copy of a gene (localized on autosome) dominates over the normal one. For the symptoms to occur, presence of only one defective copy is sufficient.

Autosomal recessive inheritance (AR)—type of Mendelian inheritance of a trait in which two copies of defective gene (localized on autosomes) are required in order for the disease to develop.

***DFNB*1 locus**—most common locus causative for nonsyndromic hearing loss, containing *GJB*2 and *GJB*6 genes.

Direct sequencing—a technology allowing to determine the sequence of nucleotides in DNA invented in 1977 by Frederic Sanger and Alan R. Coulson, based on the chain-dideoxy terminator method, also called Sanger sequencing.

Genetic pedigree—illustration of genetic relationship of a family, including information about health history of the family members.

Heteroplasmy—coexistence of more than one mtDNA type within an individual.

Homoplasmy—presence of a uniform type of mtDNA within an individual.

Mendelian inheritance—type of transmission of genes according to Gregor Mendel's set of laws, also called classical inheritance. Mendelian inheritance comprises of autosomal dominant, autosomal recessive, and X-linked type of inheritance.

Mitochondrial DNA (mtDNA)—small circular genome localized in the mitochondria.

Mitochondrial inheritance—non-Mendelian type of inheritance, occurring when a defective gene is located within the mitochondrial genome, inheritance of a trait encoded by this gene takes place exclusively from mother to offspring.

Next generation sequencing (NGS)—also known as high-throughput sequencing, a technology allowing to establish the sequence of DNA larger than 1 million base pairs in a single experiment.

Nonsyndromic deafness—deafness not associated with pathological symptoms/signs from other systems.

Partial deafness—hearing loss assessed by an audiometric test as a normal or little elevated hearing threshold within low frequencies and significantly raised hearing threshold in high frequencies.

Post-lingual hearing loss—hearing loss with late onset (after speech development).

Prelingual hearing loss—hearing loss with early onset (before speech development).

Sex-linked inheritance—type of the Mendelian inheritance of a trait in which the defective gene is located on X or Y chromosome.

Syndromic deafness—deafness as a part of a syndrome i.e., associated with pathological symptoms/signs from other organs.

Whole exome sequencing (WES)—approach based on NGS technology, allowing to sequence all protein-coding regions (exons).

Whole genome sequencing (WGS)—approach based on NGS technology allowing to analyze the whole genome DNA sequence.

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Chapter 3

Hearing Loss in Congenital Microtia

Kenichi Takano

Additional information is available at the end of the chapter

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Abstract

Congenital microtia occurs in approximately one in 10,000–20,000 live births as a result of the aberrant development of the first and second branchial arches. However, the exact pathogenesis of microtia remains unknown; it is considered a multifactorial disease where both environmental and genetic factors play a role. Microtia and aural atresia are known to be associated with conductive or mixed hearing loss caused by the developmental failure of the auricle, the external auditory canal (EAC), and middle ear structures. Cholesteatoma and mandibular dysplasia are also known to occur in microtia and atresia, as well as rare conditions, such as facial nerve paralysis, chorda tympani dysfunction, and inner ear deformity. The first branchial arch is the origin of the malleus head and the incus body as well as of the mandible, and the second arch derivatives include the stapes bone, the long process of the incus, and the manubrium of the malleus. It has been reported that the grade of microtia and the severity of middle ear abnormalities are correlated, and it is thought that better development indicates more developed middle ear structures. The existence of additional structural anomalies is suggestive of a broader developmental problem in most patients with microtia. This chapter will focus on hearing loss and structural anomalies in congenital microtia.

Keywords: microtia, atresia, facial nerve, taste disorder, hearing

1. Introduction

Congenital microtia occurs in approximately one in 10,000–20,000 live births as a result of aberrant development of the first and second branchial arches [1]. The exact pathogenesis of microtia remains unclear, but it is considered to be a multifactorial disease in which both environmental and genetic factors are thought to be associated with its pathogenesis. Microtia and aural atresia are known to be associated with conductive or mixed hearing loss and are caused by developmental failure of the auricle, the external auditory canal (EAC), and structures

of the middle ear [2, 3]. Other complications, such as cholesteatoma and mandibular dysplasia, are also known to occur in microtia and atresia, as well as rare conditions such as inner ear deformity, facial nerve paralysis, and chorda tympani dysfunction [4, 5]. It is well known that the first branchial arch is the origin of the head of the malleus, body of the incus, and the mandible, and the derivatives of the second arch include the stapes bone, the long process of the incus, and the manubrium of the malleus [2, 3]. Developmental abnormalities of the first and second branchial arches can give rise to congenital microtia and atresia, which have a significant effect on the development of the ear, including the course of the facial nerve.

Most children with congenital microtia are identified by an obvious anomaly at birth; however, they do not always receive the necessary medical care. Although otolaryngologists frequently examine only the hearing level of patients with microtia, those born with both microtia and aural atresia have a complex craniofacial condition that may affect all aspects of their lives, requiring up-to-date and unbiased patient information.

Patients with microtia are unable to undergo corrective plastic surgery until they are in their early teens since their rib bones need to be of a sufficient size for harvesting in order to create an adequately sized graft. Otolaryngologists are responsible for providing care and support to them throughout their lives.

In this chapter, we present the clinical characteristics of congenital microtia and atresia and associated complications observed at our hospital for the benefit of medical staff involved in the care of patients with these conditions.

2. Clinical characteristics and embryology of congenital microtia

The grade of microtia and the severity of middle ear abnormalities are correlated, and it is thought that better development indicates more developed middle ear structures. We investigated 172 patients (191 ears) who underwent reconstructive surgery for their external ear malformations at our university. Consistent with a previous study [1], there was a predominance of right-sided microtia (62%) and boys (64%) (**Table 1**). Although the basis for the sex discrepancy in microtia incidence has not been determined, the difference appears to be more common in Asia. Only 11% of patients had bilateral involvement. **Figure 1** shows the distribution of microtia according to severity using the Marx system proposed by Marx in 1926 [6]. Briefly, grade I microtia corresponds to a normal-shaped but small pinna, grade II to a residual vertical ridge of the tissue, and grade III to the complete absence of the pinna or the presence of only rudimentary soft tissue. The distribution was as follows: 3% was classified as grade I, 27% as grade II, and 78% as grade III (**Table 1**). It has been reported that 74% of cases of microtia are complicated with narrow external auditory atresia [2, 3], and one in five cases with congenital external auditory stenosis are complicated with ear canal cholesteatoma [6]. In our patients, narrow external auditory atresia described as complete atresia was present in approximately 70%, and external auditory stenosis affected 30%.

Careful observation is required to detect external auditory stenosis patients with ear canal cholesteatoma.

Embryologically, the auricle is formed from several protuberances in the first and second branchial arches. These protuberances, known as auricular hillocks, surround the first branchial cleft, which is the space between the first and second branchial arches [8]. Each of the hillocks contributes to a specific component of the auricle, and those in the second branchial arch form most of the ear structure. The external auditory canal and lateral tympanic membrane are derived from the ectoderm of the first branchial cleft and the epithelium of the middle ear cavity, which is derived from the endoderm of the first pharyngeal pouch. The ossicles develop from the mesenchyme of the proximal area of the branchial arches, and the malleus and incus both derive from the first branchial arch (mandibular area and maxillary area, respectively), while the stapes is formed from the second branchial arch.

Marx's classification	**%**
Grade I	3
Grade II	27
Grade III	78
Sex	
Male	64
Female	36
Laterally	
Right	62
Left	27
Bilateral	11

Table 1. Characteristics of patients with congenital microtia.

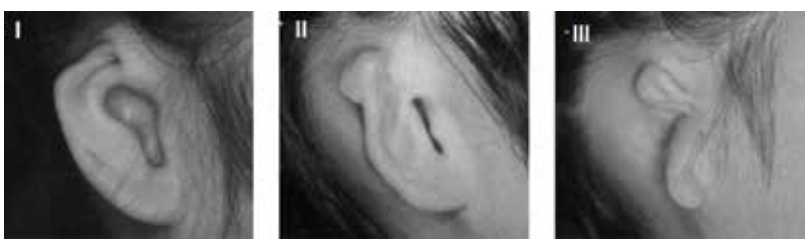

Figure 1. Marx system. Grade I: A normal-shaped but small pinna. Grade II: A residual vertical ridge of the tissue. Grade III: Complete absence of the pinna or the presence of only rudimentary soft tissue.

3. Hearing level

The pure-tone hearing average (average air conduction threshold at 0.5, 1, and 2 kHz) is used as a representative value for the hearing level, and the normal hearing range is generally defined as greater than 20 dB with an air-bone gap within 15 dB. We investigated the hearing levels for our patients with congenital microtia and compared these hearing levels with Marx's classification results (**Table 2**). Marx's classification scores did not show a correlation with the pure-tone hearing level. A previous report also found that the hearing level in microtic ears does not correlate with the degree of microtia [7].

Marx's classification	Air conduction threshold (dB)	Bone conduction threshold (dB)	Air-bone gap (dB)
Grade I	27.5	5.8	21.7
Grade II	60.9	12.8	48.1
Grade III	76.8	11.9	64.9

Table 2. Average hearing level in patients with microtia.

4. Facial nerve and chorda tympani nerve palsy

Facial nerve palsy and chorda tympani are also known to occur in some cases of congenital microtia. In our study [5], facial nerve paralysis (House-Brackmann grade more than III) and change in taste detection threshold due to chorda tympani nerve dysfunction were found in 8 and 10% of patients with microtia, respectively. We found that chorda tympani nerve dysfunction did not correlate significantly with the anatomic structure of the ear anomalies based on Jahrsdoerfer scores. On the other hand, facial nerve paralysis was significantly correlated with the presence of a malleus-incus complex, a pneumatized mastoid, an incus-stapes connection, and an external auditory canal, and facial nerve paralysis patients had a higher Jahrsdoerfer score than the chorda tympani nerve dysfunction patients.

The facial nerve canal arises initially as a sulcus in the cartilaginous otic capsule, and ossification begins from two distinct sites, such as anteriorly near the apex of the cochlea and posteriorly at the pyramidal eminence, at 20 and 25 weeks' gestation, respectively. The bone progressively covers the facial nerve, and the process is usually complete by 3 months after birth. Since the mastoid process and tympanic ring grow after birth, they displace the nerve medially. Therefore, the development of the facial nerve is closely related to the development of the middle ear and the mastoid process. Meanwhile, the chorda tympani branches from the facial nerve at 5 weeks' gestation and subsequently separates the stapes primordium and the incus primordium from the hyoid visceral bar. Unlike the facial nerve, the chorda tympani in the middle ear is not encased by a bony wall. This early branching and development of the chorda tympani may be one of the reasons why our study did not show a significant correlation between chorda tympani nerve dysfunction and facial nerve paralysis; 83% of patients

with chorda tympani nerve dysfunction did not have facial nerve paralysis. In addition, there was no significant difference in Jahrsdoerfer scores for the facial nerve between those with and without chorda tympani nerve dysfunction [5]. It is speculated that facial nerve paralysis, probably including chorda tympani nerve dysfunction, does not always correspond to an anatomic abnormality of the nerve tract.

5. Management of patients with congenital microtia

Because approximately 20–60% of patients with congenital microtia are known to have associated anomalies or an identifiable syndrome [8], patients with microtia should be examined for other dysmorphic features. In our patients, although there were no cases complicated by anomalies in the kidney and spine, there were some children complicated by esophageal atresia, ventricular septal defect, funnel chest, and cleft lip and palate. Especially, symptomatic microtia, which includes Goldenhar syndrome, hemifacial microsomia, trisomy 21, trisomy 18, and Treacher Collins syndrome, may have additional associated congenital anomalies.

Gorlin et al. [9] proposed an encompassing term "oculo-auriculo-vertebral spectrum (OAVS)," which is characterized by facial asymmetry, microtia, ear and facial tags, epibulbar dermoids, microphthalmia, and macrostomia. Hemifacial microsomia, Goldenhar syndrome, and all of its associated anomalies and variations are thought to be included in this spectrum. Extracranial features include renal, cardiac, and vertebral anomalies; at present, there is no consensus on the minimal diagnostic criteria for OAVS [10]. OAVS and microtia share the following characteristics: (1) variable phenotypic expression, (2) asymmetric involvement of facial structures, (3) right-side preponderance, (4) male predilection, and (5) familial occurrence of microtia or related anomalies, such as preauricular tags and pits [10]. Thus, isolated microtia represents a milder phenotype of OAVS.

The clinical expression of congenital microtia and OAVS overlap; hence, clinicians should consider multiple medical assessments when examining patients with microtia. First, all patients with microtia should have a diagnostic ear-specific hearing assessment within the first 6 months of age, to identify hearing loss and to assess the type and severity of hearing impairment. In children with conductive hearing loss, high-resolution CT examination of the temporal bone is useful for evaluating the middle and inner ear structures when the child is of preschool or school age. Renal ultrasound, cardiovascular examination at diagnosis, and cervical spine films at the age of 3 years are also recommended [11]. Treatment for atresia should be considered in the context of hearing, speech and language development, and reconstructive surgery at approximately 10 years of age.

Since lack of landmarks, abnormal anatomies of the facial nerve and middle ear structures, and limited space for sound reconstruction, surgical correction of hearing improvement is sometimes difficult and challenging. Therefore, not only surgery but also hearing acquisition through the use of a device should be considered. To date, osseointegrated implants known as bone-anchored hearing aids (BAHA® by Cochlear) and active middle ear implants known as Vibrant Soundbridge® (VSB by Med-El) have been the most reliable method of hearing

habilitation. These devices have been shown to improve hearing outcomes and quality of life in patients with microtia who might not otherwise benefit from traditional hearing aids. However, in order to use these implants, patients need to underwent surgery, and the portion of the implant exposed to open air has a risk of infection.

More recently, a new hearing device utilizing cartilage conduction has been developed [12]. Since the transducer is not necessarily fixed with pressure, the attachment causes no pain, unlike conventional bone conduction. Moreover, this cartilage conduction device does not require surgery. Cartilage conduction hearing aids have a potential as a useful amplification device for patients with congenital microtia and aural atresia.

6. Conclusion

We conclude that longitudinal care is required for patients with congenital microtia. This care involves the precise and regular evaluation of hearing levels from birth and investigation of malformations of the external auditory canal, middle ear, and inner ear, as well as cholesteatoma and abnormal occlusions occurring at predictable times in relationship with craniofacial growth and development. Microtia can be associated with other congenital abnormalities that are not obvious at birth. Furthermore, the external surface malformations frequently cause adverse psychosocial effects during children's growth process. Patients and their families should be supported in an unbiased manner when making decisions regarding which treatments are the most appropriate for the patient at a particular point of development, and this support must continue throughout the patients' life. In addition, means of hearing improvement should not simply be a difficult operation and instead involve careful consideration of the patient's interests and careful selection among the various options.

Terminology index

Atresia: The absence or closure of the external auditory canal

Auricular hillocks: Six (three-paired) mesenchymal condensations around the first pharyngeal cleft

Branchial arch: Paired structures associated with the pharynx that contribute greatly to the formation of the head and neck

Branchial cleft: The slit-like openings in the gills of fish between the branchial arches

Ectoderm: One of the three primary germ layers in the early embryo

Goldenhar syndrome: A complex congenital anomaly characterized by abnormal development of the eye, ear, and spine

Hemifacial microsomia: A congenital condition in which one or more parts of the face are underdeveloped

Pharyngeal pouch: Saclike diverticula that formed on the endodermal side between the pharyngeal arches

Primordium: An organ or part in the earliest recognizable stage of development

Mesenchyme: A type of undifferentiated connective tissue comprised of loose cells embedded in the extracellular matrix

Microtia: A congenital malformation of variable severity of the ear

Otic capsule: The cartilage that surrounds the developing otic vesicle and develops into the bony labyrinth of the internal ear

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Chapter 4

Characterization of Hearing Loss in Children with Mucopolysaccharidosis

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Additional information is available at the end of the chapter

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Abstract

Hearing impairment is common in patients with mucopolysaccharidoses (MPS) in the preschool age. Conductive or mixed hearing loss is the most frequent occurrence while the involvement of the inner ear or central auditory pathways may occur in more severe forms. A retrospective review of 82 children with MPS admitted at the Pediatric Department of the University of Milano Bicocca was performed to determine the incidence of otological symptoms. We focused particularly on audiological investigations in a subgroup of 47 children diagnosed before 6 years of age (MPS I, n = 11 patients; MPS II, n = 10; MPS III, n = 7; MPS IV, n = 14; MPS VI, n = 5). In 37 children, a magnetic resonance imaging (MRI) of the brain and cervical spine was also performed in order to correlate the audiological findings with the imaging of the middle and inner ear. A total of 40 out of 47 children (86%) showed some degree of hearing impairment: sensorineural or mixed hearing loss in 23 cases (48.93%) and retrocochlear in 4 (8.51%). MRI ascertained multiple CNS abnormalities in 13 (35.3%): dilated perivascular spaces in 5 (38.5%); dilated ventricular cavities in 5 (38.5%); demyelinated and gliotic areas in 3 (23.0%). Conversely, one-fourth of the children's inner ears showed some morphological anomaly (24.3%).

Keywords: mucopolysaccharidoses, hearing loss, auditory brainstem responses (ABR), transient-evoked otoacoustic emissions (TEOAE), MRI

1. Introduction

Mucopolysaccharidoses (MPSs) are a group of rare inherited metabolic disorders resulting from deficiencies of enzymes involved in the breakdown of glycosaminoglycans (GAGs).

MPS disorders have an overall incidence reported of 1.53 per 100,000 live births ranging from 1 in 150,000 to as high as 1 in 10,000 live births [1]. The highest birth prevalence was 0.84 for MPS II, accounting for 55% of all MPS. MPS I, III, and IV accounted for 15, 16, and 10%, respectively. MPS VI and VII were more rare and accounted for 1.7 and 1.3%, respectively.

The majority are characterized by an autosomal recessive pattern (except for X-linked MPS II type). The deficiency of one of the enzymes participating in the GAGs degradation pathway causes progressive storage in the lysosomes, leading to cellular, tissues and organs dysfunction. The damage is both direct or by activation of secondary and tertiary pathways among which a role is played by inflammation.

Nowadays 11 different enzyme deficiencies are known to be involved in MPSs producing seven distinct clinical phenotypes. In contrast to a recent past when there was only palliative treatment for these diseases, now many specific treatments like hematopoietic stem cell transplantation (HSCT) in selected cases (severe MPS I) and enzyme replacement therapy (ERT) for MPS I, II, IV and VI are available.

MPSs can manifest as severe or attenuated clinical picture. The "severe" forms frequently appear in the first 2–3 years of life with skeletal abnormalities often accompanied by dysmorphic facies, organomegaly, multiple hernias (inguinal, umbilical), abnormally frequent and severe upper airways infections, otitis media and chronic rhinitis. In the "attenuated" forms of the disease instead, the progression of signs and symptoms is much slower [2, 3].

These patients may show the prevalent involvement of a single organ and are often seen by one or two specialists for years before reaching the diagnosis [2, 3].

The most frequent signs of presentation are cardiac valve disease, eye disease, hearing loss, carpal tunnel syndrome and functional limitation of major joints [4–6].

In both forms, the disease invariably progresses with time. MRI of the brain and cervical spine is recommended at the time of diagnosis and at regular intervals thereafter [7].

Surgery to stabilize the spine by posterior fusion can be life-saving. Both central and peripheral nervous systems are affected in the MPSs. Prominent perivascular spaces, hydrocephalus, brain atrophy, gliosis and white matter changes are common [8, 9].

The communicating hydrocephalus that occurs in MPSs is usually slowly progressive, with mild or absent clinical symptoms. Corneal clouding in MPS I, IV, VI and VII may lead to significant visual disability. Glaucoma and cataracts have been reported in MPS I and MPS VI and in MPS III and IV respectively [10].

In the ENT field, these patients often present obstructive sleep apnea/hypopnea (OSAHS), noisy breathing, upper respiratory tract infections, chronic rhinitis, frequent middle ear infections and mixed (conductive + sensorineural) hearing loss. The conductive component is explained by Eustachian tube obstruction or insufficiency by macroglossia, pharyngeal and soft palate mucosal swelling, hyperplasia of adenoids and tonsils. Occasionally, congenital deformities

of the middle ear ossicles are observed. Treatments with continuous positive airways pressure (CPAP) during the night sleep, adenotonsillectomy, grommets insertion and hearing aids may be needed [11]. The sporadic finding of sensorineural hearing loss is related to the central and peripheral nervous systems involvement; in some instances it is retrocochlear in nature [12], and it slowly worsens over time [13]. In this study, we reviewed the clinical data of a consecutive series of patients with MPSs, focusing on the early involvement of the auditory pathways.

2. Materials and methods

A retrospective chart review was undertaken to document the otological clinical features and the hearing status of a group of 82 children affected by MPS who were consecutively admitted at the Department of Pediatrics of the San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy, for diagnostic purposes. The young patients were included in the study at the end of the diagnostic process, when the disease had been already characterized by its enzymatic and genetic substrate. Thus, the diagnosis was definite in all cases. We then selected to restrict the investigation to a subgroup of 47 younger children, aged less than 6 years, in order to define audiological profiles with an early prognostic value and early treatment.

We classified the 47 children according to the known MPS types (**Table 1**).

All children underwent an ENT examination during their in-hospital admission, including fiberoptic endoscopy of the upper airways and otomicroscopy. The audiological workup included:

1. Either behavioral audiometry (children <4 years of age) or pure-tone audiometry (children >4 years of age): they were conducted in a soundproof booth, with procedures adequate for the child's age: (a) infants: conditioned oriented responses—COR; (b) toddlers: play audiometry; (c) older children: air (AC) and bone conducted (BC) six frequencies pure tone threshold determination with conventional procedures
2. Middle ear impedance testing: tympanograms and contralateral stapedial reflexes
3. Auditory brainstem responses (ABR): responses elicited by 0.1 ms alternated polarity clicks at intensities decreasing by 10 dB-steps starting from 120 dB p.e.SPL, via ER3A inserts; the electrodes setup was A1/A2-Cz-Fpz; the electrodes impedance <5 kOhm; threshold estimation was obtained by visually checking the wave V latencies and by a test/retest procedure of the lowest amplitude recognizable of the Vth peak. In younger children the procedure was performed during spontaneous sleep; in selected instances, it was obtained during the sedation required for the MR imaging.

   Criteria for labeling a response as "abnormal" were the following:

- Absence of any of the III main wave peaks
- Increased latency of any peak, compared with the normative data for the corresponding age groups at the Audiology Service

- Increased interpeak latency (IPI) compared with the normative data
- Interaural latency difference greater than 0.20 ms

A test/retest procedure was applied at 120 dB SPL stimulation and at the wave V threshold tracing.

A control group of 20 normally hearing children aged 1 year (*normative 1*), 20 children aged 18–24 months (*normative 2*) and 20 aged 3–6 years (*normative 3*) provided the ABR waves latencies normative data.

Therefore, we selected to restrict the investigation to a subgroup of younger children, aged less than 6 years. A full set of audiological data was then gathered for these 47 younger children; among them, 37 (80.43%) underwent also an MRI of the brain and ear. It was therefore possible to cross-check the outcomes of the hearing test and neuroradiological imaging in this subgroup of 37 children. They were 21 males and 16 females with a median age at admission of 3.2 years, ranging between 12 months and 6 years. **Figure 1** shows the flowchart of the study protocol.

In the majority of cases the MRIs of the brain and ear were performed under slight sedation (infants, toddlers and uncooperative children). The MRIs were obtained by a basic protocol

Disease	Number of observed cases	Defective enzyme	GAG storage material	Estimated incidence
MPS-I (Hurler, Hurler/Scheie Scheie)	11	α-L-Iduronidase	Dermatan sulfate, heparan sulfate	1:84,000
MPS-II (Hunter)	10	Iduronate-2-sulfatase	Dermatan sulfate, heparan sulfate	1:196,000
MPS-IIIa (Sanfilippo A)	7	Heparan N-sulfatase	Heparan sulfate	1:92,000
MPS-IIIb (Sanfilippo B)		N-Acetyl-α-glucosaminidase	Heparan sulfate	1:157,000
MPS-IIIc (Sanfilippo C)		Acetyl-CoA:α-glucosamide N-acetyltransferase	Heparan sulfate	1:714,000
MPS-IIId (Sanfilippo D)	0	N-Acetylglucosamine-6-sulfatase	Heparan sulfate	1:1,000,000
MPS-IVA (Morquio A)	14	Galactose-6-sulfatase	Keratan sulfate, chondroitin-6-sulfate	1:131,000
MPS-IVB (Morquio B)		Beta-galactoidase	Keratan sulfate	1:130,000
MPS-VI (Maroteaux-Lamy)	5	Arylsulfatase B	Dermatan sulfate	1:120,000

Table 1. Clinical types of mucopolysaccharidosis (MPSs) with their underlying enzyme deficiency, accumulated substrate, and relative incidence.

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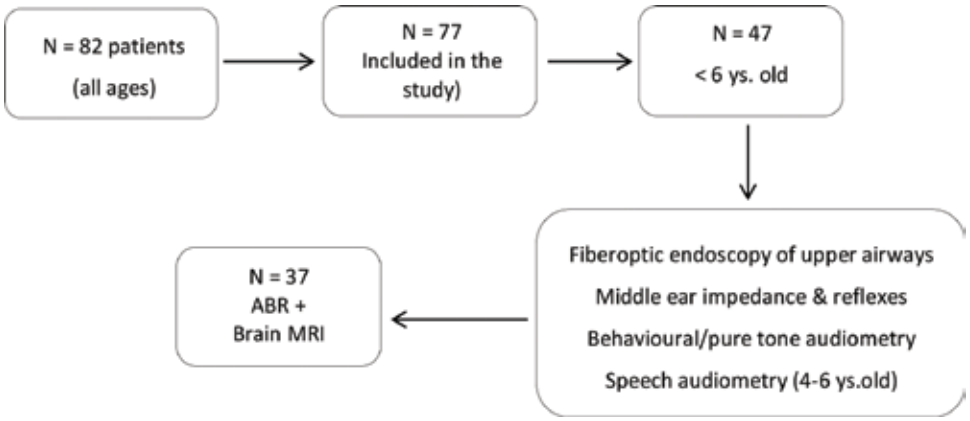

Figure 1. Flowchart showing the young patients' distribution according to the tests performed in the current study.

including axial, coronal and sagittal 3D–Steady-State Free Procession sequence (SSFP), T1-weighted Fast Spin-Echo (FSE) sequence, and T2-weighted 3D Fluid Attenuated Inversion Recovery (FLAIR) sequence. MRI scans were extended from top of the skull to C7. No intravenous injection of contrast medium was applied as a standard procedure. An expert senior Neuroradiologist categorized the findings according to the three most prevalent patterns: (a) dilated perivascular spaces; (b) dilated ventricular cavities; (c) demyelinated and gliotic areas.

After establishing an audiological diagnosis in terms of presence and type of hearing loss (conductive, mixed, sensorineural → cochlear or retrocochlear), degree of loss, laterality, and checking the eardrum morphology at otomicroscopy, these data were contrasted with the MRI findings.

Children were divided in two groups according to the type of hearing loss: "C" = purely conductive; "S" = sensorineural or mixed that is reported in **Figure 2**.

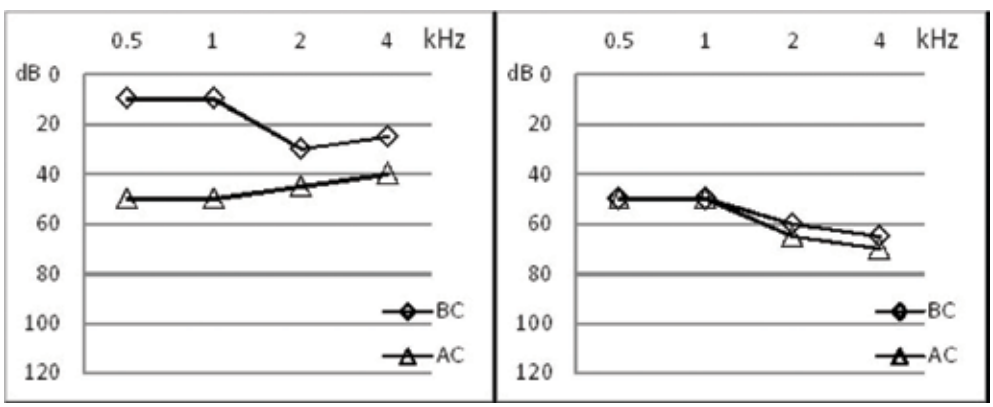

Figure 2. Mean hearing thresholds levels in the "mixed" (left panel) and in the "sensorineural" hearing loss group (right panel). n = 47.

3. Results

3.1. Audiological workup

Some degree of hearing impairment was present in 61 children (74.4%) of the whole cohort of 82 young patients (up to 14 years of age). A total of 21 children (25.6%) were normally hearing. Approximately the same rate of hearing impairment was found in 36 children of the cohort 47 under 6 years of age (76.6%) rather than at older ages; it was sensorineural or mixed in almost half of the ears (47.44%) and purely conductive in about one-third (27.02%). Hearing loss was always symmetrical in the two ears (within 10 dB differences between ears at same frequencies).

Five children presented with normal hearing at admission (mean PTA <20 dB HL bilaterally). The average AC threshold in the "C" group was 44 dB HL with an air-bone gap (ABG) of 21 dB HL; the "S" group showed an AC threshold PTA = 62.5 dB HL with an ABG of 2.3 dB HL. In 7 children (18.9%), the tympanograms were normal (type "A") at the time of the initial assessment and contralateral stapedial reflexes showed a normal threshold and morphology; in the other 30 (81.0%) they were pathological in both ears (Type "B" n = 14; type "C" n = 16).

Transient evoked otoacoustic emissions (TEOAE) were absent bilaterally in all children with a hearing threshold worse than 25 dB HL; normal otoacoustic emission responses were obtained in 9 out of 10 normally hearing ears.

Normative latencies for the three main ABR peaks in normally hearing children of different ages are reported in **Table 2**, and compared to those obtained in the MPS cohort stratified in the same three age groups. Statistical analysis was performed by means of Wilcoxon signed rank test; $p < 0.005$ was considered statistically significant.

In MPS children, ABRs to click stimuli were morphologically normal with peak latencies within normal limits (avg ± 1 SD) in 25 out of 47 subjects (53.2%), whereas 22 tracings showed abnormalities (46.8%). A typical waveform with the 3 main peaks was recognizable or only wave I was missing in 18 of these 22 cases at a stimulus intensity of 90 dB HL, but the amplitudes were reduced and all the latencies delayed ("cochlear" site of lesion); in 7 children no

Wave latencies	MPS 12 mo	Norm 1	p	MPS 18–24 mo	Norm 2	p	MPS 2–6 ys	Norm 3	p
Wave I	1.89 ± 0.21	1.62 ± 0.31	0.046	2.01 ± 0.18	1.88 ± 0.26	n.s.	2.18 ± 0.29	1.99 ± 0.48	n.s.
Wave III	4.30 ± 0.12	4.00 ± 0.34	n.s.	4.51 ± 0.25	4.12 ± 0.11	0.0001	4.45 ± 0.22	4.17 ± 0.3	0.0001
Wave V	6.39 ± 0.18	5.92 ± 0.25	0.0001	7.02 ± 0.2	5.96 ± 0.28	0.0001	7.39 ± 0.26	5.98 ± 0.11	0.0001
IPI I–III	2.40 ± 0.22	2.37 ± 0.21	n.s.	2.50 ± 0.31	2.24 ± 0.25	n.s.	2.27 ± 0.22	2.18 ± 0.21	n.s.
IPI I–V	4.33 ± 0.1	4.31 ± 0.16	n.s.	5.01 ± 0.18	4.98 ± 0.16	n.s.	5.21 ± 0.1	4.0 ± 0.26	0.0001

Latency values expressed in ms. Wilcoxon signed rank test, statistical significance at $p < 0.005$.

Table 2. ABR's absolute wave latencies (ms) and inter-peak intervals (IPI, ms) in the MPS cohort stratified by age and compared to those obtained in the normally hearing age-matched children (control groups Norm 1-2-3).

identifiable response was obtained: in 3 of them, the hearing threshold was severe enough to explain the absence of the response; in 4 cases a retrocochlear involvement was suspected. Overall, a retrocochlear involvement was likely in 8.5% of MPS children.

The relationship between the MPS types and the ABR findings is shown in **Table 3**: all children with MPS III demonstrated an altered ABR; the greatest majority of MPS II also proved pathological, as well as half of the MPS I. None of the patients affected by MPS IVA and VI revealed abnormal ABR tracings.

According to ABR response, the hearing loss was of the "cochlear" type in 83.3, 77.8 and 85.7% of MPS I, MPS II and MPS III, respectively. One case of absent wave I plus absent or delayed wave III and V were observed in MPS I and III, similarly to two cases of MPS II. In no instance an isolated delay of wave V was observed, thus excluding purely "central" site of lesions.

In most MPS children with hearing loss, the hearing threshold derived from the ABRs wave V thresholds ranged between 70 and 90 dB SPL (40–60 dB HL) with an average of 85.62 dB SPL.

3.2. Neuroimaging

Among the 37 MRI, 14 (37.84%) were normal, whereas 23 (62.16%) were pathologic. The most frequent abnormal neuroradiological findings were represented by dilated perivascular spaces (due to extracellular storage of GAGs) in = 12 (32.43%); dilated ventricular cavities n = 15 (40.54%); demyelinated and gliotic areas n = 9 (24.32%). The frequent observation of a J-shaped sella was considered a non-pathological anatomical variant.

We reviewed all MRI with a particular attention on the middle and inner ear findings, although imaging was a standard brain study, not addressing the ear morphology per se. We ascertained five cases of globose internal auditory canal (IAC), and one case of cystic cochlear

MPS type	Normal latencies (all peaks recognizable)	Abnormal ABR	Absent wave I or delayed wave I-III-V (cochlear hearing loss (IPI within normal range)	Absent wave I and absent or delayed wave III and V	Delayed wave V only
MPS-I (n = 11)	5 (46.5%)	6 (54.5%)	5	1	0
MPS-II (n = 10)	1 (10%)	9 (90%)	7	2	0
MPS III (n = 7)	0	7 (100%)	6	1	0
MPS IV (n = 14)	14	0	0	0	0
MPS VI (n = 5)	5	0	0	0	0
Total	25/47 (53.2%)	22/47 (46.8%)	18 (81.8%)	4 (8.5%)	0

Table 3. Distribution of abnormal ABR findings according to MPS type (n = 47).

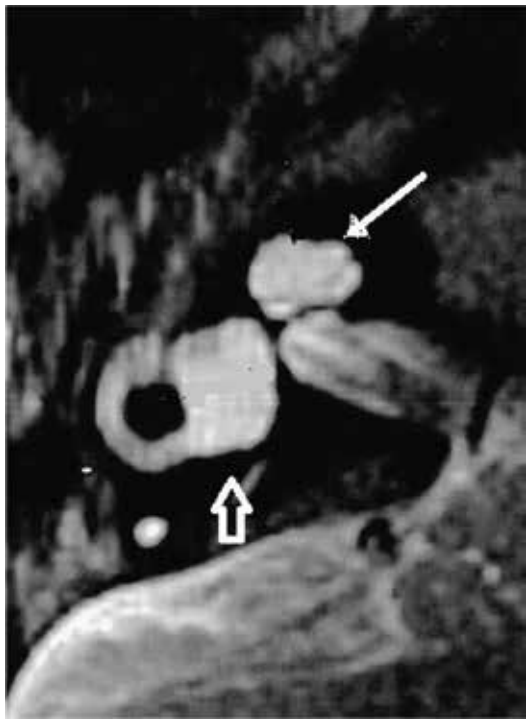

Figure 3. Detail of axial T2-weighted MRI scan of the right ear of patient #14, showing cystic cochlear apex (thin arrow) and enlarged vestibule (empty arrow).

apex and dilated vestibule, which is shown in **Figure 3**. All detected anomalies were bilateral except for the dilated vestibule (right ear, pt. # 14). The middle ear pathological findings consisted in 15 cases of sero-mucinous effusion in the mastoid cells and in the tympanic cavity, 9 bilateral and 4 unilateral (always the right side). In no instance an enlarged vestibular aqueduct was detected. Similarly, no pathological conditions were identified along the central auditory pathways in any young MPS patients.

We further stratified the 37 MR+ patients in 3 subgroups related to age: 5 (13.51%) patients were under 1 years old, only 2 children (5.4%) were between 1 and 2 years old and 30 children

Age	# of patients (%)	Rate of pathological ABRs	Rate of pathological brain MRIs
<1 year	5	2 (40%)	3 (60%)
1–2 years	2	2 (100%)	1 (100%)
2–6 years	30	23 (77.7%)	22 (72.2%)
Total	37	27 (72.9%)	26 (70.2%)

Table 4. Incidence of pathological ABRs and MRIs at different ages in the subgroup of 37 MPS patients who underwent both investigations.

(81.08%) were between 2 and 6 years old. By contrasting the rate of pathological ABR and the MRI findings according to the age layers we obtained the outcomes illustrated in **Table 4**. Noticeably, the majority of children underwent an ABR after 2 years of age, when, theoretically, the physiological maturation of the central auditory pathways should be completed.

4. Discussion

The MPSs are a group of monogenic disorders due to lysosomal storage of glycosaminoglycans (GAGs), previously called mucopolysaccharides [14]. The deficiency of one of the enzymes participating in the GAGs degradation pathway causes progressive storage in the lysosomes and cytoplasm, leading to cell swelling and multiple organs dysfunction. The damage is both direct or by activation of secondary and tertiary pathways among which a role is played by inflammation. [15] All MPSs have an autosomal recessive transmission with the exception of MPS type II (Hunter syndrome) which is X-linked [16].

The incidence of MPSs as a group is reported between 1:25,000 and 1:45,000 [17]. At present, 11 different enzyme deficiencies are involved in MPSs producing 7 distinct clinical phenotypes [14] (**Table 1**). Depending on the enzyme deficiency, the catabolism of dermatan sulfate, heparin sulfate, keratin sulfate, chondroitin sulfate, or hyaluronan may be impaired, singularly or in combination.

MPSs virtually affect all organs and tissues and show a progressive worsening with time. Diagnosis is suspected clinically on the basis of rather constant physical appearance (signs can be subtle or overt) such as: coarse facial features; short stature; "claw hand" and/or joint stiffness or ligamentous laxity (seen in MPS VI); corneal clouding (from very mild to severe), retinopathy, glaucoma; chronic nasal congestion, noisy breathing; abdominal protuberance owing to liver and spleen enlargement; spinal deformity (gibbus, scoliosis, kyphosis, lordosis); abnormal gait (e.g., toe walking); hearing deficits and brain involvement with progressive cognitive delay. In MPS III and II, mental retardation at 2–3 years may be the only, or most evident, presenting sign. Heart failure and severe valve disease in the first year of life are reported as the first presenting symptom in the *severe* forms [18–20]. In these patients, quality of life and life span are generally substantially reduced [21, 22].

The *attenuated* forms have widely variable clinical presentations with different presenting signs at different ages, often one or few organs only clinically manifest the disease [2, 3]. In these milder forms the progression of signs and symptoms is much slower than in the severe ones. These patients may have a presentation apparently limited to one organ only and are often seen by a specialist for years before reaching the diagnosis [2, 3], that is usually accomplished by means of biochemical, enzymatic and molecular tests.

Currently, specific treatments such as hematopoietic stem cell transplantation in selected cases of severe MPS I and enzyme replacement therapy for MPS I, II, IV and VI are available [23]. These treatments are able to improve the clinical course of the disease if started early. This brings along the responsibility for the clinician to recognize these diseases at the first signs to allow access to treatment before a severe damage has been established.

Although similar, each type of MPSs has a peculiar phenotypic expression [14]; besides, within the same type of MPSs, the phenotypic spectrum is largely variable, as a result of the different severity of mutations and overall genetic background of the single individual.

The otorhinolaryngological involvement is represented by otitis media with effusion, progressive mixed hearing loss, OSAHS, pathology of the Waldeyer lymphatic ring and difficulties during intubation [24].

In the *severe* forms, which most frequently present in the first 2–3 years of life with skeletal abnormalities dysmorphic facies, organomegaly and multiple hernias, children suffer abnormally frequent and severe upper airways infections, chronic rhinitis and otitis media. Hearing loss is a frequent feature of the more severe forms of MPS; therefore, it should be identified as early as possible in order to help assessing a correct diagnosis and provide an etiological treatment [33].

It occurs frequently in the early childhood, mainly as a consequence of recurrent episodes of otitis media. It is often discovered occasionally, during an otorhinolaryngological referral requested for the control of the upper airways. OME is the most frequent finding: if the clinical history is silent, it may be overlooked; its incidence in children affected by MPS is higher than in the general population [24].

A middle ear effusion can easily mask an underlying sensorineural hearing loss. The inner ear involvement has been generally neglected in the literature; the major pathologic alterations have been found in the Corti organ, tectorial and Reissner's membranes, ciliated cells and auditory nerve [13]. In the *attenuated* forms of MPS, hearing loss occurs more frequently at a later stage, but it sometimes develops already in first infancy. If correctly recognized, it can be effectively rehabilitated with hearing aids, reducing the already existing disability related with the multi-organ dysfunction.

In our series, 32% of the young patients were affected by mixed hearing loss, 28% by purely conductive, 16% by sensorineural type and 24% were normally hearing. This distribution is coherent with other reports [25, 26]. The degree of hearing loss in purely sensorineural involvement ranged between 40 and 60 dB (average 55.62 dB HL).

In our MPS children, auditory brainstem responses to click stimuli were morphologically normal with peak latencies within normal limits (avg ± 1 SD) in 25 out of 47 subjects (53.2%), whereas 22 tracings showed abnormalities (46.8%). At a stimulus intensity of 90 dB HL, the 3 main peaks of the typical ABR waveform were recognizable, or only wave I was missing, in 18 of these 22 cases. Reduced amplitudes and delayed latencies with regular interpeak latencies indicated a "cochlear" site of lesion; in 7 children no identifiable response was obtained: in 3 of them the hearing threshold was severe enough to explain the absence of the response; in 4 cases a retrocochlear involvement was suspected. Overall, a retrocochlear involvement was likely in 8.5% of MPS children.

The relationship between the MPS types and the ABR findings is shown in **Table 3**: all children with MPS III demonstrated an altered ABR; the greatest majority of MPS II also proved pathological, as well as half of the MPS I. None of the patients affected by MPS IVA and VI revealed abnormal ABR tracings. On a speculative basis, this might reflect a more severe compromise of the auditory periphery in MPS I-II and III.

Based on the ABR response, the hearing loss was of the "cochlear" type in 83.3, 77.8 and 85.7% of MPS I, MPS II and MPS III, respectively; purely "central" lesions were excluded.

The retrocochlear patterns of auditory evoked potentials observed in four of our patients with sensorineural hearing loss highlighted a conduction delay within the central auditory system, possibly related to progressive storage of GAGs.

Up to date, the reason for the sensorineural component of the hearing loss has not been fully ascertained: some alterations, such as the presence of lysosomal deposit in the outer and /or inner hair cells suggest a dysfunction of the cochlear sensorial structures; conversely, the findings of PAS+ material occupying the cytoplasm of the spiral and vestibular ganglion cells might indicate an altered neural transmission [27, 28]. Furthermore, animal studies also showed an alteration in the mechanical properties of the Reissner's and Basilar membranes [12].

The most characteristic modification in the CNS is the dilatation of the perivascular spaces, caused by extracellular storage of GAGs; it appears as a variable amount of tiny spot-like cystic lesions with CSF-like signal in all sequences. It is probably determined by large GAG inclusions between vascular adventitial cells, typically at basal ganglia, subcortical parietal and occipital white matter, and in the corpus callosum, with radial orientation along the vascular developmental lines [29]. Widening of liquoral spaces and hydrocephalus, secondary to pathologic leptomeningeal thickening with resorption deficit by the Pacchioni's granulations and/or obstruction of the CSF flow, can lead to severe neurologic compromise (requiring a shunt) or to neuronal loss and decrease of association fibers and atrophy [30]. The expression of white matter dystrophy in mucopolysaccharidoses, probably on a microvascular basis, is common also to several other diseases that share the same vulnerable areas, such as the peritrigonal white matter. Compared to dilated perivascular spaces, these lesions show brighter (hyperintense) signals both in T_2-weighted and FLAIR images.

In our series of 37 MPS children who underwent MRI, 14 (37.84%) were normal, whereas 23 (62.16%) showed some abnormalities such as dilated perivascular spaces in 12 (32.43%), dilated ventricular cavities in 15 (40.54%), demyelinated and gliotic areas in 9 (24.32%). A globose internal auditory canal was observed in five cases of IAC, and a cystic cochlear apex and dilated vestibule in 1 child. The middle ear pathological findings consisted in 15 cases of sero-mucinous effusion in the mastoid cells and in the tympanic cavity. The limited number of children tested under 2 years of age does not allow to draw general conclusions. Instead, within the group of 30 children aged 2–6 years, the rate of pathological ABRs (77.7%) and of pathological MRI of the brain (72.2%) showed a high degree of correlation. Assuming that the physiological maturation of the central auditory pathways is being completed during this age range, the ABR abnormalities would possibly be attributed no longer to a delayed myelinization. Therefore, the "retrocochlear" ABR findings might be a real expression of "central" auditory dysfunction, although the MRI abnormalities did not seem to involve directly the auditory pathways.

The interpretation of these neuroimaging findings is somehow challenging, because a clear relationship with cognitive insufficiency in MPS patients is lacking [30, 31], although mental retardation has been reported in the more severe forms of MPS 1 [32–37].

Similarly, the relationship with hearing loss is not clear. Nevertheless, a prompt recognition of the hearing difficulties, which can be among the first manifestations of the disease, might help assessing an earlier diagnosis and, therefore, provide a timely treatment.

5. Conclusions

Inner ear and retrocochlear involvement in MPS patients is more frequent than initially suspected. Observation of seromucinous effusion in the middle ear does not exclude the presence of a sensorineural hearing loss. An otological and audiological investigation should be warranted to all defined or suspected MPS patients. Inner ear or central auditory lesions detected by the audiological tests should be further investigated by specific MR imaging processing algorithms.

Early identification of hearing loss not only enables proper acoustic rehabilitation, but also supports the diagnosis of MPS, especially in its milder forms and/or initial stages.

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Conflicts of interest

The authors report no financial interest in the subject matter, no actual/potential conflict of interest.

Abbreviations

ABR	auditory brainstem responses (acoustically evoked potentials)
AC	air conduction (pure tone audiometry)
avg.	average
BC	bone conduction (pure tone audiometry)
CNS	central nervous system
COR	conditioned oriented responses (test of hearing for babies)
CPAP	continuous positive airways pressure

dB	decibel
ENT	ear, nose and throat (otorhinolaryngology)
ERT	enzyme replacement therapy
FLAIR	fluid attenuated inversion recovery sequence
FSE	Fast Spin-Echo sequence
GAG	glycosaminoglycans
HL	hearing level
HSCT	hematopoietic stem cell transplantation
IAC	internal auditory canal
MPS	mucopolysaccharidoses
MRI	magnetic resonance imaging
MR+	positive at MRI
OME	otitis media with effusion
OSAHS	obstructive sleep apnea/hypopnea syndrome
p.e.SPL	peak-equivalent sound pressure level
PTA	pure tone average (average of thresholds to pure tone stimuli at 0.5–1–2-3 kHz; value expressed in dB HL)
SD	standard deviation
SSFP	3D–Steady-State Free Procession sequence
TEOAE	transient-evoked oto-acoustic emissions

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Chapter 5

Sudden Sensorineural Hearing Loss

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Additional information is available at the end of the chapter

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Abstract

Sudden hearing loss (SHL) is a common disease in the daily practice of ear-nose-throat (ENT) and audiology clinics. It is usually defined as a sensorineural type hearing loss of 30 dB or greater in three contiguous frequencies. Although several factors were suggested for the etiology of SHL, in most of the cases, no cause could be detected and they were diagnosed as idiopathic cases. Although certain specific treatments might be applied in patients with known etiology, corticosteroids are the main component in the treatment of idiopathic SHL. Many experts and centers have developed different treatment protocols with similar approaches. SHL is considered as an emergency in ENT, as it may cause a permanent loss in hair cells, if it is not treated or the treatment is not initiated at the right time. For patients, who did not or partially benefit from the initial treatment, different salvage treatment protocols had been developed. As SHL severely affects the patient's quality of life, its diagnosis and treatment should be thoroughly deliberated.

Keywords: idiopathic hearing loss, salvage treatment, sudden deafness, sudden hearing loss, treatment

1. Definition

Sudden hearing loss (SHL) is an ear-nose-throat (ENT) emergency and as sensorineural hearing loss of 30 dB or greater in three contiguous audiometric frequencies occurring over 72 h. SHL was first described by Dekleyn in [1] (**Figure 1A**). Although the definition mentioned above involves the widely accepted diagnostic criteria of SHL, it actually develops within hours or minutes and is usually noticed by the patient early in the morning or during a telephone conversation. With an approach from a broader perspective, we may consider all identifiable and measurable hearing losses, which are noticed within minutes or within few days, as SHL. Patients usually visit an ENT specialist in a great panic, thinking they became deaf.

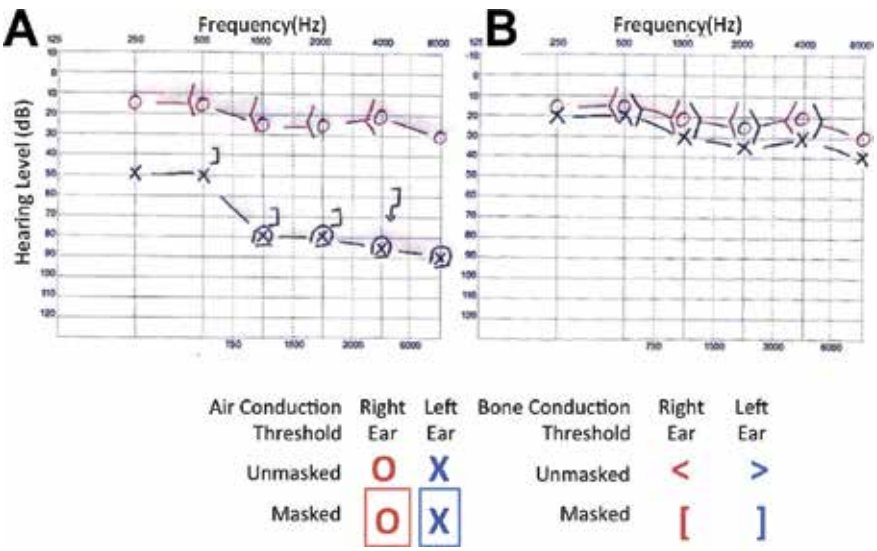

Figure 1. A: Sudden hearing loss sample audiogram. B: After treatment normal hearing level.

The physician, first of all, should calm the patient and then examine his/her medical condition, proceed immediately with the diagnostic procedures, identify—if possible—the etiology and initiate without delay the proper treatment.

2. Epidemiology

Although SHL constitutes approx. 1% of all sensorineural hearing losses, its incidence changes between 5 and 20/100,000 in different sources [2]. However, high rates such as 160/100,000 had also been reported in the literature and 40,000 new cases were diagnosed every year in the USA [3]. The incidence and prevalence of SHL are probably slightly higher than the calculated values, because of the rapid development of SHL and the high rate of spontaneous regression. Many studies reported that SHL had no correlation with gender and that the female/male ratio was equal or insignificantly different. In this regard, it seems safe to say that gender is not a risk factor. Similarly, no significant left/right ear distinction was detected. Although SHL is usually unilateral, bilateral involvement is emerging in a small percentage of patients (1–2%) [4]. Nevertheless, bilateral SHL is a more serious condition compared to the unilateral form and is often related to systemic disorders and has a relatively worse prognosis [5, 6].

3. Physiopathology

Among the mechanisms causing SHL, in particular, intracochlear hypoxia and/or inflammation in the inner ear play a major role. Several causes, which were suggested regarding the

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pathogenesis of SHL, can be classified into four main groups. Vascular factors, viral infections, autoimmune processes, and intracochlear membrane rupture.

3.1. Vascular factors

As it is well known, the cochlea is an end-organ perfused by the labyrinthine artery, which is a branch of the basilar artery and does not have collateral circulation [7]. The labyrinthine artery divides into two branches (vestibular and cochlear arteries) after entering through the internal acoustic meatus. The cochlear artery enters the cochlea after the division of its branch the vestibulocochlear artery [8]. Therefore, factors such as thrombi, emboli, atherosclerosis, vasospasm, and decreased blood flow may end up with vascular insufficiency and consequently a loss of function in the cochlea. A sudden interruption of the blood flow to the cochlea may induce the development of SHL, which will cause a complete restriction of the oxygen supply.

The obstructions in the vertebrobasilar system may also cause SHL. Here, it should be noticed that a bilateral SHL emerges, in these cases, as the basilar artery, which is the only artery supplying that region. Kim et al. [9] detected a thrombus in the bilateral distal vertebral artery in a patient with bilateral SHL and observed improvement after the restoration of the circulation with a stent. In his experimental study, Perlman [10] stated that the occlusion of the internal auditory artery caused changes in the cochlea secondary to the ischemia and some of these changes were irreversible. The difference of this study from SHL patients is that the findings in SHL are reversible. In a recent study similar to these studies, Chung [11] found out a relation between increased arterial stiffness and SHL development and the response to the treatment and drew attention to the development of SHL with vascular causes. Subclinical atherosclerosis has also been reported in the literature, as a cause of SHL [12].

It is understandable that the temporary and permanent problems in the cochlear microcirculation may cause SHL depending on the damage in the cochlear hair cells [13]. Also, in cases of hypercoagulopathy, a possible intravascular obstruction may cause damage to the inner ear in the same way. Bernhard [14] investigated the effects of experimental hyperfibrinogenemia on the development of SHL and stated that although they did not respond to corticosteroids, intravenous defibrinogenation (ancrod) improved the process markedly. He suggested that defibrinogenation therapy should be considered in non-responding SHL patients. Similarly, the relation of SHL to the factors capable of intravenous obstruction such as sickle cell anemia, Waldenström's macroglobulinemia or contraceptive drugs have been reported in the literature [15]. Although, some studies have suggested that there is a relationship between Factor V Leiden mutation and SHL, it was shown with a meta-analysis that there is no clear relationship between these two pathologies [16]. It is clear that these diseases will not respond to corticosteroids and the main treatment should be targeted to the underlying cause. Cochlear damage may emerge due to the acute emboli after the cardiopulmonary bypass or non-otological, non-coronary operations and may result consequently in SHL [17]. Any obstruction due to any reason in the cochlear microcirculation will manifest itself with the symptoms corresponding to the level of the obstructed artery. For example, although hearing loss is the only finding in the presence of the cochlear artery obstructions, vestibular symptoms like vertigo and tinnitus will also emerge in the labyrinthine artery obstructions along with hearing loss.

Cappacio [18] suggested that dyslipidemia may be associated with SHL pathogenesis and that impaired serum lipid profile might be an important factor in the development of SHL. There are also other studies in the literature linking serum lipid levels with SHL [19]. However, Chang [20] reported in his meta-analysis that serum lipid profile did not have any correlation with the SHL development and its prognosis.

3.2. Viral infections

Viral infections are the most common factor worldwide in the etiology of SHL in the world [21]. In 1954, Lindsay and Hemenway [22] detected degeneration in the tectorial membrane, corti organ, and stria vascularis during their cochlear histopathological examination and determined findings of measles virus in the cochlea in the same study. Shortly thereafter, Lindsay [23] found that the mumps virus could also do similar damage to the inner ear. So, the relationship between hearing loss and viral infections is well known. In a meta-analysis, it has been reported that 40% of the congenital hearing loss is associated with viruses and the most common responsible agent is cytomegalovirus (CMV) along with some other viral in utero infections [24]. Similarly, Van Dishoeck [25] suggested that there might be a link between upper airway infections and SHL and those upper airway viruses, which might penetrate the inner ear through neighborhood or blood circulation, might cause an immune response and an eventual damage in the inner ear. Especially, the herpes family of viruses, influenza, and enteroviruses are frequently blamed viral agents in the SHL etiology [26]. In a study conducted by Wilson [27], he found out that viral serology titration in SHL patients was two times higher than in the control group. It is believed that the penetration of the virus itself or the viral antigens to the membranous labyrinth cause an immune response and the resulting inflammation the formation of SHL. As the emerged cochleitis causes hearing loss, it is believed that the presence of vertigo, which is considered as a sign of bad prognosis for SHL, depends on the labyrinthitis emerging concomitantly.

In addition to the viral infections, bacteria can also cause the formation of SHL. In the USA, the two most common bacterial diseases causing SHL are Lyme disease and syphilis [28]. Lyme disease is caused by Borrelia burgdorferi and in long-term it may involve neurologic structures, especially the seventh nerve, which may cause facial paralysis. It may also cause hearing loss due to the involvement of the eighth nerve [28]. Although some studies showed that the incidence of Lyme disease is relatively high in SHL (up to 20%), some other reported very low rates [29, 30]. Syphilis is a systemic infection caused by *Treponema pallidum* and may present diverse clinical manifestations. Especially at the stage of neurosyphilis, if the neuritis of eighth nerve and cochleitis are added to the picture, it is called as otosyphilis. Otosyphilis may be encountered in different forms such as SHL, progressive hearing loss, fluctuating hearing loss or Meniere's syndrome [31].

In fact, viral infection hypothesis depends on three possible mechanisms considering its relation to the hearing loss [32]. The first of them, as mentioned above, is that the virus itself or its antigens, which may induce an immune response, penetrate the inner ear, and may cause cochleitis and neuritis in the cochlear nerve. The path may be hematogenous, but it may also spread directly through the neighborhood. The cerebrospinal fluid may be also a vehicle for

the spread of the virus. The second hypothesis is that the latent virus infection in the inner ear may reactivate due to several reasons and cause SHL. Especially, it is a fact that *Varicella zoster* and other neurotropic viruses may cause latent virus infections, which strengthens this hypothesis. The next hypothesis is more complicated than the first two hypotheses and is indirectly related to viruses as well. As follows: the antibodies found in the systemic circulation and secreted against the viral antigens outside the inner ear may cause the development of a cross-reaction against the structural antigens in the inner ear, which may damage the inner ear and consequently cause hearing loss. In one respect, this last theory is an example of the relation between SHL and autoimmunity.

These findings, clinical, and histopathological studies eventually give the impression that viral etiology is one of the main etiologies in SHL. Nevertheless, it is also believed that the corticosteroids, which constitute the main therapeutic approach to SHL, have an anti-inflammatory effect in the inner ear, cures the emerged cochleitis, and enable healing through these mechanisms.

3.3. Autoimmunity

Autoimmunity theory is based on the main principle of the cross-reaction of the circulating antibodies or activated-cytotoxic T cells with the inner ear antigens [33]. The antibodies in the systemic circulation may be formed not only against a virus or bacterium, but also against several allergens. Eventually, these antibodies may become sensitive to the target antigens in the inner ear such as Type 2 collagen, tectorin, and beta-actin. The best documented among these antigens is the choline transporters like protein 2 (CTL-2) an inner ear glycoprotein [34–38]. In a study, antibodies formed against CLK-2 were detected in the systemic circulation in 9 of 20 patients [39]. In an experimental study on mice with Cogan syndrome, it was shown that the antibodies, which were formed against some supportive cells called CD148 and against connexin 26 (a well-known gap-junction protein), caused hearing loss [40].

In some SHL patients, antibodies against some cochlear proteins (p30, p80) and against some antigens such as Type 2 collagen and cardiolipin in the membranous labyrinth [41–43]. In some studies, it was also found out that the levels of some T-lymphocyte substances like C3b were increased in SHL [44]. Anti-endothelial antibodies (AECA) present another example. These antibodies are a group of heterogeneous autoantibodies that develop against endothelial cells and cause damage to the vessel walls. These antibodies may cause inflammation in the vascular endothelial cells in many different regions of the body via the immune system. They were also associated with many connective tissue disorders and systemic vasculitis; therewith, they got specific terminological naming [45]. The relationship between AECA and SHL was demonstrated with several studies [46, 47]. Harris reported that the relationship between circulating antibodies and bilateral, progressive, and fluctuating SHL was sufficiently evident [48]. In this study, although he detected antibodies against an antigen, which he thought was specific to the inner ear. He concluded that his further analyses revealed that this antigen was heat-shock protein 70 (Hsp-70) and that it existed not only in the inner ear, but also in different regions of the body. The relationship between the anti-Hsp70 antibodies and SHL were tried to be confirmed by further studies [49, 50].

It has also been reported in the literature that there is a relation between systemic lupus erythematosus (SLE) and SHL. It was reported that circulating autoantibodies might enter into the reaction directly with the inner ear antigens in SLE patients and the activated T cells might increase the levels of intracellular interferon gamma and some other cytokines and thus cause cellular damage [51]. Additionally, it is well known that in SLE, circulation antibodies such as anticardiolipin antibody, lupus anticoagulant, and anti-β2 GP1, antiphospholipid antibodies cause emboli and microinfarcts in the systemic circulation. As these antibodies may cause the same problems in the cochlear microcirculation, they may also cause SHL with the mechanism explained in the vascular hypothesis of SHL. Meanwhile, it was also stated in the literature that the SHL, which is believed to be developed due to SLE, might improve with a proper anticoagulant treatment [52, 53].

Hearing losses, which are believed that they develop in relationship with autoimmunity and manifest themselves with progressive, recurrent, and fluctuating clinical picture, are also called autoimmune hearing loss or autoimmune inner ear disease [54]. Yoo [41] created hearing loss in rats with Type 2 collagen immunization and showed the monoclonal antibodies, which were formed against the antigen related to the otic capsule, with radioimmunoassay. Harris [55] identified five antibodies formed against the inner ear antigens and suggested that the inner ear might have its own immunoreactive mechanism apart from the systemic immune response, but this was not supported by studies conducted after this hypothesis was introduced. Lymphocyte transformation and Western-blot tests are recommended for the diagnosis of the autoimmune hearing loss. Heywood [56] used infliximab in the treatment of fluctuating and progressive high-frequency recurrent hearing loss and reported that the patients benefited from this anti-TNF-alpha agent. Although all these findings might show the place of the autoimmunity in the etiology of SHL, there is still a need for further studies with larger samples size, as the sample sizes in the available studies are relatively small.

3.4. Intracochlear membrane rupture

Round- and oval-window membranes are two anatomical structures that separate the inner and middle ear from each other. These structures are responsible for restricting the endolymph to the inner ear and for preventing its penetration to the middle ear. There are other additional membranes in the inner ear that prevent the endolymph from interfering with the perilymph, and it is well known that their rupture will cause hearing loss. Goodhill [57] detected a perilymph fistula in three patients with SHL. Simmons [58] was one of the earliest authors, who suggested that the labyrinthine membrane damages might play a role in the etiology of SHL. Gussen [59] has identified healed Reissner membrane in the temporal bone dissections and succeeded to reveal membrane ruptures in the SHL etiology. Similarly, Kamerer [60] demonstrated microfissures between the posterior canal ampulla and the round-window niche during his temporal bone studies. Although there are other studies with small patient sizes, the main question is whether the hearing losses depending on membrane ruptures should be classified as SHL. Because, in that case, we have to assume that SHL arises from a mechanical problem and the treatment procedure should be based mainly on surgical

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or conservative procedures. But, the main thing that should be known about these patients is that they will not respond to standard SHL treatment protocols. However, if we look at the classic definition of SHL, they also conform to the SHL definition.

4. Histopathology

The histopathology of SHL is quite diverse because of the several factors blamed regarding its etiology. In the temporal bone studies, as mentioned above, along with the membrane ruptures, degenerative findings such as atrophy in the corti organ, loss of cochlear neurons, and neuron fibrils might be encountered in the viral etiology. On the other hand, histopathological findings such as labyrinthine fibrosis and new bone formation are the predominant histopathological findings in vascular events. Yood [61] observed certain changes in 7 of 11 temporal bones in his histopathological study. These changes include especially damage to the corti organ or loss of total corti organ; even it may differ according to the etiology. On the other hand, Vasama [62] determined in his study on 12 temporal bones degeneration and loss in the spiral ligament and stria vascularis. He also observed cochlear ossification in one patient. Since SHL's etiology is multifactorial, multiple histopathological findings are expected and it can be suggested that majority of these findings might be reversible regarding the spontaneous healing rates of SHL.

5. Etiology

Although an etiological factor could be determined only in a small number of SHL patients, a wide spectrum of etiologic factors and diseases were blamed. Among these, infectious cause being in the first place, vascular causes, endothelial dysfunctions, hyperlipidemia, hypercoagulopathy, increased oxidative stress, autoimmunity, trauma, neurological disorders, endocrinopathies, iron deficiency anemia, neoplastic causes, paraneoplastic causes, and toxic causes are the most important factors. The most blamed causes in the SHL etiology are shown in **Table 1**. But it should be emphasized that none of these factors has been confirmed as a cause of SHL and idiosyncrasy is still the most common category in SHL (**Table 1**).

Vascular Causes	**Trauma**
Hypercoagulopathy	Perilymph fistula
Vertebrobasilar Insufficiency	Round window rupture
Thrombo-embolism	Rupture of the oval window
Sickle Cell Anemia	Intralabyrinthine hemorrhage
Moyamoya disease	Temporal bone fractures
Polycythemia vera	Previous otological surgeries

Atherosclerotic disorders	Previous cardiopulmonary surgeries
Arteriovenous malformations	Acoustic trauma
Aneurysm	
Erythrocyte Deformities	**Neoplastic Causes**
Infection	Acoustic Schwannoma
Viral Causes	Multiple Myeloma
Herpes viridea family (HSV Type 1, 2; VZV, CMV, EBV)	Metastatic tumors
Mumps	Meningeal carcinomatosis
Rubella	
Rubeola	
HIV	**Endocrine Causes**
Influenza family	Hypothyroidism
Enteroviridea family	Iron deficiency anemia
Adenovirus	Diabetes mellitus
Human Spumaretrovirus	**Toxic Causes**
Bacteria-Parasite	Aminoglycosides
Treponema pallidum	Gold
Borrelia burgdorferi	Quinine
Toxoplasma gondii	Iron-containing drugs
Mycoplasma spp.	ACE inhibitors
Cryptococcus spp.	Loop Diuretics
Meningococci	Cisplatin
Enterobacteriae	Aspirin
Autoimmune Causes	Chemotherapeutic agents
Autoimmune inner ear disease	Phosphodiesterase Type-5 inhibitors
Crohn's Disease	Heroin
Ulcerative Colitis	Narcotic analgesics
SLE	Benzodiazepines
Small vessel vasculitis	**Neurological Causes**
Cogan syndrome	Multiple Sclerosis
Antiphospholipid Antibody Syndrome	**Psychiatric Causes**
Sarcoidosis	Histrionic (somatoform) deafness
Endolymphatic hydrops	**İdiosyncrasy** (most common cause)

Table 1. Etiology of sudden hearing loss.

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6. Medical history and physical examination

Medical history is typical in SHL. Patients usually notice in the morning, during a telephone conversation, after exiting a noisy environment that their hearing sense is suddenly disappeared and generally they visit panicked the nearest physician with a fear of being deaf. In sudden hearing loss, as patients consult immediately a physician, early diagnosis and treatment are possible. During the physical examination, as no SHL-specific finding can be detected during the bilateral otomicroscopic examination, otoscopic examination is usually normal. In some cases, there can be an obstructive ear plug, which may be removed with difficulty. At the same time, in patients with otological disorders like chronic otitis media and tympanic membrane retraction, previous audiometry reports might be needed for the diagnosis and especially in patients with presbyacusis and missing audiometry reports, diagnosing is relatively difficult. In such cases, we have to depend only on the anamnesis. In the anamnesis, the important points are the presence of tinnitus and ringing, the presence of concomitant vertigo, and presence of a similar event in the past. Questioning of these aspects will provide useful information regarding the differential diagnosis. The patients should also be evaluated for the known chronic diseases and used medication. Especially autoimmune disorders, coagulation disorders, cardiovascular diseases, previous infectious diseases, and trauma should be questioned. Following the physical examination, hearing examination (Weber, Rinne) should be carried out in order to evaluate the type and severity of the hearing loss. Afterwards, the diagnosis should be confirmed with pure-tone audiometry.

7. Diagnosis

7.1. Audiology

The audiological examination is the most important process regarding the diagnosis. Pure-tone audiometry may enable a definitive diagnosis and also provide information about the severity of the hearing loss and the type of the audiological curve with additional data related to both differential diagnosis and prognosis. In addition to the pure-tone audiometry, tympanometric examination, acoustic reflex, speech audiometry may support the diagnosis. Such additional tests are not always needed. They are only recommended if there is a clinical necessity. In patients who cannot comply with the audiometry process ABR might be useful for the diagnosis. A definitive diagnosis of SHL can be made, if a hearing loss of 30 dB or greater is observed in three contiguous frequencies.

7.2. Laboratory analysis

As several different causes were suggested in respect of SHL etiology, the necessity of routine laboratory examination is still disputable regarding the diagnosis. The general consensus is that laboratory examination should be carried out only for the suspected etiological factors. If a viral involvement is suspected, viral antigen titration; if an autoimmune mechanism is

suspected, levels of the relevant auto-antibodies; thyroid function tests, homocysteine, PT, APTT, INR or markers like specific factor levels, Elisa for HIV, HCV viruses, fasting blood sugar level, HbA1C, lipid profile, VDRL, RPR for syphilis, Lyme titration, serum iron levels can be checked. The control of all these parameters in each patient is not reasonable and also not always possible so that it is much more appropriate to make these analyses only in suspected etiological cases.

7.3. Radiology

In SHL, unlike the laboratory examinations, a radiological examination should be definitely performed considering the differential diagnosis. Approximately in 1% of patients diagnosed with SHL, a tumor was identified in the cerebellopontine angle. Therefore, a contrast-enhanced, thin-sectioned temporal MRI must be carried out regarding the differential diagnosis and to determine the etiological factor. In MRI examination, we may observe a space-occupying mass lesion and also in SHL cases with vascular pattern, we may also observe hyperintensity in the pre-contrast examinations depending on the methemoglobin accumulated in the inner ear. In the presence of inflammation, hyperintensity might be observed in the 3D-flair sequence depending on the accumulation of the proteinous materials in the dense exudation [63]. Regarding the literature, the rate of the patients with MRI findings related to SHL was between 27 and 53% [64, 65]. In addition, MRI may also enable the identification of AICA aneurysms and vertebrobasilar system anomalies.

8. Treatment

As the etiological factor is mostly not identifiable in SHL, its treatment is arranged in certain protocols. Several therapeutic modalities clinically different but similar in respect of main aspects have been developed. Systemic corticosteroids are beyond dispute the main therapeutic agents and they are also considered as the golden standard in the literature. Moreover, multiple medical agents can be used in the treatment. In patients, who did not respond or partially respond to the primary treatment, salvage treatment should be implemented. Although these treatments may change according to the patient and physician's algorithm, it should be initiated with the primary treatment. In SHL cases with identified etiology, treatment should be targeted to the underlying disorder. Hereinafter, the treatment protocols especially for the idiopathic SHL will be discussed.

8.1. Medical treatment

8.1.1. Systemic corticosteroids

They are currently the main therapeutic agents (**Figure 1B**). They should be included in the treatment protocols of SHL cases with unknown etiology. Although the mechanism of action of the corticosteroids considering the SHL pathogenesis is not fully elucidated, it is believed that they decrease the inflammation in the inner ear and accelerate the regeneration. An early initiation

of the systemic corticosteroid therapy enables a relatively better respond to the treatment [66]. Wilson [66], in his randomized double-blind placebo-controlled study, showed clearly the positive effect of the corticosteroids on the SHL. The following numerous studies confirmed these findings. Although there are few studies in the literature reporting that corticosteroids are ineffective, we observed in our clinical practice, that they are highly effective and included them in our routine treatment protocol. Systemic corticosteroid therapy is a short-term treatment, which is initiated with a dose of 1 mg/kg and continued with a gradual dose reduction. This treatment with gradually declining dosage enables that the suppressed adrenal glands have enough time to produce steroids again. The SHL treatment guideline, which was published by the American Otolaryngology Academia in 2012, indicated the corticosteroids as the first-line therapy. It was stated that a dose of 1 mg/kg for approx. 10–14 days is sufficient for the treatment of SHL [67]. Systemic corticosteroids have diverse side effects. The most common side effects are acne, blurred vision, cataract or glaucoma, sleeping problems, hypertension, increased appetite, hypertrichosis, insomnia, immunosuppression, muscle weakness, irritability, uneasiness, osteoporosis, increase of insulin need in diabetic patients, diffuse edema due to the water and salt retention in kidneys, aseptic necrosis in the femur head. Steroids should be used carefully particularly in patients with comorbidity and in the pregnant and the risk-benefit of the therapy should be thoroughly evaluated. If in these patients corticosteroid use is risky, intratympanic corticosteroid injection should be considered in the primary treatment [68, 69].

8.1.2. Antiviral agents

Antiviral agents were added to the treatment protocols in many clinics in respect of the findings related to the role of viruses in the etiology of SHL. Even though the responsible virus mostly cannot be isolated, they are used in combination with corticosteroids. Stookross created labyrinthitis with HSV-1 antigens in an experimental animal study and applied corticosteroids as monotherapy or in combination with acyclovir. He observed that the viral replication was suppressed in the 14th day of the treatment and discontinued the application. He concluded that acyclovir and corticosteroid combination provided better recovery compared to the corticosteroid monotherapy [70]. Park [71] conducted a study with 85 patients and administered a combination of steroid + antiviral + anticoagulant + stellar ganglion blockage to one group and corticosteroid monotherapy to another group. He observed better recovery in the combination group. In contrary, Westerlaken [72] conducted a placebo-controlled randomized study with 91 patients and administered acyclovir + corticosteroid combination in one group and corticosteroid alone in the other group. He concluded that antiviral agents did not provide additional benefit. Similarly, Tucci [73] concluded in his study conducted with 105 patients that the addition of valacyclovir to the corticosteroid therapy did not provide additional benefit and that antiviral treatment is ineffective in SHL. Antiviral agents like valacyclovir and famciclovir might be used instead acyclovir.

8.1.3. Vasodilators and plasma expanders

The goal of this treatment is to increase the blood perfusion in the inner ear and the oxygenation. In order to obtain this, either the arteries in the inner ear should be dilated or the viscosity

of the blood should be decreased in order to increase its fluidity. Papaverine, histamine, and carbogen (mixture of 5% CO_2 and 95% O_2) were used for this purpose in the literature. In particular, agents such as histamine and papaverine have found effective as they reduced systemic vascular pressure [74]. Compared to these agents, carbogen treatment is more effective and provides a safer treatment option, which means that the oxygenation of the perilymph changes depending on the blood concentration of O_2 and CO_2 and systemic vascular resistance. Especially, the partial CO_2 level in the peripheral blood is an important stimulator of the perilymphatic oxygenation. Kallinen demonstrated that carbogen treatment increased the perilymphatic oxygenation more than 100% O_2 [75]. There are plenty of studies conducted with piracetam, prostaglandin E1, dextran (plasma expander) and various rheological agents. These agents are not used alone in the idiopathic SHL but added to the systemic corticosteroid therapy protocol as adjuvant agents [76].

8.1.4. Diuretics

If endolymphatic hydrops is responsible for SHL, diuretics may be used in the treatment. Besides this, they are not included in the standard treatment protocols.

8.1.5. Magnesium

Nageris [77] showed that corticosteroid and magnesium combination is more effective in SHL compared to the corticosteroid and placebo combination. Similarly, Gordin [78] determined also that magnesium treatment had positive effects on the recovery in SHL via antioxidant effects and recommended the addition of magnesium to the treatment regimes as an antioxidant.

8.1.6. Low-density lipoprotein apheresis

Low-density lipoproteins may cause the development of SHL, if their elevated concentrations increase the plasma viscosity. In a study with a large sample size, it was reported that the treatment with low-density lipoprotein apheresis and fibrinogen increased the recovery rate in SHL although the result was not statistically significant [79].

8.1.7. Ozone therapy

Ragab [92] conducted a study with 45 patients and reinjected the 100 ml blood, which he had taken from the patients and exposed to a 1:1 gas mixture of oxygen and ozone. After the implementation of this treatment protocol for a total of 10 sessions twice a week, he compared the ozone group with the placebo group. He concluded that a significant recovery was observed in the ozone group.

8.2. Salvage therapies

If known treatment protocols provided no or limited response in SHL patients, salvage treatments should be considered. The efficacy of the salvage treatments, which became popular

in the recent years, was shown in different studies with control groups. Hyperbaric O_2 and intratympanic steroid treatment can be mentioned among these treatment principles.

8.2.1. Intratympanic steroid therapy (ITS)

We already mentioned that corticosteroids had a well-established efficacy in the treatment of SHL. In patients, in whom corticosteroids have limited use or efficacy, they may be administered intratympanically with different methods. Thus corticosteroids penetrate through the middle ear membranes to the inner ear and achieve high concentrations, which consequently increased the recovery rate [80]. ITS is a treatment method, which has an ongoing increase in popularity, minimizes the side effects of corticosteroids and enables achievement of therapeutic steroid concentrations with low doses. ITS is not only effective as a salvage therapy, but it also enables good results if it is combined with systemic corticosteroids during the primary treatment or administered as the primary treatment agent in patients, who cannot tolerate systemic steroids [81–84].

8.2.2. Hyperbaric oxygen therapy

Hyperbaric O_2 therapy (HBO) is another salvage therapy method and investigated with a large number of studies. The basic principle is to increase the partial O_2 pressure, which is decreased in the perilymph and cochlea in patients with SHL. Experimental studies have demonstrated that HBO increased the partial O_2 pressure in the inner ear [85]. The increased partial O_2 pressure in the inner ear supplies the needed O_2 even if the blood flow is decreased and stimulates the cells. It decreases the platelet aggregation and increases the flexibility of the erythrocytes which positively affects the nutrition of the inner ear. Several recent studies demonstrated that the combined use of HBO therapy and corticosteroids or the use of HBO as a salvage therapy had positive effects on SHL [86–91]. The basic principle of the HBO therapy is to apply 100% O_2 with a 2–3 atm pressure in repeated doses and to increase the O_2 pressure in the inner ear with a controlled process. During the application of this procedure, the possible damage of the free O_2 radicals should be taken into consideration.

8.3. Surgical treatment

Surgical treatment can only be carried out in a subgroup of patients with a known etiology. Cases with membrane ruptures, intracochlear membrane ruptures, endolymphatic hydrops, and acoustic neuroma can be treated with surgical interventions.

9. Prognosis

As SHL has a multifactorial etiology, the prognosis is variable. Considering all SHL cases, spontaneous regression rate is over 60%. In addition, some factors, which have positive or negative effects on the prognosis, have been described. Even though these factors do not change the treatment, they provide useful information about the course of the disease.

The most important criterion is the time between the emergence of the symptoms and the initiation of the treatment. The prognosis is much better in patients started treatment early. Another factor is the age of the patient. An age less than 15 or greater than 65 years indicates a bad prognosis. The prognosis worsens with the severity of the hearing loss. Although the prognosis is relatively better in the low-frequency hearing loss compared to the high-frequency hearing loss, an ascendant type audiometric curve promises a better prognosis than the descendant type audiometric curve. The presence of vertigo and nystagmus, which shows that vestibular system is also affected, is a sign of bad prognosis. In contrary, tinnitus indicates a good prognosis in SHL, because tinnitus is considered as a sign that the hair cells in the inner ear are not completely destroyed. Bilateral SHL has a relatively worse prognosis. Increased sedimentation rate and an increase in the high sensitive CRP levels are related to the severity of the inflammation and thus to the bad prognosis. In SHL, recovery can be observed within 6 months to 1 year, it is wise to arrange the pre-rehabilitation follow-up plan according to this duration. In SHL patients, who did not show any recovery after 1 year, hearing rehabilitation can be planned upon the patient's request and according to the severity of the hearing loss.

10. Conclusion

As we have seen, SHL preserves its darkness as an enigma of ENT world. There are several already-published and a large number of ongoing studies on the etiology and treatment of SHL in the literature. Although certain diagnosis and treatment algorithms developed for SHL are already available, they cannot be implemented in all SHL cases. If corticosteroids cannot deliver sufficient results, there are not much treatment choices. Further studies for a full elucidation of the physiopathology, etiology, and treatment of SHL are required.

Abbreviations

SHL	Sudden hearing loss
ENT	Ear-nose-throat
CMV	Cytomegalovirus
CTL-2	Choline transporters like protein 2
AECA	Anti-endothelial antibodies
Hsp-70	Heat-shock protein 70
SLE	Systemic lupus erythematosus
ITS	Intratympanic steroid therapy
HBO	Hyperbaric O_2 therapy

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Section 2

Early Diagnosis and Prevention of Hearing Loss

Chapter 6

Hearing Loss at High Frequencies and Oxidative Stress: A New Paradigm for Different Etiologies

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Abstract

The clinical assessment of hearing loss has been transformed and revised in terms of interpreting the characteristics of patterns found in relation to the relative frequency of certain diseases. However, increasing the threshold to 4 kHz as a starting point for hearing loss has shown to be common to different diseases such as noise-induced hearing loss. In noise-induced hearing loss, for example, six mechanisms can be considered: conversion of sound pressure level into hearing level, vascular failure in the cochlear region responsible for hearing at 4 kHz, sound wave propagation velocity is very high and causes the displacement amplitude in the cochlear duct, the structure anatomy of the cochlea causes a collision of fluids in the first curve of the cochlea, characteristics of auricular pavilion resonance and external auditory canal, and sound attenuation of the acoustic reflex. It is hoped that this new paradigm for the different hearing losses will result in a different approach to the physiological changes that affect the auditory system in the form of high-frequency hearing loss. As such, preventing, treating, and avoiding exacerbations are possibilities to be investigated in order to guarantee efficient communication and quality of life for individuals.

Keywords: hearing loss, noise-induced hearing loss, oxidative stress, presbycusis, chronic kidney disease

1. Introduction

Hearing is one of the primary means of human contact with the world, from the perception of acoustic signals that indicate danger through an alert system to the development of language and intellect. In the evolutionary process, the human auditory system underwent transformations that enabled it to capture, amplify (magnify), perceive, and discriminate sound, the last two achieved from the inner ear (cochlea) to the auditory cortex.

Human hearing perceives sounds ranging from 20 Hz to 16 kHz, and exhibits tonotopy from the cochlea to the auditory cortex, such that hearing frequencies are recognized in an organized manner along the auditory pathway. Under certain conditions that lead to hearing loss, initial and selective damage may occur at certain sound frequencies. This pattern of selective damage can be observed in a number of pathological conditions whose physiopathological foundation may be based on an oxidative stress model. Among these conditions are noise-induced hearing loss (NIHL), age-related hearing loss (presbycusis), ototoxic hearing loss, and hearing loss associated with chronic kidney disease (CKD).

2. Oxidative stress

Free radicals are species (molecules, ions) that contain free electrons (unpaired) in their structure and, as such, are usually highly reactive with other molecules [1]. Due to this reactivity, radicals can damage membranes and other cellular structures under oxidative stress conditions.

Oxidation reactions cause the formation of a variety of unstable reactive species that can trigger chain reactions in milliseconds, leading to disease and programmed cell death (apoptosis) [2]. Among the reactive species formed are reactive oxygen species (ROS), which participate in several physiological and pathological processes in the organism.

With the evolution of the cell and the use of molecular oxygen in energy metabolism, ROS began to play increasingly studied and significant roles in a number of diseases [3]. The main ROS are the superoxide anion radical (O_2^-), hydrogen peroxide (H_2O_2), and the hydroxyl radical (OH), the last being the most reactive and harmful [1].

Given that free radical production occurs naturally in the organism, an elaborate endogenous antioxidant system evolved to control the harmful effect of reactive species. This system includes antioxidant scavenger enzymes such as superoxide-dismutase (SOD) 1 and 2, catalase, glutathione (GSH), and related enzymes, including glutathione peroxidase (GPx), glutathione S-transferase (GST), and glutathione reductase (GSH-Red), which converts ROS into neutral, non-reactive molecules.

Thus, hearing losses with different etiologies have been studied at the cellular and molecular level, and there is a convergent tendency with respect to the association between them and oxidative stress.

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3. Hearing losses

Over the centuries, man has advanced in a number of ways, but this progress has also introduced lifestyle habits that sometimes cause new risk factors for hearing loss.

Exposure to high levels of sound pressure (noise), both professionally and at leisure, can cause irreversible hearing loss, which is often progressive when an individual remains in contact with a daily sound source [4, 5].

Increased life expectancy means age-related hearing loss (presbycusis) has become more common and is one of the most prevalent chronic diseases worldwide.

The emergence of new drugs has led to the cure of numerous hitherto lethal diseases; however, the ototoxic effect of certain medications causes hearing loss and leaves sequelae in children and adults alike [6, 7].

Chronic kidney disease (CKD), which has multiple etiologies, can evolve with progressive hearing loss, representing yet another disability for kidney patients and compromising their quality of life. Moreover, the use of certain drugs for patients with CKD may worsen auditory function and be an aggravating factor for hearing loss [8].

These hearing disorders exhibit a sensorineural pattern due to the sites affected, which vary from the cochlea to the auditory cortical regions, with a preference for high sound frequencies. However, high-frequency damage is a starting point, and 4 kHz is seen as the border between frequencies that often remain preserved and those affected.

Assessment of the physiopathological model of these hearing losses shows that oxidative stress occurs under all the aforementioned conditions and emerges as a new paradigm that more deeply connects characteristic acoustic aspects common to all of them. The real reason for which hearing loss arises, preferentially and usually around 4 kHz, is not fully understood, but there may be a common point in molecular and physiopathological terms that leads to this spectral selectivity.

Starting with a model that considers oxidative stress, we will discuss each of the hearing loss conditions influenced by excess free radicals and expressed by an increase in high-frequency hearing thresholds.

3.1. Noise-induced hearing loss

Excessive exposure to noise induces sensorineural hearing loss resulting from damage to cochlear and neural structures in the inner ear, denominated NIHL. NIHL can be temporally classified into two types: hearing loss induced by chronic noise and acute acoustic trauma. Chronic NIHL is a hearing deficiency caused by continuous exposure to high levels of sound pressure that exert an average of 90 dBA, for eight hours a day, over several years or more [4], whereas acute acoustic trauma is hearing loss caused by short exposure to excessively loud sounds (100–150 dBA, decibel weighting curve A) [9].

Exposure to different sound levels leads to metabolic and mechanical damage. Metabolic damage could occur after exposure to noise between 85 and 115 dBA, whereas mechanical damage can emerge after exposure to sound levels above 115 dBA. Noise-induced hearing loss is due primarily to neural degeneration, which starts immediately after exposure to noise and progresses for several years after exposure [10].

Susceptibility to the harmful effects of noise differs significantly among individuals, that is, after identical exposure to noise, not all people suffer hearing loss, and when they do, the degree can vary. Thus, NIHL was classified as a disease resulting from external (environmental) causes, in addition to genetic predisposition [11].

Ciliated cells, particularly the more vulnerable external variety, are compromised in NIHL. There are around 12,000 external ciliated cells arranged in three rows in the basal region of the cochlea and in four or five rows in the apical region [12]. Thus, there are fewer ciliated cells at the cochlear base than the apex. With a sharp loss of ciliated cells, secondary neural degeneration is reflected in the auditory nerve and brainstem auditory nuclei [13].

The cochlea is a metabolically active organ and oxidative stress plays an important role in the pathogenic mechanisms of NIHL. The mitochondria generate energy to maintain cochlear metabolism; however, they are also the primary ROS generator. The fact that ciliated cells are highly energy-demanding during and after exposure to noise leads to a prolonged local release of free radicals, which may damage the cochlear epithelium, particularly if the antioxidant defense system is not efficient enough to neutralize them [11]. However, due to this exposure to ROS, as well as harmful environmental influences (noise), mitochondrial DNA (mtDNA) run the risk of maintaining mutations that may hinder the function of different organelles and lead to chronic diseases such as NIHL [14, 15].

Organ of Corti lesions occur primarily at the basal turn (Rosenthal's canal), in the area responsible for sounds between 3 and 6 kHz, regardless of the frequency range of aggressor noise, caused by six possible mechanisms [5]:

1. Conversion of dBA for sound intensity under the international guidelines to protect the auditory system into dBHL for hearing level;
2. Vascular failure in the cochlear region responsible for hearing at 4 kHz;
3. Sound wave propagation velocity is very high and causes the displacement amplitude in the cochlear duct to begin to grow in the 4 kHz region;
4. The structure anatomy of the cochlea causes a collision of fluids in the first curve of the cochlea;
5. Characteristics of auricular pavilion resonance and external auditory canal cause injury in the 4 kHz region.
6. Sound attenuation of the acoustic reflex occurs only for low frequencies.

The first mechanism raises the most speculation due to the dynamics of noise that exhibits the same intensity in dBA (decibel weighting curve A). This occurs because sound measures in dBA are the result of a weighted average of the amplitudes of each frequency that makes up

the sound measured [16, 17]. **Table 1** illustrates an example of the necessary correction in dB in order to calculate sound intensity in dBA.

Table 1 shows that for a pure tone of 500 Hz to emit 100 dBA, it must exhibit 108.6 dB SPL. If the frequency were 4 kHz, sound should produce 101 dB SPL. As can be observed, for a complex sound to emit 100 dBA, different possible combinations of amplitudes by frequency exist.

The guidelines that protect workers in most of the countries that have such legislation include dB and weighting curve A as intensity measures. However, auditory assessments are conducted at dB hearing levels and depend on the specific earphones used in the assessment in order to match the dB hearing level and dB SPL. **Table 2** contains the reference values corresponding to 0 dBHL, by frequency, using Telephonics TDH-39 earphones, the most commonly found in audiometers.

Thus, for a person to have the sensation of hearing 0 dBHL, the sound must emit 7 dB SPL, if its frequency is 1 kHz. As such, for them to hear at 30 dBHL, at this frequency, the sound must produce 37 dB SPL [18].

Finally, **Figure 1** exhibits the correspondence curves, by frequency, for a sound in dBA, listened to through TDH-39 earphones and the matching result from one unit to another.

Figure 1 shows that the weighting differences and adjustments to dBHL result in greater weight for sound frequencies between 0.5 and 4 kHz. Thus, a sound that has different frequencies could exhibit higher physical intensities in the dB SPL band particularly, and more energy

Frequency (Hz)	dB SPL correction for dBA
250	−8.6
500	−3.2
1000	0
2000	1.2
4000	1
8000	−1.1

Table 1. dB correction to calculate intensity in dBA, by frequency.

Frequency (Hz)	Reference (dB SPL)
250	25.5
500	11.5
1000	7
2000	9
4000	9.5
8000	13

Table 2. Reference levels (dB SPL) for an intensity of 0 dBNA, by frequency.

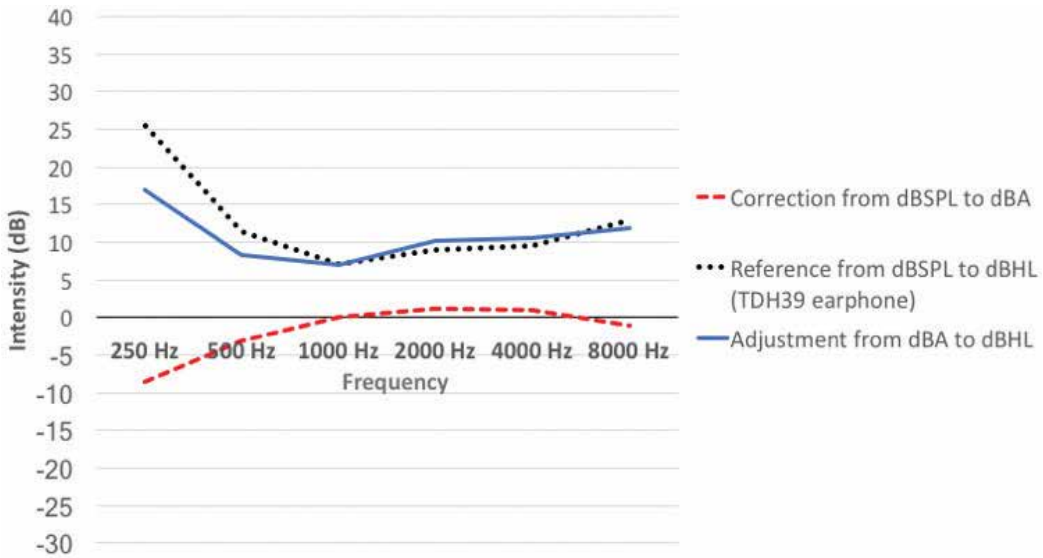

Figure 1. Adjustment from dBA to dBHL (TDH39 earphone).

could cause greater damage. However, it is necessary to know the other mechanisms in order to have a clearer understanding of the implications in the present topic.

The second, third, and fourth mechanisms described earlier explain why a frequency of 4 kHz is the first and most affected in terms of the degree of hearing loss [4, 5]. Furthermore, ciliated cells from the basal turn, the area responsible for high frequencies, are more susceptible to oxidative stress than those from the cochlear apex [19].

Even at a low oxidative stress levels, external ciliated cells from the basal turn are more vulnerable to damage, while internal and external ciliated cells from the middle and apical turns are more preserved [20]. The difference in antioxidant levels in basal turn to apical turn cells explains this greater susceptibility to lesions caused by ciliated cells from the base of the cochlea [19]. At the enzyme level, exposure to noise increases oxidase NADPHA (NOX) levels in the cochlea and a decline in SOD increases susceptibility to acoustic lesions. The accumulation of ROS subsequently triggers a complex cascade of biochemical processes including activation of c-Jun N-terminal kinase (JNK) and p38MAPK, the release of cytochrome and mitochondria and proca spase activation [3, 8, 9] (intrinsic apoptotic pathway) [21, 22].

Furthermore, the physiological mechanisms of resonance in the auditory system, primarily the concha and external auditory canal, are highly relevant in the audiometric configuration process of noise-induced hearing loss, especially at strong intensities [10]. The physiology of hearing studies the resonance in tubes in order to understand sound reception.

Resonance is closely related to the formation of stationary waves, which originate from a combination of two physical phenomena: reflection and interference [23] Resonance in the external auditory canal, calculated by the expression Vsound/4L (L = length of the canal), is around 3800 Hz, which can vary with temperature and be slightly higher or lower, due to the mobility of the tympanic membrane and the anatomic differences between subjects. As such, it

can be concluded that, of the different sound frequencies that reach the ears, those around 3800 Hz are extraordinarily amplified. Since 3.8 kHz is not assessed in audiometry, these reflexes can be found at 4 and 3 kHz. **Figure 2** presents the results of pavilion (concha), external auditory canal (outer ear), and middle ear resonance studies, as well as attenuation caused by the stapedius reflex, which only has an effect at low frequencies [24–26]. **Figure 3** shows the gains resulting from the three physiological mechanisms.

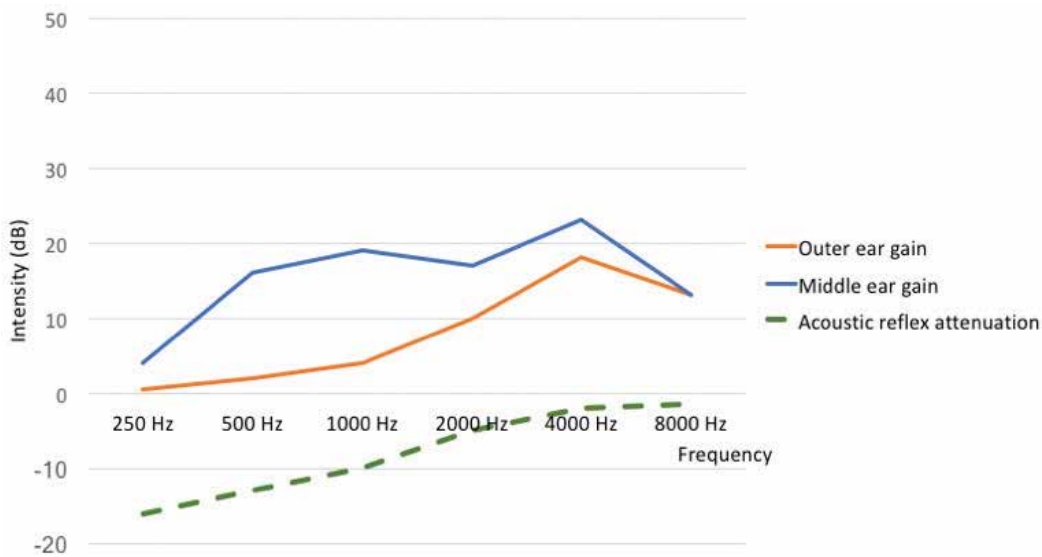

Figure 2. Outer/middle ear gain and acoustic reflex attenuation.

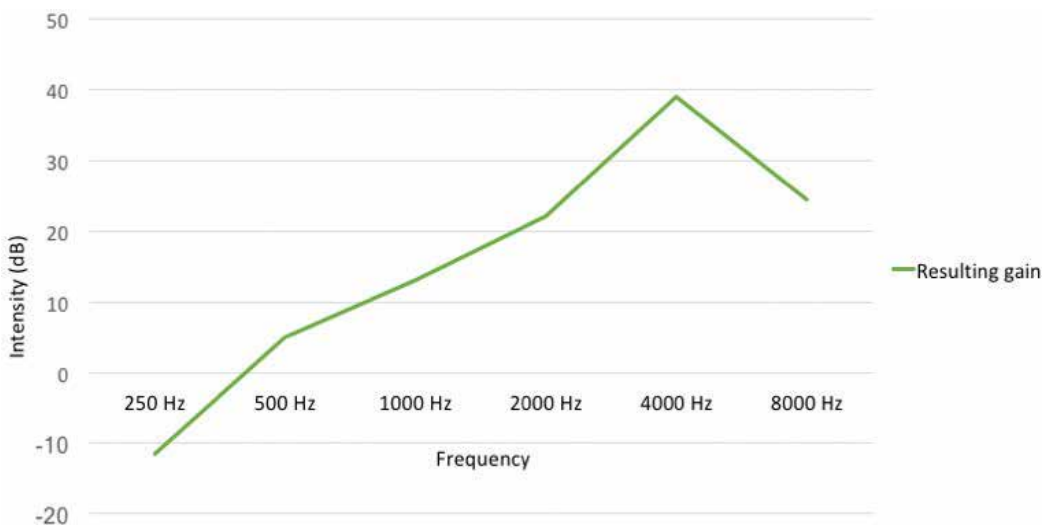

Figure 3. Resulting gain caused by the three physiological mechanisms.

Finally, relating the final physiological gain and the differences in adjustment between dBA and dBHL, despite knowing that there may be overlapping effects, and attempting to minimize errors and approach reality, **Figure 4**, which exhibits the result of the three physiological mechanisms, the dBA to dBHL adjustment, and the final result (orange line).

Finally, a sound input of 100 dBA illustrates how sound interacts with the auditory system and the spectrum resulting from this interaction (green line), as shown in **Figure 5**.

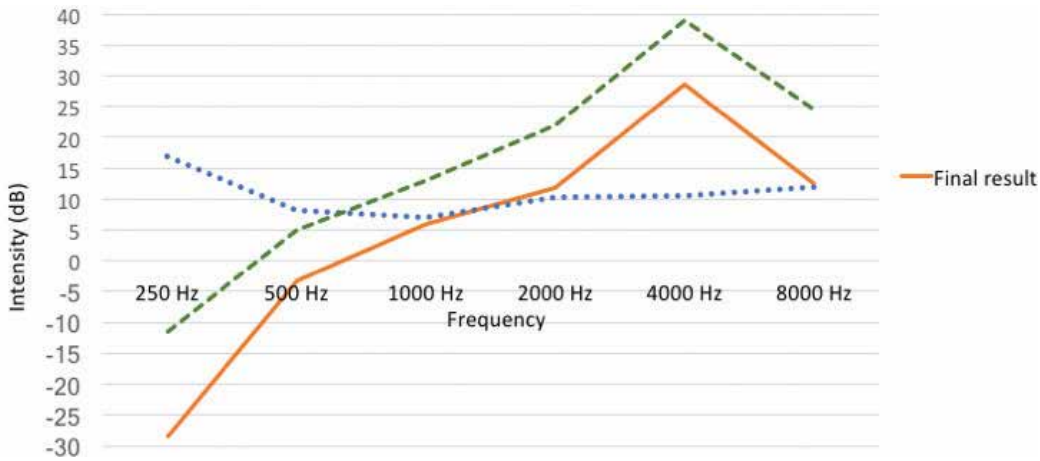

Figure 4. Final outcome, adjustment from dBA to dBHL, and physiological mechanisms.

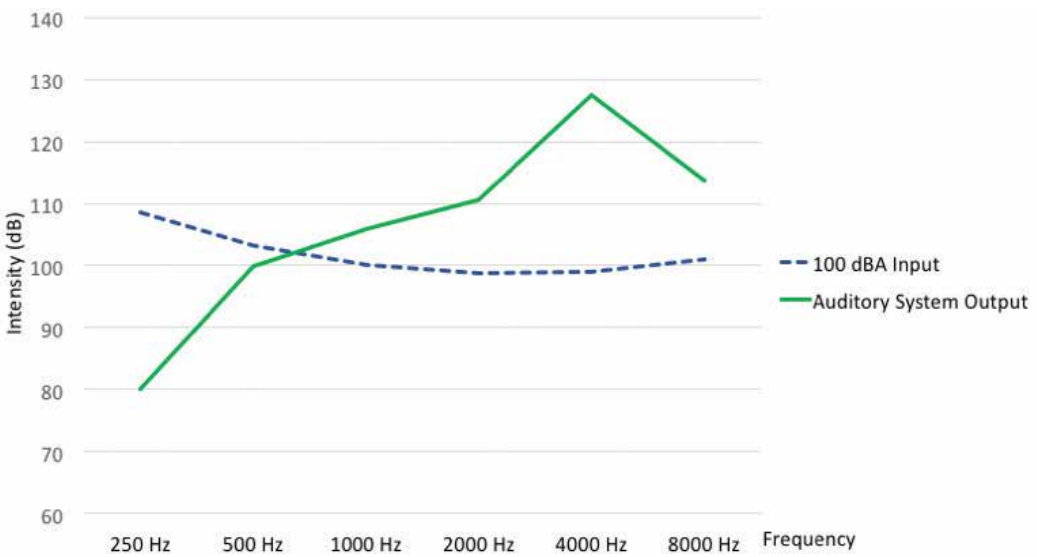

Figure 5. Final outcome: example of a 100 dBA input stimulus.

An input sound level of 100 dBA, resulting from weighting of 108.6, 103.2, 100, 98.8, 98, and 101.1 dB for 250, 500, 1, 2, 4, and 8 kHz, respectively, has an output of 80.2, 99.9, 106, 110.6, 127.5, and 113.7 dB, respectively. In other words, 4 kHz receives around 30 dB more than the original input, while at a frequency of 250 Hz, the intensity is approximately 28 dB lower.

Thus, considering the six aforementioned mechanisms, in addition to the lower number of external ciliated cells at the base of the cochlea and their increased susceptibility to oxidative stress, the audiometric profile of NIHL is defined as being at high frequencies, with the greatest effect at 4 kHz.

3.2. Presbycusis

Presbycusis is a highly complex multifactorial process involving hearing loss at high frequencies concomitantly with physical signs of aging [27].

It is the most common sensory disorder in the elderly, occurring in 25–40% of individuals aged 65 years or older and the prevalence tends to increase with age, ranging from 40 to 66% of people over 75 years old and more than 80% in those over the age of 85. The number of people with this disorder is expected to grow substantially due to the increase in life expectancy [28, 29].

Individuals with presbycusis exhibit reduced sensitivity and hearing comprehension in noisy environments, slow central processing of acoustic information and compromised sound source localization. As such, the limitations that emerge are proportional to the degree of auditory deficiency, affecting dialogue, musical appreciation, identification of warning signs, and, finally, participation in social activities [28] (**Table 3**).

The pathogenesis of presbycusis is not well understood. There is an association with extrinsic (noise, exposure to environmental ototoxic agents, traumatism, vascular injury, and diet), and intrinsic risk factors (metabolic changes, genetic factors, and physiological aging process) [31]. Furthermore, other changes have been proposed, such as altered vascular characteristics, a decrease in oxygen and nutrient supply and residue elimination, genetic mutations, and a significant increase in ROS production [28].

As stated earlier, mitochondria play a crucial role in maintaining cochlear energy homeostasis. Over the course of aging, a number of changes occur in the mitochondria and mitochondrial DNA (mtDNA), including (1) an increase in mitochondrial structural disorganization, (2)

Sensory	Atrophy occurs with loss of ciliated cells and supporting cells of the organ of Corti, starting in the basal turn of the cochlea and progressing slowly toward the apex
Neural	Neuronal atrophy occurs in the cochlea and central neural pathways. It is estimated that 2100 neurons are lost each decade
Metabolic/ strial	Atrophy occurs in the stria vascularis, which normally maintains chemical, bioelectrical and metabolic equilibrium of the cochlea
Mechanical	Thickening of the basilar membrane occurs, more severely in the basal turn of the cochlea, where the basilar membrane is narrow

Table 3. Histologically, there are four types of presbycusis [23].

decline in their oxidative phosphorylation, (3) accumulation of mutations in the mtDNA, (4) rise in mitochondrial ROS production, and (5) increase in oxidative DNA, protein, and lipid damage [14].

Thus, the cellular environment in oxidative stress due to noise exposure is one of the main determinants of NIHL, since there may be multiple conditions causing this stress, all contributing to presbycusis in a same individual. The sensory and metabolic forms display a history of exposure to noise and the degree of impairment is greater at high frequencies [32]. In addition, the two forms exhibit an intrinsic cause and effect relationship with oxidative stress, while the mechanical and neural forms display different physiopathological mechanisms but are not exempt from the influence of excessive free radicals.

3.3. Ototoxic hearing loss

Ototoxic hearing loss is caused by the cochleotoxic effect of certain substances widely used in clinical practice. However, other substances present in professional activities also have harmful effects on the cochlea [33]. In addition to the cochleotoxic capacity of the drug, hearing loss is determined by other factors, including exposure to noise, genetic predisposition, malnutrition, advanced age, overall poor health, hypoacusis, and ringing in the ears [33, 34]. Genetic predisposition involves mitochondrial inheritance and oxidative stress [33] (**Table 4**).

The following drugs exhibit a cochleotoxic effect [33, 35–37].

Once inside the cell, aminoglycosides induce ROS production. They are considered "redox-inactive compounds" and, as such, need to be converted into the redox-active form to induce ROS formation. ROS generation involves the formation of an aminoglycoside-iron complex that catalyzes the oxidation of unsaturated fatty acids located in the internal layer of the plasma membrane [27].

The increase in ROS may be due to the depletion of thiol and antioxidant enzyme-reducing buffers and/or direct activation of ROS-producing systems. Cisplatin administration leads to reduced glutathione concentration in the cochlea and a significant decline in SOD activities, catalase, cochlear glutathione peroxidase, and glutathione reductase [27].

Aminoglycosides	Dihydrostreptomycin, neomycin, amikacin, and kanamycins A and B
Beta blocker	Propranolol
Diuretics	Etacrynic acid and furosemide cause reversible hearing loss and can exacerbate hearing loss caused by aminoglycosides
Non-steroidal anti-inflammatories	Salicylates and acetylsalicylic acid. Hearing loss is normally reversible
Cisplatin	Used in chemotherapy against cancer in both children and adults. In children, it can lead to delayed language development

Table 4. The following drugs exhibit a cochleotoxic effect [26, 28–30].

Under certain conditions, base disease in itself causes a condition of permanent oxidative stress in patients. Type 1 diabetes, pancreatitis, different metabolic syndromes, cardiovascular diseases, and chronic kidney failure are frequent examples of pathological conditions with permanent oxidative stress in which patients are more susceptible to hearing loss, and can be aggravated by the use of ototoxic drugs [38]. Hearing loss is normally bilateral, symmetrical, and greater at high frequencies.

3.4. Hearing loss associated with chronic kidney disease

Chronic kidney disease (CKD) is a metabolic syndrome caused by the progressive, irreversible and generally slow loss of renal excretory capacity [39]. In 2013, it was estimated that 2.5 million patients were in dialysis worldwide, a number that is expected to reach 6.5 million by 2030 [40].

The prevalence of hearing loss in patients with CKD, even children [41–45], is higher than in the general population [41]. The best-known association between CKD and hearing loss is Alport syndrome, which has a genetic origin [46]. However, in most cases, hearing loss in patients with CKD has no genetic origin but is due to anatomical, physiological, and pathological similarities between the nephron and stria vascularis of the cochlea [47]. Of CKD cases, 35% are caused by systemic hypertension (SHT) and 29% by diabetes mellitus (DM) [48].

Several factors lead to permanent oxidative stress in CKD, such as the base disease (hypertension, diabetes) that caused CKD, namely uremia. This state of oxidative stress can be aggravated in the inner ear when drugs with a potential ototoxic effect are used [38].

The primary lesion site of hearing loss in CKD is the cochlea [49]; however, some studies also report the involvement of retrocochlear pathways and the central nervous system [41, 50]. Hearing loss normally occurs symmetrically at high frequencies [8, 43, 51].

4. Oxidative stress as a new paradigm in hearing loss at high frequencies in different etiologies

The hearing losses under study are examples of pathological conditions in the inner ear that are clinically distinct, and often accumulate over a lifetime. Final expression is determined by molecular mechanisms based on oxidative stress. Assessing the different aspects such as etiology, clinical picture and treatment of these hearing disorders should not be restricted to pre-established immutable models that treat each of them separately without including the intrinsic and extrinsic factors that significantly influence auditory damage.

Prevention possibilities and rehabilitation perspectives for these hearing disorders have been discussed for decades. It is important to prevent NIHL by non-exposure to damaging sound levels, but this is not enough, since factors such as genetic predisposition to hearing loss and the use of ototoxic drugs may exacerbate the final audiological clinical condition. Presbycusis

is the final product of different factors that are harmful to hearing during an individual's lifetime, such that its prevention is hindered by the limits in controlling these factors from childhood onward. Avoiding hearing loss caused by the use of ototoxic drugs is a challenge, since they cannot always be substituted by non-cochleotoxic medication due to the greater efficacy of the former in treating serious diseases, such as cancer. Maintaining good auditory acuity in chronic kidney patients is essential, since hearing loss becomes one more disorder for patients who depend on care and need good communication. Hearing loss related to CKD leads to restricted participation, as well as social and emotional impacts; however, the physiopathology of CKD causes progressive and irreversible cochlear damage.

Some cell factors characterize the basal turn of the cochlea as a risk zone, justifying selective hearing loss at high frequencies in NIHL, presbycusis, ototoxic hearing loss, and CKD. The lower number of ciliated cells and their greater susceptibility in the basal turn make it a risk zone under aggressor conditions (noise, aging, ototoxic, CKD).

Furthermore, the acoustic reflex is efficient in protecting at frequencies below 2 kHz, leaving high frequencies under unfavorable conditions [52]. This reflex is defined as the contraction of middle ear muscles induced by intense acoustic stimulation. The tensor tympani muscle pulls the malleus (hammer) away from the eardrum and the stapedius muscle exerts force behind the stirrup, causing greater stiffness in the system and reducing sound transmission, primarily at low frequencies, that is, below 1 kHz. Thus, changes in middle-ear impedance, due to the aforementioned contractions, have little or no effect on frequencies above 2 kHz [53].

Studying hearing loss using a new model based on oxidative stress leads to new perspectives on how to prevent this disorder. Several factors display important limitations with respect to preventing auditory damage. However, when oxidative stress is present, understanding how it occurs and devising therapies to minimize it is a new prevention strategy that could be applied to workers exposed to intense noise, individuals with a family history of presbycusis, patients using ototoxic drugs and chronic kidney patients. Adjuvant antioxidant therapies represent a new method to help prevent hearing loss. This model serves as a potential alternative to treat the forms of hearing loss under study, and should be assessed more thoroughly for these and other hearing disorders.

5. Conclusions

NIHL, presbycusis, ototoxic hearing loss, and hearing loss associated with CKD may seem disconnected and quite different from one another, but oxidative stress emerges as a paradigm that helps reassess the reasoning behind these losses and better understand the environment of the cochlea when exposed to harmful intrinsic and extrinsic factors.

It is hoped that this new paradigm for the different hearing losses will result in a different approach to the physiological changes that affect the auditory system in the form of high-frequency hearing

loss. As such, preventing, treating, and avoiding exacerbations are possibilities to be investigated in order to guarantee efficient communication and quality of life for individuals.

Conflict of interest

There is no conflict of interest.

List of the technical terms

CKD	chronic kidney disease
dBA	decibel weighting curve A
dBHL	decibel hearing level
DM	diabetes mellitus
GPx	glutathione peroxidase
GSH	glutathione
GSH-Red	glutathione reductase
GST	glutathione S-transferase
JNK	c-Jun N-terminal kinase
Hz	hertz
kHz	kilo hertz
L	length of the ear canal
NIHL	noise-induced hearing loss
NOX	noise increases oxidase
mtDNA	mitochondrial DNA
p38MAPK	the release of cytochrome and mitochondria and procaspase activation
ROS	reactive oxygen species
SHT	systemic hypertension

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Chapter 7

Hearing Screening around the World

Piotr Henryk Skarżyński and Maciej Ludwikowski

Additional information is available at the end of the chapter

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Abstract

Newborn hearing screening programs for congenital disorders and chronic diseases are expanding worldwide, and children are identified at the earliest possible stage. However, the practice is limited or absent in much of the developing world, such as Africa. Recent epidemiological studies show significant increase of hearing impairments in school-age children (around 20 in 100). Hearing disorders disturb the child's perception of sound, as well as the development of speech which in consequence negatively affects the child relations in society. The early detection of hearing impairments in children enables the effective implementation of medical and rehabilitation procedures or preventive treatment. According to the guidelines of the European Scientific Consensus on Hearing, the detection and treatment of hearing disorders in early school-age children are of the highest importance. That idea was one of the priorities during Polish Presidency of the Council of the European Union (the second half of 2011). The Institute team, in collaboration with numerous national centers, has laid the groundwork for screening programs and developed methods, procedures, and devices for carrying them out. In addition, the Institute was the coordinator and producer of many programs. Based on this, two screening models have been created—newborn and school-age children.

Keywords: hearing screening, hearing impairment, school-age children

1. Introduction

Nowadays, audiology and otolaryngology, which are included in preventive medicine, have many possibilities to assist patients with hearing impairment. However, in order to make full use of these opportunities, hearing disorders or damage should be detected in the early stages. Hence, screening programs for early detection of hearing defects are of great importance. In an optimal healthcare system, hearing screening should be conducted not only during the

neonatal or infancy but also in the subsequent years of the child's life. In this way, both congenital and acquired hearing defects can be detected.

Timely intervention is an important component of Early Hearing Detection and Intervention (EHDI) screening program. In Poland, neonatal screening program (NHS) is carried out. The first projects were performed over 25 years ago [1]. The result of the Polish EHDI/NHS program shows that the prevalence of congenital hearing impairment ranges from 2 to 7 per 1000 births [2]. The National Institute on Deafness and Other Communication Disorders (NIDCD) adduces that 6–7/1000 children have permanent hearing loss in addition to the 3/1000 likely to be diagnosed in short period after birth [3]. From the official database of the National Health & Nutrition Evaluation Studies (NHANES) for screened children who are 6–19 years, it is indicated that approximated 3/1000 prevalence of permanent hearing loss in infants can be expected to increase to 9–10/1000 children in the school-age population.

In years 2007–2016, the Institute of Physiology and Pathology of Hearing screened over million pupils from class I to VI primary school in Poland and approximately~ million children around the world [4]. This experience provided an opportunity to screen a significant number of school-age children and also created the international infrastructure for screening which makes it a suitable solution for place even in remote rural areas.

2. Etiology of hearing loss in school-aged children

Moderate-to-profound degrees of hearing loss are targeted in our newborn screening programs; however, lesser degrees of loss are often not identified until school age. The late age of identification of mild hearing loss may contribute to our lack of knowledge about causative factors. That is, in some cases, a delay in identification of hearing loss may limit our ability to interpret etiologic evaluations reliably or may affect parental memory of possible illnesses or injuries that could account for the loss [5].

As discussed by Ross et al. [6], newborn screening programs are designed to identify hearing losses that are of moderate degree or greater. As such, the equipment and protocols used for newborn screening (e.g., otoacoustic emission (OAE)) are dedicated to identify impairment greater than approximately 40 dB HL. Moreover, a lot of factors appear after newborn screening:

1. Genetic—connexin [7], mitochondrial [8]
2. Enlarged vestibular aqueduct (EVA) syndrome [9]
3. Sudden idiopathic [10]
4. Auditory neuropathy/dyssynchrony [11]
5. Noise inducted [12]
6. Viral/bacterial—mumps [13], otitis media with effusion [13]; meningitis, measles, chicken pox, influenza, encephalitis, rubella
7. Head trauma

8. Ototoxic (damaging to the auditory system) drugs

Acquired hearing loss is a hearing loss which appears after birth, at any time in one's life, as a result of a disease, a condition, or an injury. In fact, the most common cause of hearing loss in young children is otitis media. Fluctuating conductive hearing loss nearly always occurs with all types of otitis media [14]. Symptoms, severity, frequency, and length of the condition vary. At one extreme is a single short period of thin, clear, no infected fluid without any pain or fever but with a slight decrease in hearing ability. At the other extreme are repeated bouts with infection, thick "glue-like" fluid, and possible complications such as permanent hearing loss. Therefore, a hearing screening in school-age children is very important [15].

3. The impact of hearing loss on child's development

It is recommended that hearing loss in infants be identified, and when possible treated, prior to 6 months of age. This recommendation is based on studies that have shown that children identified with hearing loss prior to 6 months of age have a better chance of developing skills equivalent to their peers by the time they enter kindergarten.

Following the guidelines for hearing screening, hearing deficits in children can interfere with normal speech and language development, communication, and the ability to learn.

Failure to identify children with congenital or acquired hearing impairment can lead to lifelong consequences including deficits in speech and language abilities, cognition delays [16], poor academic performance [17], insufficient psychosocial skills, underemployment, and psychological distress [18].

Classroom is an auditory verbal environment where precise transmission and reception of speech is critical for effective learning to occur [19]. For instance, being able to hear all sounds is fundamental when learning to read. The behavioral effects of hearing impairment are frequently subtle and look similar to those of children who experience attention-deficit disorders, learning disabilities, language, and cognitive delays. Commonly cited behaviors include the following [20]: difficulty attending to spoken or other auditory information; often requests repetition; tired easily when listening; gives not suitable answer; avoids contacts with peers; difficulty with reading skills and written language; and easily frustrated. Children with mild unilateral hearing impairment can cause difficulties in sound-source location and problem with speech perception in background noise. In addition, problem associated with the loss of binaural summation and sound localization is delays in speech-language development and school achievements. Lack of binaural hearing may decrease accidental learning due to background noise interferes with overheard speech. Therefore, only such early identification results in early intervention via hearing aids, cochlear implants, and various assistive listening devices. The intervention allows for speech and language development and academic achievements to remain on target.

What is important, there are many factors that affect the speech and language acquisition, academic achievements of each child. Level of hearing loss (mild, moderate, severe, or

profound) based on the pure-tone threshold does not predict handicap or success in school. Some children have severe hearing loss; however, their speech is comprehensible and they get good grades. But on the other hand, other children with mild hearing loss and lack of family support exhibit considerable academic failure. Therefore, any hearing impairment, no matter how mild, needs to be assessed in order to assert confidently attention to any barrier of learning.

Children with unilateral hearing loss (UHL) appear to have an increased rate of grade failures, need for additional educational assistance, and perceived behavioral issues in the classroom. Possible risk factors include lower cognitive ability, right-ear hearing loss, and severe-to-profound hearing loss. Speech and language development may be delayed in some children with UHL, but it is unclear if children "catch up" as they grow older.

4. Screening methods around the world

As part of a hearing evaluation, child's healthcare provider will do a complete medical history and physical exam. In addition, there are many different types of hearing tests. Some of them may be used on all ages, while others are used based on child's age and level of understanding. Moreover, a variety of objective tools have been developed for screening tools. Hearing screening test should be conducted in a quiet area where visual and auditory distractions are minimal.

4.1. Questionnaires

Newton et al. [21] developed an eight-item questionnaire for hearing screening of children in Kenya. This tool is based on typical behavioral reaction to sound and communication ability. The main aim of this questionnaires was to identify children who may have bilateral hearing loss of a moderate degree or greater. It was designed for children of 3–8 years old and completed by teachers, parents, or community nurses, but authors recommended this tool for use only when administered by community health nurses. This questionnaire showed a high sensitivity of 100% but lower specificity of 75%. In addition, all young patients were invited to have an evaluation by ear-nose-throat physician and to have pure-tone audiometry completed.

Olusanya [22] created a questionnaire to screen children at school entry in Nigeria, Lagos. In this study was compared audiometry to results of questionnaires, otoscopy, and also tympanometry for each child. First step was a full physical exam on the children and then the parents were interviewed using a structured questionnaire that explored past medical/developmental history and family history of hearing loss. The parent questionnaire showed high specificity of 94% but low sensitivity of only 10%. The author noted that given limited resources in developing countries there is a need for a low-cost method that requires minimal training and that a questionnaire is a feasible approach. Moreover, the authors recommended the use of the questionnaire for mass screening when administered by trained teachers.

Samelli et al. [23] developed a 14-item questionnaire to identify children at risk for screening in Sao Paulo in Brazil. This tool is dedicated to children of 2–10 years old. In this study, a parent-completed questionnaire was compared with the results of an audiological assessment.

Conduction analyses show that this questionnaire from all of the children identified only with permanent severe-to-profound hearing loss. This tool showed low sensitivity of 44% and specificity of 87%. Researchers recommended the questionnaire for use in healthcare settings.

To conclude, all questionnaires were designed as a tool to identify children with hearing problems so that appropriate treatment and/or intervention could be provided; there were differences in the extent of hearing loss being targeted by the questionnaire. The purpose of population-based hearing screening is to identify those who need further testing from those who do not, with a minimum of false positives (failing the questionnaire when hearing is normal) and false negatives (passing the questionnaire when hearing loss exists).

4.2. Evoked otoacoustic emission

Physiologic test specifically measures outer hair cell response to presentation of a click stimulus (transient evoked OAEs). The test is that acoustic signals generated from within the cochlea travel in a reverse direction through the middle-ear space and tympanic membrane out of the ear. OAEs use a tiny, flexible plug that is inserted into the baby's ear. Sounds are sent through the plug. A microphone in the plug records the otoacoustic emissions (responses) of the normal ear in reaction to the sounds. There are no emissions in a baby with hearing loss. This test is painless and usually takes just a few minutes, while the baby sleeps.

1. **Advantages:** quick time test; ear-specific results; not dependent on whether patient is asleep or awake
2. **Limitations:** infant or child must be relatively inactive during the test; not a comprehensive test of hearing, because it does not assess cortical processing of sound; OAEs are very sensitive to middle-ear effusions and cerumen or vernix in the ear canal
3. **Average time:** 10-min test

4.3. Automated auditory brainstem response

Auditory brainstem responses (ABR) are measures of electrical events generated within the auditory brainstem pathway. These ABRs are used to assess brainstem function at different levels of the auditory pathway and are typically evoked by rapid multi-frequency clicks or chirps. Small metal discs with thin electrodes (wires) are placed on the baby's scalp, and then send signals to a computer to record the results. One objective physiologic means of screening hearing is the automated ABR. This instrument measures cochlear response in the 1- to 4-kHz range with a broadband click stimulus in the ear. While the baby sleeps, clicking sounds are made through tiny earphones in the baby's ears. As in OAEs, this test is painless.

1. **Advantages:** ear-specific results; responses not dependent on patient cooperation
2. **Limitations:** infant or child must remain quiet during the test (sedation is often required); not a comprehensive test of hearing, because it does not assess cortical processing of sound
3. **Average time:** 15-min test

4.4. Play audiometry

Behavioral test of auditory thresholds in response to speech and frequency-specific stimuli is presented through earphones and/or bone vibrator. This test is dedicated to children of 2–4 years old. A test that uses a special audiometer which is able to transmit sounds at different volumes and pitches into child's ears. This test is modified slightly in the toddler age group and made into a game. The toddler is asked to do something with a toy (such as touch or move a toy) every time when a sound is heard through earphones. Air-conduction hearing threshold levels of greater than 20 dB at any of these frequencies indicate possible hearing impairment. This test relies on the cooperation of the child, which may not always be given.

1. **Advantages:** ear-specific results; assesses auditory perception of child
2. **Limitations**: attention span of child may limit the amount of information obtained
3. **Average time:** 15–30 min test

4.5. Pure-tone audiometry

Behavioral test measuring auditory thresholds in response to frequency-specific stimuli is presented through earphones for children of 4 years and older. A test that uses a audiometer which is able to produces sounds at different frequently and intensity into child's ears. The child usually wears some type of earphones. Each ear should be tested at 500, 1000, 2000, and 4000 Hz. Results greater than 20 dB at any frequencies indicate possible hearing loss. In this age group, the child is simply asked to respond in some way when the tone is heard in the earphone. In that test, the most important is the cooperation of the child.

1. **Advantages:** ear-specific results; assesses auditory perception of child
2. **Limitations**: depends on the level of understanding and cooperation of the child
3. **Average time:** 15- to 30-min test

5. Hearing screening programs around the world

The major aim of hearing screening program is to detect a disease at a stage when treatment can be effective in reducing long-term complications [24]. According to the estimates provided by the World Health Organization (WHO), nearly 7.5 million children suffer from hearing loss [25]. Around 80% of them live in low- to middle-income countries [26].

In the absence of a systematic effort to screen infants with hearing loss, the average age of detection is well over 2 years, and detection may be as late as 6 years in sub-Saharan Africa [27]. In Kenya, many children with hearing impairment are not identified until 5–7 years old due to stigma, while some are hidden and are never diagnosed [28].

India launched the National Programme for Prevention and Control of Deafness. Under this program, the following two-part protocol for infant hearing screening is being complemented: institution- and community-based screening. First, screen every baby born in a hospital or

admitted there soon after birth using OAE and second, screen babies who are not born in a hospital; screening is carried out using a brief questionnaire and behavioral testing.

In 2011, 97.9% of babies born in the United States had their hearing screened in the first few weeks of life according to Centers for Disease Control and Prevention (CDC) [29].

In Europe and England, two models are used: first, in hospital before discharge, if discharge takes place before the test is completed, a letter is sent asking the mother to attend an appointment for the screening test and second, in some areas, the test is done at home by a health visitor nurse.

Although newborn hearing screening programs have greatly improved outcomes for those diagnosed with hearing loss in the immediate newborn period, there is no objective universal screening protocol in place during the critical early development years [28]. Unfortunately, school-age children are rarely screened for hearing loss during routine clinical examination, and health authorities pay little attention to audiometric evaluation particularly in primary schools.

5.1. Comprehensive approach to hearing screening in Poland

One of the priority activities of the Institute of Physiology and Pathology of Hearing in Kajetany is a screening program for children of all ages. The Institute team, in collaboration with numerous national centers, has laid the groundwork for screening programs and developed methods, procedures, and devices for carrying out them. He was the coordinator and producer of many programs. Based on this, two screening models have been created—newborn and school-age children.

5.1.1. Newborn hearing screening

The foundation on which the modern screening system was based was a research program for 150,000 newborns with funds in 15 neonatal and infants' centers in Warsaw. It was realized in 1992–1994 under the direction of Professor Maria Góralowna, and we cooperate with the team Diagnostic-Therapeutic and Rehabilitation Center "Cochlear Center" headed by Professor H. Skarżyński.

In the years 1995–1998, under the direction of Professor H. Skarżyński, a grant awarded to the Minister of Health, "Development of a unified screening program for neonates with hearing defects" was implemented. As part of the program, methods and procedures for screening hearing in newborns were developed, as well as their models - universal and intended for newborns at risk. At the end of the project, a draft of the Minister of Health was prepared for hearing screening in neonates.

In 1998, the grants were awarded the team award of the Minister of Health first degree. Another important initiative was implemented in 1996-1998, when the Institute of Physiology and Pathology of Hearing participated in the European program "European Concerted Action AHEAD (*Advancement of Hearing Assessment Methods and Devices*). This program aimed to develop a common European position on hearing screening for newborns.

In 1998, in Milan, a consensus on universal screening of hearing in newborns in Europe was signed. The signature on the Polish side was by Professor H. Skarżyński.

In the years 1998–2001, in the framework of the Government Action Plan for Disability Achievement, in which several dozen centers participated, hearing screening were disseminated and enriched. Alternative diagnostic, therapeutic, and rehabilitation facilities have been created for future screening programs. In 70 centers, more than 60,000 newborns and infants were examined.

5.1.2. School-aged children hearing screening

In 1999, the team of the Institute of Physiology and Pathology of Hearing collaborated with Brigham Young University of the United States and University of Michigan. M. Curie-Skłodowska from Lublin conducted pioneering screening of hearing in various regions of the country in a group of about 6000 children and adolescents in school age. Studies have shown that every 5 children aged 6–18 have hearing problems.

As part of the implementation of various programs (e.g., the Ministry of Health—the "Program for the Care of Persons with Hearing Loss in Poland"—the Mazovian Regional Health Service, the Ministry of National Education and Sport) conducted by the Institute of Physiology and Hearing Pathology in the years 2000–2006 in cooperation with the dozens of centers around the country, modern multimedia tools are developed for hearing screening. To use the program "I hear …" has trained over 3500 people and screened many centers. In cooperation with the Gdansk University of Technology, highly specialized systems such as "I can hear…," "I can see…," and "I can speak…" have been developed. About 16 million people from 62 countries have used the Internet.

Since 2007, a hearing screening program has been launched in Warsaw for children in class VI. Since 2011, the program also includes children in first grades. In total, these programs have covered up to now more than 56,000 children in Warsaw.

In the years 2008–2011, the programs were conducted by the Institute of Physiology and Pathology of Hearing in cooperation with the Contribution Fund of Social Insurance of Farmers and the Agricultural Insurance Fund Social screening in rural centers and small towns. Within these programs, nearly 300,000 children were studied.

In 2008, new multimedia tool—Platform for Sense Examination—used in screening was developed by the Institute of Physiology and Hearing Pathology in cooperation with the Institute of Sensory Organs. In addition, local screening programs were implemented, within the Ministry of National Education, which involved around 500 psychological and pedagogical clinics throughout the country.

In June 2007, the Institute team organized an exhibition at the European Parliament in Brussels. "HEAR-VISION-SPEAK" is the basis of communication and integration of the young generation of Europe. The exhibit was accompanied by a series of lectures, and numerous audiophiles and audiologists were examined by MEPs. The abovementioned actions aimed to draw Europeans' attention to the major social problem of communication disorders.

The exhibition was an introduction to further European activity. More than 3 years of negotiations and preparations resulted in the signing of the European Consensus on Audiology, Vision and Speech Screening in preschool and school children on June 22, 2011. There was great support during the Polish Presidency and an important argument for the adoption of the

"EU Council Conclusions on Early Detection and Treatment of Communication Disorders in Children, including the use of eHealth tools and innovative solutions".

Thanks to all these activities, Poland is currently at the forefront of countries that perform hearing screening in children of all ages.

5.1.3. System of integrated communication operations "SZOK"®

Every large-scale project involving children or adults is a great opportunity for early detection of congenital or acquired defects. In response to social needs related to the early detection of birth defects and acquired by detection and prevention, the Institute of Physiology and Hearing Pathology was involved in the implementation of the project, which was named System of Integrated Communication Operations "SZOK"®.

The project's innovation is the use of a system to assist patients with remote diagnosis and to transfer the results of their research to the health services sector. Integrating patient data into the "SZOK"® system will allow for quick service and thus shorten patient waiting times for visits to IFPS or other specialized facilities and as a comprehensive patient medical base. The system can also be successfully used in other healthcare and other medical fields. It is a unique solution in the field of telemedicine and e-health and is an excellent starting point for the Center for Screening.

Moreover, a standard for the transmission of audiological screening results has been implemented in the "SZOK"® system, which is developed within the Institute's project, so that it is adapted to obtain research results from other institutions and collect them in one place (**Figure 1**).

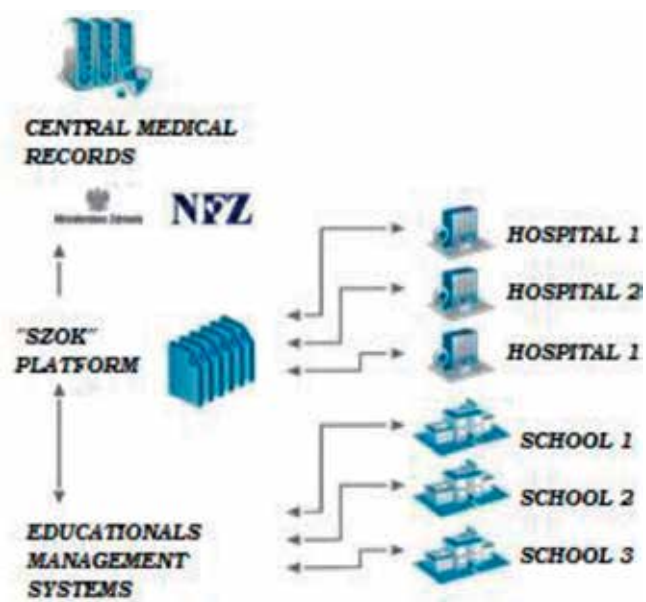

Figure 1. System of integrated communication operations "SZOK"®.

5.1.4. Platform for sense organ examination

In 2008, new multimedia tool used in screening—Platform for Sense Organs Screening—was developed by the Institute of Physiology and Hearing Pathology in cooperation with the Institute of Sensory Organs(**Figure 2**).

The platform is built around an Internet network solution, interfacing a central computer system and a series of portable computers (remote client devices) equipped with audiometric headphones and a response-button interface. The platform allows the user to conduct the following tests:

1. **Audiometric testing**: This feature allows the user to perform air conduction audiometric testing for each ear separately, in a tone frequency range from 250 to 8000 Hz, and for hearing threshold levels not exceeding 80 dB HL.
2. **Speech screening:** The speech test is carried out to obtain reliable information on: (1) the quality of verbal behavior of the child and (2) the degree of speech development (or of any potential delays) and any pathological linguistic phenomena occurring in the speech of the child.
3. **Audiological survey:** This module allows the user to conduct a general survey regarding the hearing, sight, and speech of a patient. The surveys were developed by specialists based on years of experience in specific areas, and they provide reliable information on the tested person.
4. **Test module DDT**: This is a dichotic listening test. During the test, pairs of sounds are presented to each ear and the task of the tested subjects is to repeat what they heard in one or both ears.
5. **Test module FPT**: This is a frequency pattern test. The test items are sequences of three tone bursts that are presented to one or both ears. In each of the sequences, two tone bursts

Figure 2. Platform for sense organs examinations.

are of the same frequency, while the third tone is of a different frequency. There are just two different frequencies used in this test: one is a high-frequency sound and the other a low-frequency sound pattern test.

6. **Test module DPT:** This is a duration pattern test. Test consists of sequences of three tones, one of which differs from the other two in the sequences by being either longer or shorter.

7. **Test module GIN**: This test allows assessment of the potential of perception of gaps in noise. During the test, the noise is presented with constantly emerging gaps of varying lengths.

5.2. Protocol used in the hearing screening in school-age children around the world conducted by world hearing Centre in Kajetany, Poland

Large-scale hearing screening experience called for a European Scientific Consensus agreement, which was defined and signed during the European Federation of Audiology Societies (EFAS) meeting in 2011 under auspices of the Institute of Physiology and Pathology of Hearing. As a result of this, a number of pilot hearing screening programs were started in various countries. Countries in which the team from the Institute of Physiology and Pathology of Hearing in Kajetany conducted hearing screening were presented in the **Table 1**.

Country in which IFPS conducted hearing screening	Children's age	Number of tested children	Universal Newborn Hearing Screening in this country
Armenia	6–9	200	No information
Azerbaijan	6–8	200	No screening program
Cameroon	5–15	220	No screening program
Columbia	6–8	150	In some district
Congo	6–8	200	No screening program
Ivory Coast	6–8	130	No screening program
Kazakhstan	7–8	212	No screening program
Kyrgyzstan	6–7	300	No screening program
Moldova	6–7	179	No information
Nigeria	4–7	200	Pilot project
Romania	6–7	130	No screening program
Russia	6–12	166	No screening program
Rwanda	6–15	195	No screening program
Senegal	6–10	200	No screening program
Tajikistan	7–8	143	No screening program
Tanzania	6–11	200	No screening program
Ukraine	6–11	184	No screening program

Table 1. Overview of hearing screening around the world conducted by the Institute Physiology and Pathology of Hearing.

School-entry hearing screening is especially important. That screening may actually be the first point of access to detect childhood hearing impairment.

Prior to testing, the children's parents were informed of the testing procedures and provided their written consent. The results of the audiometric tests were supplemented by the results of the questionnaire completed by the parents. This questionnaire included questions concerning data on the potential causes of the child's hearing problems, medical history, possible presence of tinnitus, and any presence of learning difficulties.

A hearing screening protocol used by a team from the Institute of Physiology and Pathology of Hearing in Kajetany, while screening in different countries includes three steps (**Figure 3**).

The first step is video-otoscopy. In this test, the specialist otolaryngologist views the middle ear on the monitor. This is the most accurate visual cure repair method and structure of the outer ear. This examination allows the diagnose change in the outer and middle ear such as excessive earwax, acute or chronic otitis media, fungal infection and changes in the tympanic membrane.

Second step is otoacoustic emission (OAE). It is an objective method of assessment—technically not a test of hearing but rather a reflection of inner ear mechanism. OAEs are sounds detected in the external ear canal that are generated by the outer hair cells within the cochlea. If the otoacoustic emission is absent, then we perform the third step—pure-tone audiometry.

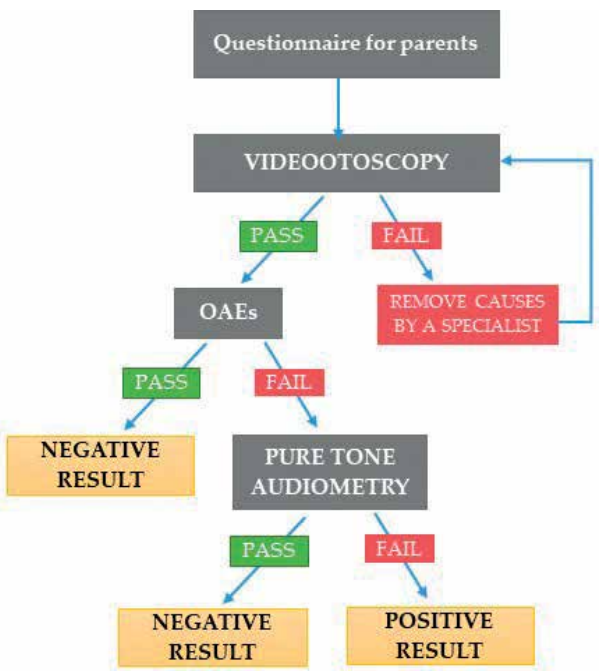

Figure 3. Schema of hearing screening protocol in school-age children used in the institute physiology and pathology of hearing.

Pure-tone audiometry (PTA) was performed using the modern platform elaborated by the Institute of Sense Organs and is fundamental for the inexpensive and universal screening in large populations of children—a platform for sense organs' screening. In addition, PTA was performed using SZOK described previously. The threshold for air conduction in the frequency range of 500–8000 Hz was determined. For abnormal test results, a hearing threshold value of 25 dB and above was used for at least one frequency in at least one ear.

The proposed screening procedure allows the detection not only of children with hearing loss but also of those with other hearing disorders, such as tinnitus. According to data study conducted by the team, led by Professor H. Skarżyńskiego, the incidence of tinnitus in school-age children is approximately 13–37.7% [30].

Moreover, the Institute of Physiology and Pathology of Hearing has their own truck that they are currently using for running a rural hearing health study—called Mobile Hearing Center. Inside, the truck functions as a regular audiology clinic, only on a much smaller scale. The larger of the two booths has a typical audiology setup with video-otoscopy. They were able to conduct assessment of the external and middle ears. The smaller booth is strictly used for testing adults. It may appear to be a small space; however, it is relatively spacious inside for the patient. Currently, we conduct only hearing screening, but in future, they hope to have Internet on the truck, so when they encounter a situation (e.g., with video otoscopy), they can evaluate the patient remotely. In that case, it would be a combination of two delivery types. Right now, it is a completely contained mobile audiology clinic, delivering the same level of service as you would expect in a brick-and-mortar clinic, except that they are able to bring hearing care services to the local community.

6. Summary

The positive impact of early identification and intervention for children with hearing loss is well established, and the primary care provider plays a vital role in screening children who require such services. Without prompt intervention, hearing loss in early childhood can cause significant delays in speech development, socioemotional growth, and school achievement.

Index of technical terms

Acute Otitis Media—painful type of ear infection. It occurs when the area behind the eardrum called the middle ear is inflamed and infected.

Auditory Brainstem Response (ABR)—neurologic test which gives information about the inner ear and brain pathways for hearing. The ABR is performed by pasting electrodes on the head—similar to electrodes placed around the heart when an electrocardiogram is run—and recording brain wave activity in response to sound.

Auditory Neuropathy/Dyssynchrony—hearing disorder in which sound enters the inner ear normally but the transmission of signals from the inner ear to the brain is impaired. People with auditory neuropathy may have normal hearing, or hearing loss ranges from mild to severe but they always have poor speech-perception abilities.

Behavioral Test–test investigates propensities toward certain kinds of behavior and styles of interaction with others.

Cerumen (Earwax)—brown, gray, or yellowish waxy substance secreted in the ear canal. It protects the skin of the human ear canal, assists in cleaning and lubrication, and also provides some protection against bacteria, fungi, insects, and water.

Chickenpox (Varicella)—a virus infection, commonly of children, caused by the varicella zoster virus and characterized by mild headache and fever, malaise, and eruption of blisters on the skin and mucous membranes.

Chronic Otitis Media—a long-standing, persistently draining perforation of the eardrum.

Cochlea—the auditory portion of the inner ear situated in the temporal bone. The cochlea interacts with the middle ear via two holes that are closed by membranes: the oval window, which is located at the base of the scala vestibuli and which undergoes pressure from the stapes, and the round window, which seals the base of the tympanic membrane and is used to relieve pressure. The cochlea is filled with a watery liquid, the perilymph, which moves in response to the vibrations coming from the middle ear via the oval window.

Cochlear Implant—a device that provides direct electrical stimulation to the auditory (hearing) nerve in the inner ear. Children and adults with a severe-to-profound sensorineural hearing loss who cannot be helped with hearing aids may be helped with cochlear implants. Cochlear implants have external (outside) parts and internal (surgically implanted) parts that work together to allow the user to perceive sound.

Congenital Hearing Impairment—it means that the hearing impairment is present at birth. Congenital hearing loss can be caused by genetic or nongenetic factors.

Connexin—structurally related transmembrane proteins that assemble to form vertebrate gap junctions.

Dichotic Listening Test—a psychological test commonly used to investigate selective attention within the auditory. Specifically, it is used as a behavioral test for hemispheric lateralization of speech sound perception. During a standard dichotic listening test, a participant is presented with two different auditory stimuli simultaneously (usually speech). The different stimuli are directed into different ears over headphones.

Duration Pattern Test—standard version is an auditory processing disorder test for ages 11 and over using nonverbal stimuli. The duration patterns are composed of three 1000-Hz tones and two 300-ms intertone intervals.

Ear Canal—it is a tube running from the outer ear to the middle ear. The adult human ear canal extends from the pinna to the eardrum and is about 2.5 cm (1 in) in length and 0.7 cm (0.3 in) in diameter.

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Encephalitis—inflammation of the brain tissue. The most common cause is viral infections. In rare cases, it can be caused by bacteria or even fungi. Symptoms may include headache, fever, confusion, a stiff neck, and vomiting.

Enlarged Vestibular Aqueduct (EVA) Syndrome—a syndromic form of hearing loss, caused by the enlargement of the vestibular aqueduct in the inner ear. It is one of the most common inner ear deformities, which results in hearing loss during childhood.

Evoked Otoacoustic Emission (OAE)—sounds of cochlear origin, which can be recorded by a microphone fitted into the ear canal. They are caused by the motion of the cochlea's sensory hair cells as they energetically respond to auditory stimulation.

Frequency Pattern Test—an auditory processing disorder test for ages 8 and over using nonverbal stimuli. The frequency pattern test consists of 880 Hz (low) and 1122 Hz (high) tones that are 200 ms in duration and have an interstimulus interval of 150 ms and a 10-ms rise fall time.

Fungal infection—fungal infections occur when an invading fungus takes over an area of the body and is too much for the immune system to handle.

Gaps in noise—test auditory processing disorder test for ages 7 and older using nonverbal stimuli. It is designed to measure temporal resolution which resolution refers to the ability to detect changes in either the duration of an auditory stimulus and/or the time intervals or gaps of silence embedded within an auditory stimulus. The ability to detect small silent intervals is an important factor in speech perception.

Head trauma—any injury that results in trauma to the skull or brain.

Hearing aid—a device designed to improve hearing. Hearing aids are incapable of truly correcting a hearing loss; they are an aid to make sounds more accessible.

Hearing deficits—it is a partial or total inability to hear.

Influenza—an infectious disease caused by an influenza virus. It is characterized by a sudden onset of fever, cough (usually dry), headache, muscle and joint pain, severe malaise (feeling unwell), sore throat, and a runny nose. The cough can be severe and can last 2 or more weeks.

Measles—a highly contagious infection caused by the measles virus. Initial signs and symptoms typically include fever, often greater than 40°C (104.0°F), cough, runny nose, and inflamed eyes. Two or three days after the start of symptoms, small white spots may form inside the mouth. A red, flat rash which usually starts on the face and then spreads to the rest of the body typically begins 3–5 days after the start of symptoms.

Medical History—information gained by a physician by asking specific questions, either of the patient or of other people who know the person and can give suitable information with the aim of obtaining information useful in formulating a diagnosis and providing medical care to the patient. The medically relevant complaints reported by the patient or others familiar with the patient are referred to as symptoms, in contrast with clinical signs, which are ascertained by direct examination on the part of medical personnel.

Meningitis—an acute inflammation of the protective membranes covering the brain and spinal cord, collectively known as the meninges. The most common symptoms are fever,

headache, and neck stiffness. The inflammation may be caused by infection with viruses, bacteria, or other microorganisms, and less commonly by certain drugs.

Middle Ear—the portion of the ear internal to the eardrum, and external to the oval window of the inner ear. The mammalian middle ear contains three ossicles, which transfer the vibrations of the eardrum into waves in the fluid and membranes of the inner ear. It joins the tympanic cavity with the nasal cavity, allowing pressure to equalize between the middle ear and throat. The hollow space of the middle ear is also known as the tympanic cavity. The primary function of the middle ear is to efficiently transfer acoustic energy from compression waves in air to fluid-membrane waves within the cochlea.

Mitochondrial Hearing Loss—nonsyndromic deafness caused by mutations in both nuclear and mitochondrial genes. Nonsyndromic mitochondrial hearing loss is characterized by moderate to profound hearing loss, and a maternally inherited mutation in either the MTRNR1 or MTTS1 gene.

Mumps—a viral disease caused by the mumps virus. Initial signs and symptoms often include fever, muscle pain, headache, and feeling tired. This is then usually followed by painful swelling of one or both parotid salivary glands. Symptoms typically occur 16—18 days after exposure and resolve after 7–10 days. Symptoms in adults are often more severe than those in children. Complications may include meningitis, pancreatitis, permanent deafness, and testicular inflammation, which uncommonly results in infertility.

Noise-induced Hearing Loss—hearing impairment resulting from exposure to loud sound. People may have a loss of perception of a narrow range of frequencies, impaired cognitive perception of sound, or other impairment, including sensitivity to sound or ringing in the ears. Hearing may deteriorate gradually from chronic and repeated noise exposure or suddenly from a short high intensity noise. In both types, loud sound overstimulates delicate hearing cells, leading to the permanent injury or death of the cells.

Otitis Media with Effusion—when there is thick or sticky fluid behind the eardrum in the middle ear, but there is no ear infection. Normally, the Eustachian tube drains fluid from your ears to the back of your throat. If it clogs, otitis media with effusion (OME) can occur. This condition most often affects children. Muffled hearing is a common symptom.

Ototoxic Drugs—medications which can damage the ear, resulting in hearing loss, ringing in the ear, or balance disorders. The effects of ototoxicity can be reversible and temporary, or irreversible and permanent. Ototoxic drugs include, for example, antibiotics (gentamicin), loop diuretics (furosemide), and platinum-based hemotherapy (cisplatin). Outer hair cells.

Outer Hair Cells—called acoustical preamplifiers. In mammalian outer hair cells, the receptor potential triggers active vibrations of the cell body. This mechanical response to electrical signals is termed somatic electromotility and drives oscillations in the cell's length, which occur at the frequency of the incoming sound and provide mechanical feedback amplification. They also improve frequency selectivity.

Platform for Sense Examination—a portable device for screening hearing, sight and speech and hearing and speech rehabilitation in children (also with special educational needs),

adolescents and adults. The device is built on the basis of an advanced central computer system and a portable computer equipped with additional accessories enabling the test.

Play Audiometry—it allows an audiologist to test the hearing of very young toddlers and preschoolers. CPA uses behavioral conditioning to get kids to respond to sounds. It is designed for children usually between 2 and 5 years of age. It measures hearing sensitivity to determine both a child's type and degree of hearing loss, if any. The audiologist can then refer parents to another specialist, if necessary.

Pure Tone Audiometry (**PTA**)—the key hearing test used to identify hearing threshold levels of an individual, enabling determination of the degree, type and configuration of a hearing loss, thus providing the basis for diagnosis and management. PTA is a subjective, behavioral measurement of hearing threshold, as it relies on patient response to pure tone stimuli. Therefore, PTA is used on adults and children old enough to cooperate with the test procedure.

Questionnaire—a research instrument consisting of a series of questions (or other types of prompts) for the purpose of gathering information from respondents. Although questionnaires are often designed for statistical analysis of the responses, this is not always the case.

Rubella—is an infection caused by the rubella virus. This disease is often mild with half of people not realizing that they are sick. A rash may start around 2 weeks after exposure and last for 3 days. Complications may include bleeding problems, testicular swelling, and inflammation of nerves. Infection during early pregnancy may result in a child born with congenital rubella syndrome (CRS) or miscarriage.

Sensitivity—the ability of an organism or organ to respond to external stimuli. For example, auditory hypersensitivity occurs when a person has a collapsed tolerance to normal environmental sound. The term commonly used to describe this condition is "hyperacusis."

Sound-source location—a listener's ability to identify the location or origin of a detected sound in direction and distance. The auditory system uses several cues for sound source localization, including time and level differences (or intensity-difference) between both ears, spectral information, timing analysis, correlation analysis, and pattern matching.

Specificity—In medicine, it means the extent to which a diagnostic test is specific for a particular condition, trait, and so on.

Sudden Idiopathic Hearing Loss—defined as greater than 30 dB hearing reduction, over at least three contiguous frequencies, occurring over a period of 72 h or less. Some patients describe that the hearing loss was noticed instantaneously in the morning, and others report that it rapidly developed over a period of hours or days. Only one ear is usually affected. About half of people recover some or all of their hearing spontaneously, and some people need a treatment from an otolaryngologist.

System of Integrated Communication Operations "SZOK"®—a world-class solution—is a revolution in the creation of IT infrastructure and data management. The project's innovativeness is based on the use of a system supporting patient diagnosis at a distance and the transfer of research results to the health services sector. Integrating patient data into the

system platform will allow for better and faster service and will reduce patient waiting times for visits to an institute.

Teleaudiology—it is the utilization of telehealth to provide audiological services and may include the full scope of audiological practice. The innovation that is currently being developed broadens teleaudiology and hearing care practice to virtual care modalities such as clinical video telehealth, store-and-forward telehealth, home telehealth, mobile health applications, secure messaging, and electronic consults.

Telemedicine—the use of telecommunication and information technology to provide clinical healthcare from a distance. It has been used to overcome distance barriers and to improve access to medical services that would often not be consistently available in distant rural communities. It is also used to save lives in critical care and emergency situations.

Tinnitus—the hearing of sound when no external sound is present. While often described as a ringing, it may also sound like a clicking, hiss, or roaring. Rarely, unclear voices or music are heard. The sound may be soft or loud, low pitched or high pitched and appear to be coming from one ear or both. Most of the time, it comes on gradually. In some people, the sound causes depression or anxiety and can interfere with concentration.

Tympanic Membrane—a thin, cone-shaped membrane that separates the external ear from the middle ear. Its function is to transmit sound from the air to the ossicles inside the middle ear and then to the oval window in the fluid-filled cochlea. Hence, it ultimately converts and amplifies vibration in air to vibration in fluid. Rupture or perforation of the eardrum can lead to conductive hearing loss.

Unilateral Hearing Loss (UHL)—a type of hearing impairment where there is normal hearing in one ear and impaired hearing in the other ear. Patients with unilateral hearing loss have difficulty in hearing conversation on their impaired side, localizing sound, understanding speech in the presence of background noise, interpersonal and social relations. Using for example CROS hearing aids or BAHA implant can help to resist better hearing functioning.

Universal Screening Protocol—it is the largest preventive health program in Poland. Its primary goal is to examine each newborn baby to except possible hearing impairment and to analyze risk factors that predispose to hearing loss.

Vernix—the waxy or cheese-like white substance found coating the skin of newborn human babies. It is produced by dedicated cells and is thought to have some protective roles during fetal development and for a few hours after birth. Vernix is theorized to serve several purposes, including moisturizing the infant's skin, and facilitating passage through the bacteria. It serves to conserve heat and protect the delicate newborn skin from environmental stress.

Video-otoscopy—video-otoscopy is the use of an otoscope (this is an instrument used to look in the ears) that has a very tiny video camera that transmits images to a television screen. These scopes use fiber optics to transmit a very bright light that illuminates the ear canal. The video otoscope allows the doctor to see in the ear much better than a traditional handheld otoscope. With the irrigating function, debris can be cleaned deep within the ear that would be impossible to remove any other way.

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Section 3

Treatment Strategies for Hearing Loss

Chapter 8

Cochlear Implants: An Excursus into the Technologies and Clinical Applications

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Additional information is available at the end of the chapter

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Abstract

Hearing loss causes severe alterations in social function and daily communications. Cochlear device implantation (CDI) is the only beneficiary method for auditory rehabilitation in patients with severe to profound sensorineural hearing loss (SNHL). Regarding a report in 2014, over 300,000 people had received cochlear implants throughout the world since December 2012 among which about 60,000 were adults and 40,000 were children in the United States. In this chapter, we discuss the history, origin, mechanism of action, and type of cochlear implants, as well as method of surgery and complications.

Keywords: cochlear implantation, hearing loss, complications, clinical applications, surgical technique, epidemiology

1. History and introduction

Most of the patients with significant social dysfunction due to hearing loss can be treated by nonsurgical interventions. Many ways such as selective seating closer or with the better ear near important sound sources or using hearing aids can be utilized for these situations [1].

Cochlear device implantation (CDI) is the only beneficiary method for auditory rehabilitation in patients with severe to profound sensorineural hearing loss (SNHL). Regarding a report in 2014, over 300,000 people had received cochlear implants throughout the world since December 2012, among which about 60,000 were adults and 40,000 were children in the United States [2].

A 60-year-old history protects cochlear implantation technology, which has experienced multiple changes in devices and speech processing strategies. It was about 200 years ago when Alessandro Volta described the early auditory percepts induced by applying a large voltage between his own ears in 1790 [3–6]. Further investigations by Weaver and Bray were focused and resulted in this concept that it might be possible to generate electrical signals mimicking auditory input stimulus [7].

In 1957, an electrode with receiver coil was successfully implanted for a patient with resected cochlear nerve due to cholesteatoma, which was able to stimulate the apparatus for months, and shockingly, the patient had sound awareness and simple word recognition [8–10]. Following Djourno and Eyries, House started his work in the early 1960s who implanted simple wires, wires with ball electrodes, and even simple arrays into the scala tympani, which finally led into production of implantable device in 1972; this was a beginning point for clinical trials [3, 11].

At the beginning, there was a resistance from scientific community especially neurophysiologists and otologists against CI; however, the national institute of health (NIH) approved the use of electrical stimulation of auditory nerves as a rehabilitation method in 1977, while evaluating the outcome in patients with single channel implants [3, 4, 12, 13].

Multichannel CIs were produced in greater numbers due to the food and drug administration (FDA) approval because of their ability of open-set word recognition and better frequency spectrum percepts [3, 6, 14]. Another remarkable progress was occurred in 1991, while continuous interleaved sampling (CIS) strategy was introduced, which developed improved open-set word recognition in comparison with previous analogue methods, so that all currently available strategies are based on CIS [15].

2. Structure and mechanism of action

Sensory hair cells within the cochlea have the responsibility for transforming sound vibration to neural signal in healthy individuals; then, the signal continues its way to auditory cortex through cochlear nerve. Cochlear implants take the place of these cells using electrodes which stimulate the nerve fiber electrically. **Figure 1** illustrates a cochlear implant device. Common cochlear implants have two parts: external component as a hearing aid and internal component which is surgically inserted in mastoid [16].

The external part is consisted of three parts: a microphone for gathering sounds, a speech processor analyzing and encoding sound into a digital code, and a magnetic headpiece which transmits coded signals by a transcutaneous radiofrequency link to the internal part.

The internal part has a receiver stimulator which receives and decodes the data and conducts decoded signal to the electrode array. In the next step, there is a flexible silicone carrier, which has variable number of electrodes. The remaining cochlear nerve fibers are stimulated by the electrode array, which is surgically implanted in scala tympani of the cochlea.

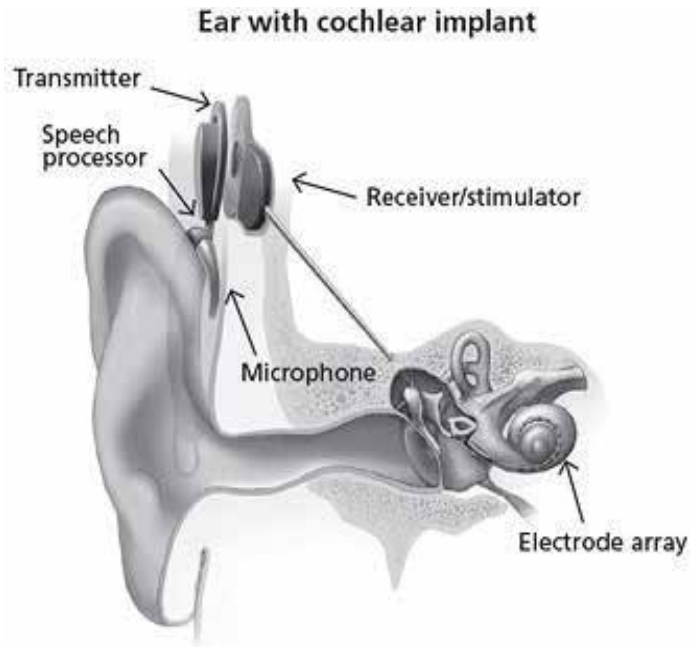

Figure 1. Different parts of cochlear implant (source: NIH/NIDCD https://www.nidcd.nih.gov/health/cochlear-implants).

3. Types of cochlear implants

3.1. Totally implantable cochlear implants

Currently available implants have an external part and need patients to wear it consisted of an external microphone, processor, and transmitting coil for empowering the electrode, which needs a dry and stable environment. Thus, development of totally implantable cochlear implants that make the whole system available underneath the skin is a new area of research. There are several challenges and requirements in the way of this progress including a tiny and sensitive microphone with ability to filter the endogenous noises, as well as a rechargeable battery with appropriate long life. There is a report of three patients with totally implantable cochlear implants [17].

3.2. Unilateral or bilateral cochlear implantation

Unilateral cochlear implantation was the only option offered at the beginning. Later, it was questioned if the patients would take more benefits from bilateral cochlear implants. Surprisingly, it was revealed that patients with bilateral cochlear implantation show better speech perception and improvement in "hearing in noise." Also, these patients showed a significantly better sound localization in comparison with their single-side implantation condition [18, 19].

Previous studies have concluded that there is no significant difference for audiologic outcomes between unilateral and bilateral cochlear implantation regarding surgical timing, as both ears can be implanted simultaneously or sequentially. Adult studies have shown that the second ear matches the first ear performance at 6 months [20]. The story has a difference when it comes to children, as it has been concluded that patients with simultaneous bilateral cochlear implantation have improved speech recognition and language when compared to children who were implanted sequentially [21].

The cost-effectiveness of bilateral cochlear implantation has remained controversial despite evident advantages of binaural stimulation. A Canadian study has reported that cochlear implantation is cost-effective in adults compared to no implantation; however, sequential bilateral cochlear implantation has a slight superiority in comparison with unilateral implantation [22]. Other studies have approved cost effectiveness of bilateral simultaneous pediatric implantation and unilateral adult cochlear implantation, although they have not approved cost-effectiveness of bilateral sequential pediatric implantation and bilateral (sequential or simultaneous) adult implantation [23].

4. Candidacy and patient selection

Selecting the right patient is the building block of a successful cochlear implantation. Therefore, a complete medical and audiologic workup is needed for evaluating candidacy of cochlear implantation and to make sure that the patient can tolerate anesthesia and surgical process. Patients are considered to take benefit from CI when they suffer from bilateral moderate to profound sensorineural hearing loss and when hearing aids cannot help them [24]. A combination of objective and subjective hearing tests is conducted to accurately identify the degree of hearing loss within audiometric frequencies. Currently available guidelines mention that children up to 2 years of age should have a bilateral profound sensorineural hearing loss, which is indicated by a pure tone audiometry (PTA) more than 90 dBHL for 500, 1000, and 2000 Hz frequencies, while patients older than 2 years of age should have bilateral sever to profound SNHL indicated by PTA more than 75 dBHL for 500, 1000, and 2000 Hz frequencies [25, 26]. Preoperative speech and language evaluation has the same importance for decision making regarding rehabilitation strategies and programs, as well as appropriateness of auditory performance, speech production, and mode of communication. Hearing loss is categorized to prelingual, postlingual, and perilingual types based on the time of onset. In prelingually deaf patients, hearing impairment occurs before gaining speaking skills, which is usually before 2 years of age, while it occurs after gaining complete speaking skills in postlingual patients which is usually after age of 5 years. In perilingual patients, hearing impairment occurs when some speaking skills are gained but are not completed usually between 2 and 5 years of age [16].

In addition, preoperative imaging and auditory testing are needed. Imaging modalities such as computed tomography (CT) scan, for assessing temporal bone, and magnetic resonance imaging (MRI), for evaluating brain anatomy and ruling out abnormalities of cochlear nerve, are conducted [15]. After scheduling patient for surgery, pneumococcal vaccines are administered according to FDA guidelines.

Current contraindications for cochlear implantation are two absolute and relative categories. Absence of cochlear development, deafness due to lesions of the central auditory pathway, and massive cochlear ossification that prevents electrode insertion are among absolute contraindications. Relative contraindications include aplasia of the acoustic nerve and medical conditions or developmental delays that would severely limit participation in aural rehabilitation.

5. Surgery

Cochlear implantation procedure is performed under general anesthesia associated with facial nerve monitoring. Surgeon needs to expose the mastoid, so a postauricular incision is made and soft tissue is dissected; latter, the surgeon makes a subperiosteal pocket for placement of implant magnet. A cortical mastoidectomy is performed associated with finding landmarks of temporal bone, such as incus, tegmen tympani, lateral semicircular canal, and sigmoid sinus. Then, the surgeon opens the facial recess, which is surrounded by chorda tympani, facial nerve, and incus buttress as its boundaries to identify the round window niche through the recess.

There are different methods for accessing scala tympani after finding the round window; in cochleostomy, the surgeon drills a separate hole and the anterior limit of the round window in extended cochleostomy. The implant is inserted into the cochlea, once the cochlea is opened. For making sure of the proper function of implant, an integrity test is performed by an audiologist at the end of the procedure. X-ray radiography is used to ensure proper location of cochlear implant by some surgeons. At the end, the patient is discharged the same day, and cochlear implant is usually activated 2–4 weeks postoperatively.

6. Complications

Cochlear implantation is generally a safe performed surgical procedure throughout the world with globally estimated complication rate of 16% [18]. Requiring additional surgery or cochlear explantation is categorized as major, and complications needing conservative medical management are classified as minor complications. Now, complication rates are decreasing due to improved experience, using smaller incisions and improvements in designing devices, and are generally calculated to be 11.8% for minor and 3.2% for major complications [27].

Infection is one of the most important major complications of cochlear implantation. Skin infection and acute otitis media are the most common type of implant-related infections ranging from 1 to 12% in the literature. Otitis media and soft tissue infection increase the risk of cochlear implant removal if leading to receiver stimulator infection. Also, it has been reported that cochlear implantation increases the risk of bacterial meningitis as 30-fold greater than general population; however, dawn of vaccination has made these cases sporadic [28]. Facial nerve palsy is another major complication of cochlear implantation, which is estimated to occur in 0.7% of cases due to heat induced by drill, cochleostomy, or reactivation of herpes virus as a result of surgery stress [29]. Finally, device failure is another major complication of cochlear

implantation occurring in 2.5–6% of cases [18, 27]. Vestibular symptoms, such as vertigo and disequilibrium, are present in about one-third of patients postoperatively and are believed to last for more than 1 week after surgery. Most of these symptoms are resolved in weeks; however, patients over 70 years of age are more likely to have permanent vestibular weakness [30].

7. Hearing after cochlear implantation

Acoustic hearing remains preserved in more than half of the patients after cochlear implantation; however, previously, it was believed that insertion of electrode into the cochlea destroys the natural mechanism of hearing [31]. Preserving physiologic pathway of hearing has several advantages such as ability to localize the sound, recognize the speech, and hear in complex listening environments [32]. A variety of factors and approaches have been considered for improving hearing preservation after cochlear implantation. Previous studies have reported that full electrode insertion makes the hearing preservation possible; however, electrode insertion depth and length are determining factors for intracochlear trauma [24, 33].

Studies believe that the most hearing preservation achieves when the electrode is entirely located in scala tympani [34]. The most appropriate surgical approach has remained controversial; some previous studies have mentioned that there is no significant difference between round window and cochleostomy approaches regarding hearing outcomes [35, 36], while others reported that each method is superior for maximizing atraumatic scala tympani insertion. Eventually, preoperative prescription of steroids and steroid-eluting implants have been reported to improve hearing preservation up to 1 year from implantation [32].

In another retrospective analysis of cochlear implanted patients, researchers investigated the impact of related factors on hearing preservation. They reported an overall preservation likelihood of 39% for patients operated by refined soft surgery technique with a higher conservation rate at low frequencies when compared to high frequencies [37]. Age at the time of implantation, etiology of deafness, side of implant, electrode array model, and insertion technique, as well as type of cochleostomy, are investigated factors, which are considered to possibly affect hearing preservation; however, there are a variety of opinions on their effects, and further studies are required for conclusive results [36, 38–52].

8. Other applications of cochlear implant

8.1. Cochlear implantation for single-sided sensorineural hearing loss

Recently, a new topic has come up about cochlear implantation in setting of single-sided sensorineural hearing loss [53]. So far, options such as hearing aids, bone-anchored implants, and contralateral routing of signal (CROS) devices were applied for single-side deaf patients. While these options improve hearing by healthy ear, cochlear implantation restores hearing by deaf ear. Sound localization is a special challenge for patients with unilateral hearing loss.

A proper localization involves a good bilateral hearing and sound stimulation, as well as intraaural time differences, which allow complex processing of sounds. Recent studies have mentioned some advantages for cochlear implantation in unilateral hearing loss, and some has reported a better sound localization in comparison with bone-anchored implants [54]. Additionally, it has been shown that cochlear implants resolve tinnitus up to an acceptable extent in patients with single-sided deafness and may improve speech perception [34, 55].

8.2. Hybrid cochlear implants

A hybrid cochlear implant was developed by Gantz et al. with the aim of preserving residual hearing, which has only 10 mm of height [56]. This provides the possibility for stimulating the region responsible for high-frequency hearing in cochlea without stimulating regions responsible for low frequency hearing. Primary studies have revealed that hybrid implant application is associated with better hearing preservation and increased speech perception [35, 36, 57, 58]. In addition to the comparable performance of hybrid implants with conventional ones, patients with hybrid implants had improved music appreciation as a result of acoustic and electrical stimulation combination [56, 57]. Replacement of hybrid implant with full-length implant in a progressive hearing loss improves hearing and word recognition; however, it is associated with a notable additional cost [59, 60].

8.3. Cochlear implantation and Meniere's disease

Cochlear implantation has been utilized for Meniere's disease, a condition consisted of episodic attacks of tinnitus, hearing loss, and debilitating vertigo spells. Previous studies have shown resolution of related symptoms after cochlear implantation in Meniere's disease patients, although the hearing outcomes are not as acceptable as patients implanted for other reasons [61, 62].

9. Prospective of cochlear implantation

So far, some in vitro and animal studies have been conducted to resolve the hearing impairment problem using regenerative medicine; nevertheless, cochlear implantation remains as the most effective current treatment method. Further efforts are being put to cochlear implantation technology field in order to improve understanding speech in noise and music appreciations.

Abbreviations

CI	cochlear implant
CROS	contralateral routing of signal
dBHL	decibels hearing level

Hz	Hertz; unit of frequency
PTA	pure tone audiometry
SNHL	sensory-neural hearing loss

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Chapter 9

Hearing Aids

Ryota Shimokura

Additional information is available at the end of the chapter

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"Blindness cuts you off from things; deafness cuts you off from people."

Immanuel Kant (Philosopher, 1724–1804).

Abstract

This chapter presents an overview of the current state of a hearing aid tracing back through the history. The hearing aid, which was just a sound collector in the sixteenth century, has continued to develop until the current digital hearing aid for realizing the downsizing and digital signal processing, and this is the age of implanted hearing devices. However, currently popular implanted hearing devices are a fairly large burden for people soon after they become aware of their hearing loss, although auditory stimulation to the nerve in the early stage can avoid accelerated cognitive decline and an increased risk of incident all-cause dementia. For this reason, we tend to stick to wearable hearing aids that are easy to be put on and take off. Although the digital hearing aid has already reached the technical ceiling, the noninvasive hearing aids have some severe problems that are yet to be resolved. In the second half of this chapter, we discuss the scientific and technical solutions to broaden the range of permissible users of hearing aids.

Keywords: dementia, EuroTrak, bone-conducted ultrasonic hearing aid, cartilage conduction hearing aid, autocorrelation analysis

1. Introduction

When the ability to hear declines, people become uncomfortable during conversations and gradually begin to speak less and less. This worsening situation can lead to depression and an increased risk of dementia. In 2015, the Ministry of Health, Labour and Welfare in Japan published an initiative for preventing dementia (New Orange Plan), which states that hearing loss is a risk for declining cognitive function [1]. The first report to show the relationship between

hearing impairment and dementia was published in 1989 [2], and several longitudinal studies that included auditory and nonauditory cognitive testing have shown that people with hearing loss have a 30–40% rate of accelerated cognitive decline [3] and an increased risk of incident all-cause dementia [4, 5]. The implications are that auditory stimulation that reaches the brain can delay aging of the brain and allow communication with family and society to continue. Thus, the earlier that people can receive audiological treatment and hearing aid prescriptions, the better.

2. The history of hearing aids

When we cannot hear what someone nearby is saying, we cup our hand behind our ears. This is actually a type of hand reflector, which can aid hearing by emphasizing in the middle and high frequency range (>500 Hz) between 5 and 10 dB and by blocking unnecessary noise from extraneous directions. The first documented evidence of a hearing aid dates back to the sixteenth century [6] and describes wooden panels that imitated animal auricles and were meant to be worn behind the ear. **Figure 1** shows a 1673 sketch depicting a hearing device called the "*Ellipsis Otica.*" This is one of the oldest illustrations of a hearing aid and was published in *Phonurgia nova*, the first known book to deal with the nature of sound, acoustics, and music in 1673 [7]. Horn-shaped hearing aids called "*Ear Trumpets*" (**Figure 2**) became a common remedy for hearing loss for the next 300 years [8] until the development of electric hearing devices. Before the twentieth century, hearing aids were always thought of as sound collectors. The narrow end of the ear trumpet was inserted in the user's ear, and the broad end faced toward the speaker. Thus, like a cupped hand, the ear trumpet was used between two people standing at close range.

Early on, ear trumpets were made from animal horn, but over time people began making them from wood and metal. The preferred color was black because it blended in with the dark clothes that were often worn by European people of that time. This was perhaps an effort to avoid drawing attention to the horn for fear that one's hearing loss would be exposed. In the eighteenth and nineteenth centuries, hearing aids were designed to be hidden from public view, as can be seen in **Figure 3**. For females, the hearing aid body was placed into a hair band (**Figure 3a**, *Aurolese Phones*) or a handy fan (**Figure 3b**, air conduction fan), which they used in daily life. For men, the hearing aid body was covered by their own beard (**Figure 3c**). The

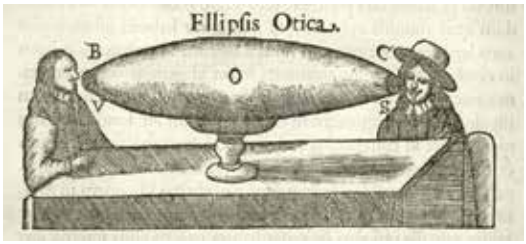

Figure 1. Speaking tubes (*Ellipsis Otica*) from *Phonurgia nova* (1673) [7].

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Figure 2. Illustrations of *Ear Trumpets* in *A clinical manual of the diseases of the ear* (1887) [8].

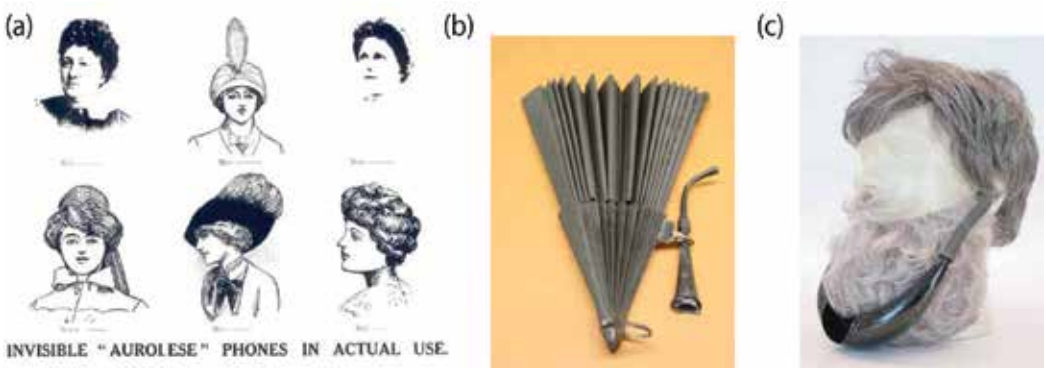

Figure 3. (a) *Aurolese Phones* simulated in hair bands (F. C. Rein co.) from the 1810s. (b) Acoustic fan with ear trumpet from the 1850s. (c) Beard receptacle (Hawksley co.) from the 1830s.

desire to hide hearing aids has not changed with new technology, as evidenced by the current popularity of small, skin-colored hearing aids.

In contrast to the wearable hearing aids described earlier, larger types of hearing aids were placed or mounted on furniture. **Figures 4a** and **b** show a flower-vase-type hearing aid that was placed in the center of a table to collect sound from a number of people conversing during a meal, while the user put the end of tube on his ear. **Figure 4c** shows a chair that was designed to function as a hearing aid. The mouths of the lions carved at the front of the wooden armrests gathered sound, and hollow cavities running through the armrests transmitted the amplified sound to the end of the tube that the user inserted into his ear. Because wearable hearing aids required the speakers to be at very close proximity, those in high positions or peerage used these types of acoustic thrones to keep a suitable distance from unknown speakers that might make them uncomfortable.

In the latter part of the nineteenth century, the invention of the telephone and microphone had a tremendous impact on hearing aid design. Once sound signals (longitudinal wave in air) could be converted into electric signals, hearing aids changed from classical sound collectors

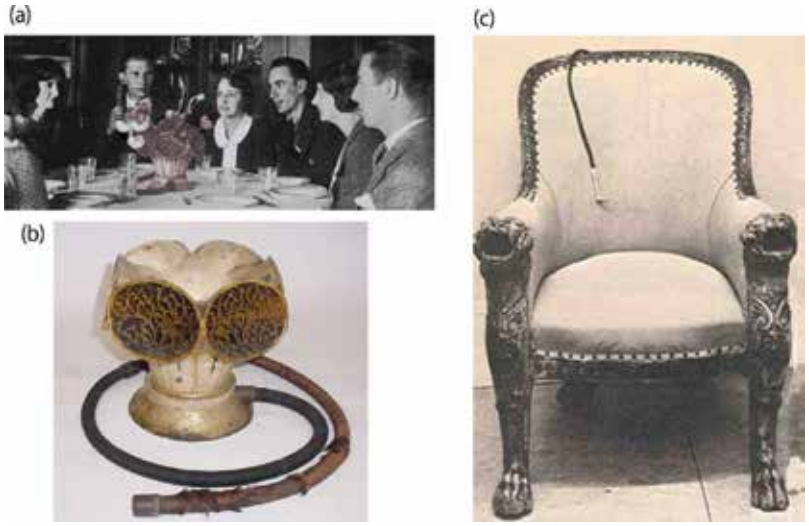

Figure 4. (a) and (b) Flower-vase-type hearing aid for gathering multiple speakers' voices (F. C. Rein Co.) in 1810. (c) Acoustic throne for European royalty in 1819.

to devices that could amplify sound through an electric circuit. The history of the electronic hearing aid is thus very similar to that of the technological evolution of the microphone, amplifier, and battery cell. Between 1989 and 1900, the Akouphone Company produced the first electronic hearing aids called "*Akoulallion*" and "*Akouphone,*" introducing a carbon microphone technique. The carbon transmitter was able to use an electric current to amplify weak signals by 20–30 dB [9]. The *Akoulallion* was large and was used on a table, while the *Akouphone* was portable. Miler Reese Hutchison—one of the company's founding presidents—established the Hutchison Acoustic Company in 1903 and produced "*Acousticon,*" an improved electric hearing aid that was further miniaturized (**Figure 5a**). Users wore the microphone and main body, put the battery in a bag, and held the earphone in their hands. The Danish company *Oticon* and the German company *Siemens* are two current makers of hearing aids that begun operations during this period.

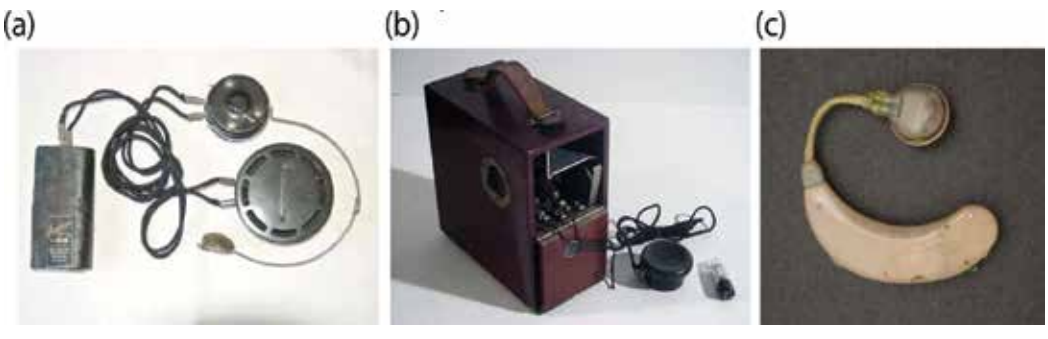

Figure 5. (a) Early electronic hearing aid with carbon components: *Acousticon* model A (Hutchison Acoustic Company, 1905). (b) Early vacuum tube hearing aid: *Vactuphone* (Globe Ear-phone Company, 1921). (c) Behind-the-ear hearing aid-embedded transistor amplifier (Zenith Diplomat Company, 1956).

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In 1920, a new type of hearing aid was developed using vacuum tubes to amplify sound by 70–130 dB. The vacuum tube aid contains a filament (heated electron-emitting cathode) and a plate (the anode), and the amount of applied voltage can control the current traveling from cathode to anode. Although the vacuum tube hearing aid was able to have a high gain and accurate frequency response, it was quite large because two batteries were needed for heating the filament and controlling the electric circuit, and batteries at that time were not small. **Figure 5b** shows the earliest vacuum tube hearing aid, called the "*Vactuphone*" (1921). Because the body was about the same size as the box camera of its day, the "*Vactuphone*" included an unnecessary lens that helped disguise it as a box camera.

Over time, advances in vacuum tube and battery technology allowed hearing aids to be made much smaller, until eventually the vacuum tube hearing aid was small enough to be worn. However, the invention of the transistor 1952 put an end to the vacuum tube era. The transistor is a semiconductor device used to amplify or switch electronic signals and electrical power. The transistor was much smaller than the vacuum tube, consumed much less power, and thus allowed for much smaller battery sizes. A predecessor of a current behind-the-ear (BTE) hearing aid appeared in this period (**Figure 5c**). By wearing it on the head, noise from moving clothes was avoided, the direction of sound could be partially perceived, and the cord could be as short as possible. As technology advanced further with the integrated circuit (IC) and button-sized zinc-air battery (1960s–1970s), miniaturization and technical performance were further improved. The end of the twentieth century saw a steady progression of innovation from in-the-ear (ITE) hearing aids that fit into the concha (1980s) to in-the-canal (ITC) and completely-in-the-canal (CIC) hearing aids (1990s). ITC and CIC hearing aids allowed maximized sound collection from the auricle and sound insulation from environmental noises, as well as cut out wind noise. With these inventions, sound could be amplified by more than 100 dB and people with hearing loss could completely hide their problem with an invisible hearing aid.

3. Digital hearing aid

After achieving this level of hearing aid output gain and miniaturization, scientists and engineers began looking for further ways to improve hearing-aid convenience. For example, analog hearing aids amplify sound from all frequency ranges, which means that both speech and unnecessary background noises are amplified equally. Another problem was that the small size of the devices caused the speaker and microphone to be too close, and acoustic feedback generated uncomfortable levels of amplified sound. In 1996, these problems began to be addressed when hearing aids entered the age of digital sound. The digital hearing aid converts sound into a binary digital signal, which can then be modified by computer software. This type of signal modification is called digital signal processing (DSP) and is the biggest advantage of the digital hearing aid.

Figure 6 shows a computer interface through which the DSP installed in a hearing aid can be controlled after connecting the hearing aid to the computer. The most beneficial aspect

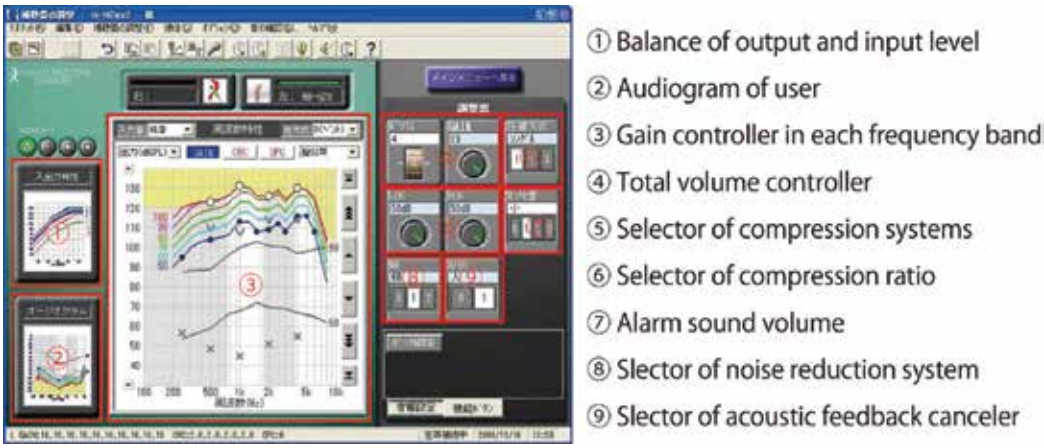

Figure 6. Example of software used to adjust a hearing aid's digital signal processing.

of the DSP is the ability to adjust the output gain in each one or one-third octave frequency band. The computer program designs the shape of a digital filter and modifies the signal passing through the filter (multichannel analysis). Because sound energy in human voice is distributed in a frequency range of 200 Hz to 4 kHz, unwanted noise can be weakened by amplifying only the desired frequency range. Audiograms of people with hearing loss differ according to individual sensitivity to each frequency band (e.g., high tone deafness, horizontal deafness, convex deafness, or concave deafness). The multichannel output can thus limit compensation to the frequency bands for which a person has difficulty in hearing.

The multichannel output is also useful for suppressing acoustic feedback. Acoustic feedback occurs when the following happens simultaneously: (1) attenuation of the speaker's voice by the time it reaches the microphone is less than the amount of sound gain and (2) the phases of the original and feedback signals are mostly overlapped. ITC and CIC hearing aids have a vent to reduce the uncomfortable feeling that can occur in the occluded ear, and the output sound transmitted through the vent can cause acoustic feedback. The solution is a feedback canceller in the hearing aid that identifies the offending frequency-repeating amplification and reduces the sound gain in the corresponding band.

The other important role of DSP is to create a compression system for the output sound. If a hearing aid amplifies sound linearly, it makes already loud sounds excessively loud. Patients with sensorineural hearing loss hear sounds above a certain sound level louder than normal listeners (recruitment hearing). Thus, the sound of a closing door or a cry from a child can annoy hearing aid users. The compression system suppresses the amplification of sounds above a certain sound level and instead fits them within the restricted dynamic range of the user. This system can therefore avoid unpleasant sounds, normalizes the perceived loudness, and improves speech intelligibility.

Another advantage of digital hearing aids is their ability to work wirelessly. In their times, the BTE hearing aid only had a short cord, and the ITC and CIC hearing aids did not

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require any cords or cables. However, in modern society, wireless function is increasingly useful for connecting hearing aids to other electronic devices. For example, because holding a smartphone near one's ear is difficult when wearing a hearing aid, the wireless hearing aid can receive speech signals directly from the smartphone using Bluetooth technology. In the near future, users will be able to control the DSP from a smartphone app. Wireless hearing aids can also help when watching television. By wirelessly connecting to the TV, users can hear clear sound from a TV program without the sound needing to travel through the air. Thus, environmental noise can be minimized and reverberations in a room can be ignored.

Digital hearing aids will likely continue to evolve and add new features and functions. For example, a hearing aid with Global Positioning System will make it easier to be found if it gets lost or misplaced. Like other wearable electronics, if hearing aids incorporate functions for measuring heart rate, step counts, and burned calories, they will become a type of wearable device that supports lifelong health.

4. User subjective assessment of hearing aids

Against a background of various technological advances, the hearing aid has continued to respond to user expectations. Are users today satisfied with the current hearing aid? Countries in Europe and Japan have conducted large-scale market research surveys called *EuroTrak* and *JapanTrak* since 2009 [10]. According to JapanTrak 2015, 1306 people with hearing loss filled out their marketing surveys. Along with a corresponding survey in the US (*MarkeTrak IX* in 2014), we can discuss how satisfied hearing-aid users are in countries whose citizens have access to the latest technology.

Figure 7 shows basic demographic information. The percentage of people with hearing loss is higher for countries with aging populations (i.e., Germany, Italy, and Japan). However, the percentage of people with hearing loss who own hearing aids is lower in these countries than

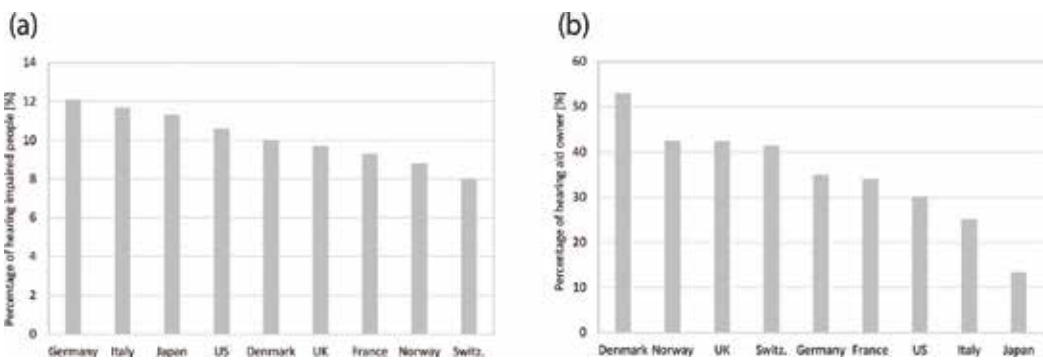

Figure 7. (a) Percentage of people with hearing loss in several high-tech countries. (b) Percentage of people using hearing aids to the number of people with hearing loss in each country.

Country	Amount granted
Denmark, Norway, UK	All expenses paid
Germany	840 Euro
Switzerland	840 CHF (about 740 Euro)
Italy	600 Euro
France	120 Euro
US	Almost none
Japan	Almost none

Table 1. Amount of money granted by governments for hearing aids.

in other countries. This trend is easy to understand after considering how much support people receive to mitigate the cost of hearings aids. **Table 1** shows public financial support for the purchase of hearing aids for each country listed in **Figure 7**. Not surprisingly, the countries showing the highest percentages of people with hearing aids are Denmark, Norway, and the UK, all of which prescribe hearing aids at no cost when a patient is diagnosed with hearing loss. We can thus say that government aid is needed to increase hearing aid distribution or the cost for these hearings aids is too high.

Figure 8 shows the percentage of people in each country who are satisfied with their hearing aids. It is interesting that people in different countries have different views about the performance of their hearing aids, even though the specification criteria are almost the same in all these countries. The countries with established social security systems are ranked in the bottom half, while more than 80% of the people with hearing loss in France, the US, and

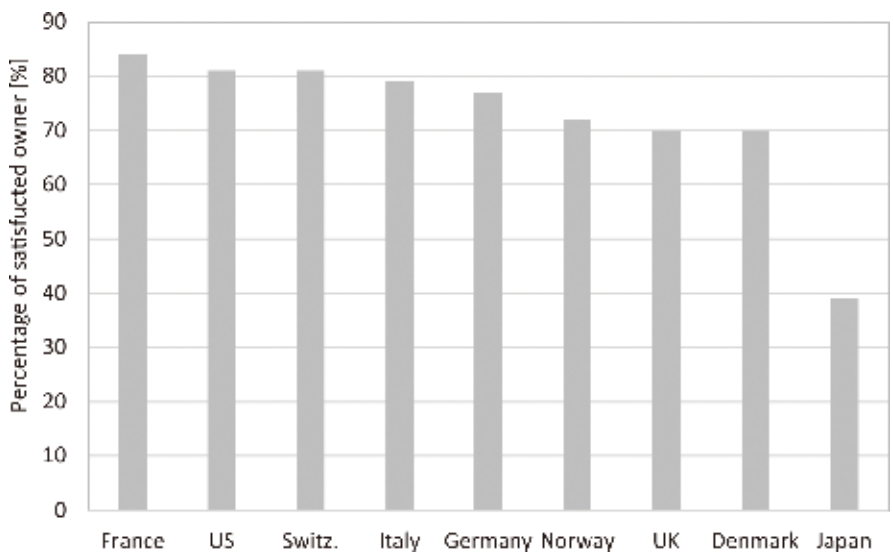

Figure 8. Percentage of people in each country who are satisfied with their hearing aids.

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Switzerland (whose out-of-pocket expenses are higher) were satisfied with their hearing aids. This result seems to support the idea that the user's own expense adds value to the hearing aid. However, users in Japan who receive no public assistance feel the most dissatisfied among the surveyed countries and have one of the lowest percentages of people with hearing aids (**Figure 7b**). Aside from Japan, other countries believe that rehabilitation for hearing loss is a medical practice, and only a state-certified technician can permit a hearing aid to be sold or adjusted. In Japan, however, a private association (The Association for Technical Aids) certifies hearing aid technicians, who can then recommend people to buy hearing aids or to have their hearing aids adjusted. These data imply that a government guarantee earns the trust of hearing aid owners and is related to satisfaction. In terms of hearing aids, the role of government is not to disburse tax money but to make people with hearing loss feel secure. Thus, the current digital hearing aid has already reached the technical ceiling, and satisfaction will depend only on the user's feelings.

5. Implanted hearing devices

Although wearable hearing aids come close to the goal desired by people with hearing loss, implanted hearing devices allow room for further improvements. Several types of implanted hearing devices exist, with one being the bone-anchored hearing aid (BAHA), shown in **Figure 9a**. People have known for centuries that we can perceive sound when our skull bones vibrate, and bone conduction hearing was first described in the sixteenth century [11]. Currently, some commercially available hearing aids utilize bone conduction, and the user fixes a vibrator over the mastoid bone using a hair band. However, vibrating the skull through skin and fat tissue effectively is difficult. Therefore, the BAHA implants a titanium anchor on the temporal bone (behind the ear) to work as a bridge for vibration transmission [12, 13]. The other end of the anchor appears on the skin, and the user attaches the vibrator and receiver to the edge. Compared with previous bone

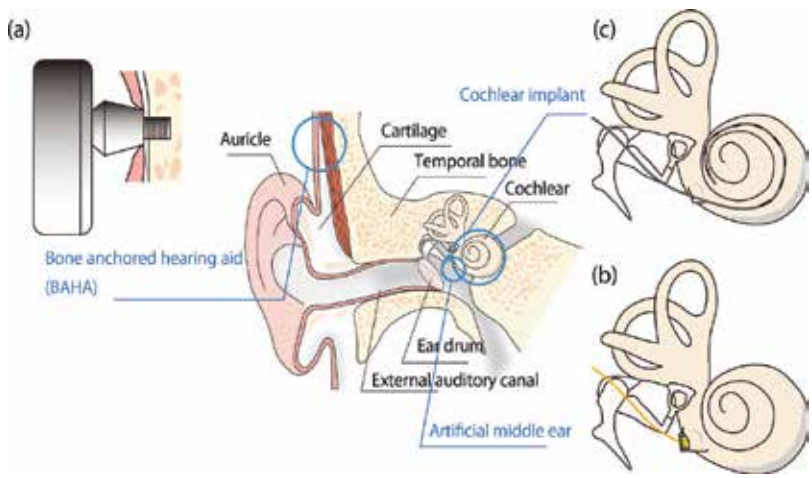

Figure 9. Implanted hearing devices: (a) bone-anchored hearing aid, (b) artificial middle ear and (c) cochlear implant.

conduction hearing aids, this technique has better amplification of higher frequency ranges, which improves speech intelligibility [14, 15].

Another implanted device is the artificial middle ear, which is used when vibration from the ear drum does not smoothly travel through the ear ossicles even after tympanoplasty operations (**Figure 9b**). A sound receiver with a built-in transmitting coil is magnetically attached behind the ear to an implanted receiving coil on the temporal bone, and the signal is transmitted through the skin by the reciprocation of the two coils. The receiving coil activates a transducer that touches the round window of the cochlea, which directly stimulates the basilar membrane. The artificial middle ear was originally developed by a Japanese hearing aid maker (RION Co., LTD.) in 1983, and other makers are currently developing a new stimulation approach using artificial ear ossicles [16].

A third device is the cochlear implant, which converts sound into an electrical current and directly stimulates hair cells in the cochlea using an implanted electrode (**Figure 9c**). The first prototype cochlear implant was conducted by William House and John Doyle in 1961 [17], making the history of this method older than either the BAHA or the artificial middle ear. Subsequently, Clark developed a multichannel electrode cochlear implant in 1977 and produced the first commercialized multielectrode device in 1978 [18]. The cochlear implant is adaptive for profound deafness (hearing level > 90 dB) in Japan. The cochlear implant is reported to be especially useful for children who have not acquired language skills for the linguistic development in the future.

Unlike implanted hearing devices, another future option could utilize stem cells, as inner ear stem cells were found in 1999 [19], and studies in regenerative medicine have developed even further since that time. This means that surgical approaches might become mainstream hearing-loss treatments. One irony is that in Japan, medical expenses for implanted hearing devices are more economic for the individual than the cost of hearing aids because they are considered within the scope of the health-care system.

6. Future of hearing aids

Although implanted hearing devices are a rapidly evolving research field and market, noninvasive hearing aids remain the first approach for treating hearing loss. Although these hearing aids have approximately achieved their aim, three severe problems are yet to be resolved.

The first is the adaptation for profound hearing loss (hearing level > 90 dB). Hearing aids are recommended when hearing level is higher than 40 dB but do not have much effect for profound hearing loss. The exception is the cochlear implant, which can work in some instances.

The second problem concerns how the hearing aids are worn. In the long history of hearing aids, some part is always inserted in the ear. The earplug occludes the external auditory canal, and the annoyance this causes is always a high-ranking reason for discontinuing use. Although the vent in CIC hearing aids as well as open-fitting hearing aids seems to reduce this feeling and the accentuation of the user's voice, they lead to acoustic feedback. Additionally,

earplugs are not possible for patients with atresia of the external auditory canal or microtia, who do not have enough space to insert it.

The third problem deals with the adaptation for sensorineural hearing loss. Unlike conductive hearing loss that affects sound waves conduction anywhere along the route through the outer ear, tympanic membrane, and middle ear, the root cause of sensorineural hearing loss lies in the inner ear or between the auditory nerves and audio cortex in the brain. Some types of hearing loss, like presbycusis, have mixed causes. Patients with conductive hearing loss are able to achieve nearly 100% accuracy on speech intelligibility tests when the speech is presented at a sufficiently loud volume. However, patients with sensorineural hearing loss including presbycusis can only achieve the maximum peak accuracy between 40 and 80%, even when the speech is presented at an optimal volume. In this condition, patients can hear but cannot identify the syllables. Because the main function of a hearing aid is to amplify sound, it may offer limited benefits for sensorineural and mixed hearing loss when used during conversation.

The following subsections describe the solutions or potential clues for solving these three problems and introduce the next-generation hearing aids.

6.1. Bone-conducted ultrasonic hearing aid

Ultrasonic sound waves are those with frequencies greater than 20 kHz, which is the audible limit of human hearing. Although airborne ultrasound cannot be perceived, we can hear ultrasound delivered to the mastoid bone of the skull via a transducer [20]. Importantly, bone-conducted ultrasound can even be perceived by people with profound hearing impairment. One study has reported that these individuals are able to identify ultrasound amplitude-modulated speech signals as speech [21]. Additionally, Hosoi used magnetoencephalography and positron-emission tomography to show that bone-conducted ultrasound can activate auditory cortex of people with profound hearing loss [22]. Although the mechanisms underlying this phenomenon are still only hypotheses, the best guess at the moment is that bone-conducted ultrasound stimulates residual inner hair cells in the base of basilar membrane [23, 24].

An accumulation of research has led to the development of several different bone-conducted ultrasonic hearing aids (**Figure 10**). The HD-GU was a test model developed by Nara Medical University in Japan. Connected to a computer, parameters from various digital signal processors (e.g., noise reduction and nonlinear gain) were controlled on a monitor via software. AIST-BCUHA-003 and AIST-BCUHA-005 were developed by the National Institute of Advanced Industrial Science and Technology (AIST) in Japan [25]. AIST-BCUHA-003 was able to control amplitude and carrier frequency (i.e., ultrasound), while the AIST-BCUHA-005 contained digital signal processors and could control the degree of modulation. Another device was HiSonic, a commercial product that controlled sound amplitude for hearing aids and as therapy for suppressing tinnitus [26, 27]. Using these models, Shimokura was able to see vast improvement in speech intelligibility in a woman with profound hearing loss who he advised to try bone-conducted ultrasonic hearing aids. [28]. The results demonstrated significant improvement from the outset of therapy, and her perceived-speech intelligibility reached 60%, as measured by correctly answered questions in a closed-set test of word intelligibility

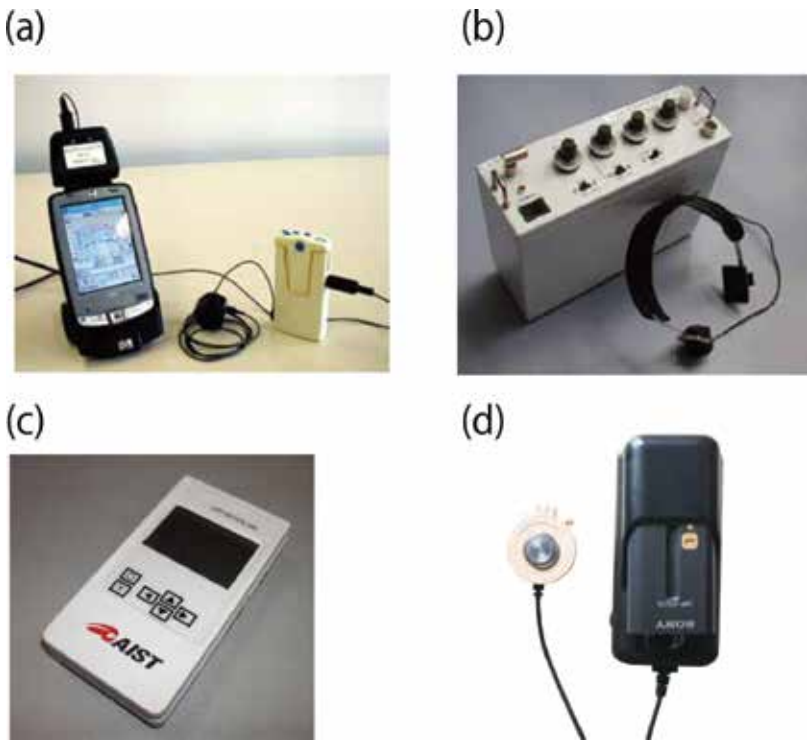

Figure 10. Bone-conducted hearing aids: (a) HD-GU, (b) AIST-BCUHA-003, (c) AIST-BCHA-005, and (d) HiSonic.

with three options. For patients with profound hearing loss, the bone-conducted ultrasonic hearing aid might be a good option before risking cochlear implant surgery.

6.2. Cartilage conduction hearing aid

The uncomfortable feeling that results from an occluded ear is a major hurdle for hearing aid users, and this feeling is always a top reason for discontinuing hearing-aid use. One study tried using active noise control to reduce this feeling [29]. Unlike this digital approach, a cartilage conduction hearing aid reduces the "full ear" feeling with an analog procedure. In 2004, Hosoi found that a specific type of transducer could be used to create clear audible sound when gently placed on aural cartilage [30, 31]. Aural cartilage comprises the outer ear and is distributed around the exterior half of the external auditory canal. Transducer-induced cartilage vibration generates sound directly in the external auditory canal as shown in **Figure 11b** [32–35]. In this case, the cartilage and transducer play the roles of a diaphragm and a loudspeaker voice coil, respectively. When the transducer is ring shaped, it can amplify the sound without occluding the ears (**Figure 11a**). Sound pressure levels in the canal show that the ring-shaped transducer produces an average gain of 35 dB for frequencies below 1 kHz [32]. Although the cartilage conduction hearing aid does not work for those with profound hearing loss, it can help those with moderate loss of hearing. One advantage of cartilage-conducted sound is its unique property of remaining in the canal regardless of the amount of ventilation, and the less sound leakage reduces the risk of acoustical feedback [36].

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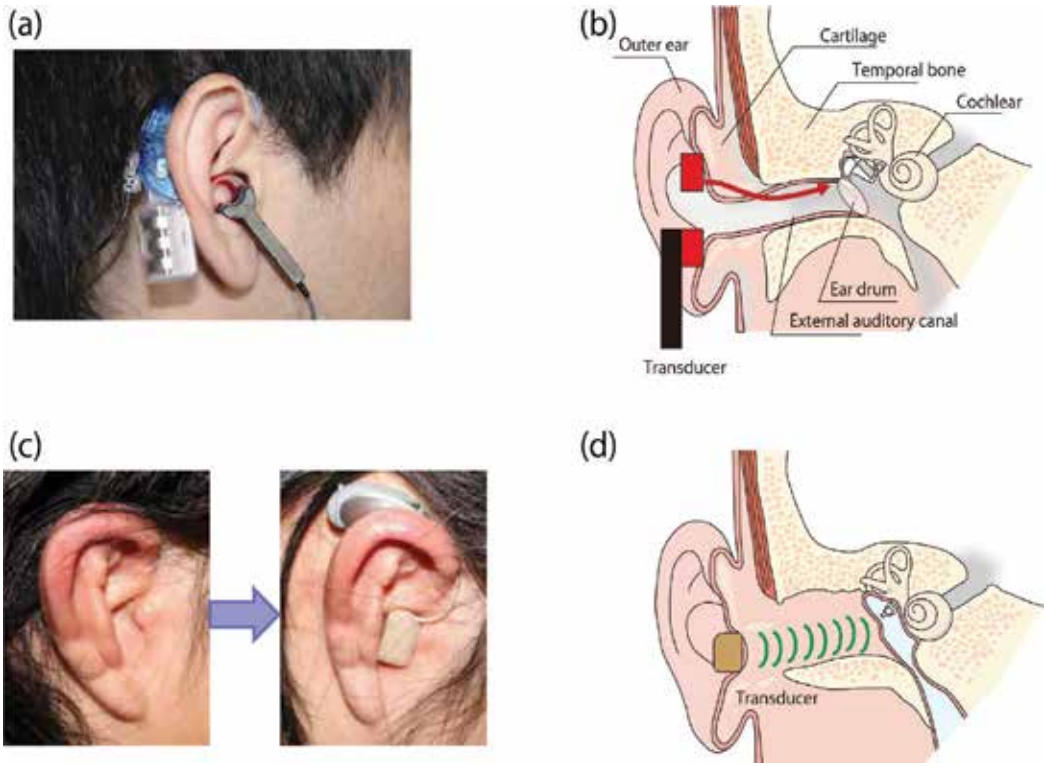

Figure 11. (a) Cartilage conduction hearing aid with a ring-shaped transducer. (b) Sound-transmission pathway in the ear. (c) Cartilage conduction hearing aid with a small transducer. (d) Sound-transmission pathway for people with atresia of the external auditory canal.

The cartilage conduction hearing aid can be used by patients with atresia of the external auditory canal [37, 38]. Because patients whose canal is occluded by fibrotic tissue cannot use a conventional hearing aid because they lack a sound pathway (**Figure 11c** and **d**), they are usually advised to use a bone conduction hearing aid or a BAHA. However, the bone conduction transducer must be pushed tightly against the head insufferably when using it for a long period of time, and the BAHA needs surgery. In contrast, the cartilage conduction transducer only needs to be softly put on the end of the canal because the excitation force required for light cartilage is much smaller than that for heavy skull bone. Despite this, hearing levels for bone and cartilage conduction are almost equivalent at frequencies below 2 kHz [38].

6.3. Autocorrelation analysis of speech signals

The third problem is the speech intelligibility for people with sensorineural hearing loss. As mentioned earlier, patients with sensorineural hearing loss can perceive sound but cannot recognize speech. For example, all Japanese medical institutions use the same list of monosyllable signals for an intelligibility test, which are delivered by a professional female speaker, and studies investigating speech intelligibility in patients with sensorineural hearing loss have identified the less discernible consonants within Japanese monosyllables [39–41]. According to [41], 90% of patients identified monosyllable /i/ correctly, while only 10% could identify /de/.

To explain the difference, studies have investigated several physical parameters. For example, voice onset time (VOT) is the length of time in milliseconds that passes between the release of a stop consonant and the onset of voicing [42]. Another example is the speech intelligibility index (SII), which is a measure of the proportion of a speech sound that is discernible under different listening conditions, such as filtering related to hearing decline or reverberation [43]. Loudness level [phon] can be calculated based on the averaged spectra of a signal, but the masking effects of neighboring auditory filters may be included [44].

All these parameters are related to mechanisms of peripheral perception in the auditory pathway. However, the causes of sensorineural hearing loss are in the inner ear or the auditory nerve. Therefore, subsequent processing after peripheral functions is complete and has to be considered when trying to explain speech intelligibility. A major candidate for imitating subsequent processing is autocorrelation function (ACF). ACF is an established method for temporally analyzing auditory nerve processes [45]. Neural representations that resemble the ACF of an acoustic stimulus have been detected in distributions of all-order interspike intervals in the auditory nerve [46, 47]. Mathematically, the normalized ACF and ACF can be represented by

$$\varnothing(\tau) = \frac{\Phi(\tau)}{\Phi(0)} \tag{1}$$

where $\Phi(\tau) = \frac{1}{2T}\int_{-T}^{T} p'(t)\,p'(t+\tau)dt$ and where 2 T is the integral interval, τ is the time delay, and $p'(t)$ is the signal after it is passed through an A-weighting filter. **Figure 12** shows an example of the calculated monosyllable /sa/. In this case, the ACF was calculated for the integral interval (2 T = 80 ms) that moves with the duration of the monosyllable (running ACF). In the fricative consonant part of the sound (before 0.3 s), the normalized ACF decays suddenly to 0, while in the extended vowel portion of the sound (after 0.3 s), it gradually decays as a function of the delay time. To evaluate the slope of the decay, an effective duration (τ_e) has been proposed [48] that is defined by the delay such that the envelope of the normalized ACF becomes smaller than 0.1. When the consonant component-containing noise element (e.g., /s/ and /d/) occupies the monosyllable, τ_e becomes shorter because it expresses the amount of noise (i.e., $\tau_e = 0$ for white noise and $\tau_e = \infty$ for a pure tone). Indeed, τ_e represents the SN ratio (S: speech and N: noise or reverberation) of a monosyllable itself.

Figure 13 shows the relationships between the physical parameters and the percent of monosyllables articulation presented to patients with sensorineural hearing loss at an optimal volume [49]. Each symbol is the average for a consonant, and $(\tau_e)_{med}$ indicates the median of the time-varied τ_e of the running ACF. Among the four physical measures examined, only τ_e was correlated with speech intelligibility. Effective duration is a measure of temporal pattern persistence, that is, the duration over which a waveform maintains a stable pattern. These data have led to the hypothesis that poor speech recognition is related to the degraded perception of temporal fluctuation patterns. DSPs that prolong the effective duration (e.g., shorten the consonant length or smoothen the voicing frequency) may therefore improve speech intelligibility for those with sensorineural hearing loss.

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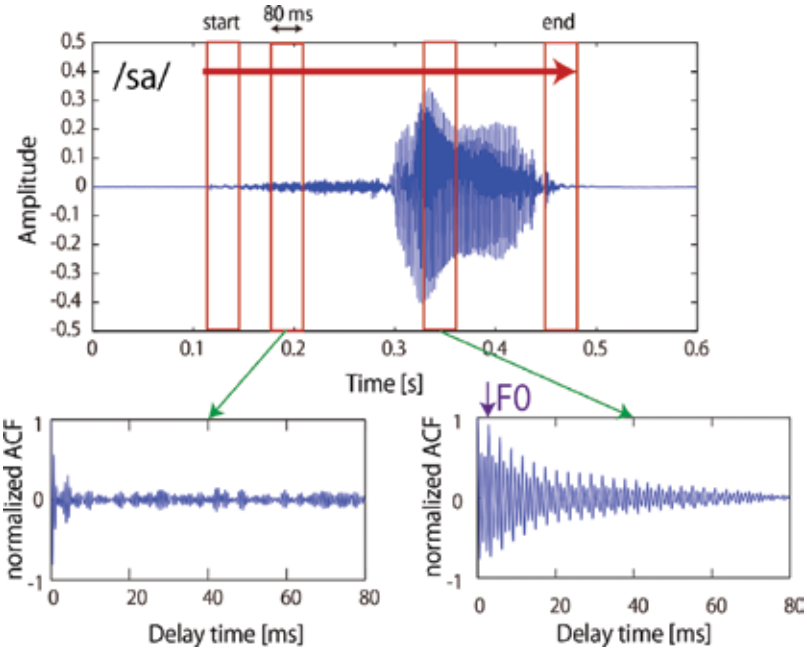

Figure 12. Example of an autocorrelation function calculated for the Japanese monosyllable /sa/ (F0: Fundamental frequency of voice).

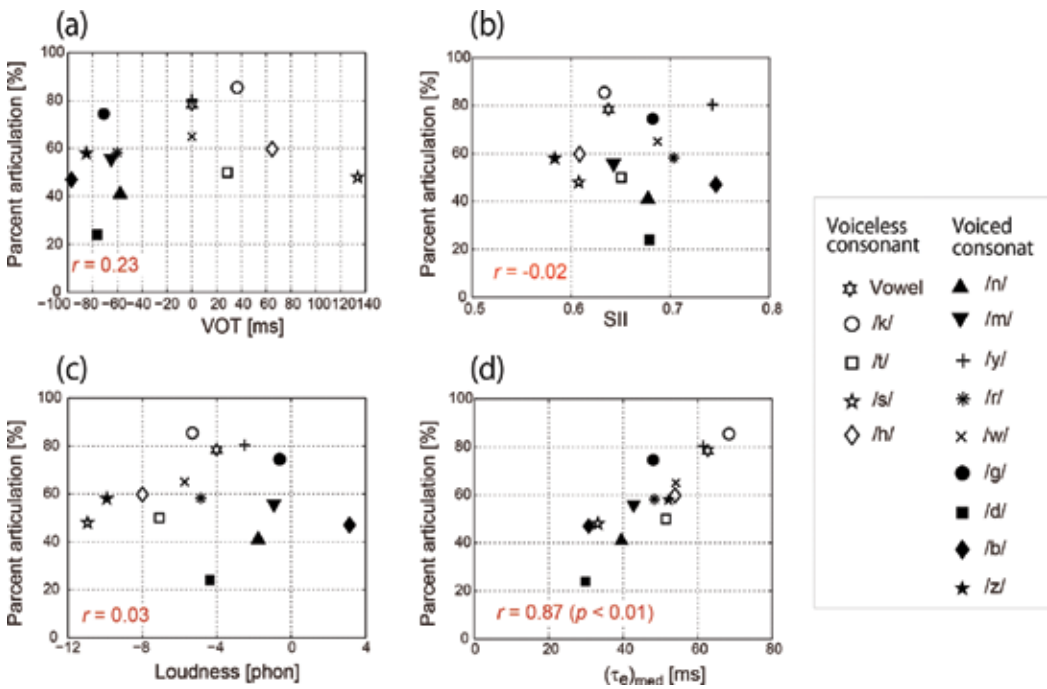

Figure 13. Relationship between the percent of articulation and four physical parameters: (a) VOT, (b) SII, (c) loudness, and (d) $(\tau_e)_{med}$ (R: Correlation coefficient). The different symbols indicate different consonants. Reproduced from (**Figure 5**) in [49].

7. Concluding comments

To avoid advanced hearing loss and instances of hearing loss-related dementia, it is important to recognize hearing loss at an early stage and provide treatment that prevents the loss of hair-cell or auditory-nerve stimulation. In particular, for those who wear hearing aids in only one ear, speech intelligibility is known to degrade more in the other ear [50, 51]. However, currently popular implanted hearing devices are a fairly large burden for people soon after they become aware of their hearing loss. For this reason, we tend to stick to wearable hearing aids that are easy to be put on and take off. Researches are therefore using the scientific method to remove technical barriers for hearing aids. Further, governments should try to remove other barriers by providing services such as financial support or public qualification for handling hearing aids, and companies that make hearing aids should charge less money. This will help slow down hearing loss and lead to a healthier society.

Index of technical terms

Active noise control, p11	Active noise control is a technique for minimizing undesired sound by acoustic interference with a secondary sound source.
Audiogram, p5	Audiogram represents hearing thresholds for standardized frequencies in a dB-scale.
Aural cartilage, p11	Aural cartilage is flexible fibrous tissue shaping an auricle and a part of external auditory canal.
Autocorrelation function (ACF), p12	Autocorrelation function is correlation of a signal with decayed copy of itself as a function of decay.
A-weighting filter, p12	A-weighting filter is designed by a loudness curve (IEC 61672:2003) around 40 phone, and the filtered sound pressure level can quantify the loudness partly.
Bone conducted ultrasonic hearing aid, p10	Bone conducted ultrasonic hearing aid has an ultrasonic transducer which is attached to a mastoid to transmit vibration in ultrasonic range modulated by speech waveform.
Bone-anchored hearing aid (BAHA), p8, p11	Bone-anchored hearing aid is a hearing device which transmit vibration to skull bone through the intermediary of an implanted titanium projection.

Cartilage conduction hearing aid, p11	Cartilage conduction hearing aid transmits sound information by vibrating aural cartilage.
Cochlear implant, p8	Cochlear implant bypasses the normal hearing process and stimulates hair cells in the cochlea using an implanted electrode directly.
Conductive hearing loss, p9	Conductive hearing loss occurs when there is a problem conducting sound waves anywhere along the route through the outer ear, tympanic membrane (eardrum), or middle ear (ossicles).
Effective duration (τ_e), p12	Effective duration is defined by the delay time at which the envelope along the early decay of the normalized autocorrelation becomes below 0.1, and signifies the degree of periodicity contained in a signal.
Fricative consonant, p12	Fricative consonant is produced by forcing air through a narrow channel made by placing two articulators close together.
Full ear, p11	Full ear is uncomfortable feeling when ears are occluded by something, and it emphasize excessively own voice and sound of mastication during a meal.
Loudness level, p12	Loudness level [phon] quantifies the subjective perception of sound pressure and is calculated by spectral energy applied to the equal loudness chart for each 1/3-octave band (ISO 532).
Magnetoencephalography, p10	Magnetoencephalography (MEG) is a noninvasive technique for measuring neuromagnetic signals generated by the brain.
Open-fitting hearing aid, p9	Open-fitting hearing aid has an earplug with a significant leak venting for the purpose of reducing the full ear.
Positron-emission tomography, p10	Positron-emission tomography is noninvasive technique for measuring a positron (positive electron) emitted by a nucleus after blood flow, metabolism, neurotransmitters, and radiolabelled drugs.
Profound hearing loss, p9	Profound hearing loss is an inability to hear sound even in 90 dB in silent condition.

Recruitment hearing, p6	Recruitment hearing is an auditory disorder to exaggerate loudness for sound over a certain amount of sound pressure.
Sensorineural hearing loss, p6, p9, p12	Sensorineural hearing loss is a type of hearing loss, in which the root cause lies in the inner ear or sensory organ (cochlea and associated structures) or the vestibulocochlear nerve (cranial nerve VIII) or neural part.
SN ratio, p13	Signal-to-noise (SN) ratio compares the level of a desired signal to the level of background noise.
Speech intelligibility index (SII), p12	Speech intelligibility index (SII) is a measure of the proportion of a speech sound that is discernible under different listening conditions, and is calculated according to the signal (i.e., speech) to noise (i.e., environmental noise) ratio and the hearing threshold (i.e., audiogram) of each 1/3-octave band.
Voice onset time (VOT), p12	Voice onset time (VOT) is the length of time in milliseconds that passes between the release of a stop consonant and the onset of voicing.

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Chapter 10

Controlling the Biocompatibility and Mechanical Effects of Implantable Microelectrodes to Improve Chronic Neural Recordings in the Auditory Nervous System

Payton Lin, Yu Tsao and Li-Wei Kuo

Additional information is available at the end of the chapter

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Abstract

Implantable microelectrodes are useful for monitoring neural response patterns in the auditory cortex, however chronic neural recordings can often deteriorate with time (e.g. impedance measures across electrode arrays generally increase monotonically over the first 7 days post-implant). This problem is caused by the increasing spatial distribution of reactive tissue responses (corresponding to changes in impedance spectra along the electrode-tissue-interface). Therefore, the design of microelectrode probes must ensure that the neuronal ensembles lie within a cylindrical radius of the recording electrodes. In this chapter, chronic neural recording failure is examined via cortical spike patterns, histological analyses, indentation experiments, and finite element models. Next, the microfabrication of the "Utah" electrode array and the "Michigan" probe is compared to determine how their size, shape, and geometry address: (1) the spatial distribution of neurons (as related to recording quality); (2) the initial penetrating profile (as related to insertion killzones); (3) the reactive cell responses (as related to glial encapsulation); (4) the anchoring of the probe's position in the tissue (as related to micromotions) and (5) the embedding of various bioactive reagents (ex: growth factors, anti-inflammatory drugs, etc.). Finally, a novel hydrogel "Dropping Method" is proposed for controlling the biocompatibility and mechanical properties at the electrode-tissue-interface.

Keywords: auditory cortex, implantable microelectrode array, chronic neural recording, neural probe, brain machine interface, inflammatory response, biocompatibility, insertion killzone, glial encapsulation, micromotion, finite element model, hydrogel

1. Introduction

Brain machine interfaces connect the human brain to electronic devices and computer software [1]. Machine intelligence can offer the inherent advantages of greater processing speeds, computing power, memory capabilities, and even unrestricted sensory perception (e.g. infrared, ultra violet, X-ray, and ultrasonic spectra). With the emergence of deep brain stimulation, neuroprosthesis, neurofeedback, and exoskeleton technologies, science fiction is being bridged into a modern reality. However, the ultimate realization of a brain machine interface is to have a computer system that can chronically interface with the neural tissues. This neurotechnology will require neuroscientists and engineers to work together to address the technical challenges of accessing neural communication channels (for data routing and transmission), preserving the *biocompatibility* (to interface electronic components within the biological neural tissues), and maintaining the bio-signal processing (for selecting the appropriate control signals).

This chapter will focus on the *microelectrode*: a neural probe used in neurophysiology for either recording neural representations in the brain or for electrically stimulating the nervous tissue. Micromachined electrodes and microwires are often used to monitor the neuronal activities by characterizing extracellular field potentials of multiple active neurons. These neural interfaces are artificially-engineered extensions of the nervous system that must coexist in the precise connections of supporting glial cells, oligodendrocytes, astrocytes, and microglia (**Figure 1A**).

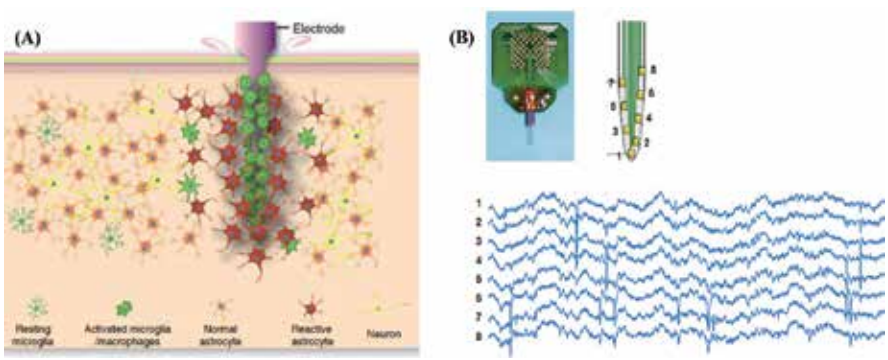

Figure 1. (A) Depiction of cellular changes induced by an implanted electrode and (B) multichannel neural recordings.

Multichannel microelectrodes (**Figure 1B**) can be used to monitor the activity in the *auditory cortex* and to investigate the functional organization of the auditory system [2–4]. For example, a chronic microelectrode investigation of the human auditory cortex [5] revealed a "tonotopic" pattern where the sound-driven units had excitatory receptive fields with sharply tuned best-frequency response over a range of frequencies. These micro-machined devices are currently being developed to control brain machine interfaces [6–8] and can benefit many applications in medicine, communication, entertainment, military, and education. However, there has been one limiting factor that has obstructed their reliability as a fully-implantable neural prosthesis: *chronic neural recordings* have been shown to deteriorate [9, 10] with time (**Figure 2**).

In Section 2, chronic neural recording failure is examined by reviewing cortical spike patterns, histological analyses, indentation experiments, and *finite element models* (FEM). For instance, probe impedance measures have been shown to increase, histological analyses have indicated that changes in the impedance spectra along the electrode-tissue interface are caused by the increasing spatial distribution of the reactive tissue responses, indentation experiments have shown persistent *inflammatory reactions* on the indwelling microelectrodes, and FEMs have simulated that surrounding tissues are compressed by the large stiffness mismatch of the implanted substrates (with pressure profiles revealing extensive tension at the probe tip).

In Section 3, the microfabrication of the *"Utah" electrode array* and the *"Michigan" neural probe* is compared by reviewing how their different sizes, shapes, and geometries can be redesigned to address: (1) the spatial distribution of neurons (as related to improving the recording quality); (2) the initial penetrating profile (as related to minimizing the *insertion killzone*); (3) the reactive cell responses (as related to preventing *glial encapsulation*); (4) the anchoring of a neural probe's position in the tissue (as related to reducing *electrode micromotion*) and (5) the embedding of various bioactive reagents (as related to eluting growth factors, anti-inflammatory drugs, etc.).

In Section 4, a *hydrogel coating* layer is proposed for improving the mechanical properties and *biocompatibility* at the electrode-tissue interface. Hydrogel coatings can be tailored to provide a buffer layer (for reducing stiffness mismatch), and to control the swelling properties to anchor the position of the probe in the tissue. In addition, a novel hydrogel coating method called the "*Dropping Method*" is proposed to control the mechanical properties at the electrode-tissue-interface. The Dropping Method will be compared versus the traditional "*Dipping Method*."

2. Chronic neural recording failure

2.1. Deterioration of neural recordings over time

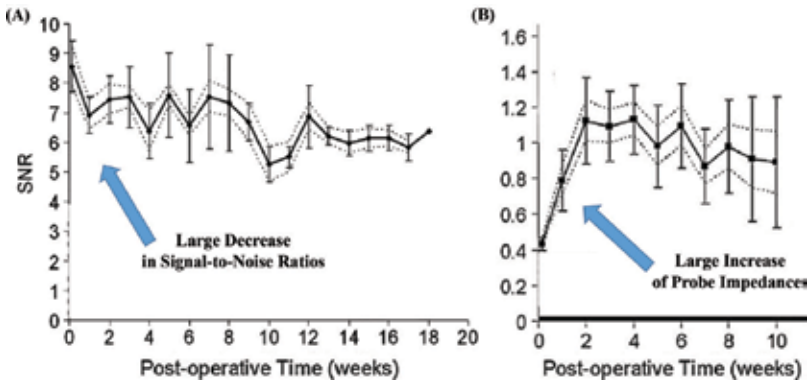

Figure 2. (A) Mean SNR across implanted probes over time and (B) mean impedance values. Reproduced from [10].

Silicon-substrate micromachined probes can provide high-quality multichannel spike activity recordings and local field potentials in the auditory cortex. For acute neural recordings, these measurements are generally stable. However, chronic long-term recordings are limited by the foreign body responses that occur during the wound healing process [9]. Previous research showed signal-to-noise-ratios (SNR) decreased as a function of postoperative time (**Figure 2A**) [10]. Impedance measures across electrode arrays were also shown to increase monotonically over the first 2 weeks (**Figure 2B**). This problem (of electrical signals gradually decreasing over time post-implant) must be solved to improve the chronic recording of neural activity.

Histological analyses have revealed tissue reactions to the implanted probe shanks during the assessment periods. For instance, confocal microscopy and immunohistochemistry protocols were used to measure the cellular density around the implanted electrodes and confirmed that a region of extensive reactive responses occurs around each individual electrode track [11]. By differentiating the spatial distribution of reactive tissue responses corresponding to changes in impedance spectra along the electrode-tissue interface, these findings confirm that reactive tissue responses directly influence the impedance spectra over time.

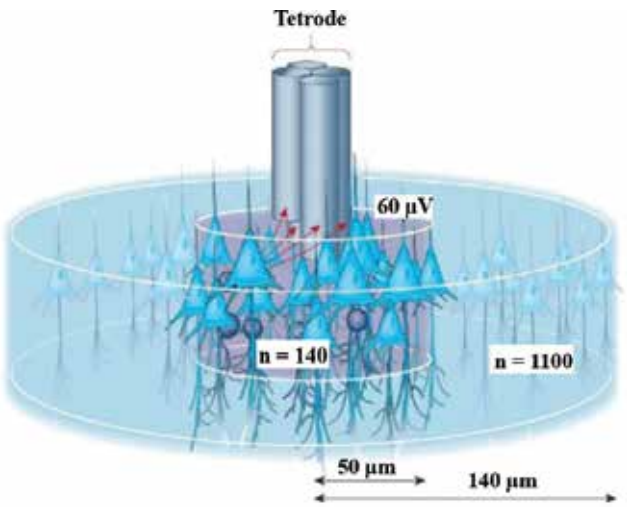

Figure 3. Unit isolation quality varies as a function of distance from the electrode. The spike amplitudes of the neuronal ensembles must lie within a cylindrical radius (n = 140 µm) to be detected. Reproduced from [12].

The recorded spike amplitudes were also measured as a function of the distance between the neuron and the electrode (by making comparisons from a multisite tetrode wire [12]). **Figure 3** shows that the extracellularly recorded spike amplitudes decreased rapidly with distance (a finding that indicates that the neuronal ensembles must lie within a cylindrical radius of ~140 µm of the recording electrode to effectively monitor the extracellular spike amplitudes). These *"cylindrical radius"* distances will be important to consider since previous studies have shown that the inflammatory responses can extend to ~100 µm.

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2.2. Insertion killzone

When inserting a microelectrode, the microshaft must penetrate through arteries, veins, tight junction cells, collagen, and smaller vessels in the pia. The shaft must then penetrate through tissues composed of neurons, glial cells, capillaries, arterioles, and venules. The tip of the shaft must be sharp enough to puncture through the microtubules and the fibrous structures within the neurofilaments. This electrode insertion process inevitably causes death and degeneration of its neighboring neurons and capillaries during the surgical implantation [13]. The *insertion killzone* is defined as the region around the shaft where the local neuron density is lower than the expected neuron density by a 90% confidence interval (**Figure 4A**). The tearing of neurons will cause the temporary loss of action potential capability and cell death due to the influx of calcium. The cutting of vessels and capillaries will cause microhemorrhages that can displace the neural tissue. If the neural tissue is compressed or stretched, the leakage of ions can lead to the loss of cellular homeostasis. Therefore, the penetrating shafts should be carefully fixed to a manipulator to prevent significant misalignment and to minimize the killzone (**Figure 4B**).

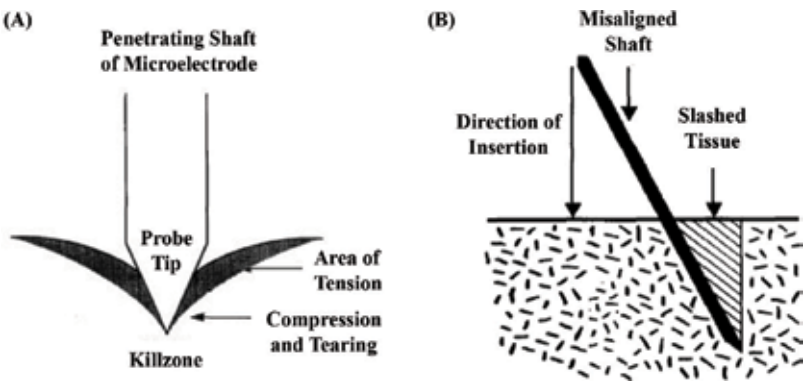

Figure 4. (A) Damage during insertion of a sharp microelectrode (where the shaft stretches the tissue beyond its elastic limits while passing through) and (B) significant axial misalignment of a shaft creates a swath of damage during insertion.

Penetrating shafts should be designed to minimize the initial mechanical trauma, to preserve the neuronal density in a local area around the implanted array, and to minimize the early reactive responses caused by the pathway of tissue damage. Indentation experiments have shown that immediate vascular and brain damage results in the recruitment of cells from the peripheral immune system and the activation of resident astrocytes or microglia. The reactive responses can be compared by immunochemically labelling for glial fibrillary acidic protein (GFAP), vimentin (for astrocytes), or ED1 (for microglia). When devices of different size were inserted, it was found that the volume of the reactive tissue responses was proportional to the cross-sectional area [14]. For instance, the smallest device (smallest cross-sectional area) with smooth surfaces and rounded corners caused less damage to the tissue, produced a smaller volume of reactive tissue, and left a smaller hole when removed from the tissue 1 week later.

2.3. Prolonged injury response

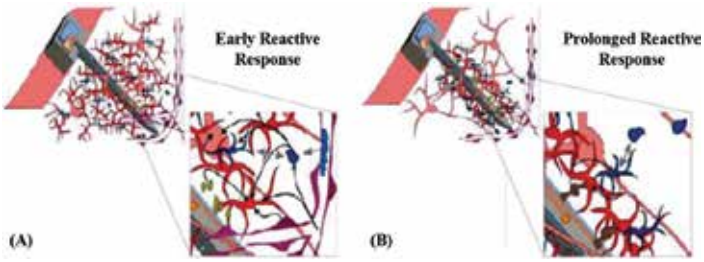

Figure 5. (A) Early reactive responses and (B) prolonged reactive responses to a chronically implant. Reproduced from [14].

An immunohistochemistry experiment [14] showed that the early reactive response (within 1 week (**Figure 5A**)) was associated with the amount of damage generated during the insertion (which depends on the device size or shape). However, this same study also showed that the prolonged reactive responses (after 4 weeks (**Figure 5B**)) eventually became similar (ultimately resulting in a compact cellular sheath containing astrocytes and microglia). While it is always better to minimize the insertion killzone, these results clearly indicate that a second sustained response occurs that is related to the tissue-device interactions. For instance, a long-term study [15] showed that the persistent ED1 up-regulation and neuronal loss (associated with the foreign body responses) were not observed in microelectrode stab controls (which indicates that the phenotype did not result from the initial mechanical trauma of the electrode implantation). Moreover, chronically-implanted electrodes were also covered in ED1/MAC-1 immunoreactive cells and released the pro-inflammatory cytokines MCP-1 and TNF-α (which are only characteristics of chronic inflammatory reactions). **Figure 6** shows that the zones of astrocytosis and connective tissue vary in proportion to an implant's reactivity [16]. Although the normal long-term response to an indwelling microelectrode is to develop a reactive glial tissue (that eventually forms into a fibrotic encapsulation layer or a glial scar), this sustained injury response has also been associated with chronic recording failure since the encapsulation (from persistent inflammatory reactions) isolates the electrodes from the surrounding neurons and decreases the stability and quality of the neural recordings.

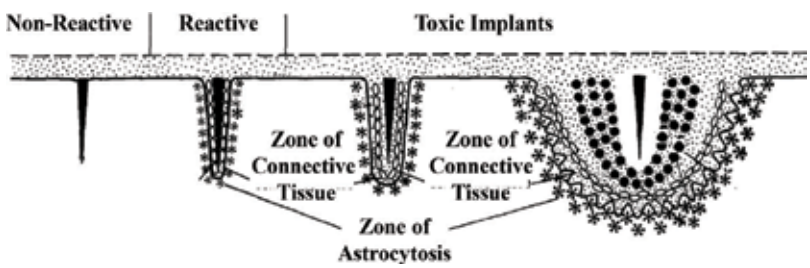

Figure 6. Histopathological changes that occur around a non-reactive implant, a reactive implant, and toxic implants.

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2.4. Micromotion

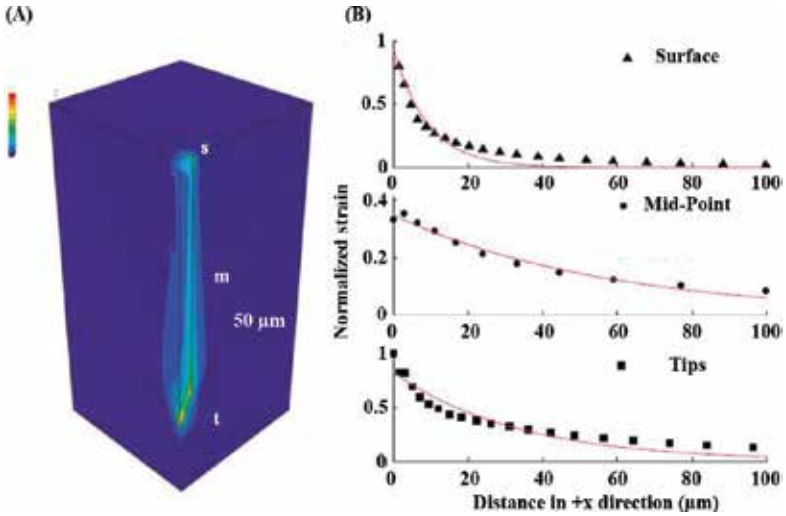

Figure 7. (A) Finite element model (FEM) strain profile of the radial tethering forces in the brain tissue that results from a 1 μm displacement of a silicon probe extended to 100 μm from the interface (s = surface, m = midpoint, t = tip). (B) Normalized strain values decreased exponentially as a function of distance in the brain tissue. Reproduced from [18].

The mechanical properties of the brain can be researched by mathematical simulation models that faithfully represent the geometry, material properties, and boundary or load conditions. For instance, an in-vivo indentation experiment [17] described the soft tissue deformation with a three-dimensional non-linear finite element model (FEM) of geometric information from the brain (obtained via magnetic resonance imaging techniques). Another FEM study measured the effects of tethering forces, probe-tissue adhesion, and the stiffness of the probe substrate on the interfacial strains induced around the implant site [18]. The results indicated that the interfacial strains were created by *micromotions* of the chronically implanted electrode, and that these mechanical strains around the implant site are likely responsible for the sustained tissue responses in chronic implants. In addition, the elevated strains at the probe tip were shown to cause poor probe-tissue adhesion and delamination of the tissue from the probe. The simulated probes also induced strain fields that displayed high radial tethering forces, with pressure profiles revealing extensive tension and maximum frictional shear stress at the tips of the arrays (**Figure 7**). Therefore, these findings indicate that softer substrates should be used to reduce the strain at the probe-tissue interface (to reduce tissue responses in chronic implants). Specifically, the magnitude of the micromotions should be reduced at the microelectrode's tip position to ensure the stability of the recordings at the cortical surface since gliosis is typically observed at the probe tips [13] (with up to a three-fold increase in the size of the surrounding glial sheath compared to at other areas of the arrays [19]). Micromotions and cortical surface displacements can also result from respiratory pulsations [20], behavioral sources [21], and the translational movements of the electrode's tethering lead wire [22] (which can occur due to the rotational acceleration of the head [23]).

3. Comparing "Utah" electrode arrays versus "Michigan" neural probes

Implantable probe designs have primarily focused on modifying the size, shape, or geometry to minimize reactive cell responses. For the *"Utah" electrode array* [24] and the *"Michigan" neural probe* [25], Section 3.1 compares the spatial distribution of neurons (as related to improving recording quality), Section 3.2 compares the initial penetrating profile (as related to minimizing the insertion kill-zone), Section 3.3 compares the reactive responses (as related to preventing glial encapsulation), Section 3.4 compares the anchoring of the probe's position in the tissue (as related to reducing electrode micromotion), Section 3.5 compares the embedding of bioactive reagents (as related to eluting growth factors, anti-inflammatory drugs, etc.).

3.1. Spatial distribution of neurons

3.1.1. Utah electrode array

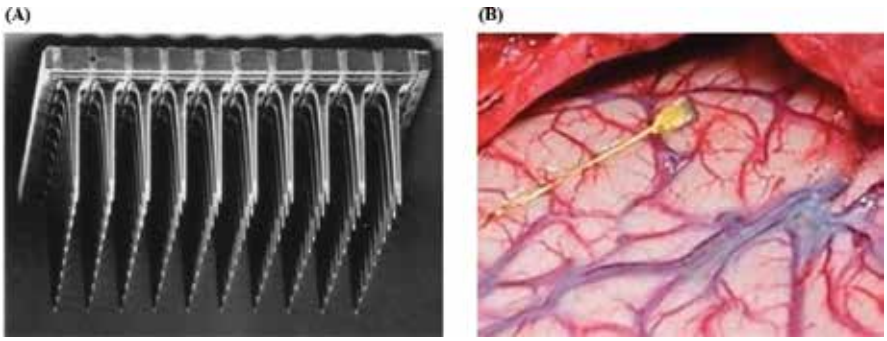

Figure 8. (A) The 100 microelectrode Utah electrode array and (B) the electrode probe tips implanted into the cortex.

The Utah array was designed from the ground up (with new manufacturing techniques [26]) to meet the specific needs of a multichannel neural interface [24]. Psychophysical experiments usually require evoking discriminable patterned percepts from many electrodes. Therefore, the Utah array (**Figure 8A**) was designed to possess a large number (~100) of large electrodes (~1.5 mm) that are typically in a square grid that projects out from a thin (~0.2 mm) substrate. **Figure 8B** shows the tapered electrodes suspended in a "sea of glass" substrate (that isolates each of the individual electrodes in the array from each other (~0.4 mm separation) to form a very effective dielectric insulating layer between the adjacent electrodes). The electrode probe tips are coated with platinum, gold, or iridium to facilitate the electronic to ionic transduction. The array's substrate was designed to be thick enough to prevent breaking upon insertion, but thin enough to rest on the cortical surface without producing a constant downward force on the array that could push it further into the cortex.

3.1.2. Michigan neural probe

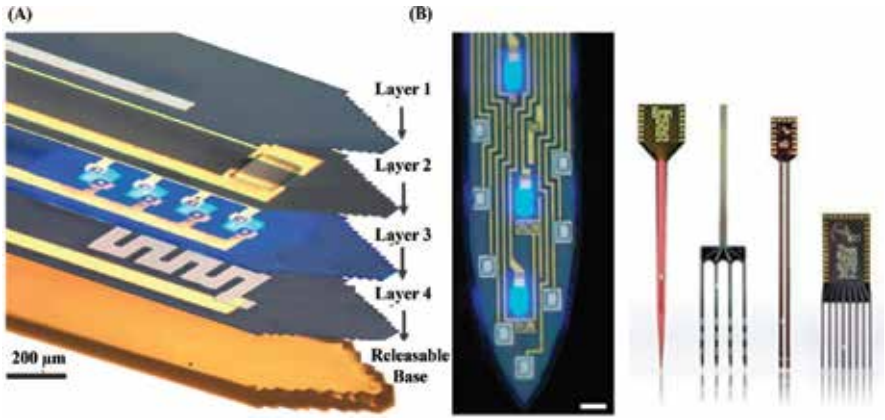

Figure 9. (A) Silicon-substrate Michigan probe and (B) microfabrication borrows semiconductors manufacturing methods.

Unlike the Utah electrode array [23], the planar Michigan probe [27] was only designed to take advantage of photolithographic manufacturing techniques from the semiconductor industry (**Figure 9A**). The extensibility of this platform technology enables these micromachined probes to be built with batch fabrication, easy customization of recording site placements or substrate shape, high reproducibility of geometrical/electrical characteristics, and the ability to integrate with ribbon cables or to incorporate on-chip electronics for signal conditioning (**Figure 9B**).

Unfortunately, the Michigan probes are known to induce a chronic breach of the blood–brain barrier [28] which leads to more chronic inflammation and culminates in neurodegeneration and ultimately to electrode failure (as described in Section 2). For instance, Michigan probes showed a significantly higher breach and worse wound-healing in comparison to microwires.

Since there is a trade-off between the size (spatial selectivity) and quality of signal recordings (sensitivity) in a neural microelectrode, previous research have altered the electrical properties by synthesizing biocompatible conducting polymers (**Figure 10A**) such as polypyrrole (PPy) and poly(3,4-ethylenedioxythiophene) (PEDOT) directly onto the electrode. Electrochemical deposition (**Figure 10B**) allows polymer films to be formed in a one-step process with a high degree of control over the film thickness and surface properties (e.g. with nanotubes in [27]).

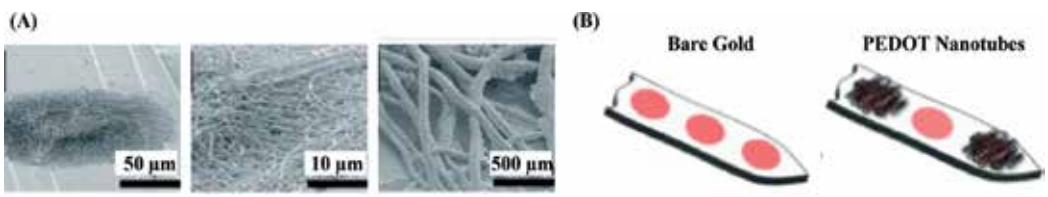

Figure 10. (A) Scanning electron microscope of deposited polymer and (B) uncoated vs. PEDOT nanotube (NT) electrodes.

3.2. Initial penetrating profile

3.2.1. Utah electrode array

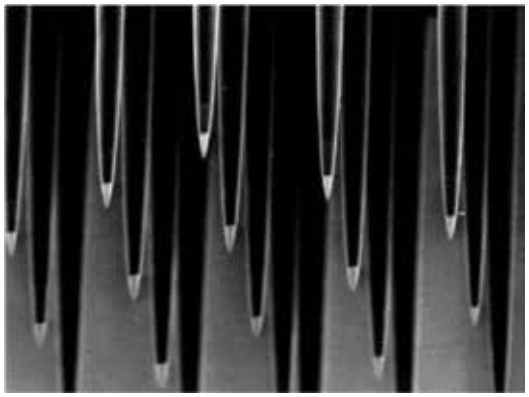

Figure 11. Penetrating shafts of the Utah electrode array with probe tips coated with platinum, gold, or iridium.

The penetrating electrodes of the Utah array (**Figure 11**) were designed to be slender enough to retain sufficient strength for withstanding the implantation procedure, yet to compromise as little cortical volume as possible (only 80 μm in diameter at the base). The needles were intentionally designed to have a cylindrical/conical geometry (rather than a planar geometry) to displace the tissues they are inserted (rather than cutting their way through). In addition, an "Impact Insertion" technique was designed to inject the array into the cortex at a high velocity [26]. This momentum transfer tool preserves uniformity and prevents dimpling of the cortex.

3.2.2. Michigan neural probe

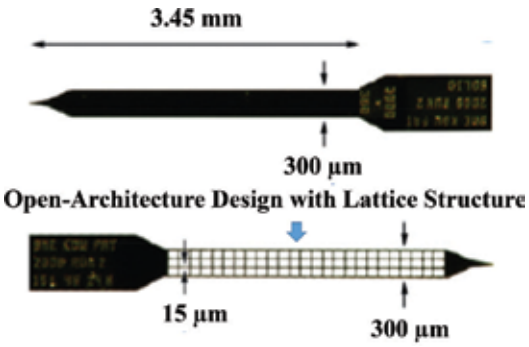

Figure 12. Comparison of a solid shank vs. the open-architecture design with a lattice structure. Reproduced from [25].

Despite evidence that smaller implants can increase the survival of neurons [29], the research direction for Michigan probes has been primarily guided by the *critical surface area model* [25]. This theory is supported by results showing microelectrodes with lattice structures (**Figure 12**)

exhibited less inflammation-related biomarker distribution in tissues compared to the solid shanks (even though both have identical penetrating profiles). However, Section 3.4.2 will show the alternative theory of *mechanical property differences* [30] can also explain these results.

3.3. Reactive processes

3.3.1. Utah electrode array

The electrodes are built from biocompatible materials such as silicon, silicon nitride, silicon dioxide, platinum, titanium, tungsten, and silicone. Histological analyses show the neuronal cell bodies remain in close apposition to the electrode tracks (especially in sections where the tracks are similar in diameter to blood vessels). The benign tissue response showed that a thin capsule (~2–5 microns) forms around each electrode track. Histological samples also revealed gliosis, fibrotic-tissue buildup between the array and the meninges, bleeding in some tracks, and some array displacement through the cortex. Despite these reactive responses, electrodes were shown to be able to record single- and multi-unit responses in the cortex for over 3 years (the longest intervals studied). Therefore, the stability of these units over periods of months provides the most compelling evidence for the biocompatibility [23].

3.3.2. Michigan neural probe

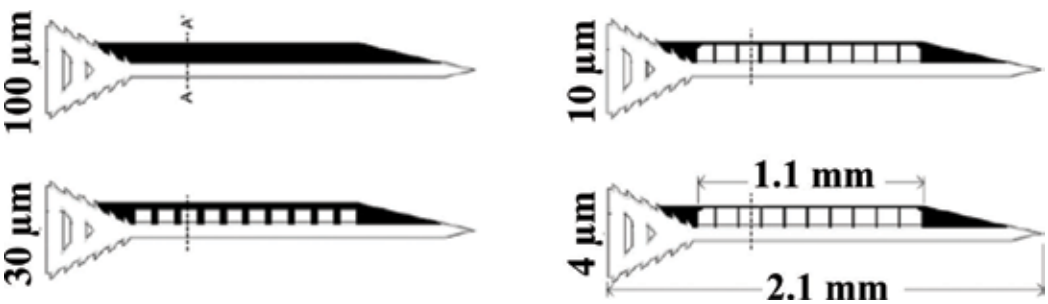

Figure 13. Comparison of a solid shank vs. open-architecture designs with varying lattice sizes. Reproduced from [30].

Glial sheaths (consisting of activated microglia and hypertrophied astrocytes, meningeal cells, and oligodendrocyte precursors that produce extracellular proteins that hinder local nerve regeneration) have been shown to form around the probe tract. As mentioned in Section 2, this tissue encapsulation is concomitant with a decrease in signal quality for neural recordings. Therefore, probe geometry has been investigated as a parameter for reducing chronic tissue encapsulation. Open-architectures (**Figure 13**) can reduce tissue encapsulation by presenting a narrow edge of surface area to prevent the prototypical attachment and spreading of foreign body responses (as cells would theoretically be unable to attach or create cytoskeleton tension below a certain dimension [30]). The tissue reactivity around the smallest lattice structure was expected to induce the least encapsulation. However, the comparison between probe designs indicated that the differences in encapsulation and neuronal loss was insignificant. Qualitative histology also showed similar responses inside the lattice region and around the shank. This has led to the *mechanical property differences* theory (which is discussed further in Section 3.4.2).

3.4. Anchoring of the probe's position

3.4.1. Utah electrode array

The large number of penetrating electrodes presents a very large surface area to the cortex and the implanted array tends to self-anchor to the cortical tissues. More importantly, the "sea of glass" allows the array to float in the cortical tissues as the cortex moves due to respiration, blood pumping, and skeletal displacements. This design feature produces an extremely stable interface with the surrounding neurons as it moves with the cortex and thereby produces very little micromotion between the electrode tips and the neurons near its active tips. In addition, GFAP staining showed that a fixation mode that un-tethers the implant from the skull elicits a smaller tissue reaction and results in the survival of a larger number of neurons in the region closest to the tissue interface [29].

3.4.2. Michigan neural probe

In Sections 3.2.2 and 3.3.2, the *critical surface model* was used to explain the benefits of open-architecture designs [25, 30]. However, an alternative theory [30] was offered to explain how the open-architecture designs reduce tissue encapsulations compared to the solid shanks. The theory of *mechanical property differences* assumes that lattice structures reduce the induced strain from relative movements (e.g. micromotion) between the probe and the tissue (occurring from the continual pulsations of vascular and respiratory oscillations). In other words, the adjoining lattice structure is assumed to present a more flexible mechanical interface that can improve the mechanical surface properties (relative to the solid probe shank). This competing theory of *mechanical property differences* is supported by FEM results that demonstrate that the shape of the electrode substantially influences the local pattern and the magnitude of strain around the electrode (especially at the electrode tip where the shank has a spear-head shape or at regions that have discontinuous or sharp edges [31]).

The theory of *mechanical property differences* is also supported by electrophysiological data [28] showing the Michigan electrode's recording performance failed faster relative to a microwire electrode. Since persistent micromotions are known to trigger a complex cascade of events, it was hypothesized that the different material properties and design of the Michigan electrode was the cause for the diminished wound healing response, the increased inflammation, the enhanced blood–brain barrier permeability, and the infiltration of inflammatory myeloid cells. For instance, a genomic analysis revealed an upregulation of MMP-2 (for facilitating wound healing and promoting neuronal regeneration) and blood–brain barrier stabilizing proteins in microwire electrodes (indicating enhanced stability and reduced micromotions compared to Michigan electrodes). Despite these findings, the *critical surface area model* theory is preferred over the theory of *mechanical property differences* because of previous results that have shown negligible differences in glial encapsulation between the soft and flexible parylene/SU-8-based structures in [30] and the silicon-based arrays (that are orders of magnitude stiffer) in [25].

3.5. Embedding of bioactive reagents

3.5.1. Utah electrode array

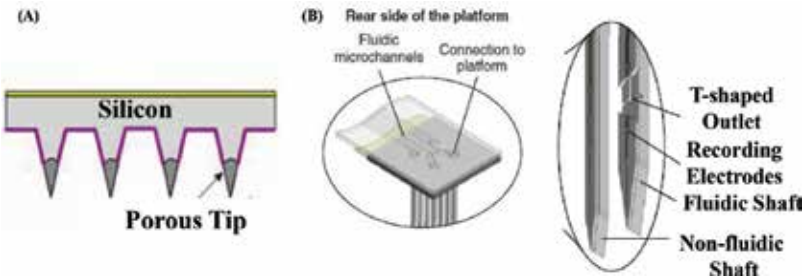

Figure 14. Platinum coated tips of the Utah electrode. Scale bar = 0.5 mm. Reproduced from [32, 33].

The microneedle array can be fabricated with porous tips that can be loaded with drugs that have a high molecular weight [32]. These porous tips are nano-structured silicon (**Figure 14A**), a material that is biocompatible, bioactive, biodegradable, and appropriate for the cultivation of adherent cells in-vivo without noticeable toxicity for biological applications. Drug delivery is also possible in the 3D floating silicon array by using a silicon platform that has microfluidic cables with adapters used for liquid supply [33]. Selected shafts can be equipped with fluidic integration (**Figure 14B**) with either one independent fluidic channel (to maximize the volume coverage) or two independent microchannels (to infuse both a drug and a buffer reference at the same location) when combining drug delivery within the array of recording electrodes.

3.5.2. Michigan neural probe

Planar microelectrodes can directly utilize innovations from micro-fabrication technology and lab-on-a-chip delivery devices. For instance, aerosol jet printing technology can be utilized to directly construct a patterned neural interface with anti-inflammatory nanocarriers [34]. 3D probe structures with microfluidic channels can also be fabricated via surface micromachining and deep reactive ion etching (DRIE) [35]. Neural probe designs (**Figure 15**) can also be bulk-microfabricated to include microchannels along the shanks for microscale and controlled fluid delivery through the blood–brain barrier [36].

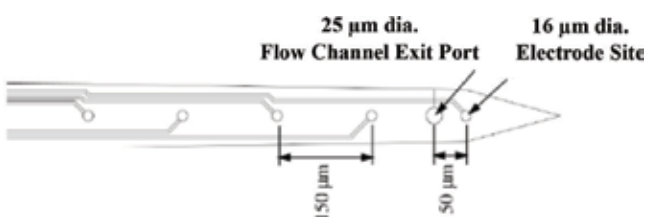

Figure 15. Probe design with microchannels along the shanks for controlled fluid delivery. Reproduced from [36].

4. Hydrogel improves biocompatibility and mechanical properties

4.1. Improved biocompatibility

Hydrogels such as Alginate are naturally occurring polysaccharides that are typically obtained from brown algae seaweed (**Figure 16**). These water-soluble biomaterials have many versatile properties such as gelling and film-forming. Hydrogels are biocompatible and are commonly used in biomedical or tissue engineering applications. Hydrogels are formed by cross-linking hydrophilic organic components and can respond to specific environmental changes [37]. This makes hydrogels the ideal polymer matrix for controlling the delivery of drugs and bioactive components into a complex biologic system.

Alginate hydrogels have been successfully applied as a coating on the Michigan probes. One study [38] showed that biodegradable neurotrophin-eluting hydrogels can be applied on the microelectrode arrays to attract neurites to the surface of the electrodes (for improved neuron-electrode proximity). Hydrogels can also be loaded with nanoparticles of anti-inflammatory agent dexamethasone (DEX) for drug delivery [39]. In-vitro drug release kinetics has revealed that 90% of the DEX can be successfully released from entrapped nanoparticles over 2 weeks. In addition, the impedance of the nanoparticle-loaded hydrogel coatings on microfabricated neural probes were equivalent to the unmodified/uncoated probes controls (indicating that the loaded-nanoparticles do not hinder electrical transport). Most importantly, the chronically implanted electrodes loaded with DEX were shown to maintain impedances in-vivo (unlike the control electrodes that showed increases after 2 weeks of implantation). This improvement in chronic neural recordings indicates the DEX-modified neural probes reduced the amount of glial inflammation via local administration of therapeutic agents. Hydrogels can also be used as a scaffold to encapsulate drug-incorporated biodegradable nanofibers for a more sustained and slower release (to reduce the burst effect [40]).

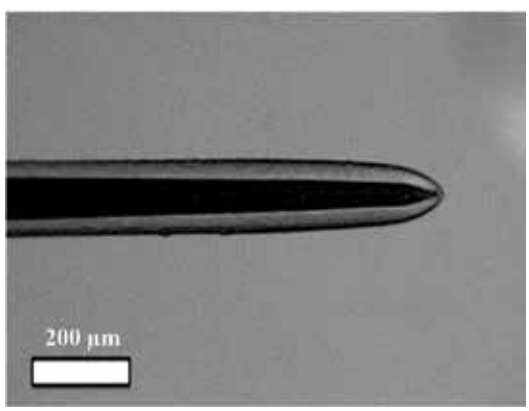

Figure 16. Optical microscopy image of an Alginate hydrogel coating on a Michigan probe. Reproduced from [41].

4.2. Improved mechanical properties

Hydrogels have also been proposed to improve the mechanical properties of the implantable microelectrodes. First, hydrogel coatings can be dehydrated to minimize the initial penetrating profile [41]. Second, the degree of reswelling can be controlled by using different cross-linking molecules to better anchor the position of the probe in the tissue after the implantation [42]. Third, the shear moduli of a hydrogel can be tightly regulated by controlling the cross-linking densities to reduce the stiffness mismatch between the hard silicon-based probes (~100 GPa) and the soft tissue (~10 kPa). Fourth, the uniformity of the hydrogel coating can be controlled by changing the concentration of the solution. Lastly, the hydrogel thickness can be controlled by quickly drying the coated surfaces in air and then overlaying additional layers on top.

Despite the many advantages of hydrogels, the spatial distribution of neurons (as it relates to recording quality) has been a barrier to the practical implementation of hydrogel coatings on microelectrodes. For instance, neural recordings in the auditory cortex showed a significant loss in functionality (as determined by the number of clearly detectable units and the average signal-to-noise ratios [43]). In fact, in-vivo experiments showed that only 30% of the electrode sites (with 80 μm thick hydrogel coatings) could record detectable signals from surrounding neurons and that the average signal-to-noise ratio dramatically decreased (even for 5 μm thick coatings). The loss in neural recording quality is hypothesized to be caused by the reswelling properties of the dehydrated hydrogel coatings (which can affect the spatial distribution of the target neurons around the implanted electrode). In other words, the low signal detection is hypothesized to be caused by the post-implantation water absorption which pushes the target neurons away from the electrode surfaces as they rehydrate (and beyond the *cylindrical radius* distances in [12] that are required for effective electrode recording, as illustrated in **Figure 3**).

To solve the hydrogel swelling problem, [44] proposed to modify the electrode design to place the recording sites in closer proximity to the hydrogel's surface (**Figure 17**). The deposition of conducting polymer PEDOT has also been shown to restore some of the lost functionality of electrode sites with thicker hydrogel coatings [43]. Alternatively, fibrin can be selected (rather than Alginate) to be reabsorbed in the surrounding tissues 7 days after the implantation [45].

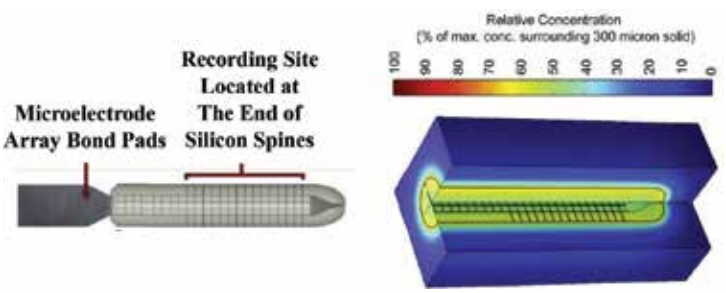

Figure 17. Electrode design with recording sites in closer proximity to the hydrogel's surface. Reproduced from [44].

4.3. The "Dipping Method"

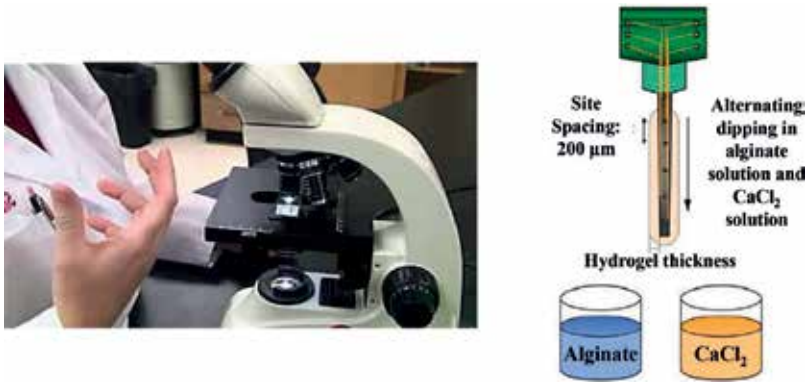

Figure 18. Dipping Method for hydrogel coating of neural electrodes with optical microscopy. Reproduced from [43].

While previous solutions to the hydrogel swelling problem have mostly proposed physical changes to the actual microelectrode or the hydrogel [39–45], most attempts still rely on the "*Dipping Method*" for depositing the hydrogel coatings onto the microelectrodes (as proposed in [41]). **Figure 18** shows the Dipping Method involves the repetitive dipping of electrodes (e.g. via an inverted fine-tooth syringe pump [44]) into an alginate solution followed by immersion in a $CaCl_2$ solution until a desired coating thickness is achieved. The thickness of the hydrogel coating is roughly controlled by monitoring the sample as a function of the number of dips with an optical microscope [43]. For instance, 1 dip is sufficient for a thin coating, and roughly 20 dips are needed to obtain a thick diameter coating. The hydrogel-coated electrodes are then dried in a laminar hood [43] or by exchanging ethanol and drying in an air stream [40].

In practice, the Dipping Method has several problems. First, lateral movements of the neural electrode effect the reproducibility of the alginate coating around the shank of the probe [40]. Second, it is impossible to control the average thickness by just approximating the number of dipping cycles (as verified by ellipsometry data in Figure 4B of [44]). Third, it is impossible to control the maximum radial thickness by just altering the number of dips (as demonstrated in Figure 2C of [45]). Fourth, the speed of dipping effects the uniformity of the alginate coating around the shank of the probe [40]. These limitations of the Dipping Method are confounding and counter-productive when considering that the entire rationale for using hydrogel coatings was to control the mechanical properties of the electrodes in [41]. Furthermore, the Dipping Method requires a human observer to subjectively monitor the entire dipping process with an optical microscope [43]. Therefore, this proposed Dipping Method essentially eliminates one of the primary advantage of the Michigan probes: exploiting semiconductor manufacturing techniques to allow batch fabrication for the high reproducibility of geometrical/electrical characteristics (as highlighted in Section 3.1.2).

4.4. The "Dropping Method"

Techniques for coating hydrogels onto microelectrodes include spray coating, brush coating, Dipping Methods [39–45], and micropipetting [38]. Unfortunately, none of these methods can produce uniform coatings in a reproducible manner [46]. Therefore, novel strategies such as the Molding Method (which involves the photopolymerization of hydrogels in a polyethylene tube) have been proposed to provide hydrogel coatings that are more reproducible and have a means to control coating uniformity and thickness (e.g. by varying the polyethylene tubing).

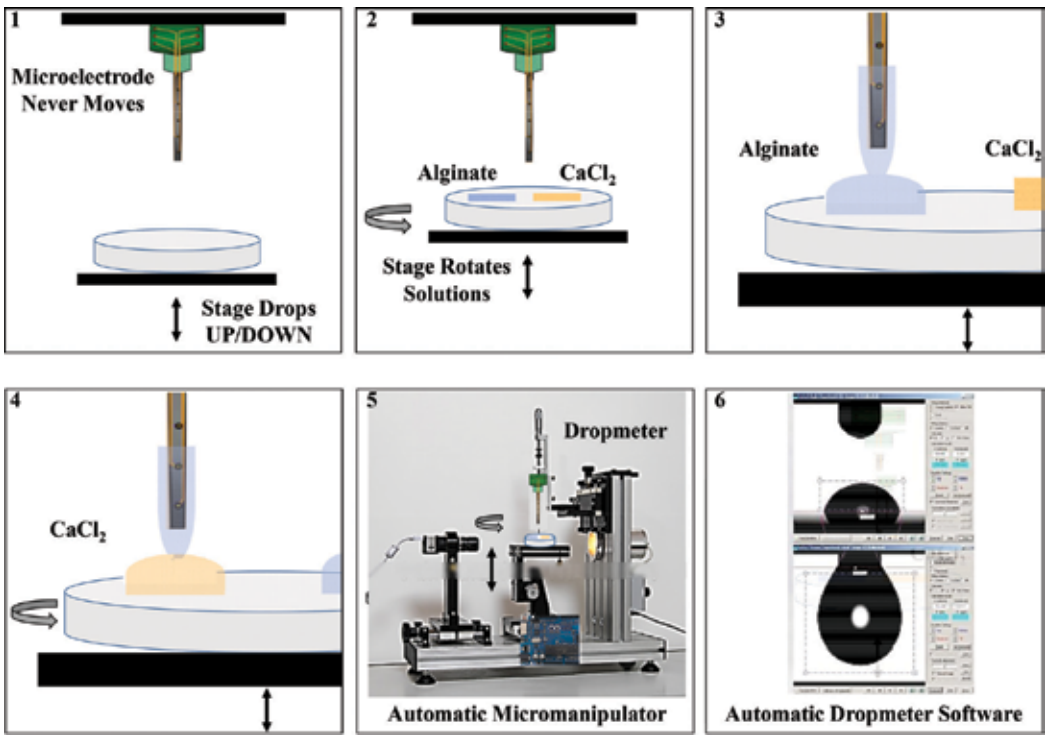

Figure 19. Dropping Method for hydrogel coating of neural electrodes with a fully-automated procedure.

Figure 19 proposes a novel procedure called the "Dropping Method" to address the reported limitations of the Dipping Method. First, the microelectrode is permanently attached in one location to eliminate lateral movements (to improve reproducibility [40]). Second, a stage that contains solutions is automatically revolved to eliminate the requirement of approximating movements (to improve the average thickness [44]). Third, the stage is dropped downward to allow gravity to align the droplets and to evenly pull down the edges (to improve the radial thickness [45]). Fourth, the speed of dropping is automated by a digital micromanipulator (to improve the uniformity of the alginate coating around the shank of the probe [40]). Finally, the optimal contact angle is automated on a Dropmeter stage via programmable software (instead of relying on subjective interpretations of a human observer via optical microscopy as in [43]).

FEM and histological analyses have shown that elevated local strains correspond to increases in gliosis (with a three-fold increase in gliosis at the probe tips compared to other areas of the explanted arrays [19]). In addition, FEM pressure profiles predict that the strain at the tip can be reduced by utilizing more flexible or softer substrates, reducing the opening angle of the probe face, and by promoting tissue integration to reduce excessive adhesion. Therefore, the Dropping Method is recommended for coating hydrogel at the tips of the microelectrodes to optimize the mechanical effects for improved chronic recording stability. Applying hydrogel coatings on the probe tips should stabilize the mechanical interface and lower the interfacial tension with the surrounding biological environment. Constraining hydrogel coating depths to just the tips will also avoid the electrode coverage issue [12]. Finally, the initial penetrating profile should be reduced since only the dehydrated probe tips will reswell in thickness upon water absorption (unlike previous studies that coated the hydrogel layers along the entire length of the neural electrode shanks in efforts to reduce the sustained injury responses).

5. Conclusions

This chapter reviewed how controlling the biocompatibility and mechanical properties of a microelectrode is critical when implanting deeper within the auditory system. To effectively monitor extracellular spike amplitudes in the cortex, several design considerations should be factored to ensure that the neuronal ensembles lie within a cylindrical radius of the recording electrode. First, penetrating shafts should reduce the initial mechanical trauma during surgical implantation (to minimize the reactive responses caused by the pathway of tissue damage). Second, the indwelling microelectrodes should embed bioactive reagents since chronic neural recording failure is associated with sustained injury responses from persistent inflammatory reactions. Third, the mechanical properties should be controlled since micromotions can cause shearing and compression to the surrounding tissues (due to the large stiffness mismatch of the implanted substrates). This chapter also describes how hydrogels can minimize the cross-sectional area while ensuring the neuronal density is maintained in local areas surrounding the implant. A novel hydrogel coating "Dropping Method" is proposed instead of the Dipping Method to eliminate the problems of lateral movements, approximated cycles, and uniformity.

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Glossary

Auditory cortex: region of the temporal lobe that is responsible for processing auditory information.

Biocompatibility: ability of a biomaterial to perform with an appropriate host response in the body.

Brain machine interface: technology that allows direct communication pathways between the brain.

Chronic neural recordings: long-term neural recordings by implantable (e.g. intracortical) electrodes.

Critical surface area model: theory of minimizing electrode surfaces to reduce tissue encapsulations.

Cylindrical radius: neuronal ensembles must lie within ~140 μm of the recording electrode [12].

Dipping method: hydrogel coating as a function of the number of dips (via optical microscopy).

Dropping Method: hydrogel coating automated on Dropmeter stage (via programmable software).

Electrode micromotion: induced strain from relative movements between the probe and the tissue.

Finite element model: numerical analysis that can approximate the behavior of mechanical systems.

Glial encapsulation: formation of a fibrotic encapsulation layer or a glial scar surrounding an implant.

Hydrogel coating: biomaterials with many versatile properties such as gelling and film-forming.

Inflammatory reactions: complex biological responses of tissues that protect from harmful stimuli.

Insertion killzone: region around the shaft where the local neuron density is lower than expected.

Utah electrode array: 3D arrays consisting of conductive needles (designed at University of Utah).

Mechanical property difference: theory of minimizing micromotions to reduce tissue encapsulation.

Michigan probe: planar shanks from semiconductor platforms (designed at University of Michigan).

Microelectrode: electrical conductor used for recording neural representations in the brain.

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